Skin Tumors and Reactions to Cancer Therapy in Children

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Preface

Although cancer in children is rare, it is the leading cause of death by disease past infancy among children in the United States [1]. Fortunately, therapeutic advancements have improved the outlook of children with cancer, with a decline in cancer mortality rate by more than 50% from 1975–1977 to 2007–2010 [2]. However, with the development of novel anticancer therapies and increase in cancer survivorship, there is a growing need for multidisciplinary care to manage both acute and long-term complications of therapy. Dermatologists play important roles in this care, from the recognition of cutaneous reactions to therapy requiring only symptomatic relief, to the detection of life-threatening secondary skin cancers and treatment side effects.

Cutaneous malignancies are particularly rare in children and thus may pose significant diagnostic or therapeutic dilemmas when encountered. While many skin cancers can be seen across ages, there are special considerations in clinical presentation (e.g., modified ABCDs of pediatric melanoma), risk factors (e.g., genetic predisposition syndromes associated with nonmelanoma skin cancer), and therapeutic response (e.g., phototherapy in cutaneous T cell lymphoma) in children that are important to recognize [3–5]. In addition, there are cutaneous proliferations with uncertain prognosis, such as pityriasis lichenoides chronica, skin-limited Langerhans cell histiocytosis, and cutaneous mastocytosis that demand further attention and research.

Our book strives to address the most pertinent issues that dermatologists face in the care of children with oncologic conditions. We begin by discussing various cutaneous malignancies and tumors with malignant potential. We then focus on acute complications of therapy, including drug reactions, graft-versus-host disease, and opportunistic skin infections. We conclude with a chapter on malignant and nonmalignant late effects of the skin in childhood cancer survivors.

We hope that this book will be a guide for practicing dermatologists on the care of children with oncologic conditions and serve as an impetus for future research and future texts as the important niche of oncodermatology evolves.

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Melanoma and Spitz Nevi in Children

1

Catherine Warner and Melinda Jen

Melanocytic nevi are common skin neoplasms and can be either congenital or acquired. While congenital nevi can be present at birth or appear shortly thereafter, acquired nevi continue to develop through childhood and into early adulthood. In a large cross-sectional study of kindergarten children in Germany, nevi were noted to increase in number from a median of 3 at 2 years of age to 19 at 7 years of age [1]. Variations in mean nevi number across geographic locations has been noted to be inversely associated with latitude and supports the role of sun exposure in nevi development. A study comparing the number of nevi over time in children born in Scotland versus Australia found a similar frequency of nevi at birth but a significant difference in the number of nevi over time. At 2 years of age, 100% of the children in Australia had nevi compared to 62% of children in Scotland [2]. Since these two groups have similar skin types, this highlights the role of sun exposure in the development of nevi.

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In addition to the development of new nevi, existing nevi naturally evolve throughout childhood, and a change in appearance may be not be concerning for melanoma [3–5]. Although pediatric melanoma is uncommon, identifying clinically suspicious lesions is essential for timely diagnosis and treatment. Appropriately identifying concerning lesions is especially important in the pediatric population where biopsies may be relatively more emotionally or psychologically stressful. Spitz nevi and atypical Spitz nevi pose a particular challenge clinically and histologically because of features that overlap with melanoma. Research has focused on histologic, immunohistochemical, and genomic methods to differentiate between these three entities.

Spitz Nevi

Key Points

- Most commonly found in the pediatric population.
- Present as smooth pink, red, brown, or black papules that initially grow rapidly and then stabilize.
- Composed of epithelioid and/or spindle cells.

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In 1948, Dr. Sophie Spitz described a subset of pediatric melanocytic tumors that had features of melanoma but lacked their aggressive clinical characteristics [6]. Although previously called "benign juvenile melanoma," this tumor is now called "spindle and epithelioid cell nevus" or, more commonly, "Spitz nevus." A variant of the Spitz nevus is the pigmented spindle cell nevus (pigmented cell tumor of Reed, Reed nevus, pigmented Spitz nevus).

Clinical

Spitz nevi most commonly arise in patients less than 20 years of age [7–9]. They present as well-circumscribed pink, red, brown, or black papules. They are generally smooth and dome shaped, though can sometimes be verrucous, and are less than 1 cm in diameter and solitary. A period of initial rapid growth is often followed by stability in size. A common clinical scenario is that of a new onset pink papule with rapid growth initially and then stabilizes in size in a young child (Fig. 1.1). Spitz nevi are most often found on the lower extremities and the trunk [8–12]. Regression of Spitz nevi over years to months has been observed [13, 14]. In comparison, pigmented spindle cell nevi are uniformly dark brown to black macules or thin papules. They are usually less than 6 mm in diameter and most commonly found on the extremities [15].

On dermoscopy, Spitz nevi have several common patterns, including starburst, globular, homogeneous, negative network, and reticular patterns (Fig. 1.2) [17]. The starburst pattern is demonstrated in more than 50% of biopsied Spitz nevi and is associated with 96% diagnostic sensitivity. This pattern was named for its exploding star-type appearance and can be composed of streaks (pseudopods or radial streaming) or multiple rows of peripheral globules [18]. The starburst pattern signifies an initial radial growth phase before transitioning to a homogeneous pattern with a blue-white veil [19]. The starburst pattern also characterizes pigmented spindle cell nevi [20]. Common melanoma-specific structures, such as atypical pigment network, negative network, crystalline structures, blue-white veil, and irregular vessels, have been described in Spitz nevi but are more likely to be symmetric and organized.

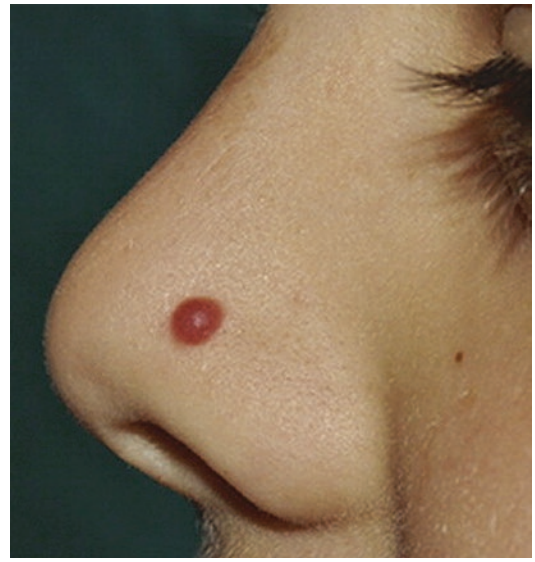

Fig. 1.1 Characteristic appearance of a Spitz nevus as a smooth dome-shaped pink papule [16]. Reprinted from Journal of the American Academy of Dermatology, Vol. 65, No. 6, Luo S, Sepehr A, Tsao H, Spitz nevi and other Spitzoid lesions: Part I. Background and Diagnoses, pages 1073–1084, © 2011, with permission from Elsevier

Histology

While the majority of Spitz nevi are compound, they can also be junctional or intradermal. At low power, Spitz nevi are dome or wedge shaped, symmetric, and well-circumscribed. At higher power, Spitz nevi have characteristic epithelioid and/or spindled melanocytes with prominent cytoplasm. Junctional cells are nested and often have clefts separating individual cells or nests from adjacent epidermis. Cells mature to become small individual melanocytes deeper in the dermis. Kamino bodies are acellular pale eosinophilic structures often found within the epidermis and are composed of basement membrane material. Epidermal hyperplasia, hyperkeratosis, and hypergranulosis are commonly seen. Occasional mitotic figures can be seen within the epidermis

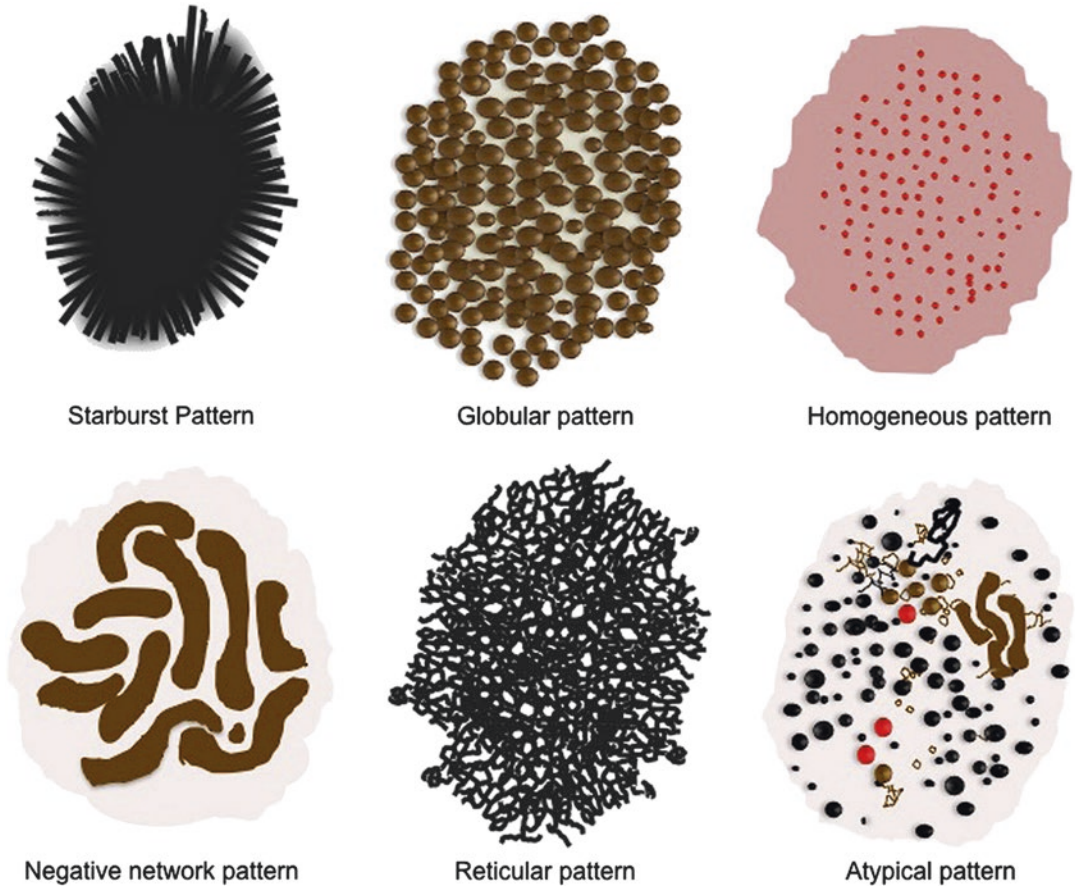

Fig. 1.2 Common dermoscopy patterns seen in Spitz nevi [17]. Reprinted from Dermatologic Clinics, Vol. 31, No. 2, Kerner M, Jaimes N, Scope A, Marghoob AA, Spitz nevi: a bridge between dermoscopic morphology and histopathology, pages 327–335, © 2013, with permission from Elsevier

or superficial dermis, although deep mitoses can indicate a more atypical tumor (Fig. 1.3a, b). Pigmented spindle cell nevi resemble Spitz nevi histologically but have prominent cytoplasmic pigmentation.

Genetics

Approximately 20% of Spitz nevi demonstrate an increase in chromosome 11p, which is the site of the *HRAS* gene [21]. Gain of this genetic locus is very rare in cutaneous melanoma. Gain of chromosome 11p therefore suggests a more benign etiology (see Genetics and Molecular Analysis below). Apart from an occasional gain in *HRAS*, genetic gains or losses are rare in Spitz nevi.

Management

Although generally considered to be benign, controversy exists surrounding the management of Spitz nevi. For classic appearing Spitz nevi in school-aged children, some advocate for clinical observation, while others advocate a biopsy of any Spitzoid lesion [22–29]. There is consensus throughout the literature, however, that biopsy should be performed for any lesion with atypical features, rapid evolution, asymmetry, or ulceration. A partial biopsy should be avoided because overall architecture is an important criterion for diagnosis of a Spitz nevus. If clinically visible tumor remains after initial biopsy, then most clinicians would recommend re-excision. If only the histologic margins of a biopsy are positive, the need for re-excision is

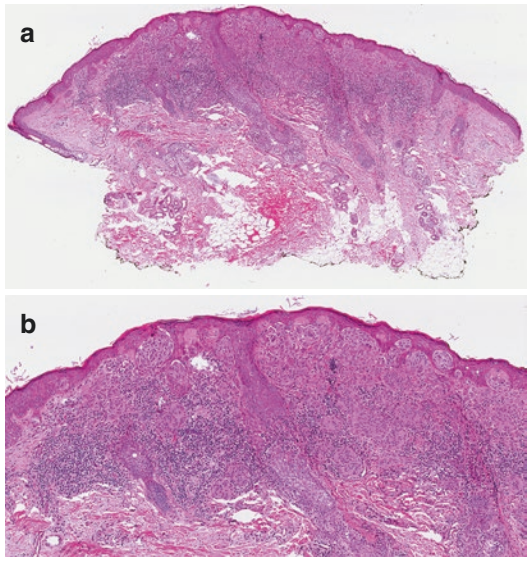

Fig. 1.3 Spitz nevus. (**a**) At low power, the characteristic wedge-shaped, symmetric, well-circumscribed architecture of a Spitz nevus is seen (H&E, 40×). (**b**) Junctional and dermal nests of mostly epithelioid and some spindled melanocytes are seen. Eosinophilic globules (Kamino bodies) are in the epidermis, and there is mild epidermal hyperplasia. Lymphohistiocytic inflammation is present in the dermis (H&E, 100×) (Image courtesy of Adam I. Rubin, MD)

controversial. In a survey of pediatric dermatologists, approximately one-third of respondents would re-excise a Spitz nevus after partial biopsy, which is similar to the results of a survey of general dermatologists [28–30]. Though, if re-excision is pursued, narrow 1–2 mm margins are adequate.

Atypical Spitz Tumors

Key Points

- Histologic features overlapping with Spitz nevi and melanoma.
- Molecular testing with fluorescence in situ hybridization and/or comparative genomic hybridization is an adjunct to histologic evaluation.
- HRAS mutations, BAP1 mutations, and kinase fusions have been identified in these tumors.

Atypical Spitz tumors (AST), also called Spitzoid tumors of uncertain malignant potential (STUMP), are challenging because they have histologic features that overlap with both classic Spitz nevi and with melanoma. Consequently, the diagnosis and management of these tumors are controversial and still evolving.

Atypical Spitz tumors are often considered within the larger category of "borderline melanocytic tumors" or "melanocytic tumors of unknown malignant potential" (MelTUMP). The term "MelTUMP" was first used by Elder and Xu to encompass a wide spectrum of lesions that demonstrate features of both benign melanocytic nevi and melanoma [31]. In addition to AST, pigmented epithelioid melanocytoma, deep penetrating nevus, and cellular blue nevus are the most common neoplasms included in this group.

Clinical

Atypical Spitz tumors have a varied clinical appearance. They can be indistinguishable from benign Spitz nevi and present as growing pink, red, brown, or black papules. In other cases, AST can have concerning clinical characteristics, such as rapid growth, irregular pigmentation, ulceration, nodularity, or easy bleeding. AST can be found anywhere on the body but are most often on the trunk or extremities [32].

Genetics

Several mutations have been identified in ASTs, including *HRAS* mutations, *BAP1* mutations, and kinase fusions. These mutations are not unique to AST and are often not definitive for distinguishing an AST from a Spitz nevus or melanoma. Comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) are being used to further identify chromosomal aberrations in tumors to aid in diagnosis (see Molecular Analysis below).

ASTs with *HRAS* mutations have an increase in chromosome 11p copy number and consequently *HRAS* gain of function. *HRAS* is an

oncogene that activates both the MAP/ERK and PI3K/AKT/mTOR pathways allowing for cell proliferation. *HRAS* mutations are rarely found in melanoma [33–36] and, when found in AST, tend to have a good prognosis [37]. On histology, these tumors are predominantly intradermal and comprised of large, pleomorphic melanocytes that have an infiltrating growth pattern at the base. There is marked stromal desmoplasia and sclerosis [35].

BAP1 (BRCA1-associated protein 1) is a nuclear protein that functions as a tumor suppressor and has a role in DNA damage repair, cellular differentiation, transcription, and cell cycle control. Germline *BAP1* mutations are found in cancer predisposition syndrome, but somatic loss of *BAP1* has been identified in some ASTs. These tumors generally also harbor *BRAF* mutations [38]. *BAP1* inactivated tumors have also been known as *BAP1*-inactivated Spitzoid nevus, BAP-oma, nevoid melanoma-like melanocytic proliferation (NEMMP), and melanocytic *BAP1*-mutated atypical intradermal tumors (MBAIT) [39]. *BAP1* inactivated tumors tend to be skin-colored or dome-shaped papules or nodules. Histologically, *BAP1*-inactivated tumors are predominantly dermal tumors comprised of large epithelioid cells with abundant amphophilic cytoplasm, nuclear pleomorphism, and prominent nucleoli [39]. Loss of *BAP1* staining on immunohistochemistry can be used to identify these tumors.

Kinase fusion proteins involving the tyrosine kinases *ALK, ROS1, NTRK1, RET,* and *MET* and the threonine kinase *BRAF* have been identified in approximately 50% of AST [40, 41]. The fusion of these kinase genes with another gene creates an enzyme that is constitutively active. *ALK* fusion proteins are present in 5–15% of AST and are most commonly fused with *TPM3* and *DCTN1* [41–43]. *ALK*-positive tumors typically have a plexiform growth pattern with fascicles of fusiform melanocytes in the dermis [42, 43]. ALK immunohistochemical staining is positive in these tumors. *ROS1* fusion proteins are present in 6% of AST [41]. These tumors have no characteristic clinical or histologic appearance, and ROS1 staining has low sensitivity and specificity. *NTRK1* fusion proteins have been identified in up to 25% of AST [40]. NTRK1 staining has high sensitivity and specificity and can be useful in identifying ASTs that otherwise have no characteristic clinical or histologic findings. *RET, MET,* and *BRAF* fusions are less commonly found in AST [40, 41, 44].

Histology

Histopathologic criteria for AST have not been established. There is frequently variability between pathologists as to the whether a tumor is a benign Spitz nevus or an AST and whether a tumor is an AST or Spitzoid melanoma. In one study, there was poor agreement between 13 expert dermatopathologists asked to evaluate a cohort of atypical tumors [45]. Molecular genetic analyses have been pursued as a way to more precisely define and distinguish between these entities.

Compared to the classic histology of Spitz nevi, AST may demonstrate greater cytologic atypia, ulceration, cellular density, lack of maturation, deep mitoses, and larger size. Histologic features that would be considered more consistent with a diagnosis of melanoma include a mitotic rate above 6 mitoses/mm^2, significant asymmetry, and tumor extension to the subcutaneous fat [46].

Immunohistochemical stains for HMB-45 (Gp-100), Ki-67 (MIB-1), and p16 can be used together to further assess these tumors. HMB-45 is a melanocyte stain that can be used to assess the maturation of a tumor. Spitz nevi demonstrate maturation with depth, so HMB-45 expression decreases toward the base. On the other hand, melanoma demonstrates a more uniform or scattered HMB-45 distribution throughout. Ki-67 is a marker of cellular proliferation and in benign nevi is usually present in the epidermis but is absent in the deep dermis, also reflecting melanocyte maturation. Increased Ki-67 expression in deep dermal melanocytes is seen in melanoma [47]. *CDKN2A* on chromosome 9p21 encodes for the tumor suppressor p16 and has been found to be associated with more clinically aggressive AST [44, 48–51].

If staining for p16 is lost, it is indicative of a homozygous loss of 9p21 and may be associated with more aggressive behavior [44].

Molecular Analysis

As the genetic landscape of melanocytic tumors has become more defined, chromosomal analysis is used to distinguish between Spitz nevi, AST, and melanoma. FISH and array CGH are molecular techniques that identify genetic aberrations in tumors. FISH utilizes fluorescently labeled short fragments of DNA (probes) that bind to tumor DNA. Each nucleus should bind two probes and thus have two fluorescent dots. If there is chromosomal gain or loss corresponding to the probes, then there will be more or less than two dots, respectively. Array CGH is similar, though able to detect chromosomal gain and loss over the entire genome through binding to a DNA microarray.

Current FISH testing includes the five probes, *RREB1*/6p25, *MYC*/8q24, *CDKN2A*/p16/9p21, *CCND1*/11q13, and *Cen9*/centromere 9. This set of probes have been shown to have a sensitivity of 94% and specificity of 98% for detecting Spitzoid melanomas [52]. Studies have found clinical patterns based on FISH testing that can help prognosticate AST (Table 1.1).

AST with isolated homozygous loss of 9p21 exhibit more aggressive behavior, with a greater likelihood of tumor spread to lymph nodes and death due to disease [44, 48–51]. Because of this aggressive behavior, the term "Spitzoid melanoma with isolated homozygous loss of 9p21" has been proposed for these tumors [44, 48]. Although more aggressive, these tumors seem to have a better prognosis than conventional melanomas [44, 48]. AST with isolated heterozygous loss of 9p21 have a more benign clinical course, with no tendency for metastasis and with a prognosis similar to tumors with negative FISH [44, 48–51]. Tumors with isolated heterozygous loss of 9p21 have less cytologic atypia, less atypical dermal mitoses, less nodular growth, and more Kamino bodies compared to those with homozygous loss of 9p21 [44]. Gain of 6p25 or 11q13 also exhibits aggressive behavior but may be less aggressive than tumors with homozygous 9p21 loss [48]. Gain of 8q24 has been rarely identified in AST, appears as amelanotic papules or nodules, and histologically has sheets of small- to intermediate-sized melanocytes with monotonous cytologic appearance, nuclear atypia, and prominent mitoses [49]. Because these tumors are so rare, it is difficult to assess their risk. In the past, a probe for *MYB*/6q23 was included in FISH panels but has been replaced with 8q24. Though AST with isolated loss of 6q23 could have positive sentinel lymph nodes, these tumors tend not to spread beyond the sentinel node or have metastasis [48, 49, 53].

Array CGH identifies copy number alterations over the entire genome of a tumor. In general, benign nevi lack copy number alterations, while melanomas have multiple copy number alterations, sometimes involving a portion of a chromosome but other times entire chromosomes [54, 55]. Melanomas often have amplification of oncogenic genes (*BRAF*/7q34 and *MITF*/3p13) or gain in larger oncogenic regions (6p, 7, and 8q). Homozygous loss of tumor suppressor genes (*CDKN2A*/9p21 and *PTEN*/10q23) and tumor suppressor regions (6q, 8p, 9p, 10) are commonly seen. The more atypical Spitzoid tumors have more chromosomal aberrations.

Management

No guidelines for management exist for these extremely challenging tumors. Because AST have an uncertain malignant potential, complete

Table 1.1 Risk stratification of atypical Spitz tumors based on fluorescence in situ hybridization results

High risk	Intermediate risk	Low risk
Isolated homozygous loss of 9p21	Isolated gain 6p25 or gain 11q13	Heterozygous loss 9p21 Isolated loss of 6q23 Negative FISH

excision is recommended. The role of sentinel lymph node (SLN) biopsy for the diagnosis and management of AST is controversial. Some have advocated for the use of SLN biopsy to aid in diagnosis, with the presence of tumoral deposits in the lymph node as evidence for malignancy. The interpretation of finding atypical cells in the SLN is complicated by the fact that deposits of benign nevi, including Spitz and blue nevi, can be found within local lymph nodes [56–60]. Furthermore, there is mounting evidence that SLN biopsy is not useful for diagnosis or management for AST. Even when the SLN is positive, multiple studies have found that it does not indicate an increased risk for metastasis or increased mortality [61–66]. In pediatric patients with AST treated with excision with clear margins alone and without SLN biopsy, a follow-up study showed excellent prognosis, with no recurrence, metastasis, or death from disease [65]. Patients with a history of AST should continue to have close clinical follow-up 1–2 times a year.

Pediatric Melanoma

Key Points

- Uncommon and decreasing in incidence.
- Three age categories: congenital (in utero to birth), childhood (<10 years of age), and adolescent (10–19 years of age).
- Additional ABCD criteria of pediatric melanoma (amelanotic, bleeding, bump, color uniformity, de novo, of any diameter) aids in identifying suspicious lesions.

Pediatric melanoma is an uncommon diagnosis and accounts for about 6% of cancers in adolescents between 15 and 19 years of age. The incidence of melanoma in individuals under 20 years of age is 0.37 per 100,000 person years, with the incidence increasing with age [67]. Fortunately, the incidence of pediatric melanoma has been decreasing up to 11% annually in the United States [68–70]. This decrease may be due to improved public health programs educating about the risks of indoor tanning and advocating for sun safety and sun protection. After Australia instituted a skin cancer educational program, a similar decrease in incidence was documented [71].

Clinical

Pediatric melanoma can be subdivided into three age groups: congenital (in utero to birth), childhood (<10 years of age), and adolescent (10–19 years of age). Congenital melanoma is extremely rare, with only 23 cases reported between 1925 and 2002 [72]. It can occur within a congenital melanocytic nevus or secondary to transplacental transmission of maternal melanoma. Childhood and adolescent melanoma can occur de novo or in association with another nevus.

The clinical presentation of melanoma in children differs from that in adults. A study evaluating the usefulness of the classic ABCDE criteria (**a**symmetry, irregular **b**orders, multiple or irregular **c**olor, **d**iameter >6 mm, **e**volution) in the pediatric population found it failed to identify melanoma in 60% of cases in patients less than 10 years of age. Additional ABCD criteria were recommended in this prepubertal age group: **a**melanotic, **b**leeding, **b**ump, **c**olor uniformity, **d**e novo, of any **d**iameter [73].

Overall, there is a female preponderance for pediatric melanoma, though more common in males in the prepubertal (<10 years of age) age group and females in adolescence [74]. Tumors in the younger age group tend to be significantly thicker and diagnosed at a more advanced stage than in adolescence [74]. This difference is likely related to the delay in diagnosis because of the low index of suspicion for melanoma in younger age groups and difficulty or reluctance to biopsy children. Head and neck melanoma is more common in the very young, while the trunk is more common in adolescence [69].

Risk Factors

Risk factors for the development of melanoma in children are fair skin, blue or green eyes, blond or red hair, tendency to freckle, intermittent intense sun exposure, family history of melanoma, personal history of atypical nevi, and systemic immunosuppression. Additional risk factors include large congenital melanocytic nevi, familial atypical multiple mole melanoma syndrome, *BAP1* tumor predisposition syndrome, and xeroderma pigmentosum.

Congenital melanocytic nevi (CMN) are categorized based on their projected final adult size, with small CMN measuring less than 1.5 cm, medium-sized CMN 1.5–20 cm, and large CMN greater than 20 cm. Small and medium CMN have a lifetime risk of less than 1%, though the general risk of melanoma in the United States is about 2% [67, 75–81]. The reported risk of melanoma in large CMN ranges from 0 to 50%, though the risk is likely closer to 5–10% [77, 82–92]. Importantly, prophylactic excision of CMN does not entirely eliminate the risk of melanoma [91, 93].

Familial atypical multiple mole melanoma (FAMMM) syndrome is characterized by the development of atypical nevi starting early in life and an increased lifetime risk of melanoma. Inherited, in an autosomal dominant manner, FAMMM is caused by a mutation in *CDKN2A*, which encodes for p16, a tumor suppressor. In addition to the risk for cutaneous melanoma, patients with FAMM have an increased risk of developing ocular melanoma and other internal malignancies, most commonly pancreatic cancer. Up to 10% of melanomas in this group occur in individuals before the age of 20, making the identification of at-risk children imperative [94]. Melanoma astrocytoma syndrome (MAS) is a variant of FAMMM that is also caused by a mutation in *CDKN2A*. *CDKN2A* encodes for two proteins, p16 and p14, both tumor suppressors, and MAS is caused by a mutation in p14. Patients with MAS are at risk for melanoma and for a number of central nervous system tumors, including astrocytoma and meningioma.

As noted above, mutations in BRCA1-associated protein 1 (BAP1) has been identified as a risk factor for multiple malignancies. In addition to characteristic BAP1-inactivated tumors described above (see Atypical Spitz Nevus), patients with *BAP1* tumor predisposition syndrome develop cutaneous and uveal melanomas, mesothelioma, clear cell renal cell carcinoma, and basal cell carcinoma.

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder caused by mutations in the DNA repair mechanism, so patients are unable to repair UV-induced DNA damage. Patients with XP are at an increased risk of developing multiple types of skin cancer, including melanoma. Melanoma develops in approximately 5% of patients with XP, often at younger than 20 years of age [95].

Genetics

Pediatric conventional melanoma has the greatest number of single-nucleotide variations of any pediatric cancer [96]. Mutations in *TERT* (telomerase reverse transcriptase core promoter) are found in all pediatric conventional melanoma [96]. Eighty-seven percent of conventional melanoma also has *BRAF* V600 mutations, commonly in association with a *PTEN* mutation [96]. Interestingly, *BRAF* V600E mutations have been found in a higher proportion of adolescents with histologically conventional melanomas than in the adult population [97]. Melanoma arising in a congenital nevus tends to have mutations in *NRAS*. Some Spitzoid melanomas have kinase fusions, and another subset with *TERT* mutations is at increased risk for metastasis and poor prognosis [96, 98].

Management

Staging of pediatric melanoma utilizes the adult staging system recommended by the American Joint Commission on Cancer (Tables 1.2 and 1.3) [99]. All melanoma should be completely excised, with excision margins identical to those

Table 1.2 (**a**–**c**) American Joint Commission on Cancer 2009 melanoma TNM staging categories [99]

a. Tumor classification		
Classification	Thickness (mm)	Ulceration status/mitoses
Tis	N/A	N/A
T1	≤1	a: Without ulceration and mitoses <1mm^2 b: With ulceration or mitoses ≥1mm^2
T2	1.01–2	a: Without ulceration b: With ulceration
T3	2.01–4	a: Without ulceration b: With ulceration
T4	>4	a: Without ulceration b: With ulceration
b. Regional lymph node classification		
Classification	Number of metastatic nodes	Nodal metastatic burden
N0	None	N/A
N1	1	a: Micrometastasis b: Macrometastasis
N2	2–3	a: Micrometastasis b: Macrometastasis c: In-transit met(s)/satellite(s) without metastatic nodes
N3	4+ Metastatic nodes, matted nodes, in-transit met(s)/satellite(s) with metastatic node(s)	
c. Distant metastasis classification		
Classification	Site	Serum LDH
M0	No distant metastases	N/A
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

recommended for melanoma excision in adults (0.5 cm for in situ, 1 cm for tumors <1 mm thick, 1–2 cm for tumors 1–2 mm thick, and 2 cm for tumors >2 cm thick) [100, 101].

As in adults, sentinel lymph node biopsy is recommended for melanomas greater than 1 mm in depth or those less than 1 mm with ulceration and Clark level IV or V. Support for SLN biopsy in the pediatric literature has been based on the fact that multiple series showed mortality only in patients with positive lymph nodes [102–104]. Notably, several studies have shown no difference in overall survival between node-positive and node-negative pediatric patients [102, 103, 105, 106]. Intriguingly, rates of positive SNL biopsy are higher in the pediatric than adult population (around 40% in pediatric patients vs. 20% in adults), while disease-free survival is superior [103, 107–110]. Some authors have suggested the better prognosis stems from age-related differences in lymphatic flow and immune system [111]. An association between methylation of tumor-related genes in positive SLNs of pediatric patients and worse outcomes needs to be further investigated [112]. The ability to stratify pediatric patients into high- and low-risk groups based on SLN biopsy may prove helpful in the future. While the utility of SNL biopsy in pediatric melanoma is further investigated, it remains a part of tumor staging. If the SLN is positive, the role for complete lymphadenectomy remains unclear. Studies have shown that a positive SLN is not

Table 1.3 American Joint Commission on Cancer 2009 melanoma anatomic staging categories [99]

Clinical staging				Pathologic staging			
0	Tis	N0	M0	0	Tis	N0	M0
1A	T1a	N0	M0	1A	T1a	N0	M0
1B	T1b	N0	M0	1B	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	≥N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	Any M	IV	Any T	Any N	M1

associated with additional positive nodes, and complete lymph node dissection can have considerable morbidity while not altering prognosis [103, 108, 113].

Adjuvant therapy in pediatric patients is limited primarily due to lack of FDA-approved therapies, though there are several clinical trials in process evaluating the use of newer therapies. Interferon-α2b is most commonly used, with evidence showing its safety and tolerability in children [114]. Other newer classes of therapies include immunotherapies and targeted therapies. For melanomas with *BRAF* mutations, BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) target the mutated protein that leads to uninhibited cell proliferation. MEK inhibitors (trametinib, cobimetinib) block the RAS/RAF/MEK/ERK pathway downstream from mutant proteins in tumors caused by *BRAF* and *NRAS* mutations. For tumors that are *BRAF* negative, immunotherapy can be considered. These treatments stimulate the immune system to recognize and target melanoma cells. PD-1 inhibitors (pembrolizumab, nivolumab) and CTLA-4 inhibitors (ipilimumab) are checkpoint inhibitors that allow the immune system to identify and target melanoma cells. Other targeted therapies in development include MEK inhibitors with or without CDK4/6 inhibitors for *NRAS* mutant melanomas, mTOR and MEK inhibitors for NF-1 mutant melanoma, and tyrosine kinase inhibition for *KIT*-mutated melanoma.

Prognosis

Overall age-adjusted mortality rate for pediatric melanoma is 2.25 deaths per year [115]. One registry analysis of 365 patients found 5-year survival to be 97, 88, 84, and 40% in patients with stage I, II, III, and IV disease, respectively [75]. Factors associated with a poor prognosis include

ulceration, higher Clark level, higher tumor thickness, lymph node metastasis, and higher tumor stage [74, 102, 105, 116]. Though studies have shown conflicting results, it appears that younger age at diagnosis is associated with better prognosis [74, 75, 102, 105, 106, 115–118]. Spitzoid melanoma has a better prognosis compared to conventional melanoma of the same stage [61, 119].

Summary

Since Sophie Spitz's initial description of Spitz nevi as "benign juvenile melanoma," much has changed in the way we think about Spitz nevi and pediatric melanoma. The spectrum of melanocytic tumors ranging from Spitz nevi, to atypical Spitz tumors, to melanoma, has been better defined, though much still needs to be understood. Adjunctive histologic and molecular testing has helped to better categorize melanocytic tumors within this spectrum. As we continue to define the genomic landscape of Spitzoid tumors and melanoma, more definitive methods of diagnosis will hopefully become available and, importantly, a better understanding on how to counsel families on the nature and prognosis of these tumors.

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Congenital Nevi

2

Johanna S. Song, Diana Bartenstein, and Elena B. Hawryluk

Background and Diagnosis

Key Points

- Congenital melanocytic nevi are present in 1% of newborns.
- Most CMN likely occur due to postzygotic somatic mutations.
- CMN are classified by their projected adult size into categories: small, medium, large, and giant, which inform associated risks of melanoma and neurocutaneous melanocytosis.

Overview

Congenital melanocytic nevi (CMN) are pigmented lesions that form in utero (5th–24th week of gestation) and are present at birth or appear within the first weeks of life as melanin develops [1, 2]. Approximately 1% of newborns [3] have a CMN of any size, but larger lesions are far rarer than smaller ones. CMN over 20 cm are estimated to occur in only 1 out of every 20,000–500,000 newborns [4]. Historically, giant CMN (over 40 cm) have also been called other names based on their distribution and visual features, including garment nevus, bathing trunk nevus, giant hairy nevus, giant pigmented nevus, nevus pigmentosus, and nevus pilosus [3].

Pathogenesis

CMN are thought to develop from cutaneous stem cells in a process independent of normal melanocyte differentiation [5]. In ordinary skin, melanoblasts migrate from the neural crest to the embryonic dermis and subsequently to the epidermis where they differentiate [6]. An observation of normal basal layer epidermal melanocytes overlying dermal CMN suggests that CMN cells have a unique pathogenesis [5].

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Genetics

Most CMN occur sporadically due to postzygotic somatic mutations. Mutations in *NRAS* and *BRAF*, genes part of the mitogen-activated protein kinase pathway, have been identified as drivers of CMN melanocyte proliferation [7]. NRAS and BRAF normally activate oncogene-induced senescence following melanocyte proliferation; this process may be delayed with *NRAS* or *BRAF* mutations [8]. There have been attempts to associate specific mutations with CMN phenotypes, and 77.2–94.7% of large and giant CMN have been found to harbor *NRAS* mutations, in contrast to 62.5–70% of small-medium CMN [9, 10]. While these data suggest that *NRAS* may be an important driver of large CMN, 5.2–8.8% of large-giant CMN harbor *BRAF* mutations without an *NRAS* mutation, and up to 12.3% of samples have been identified with no mutations. Accordingly, *NRAS* mutations may not be as universal in large CMN as previously thought.

Evidence for genetic mosaicism in CMN patients comes from research demonstrating that patients with multiple CMN and/or associated neurologic lesions, harboring a single persistent *NRAS* mutation within their cutaneous lesions and neurologic samples, do not have this mutation present in non-lesional skin and blood samples [11].

However, a few rare cases of CMN familial clustering indicate that paradominant inheritance may be possible [12, 13]. In paradominant inheritance, heterozygous individuals are phenotypically unaffected; paradominant traits develop only in individuals who have a postzygotic loss of heterozygosity [14]. This theory of non-Mendelian inheritance has been posited in other rare diseases such as cutis marmorata telangiectatica [15] and Klippel-Trenaunay syndrome [16] and would explain both familial clustering as well as mosaicism observed in the CMN patients' skin.

Germline *RAS* mutations have been associated with severe growth and hormonal disorders [17–20], and patients with CMN may be susceptible to endocrine disturbance. A recent study showed that the body mass index of CMN patients was almost double that of their non-affected peers, and CMN patients had increased adiposity as well as insulin insensitivity [21]. Premature thelarche and undescended testes were also observed in several CMN patients, though puberty was otherwise unaffected, and these results raise the possibility of an underlying genetic defect in CMN patients [21].

Classification

Historically, various guidelines have been used to classify CMN based on size, depth, percent of body surface area, anatomical distribution, and satellite lesions [22]. CMN are primarily classified by their projected adult size, based on the observation that CMN grow proportionally with children [22]. Despite long-term overall proportional growth, there may be disproportionate rapid expansion during infancy [23]. Based on projected adult size, small CMN are <1.5 cm, medium lesions are 1.5–20 cm, large lesions are 20–40 cm, and giant lesions are greater than 40 cm (Table 2.1).

The following enlargement factors can be used to estimate the adult size of a CMN from its size at birth: 1.7 times for the head, 2.8 times for the trunk or arms, and 3.3 times for legs (Fig. 2.1) [22]. Krengel and colleagues propose a consensus-based, detailed classification to help clinicians identify patients at greatest risk and requiring close follow-up. These characteristics include CMN anatomic location and other morphologic features common in CMN: presence of satellite lesions, color heterogeneity, rugosity, nodules, and hypertrichosis [22]. Satellite lesions are melanocytic nevi that surround a CMN. They may exist as single or multiple lesions, and the following classification exists: S0 for no satellites present, S1 for less than 20 satellites, S2 for 20–50 satellites, or S3 for more than 50 satellites (Fig. 2.2). Color heterogeneity is classified as C0 for none, C1 for moderate, or C2 for marked variation of hue. Surface rugosity, which captures the amount of

Table 2.1 Standard classification of CMN features [22]

CMN size	
Small	<1.5 cm projected adult size
Medium	
M1	1.5–10 cm projected adult size
M2	>10–20 cm projected adult size
Large	
L1	>20–30 cm projected adult size
L2	>30–40 cm projected adult size
Giant	
G1	>40–60 cm projected adult size
G2	>60 cm projected adult size
Multiple medium	≥3 medium CMN without a single, predominant CMN
Satellite nevi	
S0	No satellites
S1	<20 satellites
S2	20–50 satellites
S3	>50 satellites
Color heterogeneity	
C0	No color heterogeneity
C1	Moderate color heterogeneity
C2	Marked color heterogeneity
Surface rugosity	
R0	No rugosity
R1	Moderate rugosity
R2	Marked rugosity
Proliferative nodules	
N0	No nodules
N1	Scattered nodules
N2	Extensive nodules
Hypertrichosis	
H0	No hairiness
H1	Notable hairiness
H2	Marked hairiness
Anatomic distribution	
Head	Face, scalp
Trunk	Neck, shoulder, upper back, middle back, lower back, breast/chest, abdomen, flank, gluteal region, genital region
Extremities	Upper arm, forearm, hand, thigh, lower leg, foot

Reprinted and adapted from *Journal of the American Academy of Dermatology*, Vol. 68/No. 3, Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA, New Recommendations for the categorization of cutaneous features of congenital melanocytic nevi, pages 441–451, © 2013, with permission from Elsevier

surface texture or "wrinkles" present, is classified as: R0 for none, R1 for moderate, or R2 for marked. Nodules are benign, secondary proliferative lesions that can develop in CMN, and are classified as N0 for none, N1 for scattered, or N2 for extensive dermal or subcutaneous nodules. Finally, hypertrichosis indicates amount of hair present and is classified as H0 for none, H1 for notable, or H2 for marked presence of hair (Fig. 2.3). This classification system has shown moderate to excellent interobserver agreement (kappa values 0.54–0.93), and its use is important for the consistency and reliability of future research [22].

Congenital Melanocytic Nevus Syndrome

Observations about the prevalence of certain extracutaneous features associated with CMN have led to the proposal of the entity "congenital melanocytic nevus syndrome," and bring into question whether genes associated with CMN have widespread effects. For example, Kinsler and colleagues found that children with CMN were more likely to have the following facial characteristics compared to a control population: wide or prominent forehead, apparent hypertelorism, eyebrow variants, periorbital fullness, small/short nose, narrow nasal ridge, anteverted nares, broad nasal tip, broad or round face, full cheeks, prominent premaxilla, open-mouth appearance, prominent or long philtrum, and prominent everted lower lip [24]. Neurologic abnormalities, whether identified clinically or by imaging, are also common in patients with CMN (see section on "Neurocutaneous Melanocytosis"). It is suggested that patients who meet both of the following criteria be considered patients with CMN syndrome: 1) CMN with projected adult size of more than 5 cm or presence of two or more CMN and 2) neurologic involvement or three or more of the characteristic CMN facial features described above [24]. Further research

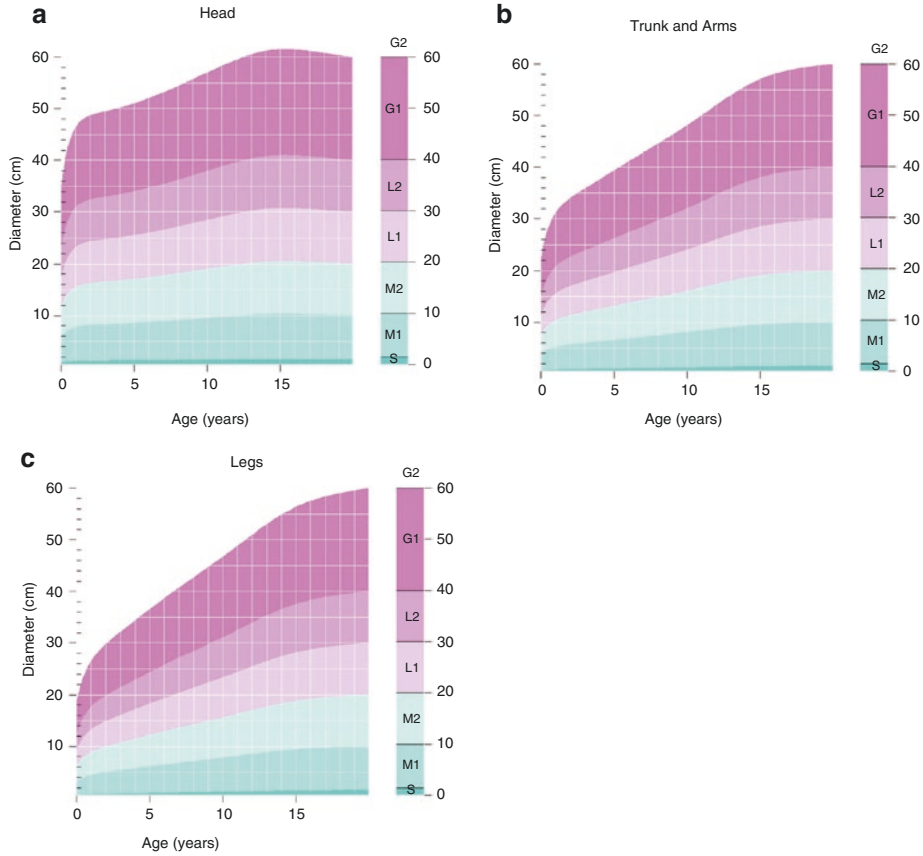


Fig. 2.1 Anticipated CMN growth. These charts are useful for determining CMN size classification, as CMN size categories are defined by projected adult size (small, medium, large, giant, categories depicted as S, M, L, G, respectively) [22]. Reprinted from *Journal of the American Academy of Dermatology*, Vol. 68/No. 3, Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA, New Recommendations for the categorization of cutaneous features of congenital melanocytic nevi, pages 441–451, © 2013, with permission from Elsevier

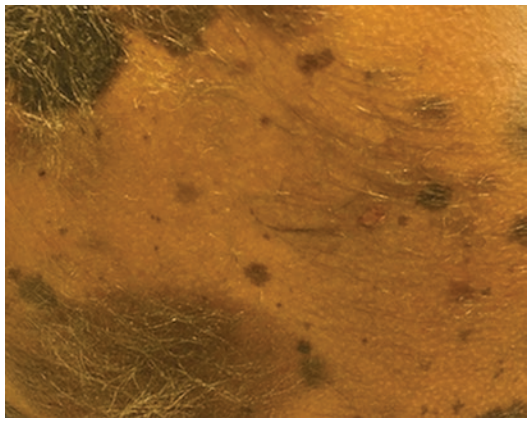


Fig. 2.2 Adult patient with multiple CMN and satellite lesions. CMN are hypertrichotic (H2) and vary in color; some papules have faded as the patient aged

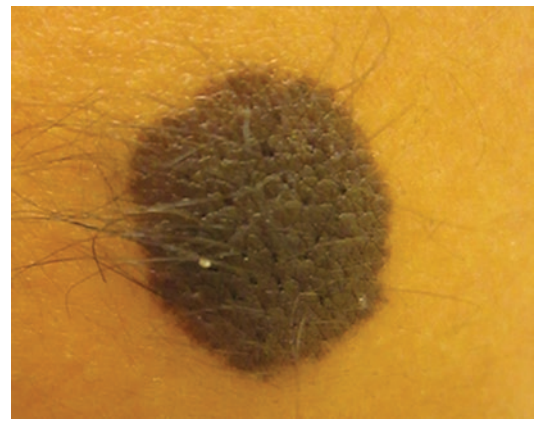


Fig. 2.3 Small CMN with marked hypertrichosis; H2 classification

on CMN syndrome may yield important insight about CMN genetics and patient outcomes to improve counseling regarding prognosis and expected course.

Differential Diagnosis

When evaluating CMN at their initial presentation, a broad differential should be considered. In one study, infantile pigmented lesions were biopsied, and many conditions other than CMN were found including café au lait spots, fibrosis and increased capillaries, toxic erythema of the newborn, congenital dermal melanocytosis, nevus sebaceous, and leiomyoma [25]. The differential diagnosis for CMN additionally includes Becker's nevus, hamartoma, pigmentary mosaicism, mastocytoma, and melanoma.

Later in life, CMN may be confused with common acquired nevi. While certain histologic and dermoscopic features may be characteristic of CMN, clinical history provides the best evidence for CMN diagnosis. If biopsy is performed, the following features are often found in CMN: nevomelanocytes that are located deeper than melanocytes of acquired nevi, within the lower two-thirds of the dermis and subcutaneous tissue [26], and nevomelanocytes that are spread between collagen bundles of the reticular dermis and other dermal apparatus, nerves, and vessels [27]. In some cases, CMN nevomelanocytes display a perivascular and perifollicular distribution and can disturb the normal development of arrector pili [3]. On dermoscopy, CMN may have a globular, reticular, complex (reticular-globular), or homogenous pattern [2, 28–30], but CMN less than 3 cm do not have dermoscopic features that distinguish them from nevi acquired during the first two years of life [30]. Likewise, it is quite common for nevi acquired at an early age to have congenital histologic features [31]. Acquired melanocytic nevi that have features of CMN have been called "tardive congenital nevi" as well as "congenital nevus-like nevi"; whether their pathogenesis is the same or distinct from that of CMN is unknown.

Evolution and Complications

Key Points

- The natural evolution of CMN includes a number of benign changes, including development of proliferative nodules.
- CMN may be associated with vitiligo, secondary skin conditions, and musculoskeletal changes.
- Serious complications include neurologic abnormalities and melanoma.

Benign Changes

CMN frequently evolve over the course of a lifetime. Benign and anticipated changes can include pruritus, increasing thickness, development of rugosity or hypertrichosis, and proliferation of nodules [2, 32–40]. Xerotic and eczematous changes may occur due to modified sebaceous glands in CMN [7]. Color lightening or darkening may also occur, though most untreated CMN lighten [41]. Some may even lighten so markedly that they are no longer visible—spontaneous involution of CMN has been reported and is particularly common on the scalp [33].

Proliferative Nodules

Proliferative nodules within CMN are a benign occurrence, though the growths are commonly mistaken for melanoma [39]. The development of proliferative nodules within a CMN is far more common than development of a melanoma. Clinically, reassuring features include the presence of multiple nodules and lack of ulceration [35]. Histologically, proliferative nodules often have lower mitotic counts, less expansile growth, and no epidermal involvement [35, 36]. Immunohistochemistry and fluorescence in situ hybridization have not shown to be reliable in differentiating between benign and malignant processes [42]. Melanomas arising in CMN may be distinguished from benign proliferative nodules by the presence of partial chromosome

gains or losses [35], though melanoma without this feature has been reported [43]. Preliminary results suggest that DNA methylation may also be utilized for diagnostic clarification. In one study, 90.65% of proliferative nodules expressed high levels of the epigenetic marker 5-hydroxymethylcytosine, whereas only 7.87% melanomas showed expression [44].

Proliferative nodules are thought to originate from a unique clonal population of cells within CMN, as nodule tissue stains intensely for c-kit while surrounding CMN tissue does not [37]. Over time, proliferative nodules may transform further—clinically, they have been observed to soften or decrease in size and pigmentation [37]. Additional findings of soft nodules and large neurofibroma-like plaques may result from peripheral nerve sheath differentiation of dermal melanocytes [45].

Autoimmune Response

Large CMN may be associated with a greater antigen burden that can trigger an autoimmune response against melanocytes. Halos, or areas of depigmentation, have been observed to surround CMN prior to spontaneous regression [34, 46], and vitiligo may be associated with CMN (Fig. 2.4). In a review of 92 patients with large CMN, 8.7% of patients had areas of depigmentation [47]—a large number in comparison to the worldwide incidence of vitiligo—which is 0.5–2.0% [48]. Furthermore, in patients with both vitiligo and halo CMN, vitiligo has been reported to resolve following excision of the halo CMN [34, 49, 50]. While CMN are suspected to trigger autoimmune disruption, the mechanism is not well understood [51].

Secondary Cutaneous Processes

CMN are subject to secondary infections and several other skin processes, similar to the surrounding skin. Potentially related to disturbance of the normal skin architecture, there have been reports of molluscum, warts (Fig. 2.5), and eczema (termed the Meyerson phenomenon) affecting CMN [52, 53]. One case report describes a rhabdomyosarcoma arising in a CMN [54]. Therefore, clinicians should consider a wide variety of etiologies, apart from melanoma, when CMN evolution is observed.

Fig. 2.4 Medium CMN with development of surrounding depigmented macules and patches

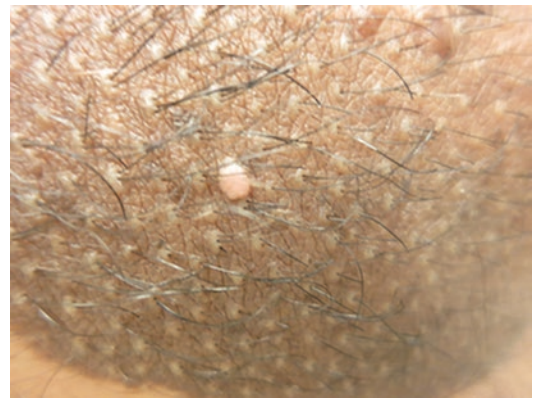


Fig. 2.5 CMN with follicular prominence and overlying verrucous pink papule. Subsequent biopsy demonstrated histopathologic findings consistent with wart

Musculoskeletal Effects

CMN can also present with musculoskeletal changes. Atrophy underlying CMN has been

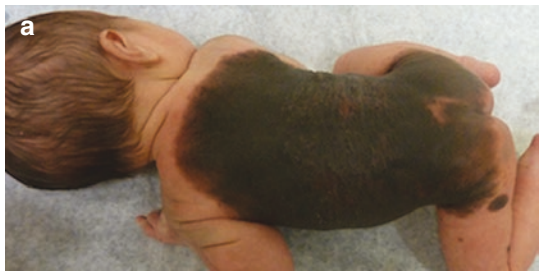
reported [55, 56], and whole-body dual-energy X-ray absorptiometry (DXA) scanning shows that there is often a reduction of fat and muscle underlying large CMN, with no change in bone development [21].

Neurocutaneous Melanocytosis (NCM)

NCM is a condition in which patients have CMN as well as melanocytes present in the meninges [57], first described by Rokitansky in 1861 and termed by Van Bogaert in 1948 (though the 1948 article was referring to heredofamilial melanosis, a different disorder) [57–59]. The terms neurocutaneous melanosis and neurocutaneous melanocytosis have been used interchangeably, but neurocutaneous melanocytosis is preferred for its accuracy, as the condition involves meningeal melanocytes as opposed to melanin accumulation [60, 61]. Criteria, proposed in 1991, for diagnosis of NCM include 1) large (> 20 cm) or multiple (more than three) congenital nevi in addition to melanosis or melanoma of the leptomeninges, 2) no cutaneous melanoma except in patients with histologically benign meningeal lesions, and 3) no meningeal melanomas except in patients with histologically benign cutaneous lesions [57]. These criteria avoid the potential for confusing patients with NCM for those with metastatic cutaneous melanoma. The differential diagnosis for symptomatic NCM includes metastatic melanoma and neurofibromatosis type I (if café au lait patches are mistaken for CMN [61]).

Risk factors for NCM include larger-sized CMN, greater number of satellite nevi, and multiple small- to medium-sized CMN [57, 62–67] (Fig. 2.6a, b). Some data suggest that male gender also represents a risk factor for neurological complications [67]. Head, neck, and posterior axial CMN were previously thought to increase the likelihood of NCM [63, 64, 66], but more recent data indicate that this effect was confounded by size, as large and giant CMN are most commonly found in the posterior axial region [67, 68].

NCM incidence statistics are difficult to estimate given a paucity of prospective studies and selection bias, but the incidence of NCM found on magnetic resonance imaging (MRI) in high-risk patients is reported between 12.3% and 33% [62, 66, 68, 69]. In the largest prospective study



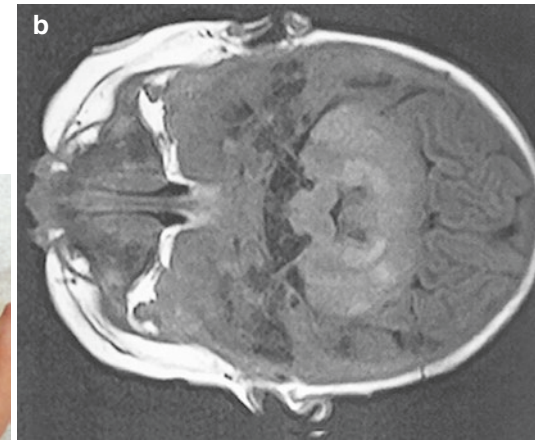


Fig. 2.6 (**a**) Infant with giant CMN. Large darkly pigmented plaque with hypertrichosis present on the entire back and extending to the anterior trunk, with some eroded areas on the right lower back, and with satellite hyperpigmented papules on the left upper posterior thigh. (**b**) (Patient from **a**) Brain magnetic resonance imaging without contrast, T1 FLAIR, revealing multiple foci of T1 shortening within the cerebellar hemispheres (shown), in addition to the dentate nuclei, pons, midbrain, and right temporal lobe, consistent with melanotic deposits. Findings are consistent with brain involvement of neurocutaneous melanocytosis

to date, 46 of 271 children (17%) with CMN demonstrated abnormalities on central nervous system MRI screening [68]. Data was collected from 1991 to 2013, and criteria for screening before 2008 was a CMN overlying the spine or brain >2 cm in size or a CMN occurring in any location equal to or larger than the patient's hand. After 2008, to reflect new results published by the group [41], researchers screened patients born with multiple CMN in any anatomic location and of any size.

NCM may present with a variety of symptoms. Symptoms most often occur in patients less than 3 years of age; however, there have also been reports of patients aged 20–30 years with presenting symptoms. These symptoms are heterogeneous; they include those associated with increased intracranial pressure and those based upon focal location of the melanocytes. Symptoms associated with increased intracranial pressure include headache, neck stiffness, photophobia, irritability, lethargy, vomiting, seizures, abnormal neurologic exam, and hydrocephalus with increased head circumference [57]. Bowel and bladder dysfunction, as well as developmental delay and behavioral changes, may also occur due to melanocytic accumulation in the brain [70–72]. Communicating hydrocephalus, a result of melanocytic accumulation in the basal cisterns preventing cerebrospinal fluid reabsorption, can lead to death [61].

In the large prospective study mentioned above, 72.2% of patients with MRI findings were symptomatic with mean follow-up time of 11 years [68]. This percentage is similar to or higher than other reported rates, ranging from 53–71% with varied follow-up times [62, 63, 71]. While symptomatic NCM was previously thought to portend an almost universally poor prognosis [57, 64], imaging advances and studies with larger sample sizes have led to lower fatality estimates [67, 68, 73]. In a study of 1008 patients with large or multiple CMN, 100% of those with head or extremity CMN and symptomatic NCM survived (0/3 deaths), 66% of those with truncal lesions and symptomatic NCM survived (10/29 deaths), and 62% of those with multiple congenital melanocytic nevi and symptomatic NCM survived (7/12 deaths) [73]. However, other large studies of patients with symptomatic CMN report that >90% of patients die from this disease and 70% of patients die before 10 years of age [40, 50, 74].

Monitoring patients with NCM includes head circumference measurements, neurodevelopmental assessments, and imaging [57]. Pediatricians and dermatologists alike must be meticulous in their physical and neurologic examinations in order to recognize early signs of NCM. MRI is the gold standard for diagnosing NCM patients and should be performed in any patient who displays delayed development or neurologic symptoms [2, 68]. Traditionally, clinicians have also pursued baseline imaging for patients with a single large CMN, multiple medium CMN, axially distributed CMN, or CMN with satellite lesions [7, 67]. A new recommendation by Waelchli and colleagues encourages baseline imaging when two or more CMN are present regardless of size, based on data suggesting that imaging a single lesion is low yield for detecting serious intracranial abnormalities [68]. While this recommendation will decrease MRI procedures for patients with a single CMN, it increases imaging for patients with multiple small CMN, whom clinicians previously considered low-risk CMN and have traditionally monitored conservatively.

It is generally recommended that baseline MRI be performed at 4–6 months of age, prior to brain myelination that may obscure radiologists' ability to see melanocytic deposits [68, 71]. While some do not endorse time sensitivity for this radiologic reason [65], parents and physicians may elect to perform a baseline MRI image early enough such that general anesthesia is not required. Unfortunately, recent observational data suggest that general anesthesia may cause cognitive changes in exposed children [75, 76]. Opponents of early imaging state that MRI is neither sensitive nor specific for symptomatic NCM; some CMN patients have neurological abnormalities in the absence of MRI changes [67, 77], and some CMN patients with positive MRI findings never develop symptoms [78]. Further, one may consider that there are no active interventions for treatment if NCM is discovered, unless

it is causing hydrocephalus, in which case the goal of relieving pressure should be addressed. Proponents of early imaging state that while false positives can lead to overtreatment, there are cases in which screening MRI can lead to prompt intervention and improved clinical outcome [68]. Further, at later points in life, the development of any focal neurologic abnormality would prompt imaging, and it is helpful to have a baseline comparison to aid in interpretation of results. At this time, these authors are supportive of early assessment of CMN patients, and if MRI can be performed prior to requirement of sedation, we have found this baseline study to be helpful in clinical management.

The most common finding on MRI is intraparenchymal melanocytosis, associated with T1 hyperintensity and T2 hypodensity [67–69, 79]. However, a wide range of central nervous system abnormalities have been reported in association with CMN, including dorsal spinal arachnoid cysts, other benign tumors, tethered cord syndrome, and various additional malformations [67–69, 71]. Accordingly, experts have suggested the terminology, "CMN syndrome," for CMN patients with any MRI changes or neurodevelopmental abnormalities [7, 68]. Waelchli and colleagues recommend that patients who have only intraparenchymal melanocytosis on MRI do not undergo serial MRI unless a clinical change occurs, but patients with additional findings on MRI require a multidisciplinary team including pediatric dermatology, neurology, neurosurgery, and neuroradiology to determine the frequency of follow-up imaging [68].

Treatment options for symptomatic NCM are primarily supportive. Treatment of CMN is discussed in the "treatment" section below. Nonmedical interventions such as speech, behavioral, and occupational therapy can attenuate developmental delay. Antiepileptic medications can control or prevent seizures. Radiation therapy can be helpful for unresectable or disfiguring lesions. Surgical removal of spinal cysts may reduce myelopathy, and ventriculoperitoneal shunts can decrease symptoms of increased intracranial pressure and prevent brain stem herniation [2, 61, 68]. Experimental therapies such as interferon, IL-2, chemotherapy, and retinoids have also been trialed in order to alleviate symptoms, but results are ambiguous [73, 80–83].

Melanoma

Melanoma is a feared complication of CMN but may be less common than previously believed. In one systematic review, the overall incidence of melanoma among CMN patients was 0.7% [84]. This data demonstrates a higher incidence of melanoma in CMN patients compared to that observed in the general pediatric population (the incidence rate in the general population was estimated at 5.93 per 1,000,000 children and adolescents, based on 2000–2010 Surveillance, Epidemiology, and End Results cancer registry data [85], but included older studies confounded by selection bias). Out of the 6571 CMN patients followed for a range of 3.4–23.7 years, 46 patients developed 49 melanomas [84]. The mean and median ages of melanoma diagnosis were 15.5 and 7 years, respectively, suggesting that CMN patients who develop melanoma are most likely to present in childhood or early adolescence.

Melanoma risk increases with CMN size; small- and medium-sized CMN have not been associated with a significantly elevated risk of melanoma [67, 78, 84, 86–89]. The lifetime melanoma risk for patients with large and giant CMN has historically been estimated at 5–15%, but newer studies report much lower incidences [90]. A recent meta-analysis including 2578 patients with large and giant CMN reported only a 2% melanoma incidence [4]. Mean age of diagnosis was 12.6 years, 14% of melanomas presented viscerally, and 55% were fatal. Melanomas most commonly occurred in patients whose CMN were greater than 40 cm (74%), were located on the trunk (68%), and had satellite lesions (94%) [4]. A retrospective study of case reports of fatal or metastasizing melanomas in children (436 patients) reported the following characteristics associated with pediatric melanoma in CMN patients (178 patients): prepubertal age (0–10 years), female gender, CMN with satellite lesions, multiple CMN, and presence of ulceration

or bleeding. On histopathology, melanomas in patients with CMN tended to be deeper in the dermis or subcutaneous fat than non-CMN melanomas [91].

Although most CMN-associated melanomas appear in childhood [4, 84], malignant melanoma can occur at any age and at any anatomical site. Congenital malignant melanoma arising in a CMN has been reported [92], and there are several reports of adult-onset melanoma associated with CMN [93–95]. Results from 1998 to 2012 National Cancer Data Base showed 976 adults with invasive melanoma in pigmented nevi more than 20 centimeters, as compared to 111,870 patients with superficial spreading melanoma and 35,962 patients with nodular melanoma [96]. In this cohort, there was an approximately normal distribution for diagnosis, around age 52 years of age, and overall survival was comparable to adults with invasive superficial spreading melanoma, despite findings that CMN patients were more likely to present with thicker Breslow depth, positive lymph nodes, and distant metastases [96].

Adult melanoma treatment algorithms have been applied to pediatric CMN patients with melanoma. Surgery is the primary treatment option, and clinicians can consider a variety of adjuvant and systemic therapies for more widespread disease (e.g., interferon-alpha2b, BRAF inhibitors, anti-PD1 therapies). Though these therapies have been studied in adults, there is minimal data for use in the pediatric population. Palliative radiation is an option for metastatic or unresectable disease [97].

One aspect of melanoma management that is unique to CMN patients is interpretation of the sentinel lymph node biopsy; CMN patients without metastatic melanoma may have large amounts of benign melanocytic deposits in subcapsular and parenchymal lymph node tissue. Even though it is commonly known that non-CMN patients (with or without melanoma) will often have small amounts of benign melanocytic deposits in their lymph nodes (termed “nevic rests”), the large amount of melanocytes that can be found in CMN patients may easily be mistaken for malignancy [98–102]. These benign melanocytic deposits must be distinguished from malignant cells by cytology and staining; these cells are typically cytologically bland, do not stain for Ki-67, and do not stain or only weakly stain for HMB-45 [103].

A second aspect of melanoma management that is unique among CMN patients is the potential utility of NRAS-targeted treatment. Melanoma in CMN patients are frequently found to have *NRAS* mutations, as opposed to the *BRAF V600* mutations suggestive of ultraviolet damage more commonly found in conventional melanoma of sun-exposed skin and the chromosomal rearrangements with activated kinase signaling found in Spitzoid melanomas [8, 104]. Enthusiasm for anti-NRAS therapy as CMN melanoma treatment, however, is tempered by the fact that an overwhelming proportion of benign large and giant CMN harbor *NRAS* mutations [9]. However, it is plausible that anti-NRAS therapy could prevent the growth of all CMN lesions and thus minimize their malignant potential.

Theorized strategies for NRAS-directed treatment include targeting NRAS by membrane localization of NRAS, reducing expression with small interfering RNAs, or inhibiting downstream signaling [105]. Recently, there have been promising results in preclinical and early clinical trials for MEK inhibitors targeting downstream signals, combined with inhibitors of the cell cycling and PI3K-AKT pathway [106]. In clinical use, there is only one case report of a MEK-inhibitor administered to a patient with NCM on a compassionate use basis, and this patient expired prior to any potential therapeutic effect [107].

In contrast to conventional melanoma, where BRAF targeted therapies have found therapeutic utility, the use of BRAF inhibitors is contraindicated in *NRAS*-positive melanoma due to the potential activation of RAS by the BRAF inhibitors [108, 109]. This is particularly relevant to CMN melanomas due to the predominance of *NRAS* mutations in these lesions.

Treatment

Key Points

- CMN may be excised for improvement of aesthetic appearance, functional limitations, and melanoma management, though universal removal for melanoma prophylaxis is not recommended, as data does not support reduction of melanoma risk with excision.
- Surgical excision must be considered on a case-by-case basis.
- Adequate psychosocial support is exceedingly important in the treatment of CMN patients.

Treatment Options and Indications

Past treatments for CMN have included observation, excision, dermatome shaving, curettage, dermabrasion, chemical peels, cryotherapy, electrosurgery, radiation therapy, ablative lasers, and pigment-specific lasers [110]. Reasons to remove CMN include distress regarding aesthetic appearance, functional limitation (such as obstruction or intractable pruritus), and management of a diagnosed melanoma [7]. Surgery is currently the recommended therapy if treatment is necessary, as evidence for the efficacy and safety of the other treatment modalities is scarce [110]. However, clinicians are increasingly favoring observation [111].

Treatment Considerations

Given that small and medium CMN are not associated with a significantly increased risk of melanoma [68, 78, 84, 86–89], observation is recommended for these lesions in the absence of another surgical indication. While clinicians historically endorsed excising large and giant CMN for prophylaxis against melanoma, the risk of these patients developing melanoma is lower than was once thought [78]. Further, there is no data to suggest that excision of CMN alters a patient's lifetime risk of melanoma, though randomized controlled data is lacking [41, 73, 84, 111, 112]. CMN patients can develop melanoma in other cutaneous sites, extracutaneous sites, or as metastatic disease of unknown primary location [62, 73, 87, 113]. In a review of 1539 patients with CMN larger than 20 cm and 49 melanomas, 33% of melanomas (16 cases) did not develop primarily within CMN. About 10% of melanomas (5 cases) occurred in cutaneous sites outside of the patient's CMN or satellite lesions, 14% (7 cases) were metastatic melanomas of unknown primary, and 8% (4 cases) were extracutaneous [84]. Furthermore, melanoma has been reported to occur in sites where CMN excision and grafting previously occurred [73, 94, 114–116], and postsurgical scars can obscure monitoring and make it more difficult for physicians to diagnose melanoma clinically and histologically (Fig. 2.7). Additionally, excision of CMN does not impact the risk of NCM development [61]. Overall, physicians are moving toward a conservative management strategy of observation and close monitoring for melanoma development [111].

The adverse outcomes associated with surgery must also be considered when recommending treatment for CMN patients. Anesthesia has serious risks in young children, including neurotoxicity and other poorly understood effects [117–120]. Data from animal studies have shown that many anesthetic agents have serious and lasting effects on the developing brain, leading to recommendations that procedures requiring general anesthesia be avoided in pediatric patients—especially children less than 3 years of age—unless the patient requires urgent attention, or failing to perform the procedure will have harmful effects later in life [75]. Surgical complications that have been reported in CMN patients include keloid formation [121], growth limitations from the fibrotic nature of scars [111], paralysis caused by iatrogenic nerve injuries [111], and darkening of remaining CMN [41]. Furthermore, some parents

report that CMN excisions worsened their child's appearance [41, 77, 122]. Surgical dissatisfaction may increase with lesion size, but the potential for unfavorable aesthetic outcome following any excision cannot be understated. Large scars may be more disfiguring than naturally appearing pigmented lesions and may create challenges for melanoma monitoring (Fig. 2.7). It has also been reported that after surgical excision, remaining CMN can become darker in color (possibly due to activation and migration of non-excised nevomelanocytes) [111]. In contrast, untreated CMN may lighten over time. In one study where CMN patients were followed for 19 years and families completed yearly questionnaires, 48 patients never received treatment for their CMN. Among these patients, 31 (65%) reported lightening, 16 (33%) reported no change, and only 1 (2%) reported darkening [41].

While excision of all CMN for the purpose of melanoma prophylaxis is not recommended [111], the decision to treat must be determined on a case-by-case basis. Any lesion with suspicious change should be biopsied for melanoma, and patients may be candidates for prophylactic excision if there is significant parental anxiety, if the lesion will be difficult to monitor, or if psychosocial factors will prevent adequate follow-up [111]; however, the risks of surgery must be addressed. If a patient elects observation, it is important to observe him or her consistently over the course of a lifetime, as thorough skin examinations and a comprehensive review of systems are crucial in detecting extracutaneous and metastatic melanomas. Patients who undergo treatment or excision also require lifelong monitoring, as the procedure may not significantly alter the risk of developing melanoma [84, 111].

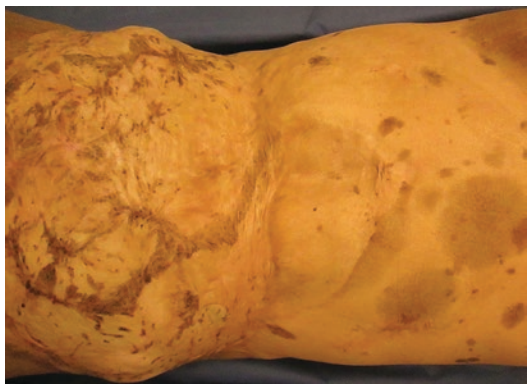


Fig. 2.7 Adult patient with a history of extensive excision and grafting for giant CMN performed in childhood. This patient has developed subcutaneous melanomas within the depicted lower back scars, despite surgical excision, and her physical exam is challenging due to the abnormal pigment patterns and substantial scar tissue

Psychosocial Considerations

To support families and recommend observation, dermatologists must effectively counsel toward acceptance of CMN appearance. Providing adequate support is crucial, given that many patients with large and giant CMN suffer psychosocial consequences and stigma from visible disease. Many parents and patients suffer anxiety from the possibility of developing NCM or melanoma in the future. Patients with extensive CMN have been found to have social, behavioral, and emotional problems, and in one study 69% of mothers of children with giant CMN agreed with the statement, "I think it is awful that my child was born with a congenital anomaly" [123].

Physicians should be aware of patient and parent-organized support organizations. These exist on the national scale and are tremendously beneficial to patients and parents alike, by providing information and allowing families to connect with each other. These organizations should also be recognized for their role in research, as several large studies on CMN have been completed with their network of patients [22, 73, 124]. As research advances, and as scientists hone in on the molecular pathways contributing to CMN development, dermatologists and other medical professionals must continue to approach patients as unique individuals, offer adequate support, and stand up as allies for this uncommon but highly visible skin condition.

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Lymphoproliferative Disorders of the Skin

3

Markus Boos and Sara Samimi

Cutaneous Lymphoid Hyperplasia/ Pseudolymphoma

Key Points

- Cutaneous lymphoid hyperplasia (CLH/pseudolymphoma) is a benign, reactive condition that can occur secondary to multiple different stimuli.
- Clinically it may be difficult to distinguish CLH from true cutaneous lymphoma, though histologic features and response to therapy can assist in proper diagnosis.

Cutaneous lymphoid hyperplasia (CLH) is a term used to describe a benign, reactive proliferation of T and B cells in the skin. Despite its indolent behavior, CLH engenders concern because it can mimic cutaneous T- and B-cell lymphomas both clinically and histologically. As such, a careful history, physical examination, and appropriate pathologic evaluation are central to establishing a proper diagnosis.

CLH traditionally presents as asymptomatic, pink- to plumb-colored papules, plaques, and nodules with minimal to no surface change. Individual lesions are either unifocal or regionally clustered, most commonly on the face and scalp [1]. Importantly, patients with CLH are typically well appearing, without evidence of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, or lab abnormalities. CLH is most frequently seen in young adults, though its existence is well documented in children, as well [1, 2].

Though most commonly considered an idiopathic condition, CLH is known to be associated with a variety of exogenous stimuli and may develop in response to specific antigenic exposures [1, 3]. These include vaccinations (particularly hepatitis A and B vaccines) [4], molluscum contagiosum [5], tattoos [6], arthropod assault, and medications. Drugs that commonly induce CLH and that are of interest in the pediatric population include antiepileptics, antihistamines, cefixime and cefuroxime, trimethoprim-sulfamethoxazole, fluoxetine, aspirin, ibuprofen, naproxen, and methylphenidate [7]. CLH also is known to occur in response to *Borrelia* infections in Europe, specifically to *B. afzelii* and *B. garinii* [8]. These so-called *Borrelia* lymphocytomas

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frequently appear on the ear and breast/areola and present similarly to conventional CLH as asymptomatic red-blue nodules.

The histology of CLH varies with its inciting cause, a discussion of which is beyond the scope of this text. In general, CLH can be divided into major categories depending on its cellular architecture and whether it is T- or B-cell predominant, though lesions often demonstrate a mixed infiltrate that may include plasma cells and eosinophils [9]. B-cell predominant CLH often exhibits a nodular pattern, though its architecture may also appear diffuse. In contrast, T-cell predominant CLH may present histologically in a band-like pattern that mimics mycosis fungoides, though it can also assume nodular or diffuse forms. In general, cellular atypia is minimal, and the cellular infiltrate is polyclonal in CLH, but immunohistochemical studies may be used to help differentiate CLH from its malignant counterparts including marginal zone lymphoma, follicle center lymphoma, and mycosis fungoides. Gene rearrangement studies lacking evidence of a T- or B-cell clone are supportive of a diagnosis of CLH, but the presence of clonal populations must always be interpreted with caution, as they (including artefactual "pseudoclones") may be suggestive of, but do not necessary define, a malignant process [10].

A variant of CLH known as pseudolymphomatous folliculitis (PLF) presents as a large, violaceous, dome-shaped or flat-topped nodule, typically on the face. In contrast to the absence of surface change in traditional CLH, PLF may present with minimal scale and follicular accentuation (Fig. 3.1) [11]. Histologically, PLF is also characterized by a dense dermal lymphocytic infiltrate, but distinguishes itself from CLH by the presence of irregular enlargement of pilosebaceous units accompanied by blurring of their epithelial lining. Atypical lymphocytes may be seen, leading to pathologic confusion with true cutaneous lymphomas. However, the presence of perifollicular histiocytes thought to represent T-cell-associated dendritic cells may be used as a clue to diagnosis [11].

A special form of CLH that is more common in children and adolescents warranting special mention is acral pseudolymphomatous angiokeratoma of children (APACHE). This clinical entity is characterized by asymptomatic red-to-violaceous grouped papules with variable overlying keratotic scale, typically at acral locations [12, 13]. Initially thought to be a vascular neoplasm, it is now accepted to represent a form of pseudolymphoma. Despite its name, APACHE has also been reported in adults at non-acral sites [14]. Histologically, APACHE is characterized by a polymorphous dermal infiltrate of lymphocytes, histiocytes, and plasma cells admixed about thick-walled blood vessels with plump endothelial cells. Epidermal changes are variable and may include hyperkeratosis, spongiosis, lymphocytic exocystosis, and vacuolization of the basal layer [12, 13]. Treatment options include excision, intralesional corticosteroid injection, cryotherapy, or radiation therapy [13].

A diagnosis of CLH can only be made via thoughtful synthesis of clinical and histopathologic findings and in some cases may only be

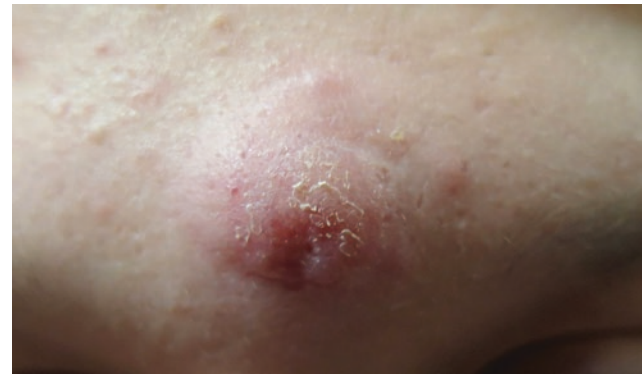

Fig. 3.1 Pseudolymphomatous folliculitis. Indurated erythematous nodule with associated follicular accentuation and scale on the forehead of an adolescent

diagnosed after prolonged monitoring with regular follow-up. A diagnosis of CLH/pseudolymphoma is suggested by the localized nature of the lesions, an absence of constitutional symptoms, and recognition of an inciting agent. Histopathology with a mixed infiltrate and the absence of marked atypia or a clonal population is also reassuring of a benign process.

Treatment mandates cessation of the inciting agent when CLH is recognized as medication induced [7]. CLH often also responds to biopsy by self-resolving. Beyond observation, however, more active interventions may include topical or intralesional corticosteroids or administration of anti-inflammatory agents such as doxycycline or methotrexate [2]. Treatment with appropriate antibiotics also causes resolution of CLH induced by *Borrelia* species [8]. In select cases, radiation therapy or surgical excision may also be considered, though this must be carefully weighed against the risks of these procedures, particularly in children. While in general CLH is believed to follow a benign course, it has been proposed that persistent antigenic stimulation may promote evolution to malignancy [3]. As such, regular clinical monitoring via physical and detailed history is warranted for all patients with CLH, even after resolution.

Pityriasis Lichenoides

Key Points

- Pityriasis lichenoides (PL) is a benign disorder that exists on a spectrum with both acute and chronic forms.
- It is typically self-limited and is not thought to predispose to malignancy but can wax and wane over months to years.
- A severe variant of PL known as febrile ulceronecrotic Mucha-Habermann disease is characterized by rapid onset of characteristic lesions with high fevers and systemic involvement; in rare cases it can be fatal.

Pityriasis lichenoides (PL) is a benign lymphoproliferative disorder that is typically classified as two main variants: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC). These two manifestations lay on a disease spectrum, with PLEVA being more acute and symptomatic and PLC being more chronic in nature, though some patients may exhibit features of both [15, 16]. Both presentations are rare and have a collective incidence of about 1/2000 people per year [17].

The average age of onset of PL is 6.5 years with rare cases reported in infancy, and even at birth, with a slight male predominance [18]. In a review by Hapa et al. of 24 patients (ages 2–14 years, with a median age of 7 years) with PL, PLC was more common than PLEVA (62.5–25%, respectively), with features of both in a small subset of patients (2.5%) [19]. In contrast, a larger retrospective review of 124 patients in 2007 identified PLEVA in 57.3% and PLC in 37% of patients, with features of both seen in the remainder [16]. Patients with PLEVA had a younger median age of onset (60 months) as compared to those with PLC (72 months), with a median duration of disease ranging from 18 months in PLEVA to 20 months in patients with PLC [16]. Both subtypes present more commonly in the spring or the fall [16, 19].

Clinically, PLEVA is characterized by the abrupt onset of pruritic and at times painful, symptomatic papulovesicles with necrotic, ulcerative, or hemorrhagic changes (Fig. 3.2). Early in its course, the condition may be confused with varicella. Patients with PLEVA, however, lack the typical fever and mucous membrane involvement seen in varicella, and the course of PLEVA is considerably more prolonged. In contrast, the hallmark of PLC is recurrent crops of asymptomatic, scaly, erythematous, or red-brown papules and plaques with central adherent scale that flatten or regress over a period of weeks. Lesions tend to be diffuse, though some patients may have truncal predominance, as well as segmental restriction of their disease [20]. Clinically, the papulosquamous appearance of this condition may resemble pityriasis rosea or hypopigmented

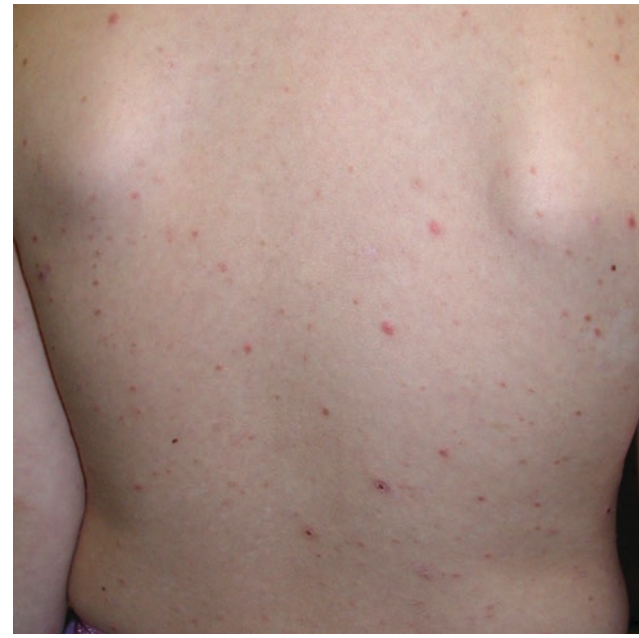

Fig. 3.2 Pityriasis lichenoides et varioliformis acuta. Multiple erythematous papules and vesicles, some with associated ulceration and hemorrhagic crusting, present on the back of a child

mycosis fungoides. Rarely, restriction to the palms and soles resembling psoriasis can occur [21]. Lesions of both PLEVA and PLC may be present at all stages of development. In both variants, the lesions usually resolve with hyper- or hypopigmentation [16]. As compared to the clinical presentation in adults, children with PL are more likely to have more prominent dyspigmentation and extensive cutaneous involvement, especially of the face [22].

Notably, the histopathology of both entities can overlap, with more subtle changes identified in PLC. Tissue examination reveals focal parakeratosis, mild to moderate acanthosis, focal areas of spongiosis, few dyskeratotic keratinocytes, vacuolar interface changes, a mild superficial perivascular lymphocytic infiltrate, and variable erythrocyte extravasation. Necrotic keratinocytes, vesiculation, and ulceration may be seen in the epidermis. Immunohistochemistry also helps to distinguish these entities, as a predominantly CD8+ T-cell lymphocytic infiltrate is present in patients with PLEVA, while the infiltrate in patients with PLC is characterized primarily by CD4+ T-cells [23].

PLEVA and PLC are regarded as benign, reactive disorders, and several theories regarding their etiology have been postulated. Specifically, PLEVA and PLC have been proposed to represent a T-cell-mediated reaction triggered by an infectious agent or medication or to occur secondary to a T-cell dyscrasia. A history of a preceding URI is reported in a third of cases and preceding drug or vaccination in 20% of cases [18, 19]. Suspected infectious triggers include VZV [24], HHV-8 [23], streptococcal pharyngitis, *Toxoplasma gondii*, parvovirus B19, Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) [25]. Implicated medications and vaccinations include subcutaneous immunoglobulin [26]; etanercept [27]; measles, mumps, and rubella (MMR) vaccine; influenza vaccine; and hepatitis B immunization [18, 28, 29]. Clonality has been detected in patients with PL, supporting an alternate theory that these entities represent a lymphoproliferative disorder rather than an inflammatory process [30, 31]. Currently, it is unclear if T-cell clonality in PL is dependent upon a specific disease trigger. It is also unknown whether those

patients identified as having a clonal population may be at increased risk of developing a secondary lymphoproliferative disease.

PL often waxes and wanes and may exhibit spontaneous resolution. Treatment is initiated due to concerns about the appearance of the eruption, associated symptoms, or to guard against long-term sequelae, such as scarring. First-line treatment options for both PLEVA and PLC include oral antibiotics with or without topical corticosteroids or topical immunomodulators. Erythromycin is commonly administered, with greater than 50% improvement in skin disease in 64% of patients at 1 month, 73% at 2 months, and 83% at 3 months [19]. It is recommended that erythromycin be continued for 2–3 months after resolution given concern for recurrence if stopped too quickly [18]. Cephalexin, amoxicillin-clavulanic acid, cefaclor, tetracycline and minocycline (both contraindicated in children younger than 8 years old), and azithromycin have also been used with some success [32, 33]. Second-line treatment options include ultraviolet B (UVB) and psoralen with ultraviolet A (PUVA) phototherapy, though their success and tolerability may vary based on the age of the patient [34]. PLC may respond better to phototherapy than PLEVA [35]. Narrowband (nb) UVB alone has been successful in 44–48% of patients with PLC [36]. A recent study demonstrated greater efficacy of nbUVB compared to broadband (bb) UVB and PUVA, as recurrence was decreased in patients who received nbUVB therapy. Patients on average achieved a response with 18.8–22 sessions. Commonly observed side effects of phototherapy include erythema, pruritus, and discomfort or pain [37]. PUVA may also be less optimal given its risk of treatment-related secondary cutaneous malignancy [38]. Third-line agents include methotrexate, acitretin, dapsone, or cyclosporine. Up to 77% of patients have evidence of disease recurrence after complete clearance with appropriate treatment [16].

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare and severe variant of PLEVA that may follow a diagnosis of PLEVA or occur de novo [39, 40]. When a patient presents with a PLEVA-like eruption with evidence of rapid clinical progression and systemic symptoms, FUMHD is probable [41]. It tends to occur more commonly in children and young adults. In contrast to adults, children may demonstrate a shorter time transforming from PLEVA to FUMHD with more frequent mucosal involvement and a more favorable outcome, [42] though fatal cases have been reported [43]. Affected patients exhibit a rapid onset of necrotic papules coalescing into large ulcerations with histologic features of PLEVA. Mucous membrane involvement is evident in about 28% of cases (including oral, genital, and conjunctival mucosae), with systemic involvement in 45%. Systemic symptoms include markedly high fevers, abdominal pain, diarrhea, arthritis, pulmonary involvement, central nervous system involvement, and sepsis [25, 43, 44]. Laboratory abnormalities may include increased leukocyte count, elevated erythrocyte sedimentation rate and C-reactive protein, anemia, mild hypergammaglobulinemia, hypoproteinemia, hypoalbuminemia, hypocalcemia, eosinophilia, lymphopenia, and positive skin and blood cultures [44]. Clinical mimickers of FUMHD include varicella, papulovesicular pityriasis rosea, leukocytoclastic vasculitis, and lymphomatoid papulosis [44, 45]. Rarely, FUMHD may clinically mimic Stevens-Johnson syndrome (SJS), given the extent of cutaneous involvement with epidermal necrosis [41]. However, distinguishing features include flexural accentuation, constitutional manifestations, and histologic appearance. Similar to PL, no clear triggers have been identified for FUHMD, though isolated cases have demonstrated seropositivity to VZV and HSV-2 [46, 47]. Treatment modalities for FUMHD may overlap with PL; however, given its severity with rapid progression, systemic complications, and potential fatality, more aggressive or combination medications are utilized. Treatment options include methotrexate [40, 41, 48, 49], TNF-alpha inhibitors [50], prednisone [41], cyclosporine [43], intravenous immune globulin (IVIG), and extracorporeal photopheresis [51].

Lymphomatoid Papulosis

Key Points

- Lymphomatoid papulosis (LyP) is a CD30+ cutaneous lymphoproliferative disorder characterized by self-healing but recurrent, ulcerative papules.
- Treatment of LyP is not thought to influence disease course or progression.
- LyP is associated with secondary malignancies in approximately 10–20% of patients.

Lymphomatoid papulosis (LyP) is a chronic primary cutaneous CD30+ lymphoproliferative disorder of intermediate malignant potential. Clinically it is distinguished by crops of pink-red papulonodules, most commonly distributed on the trunk and extremities (Fig. 3.3). LyP characteristically advances over weeks to months through stages of necrosis, ulceration, and hemorrhagic crusting before spontaneously resolving with pigmentary changes and scarring. Individual lesions are often in different stages of evolution [52]. A variant of LyP termed persistent agminated LyP (PALP) presents as multiple lesions of LyP within a circumscribed area that wax and wane in intensity but never completely resolve. As a result of this behavior, whether PALP represents a localized form of LyP or a distinct lymphoproliferative disorder on the spectrum of mycosis fungoides (MF) remains controversial [53, 54].

Although more common in older adults, LyP is also well documented in children, and its incidence may be underestimated [55]. Recent retrospective analyses and systematic literature reviews provide greater insight into the nature of pediatric LyP. In children, LyP occurs at a mean age of approximately 7–8 years, though diagnosis is often delayed by 1 year [55, 56]. Boys are somewhat more frequently afflicted than girls [55, 56]. As in adults, pediatric LyP favors the extremities and trunk, though generalized forms are not uncommon and multiple lesions (up to 75 total in some reported cases) may be seen [57]. In a series of 25 children with LyP, the majority of patients had fewer than 10 lesions that resolved over a mean time of 5 weeks, though disease duration was, on average, 18 months [55]. Approximately 25% of all patients had recurrent disease, with disease-free intervals between outbreaks lasting from less than 1–20 months [55]. Interestingly, though LyP is typically thought to be asymptomatic, children often endorse

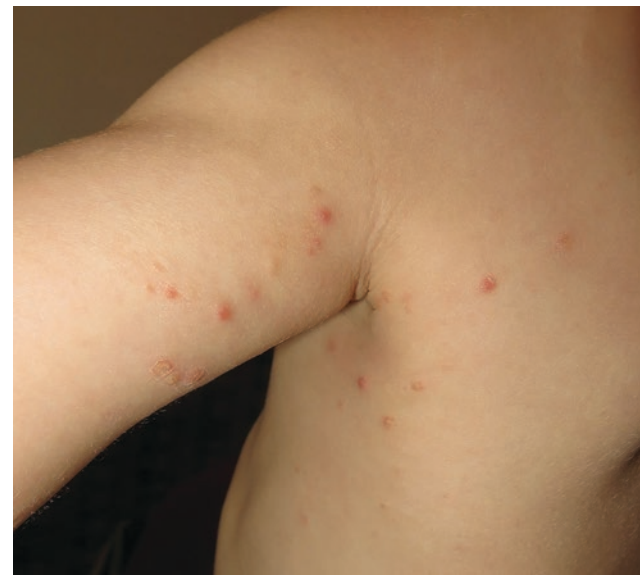

Fig. 3.3 Lymphomatoid papulosis. A crop of pink-red papulonodules with early scale and crust present on the arm and axilla of a child

associated pruritus that may lead to a misdiagnosis of arthropod assault [55, 56].

LyP can be classified histologically into different subtypes, denoted LyP types A through F [52]. Although the nuances of each histologic subtype are beyond the scope of this text, some salient features are worth noting. Among both children and adults, type A LyP appears to be the most common form [55–58]. Type A LyP demonstrates a wedge-shaped infiltrate of grouped, large, pleomorphic lymphocytes admixed among neutrophils, eosinophils, and histiocytes. These tumor cells usually possess a CD4+ T-helper cell phenotype with CD30 expression, though many cases of CD8+ LyP have been reported in the pediatric population, without evident prognostic implications [57, 58]. Type B LyP displays a superficial perivascular or band-like infiltrate of lymphocytes with cerebriform nuclei in the dermis accompanied by lymphocytic epidermotropism that is reminiscent of the histologic features of MF (see below). In this subtype, many neoplastic cells lack CD30 expression, and distinction from MF on histologic grounds alone can be difficult, requiring clinicopathologic correlation. Type C LyP is characterized by sheets of large, atypical, CD30+ lymphocytes and resembles anaplastic large-cell lymphoma [58]. Distinguishing between these two entities is difficult and requires clinicopathologic correlation. Rare, histologically unique subtypes D, E, and F have also been reported [59]. T-cell clonality is common in lesions of LyP [55, 58, 60]. Studies conflict as to whether the histologic subtype of LyP influences clinical course or prognosis, though a retrospective study of 123 patients with LyP suggests that T-cell clonality and multiple subtypes of LyP present in the same individual may indicate an increased risk of associated hematologic malignancy [61].

The etiology of LyP is unknown, though persistent antigenic stimulation of skin-resident T cells has been suggested. In support of this, up to 25% of pediatric patients who develop LyP report having an antecedent viral illness prior to disease onset, while another quarter of patients carry a diagnosis of atopic dermatitis [55, 56]. PL can also be seen concomitantly with LyP. Given that some cases of PL are identified as having a CD30+ cellular infiltrate, it has been proposed that PL and LyP are related entities, though this remains controversial [55, 56]. Importantly, approximately 10–20% of patients with LyP develop a secondary hematologic malignancy prior to, concurrently with, or after their diagnosis. MF, anaplastic large cell lymphoma (ALCL), or Hodgkin disease are the most commonly associated malignancies [52, 62]. Although MF is the most frequent LyP-associated malignancy in adults, ALCL appears to be the most common secondary hematologic malignancy in children [52, 56, 62, 63].

Initial evaluation of LyP includes skin biopsy, complete blood count (CBC) with differential, a comprehensive metabolic panel (CMP), and lactate dehydrogenase (LDH). If malignancy is considered in the differential diagnosis, more extensive evaluation may be warranted. LyP follows a spontaneous, self-resolving course. Thus, providers must carefully weigh risks and benefits when considering treatment. Treatment does not appear to influence the natural course of the condition or development of associated malignancies; no known "curative" therapies exist [52, 56, 64]. Therefore, close observation is a reasonable option in the management of LyP. Factors that may warrant active intervention include multiple cosmetically bothersome lesions, intense pruritus, or a desire to reduce the risk of subsequent scarring. For localized, infrequently recurrent disease, application of ultrapotent topical corticosteroids can help speed resolution or limit growth and ulceration of individual lesions [52]. For more widespread disease, systemic agents are more appropriate options, but their specific risks must be carefully considered in the pediatric population. For example, PUVA appears to be a useful treatment for LyP. However, given its risk for inducing cutaneous malignancy, nbUVB therapy may be a more appropriate choice in children, despite only anecdotal evidence to support its efficacy [52, 62]. Other potential treatment options include oral antibiotics (i.e., doxycycline), though low-dose methotrexate may be a safe, more effective, and therefore preferred option

[64]. Topical nitrogen mustard, as well as systemic bexarotene or interferon, may also be considered as second-line agents [52]. Owing to the risk of developing a secondary malignancy, all patients with LyP warrant regular, long-term monitoring.

Cutaneous T-Cell Lymphoma/ Mycosis Fungoides

Key Points

- Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) in children.
- The hypopigmented variant is the most common form of pediatric MF.
- Most children with MF have both limited body surface area with rare systemic involvement and have life expectancies similar to age-matched controls.

Cutaneous T-cell lymphoma (CTCL) is a general term that refers to primary extranodal T-cell neoplasms of the skin. The frequency of CTCL is estimated at 10.2 cases per million, which appears to have stabilized after many years of increasing incidence [65]. Although much more common in adults, the entire spectrum of CTCL has been reported in children [66].

Among the assorted forms of CTCL, MF is the most common variant in both adults and children. MF can present in diverse ways, from limited patch-stage disease to frank erythroderma, with variable extracutaneous involvement. Classically, MF presents as scaly, erythematous patches or plaques that favor sun-protected, "double-covered" areas including the buttocks and upper thighs (Fig. 3.4). Overlying skin atrophy may be associated. More advanced stages, which are uncommon in children, are characterized by larger tumors with a propensity toward ulceration or erythroderma with accompanying constitutional symptoms. Staging guidelines for MF are found in Table 3.1.

Other presentations of MF that have been described in children include pigmented purpuric, pityriasis lichenoides-like, isolated acral (Woringer-Kolopp), and leukemic variants [67–70]. Among children, the hypopigmented variant of MF is the most common presentation and is overrepresented relative to its incidence in adults [67, 68, 71–73]. This form is characterized by hypopigmented macules and patches, usually without secondary change, and can occur in isolation or alongside more traditional papulosquamous lesions of MF. Although more commonly recognized in darker-skinned children, hypopigmented MF is known to occur in Caucasian children, as well [68, 74, 75]. Irrespective of clinical appearance, most children present with early stage disease (IA, IB, or IIA) [67, 68, 71, 74].

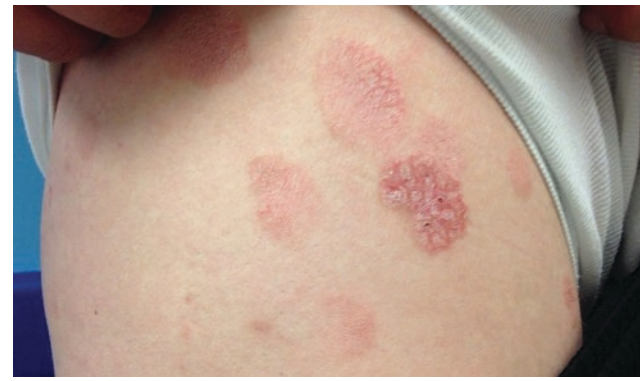

Fig. 3.4 Mycosis fungoides. Nummular, scaly, erythematous patches and thin plaques present on the upper thigh and buttocks of a teenager

Table 3.1 TNMB classification and clinical staging of mycosis fungoides [84]

Skin	Description			
TNMB classification				
T1	Patches, papules, and/or plaques covering <10% total body surface area			
T2	Patches (T2a), papules, and/or plaques (T2b) covering ≥10% total body surface area			
T3	One or more tumors (≥1 cm in diameter)			
T4	Erythroderma (erythema involving ≥80% total body surface area)			
Nodes				
N0	No clinically abnormal lymph nodes identified			
N1	Atypical lymph nodes, histopathology Dutch grade 1 or NCI LN0–2			
N2	Atypical lymph nodes, histopathology Dutch grade 2 or NCI LN 3			
N3	Atypical lymph nodes, histopathology Dutch grades 3–4 or NCI LN 4			
NX	Abnormal lymph nodes without histopathologic evaluation			
Visceral				
M0	No visceral organ involvement			
M1	Visceral involvement with histologic confirmation (specify organ)			
MX	Abnormal viscera without histologic confirmation			
Blood				
B0	Absence of significant blood involvement; ≤5% of peripheral blood lymphocytes are Sezary cells, <15% CD4+/CD26 or CD4+/CD7 cells of total lymphocytes			
B1	Low blood tumor involvement; >5% of peripheral blood lymphocytes are Sezary cells or ≥15% CD4+/CD26 or CD4+/CD7 cells of total lymphocytes but do not meet classification as B0 or B2			
B2	High blood tumor involvement; ≥1000/mcL Sezary cells or CD4/CD8 ≥ 10 or ≥40% CD4+/CD7 or ≥30% CD4+/CD26 cells of total lymphocytes			
Clinical staging of mycosis fungoides				
	T	*N*	*M*	*B*
IA	1	0	0	0–1
IB	2	0	0	0–1
IIA	1–2	1–2	0	0–1
IIB	3	0–2	0	0–1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

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Folliculotropic MF (FMF) is a rare variant that is more common in adults and clinically is characterized by acneiform lesions including comedones, milia, or cysts. Hairless patches and plaques with folliculocentric papules and variable degrees of induration are a more common presentation in children [76]. FMF deserves special consideration because its clinical appearance often overlaps with that of benign, reactive follicular mucinosis (FM). This distinction is vital as FMF in adults appears to carry a worse prognosis than classic MF, and both treatment and prognosis differ considerably between FM and FMF [77]. Historically, the clinical presentation of FM was divided into two main groups: FM limited to the head and neck in young patients and more widespread FM that was more typically seen in older adults. Importantly, the former usually follows an indolent course, while more widespread disease is thought to be more aggressive, with a greater likelihood of transformation into FMF [78, 79]. T-cell clonality does not appear to help distinguish between FM and FMF and may be of minimal prognostic value [80].

In children, FMF is believed to be uncommon. Though some contend that FM is an early form of FMF, two retrospective case series of pediatric FM demonstrated a rare association of FM with FMF, and those children who met criteria for FMF still followed a benign trajectory [80, 81]. The authors of these studies argue that in children, FM is an indolent disease with minimal risk of malignant transformation and should therefore not be considered on the spectrum of FMF. In contrast, a retrospective study of 50 patients with pediatric MF showed a higher incidence of FMF compared to both adults and comparable cohorts of children [76]. This may be secondary to difference in the interpretation of histopathologic features leading to a diagnosis of FMF versus FM in this study; regardless, FMF in this cohort behaved similarly indolently. It appears that FM and FMF in children are more indolent conditions that do not require aggressive treatment. Nevertheless, secondary malignancies have been documented in association with FM, and children diagnosed with both FM and FMF warrant long-term monitoring [80, 81].

Given its ability to mimic more common, benign pediatric dermatoses, clinical suspicion must remain high in order to successfully render a diagnosis of mycosis fungoides in a child. Classic lesions of MF may be mistaken for lesions of atopic dermatitis or nummular eczema, psoriasis, tinea corporis, or pityriasis rubra pilaris. The hypopigmented variant may clinically resemble PLC, post-inflammatory hypopigmentation, and progressive macular hypomelanosis, as well as sarcoidosis or morphea [82].

MF is also a challenging diagnosis to make histologically, particularly in early stages when its defining pathologic characteristics may not yet be evident. As such, clinicopathologic correlation is always necessary before rendering a final diagnosis. Histologic findings suggestive of a diagnosis of MF include epidermotropism of atypical lymphocytes (irregular nuclei, cerebriform cells), sometimes arranged in so-called Pautrier's microabscesses. Accompanying spongiosis is minimal to absent. A band-like infiltrate of atypical lymphocytes abutting ("tagging") the basal layer of the epidermis, along with papillary dermal fibroplasia, is another supportive feature [83]. Immunohistochemistry revealing an increased ratio of CD4+ to CD8+ cells in the epidermis and dermis is typical. Nevertheless, a predominantly CD8+ T-cell phenotype of MF appears to be overrepresented in children, though this does not seem to influence clinical course [67, 72]. Multiple biopsies may be necessary before a definitive diagnosis can be made.

Workup of children with MF is not standardized, and a thoughtful approach based upon the current National Comprehensive Cancer Network guidelines for adults is recommended [84]. A complete history with special attention to constitutional symptoms including fever, chills, drenching night sweats, overwhelming fatigue, and unintentional weight loss should be performed. A meticulous physical exam is mandatory, with attention to the morphology, distribution, and total body surface area (BSA) involved, as well as palpation for lymphadenopathy or hepatosplenomegaly. A limited laboratory workup including a CBC with differential, CMP, and LDH is recommended. For patients with early

patch-stage disease (T1) and no constitutional symptoms, no further evaluation is required. However, in patients with constitutional symptoms or more advanced disease, flow cytometry of blood and T-cell receptor gene rearrangement studies of blood and lesional skin are necessary to evaluate for clonality and peripheral blood involvement. Full body imaging via computerized tomography (CT) or positron emission tomography with CT (PET/CT) may be considered after taking into account a patient's clinical appearance and the results of the aforementioned evaluation. However, the evident risk of secondary malignancy in patients exposed to frequent CT scans must be thoughtfully weighed [85, 86]. It has been recommended that PET/CT scans be performed in patients with >20% BSA involvement of T1 or T2 disease or those with more advanced stages of disease. The exception to this is hypopigmented MF, as its typically indolent course precludes aggressive imaging studies, even with widespread BSA involvement [82]. If possible, alternative methods of staging (i.e., ultrasound of lymph nodes) should be considered to limit ionizing radiation as much as possible.

Treatment of MF is challenging, as no single agent is known to prolong survival; it is also unclear if the disease can be cured, though extended remissions occur [87, 88]. Instead, treatment should focus on symptom control, quality of life, and mitigation of therapy-associated morbidity [89]. For limited patch- or plaque-stage disease, skin-directed therapies are appropriate first-line treatment. Topical options include potent and ultrapotent corticosteroids, nitrogen mustard (NM), tazarotene, carmustine, or bexarotene [90–92]. Each of these agents carries their own associated risks, from skin irritation associated with many of these topical therapies to atrophy and potential adrenal suppression in younger children with extensive BSA involvement treated with potent topical steroids [92]. Bone marrow suppression is also an important consideration with the use of the topical alkylating agents NM and carmustine. While topical treatment with NM has not been shown to induce bone marrow suppression in adults and children, carmustine does induce mild-to-moderate myelosuppression in a subset of patients [92, 93]. In both cases, periodic monitoring with CBC and a metabolic panel should be considered [82, 92, 93]. Given the potential risks associated with even topical therapies, treatment must be carefully selected for each individual patient [91, 92]. An alternative option for patients with early-stage (IA/IB) disease is phototherapy with either nbUVB or PUVA. A recent retrospective review demonstrated the efficacy of phototherapy in children with early-stage MF, with a complete or partial response to one of these modalities in 77% of patients [71]. Though PUVA appears to induce longer periods of remission than nbUVB therapy, its use must be weighed against its potential side effects including phototoxicity, ocular damage, and the long-term risk of cutaneous malignancy [94]. Nevertheless, it may be superior for particular variants of MF, including FMF [76]. The potential long-term risks of continued nbUVB phototherapy are not known but are believed to be significantly less than with PUVA [95, 96]. With both forms of phototherapy, close monitoring for ongoing signs of skin damage and cutaneous toxicity is warranted, and treatment frequency and duration should be limited, if possible. More advanced stage disease may be more appropriately treated with systemic agents including bexarotene or interferon. For disseminated cutaneous or extracutaneous disease, consultation and potential treatment in conjunction with an experienced pediatric oncologist are recommended.

The prognosis of children with MF is typically excellent. In studies of patients aged 35 years or younger with a diagnosis of MF, overall and disease-specific survival were both better than that of older adults [97]. This appears to be related to disease stage at presentation, however, as younger patients are more likely to have limited T1 disease [97, 98]. Additionally, the hypopigmented variant of MF appears to have improved overall and disease-specific survival (as mentioned above), as well as reduced risk of disease progression compared to the classic form of MF [77, 98]. Age does not appear to be an independent predictor of survival as young patients with more advanced stages of disease

have similarly poor outcomes as older adults [97, 98]. These patients may also have an increased risk of melanoma, posited to be secondary to ongoing phototherapy treatment for MF. Patients less than 30 years of age with MF also appear to have an increased risk of secondary lymphomas, warranting regular, ongoing clinical surveillance [99]. For patients with indolent disease, evaluation every 3 months is an appropriate interval; complete restaging may be necessary with changes in clinical appearance [82].

Cutaneous B-Cell Lymphoma

Key Points

- Primary cutaneous B-cell lymphomas (PCBCLs) are exceedingly rare in children and typically have an excellent prognosis.
- Precursor B-cell lymphoblastic lymphoma (B-LBL) may also present in childhood and should be considered a diagnostic and therapeutic emergency.

Primary cutaneous B-cell lymphoma (PCBCL) is classified as a subtype of non-Hodgkin lymphoma that originates in the skin without any evidence of systemic involvement at the time of diagnosis. There are four main subtypes of PCBCL, all of which are exceedingly rare in children and adolescents [83]. Of these, primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are regarded as relatively benign entities with indolent behavior. In contrast, primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCL-L), and primary cutaneous diffuse large B-cell lymphoma, other (DLBCL), are more aggressive neoplasms with poorer survival [63, 100]. In general, all forms of PCBCL typically present as red-to-violaceous papules, plaques, or smooth nodules [100]. Owing to their rarity in children, PCFCL and DLBCL will not be discussed further in this text [63].

Primary Cutaneous Marginal Zone Lymphoma

Though still rare, PCMZL appears to be the most common form of PCBCL in children and does not exhibit a gender predilection [101]. Lesions are typically multifocal with a propensity for the trunk and extremities, especially the arms [100, 101]. In children, PCMZL appears to follow an indolent course with a minority of patients exhibiting persistent disease following treatment. Although some cases of adult PCMZL have been associated with exposure to European *Borrelia* species, this is thought to be uncommon in children [100, 101].

Histologically, PCMZL is characterized by a nodular or diffuse infiltrate of small- to medium-sized lymphocytes, lymphocytoplasmoid cells, and plasma cells with an evident grenz zone. Eosinophils and histiocytes may also be appreciated [100, 102]. At low magnification, darker cellular aggregates are often surrounded by a lighter zone of pale-staining, centrocyte-like, marginal zone B cells with minimally irregular nucleoli [83]. On immunohistochemistry, these neoplastic cells stain positively for CD19, CD20, CD70a, and Bcl-2 while lacking expression of CD5, CD10, and Bcl-6 [102]. Clonal expression of IgH genes is evident in a majority of cases [83].

Upon diagnosis of PCBCL, a complete staging workup is recommended to exclude secondary involvement of the skin by a primary systemic lymphoma [103]. Recommended evaluation includes a complete history and physical examination with specific evaluation for lymphadenopathy and hepatosplenomegaly. Laboratory evaluation includes a CBC with differential, CMP, and LDH. CT with contrast or PET/CT of the chest, abdomen, and pelvis is also recommended. In select instances, peripheral blood flow cytometry, bone marrow biopsy, and serum protein electrophoresis/quantitative immunoglobulin levels may be evaluated.

The prognosis of children with PCMZL is excellent. Treatment options for localized disease include radiotherapy and excision. Observation, topical corticosteroids, intralesional corticosteroids, or intralesional interferon alpha may also

be considered as first-line therapies [101, 103]. In cases of widespread or refractory disease, single- or multi-agent chemotherapy, as well as targeted immunotherapy with the anti-CD20 monoclonal antibody rituximab, may be useful. If association with *Borrelia* infection is suspected, appropriate antimicrobial therapy can prompt resolution [100, 103].

Precursor B-Cell Lymphoblastic Lymphoma

Lymphoblastic lymphomas are neoplastic diseases of T- or B-cell precursors. Although most precursor lymphoblastic lymphomas are of a T-cell phenotype, precursor B-cell lymphoblastic lymphomas (B-LBL) are more likely to present with cutaneous involvement [104, 105]. Clinically, cutaneous B-LBL presents as large, blue-red, asymptomatic, firm, fixed nodules, often located on the head and neck, particularly the scalp [106, 107] (Fig. 3.5). The lesions are solitary in approximately 80% of cases [63, 106]. B-LBL is seen more commonly in females than males, with patients presenting at a mean age of 5 years [106].

Histologically, B-LBL is characterized by a diffuse, monomorphic infiltrate of small- to medium-sized cells with inconspicuous nucleoli and a high mitotic index [104, 106]. Immunohistochemistry is essential in making a diagnosis of B-LBL, as neoplastic cells express TdT and other B-cell antigens including CD10, CD19, and CD79a, as well as the transcription factor Pax5. However, they often lack expression of CD20 [63, 104, 106].

Diagnosis of cutaneous B-LBL requires mandatory evaluation for evidence of B-cell acute lymphoblastic leukemia (B-ALL), which is distinguished from B-LBL by peripheral blood involvement of neoplastic cells or bone marrow aspirate demonstrating ≥25% blasts [63, 108]. As such, a complete history and physical, laboratory evaluation including a CBC with differential, CMP, and LDH, as well as a bone marrow aspirate, should be performed, and collaboration with an experienced oncologist is recommended.

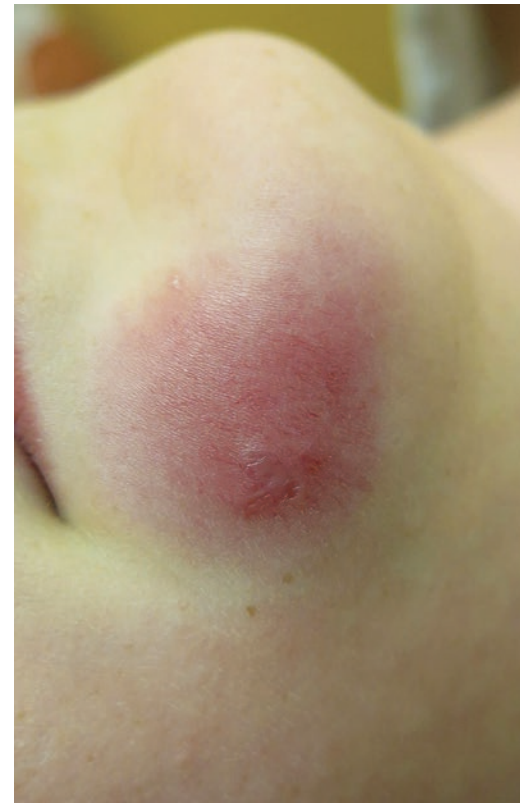

Fig. 3.5 Cutaneous precursor B-cell lymphoblastic lymphoma. A red-to-violaceous subcutaneous nodule present on the chin of a child

Flow cytometry of peripheral blood, evaluation of cerebrospinal fluid, and CT imaging are also required to evaluate for other sites of involvement including the CNS, soft tissue, and bone [105]. B-LBL should be considered a therapeutic emergency. Though prognosis is generally good, outcomes are improved if treatment is instituted early, which may reflect the benefit of a smaller tumor burden when compared to B-ALL [105, 106, 108]. Nevertheless, treatment of B-LBL, regardless of degree of involvement, requires aggressive multi-agent systemic chemotherapy [104, 106].

CLPDs are rare in children and typically mimic more common, benign dermatoses. Nevertheless, the entire spectrum of reactive and variably malignant lymphoproliferative disorders has been recognized in childhood, though these entities often require a high index of suspicion

for diagnosis. Fortunately, the majority of these conditions have favorable long-term prognoses with appropriate treatment.

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Other Proliferative Disorders of the Skin

4

Emily A. Gurnee and Leslie P. Lawley

Mastocytosis

Key Points

- Though there is a broad range of disease severity in mastocytosis, children frequently have benign cutaneous variants and do not usually require aggressive systemic workup.
- Systemic symptoms associated with cutaneous mastocytosis result from histamine release, necessitating avoidance of potential triggers of mast cell degranulation in some patients.
- Cutaneous mastocytosis tends to resolve gradually over time.

Introduction

Mast cells not only play an essential role in immunity, tissue repair, and wound healing but also contribute to the development of common disease entities like allergy and asthma. Both pathogens and allergens have the potential to aberrantly activate mast cells either directly or indirectly. The term mastocytosis encompasses a wide spectrum of disease resulting from the proliferation of mast cells; activation of these cells by various triggers leads to degranulation and downstream symptoms such as flushing, diarrhea, bronchospasm, and anaphylaxis. The World Health Organization (WHO) divides mastocytosis into nine distinct disorders: cutaneous mastocytosis (including maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, and mastocytoma of skin), indolent systemic mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis with hematologic neoplasm, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma [1]. Some authors also include telangiectasia macularis eruptiva perstans (TMEP) as a separate classification within cutaneous mastocytosis, but this is very rare in children. The majority of children with mastocytosis present with cutaneous mastocytosis (reviewed in Table 4.1), a relatively benign disorder characterized by mast cell infiltration restricted to the skin. This chapter will focus on the diagnosis, clinical features, and management of cutaneous mastocytosis, with attention to situations that require further workup for systemic mastocytosis.

Epidemiology

There are no epidemiologic studies of pediatric cutaneous mastocytosis. Overall estimates of prevalence of mastocytosis in European

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Table 4.1 Classification of pediatric cutaneous mastocytosis [2–4, 5]

Classification	Percent of pediatric cases (%)	Description	Associated signs and symptoms	Prognosis
Cutaneous solitary mastocytoma	20	Solitary macule or plaque with mast cell infiltrate	Itching, lymphadenopathy	Excellent: >90% show partial or complete regression
Urticaria pigmentosa/ maculopapular cutaneous mastocytosis	75	Multiple macules, papules, plaques, or bullae	Itching, flushing, diarrhea, dyspnea, hepatomegaly lymphadenopathy, splenomegaly	Very good: 71% show partial or complete regression
Diffuse cutaneous mastocytosis	5	Diffuse mast cell infiltration of skin, often causing peau d'orange appearance; may have overlying papules or vesicles	Itching, hepatomegaly, lymphadenopathy, splenomegaly, diarrhea	Excellent: >90% show partial or complete regression
Telangiectasia macularis eruptiva perstans (TMEP)	<1	Brown macules, often on trunk. Scant mast cell infiltrate, often with negative Darier's sign	Limited data in children, but often asymptomatic. About half of adults have associated systemic mastocytosis	Long-term prognosis unknown, reported cases have benign course

populations are around 9–13 per 100,000 [6]. Pediatric mastocytosis is largely a benign condition, with about 75% of children reported in recent literature presenting with urticaria pigmentosa, 20% with solitary mastocytoma, 5% with diffuse cutaneous mastocytosis, and <1% with TMEP [3]. Systemic and malignancy-related forms are rarely encountered in pediatric populations.

Natural History

About 90% of cases of cutaneous mastocytosis present prior to age two, with a slight male predominance [2, 3]. In children with early-onset disease, lesions tend to resolve by adolescence [7]. One case series, which followed 13 patients with UP and 2 patients with DCM for over 20 years, demonstrated that 10 of 15 showed complete resolution, and the remaining 5 showed partial or major improvement [8]. Pediatric patients with small lesions (<1 cm) show significantly later resolution that those with larger lesions, higher tryptase, and later onset of disease [9]. Across all types of pediatric mastocytosis, 67% of patients show partial or complete regression [3].

Though the majority of patient's signs and symptoms resolve or gradually improve, a smaller subset may have progressive disease. In a review of published cases, Meni et al. 2015 noted that children with UP were the most likely to have cutaneous worsening or develop systemic mastocytosis. In the same review, 2.9% of cases with follow-up data resulted in a fatal outcome; however, this is likely heavily affected by publication bias [3].

Pathogenesis

The cause of mastocytosis is unknown, but genetic factors have been proposed. Hematopoietic stem cells differentiate into mast cells in response to signaling through CD117, a transmembrane tyrosine kinase receptor [10]. Adults and children with cutaneous mastocytosis have been shown to harbor mutations in c-KIT, the gene encoding CD117, though the affected codon differs in pediatric patients in comparison to adult patients [11, 12]. In adults, KIT mutations are commonly found on exon 17, KIT D816V, whereas children demonstrate mutations in exon 8, 9, or 17 [12]. c-Kit is a receptor tyrosine kinase essential for numerous cellular signal transduction pathways [13]. The significance of genetic polymorphisms in c-Kit among pediatric patients is not yet clear, and the utility of genetic testing in clinical practice has not been established.

Symptoms of mastocytosis are largely due to the activation and degranulation of mast cells, resulting in release of a variety of mediators, including proteases, histamine, proteoglycans, cytokines, prostaglandins, and leukotrienes [14]. Histamine release from mast cells can lead to symptoms in all forms of cutaneous mastocytosis (Table 4.2), ranging from mild headache, nausea, vomiting, diarrhea, and cutaneous flushing to severe symptoms such as hypotension, anaphylaxis, and neurologic dysfunction [15].

Clinical Features

Mastocytosis has a variety of clinical manifestations from limited skin involvement to systemic signs and symptoms. The rate of anaphylaxis in children with all types of mastocytosis is estimated to be 5–9% [3, 17]. Rates in urticaria pigmentosa are lower, around 1.5%, but greater cutaneous involvement is associated with higher risk of anaphylaxis [16, 17]. In one study, 13% of adults with cutaneous mastocytosis reported a history of anaphylaxis, whereas in adults with systemic mastocytosis rates of anaphylaxis have been reported to be as high as 56% [17].

Table 4.2 Symptoms of mast cell degranulation in patients with mastocytosis [3, 16]

Skin symptoms
Itching
Flushing
Gastrointestinal symptoms
Diarrhea
Abdominal pain
Vomiting
Respiratory symptoms
Wheezing/dyspnea
Cough
Rhinorrhea
Other
Bone pain
Headache
Systemic symptoms
Irritability
Hypotension
Anaphylaxis
Syncope

Clinical manifestations may vary by mastocytosis subtypes. Pediatric cutaneous mastocytosis subtypes include solitary mastocytoma (SM), maculopapular cutaneous mastocytosis or urticaria pigmentosa (UP), diffuse cutaneous mastocytosis (DCM), and telangiectasia macularis eruptiva perstans (TMEP), with UP representing the most common variant (see Table 4.1). Rare cases of localized xanthelasmoid mastocytosis have been reported, often favoring flexural areas, with appearance similar to pseudoxanthoma elasticum or juvenile xanthogranuloma [18–20].

About 20% of cases of pediatric mastocytosis present as a solitary mastocytoma [3]. Solitary mastocytomas typically present in early childhood as a single yellow-brown lesion. Induration of skin with associated dimpling resulting from cutaneous infiltration has been referred to as having a peau d'orange (or orange skin) appearance (Fig. 4.1). Systemic symptoms are rarely encountered in association with solitary mastocytomas, and >90% of lesions will spontaneously resolve [3].

Urticaria pigmentosa presents with multiple yellow-brown macules, papules, plaques, or blisters. Lesions range from a few millimeters to 1–2 cm, tend to first appear on the trunk, and generally spare acral regions. Blistering can be seen, most prominently in association with lesions on the head [21]. Blistering tends to appear and resolve in the first few years of life [22]. In

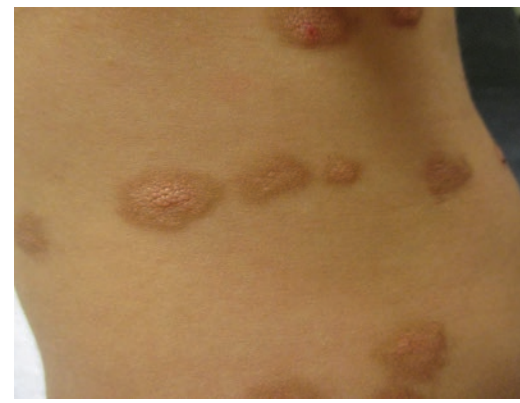


Fig. 4.1 Cutaneous mastocytosis. Several lesions in this patient exhibit peau d' orange textural changes

patients with UP, both the number and severity of skin lesions predict systemic symptoms, most commonly gastrointestinal, respiratory, or neuropsychiatric disturbances [16].

Patients with DCM present with generalized hyperpigmentation and induration of skin, as opposed to the discrete lesions seen in UP or SM. Two cutaneous manifestations of DCM have been described, including indurated plaques or blisters with background generalized erythema and yellow/orange plaques mimicking xanthomatous skin lesions [23, 24]. Systemic symptoms such as flushing, GI distress, and bone pain are more common in DCM than other forms of cutaneous mastocytosis [3, 15].

Telangiectasia macularis eruptiva perstans (TMEP) is a form of cutaneous mastocytosis seen in <1% of childhood cutaneous mastocytosis, and in up to 14% of adult cases, with median age of onset at 50 years [5]. TMEP is characterized by small red-brown telangiectatic macules more commonly located on extremities. Up to 50% of adult patients with TMEP experience systemic symptoms [5], but there is a paucity of pediatric data due to the rarity of this presentation in children.

It is important to note the distinctions in clinical features between pediatric and adult-onset mastocytosis. Adult-onset mastocytosis is much more likely to be associated with systemic manifestations, is less likely to regress, and presents with smaller, monomorphic lesions on the trunk and thighs. Children typically have larger, polymorphic macules, papules, plaques, or blisters targeting the head and neck, trunk, and extremities [21]. Interestingly, children with small (<1 cm), monomorphic maculopapular lesions may have a later onset in disease and higher likelihood of disease persistence beyond childhood [9].

Though pediatric fatalities in the perioperative period have not been reported, the perioperative period represents a clinical situation that requires special attention. While 2–4% of children with cutaneous mastocytosis may experience moderate symptoms secondary to mast cell release and/or anaphylaxis from anesthesia, such complications may be avoided with prophylactic antihistamines [25]. Importantly, there are no reported cases of anesthesia-related complications in patients with solitary mastocytoma [26]. The incidence in pediatric systemic mastocytosis is unknown due to rarity of the diagnosis. The perioperative period may introduce numerous triggers, including stress, temperature change, mechanical stress, and medications. Therefore, anesthesiologists should be aware of the patient's diagnosis and obtain a thorough history of past triggers. Most authors advocate for continued administration of maintenance mastocytosis-directed treatment, incremental administration of medications with potential for mast cell release, and substitution of fentanyl or sufentanil for known degranulators, including atracurium, mivacurium, meperidine, and morphine [26]. NSAIDs may be used, with caution, in children without known sensitivity. Regardless of procedure, medication list, or severity of cutaneous symptoms, medical providers should be prepared to respond to episodes of anaphylaxis in children with cutaneous mastocytosis undergoing anesthesia.

Diagnosis

The diagnosis of cutaneous mastocytosis is established by identifying the highly characteristic clinical exam (see Fig. 4.1) and/or with skin biopsy. Lesions of cutaneous mastocytosis are hyperpigmented, fixed macules, papules or plaques that tend to exhibit a wheal and flare reaction when stroked, known as the Darier's sign. Skin biopsy of suspected lesions demonstrates a mast cell infiltrate in the papillary dermis. Increase in mast cell number can be subtle, particularly in patients with TMEP. Giemsa, toluidine blue, or immunohistochemical stains with CD117/c-kit and tryptase can help to identify mast cells on skin biopsy.

Many experts suggest that evaluation for systemic mastocytosis is unnecessary for most children with mastocytosis, but for certain

patients with severe disease, further workup may be warranted. Though controversial, some authors recommend consideration of systemic workup in the following scenarios: organomegaly, elevated tryptase, unexplained peripheral blood abnormalities, or persistence of cutaneous lesions after puberty. Differentiation of cutaneous mastocytosis from systemic mastocytosis generally requires a bone marrow biopsy and is supported by the criteria listed in Box 4.1 [27].

Box 4.1 Criteria for the diagnosis of systemic mastocytosis, adapted from Valent et al. 2001 [27]

Major

1. >15 mast cells in aggregates on bone marrow biopsy or other extracutaneous tissue

Minor

1. 25% spindle-shaped mast cells in extracutaneous specimen or >25% atypical mast cells
2. C-kit mutation in codon 816
3. Co-expression of kit and CD2 and/or CD25 in mast cells in bone marrow, blood, or extracutaneous tissue
4. Serum tryptase persistently >20 ng/mL

One major and one minor or three minor criteria are required for the diagnosis of systemic mastocytosis.

Laboratory Findings

Recommendations for initial laboratory testing vary between authors and clinicians. Some suggest that CBC with differential and biochemistry should be obtained at diagnosis in addition to baseline tryptase in those with UP or DCM [28]. Frequency of repeat testing has not been established but likely should be based on the severity of systemic symptoms.

Monitoring of tryptase levels may be helpful in determining burden of cutaneous disease and risk for systemic involvement. Children with diffuse cutaneous mastocytosis display significantly higher levels than those with urticaria pigmentosa or solitary mastocytoma [15, 29]. Serum tryptase tends to decrease over time and correlate with improvement in symptoms. As such, increases in serum tryptase may indicate the need for further evaluation and consideration of bone marrow biopsy [30]. In a case series of 105 children evaluated for cutaneous mastocytosis, systemic mastocytosis was found only in children with both elevated tryptase (>20 ng/mL) and organomegaly, suggesting that these factors should be considered in the decision to pursue bone marrow biopsy in pediatric patients [30]. Importantly, there were no patients with elevated tryptase in the absence of organomegaly who were found to have systemic mastocytosis [30]. Plasma histamine, though elevated in most cases of CM, has not been found correlate with active disease in mastocytosis [31].

The SCORing MAstocytosis (SCORMA) index correlates with serum tryptase and has been proposed as a standardized method to grade severity of mastocytosis [32]. This index combines the anatomical area involved, intensity of cutaneous findings, and subjective symptoms reported by patients or families.

Treatment

Treatment of mastocytosis is dependent on the severity of symptoms relating to mast cell degranulation and mast cell mediator release (Table 4.3). Treatment can successfully ameliorate symptoms but does not appear to hasten resolution of mastocytosis. A detailed protocol for management is proposed by Heide et al. 2008 [33]. For patients with severe disease, avoidance of triggers of mast cell degranulation (Table 4.4) can help prevent systemic symptoms.

Table 4.3 Treatment options for cutaneous mastocytosis [33, 34]

Clinical presentation	Treatment recommendations
All forms	At least yearly follow-up with abdominal and lymph node exam Screening for systemic symptoms of mast cell degranulation
Asymptomatic cutaneous lesions	No treatment required
Cutaneous solitary mastocytoma	Topical steroids may speed partial regression [34] Consider surgical excision if severe
Urticaria pigmentosa or diffuse cutaneous mastocytosis with symptoms from histamine release (see Table 4.2)	First- and/or second-generation antihistamines Oral cromolyn sulfate Topical steroids Avoid known triggers Consider epinephrine prescription
Extensive cutaneous disease	Avoid known triggers Provide epinephrine prescription PRN

Table 4.4 Triggers of mast cell degranulation [28, 33]

Changes in temperature
Friction
Stress
Infections
NSAIDs, aspirin
Opiates, especially morphine, codeine
Dextromethorphan
Polymyxin B
Contrast media
Alcohol
Surgical or dental procedures
Vaccines
Bee/wasp stings
Any other past triggers

Table 4.5 WHO classification of hematopoietic/lymphoid tumor subsets, adapted from Campo et al. 2008 [35]

(1) Mature B cell neoplasms
(2) Mature T cell and NK cell neoplasms
(3) Hodgkin lymphoma
(4) Posttransplant lymphoproliferative disorders
(5) **Histiocytic and dendritic cell neoplasms**
– Histiocytic sarcoma
– **Langerhans cell histiocytosis**
– Langerhans cell sarcoma
– Interdigitating dendritic cell sarcoma
– Follicular dendritic cell sarcoma
– Fibroblastic reticular cell tumor
– Intermediate dendritic cell tumor
– Disseminated juvenile xanthogranuloma

Langerhans Cell Histiocytosis

Key Points

- Langerhans cell histiocytosis (LCH) is a neoplastic disorder arising from histiocytes that can affect nearly any organ system.
- Single and multisystem forms of LCH have significantly different prognoses, and evaluation for systemic involvement should be undertaken for all patients with cutaneous lesions.
- Mutations in BRAF V600E are found in many cases of LCH. A portion of BRAF V600E mutation-negative patients harbor mutations in MAP 2K1.

Introduction

Manifestations of LCH range from relatively benign collections of histiocytes in the skin or bone to multi-organ disease with a higher morbidity and mortality rate. The WHO groups LCH within the larger category of histiocytic/dendritic cell neoplasms (see Tables 4.5 and 4.6) [35, 36].

Recently, authors have advocated for a new classification scheme of LCH from the traditional eponyms into single-system (SS-LCH) and multisystem LCH (MS-LCH) (see Table 4.6). Focal osteolytic lesions, previously known as eosinophilic granuloma, and congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker) are now considered variants of SS-LCH.

Table 4.6 Historic and modern classifications of LCH [37]

Historic classification model	Modern classification
Eosinophilic granuloma (localized LCH, often of bone) **Hashimoto-Pritzker** (congenital self-healing LCH)	**Single-system LCH** (SS-LCH)
Hand-Schuller-Christian (osteolytic lesions of the skull, diabetes insipidus, and exophthalmos) **Abt-Letterer-Siwe** (acute diffuse histiocytosis)	**Multisystem LCH** (MS-LCH) -With "risk organ" involvement (liver, spleen, hematolymphatic, or respiratory system) -Without "risk organ" involvement

Epidemiology

Across subtypes, LCH occurs at a rate of about 1–4 per million children [38–40), with rates as high as 9 per million in some studies [41]. Rates are generally higher in children under age 1 (around 5–9 per million infants) [38, 39], as well as in Caucasian and Hispanic populations [38]. Most cases of LCH are sporadic, but familial and twin cases have been reported [42]. Most case series show a modest male predominance.

Natural History

LCH is predominantly a disorder of childhood, with median age at diagnosis of 4–5 years [41, 43, 44]. Skin-limited LCH has a very good prognosis, with 100% 3-year overall survival and 89% 3-year progression-free survival [45]. In contrast, 3-year progression-free survival falls to 44% for patients with multisystem disease [45]. Involvement of high-risk organs, specifically the liver, spleen, hematolymphatic, or respiratory system, portends a worse prognosis [44]. Though the mortality rate is relatively low, mortality typically affects patients with multisystem disease involving high-risk organs. For example, the 5-year survival rate for patients with liver involvement is 25% [39].

Over 70% of neonates (infants less than 28 days) presenting with cutaneous features of LCH have multisystem involvement on further investigation [46]. Single-system LCH in infants has excellent prognosis with a 94% 5-year overall survival, but survival falls to 57% for patients with multi-organ involvement [46]. Historically, authors defined a distinct benign entity in neonates known as congenital self-healing reticulohistiocytosis or Hashimoto-Pritzker. Solitary congenital lesions have been reported, generally with excellent prognosis and spontaneous resolution [47–49]. However, as no reliable factors exist at this time to predict which patients may experience progression or recurrence based on cutaneous features [50, 51], many authors now advocate to view all forms of LCH as having the potential for aggressive features and long-term sequelae [52].

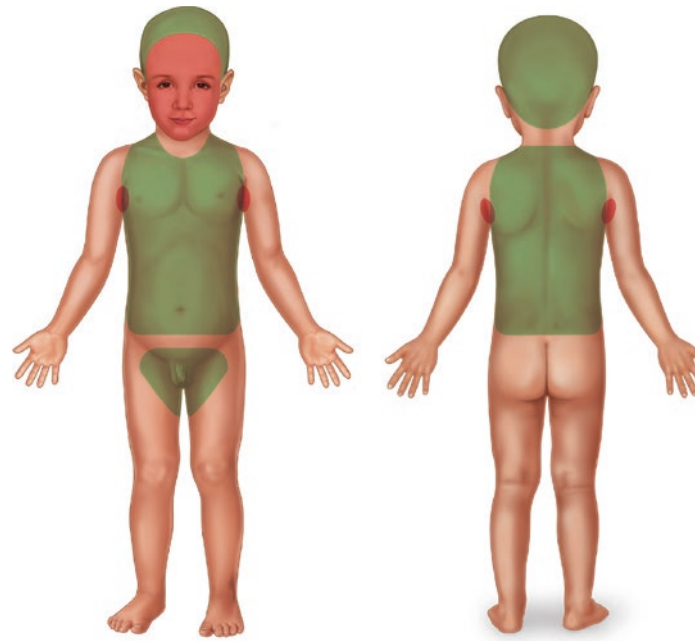
Pathogenesis

Langerhans cells are antigen-presenting cells found in the skin and other organs. Both normal Langerhans cells and LCH cells can be identified by similar phenotypic markers such as CD1a, S100, and Langerin (CD207). Though they share the same markers as epidermal Langerhans cells, lesional Langerhans cells in LCH likely arise from myeloid dendritic precursors [53]. Clonal populations of Langerhans cells have been identified in LCH, including in unifocal, multi-organ, and disseminated forms [54, 55]. Until recently, many authors debated whether the clonal proliferations seen in LCH represented a neoplastic or reactive process. In 2010, Badalian-Very et al. demonstrated high prevalence of activating BRAF mutations in patients with LCH [56], suggesting that LCH should best be defined as a neoplastic process. More recently, multiple studies have identified that about 50% LCH lesions express BRAF V600E mutations [57, 58]. Mutations in MAP 2K1,which encodes MEK1, a downstream effector protein in the BRAF signaling pathway, have been found in about half of the BRAF V600E-negative patients [59]. The clinical implications of these mutations are unclear, as no distinct disease phenotype has been found to correspond to either mutation [60].

Clinical Features

Skin lesions in LCH have a variable clinical presentation. Common cutaneous presentations include crusted, scaly papules or vesicles. Lesions often involve the seborrheic distribution, intertriginous areas, and mucosa or may resemble otitis externa [52]. LCH should be suspected in cases of seborrheic dermatitis, diaper dermatitis, and otitis externa that do not respond to standard treatments. See Fig. 4.2 for the most frequent distribution of lesions. Rarely, lesions resembling hemangiomas, varicella, or purpura have been reported [52]. In children under age 1, cutaneous findings are the most common presenting symptom [44, 46, 51].

About 30% of LCH patients present with multisystem disease, with the bone as the most frequently involved organ, followed by the skin and soft tissue [43, 44]. In addition, progression from skin-limited to multisystem LCH has been reported [61]. Signs and symptoms from extracutaneous LCH depend on organ system involved and include fever, weight loss, malaise, bone pain or swelling, loose teeth, respiratory distress, ataxia, and polydypsia/polyuria. Children with multisystem disease are more likely to have long-term sequelae such as diabetes insipidus, orthopedic abnormalities, hearing loss, or neurologic dysfunction [62].



Involved in >50% of cases (green areas)	Scalp Trunk Groin
Involved in 25–50% of cases (red areas)	Retroauricular skin Face Axilla Pubis External otitis

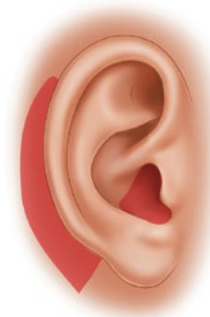


Fig. 4.2 Typical distribution of lesions in pediatric LCH [52]

Diagnosis

The Histiocytosis Society recommends a standardized workup in cases of suspected LCH, regardless of clinical variant (Box 4.2).

Box 4.2 Initial evaluation of suspected LCH, adapted from the Histiocytosis Society of Europe [37]

Physical exam: including lymph node exam and abdominal exam for evaluation of liver and spleen

Skin biopsy of suspected lesion(s)

Bloodwork
- Complete blood count with differential
- Electrolytes
- Liver function tests (albumin, total protein, bilirubin, coagulation studies, transaminases)
- ESR

Imaging
- Skeletal and chest radiographs
- Abdominal ultrasound

Whenever possible, histologic examination is essential to confirm the diagnosis of LCH, as many diseases may mimic LCH. Hematology-oncology will pursue additional studies, including bone marrow biopsy, pulmonary function tests, bronchoalveolar lavage or lung biopsy, small bowel imaging, liver biopsy, CT or MRI of brain, dental radiographs, endocrine evaluation and ENT evaluation, based on initial clinical, laboratory, and imaging findings [63].

Treatment

Treatment for single-system LCH varies based on the organ system involved and associated risk for mortality or morbidity [37]. Single-system disease can be effectively treated with observation or curettage (bone-only disease) or topical corticosteroids (skin-only disease), while multi-organ or high-risk organ involvement often necessitates initiation of chemotherapy. Protocols employing vinblastine and prednisone have been shown to effectively treat multisystem LCH [64, 65], particularly with intensified and prolonged courses of treatment [65, 66]. In patients who require chemotherapy to treat LCH, response to initial therapy predicts long-term survival [40, 66, 67]. Based on the identification of BRAF mutation in LCH, initial investigation of vemurafenib for LCH has been promising [68–70]. MEK mutations have been identified in BRAF mutant-negative patients, likely creating a role for targeted MEK inhibitors in the future [59].

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Malignancy-Associated Genodermatoses

5

Sarah N. Robinson, Hannah Song, and Jennifer T. Huang

Genodermatoses Associated with Primary Cutaneous Malignancies

Introduction

In this section, we will highlight genodermatoses associated with primary skin cancer during childhood, as opposed to those with development of skin cancer secondarily in the setting of photosensitivity or other predisposing factors such as chronic wounds. Genodermatoses will be presented according to the type(s) of skin cancer with which they are associated (basal cell carcinoma, squamous cell carcinoma, or melanoma).

Key Points

- Nevoid basal cell carcinoma syndrome (also known as Gorlin syndrome) is the genodermatosis most commonly associated with development of basal cell carcinoma in childhood.
- Ferguson-Smith syndrome is associated with eruption of keratoacanthomas and typically follows a self-limited course.
- Familial atypical multiple mole-melanoma syndrome is associated with the presence of numerous atypical nevi and predisposition to development of melanoma.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common form of nonmelanoma skin cancer (NMSC) in adults, but a rare entity in the pediatric population. The diagnosis of BCC at a young age merits a thorough investigation for underlying predisposing factors including nevus sebaceous, radiation exposure, immunosuppression, or associated genodermatoses [1, 2]. We will review two genodermatoses that are associated with development of BCCs in children or young adults: nevoid basal cell carcinoma syndrome and Bazex syndrome.

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Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome, also known as Gorlin syndrome or basal cell nevus syndrome, is an autosomal dominantly inherited genodermatosis associated with the development of numerous BCCs. Hundreds of cases have been reported in the literature to date, with large series of more than 100 patients each described in both the United States and Australia [3, 4]. The gene affected in this condition is the tumor suppressor gene PTCH1, located on chromosome 9q22–31; the mutation results in an upregulation of the Hedgehog signaling pathway [5].

Clinically, patients typically have at least one BCC and many develop hundreds or more, with onset ranging from early childhood to adulthood, averaging in the early 20s [3]. They appear as skin-colored papules, often developing in sun-exposed areas including the face, neck, and extremities, as well as the trunk with predilection for flexural regions such as the neck, axillae, and inguinal regions. While BCCs may begin as small, asymptomatic lesions during childhood (Fig. 5.1), they continue to grow in size with age and can become locally destructive. Importantly, patients with nevoid basal cell carcinoma syndrome can have a number of associated cutaneous and extracutaneous findings, several of which may be noted in early childhood prior to the development of BCCs. Additional skin findings can include palmar or plantar pits (Fig. 5.2), epidermal inclusion cysts, and milia [6]. Many children have characteristic facial features including hypertelorism, macrocephaly, and frontal bossing. Associated extracutaneous features include ophthalmologic anomalies (see Table 5.1), calcification of the falx cerebri, medulloblastoma, odontogenic keratocysts, or other skeletal or soft tissue abnormalities [6, 7]. Positive family history can also suggest this diagnosis early in life [6]. While there are no agreed upon diagnostic criteria, proposed criteria for "reasonable consideration" from the First International Colloquium on Basal Cell Nevus Syndrome held at Saint Louis University School of Medicine in 2011 were one major criterion and confirmatory genetic testing, two major criteria, or one major and two minor criteria, as outlined in Table 5.1 [7].

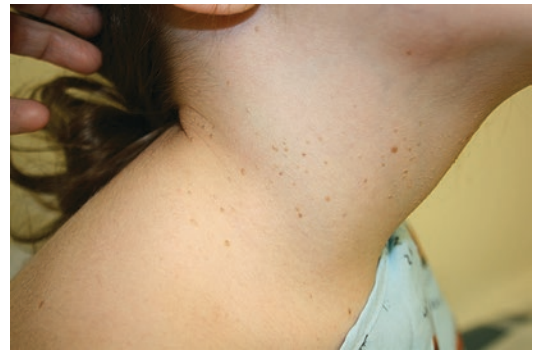

Fig. 5.1 Numerous small skin-colored, dome-shaped papules on the neck, consistent with early basal cell carcinomas in Gorlin syndrome

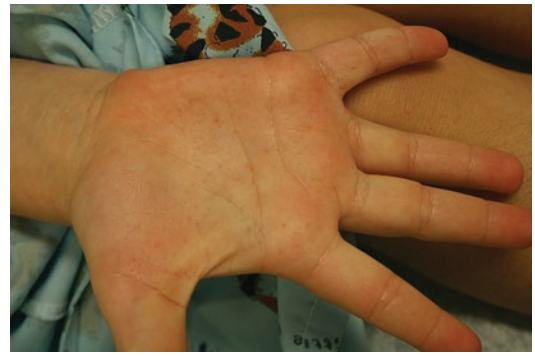

Fig. 5.2 Palmar pits, which can be subtle clinically but represent a major criterion for Gorlin syndrome

With regard to management for these patients, treatment for each individual BCC is similar to that for any other BCC, typically consisting of electrodessication and curettage (ED&C), curettage alone, excision, or Mohs micrographic surgery for nodular subtype or lesions on sites that are cosmetically sensitive and/or at higher risk for recurrence. When treating multiple BCCs within a localized area, providers should consider field treatment such as photodynamic therapy (PDT) or topical chemotherapy such as 5-fluorouracil cream for superficial lesions. For numerous, locally invasive, recurrent, or metastatic BCCs, one may also consider systemic treatment with the smoothened receptor inhibitors such as vismodegib and sonidegib, although

Table 5.1 Clinical criteria for diagnosis of Gorlin syndrome [7]

Major criteria	Minor criteria
BCC at age <20 years or multiple BCCs higher in number than would be expected based on exposures	Ocular abnormalities (i.e., hypertelorism, strabismus, congenital cataracts)
Odontogenic keratocyst during childhood	Skeletal anomalies (i.e., bifid or other rib abnormalities, vertebral fusion, short fourth metacarpals, polydactyly)
Medulloblastoma	Macrocephaly, frontal bossing
Calcification of the falx cerebri	Cleft lip/palate
Palmar or plantar pitting	Fibroma of ovary or heart
Family history of Gorlin syndrome in a first-degree relative	Abdominal cysts containing lymphatic fluid

Information compiled from Bree et al. "Consensus statement from the first international colloquium on basal cell nevus syndrome"

there is currently limited data on safety and efficacy in children [8–10].

These patients require close surveillance with routine full skin examinations every 6–12 months, radiographic surveys to assess for odontogenic keratocysts of the jaw, and counseling regarding importance of strict sun protection. The treatment team should be multidisciplinary and may include dentistry, neurology, orthopedic surgery, ophthalmology, and genetics, in addition to dermatology. While radiographs may be necessary to screen for odontogenic keratocysts or brain tumors, ionizing radiation, e.g., radiologic imaging and radiation therapy, should be used with caution in these patients as it has been shown to significantly increase risk for development of BCCs within the treatment area [11, 12]. With appropriate treatment and no internal malignancy, most patients with nevoid basal cell carcinoma syndrome can expect a normal lifespan.

Bazex Syndrome

Bazex syndrome, also known as Bazex-Dupré-Christol syndrome, is a rare genodermatosis associated with development of multiple BCCs with onset as early as the first or second decade of life [13]. It is thought to have an X-linked dominant inheritance pattern, although the causative gene remains unknown. Other characteristic cutaneous features include hypotrichosis (which is often the presenting sign as it may become apparent early in childhood), hypohidrosis, and follicular atrophoderma of the dorsal aspect of hands and feet [2, 14, 15]. While Bazex syndrome demonstrates significant overlap in clinical features with Rombo syndrome, BCCs in Rombo syndrome tend to develop during adulthood [16]. Management for patients with Bazex syndrome should emphasize education on sun protection as well as regular full skin checks with dermatology.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common form of NMSC in adults. Many consider keratoacanthomas, which classically present as rapidly enlarging nodules with a central crater containing keratin, to be on a spectrum with SCC. While they may be indistinguishable from SCC histologically, they have a tendency to erupt and then spontaneously regress clinically. Similar to BCC, SCCs are also rare in childhood and should prompt evaluation for predisposing factors. In this section, we will discuss a single genodermatosis that has been associated with development of keratoacanthomas during childhood, Ferguson-Smith syndrome, as well as give brief mention to a second entity that can have similar findings in adults, Muir-Torre syndrome.

Ferguson-Smith

Ferguson-Smith syndrome, also known as multiple self-healing squamous epitheliomas, is characterized by multiple keratoacanthomas, as its

name suggests. It has an autosomal dominant inheritance pattern and results from TGFBR1 or ALK5 mutations, resulting in a loss of function mutation in TGFbeta1 [17]. The clinical presentation includes anywhere from a few to hundreds of keratoacanthomas in adolescence or early adulthood that grow rapidly before resolving, often leaving deep scars. The disease is not associated with photosensitivity, but keratoacanthomas have a propensity to develop on sun-exposed areas. Given the spontaneous regression of keratoacanthomas, the lifespan of these patients is typically not affected.

Muir-Torre syndrome is another condition that can be associated with multiple keratoacanthomas, though the tumors typically appear in adulthood. It is an autosomal dominantly inherited condition characterized by sebaceous gland neoplasms and internal malignancies. It is considered a phenotypic variant of hereditary nonpolyposis colorectal cancer (HNPCC) that results most commonly from mutations in mismatch repair genes MLH1 and MSH2 [18]. Sebaceous adenomas, the most common skin neoplasm, are considered benign and usually present in the fifth decade but can present in adolescence [19]. Multiple keratoacanthomas do not usually occur until adulthood. The presence of sebaceous neoplasms in children should prompt screening for Muir-Torre and associated gastrointestinal malignancies [20].

Melanoma

In addition to squamous cell carcinoma in the setting of immunodeficiency, melanoma is a malignancy of the skin with potential to metastasize to internal organs, leading to death. However, when detected early, local surgical excision can be curative. There are a number of factors associated with increased risk for development of melanoma in both children and adults, including, but not limited to: skin type, sun exposure, family history, number and type of nevi, and atypical nevi [2, 15]. In addition, there are several genodermatoses associated with increased risk of melanoma including a familial mole syndrome and xeroderma pigmentosum (to be discussed in a later section), as shown in Table 5.2. In this section, we will focus on familial atypical multiple mole-melanoma syndrome, a condition associated with atypical nevi and increased risk for melanoma.

Table 5.2 Genodermatoses associated with cutaneous malignancy in childhood

BCC	Nevoid basal cell carcinoma syndrome (Gorlin) Bazex syndrome (Bazex-Dupré-Christol) Xeroderma pigmentosum Oculocutaneous albinism
SCC	Ferguson-Smith syndrome Xeroderma pigmentosum Kindler syndrome Bloom syndrome Rothmund-Thomson syndrome Oculocutaneous albinism Epidermodysplasia verruciformis Epidermolysis bullosa Incontinentia pigmenti
Melanoma	FAMMM syndrome (familial atypical multiple mole-melanoma syndrome) Xeroderma pigmentosum

Familial Atypical Multiple Mole-Melanoma Syndrome

Familial atypical multiple mole-melanoma (FAMMM) syndrome, also known as atypical mole syndrome, is an autosomal dominantly inherited genodermatosis that is most commonly associated with a mutation in CDKN2A, which encodes p16. Typical skin findings include 50 or more atypical nevi (larger in size, darker in color, and/or having irregular borders compared to banal nevi) that develop in childhood or early adulthood, with nevus counts in some individuals reaching several hundred [21]. These patients are at significantly increased risk for development of cutaneous melanoma beginning in their teenage years, as well as ocular melanoma and other internal malignancies, such as pancreatic cancer, with particular CDKN2A mutations [2, 22]. Routine screening skin exams and consideration of total body photography, in addition to sun protection, are integral management strategies to allow for early detection of melanoma in these patients and their families.

Genodermatoses Associated with Photosensitivity and Increased Risk of Skin Cancer

Introduction

Key Points

- Xeroderma pigmentosum (XP) is a genodermatosis associated with photosensitivity secondary to defects in DNA mismatch repair and increases the risk for NMSC and melanoma.
- Bloom and Rothmund-Thomson are genodermatoses associated with photosensitivity secondary to defects in DNA helicase genes and increase the risk for NMSC.
- Kindler syndrome is associated with photosensitivity due to cell matrix instability, and oculocutaneous albinism is associated with photosensitivity due to a defect in melanin biosynthesis. Both increase the risk of NMSC.

Photosensitivity is an important feature of many genodermatoses, some of which are associated with an increased risk for skin cancer and other malignancies. There are multiple underlying mechanisms for the increased risk in skin cancer, which include defects in DNA repair, cell matrix instability, and melanin production, as detailed in Table 5.3.

DNA Repair

Table 5.3 lists genodermatoses with photosensitivity with underlying defect in DNA repair.

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is an autosomal recessively inherited disease characterized by exquisite sensitivity to ultraviolet (UV) radiation. Mutations in eight genes (XPA to XPG and XPV), which correspond to complementation groups that assist in DNA repair, have been identified. The repair rate of damaged DNA depends on the specific mutation, resulting in a range of severity in disease presentations. The incidence of disease ranges from 2.3 per million in Western Europe to 1 per 20,000 in Japan and depends on the demographic of the population [23].

There are two main clinical presentations of XP, which include extreme photosensitivity with secondary changes including vesicles, bullae, and conjunctivitis, or disproportionate numbers of lentigines that appear in sun-exposed areas. The onset of these cutaneous manifestations is typically at 1–2 years of age [24]. Chronic cutaneous changes include severe xerosis and premature aging of the skin, with telangiectasias, atrophy, hypopigmentation, and hyperpigmentation. Furthermore, these patients have an increased risk of both NMSCs and melanoma in sun-exposed areas, especially in the head and neck region. These cancers can have an aggressive course, with a tendency to grow rapidly and metastasize early [25]. The median age for NMSC diagnosis is 8 years and median age for

Table 5.3 Genodermatoses with photosensitivity with underlying defect in DNA repair

Genodermatosis with photosensitivity	DNA repair gene defect
Xeroderma pigmentosum	Nucleotide excision repair: XPA-XPG, XPV UV-irradiated DNA repair: XPV
Xeroderma pigmentosum/Cockayne overlap[a]	Nucleotide excision repair: XPG, sometimes XPB or XPD
Cockayne syndrome[a]	Nucleotide excision repair: CSA, CSB
Trichothiodystrophy[a]	Nucleotide excision repair: TTDA, TTDN
Bloom syndrome	Helicase: RECQL4
Rothmund-Thomson syndrome	Helicase: RECQL2

[a]no association with increased risk for cutaneous malignancy

melanoma diagnosis is 19–22 years [26, 27]. The overall risk of NMSC is 10,000× normal, and the risk of melanoma is 2,000× normal in patients with XP [27]. Ocular tissue involvement also occurs in almost half of all these patients, resulting in changes like conjunctivitis, ectropion, corneal opacities, and neoplasms [24]. Important extracutaneous findings include progressive neuronal deterioration, which occurs in 20–25% of patients [24, 27]. In the past, diagnosis was made on the basis of clinical features and observations of defective DNA repair, but there is increased utilization of genetic testing, including whole exome sequencing [28].

Management of these patients requires rigorous photoprotection, both when the patient is indoors and outdoors. Measures like UV-resistant films on all windows in a patient's home and school environments and protective headgear, gloves, and clothing to cover all body surfaces when going outdoors are imperative, given the extraordinary risk of skin cancer in XP patients. High-dose oral isotretinoin has a chemoprophylactic effect and significantly reduces the rate of skin cancer formation during treatment, but the skin cancer formation rate increases again to the pretreatment rate once the medication is stopped [29]. Novel treatments, including a bacterial DNA repair enzyme delivered in a liposomal lotion and gene therapy, are currently under investigation [30]. Regular visits to the dermatologist and ophthalmologist for cancer surveillance are the standard of care. The most common cause of death in XP patients is skin cancer, followed by neurologic decline and internal cancers.

Rothmund-Thomson

Rothmund-Thomson (RT) is another exceedingly rare autosomal recessively inherited genodermatosis. There are about 300 cases of RT reported in the literature [31]. RT1 is a subset without a known causative gene, while RT2 has been linked to a mutation in RECQ4 and an increased risk for malignancy [32]. Mutations in the DNA helicase RecQ family of genes are responsible for Bloom, Werner, and RT, which have different clinical presentations, but share similar mutations that cause gene instability, resulting in a strong predisposition to malignancy [14]. The cutaneous findings usually manifest between 3 and 6 months of life and almost always before the first year of life, with erythema, edema, and blistering, on the cheeks and face, before spreading to the extremities and buttocks [33]. These skin changes can occur in response to ultraviolet light, but can also occur in the setting of minimal sun exposure [34]. This rash typically spares the trunk and abdomen. Chronic changes include atrophy, hyperpigmentation, hypopigmentation, and reticular telangiectasias that can persist throughout the patient's lifetime. Other cutaneous findings that would support the diagnosis of RT include diffuse hypotrichosis on the scalp and eyebrows, nail dystrophy, and palmoplantar keratosis. Squamous cell carcinoma is the most common cutaneous tumor and represents an important manifestation of RT. Important extracutaneous clues to the diagnosis include cataracts, short stature, and skeletal abnormalities.

The diagnosis of RT is primarily based on characteristic clinical findings, as well as genetic testing for RECQL4 mutations, and treatment for these patients is mainly supportive. In terms of long-term management, it is important to know that patients with RT have increased susceptibility for both osteosarcoma (most common malignancy) and cutaneous SCC. Given these associations, there should be an emphasis on photoprotection and a low threshold for work-up of musculoskeletal complaints. NMSC, especially SCC, presents at a mean age of 34 years, but surveillance with complete skin examinations should begin in adolescence [35].

Bloom Syndrome

Bloom syndrome is an autosomal recessive disease found frequently in the Ashkenazi Jewish population and associated with a mutation in the BLM gene at chromosome 15q26.1 that encodes RECQL3 helicase [36, 37]. The DNA in lymphocytes, which lack this important helicase in affected patients, demonstrate an increase in sister chromatid exchanges and therefore DNA

instability [38]. Several hundred cases have been reported in the literature. Erythema of the cheeks in a butterfly distribution after sun exposure is often the earliest cutaneous manifestation appearing within the first few weeks of life. The rash can spread over the face, but tends to spare the extremities and trunk. Photosensitivity resulting in blistering, erythema, and bleeding is commonly seen in any region exposed to UV radiation [36]. These cutaneous changes evolve into chronic changes that include mottled hypo- and hyperpigmentation, telangiectasias, atrophy, and scarring. Other important cutaneous manifestations are café au lait macules and hypopigmented macules, especially over the dorsum of the hands and forearms [39]. The most distinctive extracutaneous feature of Bloom syndrome is proportionate small stature. Other suggestive extracutaneous findings include a characteristic birdlike appearance due to lack of subcutaneous fat, recurrent bacterial infections with associated hypogammaglobulinemia, and impaired fertility in men and women. Diagnosis is ultimately made through karyotype or genetic mutation analysis [40].

The range of malignancies associated with Bloom syndrome is similar to the spectrum seen in the general population, but affects patients with an increased frequency and at a younger age. In the first decade, rare cases of Wilms tumor and osteosarcoma have been reported. In the second decade, hematologic malignancies and skin cancer become more common, and the risk of all other carcinomas, especially colon and breast cancer, increases thereafter [41]. Of note, pulmonary complications like bronchiectasis, while not malignant processes, contribute significantly to the mortality rate and are the second-leading cause of death after malignancy in these patients [41]. Dermatologic care should include photoprotection and frequent monitoring to detect skin cancers. Management can be very difficult because Bloom syndrome patients are susceptible to such a wide spectrum of malignancies, but avoidance of unnecessary radiation and early screening for the common malignancies like breast and colon cancer have been recommended [42].

Cell Matrix Instability

Kindler Syndrome

Kindler syndrome, or congenital bullous poikiloderma, is a rare subtype of epidermolysis bullosa with an autosomal recessive inheritance pattern. It is caused by a mutation in the FERMT1 gene encoding kindlin-1, resulting in dysfunctional actin cytoskeleton-extracellular matrix interaction at multiple intra- and subepidermal levels [43]. To date, there have only been 250 cases of this blistering disease reported [44]. Patients typically present at birth with severe skin fragility and new blisters forming after exposure to trauma or sunlight. Chronic changes including sclerosing features and diffuse cutaneous atrophy affecting the dorsal aspects of the hands (Fig. 5.3) increase with age [45]. Other cutaneous findings include webbing of hands and feet, hyperkeratosis of palms and soles, nail dystrophy, ectropion, gingivitis, and periodontitis leading to premature loss of teeth. Furthermore, patients develop actinic keratoses or SCCs in the third and fourth decade of life, especially on the acral surfaces and oral mucosa, most likely due to ultraviolet-induced DNA damage and chronic inflammation [45]. Extracutaneous findings include esophageal, urethral, and vaginal stenosis and colitis secondary to mucosal inflammation [46]. Given the overlap with other blistering disorders, the gold

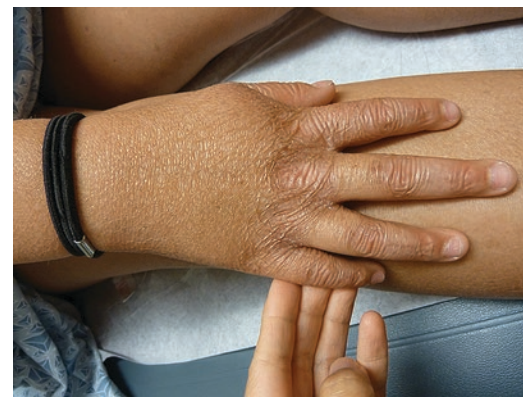

Fig. 5.3 Diffuse cutaneous atrophy of the dorsal aspect of the right hand, consistent with chronic skin changes in Kindler syndrome

standard of diagnosis is molecular genetic mutation testing for loss of function mutations in FERMT1 and supportive histological and immunofluorescence studies.

In terms of treatment, a multidisciplinary team is essential to minimize complications from strictures and scarring that can affect all mucosal surfaces. Regular dental care is necessary to monitor for and treat the gingivitis. Patients with severe dysphagia secondary to esophageal strictures may require repeat dilatations of the esophagus. Patients with severe colitis, urethral, or vaginal strictures may require surgical intervention. Photoprotection and proper wound care are the mainstays of dermatologic care. Monitoring for skin cancer with regular skin exams at least every 6–12 months, with careful attention to the oral mucosa and areas of chronic ulceration or leukoplakia, should begin at the age of 20 years [47].

Oculocutaneous Albinism

Oculocutaneous albinism (OCA) is a disease entity with autosomal recessive transmission that is caused by a defect in melanin biosynthesis and affects about 1 in 17,000 individuals in the United States [48]. There are at least seven subtypes of OCA, but OCA1 and OCA2 are the most common forms.

The clinical presentation of OCA includes hypopigmentation of the skin, hair, and eyes due to an absence or reduction in melanin biosynthesis, despite normal number of melanocytes. Reduced melanin biosynthesis results in increased sensitivity to UV radiation and a propensity for cutaneous malignancies, especially SCC and BCC. Patients develop signs of early actinic damage, as well as amelanotic or pigmented melanocytic nevi. Cutaneous malignancies develop as early as childhood and present at a mean age of the third and fourth decade of life [49]. The true incidence of melanoma in this population is controversial, but appears to be low [50, 51]. The lack of ocular pigmentation is associated with abnormal optic projections of fibers from the retina to the optic cortex. Patients present with translucency of the iris, reduced visual acuity, photophobia, nystagmus, and strabismus. Treatment should include sun avoidance and ophthalmologic care.

Genodermatoses Associated with Other Causes of Secondary Cutaneous Malignancies

Introduction

In the next section, we will discuss a somewhat heterogeneous group of genodermatoses that are not associated with photosensitivity but predispose to development of SCC, this time in the setting of chronic inflammation and/or scarring. While SCCs tend to occur slightly later in life in this context, we will discuss several genodermatoses that are associated with development of skin cancer during childhood, including epidermolysis bullosa, incontinentia pigmenti, and epidermodysplasia verruciformis.

Key Points

- In certain subtypes of epidermolysis bullosa, chronic inflammation, ulceration, and scarring predispose to the development of SCC that may behave aggressively.
- Incontinentia pigmenti is characterized by skin changes in a Blaschkoid distribution and is associated with an increased risk for SCC within affected areas.
- Epidermodysplasia verruciformis represents an interplay between a genetic mutation and HPV infection and is associated with increased risk for SCC.

Epidermolysis Bullosa

Epidermolysis bullosa (EB) refers to a group of genetic bullous disorders with onset in childhood

with variable inheritance, presentation, severity, and prognosis. Severe generalized recessive dystrophic epidermolysis bullosa (RDEB) is the subtype most commonly associated with SCC during childhood, although patients with both Herlitz- and non-Herlitz-type junctional epidermolysis bullosa are also at increased risk, especially as adults [52, 53]. In RDEB, which demonstrates abnormal type VII collagen resulting in subepidermal split, blisters and erosions may be seen diffusely on the skin, favoring extremities and other frequently traumatized areas, and mucous membranes. Over time significant scarring develops, leading to joint deformities and disability. Similar to the increased susceptibility of areas with chronic inflammation to SCC in Kindler syndrome, areas with scars and active inflammation in EB are predisposed to the development of invasive SCC, which can be treated with excision if diagnosed early. Importantly, SCCs arising within scars may have a more aggressive course, resulting in local tissue destruction or metastasis. Cases diagnosed late may require amputation or metastasize, making SCC a leading cause of mortality in patients with RDEB [2, 53].

Incontinentia Pigmenti

Incontinentia pigmenti (also known as Bloch-Sulzberger syndrome) is an X-linked dominant genodermatosis with mutations in NF-kappa-B essential modulator (NEMO), also known as inhibitor of nuclear factor kappa-B kinase subunit gamma (IKK-γ). This entity affects females and is typically lethal in males. Characteristic skin changes occur on the trunk or extremities in a Blaschkoid distribution. There are classically four distinct phases on the skin, beginning with vesicles and bullae, followed by verrucous papules, then hyperpigmented macules, and finally hypopigmented patches that may be atrophic, though patients may not exhibit all phases and the phases occur out of the classic order. Hair and nails may also be affected. Patients may have extracutaneous features including peg teeth, ocular abnormalities, and seizures [2]. There have been at least two reports in the literature of patients with incontinentia pigmenti who have developed SCC during childhood [1, 54]. Management, as with other SCCs, centers on treatment with local excision and routine screening skin exams with close assessment of scars to detect primary skin cancer or recurrence.

Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis, also known as Lewandowsky-Lutz dysplasia, is a rare genodermatosis associated with a mutation in the EVER1/EVER2 genes that predisposes to human papilloma virus (HPV) infection of numerous types including 5 and 8, which have been associated with increased risk for SCC in this population, and is inherited in an autosomal recessive manner [55]. Patients typically present with numerous thin, slightly scaly plaques that can be mistaken for flat warts or pityriasis versicolor during childhood, which progress to verrucous papules with increased risk for SCC [14]. While SCC typically presents during adulthood with this condition, cases have been described during teenage years with a predilection for the head and neck [56]. Treatment is often difficult given the number and refractory nature of lesions. Sun protection and interval screening skin exams are recommended.

Genodermatoses Associated with Extracutaneous Malignancies

Introduction

In this final section, we present a diverse group of genodermatoses with characteristic cutaneous findings that are suggestive of an underlying genetic defect strongly associated with internal tumor(s) in Table 5.4. The table includes the underlying genetic defect, cutaneous and extracutaneous findings, as well as the most common extracutaneous malignancies associated with the genodermatoses.

Table 5.4 Genodermatoses associated with extracutaneous malignancies [57–69]

Genodermatoses	Genetics, including gene (gene function)	Cutaneous manifestation: typical age of presentation	Extracutaneous manifestations	Malignancies
Neurocutaneous tumor syndromes				
Neurofibromatosis 1 (NF1)	Inheritance: AD Chromosome: 17q11.2 Gene: Neurofibromin (TS) Incidence: 1/3–4000 [57]	Café au lait macules: birth Crowe's sign with axillary freckling: childhood Neurofibromas: puberty Plexiform neurofibromas with malignant potential	Lisch nodules: pigmented ocular hamartomas seen on slit-lamp exam Most common cause of death: vascular complications [58]	Pheochromocytomas: uncommon before age 20 [58] Hematologic malignancies Optic gliomas
Neurofibromatosis 2 (NF2)	Inheritance: AD Chromosome: 22q12.2 Gene: Merlin (TS) Incidence: 1/33–40,000 [57]	Café au lait macules Schwannomas Neurofibromas	Cataracts	Bilateral acoustic neuromas: 20–30s Spinal tumors Meningiomas
Tuberous sclerosis (TS)	Inheritance: AD Chromosome: 9, 16 Gene: TSC1/hamartin, TSC2/tuberin (TS) Incidence: 1/60–10,000 [59] TSC1 milder disease	Ash leaf spots: from birth Adenoma sebaceous: 2–6 years Shagreen patch: puberty Ungual fibroma: puberty	Dental pits	Giant cell astrocytomas Renal angiomyolipomas Cardiac rhabdomyomas
Multiple endocrine neoplasia 1 (MEN 1)	Inheritance: AD Chromosome: 11q13 Gene: Menin (TS) Incidence: 1/30,000 [60]	Variable cutaneous features Facial angiofibromas: 3rd to 4th decade Collagenoma: similar to Shagreen patch, more papular Less common: lipomas, café au lait macules, hyperpigmented macules, gingival polyps, migratory necrolytic erythema		Triad 1. Pituitary 2. Pancreatic islet cells 3. Parathyroid
Multiple endocrine neoplasia 2A (MEN 2A)	Inheritance: AD Chromosome: 10q11.2 Gene: RET (proto-oncogene) Incidence (MEN 2A + 2B): 1/30,000 MEN1 milder disease [61]	Not a major feature of disease Lichen amyloidosis		Triad 1. Medullary thyroid 2. Pheochromocytoma 3. Parathyroid adenoma RET screening and thyroidectomy if positive
Multiple endocrine neoplasia 2B (MEN2B)		"Bubbly"/fleshy lips Thickened eyelids	Marfanoid: tall, pes cavum/excavatum	Triad 1. Medullary thyroid 2. Pheochromocytoma 3. Mucosal neuromas RET screening and thyroidectomy, if positive

Tumor syndromes with gastrointestinal malignancies				
Peutz-Jeghers	Inheritance: AD Chromosome: 19p13.3 Gene: STK11/LKB1 (TS) Incidence: 1/60–100,000	Blue-brown-black oral mucosal pigmentation: childhood, fades in adolescence		GI hamartomatous polyps Malignant adenocarcinoma of GI tract, breast, ovary
Gardner	Inheritance: AD Chromosome: 5q21 Gene: APC (TS) Incidence: 1/13,500 [62] for FAP syndromes	Epidermoid cysts on face and extremities: early childhood Desmoid tumors Less common: pilomatricomas, lipomas, fibromas		Polyps and adenocarcinoma by age 20 Other GI: duodenal, pancreatic, hepatoblastoma Osteomas of skull Thyroid
Turcot		Café au lait macules Basal cell carcinomas		Medulloblastomas
DNA repair disorders				
Carney complex	Inheritance: AD Chromosome: 17q-23–24 Gene: PRKAR1A (TS) Incidence: 750 total cases reported [63]	Most common: lentigines that appear in puberty, fade in adulthood, and occur on skin, conjunctiva, oral mucosa (may be confused with Peutz-Jeghers) Cutaneous myxomas: infancy to teen Spotty skin pigmentation Schwannoma		Endocrine tumors: adrenocortical, pituitary, Sertoli cell, thyroid Cardiac myxoma
Dyskeratosis congenita	Inheritance: AD or AR Chromosome: multiple Gene: Dyskerin Incidence: 1/million	Thin dystrophic nails Gray/brown pigmentation and poikilodermatous change: puberty Leukoplakia	Pulmonary, hepatic fibrosis Bone marrow failure cause of death in 60–70% of cases [64]	Associated with AML and MDS, causes death in less than 10% cases
Fanconi anemia	Inheritance: AR, more common in Ashkenazi Jewish population Chromosome: multiple Gene: 17 genes, FANCA in 2/3 cases Incidence: 1/160–400,000 [65]	Café au lait macules Hyperpigmentation Hypopigmentation	VACTERL defects: vertebral, anal atresia, cardiac, tracheoesophageal, renal, limb Bone marrow failure	Medulloblastoma AML MDS Liver tumors SCC after bone marrow transplant

(continued)

Table 5.4 (continued)

Genodermatoses	Genetics, including gene (gene function)	Cutaneous manifestation: typical age of presentation	Extracutaneous manifestations	Malignancies
Ataxia-telangiectasia	Inheritance: AR Chromosome: 11q Gene: ATM (TS) Incidence: 1/40–100,000	Mucocutaneous telangiectasia: 3–5 years Skin telangiectasias on sun-exposed areas Less specific: fat loss, progeroid change, hair graying, seborrheic dermatitis, eczema	Truncal ataxia Other CNS findings: myoclonic jerking, choreoathetosis, dysarthria	Hematologic malignancies Solid tumors: adulthood
Other				
Cowden	Inheritance: AD Chromosome: 10q22-23 Gene: PTEN (TS) Incidence: 1/200,000 [66]	Facial/mucosal trichilemmomas Oral mucosal papillomas with cobblestone buccal mucosa Palmoplantar, acral keratosis Cutaneous findings almost always evident by 2nd decade [67]	Macrocephaly Birdlike facies Deafness Benign hamartomatous growths in many different organs	Breast cancer, occurs in 25–50% Thyroid cancer Lhermitte-Duclos: hamartoma of cerebellum is pathognomonic
Birt-Hogg-Dube	Inheritance: AD Chromosome: 17q11.2 Gene: FLCN/folliculin (TS) Incidence: 200 total cases reported [68]	Facial fibrofolliculomas, trichodiscomas, acrochordons Histologically confirmed fibrofolliculuma should be referred to genetics Usually presents in 2nd decade [68]	Bilateral lung cysts Pneumothoraces	Benign and malignant renal cell tumors, with yearly MRI starting at age 20
Hereditary leiomyomatosis and renal cell cancer	Inheritance: AD Chromosome: 1q42.1 Gene: Fumarate hydratase (TS) Incidence: 100 total cases reported	Leiomyomas Skin-colored to red to purple papules/nodules in segmental distribution: 1st to 4th decades [69]	Uterine leiomyomas requiring hysterectomy before age 30 from discomfort	Papillary renal cell type II, aggressive and metastasizes early with 15% cumulative risk

AD autosomal dominant, *AML* acute myelogenous leukemia, *AR* autosomal recessive, *CNS* central nervous system, *FAP* familial adenomatous polyposis, *GI* gastrointestinal, *MDS* myelodysplastic syndrome, *MRI* magnetic resonance imaging, *SCC* squamous cell carcinoma, *TS* tumor suppressor

Key Points

- Neurofibromatosis (NF) 1, NF 2, tuberous sclerosis (TS), multiple endocrine neoplasia (MEN) 1, and MEN 2 are genodermatoses strongly associated with brain tumors or neuroendocrine tumors.
- Peutz-Jeghers, Gardner, and Turcot syndromes are genodermatoses associated with GI polyps and malignant adenocarcinomas.
- There are also genodermatoses, such as Carney complex, dyskeratosis congenita, Fanconi anemia, and ataxia-telangiectasia, with underlying DNA repair defects that are associated with a wide range of extracutaneous malignancies, especially hematologic malignancies.
- Cutaneous findings often present during childhood, which can be helpful for earlier diagnosis and screening for the internal malignancies that may develop later in life.

Summary

In summary, a careful examination for characteristic cutaneous and extracutaneous features is necessary for identification of genodermatoses and related malignancies. Mainstays of management for patients at risk for multiple skin cancers include routine skin checks for early detection and treatment, as well as sun protection.

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Malignant Soft Tissue Tumors in Children

6

Christina L. Boull and Sheilagh M. Maguiness

Introduction

Malignant soft tissue tumors in children encompass a broad and heterogeneous array of malignancies of mesenchymal origin. They account for 7–10% of all pediatric malignant solid tumors [1, 2]. In the pediatric population, malignant soft tissue tumors are primarily divided into rhabdomyosarcomas (RMS) and non-rhabdomyosarcomas (NRMS). The former (RMS) most commonly present in the neonatal and infantile period, while NRMS more classically present in adolescents and young adults.

This chapter will review the current classification of malignant soft tissue tumors in both categories, with focus on clinical presentation, histopathology, molecular classification, and prognosis. Special consideration and descriptions will be given to cutaneous manifestations of malignant soft tissue tumors to guide pediatric dermatologists with differential diagnoses, initial workup, and management for these challenging malignancies.

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Rhabdomyosarcomas

Key Points

- RMS accounts for 3.5% of all preadolescent cancers and may mimic vascular anomalies, scars, or other infiltrative neoplasms clinically. A biopsy is required for diagnosis.
- Embryonal RMS is the most common histopathologic subtype and most likely to be associated with underlying cancer predisposition syndromes such as Beckwith–Wiedemann and several RASopathy syndromes.
- Prognosis for RMS has improved over the past decade and is best in children ages 0–9 at 70–80% survival. Treatment is generally multimodal including resection, chemotherapy, and radiation.

Epidemiology

Pediatric RMS comprise 3.5% of all pediatric cancers in children 0–14 and 2% of cancers of adolescents of 14–19 years [3]. The annual incidence of RMS is approximately 4.5 cases per million, but incidence depends on the histopathologic subtype. Most cases occur in the first decade of life.

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Clinical Presentation

RMS most commonly present on the head and neck. Primary cutaneous RMS is rare; rather dermal extension of the tumor results in nodules or plaques in the skin. Differential diagnosis is broad and can include dermoid cysts, scars, infantile hemangiomas and other vascular tumors, and other infiltrative neoplasms such as leukemia, lymphoma, and other non-RMS soft tissue tumors. A skin biopsy is needed to confirm the diagnosis. RMS has historically been subdivided based on histopathology into three categories: embryonal, alveolar, and undifferentiated. The histopathologic subtype is somewhat predictive of clinical behavior.

Risk Factors

Though most cases of RMS occur de novo, there are several known associations including high birth weight/large for gestational age and several genetic syndromes. Genetic syndromes with increased incidence of RMS include Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, and several of the RASopathies including neurofibromatosis type I, Costello, and Noonan syndrome [4, 5] (see Table 6.1 for summary). There are also reports of RMS arising within giant congenital nevi [6]. As pediatric dermatologists, it is important to be aware of these associations to ensure close follow-up.

Table 6.1 Syndromes associated with rhabdomyosarcoma

Syndrome	Gene mutation and inheritance	Clinical features	RMS type and/or features	Other associated malignancies
Li–Fraumeni	P53 AD	Early onset malignancy, familial	Anaplastic RMS presents in children <3 years old	• Breast cancer • Non-RMS tumors • Brain tumors • Leukemia • Colon cancer • Others
Beckwith–Wiedemann	(1) Mutation/deletion of imprinted genes chromosome 11p15.5 (2) Heterozygous mutation in CDKN21 AD	Pediatric overgrowth syndrome with variable features: macroglossia, omphalocele, hypotonia, neonatal hypoglycemia, prominent nevus simplex	Embryonal RMS	• Wilms' tumor • Neuroblastoma • Hepatoblastoma • Adrenal carcinoma
NF type I	NF1 AD	Café au lait macules, axillary/inguinal freckling, lisch nodules, sphenoid wing dysplasia, pseudarthrosis, neurofibromas, macrocephaly, developmental delay	Embryonal RMS young age of presentation, genitourinary site	• Optic glioma • Malignant peripheral nerve sheath tumors • Meningioma • Pheochromocytoma • Pilocytic astrocytoma
Noonan	PTPN11 AD	Short stature, webbed neck, lymphatic malformations, low set ears, VSD, pulmonic stenosis	Embryonal RMS	• Malignant schwannoma
Costello	HRAS AD and sporadic	Short stature, macrocephaly, coarse facies, webbed short neck, hypertelorism, thick lips, sparse curly hair, papillomas, loose skin, acanthosis hypertrophic cardiomyopathy, pulmonic stenosis, mitral valve prolapse	Embryonal RMS, most common malignancy in Costello syndrome patients	• Neuroblastoma • Bladder carcinoma • Vestibular schwannoma

Prognosis

Prognosis for patients with RMS has improved significantly over the past decade due to multimodal chemotherapy regimens. Relapse-free survival rates are reported in the 70–80% range [7]. Children aged 1–9 have the best prognosis, with infants less than age 1 and older children showing significantly worse outcomes. The Intergroup Rhabdomyosarcoma Study Group (IRSG) recently reported that 5-year failure-free survival (FFS) was 57% for patients less than 1 year, 81% for patients aged 1–9 years, and 68% for patients older than 10 years. Five-year survival for these groups was 76%, 87%, and 76%, respectively [7].

Treatment

Treatment for RMS is multimodal and includes surgical management, chemotherapy, and often radiation. However, these chemotherapeutic regimens are associated with significant toxicity. Advances in the molecular classification of RMS may be paving the way for more targeted therapies and will be reviewed with each histopathologic subtype below [8].

Embryonal RMS (Fusion Negative)

Embryonal RMS is the most common histopathologic subtype, seen most frequently in children ages 0–4 years. It is more common in males (1.5:1) [9]. Embryonal RMS tends to occur on the head and neck or genitourinary (GU) tract. Characteristic genetic changes in embryonal RMS include loss of heterozygosity of 11p15 and gains in chromosome 8. Mutations in NRAS, KRAS, HRAS, and NF1 are present in up to a third of tumors, while mutations in other recognized genes (FGFR4, PIK3CA, CTNNB1, FBXW7, and BCOR) comprise less than 10% of cases [8].

Alveolar RMS (Fusion Positive)

The alveolar subtype of RMS tends to occur in older children/adolescents and comprises about 20% of all RMS cases [10]. It is most common on the trunk and extremities and perianal regions [10]. To be designated as alveolar, over 50% of the tumor must have the alveolar histopathologic features. The distinction between embryonal and RMS can also be made based on genetic classification. The key genetic footprint of classic RMS is the fusion protein between PAX 3 or PAX 7 and the FOXO1 gene [8].

Undifferentiated RMS (Pleomorphic, Anaplastic)

Pleomorphic and anaplastic RMS account for only 2% of all pediatric RMS, seen more commonly in the adult population. One important exception is the anaplastic RMS subtype (anRMS) which has recently been identified to occur frequently in children with Li–Fraumeni syndrome [11]. A diagnosis of anRMS in children under age 36 months should prompt investigation into underlying p53 mutations so that surveillance for other associated secondary malignancies can be undertaken [11].

Genetic Classification and Advances

Recently, extensive genomic analysis of numerous RMS tumors supports that the molecular classification is the most helpful way to categorize these tumors [8]. In their landmark paper, Shern and colleagues identified that the presence or absence of the PAX3/7–FOXO1 gene fusion is the most important prognostic indicator for any RMS. Typically, there is emerging support for molecular classification over histopathologic classification as a more precise predictor of clinical behavior. Fusion positive tumors behave clinically like alveolar RMS, and fusion negative

tumors behave as traditional embryonal RMS [12]. Interestingly, the main genetic alterations in all types of RMS seem to be within a common receptor tyrosine kinase/RAS/PIK3CA signaling pathway, either via rearrangement of the PAX gene or by the occurrence of downstream mutations [8]. Advances in this area will likely give rise to more targeted, molecularly based chemotherapies.

Primary Cutaneous RMS

Cutaneous presentations of RMS without another distinct primary site have been rarely documented in case reports with 75% occurring in the pediatric population [13]. Lesions present as grouped nodules usually less than 5 cm in size and may mimic keloid scars, cysts, dermatofibromas, sarcoidosis, basal cell carcinoma, and hematomas [14]. In children, the embryonic and alveolar subtypes predominate with a "small blue cell" pattern by histopathology.

Non-rhabdomyosarcoma

Key Points

- Non-rhabdomyosarcoma soft tissue sarcomas [NRMS] may mimic vascular tumors, morphea, or benign fibrohistiocytic tumors on clinical and radiologic exams. A biopsy is required for diagnosis.
- Surgical resectability is a key factor in overall prognosis.
- Most NRMS occurring early in life have a favorable prognosis if recognized and treated promptly.

The non-rhabdomyosarcoma soft tissue sarcomas represent 3–4% of all pediatric cancers [15, 16]. Classification is based on the International Classification of Childhood Cancers. Prognostic factors for all subtypes include extent of disease (local vs. metastatic), degree of tumor resection, maximal tumor diameter (<5 vs. >5 cm), and tumor grade [1, 17–19].

In all cases, a tissue biopsy is required to ascertain a definitive diagnosis. Tumors may be located deeper in the tissue than clinical exam suggests, so preoperative imaging is suggested. Close collaboration with an oncologist is necessary to facilitate proper cancer staging and treatment. As the lungs are the most frequent site of metastasis, chest imaging is an important component of the evaluation. Additional imaging studies should be dictated by the tumor subtype and exam findings [1].

Once the diagnosis and staging are confirmed, tumor resection is a key component of treatment. The role of neoadjuvant and adjuvant chemotherapy and radiation varies based on patient age, tumor characteristics, and the extent of resection [1, 20–22] and therefore requires the input of an oncologist who is well versed in the treatment of pediatric soft tissue tumors.

Fibrous (Connective Tissue Tumors)

Key Points

- Fibrosarcomas present as firm, nonmobile soft tissue masses. They have a bimodal age distribution. Presentation prior to age 2 years is associated with a favorable prognosis.
- Dermatofibrosarcoma protuberans is a fibrous tumor which is very rare in children. Consider underlying severe combined immunodeficiency (SCID) syndrome especially in children with multicentric lesions.

Fibrosarcoma

Epidemiology

Fibrosarcoma (FS) is the most common soft tissue tumor occurring in infancy, representing 10% of the pediatric non-rhabdomyosarcoma

soft tissue sarcomas [23]. The age distribution is bimodal with the initial peak occurring in infancy and the second in early adolescence. Infantile fibrosarcomas may be congenital or arise in the first few years of life. Most experts suggest that tumors occurring prior to the age of 2 years are of the infantile subtype [24]. The second peak in incidence occurs in the early teens, between 10 and 15 years of age, with tumor characteristics and prognosis similar to those of adult FS [23].

Clinical Characteristics

FS present as rapidly growing superficial or deep soft tissue masses. They have a predilection for the distal extremities in younger children and more axial locations in older patients [23] (Fig. 6.1). Children rarely report associated pain. The overlying skin appears glossy, tense, and erythematous and may ulcerate [23]. Presentations mimicking vascular anomalies including infantile hemangiomas and lymphatic malformations have been reported [25–27]. Unlike infantile hemangiomas which are soft and mobile, FS are infiltrative, fixed to the underlying tissue [26]. Associated hematologic abnormalities include low-level thrombocytopenia and coagulopathy mimicking Kasabach–Merritt phenomenon [26–29].

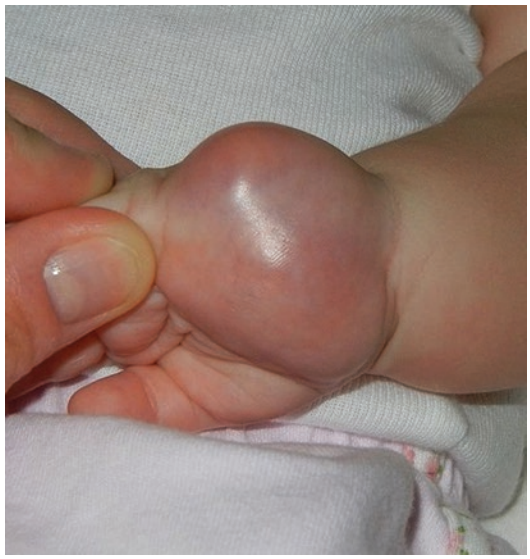

Fig. 6.1 Firm, pink tumor on the palm of an infant: infantile fibrosarcoma (Image courtesy of Jennifer T. Huang, MD)

Laboratory and Imaging Characteristics

Tumor biopsy is required for diagnosis. The cells of FS are spindled and densely packed with frequent mitoses. Highly vascular areas are common. Immunohistochemical staining is variable but is usually positive for vimentin and negative or focally positive for smooth muscle actin, desmin, S-100 protein, or CD34 [26, 30]. When infantile hemangioma is considered in the differential diagnosis, staining for GLUT-1, positive in IH but negative in FS, may be helpful. Infantile and adult FS are histologically identical [24] so molecular diagnostics may further differentiate these entities. Aberrant copies of chromosomes 8, 11, 17, and 20 are all more common in infantile FS [26, 31–33]. Recently the gene translocation t(12;15)(p13;q25) resulting in the fusion protein ETV6-NTRK3, and expression of NTRK3 (TRKC), a tyrosine kinase receptor, has been reported as a more specific marker for infantile FS [26, 30, 32–36].

Prognosis and Treatment

Patient age is the most important prognostic feature. Infantile FS have a >80–90% survival rate [23, 36], with survival falling to 50–60% in older children [23, 37]. In a series of children under the age of 2 years, the 5-year survival rate was 89%, even though only 21% underwent complete surgical resection [36]. For this reason, aggressive or deforming surgeries are only recommended when other treatment modalities have failed [36, 38].

FS are chemoresponsive [36]. Neoadjuvant chemotherapy may allow for a smaller excision with less resultant functional or cosmetic compromise and may be curative [38]. As recurrences of infantile FS tend to be local as opposed to metastatic, some authors recommend careful watchful waiting after chemotherapy as opposed to a surgical intervention.

While there have been reports of spontaneous resolution of infantile FS without treatment [39,

40], this is uncommon and should be reserved for cases of infants <3 months old with poorly operable tumors [36].

LOXO-101, an experimental drug targeting a tropomyosin-related kinase inhibitor, is a promising new treatment for infantile FS that express the NTRK3 receptor. While only one pediatric case report has been published, the response was dramatic in an otherwise refractory tumor [41]. Additional data is needed to determine the full potential of this medication.

Non-infantile fibrosarcomas require more aggressive therapy given their worse prognosis. Their predilection for axial sites makes complete resection more difficult, increasing the risk of metastasis [23]. In many cases, chemotherapy and radiation are indicated, especially in the setting of incomplete surgical resection [1, 23].

Dermatofibrosarcoma Protuberans

Epidemiology

Dermatofibrosarcoma Protuberans (DFSP) is an uncommon mesenchymal tumor of intermediate malignancy. Patients most commonly present in middle age; less than 200 cases of pediatric DFSP were reported in the literature [42]. A review of pediatric cases revealed no gender predilection. In this group, the mean age at diagnosis was 9 years, and the mean time to diagnosis was 4 years [42].

Clinical Presentation

In both adults and children, DFSP follow an indolent course of slow growth with local invasion and frequent recurrence [42]. Most tumors arise on the trunk, with nearly all congenital cases arising at this site [43]. The proximal lower extremity is also a common location. Tumors of the head and neck or upper extremities are less common.

DFSP may begin as pink macules and may appear vascular (Fig. 6.2). They slowly progress into indurated pale red-blue plaques and then nodules. Additional nodules may develop

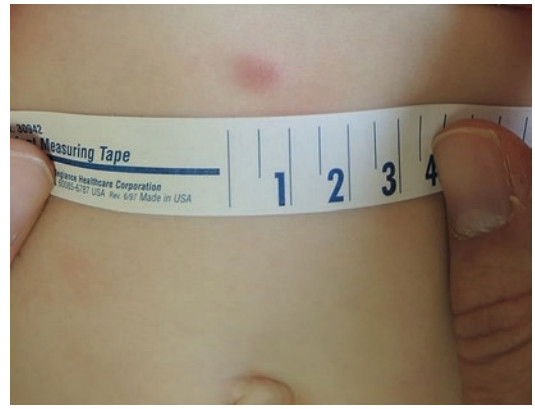

Fig. 6.2 Firm violaceous nodule in a 10-month-old: DFSP (Image courtesy of Ingrid Polcari, MD)

at the periphery giving a multilobulated appearance [42, 44, 45]. A plaque-like morphology has been described more often in pediatric cases [45]. Plaques are fixed to the skin but are mobile over underlying tissues [43, 45–47]. Tumors typically range between 1 and 5 cm in diameter but may grow significantly larger [44, 46]. They are primarily asymptomatic, but ulceration and pain can occur [42, 46, 47].

Cases of DFSP arising in children with severe combined immunodeficiency (SCID) syndrome, Fanconi anemia, Shwachman–Diamond syndrome, and Cowden syndrome have been described [48–51]. Of these potential syndromic associations, adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) syndrome is the most convincingly linked. In a series of 12 ADA-SCID patients who received skin checks, 8 were found to have DFSP, and 7 had multicentric lesions [48]. Two additional case reports have been published [52, 53]. While the cause of the association is uncertain, authors speculate that increased levels of adenosine and deoxyadenosine produce profibrotic effects and DNA strand breaks in the skin, creating a favorable environment for the development of DFSP [48]. Single cases of DFSP arising in children with Shwachman–Diamond, Fanconi anemia, and Cowden syndrome have been reported, but the associations are not well established.

Clinical mimickers of DFSP include benign lesions such as dermatofibromas, vascular malformations, pilomatricoma, morphea, atrophoderma, anetoderma, scar, keloid, infantile myofibroma, and neurofibroma [42, 54, 55]. The combination of benign appearance, lack of symptoms, and slow growth likely contributes to the often delayed diagnosis.

Laboratory and Imaging Tests

The histopathology of DFSP is characterized by a storiform collection of spindled cells extending through the dermis and into the fat. Immunohistochemical staining is positive for CD-34 and negative for factor XIIIa. A reciprocal translocation T(17;22)(q 22, q 13) is the most common gene rearrangement in pediatric DFSP and may be detected by cytogenetic testing [56].

Prognosis and Treatment

Primary treatment consists of surgical excision with wide margins. Margins of 2–3 cm in children >5 years and of 1–2 cm in younger children are suggested [57, 58]. Multiple procedures are often needed to obtain microscopically clear margins [59].

Mohs excision has been reported as a successful treatment with low risk of recurrence, but anesthetic exposure may limit its use in small children [60–62]. The recurrence rate in adults is reported at 32–76% with most recurrences occurring in the first 3 years [63]. Preoperative imaging, particularly in larger tumors, may help to delineate the tumor dimensions improving successful surgical clearance [64]. Sites of metastasis include the lungs and the lymph nodes, but metastatic disease is rare in children [45, 58, 59].

Imatinib mesylate is a tyrosine kinase inhibitor which has been used to successfully treat DFSP in adults. In children with unresectible or recurrent tumors, it has been reported as a neoadjuvant therapy, decreasing tumor size to allow for complete resection [57].

Borderline or Malignant Vascular Tumors

Key Points

- Immune suppression is an essential trigger for all Kaposi sarcoma subtypes.
- HIV-associated (epidemic) Kaposi sarcoma has now become the most common KS variant in children.
- Kaposiform hemangioendothelioma is a rare vascular tumor of infancy. It is an important cause of Kasabach–Merritt phenomenon which may be fatal even when promptly identified and treated.

Kaposi Sarcoma

Epidemiology

Kaposi sarcoma (KS) is a malignancy of endothelial cell origin occurring in the setting of immunosuppression. It was originally described in elderly males of Eastern European and Mediterranean ancestry (classic KS) but was later identified in an endemic form in portions of Africa and in an epidemic form in patients infected with HIV/AIDS. Iatrogenic cases are attributed to immune suppression following solid organ transplantation.

Pediatric KS is rare in most of the world but comprises 25–50% of pediatric soft tissue sarcomas and 2–10% of all pediatric cancers in portions of Eastern and Southern Africa [65–68]. All subtypes of KS have been reported in children [69–71]. Prior to the late 1980s, endemic KS was the most common variant seen in children, but now HIV-associated (epidemic) KS predominates [68]. Pediatric cases of classic KS remain rare with less than 50 reported cases, all occurring within the Mediterranean basin [68, 72].

Pediatric KS has a predilection for males. The mean age of onset is reported at 6.6 and 8.8 years for endemic and epidemic variants, respectively, but early onset is not uncommon [73, 74]. The timing of onset of iatrogenic KS is dependent

upon the age at transplantation. Classic KS has been described in children ranging from infancy to the teen years [68].

Clinical Characteristics

The clinical presentation of pediatric KS varies by subtype. Skin and mucosal lesions, when present, begin as purple or brown-red patches that grow into plaques and nodules. Lesions are usually painless but may Koebnerize in areas of past trauma or infection [74]. Classic KS favors acral sites in children as it does in adults. Children with endemic KS are more likely to present with lymphadenopathy and less commonly with skin or mucosal involvement, but data is limited [73]. Lymphoma, bacillary angiomatosis, and other disseminated infections associated with lymphadenopathy are clinical mimics [75].

In a series of children with primarily epidemic KS, three patterns of disease were described (listed in order of frequency):

1. KS of the head and neck with localized or generalized lymphadenopathy, 39% with skin lesions
2. KS of the genital area with inguinal lymphadenopathy, 57% with skin lesions
3. Solitary tumors localized to the extremities or the abdominal organs [74]

Laboratory and Imaging

The histopathology of KS is characterized by collections of spindled cells with slit-like vascular spaces and erythrocyte extravasation. Cells stain positive for the vascular endothelial markers CD31, CD 34, and factor VIII. The most definitive marker is positive staining for human herpesvirus 8 latency-associated nuclear antigen, present in all cases of KS [76].

HHV8 is a necessary factor in the pathogenesis of KS [66, 77]. Most individuals infected with HHV8 do not develop KS, suggesting that an acquired or inherited immunodeficiency which increases susceptibility to the virus is a necessary cofactor [68, 78].

Radiographic imaging is useful in determining disease extent. Based on sites of suspected involvement, contrast-enhanced CT or MRI is suggested. In both modalities, tumors show strong post-contrast enhancement. Scintigraphy (lymphoscintigraphy) with sequential thallium and gallium scanning may be employed to differentiate KS from infectious mimics [75].

Treatment and Prognosis

There are no consensus guidelines on the treatment of pediatric KS. In classic, epidemic, and endemic forms, chemotherapy is indicated for systemic involvement [68, 72, 79]. Intralesional chemotherapy may be considered for localized disease [68]. In children with epidemic KS, the combination of HAART with chemotherapy appears to be the most beneficial [80]. Notably, children with epidemic KS who are treated with HAART have an elevated risk of developing immune reconstitution inflammatory syndrome (IRIS) [68] and must be monitored for this complication.

Children with iatrogenic KS have a better overall prognosis than those with epidemic KS [73]. Some cases of iatrogenic KS have resolved with transition to sirolimus-based immunosuppression. Sirolimus, an mTOR inhibitor, may exert its effect by inhibiting angiogenesis and autocrine growth factor signaling within the tumor [79]. Based on a mouse model, mTOR inhibitors may be effective in all KS subtypes and better tolerated than other systemic agents, but further human trials are needed to make accurate conclusions [79, 81].

Survival in KS is dependent on HIV/AIDS status and stage of disease at presentation. Access to care may be limited and likely contributes to worse outcomes in resource-poor areas.

Kaposiform Hemangioendothelioma

Epidemiology

Kaposiform Hemangioendothelioma (KHE) is a rare, borderline malignant, infiltrative vascular tumor. KHE can cause life-threatening complications secondary to associated Kasabach–Merritt phenomenon (KMP). The estimated prevalence of KHE is 0.91 per 100,000 children with a slight male predominance ~1.33:1 [82]. Over 90% of

cases occur in infancy, usually in the first 3 months of life.

Clinical Presentation

KHE typically presents as a solitary lesion, though multifocal presentations have been described. KHE is infiltrative and may cross tissue planes from the dermis to the underlying subcutaneous tissue, muscle, and bone. The most common locations include, in order of frequency, the extremities, torso, and the head and neck. Extension to the retroperineum is often observed [82, 83]. Cutaneous features include a solitary, indurated, violaceous, or erythematous to purpuric plaque or tumor. Hypertrichosis and hyperhidrosis may also be appreciated (Fig. 6.3a).

KMP is a consumptive coagulopathy which is specifically observed in the setting of KHE or tufted angioma and is usually present at the time of diagnosis. Tufted angioma (Fig. 6.3b) shares similar clinical and histopathologic features with KHE, and the two entities are considered to represent a spectrum of severity. KMP is a life-threatening condition due to sequestration of platelets within the tumor resulting in thrombocytopenia. Though the exact etiology is not well

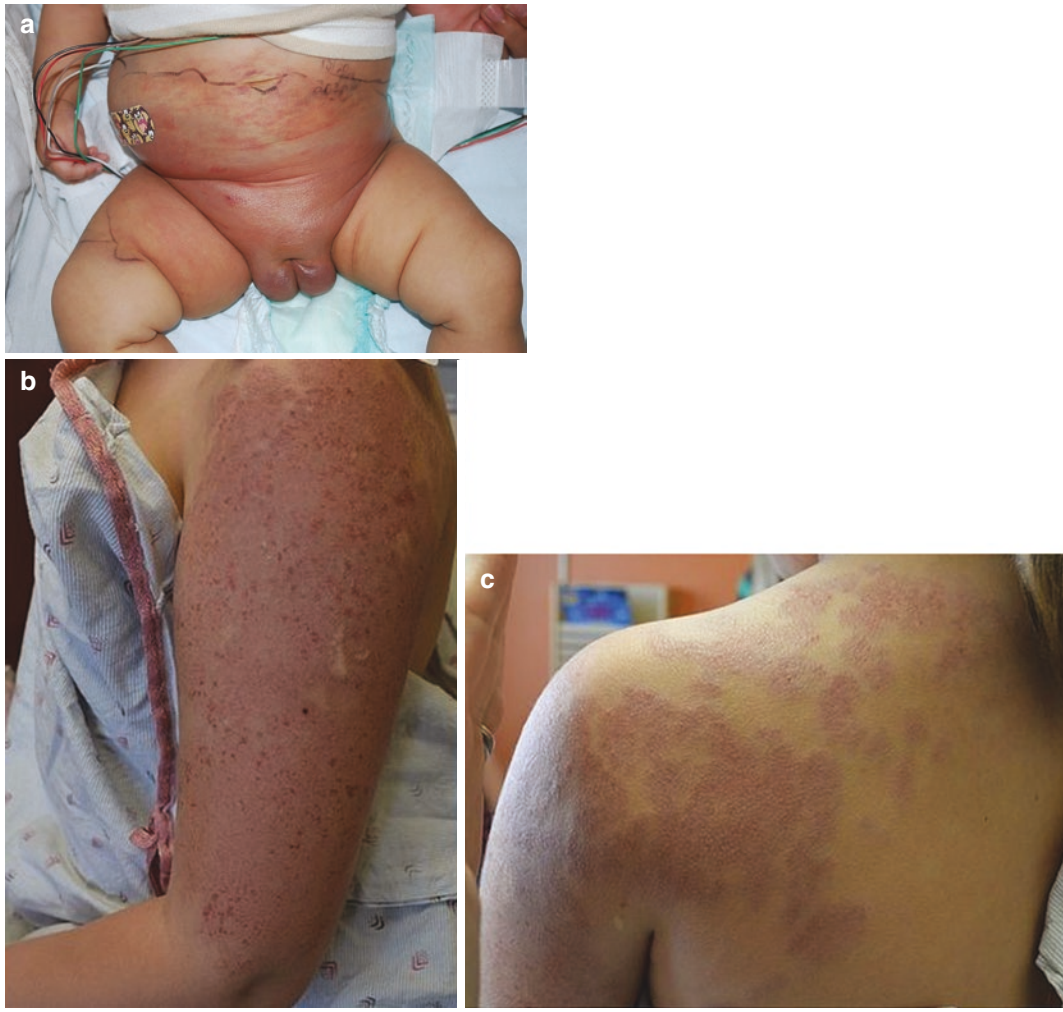

Fig. 6.3 (**a**) KHE in the perineum and lower abdomen (Image courtesy of Kristen Hook, MD). (**b** and **c**) Erythematous, indurated plaque of the upper extremity and shoulder of a 9-year-old girl: large tufted angioma previously treated with oral sirolimus

understood, it is thought that turbulent blood flow within the slit-like spaces of the KHE may lead to consumption of platelets and, when severe, can result in profound thrombocytopenia, elevated D-dimer levels, and low fibrinogen.

Initial recommended workup includes a complete blood count, coagulation studies, and baseline MRI imaging (with and without contrast) along with tissue biopsy to confirm the diagnosis.

Prognosis

There is a lack of outcome data related to the management of KHE and KMP. Historically, mortality rates in the 1980s were reported in the range of 30%, usually due to hemorrhage or other complications related to KMP [84]. However with earlier diagnosis and improved medical management, outcomes seem to have improved significantly.

Treatment

An interdisciplinary consensus statement on the management of KHE was proposed in 2013 [85]. At that time, authors advocated for initial treatment with vincristine and systemic steroids. More recently, the use of oral sirolimus in the management of KHE and KMP has been very promising [86] and may be preferable as an initial treatment due to the more favorable side effect profile and ease of administration. Sirolimus has also been reportedly successful in the late stage of KHE with softening of the tumor and improvement in pain and joint contracture [87]. A study comparing sirolimus and vincristine in the management of KHE is currently underway [86].

Neural

Key Points

- Malignant peripheral nerve sheath tumors usually arise after puberty and are strongly associated with neurofibromatosis 1.
- MPNST may be difficult to discern clinically and radiographically from a growing plexiform neurofibroma.

Malignant Peripheral Nerve Sheath Tumors (MPNSTs) (Synonyms Neurofibrosarcoma, Neurogenic Sarcoma, Malignant Schwannoma)

Epidemiology

MPNSTs form from the nerve sheaths of larger nerve trunks [21, 88, 89]. They represent 5–10% of all soft tissue tumors [90]. Less than 20%, however, present in children and usually arise after puberty [21, 91].

Neurofibromatosis type 1 is a closely linked risk factor. Even in the absence of NF-1, most MPNSTs demonstrate a pathogenic truncating mutation in the NF-1 gene [92, 93]. Approximately 10% of NF-1 patients will develop a MPNST, usually within a plexiform neurofibroma (NF), but incidence estimates vary widely [94, 95] The mean age of MPNST onset in NF-1 positive patients is 27 years, compared with 40 years in patients who are NF-1 negative [96].

Clinical Presentation

MPNST presents as a rapidly growing, firm, and sometimes painful mass. The trunk followed by the extremities is the most common site for MPNST in both patients with and without NF-1.

MPNSTs in NF-1 tend to be larger and deeper [96]. When arising from a plexiform NF, MPNSTs are associated with swelling and neurologic deficits [97]. It may be difficult to clinically distinguish a growing plexiform NF from a MPNST, as plexiform NFs often grow rapidly during adolescence [98].

Laboratory and Imaging Studies

A tissue diagnosis of MPNST requires a deep biopsy. Histologic features include a mass, often arising in a neurofibroma. Myxoid and cellular areas are admixed with bundles of irregular interlacing spindled cells and perivascular whirling. Histologic features including cellular pleomorphism, necrosis, and mitotic activity help to differentiate MPNST from its benign mimickers [89]. Staining is often positive for nerve growth factor receptor with partial or complete loss of S-100 [89, 96, 99]. There is no definitive molecular staining. While NF1, CDKN2A, and EFGR

alterations are suggestive of MPNST, they are not diagnostic [89].

Imaging may assist in differentiating MPNST from its clinical mimic of plexiform NF. MPNSTs have significantly higher uptake by FDG PET [95]. On MRI they are more likely to have an irregular shape and unclear borders, intra-tumoral lobulation, and higher signal intensity of T1-weighted imaging compared to plexiform NF [98, 100].

Prognosis and Treatment

MPNSTs may be difficult to detect and often have early distant metastases [95]. MPNSTs have a poor prognosis with a 5-year survival rate of 21% in the NF-1 population [94]. Median overall survival in the pediatric population is 30 months [21]. Negative prognostic factors include size of the tumor and recurrent disease [96]. Truncal location may also worsen prognosis [96]. While patients with NF-1 often present with larger tumors, NF-1 does not appear to be an independent risk factor for worse prognosis [96], but data is mixed [21].

Treatment options for MPNST are disappointing. Complete surgical resection has been shown to be associated with increased overall survival [21]. This is often not feasible as MPNST may be large, infiltrative, and difficult to distinguish from the plexiform NF in which they are arising. In the setting of metastatic disease, chemotherapy has been the most effective intervention but has a partial response rate of only 25–30% [101].

Targeted therapies have become an exciting new area of investigation for MPNST treatment. Drugs targeting MAPK pathway, including BRAF and MEK inhibitors, are currently under investigation for clinical use in this setting [102–104].

Lipomatous

Key Point

- Pediatric liposarcomas most commonly present on the extremities. Surgical excision is the treatment of choice.

Liposarcoma

Epidemiology

Liposarcoma is a rare malignant neoplasm of mesenchymal origin with lipomatous differentiation. While it is the most common non-RMS in the adult population, it is much rarer in children, comprising <3% of all pediatric non-RMS cases [105]. Myxoid liposarcomas carry a typical genetic translocation t(12; 16)(q13; p11), which occurs in greater than 90% of cases and can aid in diagnosis.

Clinical Presentation

One recent single institution review of pediatric liposarcomas at Sloan Kettering reported on information from 34 patients aged <22. Lesions typically presented as enlarging masses and were most commonly located in peripheral (extremity, inguinal) areas. Liposarcomas presenting in central locations (head and neck, paraspinal, retroperitoneum) were less common [106].

Prognosis

In pediatric cases of liposarcoma reviewed at one institution, survival correlated highly with tumor grade, location, and completeness of surgical resection. Histologic subtype and tumor location also significantly impact outcome, with highly pleomorphic tumors in a central location carrying the poorest prognosis. When comparing histologic subtype and survival, patients with myxoid, well-differentiated, and pleomorphic histologies had 5-year estimated survival rates of 83%, 67%, and 25%, respectively [106]. In 5.4 years of follow-up, 8/34 patients died due to progression of disease [106].

Treatment

The primary treatment for liposarcoma is surgical resection. In patients with low-grade tumors in a peripheral location, complete surgical resection with clear margins may be the only treatment required. The role of chemotherapy and radiation therapy in the setting of liposarcoma is not well delineated, but multimodal therapy is recommended in central tumors, with incomplete resection or recurrence [106].

Tumors of Unknown Origin

Key Points

- Malignant rhabdoid tumor is an aggressive malignancy with a poor prognosis, especially when arising from the kidney.
- Synovial sarcoma arises near large joints and may mimic an athletic injury. Imaging characteristics may be misinterpreted as benign, leading to a delayed diagnosis.

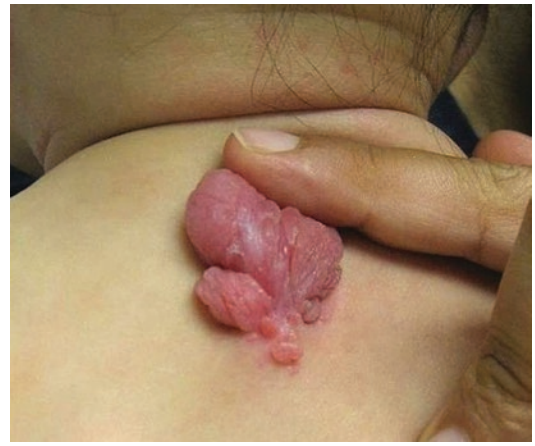

Fig. 6.4 Polypoid, vascular-appearing mass on the midback of a 9-month-old: malignant rhabdoid tumor

Malignant Rhabdoid Tumor (Atypical Teratoid/Rhabdoid Tumor)

Epidemiology

Malignant rhabdoid tumor (MRT) is an extremely rare, aggressive malignancy which presents in children less than 3 years of age. MRT is most commonly found in the kidney, CNS, and subcutis. When present in the CNS, the designation of atypical teratoid/rhabdoid tumor (ATRT) is given. ATRT accounts for 1–2% of all pediatric CNS tumors but is the most common pediatric CNS tumor presenting before 6 months of age.

Rhabdoid tumor was originally described in the late 1970s as a variant of Wilms' tumor with a rhabdomyosarcomatous component [107]. MRT can be challenging to diagnose based on histopathology but share a common genotype, the loss of expression of INI1/SMARCB, which aids in diagnosis. Germline mutations in INI1/SMARCB account for most multifocal presentations.

Risk Factors

Risk factors for MRT/ATRT are not well delineated. Germline mutations in INI1/SMARC are associated with earlier presentation and multifocal or metasynchronous disease in a constellation of findings known as rhabdoid tumor predisposition syndrome.

Clinical Presentation

The most common location for MRT is renal, followed by the CNS. Cutaneous and soft tissue presentations of MRT are extremely rare. Lesions are heterogeneous and reported to present as polypoidal masses mimicking skin tags or hamartomas (Fig. 6.4) or blue nodules mimicking vascular lesions. Multifocal nodules are also described.

Prognosis

MRT is a highly aggressive malignancy and prognosis is extremely poor. When affecting the kidney, diagnosis at age <6 months portends a very poor prognosis with overall survival being 9% at 4 years [108]. There are no long-term survival rates published for CNS lesions. Initial studies estimated an average survival of only 12 months following diagnosis. Survival is poor in the setting of subtotal resection of the primary lesion.

Treatment

There is no current consensus in management; however, surgical excision, radiation, and adjuvant chemotherapy are often used. There is some data to suggest that outcomes improve with multimodal treatment [109].

Synovial Sarcoma

Epidemiology

Synovial sarcoma (SS) is the most common of the pediatric non-rhabdomyosarcoma soft tissue tumors. Despite its name, SS does not arise from synovial tissue but, rather, from mesenchymal cells. It is a tumor of adolescents and young adults with a median age at diagnosis of 30 years and up to 1/3 of patients presenting prior to age 21 [110, 111].

Clinical Characteristics

SS favors periarticular areas near large joints. The knee, followed by the ankle, elbow, and shoulder are the most common sites. Tumors on the trunk or head/neck have been described less commonly [110, 112].

Tumors present as slowly growing tender, deep masses, usually >5 cm. Numbness or paresthesias develop if the tumor compresses or infiltrates around the nerves. In some cases, pain is the only presenting sign [113–115]. SS is the most commonly misdiagnosed soft tissue malignancy [113]. Initially, the associated pain may be mistakenly attributed to trauma or athletic injury. Clinical mimics include bursitis, tendonitis, myositis, or hematoma. Imaging characteristics are often reassuringly benign, further delaying biopsy [113–116].

Laboratory and Imaging

SS show one of three histologic patterns: (1) biphasic pattern with spindle cells and epithelial cells, (2) monophasic pattern with only spindle cells, and (3) poorly differentiated subtype of small round basophilic cells [117, 118]. Calcification and necrosis are characteristic features [117]. The t(X;18)(p11;q11) translocation is present in more than 90% of cases [110, 111].

Gadolinium-enhanced MRI is the imaging study of choice, with early enhancement consistently present. Tumors commonly appear well circumscribed and non-infiltrative, arising near the bone. Peripheral calcifications are often present. Small, peripheral SS may be more superficial and have smooth contours and homogenous texture, mimicking benign tumors. High uptake by FDG PET is associated with a worse prognosis in SS, with higher incidence of recurrence and metastasis, likely due to higher mitotic activity [118, 119].

Treatment and Prognosis

Treatment is dependent on surgical resection. Chemotherapy and radiation are often recommended in the setting of incomplete resection or metastatic disease [120]. Adjuvant chemotherapy may decrease the risk of metastasis, even when resection is complete [111]. Long-term follow-up is required given the high rate of late metastasis at 5–10 years posttreatment.

A younger age at diagnosis is a favorable prognostic factor. In a cohort of patients with SS, the 5-year event-free survival for patients younger than 17 years was 66% but dropped to 31% for those older than 30 [111].

Summary

Malignant soft tissue tumors encompass a heterogeneous group of pediatric malignancies. The main classification system divides these entities based on tissue of origin with rhabdomyosarcoma being the most common subtype. Limited information has been published regarding the cutaneous manifestations of these tumors. Often presenting as a subcutaneous mass or indurated plaque, they may mimic vascular lesions or other benign entities clinically. Biopsy is always indicated when the diagnosis is uncertain. Please see Table 6.2 for a clinical summary of some of the rarer non-RMS tumors.

Table 6.2 Other rare NRMS malignant soft tissue tumors

Tumor	Epidemiology	Clinical features	Pathology	Treatment	Prognosis
Hemangiopericytoma	Infantile subtype, <1 year of age; M > F adult subtype, >1 year	Deep soft tissue mass LE most common site Size 3–10 cm, larger for adult subtype	Mesenchymal origin Cells packed tightly around endothelium-lined vascular channels	Resection, radiation, chemotherapy	Infantile: 5-year OS 80% Adult: 5-year OS 69%
Leiomyosarcoma	Cutaneous and subcutaneous subtypes M = F Associations: immunosuppression, HIV, EBV	**Superficial:** red-pink single or clustered nodules. Ulceration may be present. Mimics: hypertrophic scar, dermatofibroma, DFSP **Subcutaneous:** firm indurated mass in the subcutis. Mimics: lipoma, cysts, neurofibroma	Smooth muscle origin Atypical spindled cells in sheets and fascicles + vimentin, desmin, SMA	Resection. Radiation is contraindicated. Chemotherapy useful only for neoadjuvant debulking	Cutaneous: recurrence rate up to 50%. Low metastatic potential Subcutaneous: 5-year OS 79% in children 30–60% incidence of metastasis
Extraosseous Ewing sarcoma (malignant primitive neuroectodermal tumor)	Most tumors are in the deep soft tissue Rare subcutaneous or cutaneous cases reported 8% of all Ewing sarcoma cases M > F	**Deep:** soft tissue mass, pelvis and trunk most common sites **Subcutaneous/cutaneous:** nodular or pedunculated polypoid mass, usually <3 cm	Neural origin Small blue cell tumor (same histology as osseous Ewing) + vimentin, CD99, EWS gene translocation	Resection, chemotherapy, +/− radiation	Deep: 5-year OS 75% (all ages) Subcutaneous/cutaneous: indolent, favorable prognosis

Abbreviations: *OS* overall survival, *DFSP* dermatofibrosarcoma protuberans, *SMA* Smooth muscle actin, *EBV* Epstein–Barr virus

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7 Cutaneous Reactions to Traditional Chemotherapy and Radiation Therapy

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Introduction

Local and systemic treatment for malignancies including chemotherapy and radiation therapy can have significant toxicities related to skin, hair, nails, and mucous membranes. While many of these have been well documented in the adult literature, cutaneous toxicities related to chemotherapies in the pediatric population have been mostly described in the form of case reports and small case series. Recognition of these cutaneous side effects is important, particularly in this complex population, and cutaneous manifestations of other underlying conditions (e.g., infection, graft-versus-host-disease, paraneoplastic phenomenon) must be differentiated from treatment effects.

This chapter describes some of the common as well as less familiar cutaneous toxicities related to traditional chemotherapeutic agents, organized by agent, as well as acute adverse reactions to radiation therapy. Newer targeted chemotherapies and associated skin reactions are discussed in the next chapter (Chap. 8).

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Antimetabolite Chemotherapeutic Agents

Key Points

- Antimetabolite agents are structural analogues of cellular metabolites, which interfere with protein, RNA, and DNA synthesis.
- Three main types of antimetabolite agents exist: (1) purine analogues, (2) pyrimidine analogues, and (3) folate antagonists.
- Common cutaneous side effects include the development of toxic erythema of chemotherapy; however many unique cutaneous side effects occur with each chemotherapeutic agent.

Antimetabolite chemotherapeutic agents are structural analogues of normal cellular metabolites that are required for cell function and replication. When incorporated into the cell, they interfere directly with normal cellular metabolism, which leads to either production of defective enzymes or end products that are necessary for either protein, RNA, or DNA synthesis. This prevents cell division, and thereby inhibits tumor growth. As such, they are cell cycle specific and exert their effect in the S phase of cell replication.

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Antimetabolite chemotherapeutic agents are often divided into three categories:

1. Purine analogues
2. Pyrimidine analogues
3. Folate antagonists

Purine Analogues

Mercaptopurine

Mercaptopurine (6-MP) competes with purine derivatives hypoxanthine and guanine for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Downstream effects lead to decreased purine synthesis and metabolism. It is commonly used to treat pediatric acute lymphoblastic leukemia (ALL) as well as non-Hodgkin's lymphoma (NHL). Many cutaneous side effects have been noted. (Table 7.1 summarizes all chemotherapeutic agents discussed in this chapter and their cutaneous toxicities.) Toxic erythema of chemotherapy (TEC) has been described in patients taking 6-MP. TEC is an umbrella term for a group of cutaneous eruptions that can be seen during the course of chemotherapy, usually appearing between 2 days and 3 weeks following administration of a wide variety of chemotherapeutic agents (Fig. 7.1). It is characterized by erythematous patches or edematous plaques of mostly the acral areas and intertriginous zones, accompanied by burning or tenderness, followed by desquamation and spontaneous resolution [1]. Pathology tends to reveal keratinocyte atypia and apoptosis, along with eccrine squamous metaplasia. This may include entities such as acral erythema, hand–foot syndrome (HFS), palmar-plantar erythrodysesthesia (PPE), intertriginous eruption associated with chemotherapy, and chemotherapy-associated neutrophilic eccrine hidradenitis (NEH). In patients receiving 6-MP, TEC tends to occur in the form of HFS or acral erythema, and onset is typically 2–4 weeks after initiation of therapy. Clinical findings can include painful desquamation and erosions, as well as tender erythema and edema of the palmar and plantar surfaces (Figs. 7.2 and 7.3) [2, 3]. In addition to occurring near the beginning of therapy, TEC can also present after up-titration of 6-MP therapy [4].

There may also be an increased risk of development of non-melanoma skin cancer (NMSC) in patients treated with thioguanines such as 6-MP or its prodrug allopurinol [5–8]. One study looked at the incidence of NMSC in patients with inflammatory bowel disease treated with thioguanines, compared to those who were not treated with similar medications, and found that development of NMSC was associated with thioguanine exposure (OR 5.0, 95% CI 1.1–22.8), mostly in Caucasian populations [9].

In addition to development of NMSC, there is an increased risk of the development of eruptive nevi in patients taking thioguanines [10–16]. In one case, a 17-year-old male with pre-B-cell ALL underwent induction chemotherapy with 6-MP, as well as other concurrent chemotherapeutic agents. Two months after completion of maintenance chemotherapy, numerous pigmented lesions were noted to develop on his trunk. Upon follow-up, numerous dysplastic nevi as well as a melanoma in situ were identified [17]. The development of eruptive pigmented lesions in both children and adults following various types of chemotherapy has been well documented [18–20]. While the mechanism of action is not clear, it may be related to immunosuppressive effects related to chemotherapy.

Fludarabine

Fludarabine is a purine analogue that inhibits DNA synthesis by inhibiting ribonucleotide reductase, DNA polymerase, and DNA primase, thereby interfering with DNA synthesis. It is commonly used in the treatment of hematologic malignancies as well as during conditioning for allogeneic hematopoietic stem cell transplantation.

Unusual cutaneous side effects can be noted with fludarabine. There are few reports in adult patients with chronic lymphocytic leukemia (CLL) or Waldenstrom's macroglobulinemia treated with fludarabine who subsequently developed paraneoplastic pemphigus (PnP), characterized by tense blistering over trunk and extremities as well as ocular and oral mucosal involvement [21–25].

Table 7.1 Summary of traditional chemotherapeutic agents, mechanisms of action, and common cutaneous reactions

Drug class	Mechanism of action	Cutaneous reaction
Antimetabolite agents	Structural analogues of cellular metabolites, incorporate with DNA and interfere with DNA, RNA and protein synthesis	
Purine analogues		
Mercaptopurine	Competes with purine derivatives for HGPRT, leads to decreased purine synthesis	TEC (HFS/acral erythema), increase in NMSC, increase in pigmented lesions, development of melanoma
Fludarabine	Inhibits ribonucleuotide reductase, DNA polymerase, and DNA primase	Paraneoplastic pemphigus, TEC (intertriginous eruption), TA-GVHD, increased growth of pre-existing skin cancers
Cladribine	Inhibits adenosine deaminase	Pruritus, rash including papules, plaques, vesicles, ulceration, TEN, TA-GVHD, extravasation injury
Pyrimidine analogues		
5-Fluorouracil	Inhibits thymidylate synthase	TEC (HFS), hyperpigmentation (persistent serpentine supravenous or erythematous eruption, acral, interphalengeal, nails, oral mucosa, reticulated pattern)
Capecitabine	Prodrug of 5-fluorouracil	TEC (HFS), cutaneous and systemic lupus erythematosus, loss of fingerprints, diffuse systemic sclerosis, localized sclerosis of hands, hyperpigmentation, longitudinal melanonychia, onycholysis
Cytarabine	Interferes with DNA polymerase	Morbilliform eruption, TEC (HFS, Ara-C ears, intertriginous papular, purpuric, pruritic eruption), TEN, neutrophilic eccrine hidradenitis
Gemcitabine	Cytosine analogue	Maculopapular rash, TEC (pseudocellulitis of lower extremities), peripheral edema, radiation recall dermatitis, drug-induced linear IgA, subacute cutaneous lupus erythematosus, SJS/TEN
Folate antagonists		
Methotrexate	Inhibits dihydrofolate reductase	Cutaneous ulceration, TEC (HFS, acral erythema)
Alkylating agents		
Cyclophosphamide	Attach alkyl group to guanine base of DNA, which interferes with DNA replication by forming intra-strand and inter-strand DNA crosslinks	Mucositis, hyperpigmentation of nail plate (diffuse, longitudinal or horizontal bands), hyperpigmentation (oral mucosa, palmar crease, dorsal hands/feet, under areas of occlusion, reticulate pattern), TEC ntertriginous eruption), facial flushing, type I hypersensitivity reaction
Ifosfamide	Isomer of cyclophosphamide	Hyperpigmentation (hands, feet, under occlusion), type I hypersensitivity reaction, oral mucositis, intertriginous and genital erythema and subsequent sloughing of skin
ThioTEPA	Forms reactive ethylenimine radical that crosslinks DNA and disrupts synthesis	HSR (including urticarial), hyperpigmentation (occluded and intertriginous areas), erythema (palms, soles), desquamation
Melphalan	Alkylates DNA nucleotide guanine	Erythema, edema, blistering, compartment syndrome, loss of nails, hyperpigmentation of nail plate
Busulfan	Creates intra-strand DNA crosslinks	Hyperpigmentation (diffuse bronze coloration: Neck, trunk, palmar crease), HSR, pruritus, injection site reaction, vasculitis

(continued)

Table 7.1 (continued)

Drug class	Mechanism of action	Cutaneous reaction
Hydroxyurea	Inhibits M2 protein subunit of ribonucleotide reductase	Xerosis, alopecia, tissue atrophy, palmoplantar keratoderma, hyperpigmentation (nails), collagen vascular disease (cutaneous and systemic lupus erythematosus, dermatomyositis-like dermatitis), cutaneous ulceration, development of NMSC
Platinum based Antineoplastics		
Cisplatin and Carboplatin	Crosslink DNA strands, inhibits DNA repair and synthesis	HSR (including urticaria), hyperpigmentation (dorsum of extremities, elbows, knees, areas of trauma or pressure, nails)
Antitumor antibiotics		
Daunorubicin and Doxorubicin	Intercalate between DNA/RNA base strands, inhibit topoisomerase II, generates oxygen free radicals	Alopecia, mucositis, extravasation injury, TEC (HFS, PPE, intertrigo-like dermatitis), follicular rash, radiation recall, formation of melanotic macules, HSR (urticaria, flushing)
Dactinomycin	Binds adjacent guanine-cytosine base pairs in DNA, inhibits RNA polymerase	Lichenoid dermatitis, mucositis, cheilitis, acne, radiation recall dermatitis, alopecia
Bleomycin	Complexes with iron and oxygen to create free radicles and DNA strand breakages	Flagellate dermatitis (erythema or hyperpigmentation), scleroderma-like fibrosis, Raynaud's phenomenon, acral gangrene, alopecia, nail changes, TEC (NEH)
Topoisomerase inhibitors		
Topoisomerase I Inhibitors		
Topotecan	Binds topoisomerase I/DNA complex to prevent resealing of DNA single strand breaks	Mucositis, alopecia, rash, pruritus, HSR (soft tissue swelling/edema, urticaria)
Irinotecan	Prodrug of topotecan	Cholinergic syndrome (diaphoresis, flushing), alopecia, mucositis
Topoisomerase II Inhibitors		
Etoposide	Forms a complex with DNA and topoisomerase II and prevents re-ligation of the DNA strands and DNA breakage	HSR (soft tissue swelling), alopecia, rash, mucositis
Tenotoposide	Causes dose-dependent single and double-stranded breaks in DNA and DNA-protein crosslinks	HSR (flushing, facial edema, urticaria), alopecia
Mitotic inhibitors		
Taxanes		
Paclitaxel	Target microtubules to induce cell cycle arrest	HSR, rash
Docetaxel	Binds the tubulin component of microtubules to inhibit the M phase of the cell cycle	TEC (HFS/PPE), nail changes (onychomadesis), HSR, fluid retention/edema, alopecia, blistering rash, acneiform eruption, non-specific rash
Vinca alkaloids		
Vincristine,Vinblastine, Vindesine, & Vinorelbine		Alopecia, rash, Raynaud's phenomenon, mucositis, urticaria, venous sclerosis

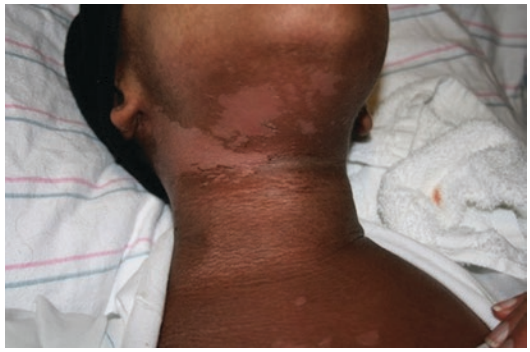

Fig. 7.1 Toxic erythema of chemotherapy presenting with edematous, erosive patches in a patient undergoing conditioning (carboplatin, etoposide, melphalan) for hematopoietic stem cell transplant (image courtesy of Jennifer T. Huang, MD)

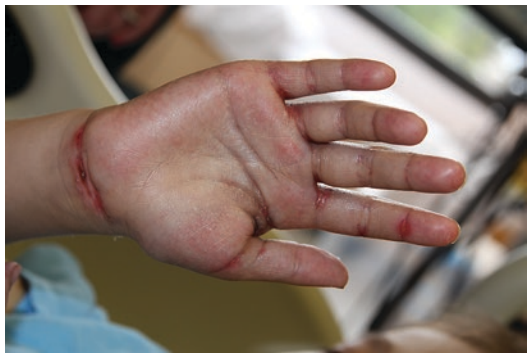

Fig. 7.2 Hand–foot syndrome characterized by erythema, edema, and fissures on bilateral palms while receiving 6-MP

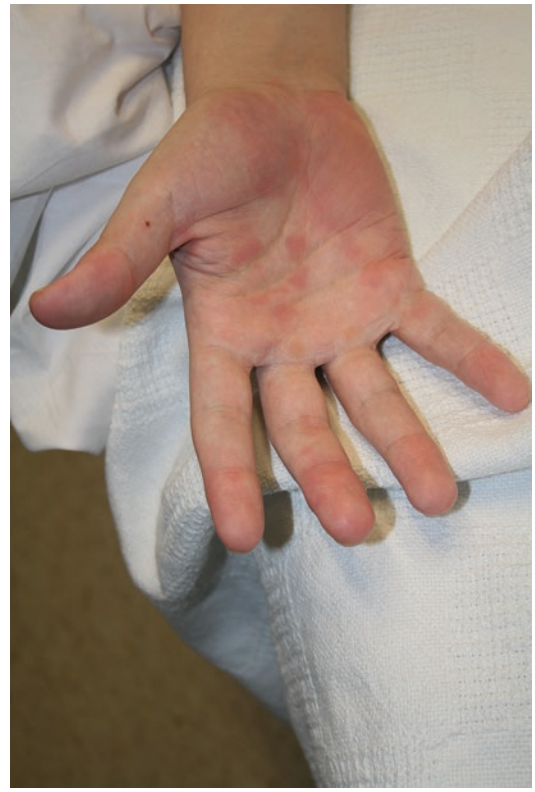

Fig. 7.3 Acral erythema presenting with erythematous patches in a patient on therapy with vincristine, doxorubicin, cytoxan, etoposide, and ifosfamide (image courtesy of Jennifer T. Huang, MD)

While CLL is associated with PnP, in all of these cases, development of blistering occurred following fludarabine administration. Several cases improved upon discontinuation of fludarabine. The mechanism for this reaction is unknown. It may represent the ability of fludarabine to induce new autoantibodies to the skin or antitumor antibodies that then cross-react with epidermal epitopes.

A study looking at the use of intravenous (IV) busulfan and fludarabine for conditioning prior to peripheral blood stem cell transplant (PBSCT) found that 57% of patients (33/58) developed TEC, ranging from 10 to 35 days following stem cell infusion [26]. In this study, the most common areas affected included intertriginous sites (21/33 patients with multiple areas of involvement), with spontaneous resolution in 2–4 weeks [26].

Transfusion-associated graft-versus-host disease (TA-GVHD) is rare, but has been noted with fludarabine administration [27–31]. TA-GVHD occurs when allogeneic lymphocytes present in blood products engraft and create an immunologic reaction against the host. Clinical findings include fever, rash, and elevated transaminases. Risk factors include severe immunodeficiency due to malignancy, use of immunosuppressive medications, congenital immunodeficiencies, infants with hemolytic disease of the newborn, or preterm birth [32]. This complication is fatal in many cases.

Fludarabine has also been associated with increased exacerbation or accelerated growth of preexisting skin cancers [33–35]. While no reports have been noted in children, it is reasonable to advocate for regular dermatologic evaluation in patients being treated with fludarabine.

Cladribine

Cladribine is used in the treatment of pediatric acute myeloid leukemia (AML) as well as histiocytic disorders like Langerhans cell histiocytosis and systemic mastocytosis. It is a purine analogue that inhibits adenosine deaminase, thereby decreasing purine DNA synthesis. It selectively targets lymphocytes and thus leads to immune suppression.

More common cutaneous side effects noted with cladribine include pruritus and erythematous macules, papules, and plaques that can ulcerate, crust, vesiculate, or become purpuric [36–38]. There is a report of toxic epidermal necrolysis (TEN) occurring after cladribine administration [39]. Onset of side effects is within 2 weeks to 2 months after initiation of medication or after subsequent cycles. Pathology reveals a perivascular dermatitis with lymphocytes, degranulated eosinophils (flame figures), collagen necrobiosis, or intra/subepidermal vesicle formation [38]. Peripheral eosinophilia may occur as well [40–44]. Other less common cutaneous side effects of cladribine include one case of TA-GVHD [45] as well as skin necrosis due to extravasation injury [46].

Pyrimidine Analogues

5-Fluorouracil and Capecitabine

5-Fluorouracil (5-FU) is a pyrimidine analogue, and acts by inhibiting thymidylate synthase, thereby interfering with de novo DNA synthesis. It is commonly used in the treatment of hepatoblastoma and other hepatobiliary malignancies. Capecitabine is an oral prodrug of 5-FU and is converted into the active form in either the liver or within the tumor itself. Therefore, the two drugs share a similar side effect profile. 5-FU and capecitabine are well known to cause TEC, in the form of HFS [47–53]. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v4.0) grading system for dermatologic toxicities is a commonly used method of grading HFS or PPE (Table 7.2) [54]. Patients taking capecitabine may experience varying severity of HFS, with some experiencing mild erythema and minimal dysesthesia (Grade I) to blister formation, desquamation, pain, and functional impairment (Grade 3). While mostly symmetric, unilateral cases have been described [47, 50]. Depending on severity, treatment can be either supportive in nature or may require dose adjustment or discontinuation of the medication. Onset is typically noted within the first two cycles of medication administration.

Capecitabine has a few distinct cutaneous side effects.There are case reports of drug-induced cutaneous and systemic lupus erythematosus secondary to capecitabine administration [55–65]. The onset is between 2 and 4 weeks of starting therapy. The morphology can range from erythematous annular scaling plaques on sun-exposed areas to more discoid lesions. Patients have shown positive antinuclear antibodies (ANAs), as well as anti-histone, Ro, and La antibodies. Other unique cutaneous side effects include the deterioration or loss of fingerprints, which can be independent of the development of HFS [66–69]. The loss of fingerprint quality can be reversible; however this may prove to be problematic for patients given difficulties with identification. There have also been reports in adults of scleroderma-like changes of the hands associated with HFS [70, 71] as well as a case of diffuse systemic sclerosis attributed to capecitabine therapy [72].

Both 5-FU and capecitabine have been associated with significant pigmentary changes. 5-FU has been known to cause pigmentary abnormalities in 2–5% of all patients [73]. Notable changes include persistent serpentine supravenous hyperpigmentation (PSSH) or erythematous eruption (PSEE), diffuse acral pigmentation and pigmented bands of the interphalangeal joints, as well as pigmentation of the nails and oral mucosa [74–77]. In PSSH and PSEE, hyperpigmentation or erythema, respectively, is noted in a linear or

Table 7.2 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 [54]

Skin and subcutaneous tissue disorders					
	Grade				
Adverse event	1	2	3	4	5
Palmar-plantar Erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema or hyperkatosis) with pain, limiting self-care ADL		
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychological impact			
Dermatitis reaction	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and crease; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

Information is from the website of the National Cancer Institute (https://www.cancer.gov)

serpentine distribution overlying the superficial venous network. A reticulated pattern of hyperpigmentation has also been noted with 5-FU [78–80]. Longitudinal melanonychia and onycholysis have also been associated with capecitabine [81–86].

Cytarabine

Cytarabine (also known as cytosine arabinoside or Ara-C) is commonly used in the treatment of leukemias and lymphomas. It interferes with DNA polymerase activity, which inhibits DNA synthesis. It is specific for the S phase of the cell cycle. Cutaneous reactions to this medication are quite common. In a study of 172 patients receiving cytarabine, 53% developed a cutaneous reaction, with a morbilliform eruption being the most common [87]. Cytarabine can commonly cause HFS, both classical and a bullous variant, both of which have been described in the pediatric literature [88, 89]. This reaction may resolve spontaneously or upon withdrawal of the medication. Ear swelling or erythema (likely a form of TEC) has been noted following cytarabine administration, leading to the term "Ara-C ears" [90]. A generalized papular, purpuric eruption or violaceous erythema has also been described related to cytarabine [91]. In a retrospective study looking at 16 patients, intertriginous involvement was common, as was pruritus. A majority of patients developed these findings following completion of therapy. No systemic symptoms were noted. Previous cytarabine use was not a risk factor of development of the eruption, or predictive of recurrence with reexposure. Two pediatric patients developed TEN following administration

of intermediate [92] and high-dose cytarabine [93], initially presenting with localized bullae that quickly generalized. Cutaneous findings were initially noted on the second and fifth days of therapy, respectively. Both cases resulted in death of the patients.

NEH has also been described with cytarabine use [94, 95]. Clinically, patients can be febrile and develop erythematous to violaceous or purpuric macules, plaques, vesicles, pustules, or nodules. Face and extremities are commonly involved. In some cases, NEH may mimic cellulitis [96]. Pathology reveals infiltration of the eccrine glands and ducts with neutrophils, as well as necrosis of the secretory epithelium [97].

Gemcitabine

Gemcitabine is a cytosine analogue that, when activated, can be incorporated into replicating DNA and lead to cell death. It is commonly used in the treatment of pediatric cancers such as Hodgkin's lymphoma and NHL, germ cell tumors, hepatocellular carcinoma, and other solid tumors. Cutaneous side effects have been well documented with gemcitabine, with the most common being the development of a fine maculopapular eruption that occurs in up to 30% of patients [98]. In a pediatric report, the eruption itself was self-limiting, but did recur upon reexposure to gemcitabine [99].

Other cutaneous findings include pseudocellulitis, mostly of the lower extremities [100–106], likely another form of TEC. Similarly, an erysipeloid-like erythema in areas of preexisting lymphedema [107] or development of peripheral edema has been noted. According to the package insert of the medication, peripheral edema has been noted in up to 20% of all patients receiving the medication [108]. These findings tend to be self-limited and rarely require discontinuation of the medication [109–111].

Notably, gemcitabine can also induce radiation-recall dermatitis. Radiation-recall dermatitis is an inflammatory reaction that can occur in a specific area of the skin or underlying tissues that was targeted with previous radiation therapy following administration of certain medications, including cytotoxic agents such as gemcitabine. Clinically, cutaneous findings can include erythema, desquamation, edema, vesiculation, ulceration, or frank necrosis localized to the area that was previously irradiated. Pain or pruritus is often noted. It tends to self-resolve without specific therapy, but topical steroids and antihistamines may offer symptomatic relief. Gemcitabine-induced radiation-recall dermatitis is unusual compared to other medications, in that it can also affect internal organs and tissues, as described by Friedlander et al. [112]. Jeter et al. looked at all reported cases of radiation-recall and found that the majority were caused by anthracyclines (41%) and taxanes (28%) [113]. In this study, 63% of radiation-recall reactions due to anthracyclines and taxanes manifested as dermatitis. The Friedlander et al. study in contrast reported only 31% of patients presented with dermatitis or mucositis, and 70% were found to have internal organ involvement [112]. In addition to internal organ involvement, myositis has also been noted to occur, including a severe case in a 14-year-old female with a right arm synovial sarcoma, treated initially with radiation and subsequently with gemcitabine and docetaxel, who developed myositis, resulting in compartment syndrome [114].

In adults, there are a few reports of more serious cutaneous side effects. Drug-induced linear IgA due to gemcitabine has been described [115]. Lesions resolved within 2 weeks of discontinuation of gemcitabine. There are also rare reports of drug-induced subacute cutaneous lupus erythematosus occurring secondary to gemcitabine [116, 117], as well as Stevens–Johnson syndrome/TEN [118–120].

Folic Acid Antagonists

Methotrexate

Methotrexate (MTX) is an inhibitor of dihydrofolate reductase (DHFR), which is necessary in tetrahydrofolate synthesis. By acting as a competitive inhibitor, the end effect results in a decrease in DNA and RNA synthesis. It is commonly used in the treatment of both hematologic and solid-organ malignancies. Most common

side effects include myelosuppression and gastrointestinal mucositis. Oral mucositis tends to occur within 3–7 days following administration. It is thought that intestinal mucosal cells are more sensitive to the medication, and MTX tends to accumulate and persist within the cells [121]. Cutaneous toxicities have been reported as well. Perhaps the most documented is the development of ulceration, oftentimes within plaques of psoriasis, which can be a presenting sign of methotrexate toxicity. It is postulated that ulcerations preferentially occur within psoriatic plaques due to the higher uptake of methotrexate by the hyperproliferative keratinocytes within psoriasis lesions [122, 123]. However ulceration of non-psoriatic skin has also been reported [124]. Risk factors for development of cutaneous ulcerations may include infection, older age, and coadministration of nonsteroidal anti-inflammatory medications [125]. There are no reported cases occurring in the pediatric population.

Ultraviolet recall reactions, which are similar to radiation-recall reactions, can be triggered by MTX. They present with erythema and can be erosive (Fig. 7.4) or vesiculobullous, akin to phototoxic reactions.

Another well-documented, although relatively uncommon, reaction to MTX is the development of HFS, or acral erythema of chemotherapy. This is characterized by the development of painful inflamed plaques on both the palms and soles oftentimes over pressure points, with even bullous lesions noted. To date, there have been nine cases of bullous acral erythema being reported in children with a variety of underlying malignancies [126–134]. Treatment options include observation, systemic steroids, or use of intravenous immunoglobulins. Other treatment options with more variable results include saline soaks, topical steroids, topical narcotics, and emollients.

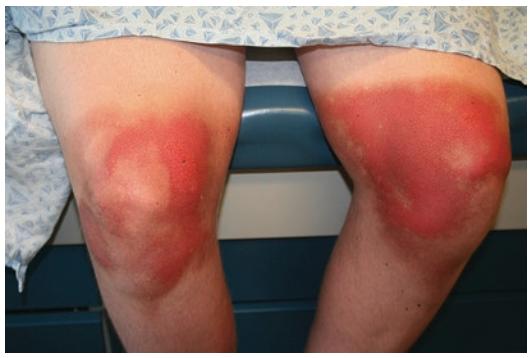

Fig. 7.4 Ultraviolet recall reaction induced by methotrexate (image courtesy of Jennifer T. Huang, MD)

Alkylating Agents

Key Points

- Alkylating agents attach an alkyl group to the guanine base of DNA.
- Cyclophosphamide causes cutaneous and nail pigmentation, along with toxic erythema of chemotherapy.
- ThioTEPA can lead to the development of a hyperpigmented intertriginous eruption.
- Hydroxyurea can cause hyperpigmentation and cutaneous ulceration, and can induce autoimmunity leading to the development of collagen vascular disease.
- Hypersensitivity reactions are common with platinum-based antineoplastic agents.

Alkylating agents attach an alkyl group to the guanine base of DNA. Through this action they prevent breakage of DNA strands and lead to death of individual cells. In addition, cells in all phases of the cell cycle are susceptible to their effects, making them useful in the treatment of various malignancies.

Cyclophosphamide

Cyclophosphamide is commonly used to treat several cancers. Notable cutaneous side effects can include alopecia, mucositis, facial flushing as well as type I hypersensitivity reactions (HSRs), and hyperpigmentation (widespread or localized). The most common location of hyperpigmentation noted with cyclophosphamide occurs

in the nail plate. In a study looking at nail pigmentation related to chemotherapy in patients with Fitzpatrick type V skin, ten women on cyclophosphamide developed diffuse black pigmentation, slate grey to black longitudinal streaks, or diffuse dark grey pigmentation proximally with overlying black transverse bands [135]. The nail pigmentation starts proximally and spreads distally, and tends to subside similarly when the medication is discontinued. Cutaneous and mucosal hyperpigmentation can also be noted, including the oral mucosa, palmar creases, and dorsal aspects of the hands and feet [136, 137]. Localized forms of pigmentation, particularly under areas of occlusion, have been noted in both pediatric and adult patients [138]. One case report described a generalized reticulate pattern of skin pigmentation, in the absence of nail findings [139]. The skin pigmentation that can occur with cyclophosphamide is usually reversible in 6–12 months following discontinuation of therapy [140].

Other cutaneous findings related to cyclophosphamide include the development of TEC. In a study describing the development of an intertriginous distribution of TEC in 16 pediatric patients, 7 patients were receiving cyclophosphamide (in combination with other chemotherapeutic agents) [141]. Cutaneous findings included dusky red papules as the primary lesions that became confluent in intertriginous areas, particularly in the axillae and groin. The onset of development was 1–25 days after receiving chemotherapy. This particular eruption was strikingly asymptomatic for all patients, and spontaneously resolved without major intervention.

Ifosfamide

Ifosfamide is an isomer of cyclophosphamide and therefore there is overlap in their cutaneous adverse reactions. Hyperpigmentation is known to occur, usually on hands and feet [142, 143] or in occluded areas [144]. Type I HSRs also occur rarely [142]. In combination with other chemotherapeutic agents such as carboplatin and etoposide, a characteristic eruption has been noted including oral mucositis, bright red erythema accentuated in intertriginous and genital areas, and subsequent sloughing and desquamation of affected areas [145].

ThioTEPA

ThioTEPA is used as a conditioning agent in patients undergoing hematopoietic stem cell transplantation. It is a derivative of nitrogen mustard and acts as an alkylating agent. Alkylation occurs by the formation of a reactive ethylenimine radical, which cross-links two strands of DNA, thereby disrupting DNA, RNA, and protein synthesis. Common side effects are pruritus as well as HSR including development of urticaria [140, 146]. Mucositis can be dose limiting for many patients.

The most common cutaneous side effect with high-dose thioTEPA, in both adults and pediatric patients, is the development of hyperpigmentation and erythema [147–150]. Less frequently, exfoliation and desquamation have also been noted [150, 151]. Other findings include erythema of the palms and soles [152] as well as hyperpigmentation specific to occluded areas [148]. Preferential areas of involvement include intertriginous zones [148, 150, 151]. ThioTEPA is thought to be excreted onto the skin by sweat, and therefore elevated drug concentrations in these areas may lead to increased risk of skin toxicity.

In a study looking at 38 pediatric patients receiving high-dose thioTEPA (in combination with other chemotherapeutic agents) for a variety of solid-organ malignancies, all developed skin toxicities [153]. Seventy nine percent developed a pattern of skin involvement, starting with mild erythema, which then progressed to generalized erythema, desquamation, and hyperpigmentation. In the other patients, features of erythema, desquamation, and hyperpigmentation were noted, although not following a specific sequence. Intertriginous or occluded areas were most often involved. Onset was on average 6.5 days following administration of thioTEPA.

Melphalan

Melphalan is an alkylating agent in the nitrogen mustard family. It exerts its mechanism of action by alkylation of DNA nucleotide guanine. This leads to DNA strand linkages, which thereby inhibits DNA and RNA synthesis, leading to cytotoxicity. Melphalan is not cell cycle specific. It is commonly used in conditioning regimens prior to hematopoietic stem cell transplantation. It is also used to treat malignancies such as multiple myeloma and retinoblastoma, as well as skin and soft-tissue tumors such as malignant melanoma or soft-tissue sarcomas.

Melphalan can be used in the treatment of localized skin and soft-tissue tumors with the technique of isolated limb infusion (ILI). In a systematic review looking at ILI with use of melphalan in combination with actinomycin D, out of 576 included patients, 46% of patients developed mild erythema or edema, while 19% had significant erythema, edema, or blistering. Extensive skin blistering/sloughing or compartment syndrome was noted in 2% of all patients [154]. Temporary loss of nails in the perfused limb can be noted. Hyperpigmentation has commonly been noted, particularly of the nails, presenting as dark bands of the nail plate [155].

Busulfan

Busulfan is an alkylsulfonate type of alkylating agent. It works by creating intra-strand DNA cross-links, which prevents DNA replication. It is commonly used in both pediatric and adult populations as a conditioning agent prior to bone marrow transplantation, as well as for treatment of leukemias, lymphomas, and other myeloproliferative disorders.

The most notable cutaneous reaction to busulfan is the development of a diffuse hyperpigmentation that can be similar in appearance to Addison's disease [156–161]. The bronze discoloration occurs more often on the neck, upper trunk, and palmar creases. It is more common in darker skinned individuals [162]. It is thought to occur due to toxic effects of the medication on melanocytes, leading to increased pigment deposition in the basal layer of keratinocytes [163].

Hydroxyurea

Hydroxyurea (HU) exerts its effects by inhibiting the M2 protein subunit of ribonucleotide reductase. This in turn inactivates the enzyme, leading to inhibition of DNA synthesis and cell death in the S phase of the cell cycle [164]. It is commonly used in the treatment of leukemias and myeloproliferative disorders, as well as for children and adults with sickle cell anemia. HU has a wide range of cutaneous toxicities. Common findings include xerosis, hyperpigmentation, alopecia, tissue atrophy, and palmoplantar keratoderma [165, 166]. Pigmentary changes of the nails have also been noted with three distinct patterns of hyperpigmentation noted: transverse or longitudinal bands of hyperpigmentation, or diffuse hyperpigmentation of the entire nail plate [167–169]. In a study looking at children on HU therapy for sickle cell anemia, nail pigmentation was noted to occur relatively quickly (mean 8–12 weeks) following initiation of HU, with relatively low doses of the medication [170]. This is in contrast to previous reports noting onset of cutaneous side effects in adult patients after prolonged HU therapy (with one study noting an average 5 years) in the treatment of myeloproliferative disorders or leukemia [171]. As patients with sickle cell anemia tend to have darker skin tones, this may highlight a predisposition to developing hyperpigmentation with HU for those who have darker skin at baseline.

Another notable cutaneous effect of HU is the development of collagen vascular disease. In a study looking at HU in the use of psoriasis and the development of autoimmune disease, patients on HU therapy had a higher rate of elevated dsDNA and anti-cardiolipin IgG antibodies, compared to their matched controls (ages not specified) [172]. Of those with positive serologies, only 14% developed cutaneous signs that may be associated with collagen vascular disease. A case report describes a 14-year-old patient with sickle cell anemia on HU therapy who

developed discoid lesions on the face and upper extremities [173]. Pathology confirmed findings consistent with discoid lupus erythematosus and laboratory evaluation revealed + ANA and antihistone antibodies. Upon discontinuation of HU, the skin lesions rapidly improved and the antibody profile soon normalized. There is also a report of development of systemic lupus erythematosus due to HU in an adult, who also noted rapid improvement in all of her symptoms following discontinuation of the medication [174]. There are many reports of HU-induced dermatomyositis (DM), or DM-like changes on the skin [175–184]. In a review of all reported drug-induced DM cases in the literature, HU accounted for 51% of all total cases [185]. In this group of patients, the average time to onset of DM was 60 months after initiation of HU therapy. None of the reported cases had associated myositis or muscle weakness. 80.6% of patients had classic pathognomonic cutaneous changes of DM on exam, including Gottron's papules, erythema of dorsal hands, and heliotrope rash.

HU has also been known to cause cutaneous ulcerations. According to manufacturer reporting, ulceration accounts for 30% of all dermatologic adverse events [186]. Common locations include the lower extremity, in particular perimalleolar area, as well as feet (dorsal surface), heel, and occasionally arms, hands, and face [187]. Ulcerations tend to be small, well demarcated, and shallow with an adherent yellow, fibrinous, necrotic base [188]. They can be bilateral and almost universally tend to have significant associated pain. Some studies suggest that development or expansion of ulcerations is dose dependent [186, 189]; however, other studies suggest that even the minimum daily dose can induce ulcer formation [190]. Pathophysiology is thought to be due to a cumulative and direct effect on basal keratinocytes, leading to atrophy and delayed wound healing [164, 171].

HU has also been implicated in the development of NMSC, predominantly in photodistributed areas and in individuals with Fitzpatrick phototype I or II skin. As HU impairs DNA repair mechanisms, it interferes with correction of UV signature mutations induced by sun exposure, which can lead to development of squamous dysplasia and eventually neoplasia. Some authors recommend using the term "HU-induced dermopathy" to encompass the spectrum of skin changes resulting from sun exposure in combination with HU therapy, ranging from sunburns to premalignant actinic keratosis to metastatic squamous cell carcinoma [191].

Platinum-Based Antineoplastic Agents: Cisplatin and Carboplatin

Platinum-based antineoplastic agents are group of chemotherapeutic drugs that are used to treat a wide range of malignancies. Their mechanism of action is to cause cross-linking of DNA strands, which inhibits DNA repair and synthesis. They are similar to alkylating agents in their end effect on DNA, but do not technically contain an alkyl group. The prototypic drug in this group of medications is cisplatin. Carboplatin is a second-generation platinum agent, thought to have a more favorable side effect profile.

A common side effect noted with platinum-based chemotherapeutic agents is HSR. Most HSRs due to platinum agents occur at the time of infusion. It is considered to be a type I hypersensitivity IgE-mediated response. In a study looking at 50 pediatric patients with low-grade gliomas receiving treatment with carboplatin and vincristine, 40% developed a HSR [192]. Of those, 45% of patients had a Grade I reaction, characterized by transient flushing or rash, and 30% had a Grade 2 reaction resulting in development of flushing, urticaria, mild bronchospasm, and dyspnea. More severe reactions with true anaphylaxis were noted in 25% of patients, resulting in the death of one patient. The mean number of carboplatin doses received at the time of first HSR was 9, which is similar to another study of pediatric brain tumor patients in which 42% of patients receiving carboplatin developed HSR, after a mean of 10.5 infusions [192, 193]. This study revealed that the cumulative risk of developing HSR increased with each subsequent infusion, and did not plateau.

In a study looking at pediatric patients receiving carboplatin for low-grade gliomas, who did have HSR, 40/55 (73%) were able to receive repeated infusions to complete therapy with either use of precautionary measures (prolonged infusion time, premedication with H1 and H2 receptor antagonists, and corticosteroids) or following desensitization therapy, allowing 34 patients to complete their planned treatment course [194]. However, successful re-challenge may be protocol specific, as other studies have reported less efficacy with desensitization regimens [195, 196].

Other cutaneous findings have been noted with platinum agents. Cisplatin in particular can cause hyperpigmentation in up to 70% of patients [136]. The distribution can be localized or patchy (corresponding to areas in close proximity to intra-arterial infusion) [197, 198], and may affect dorsal aspects of extremities, elbows, knees, sites of trauma or pressure, and nails [199, 200].

Antitumor Antibiotics

Key Points

- Antitumor antibiotics are derived from *Streptomyces* bacterium.
- Anthracycline antitumor antibiotics include daunorubicin and doxorubicin. Their major cutaneous side effects include the development of hand–foot syndrome and other forms of toxic erythema of chemotherapy.
- Dactinomycin can cause a lichenoid dermatitis in children.
- Bleomycin is known to cause a flagellate dermatitis, commonly on the upper trunk and extremities. Other cutaneous side effects include the development of Raynaud's phenomenon and a scleroderma-like fibrosis of the skin.

Antitumor antibiotics are a group of chemotherapeutic agents that are derived from *Streptomyces* bacterium. They are both antimicrobial and cytotoxic in nature. Most are not cell cycle specific and they work by interfering with a variety of cellular processes, mainly disrupting nucleic acid synthesis or inhibiting DNA/RNA synthesis.

Anthracycline Antitumor Antibiotics

Anthracycline antibiotics have three mechanisms of action:

1. Intercalating between DNA/RNA base strands to prevent DNA/RNA synthesis in rapidly growing cells
2. Inhibition of topoisomerase II, which thus inhibits relaxation of DNA supercoils, thereby blocking the function of DNA polymerase in transcription
3. Generation of free oxygen radicals that lead to DNA cellular damage

   Common anthracycline antibiotics include daunorubicin and doxorubicin.

Doxorubicin is commonly used in the treatment of NHL and other lymphomas; lung, ovarian, and breast carcinomas; sarcomas; and other pediatric solid-organ tumors. Daunorubicin is commonly used to treat leukemias, NHL, and Ewing sarcoma. Their side effect profiles are similar, though those of doxorubicin are better described. Doxorubicin, while effective, has a significant side effect profile, with use being limited by cardiac toxicity and nausea. Cutaneous side effects include alopecia, mucositis, and extravasation injury [201–203]. The development of a polyethylene glycol-coated liposomal form of doxorubicin (PLD) has allowed for overall better tolerability, with less myelosuppression and no cardiac toxicity. However, there are some unique cutaneous adverse events that can occur with PLD. One study looking at 22 pediatric patients with refractory solid-organ tumors showed that PLD-induced mucositis was dose dependent, with development and worsening of disease noted with subsequent increased doses [204]. HFS and PPE, entities within the broader spectrum of TEC, are commonly noted with PLD with pooled data showing an incidence of

up to 45% [205]. In the previously mentioned study of pediatric solid-organ tumor patients, 6/22 (27%) developed PPE [204]. Some studies suggest that the incidence increases with higher doses of PLD [206–208]. In addition to previously noted mucositis and PPE, other studies looking at cutaneous effects due to doxorubicin have noted an intertrigo-like dermatitis (again likely part of the spectrum of TEC) [209–212], diffuse follicular rash, radiation-recall, and new formation of melanotic macules [210]. HSR, characterized by urticaria, flushing, and chest pain within minutes of infusion, has also been noted [204, 209].

Dactinomycin

Dactinomycin is a polypeptide antitumor antibiotic, also isolated from *Streptomyces* species. It is composed of two cyclic peptides, attached to a phenoxazine derived from *Streptomyces*. It exerts its mechanism of action by binding adjacent guanine-cytosine base pairs in DNA and inhibiting RNA and protein synthesis via RNA polymerase. It can also cause single-stranded breaks in DNA, leading to further damage. It is cell cycle nonspecific. It is commonly used in the treatment of pediatric solid tumors, such as Wilms tumor, Ewing sarcoma, gestational trophoblastic neoplasia, and rhabdomyosarcoma.

Dactinomycin can induce a lichenoid dermatitis in children undergoing chemotherapy [213–216]. In these reports, onset occurred within 1–2 weeks of dactinomycin initiation. The appearance was varied, with some reports describing an erythematous maculopapular rash, diffuse hyperpigmentation, or brawny erythematous papules with either follicular accentuation or overlying Wickham striae. The distribution was either generalized [215, 216] or favored intertriginous areas such as axillae and inguinal folds [213, 214]. Two reports also described either oral mucositis or cheilitis [214, 215]. In three of these reports, skin biopsies revealed lichenoid dermatitis, some showing changes of syringometaplasia as well [214, 215]. The eruption resolved spontaneously in most cases over several weeks with residual hyperpigmentation. Few cases recurred following reexposure to dactinomycin.

Another cutaneous toxicity of dactinomycin is the development of severe acne, as reported in an 8-year-old prepubertal female [217]. Onset occurred 10 days into therapy and serial measurements of hormones revealed spikes in androgen levels temporally related to dactinomycin administration. Radiation-recall dermatitis has also been described related to dactinomycin [218–221]. Alopecia has been reported, as well [218].

Bleomycin

Bleomycin is a non-ribosomal glycopeptide derived from *Streptomyces verticillus*. It exerts its antitumor effect by complexing with iron and oxygen, leading to free radical formation and subsequent single- and double-stranded DNA breaks. It is cell cycle specific, working within the G2 and M phases. Common areas of toxicity include the lungs as well as the skin, as these two organs lack bleomycin hydrolase, an inactivating enzyme, predisposing to accumulation of the medication within the tissue. A commonly noted side effect of the medication is the development of flagellate erythema or hyperpigmentation. Bleomycin-induced linear hyperpigmentation was originally described in 1971 [222], and several reports describing the reaction have followed. In a study looking at 274 patients receiving bleomycin, 1/3 of patients developed hyperpigmented streaks [223]. The typical areas of involvement include upper trunk and extremities. There is usually accompanying pruritus. In some patients, areas initially appear to be more erythematous, urticarial, or vesicular, which then resolve leaving post-inflammatory hyperpigmentation [224–226]. Originally, the reaction was thought to be dose dependent, occurring in patients receiving doses higher than 100–200 mg, but there are reports of development of flagellate dermatitis with doses as low as 15 mg [224, 226, 227]. In a report of four teenage patients with nodular sclerosing Hodgkin's lymphoma who developed flagellate dermatitis during treatment

with bleomycin, the cumulative doses ranged from 60 to 150 mg [228]. Development of flagellate dermatitis has been reported with various routes of administration including intravenous, intramuscular, intrapleural, intraperitoneal, and intracutaneous injections [225, 229–233]. The eruption can occur between 1 day and 9 weeks after administration of the drug, and usually self-resolves, but can last up to 6 months after discontinuation of medication.

Raynaud's phenomenon (RP) is another potential side effect of bleomycin therapy. In a study looking at 32 men with testicular germ cell tumors being treated with combination bleomycin therapy, 44% developed RP [234]. Risk factors for development include higher cumulative doses as well as bolus administration of the drug (compared to continuous infusion) [235]. There is a pediatric report of RP occurring following intralesional bleomycin administration for treatment of verruca vulgaris [236]. Few cases describe the development of acral gangrene as a result of RP induced by bleomycin [237–239]. Scleroderma-like changes in the skin have also been reported with the use of bleomycin. Most patients have limited involvement, but few patients have developed diffuse disease [240]. Many cases develop concurrently with medication administration, but can be delayed by up to 2 years [241]. Some patients have resolution of swelling and sclerosis following discontinuation of therapy, but sclerodactyly tends to be persistent. There is a case report of a 10-year-old female receiving bleomycin for an ovarian germ cell tumor, who developed both flagellate dermatitis and morphea-like plaques over much of her trunk [242]. Other cutaneous findings include alopecia, NEH, and nail changes [243].

Topoisomerase Inhibitors

Key Points

- Topoisomerase I inhibitors most commonly cause diarrhea and myelosuppression.Cutaneous adverse effects include mucositis, alopecia, rash, and cholinergic syndrome.
- Topoisomerase II inhibitors may cause secondary leukemia in a minority of patients, which is dose related. Cutaneous adverse effects include alopecia, rash, hypersensitivity reaction, and mucositis.
- The hypersensitivity reaction caused by etoposide is thought to be due to the chemicals in its base, whereas for teniposide it is thought to be due to the active drug.

Topoisomerase inhibitors inhibit DNA synthesis by binding to topoisomerase enzymes, which function to relieve helical strain during DNA replication. There are two classes of topoisomerase inhibitors: those that act on topoisomerase I and those that act on topoisomerase II.

Topoisomerase I Inhibitors: Topotecan and Irinotecan

Topotecan and irinotecan are water-soluble derivatives of the plant alkaloid camptothecin, from the Chinese tree *Camptotheca acuminate*. They are camptothecin analogues that target the intranuclear enzyme topoisomerase I. Topoisomerase I binds to double-stranded DNA and creates a transient single-strand break to relieve torsional strain during DNA replication. It then binds covalently to the cleaved DNA, allowing the unbroken strand to pass through, and reseals the break resulting in a newly relaxed DNA double helix. The camptothecin analogues bind and stabilize the topoisomerase I and DNA complex, preventing resealing of the single-stranded break. However, this is not sufficient for cell death. The replication fork must advance to the topoisomerase I-DNA complex, which causes a lethal double-stranded break in the DNA. This induces apoptosis in the S phase. Irinotecan is a prodrug that undergoes enzymatic hydrolysis by carboxylesterase in the liver, gut, and certain tumors to

form its active metabolite, which is over 100× more effective as an antitumor agent.

Currently, both topotecan and irinotecan are only FDA approved for treatment of adult malignancies. Topotecan is approved as a second-line therapy for ovarian cancer, small-cell lung cancer, and in combination with cisplatin for cervical cancer. Irinotecan is approved for the treatment of refractory colorectal carcinoma or as initial therapy in combination with 5-fluorouracil for metastatic colorectal cancer.

Clinical trials of topotecan and irinotecan in children were initiated in the 1990s. Topotecan, despite having good blood-brain barrier penetration, has not been effective in the treatment of CNS tumors [244]. Topotecan has been shown to have complete and partial responses when used in the treatment of neuroblastoma, Ewing sarcoma, and retinoblastoma, and long-lasting minor responses or stable disease were seen in hepatoblastoma and rhabdomyosarcoma [245].

In single-agent trials with topotecan for pediatric solid tumors, myelosuppression, specifically neutropenia, was the most common dose-limiting toxicity. For pediatric leukemia trials, the dose-limiting toxicity for topotecan was mucositis [246]. In pediatric clinical trials, 1–10% of patients developed moderate-to-severe mucositis [244, 246–249]. Cutaneous adverse reactions for topotecan included alopecia, rash, and pruritus. Three to 12% of patients may develop a pruritic, recurrent, generalized erythematous maculopapular rash that can be symptomatically treated with diphenhydramine and topical corticosteroids [246, 250–253]. Alopecia is an infrequently reported side effect [247, 254].

Of note, topotecan can also be injected intraocularly into the sub-Tenon's space for the treatment of intraocular retinoblastomas. One group reported hypersensitivity reactions in 2 of 25 patients during their third intraocular injections of topotecan in a fibrin sealant [255]. The first patient developed upper lid swelling after the first two injections, and then upper lid swelling with urticaria and laryngeal edema requiring ICU admission with the third injection. Improvement was noted with administration of IV diphenhydramine and epinephrine. The second patient developed periocular edema, pruritus, and increased tearing 2 days after the third dose of intraocular topotecan, which resolved with diphenhydramine. There was no reaction noted after the fourth dose, which was compounded in the patient's own blood.

Cutaneous adverse effects of irinotecan include cholinergic syndrome, which includes diaphoresis with flushing during administration, alopecia, and mucositis. In one clinical trial, 2 of 18 children who received irinotecan experienced grade 2 mucositis [256]. In another clinical trial of children on concurrent oral irinotecan and gefitinib, 28% of patients developed grade 1/2 rash [257]. Between 6 and 50% of children have been reported to develop alopecia [256, 258].

Other systemic adverse effects include myelosuppression and diarrhea, which can be dose limiting with large, infrequent dosages [256, 259]. In protracted lower dose schedules, diarrhea and abdominal pain remained prominent [258].

Topoisomerase II Inhibitors

Etoposide and teniposide, which are epipodophyllotoxin derivatives, act on the enzyme topoisomerase II.This enzyme, like topoisomerase I, relieves helical strain during DNA replication. However, unlike topoisomerase I, topoisomerase II cleaves both strands of DNA simultaneously. It then forms a covalent linkage with each free DNA strand terminus. All topoisomerase II inhibitors stabilize the enzyme-DNA covalent complex so that the DNA strand breaks persist and cannot be resealed.

Topoisomerase II inhibitors are known for inducing rearrangements of the mixed-lineage leukemia gene (*MLL*) and causing secondary leukemias. The secondary leukemia that occurs with etoposide and teniposide can be differentiated from one occurring after treatment with alkylating agents by a shorter latency period, predominance of myelomonocytic or monoblastic

subtypes, and frequent cytogenetic abnormalities involving 11q23 (over 50%) [260]. Data suggests that higher cumulative doses of epipodophyllotoxin derivatives increase the risk of developing a secondary AML or myelodysplastic syndrome [261].

Single-agent therapies are uncommon in modern oncology treatment protocols, and epipodophyllotoxins are almost exclusively used in combination with other agents. They are generally used as part of alkylating or cisplatin-based regimens for solid tumors, and with cytarabine for leukemias [262].

Etoposide

Etoposide is a semisynthetic derivative of podophyllotoxin, which is a derivative of podophyllin. Podophyllin is an alcoholic extract of the Mayapple or mandrake plant (*Podophyllum peltatum*).

Cancers historically treated with single-agent etoposide therapy in children include Langerhans cell histiocytosis, Ewing sarcoma, Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, testicular tumor, small-cell carcinoma of the lung, malignant histiocytosis, and leukemia.

There are case reports of HSR to etoposide. One study reported that 3.8% of administrations lead to and 34% of patients developed HSR, whereas another study reported that 2% of patients developed grade 1 or 2 allergic reactions to etoposide [263–265]. This has been postulated to occur due to its base of benzyl alcohol and polysorbate 80. Etoposide phosphate does not include these vehicles, but does contain dextran 40. There is a report of HSR to etoposide phosphate; a 5-year-old female developed edema of the upper lip and face at the end of her first 1-h infusion, followed by fever. The patient was switched to etoposide and premedicated with ondansetron, methylprednisolone, and dexchlorpheniramine without further reactions [265].

Etoposide may also result in alopecia, rash, and mucositis. Between 6 and 40% of patients may develop mild alopecia [264, 266, 267]. The rash that has been reported with etoposide is nonspecific, erythematous, and pruritic [264, 266, 268]. Mucositis is uncommon, with 2 studies reporting 1 out of 20 and 28 patients developing mild mucositis [269, 270].

Teniposide

Teniposide is FDA approved for refractory childhood lymphoblastic leukemia. Like etoposide, teniposide is a semisynthetic epipodophyllotoxin derivative. Teniposide has mainly been used for pediatric ALL, but also in the treatment of pediatric solid tumors and lung cancer in adults.

HSR with teniposide administration can occur in 2–11% of patients [263]. The onset is immediate with administration and thought to be a type I reaction. It most often occurs during the second infusion, though it may even occur with the first dose. The vehicle of teniposide contains benzyl alcohol, N,N-dimethylacetamide, maleic acid, dehydrated alcohol, and cremophor EL (polyoxyethylated castor oil). These agents, especially cremophor EL, have been known to cause hypersensitivity, although the mechanism through which teniposide causes hypersensitivity is thought to occur mainly through direct mast cell degranulation by teniposide and not by IgE-dependent histamine release, or by action through its vehicles [263]. The reaction is usually immediate, although delayed reactions can occur [271]. In children, there are a handful of case series and retrospective studies that report the frequency of HSR. Between 2 and 11% of patients treated with teniposide may experience HSR. Of note, patients with neuroblastoma may have a higher incidence of HSR [272]. One study reports that 2 of 82 children with leukemia and lymphoma developed HSR, whereas 14 of 105 children with neuroblastoma developed the type I reaction [273].

Other side effects of teniposide reported in adults include myelosuppression, alopecia, and nausea/vomiting.

Mitotic Inhibitors

Key Points

- Taxanes most commonly cause myelosuppression and neuropathies. Cutaneous adverse effects include hand–foot syndrome, nail changes, hypersensitivity, alopecia, mucositis, and rash.
- The main dose-limiting toxicities for vinca alkaloids differ per agent: vincristine is neurotoxic, vinblastine is myelosuppressive, vindesine is both, and vinorelbine is myelosuppressive with mild/reversible neurotoxicity.
- Cutaneous adverse effects associated with vinca alkaloids include alopecia, rash, vein sclerosis, mucositis, and hypersensitivity reaction.

Mitotic inhibitors inhibit cell division during the G2/M phase of the cell cycle. They disrupt microtubule polymerization, which is needed to pull cells apart when they divide. There are two major subclasses of mitotic inhibitors used for chemotherapy: taxanes and vinca alkaloids. Both are originally derived from plant sources.

Taxanes: Paclitaxel and Docetaxel

Taxanes are originally derived from the Pacific yew tree (genus *Taxus*). They are among the most commonly used anticancer drugs and are used in many multidrug-based chemotherapy regimens. Paclitaxel was the first taxane known, identified in 1971 [274].

Currently, there are two taxanes available for clinical use: paclitaxel and docetaxel. Both target microtubules by binding to the beta subunit of tubulin dimers, stabilizing microtubules, which induces microtubule bundling, abnormal mitosis, and cell cycle arrest [275, 276]. This induces apoptosis, although the exact mechanism is debated [277–279]. Paclitaxel has additional mechanisms of action, including triggering kinase activation and binding to Bcl-2 and mitochondrial tubulin.

Taxanes are regarded as one of the most powerful anticancer medication classes in adult oncology. They are used as part of first-line multidrug chemotherapy regimens to treat breast, ovarian, lung, and head and neck cancers in adults. They also have successfully treated adult malignancies that are refractory to conventional chemotherapy, including lymphoma and small-cell lung cancers, as well as esophageal, gastric, endometrial, bladder, and germ cell tumors. However, taxanes have had limited success in treating pediatric malignancies.

In 1991, the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) began phase I studies of paclitaxel and docetaxel for children with refractory solid tumors and leukemia. In pediatric patients with refractory and recurrent solid tumors, there was an overall poor response rate in phase I and phase II studies from 1994 to 2006 [280–283]. More recent studies have focused on the combination of gemcitabine and docetaxel for recurrent sarcomas. Docetaxel combined with gemcitabine as rescue therapy for relapsed/refractory pediatric sarcoma has shown a more promising response rate of 50% [284]. There are case reports and case series of patients with neuroblastoma, Wilms tumors, multifocal juvenile granulosa cell tumor of the ovary, and non-Hodgkin's intestinal lymphoma who have improved on taxane-based therapy [283].

The most common side effects from taxanes are neutropenia and peripheral neuropathy. Reported cutaneous side effects to taxanes include HFS and nail changes. In the adult literature, it is reported that approximately 10% and 5% of patients who receive paclitaxel and docetaxel, respectively, develop erythematous plaques on their hand dorsa, Achilles tendon, and malleoli. In adults, nail toxicity manifesting as onycholysis, Beau's lines, onychomelanosis, subungual hemorrhage, and paronychia has been reported in relation to taxanes. In the pediatric literature, there are reports of children developing PPE, desquamation of the fingers and toes, and papules on the arms and legs with docetaxel [285–287]. In studies of docetaxel, between

2 and 18% of children have been reported to develop HFS [288–290]. Nail changes have also been reported in children on docetaxel [280, 284].

Other cutaneous reactions from taxanes include hypersensitivity, peripheral sensory neuropathy, fluid retention/edema, mucositis, and alopecia. Both docetaxel and paclitaxel have provoked HSR in children [281, 289, 291–293]. Peripheral neuropathy can be found in 1–11% of patients who take either paclitaxel or docetaxel, and the incidence increases in a dose-dependent manner [280–282, 294–297]. Fluid retention is more common in those who take docetaxel and is more likely to occur after three treatments. It can be treated with diuretics, and usually resolves after stopping the medication [280, 282, 284, 288, 298]. Alopecia also was only noted in those on docetaxel, and was more prevalent in those who were postpubertal [284].

Docetaxel may also cause a variety of rashes in children. Several reports describe blistering and desquamating dermatoses [282, 287, 293]. There are two reports of acneiform eruptions of the face and torso [280, 299], and several other reports of a painful, erythematous rash that may be found in the folds, periorbitally, under tape occlusion, and on the palms and soles [280, 287]. Paclitaxel has been reported to cause a transient, asymptomatic, papular eruption [300]. In adults, taxanes have been associated with radiation-recall dermatitis, photosensitivity, subacute cutaneous lupus erythematosus, and scleroderma; however, these entities have not been reported in children.

Vinca Alkaloids

Vinca alkaloids were originally extracted from the leaves of the Madagascar periwinkle (*Catharanthus roseus*, previously known as *Vinca rosea*). Vincristine sulfate was first approved for use by the FDA in 1963. Three vinca alkaloids have been approved for intravenous use in the United States (vincristine, vinblastine, vinorelbine) and two are used in Europe (vindesine and vinflunine).

The mechanism of action of vinca alkaloids is through binding of the tubulin component of microtubules to inhibit the M phase of the cell cycle. Their high-affinity binding with tubulin interferes with microtubule assembly, axonal transport, and secretory functions causing axonal degeneration, which contributes to neurotoxicity. In fact, one study has shown that the conduction along sensory nerves in children as measured by somatosensory-evoked potentials was prolonged after vincristine administration [301].

The main dose-limiting toxicities for vinca alkaloids differ per agent: vincristine is neurotoxic, vinblastine is myelosuppressive, vindesine is both, and vinorelbine is myelosuppressive and results in mild/reversible neurotoxicity [302]. Vinorelbine is a semisynthetic vinca alkaloid that is a more selective inhibitor of microtubules involved in mitosis than of those involved in neuronal axonal transport, which leads to less neurotoxicity. Of the vinca alkaloids, vincristine is the most neurotoxic, and there may be a genetic predisposition to susceptibility to neurotoxicity caused by vincristine. Caucasians are more likely to experience neurotoxicity and more severe neurotoxicity from vincristine than African-Americans [303], and those with low CYP3A5 expression (which may be more common in Caucasians), or a specific polymorphism of the promoter region of *CEP72*, are more likely to have vincristine-related neurotoxicity [304–306].

Vinblastine is FDA approved for use in adults to treat Hodgkin and NHL, testicular cancer, breast cancer refractory to other treatments, Kaposi sarcoma, mycosis fungoides, and choriocarcinoma refractory to other treatments. In children, it has been used as monotherapy to treat low-grade gliomas, refractory immune thrombocytopenia, and Langerhans cell histiocytosis [307]. In dermatology, additionally, vinblastine has been used for infantile hemangiomas [308]. Vincristine was primarily used to treat ALL and lymphoma; however it has shown success in treating multiple myeloma, CLL, lymphoblastic crisis of chronic myelogenous leukemia, neuroblastoma, sarcomas like rhabdomyosarcoma, small-cell lung cancer with distant metastases,

and Wilms tumor. In dermatology, vincristine has been used to treat vascular tumors such as infantile hemangiomas (especially prior to the discovery of propranolol's efficacy in treating these vascular tumors), kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon [309–316]. Vinorelbine is FDA approved to treat unresectable non-small-cell lung cancer; it is also used to treat advanced breast cancer, and Hodgkin's lymphoma [302]. In children, vinorelbine has been successful in treating childhood sarcomas. Vinca alkaloids generally are combined with other chemotherapeutics in multidrug regimens.

In adults, reported cutaneous side effects for vinca alkaloids include sensory neuropathies, alopecia, maculopapular rash, mucositis, erythema multiforme-like lesions, HFS, and local irritation and ulceration. In children, the reported cutaneous side effects are mostly the same, although there have been no reports of erythema multiforme-like lesions nor HFS, but there have been reports of vein sclerosis, HSR, and one case of RP (see below). Alopecia is a common adverse effect seen in those who receive vinca alkaloids and has been reported in association with vincristine and vinblastine. Between 11 and 100% of patients on vincristine developed alopecia ranging from mild to total alopecia [317–319]. Scalp tourniquets and every other week dosing can decrease the occurrence of alopecia [318]. Although alopecia is also seen in those on vinblastine therapy, it is seen to a lesser degree than those treated with vincristine [319–321]. Additionally, two patients who initially had alopecia when starting vinblastine therapy had significant hair regrowth while still receiving the medication [322]. There have been a handful of cases of rash reported in correlation with vincristine and vinblastine [317, 320, 323]. Mucositis has been reported in 3–9% of patients in association with vincristine, vindesine, and vinorelbine [317, 319, 324–327]. Hives and bronchospasm have been reported in three pediatric patients from vinorelbine and were adequately treated with subsequent premedication [325, 328]. There has been only one report of a child who developed RP with vincristine, which recurred with each vincristine infusion. It was treated with nifedipine [329].

Venous sclerosis, including one case of skin necrosis with vindesine, has been reported with vindesine and vinorelbine administration. It occurs mostly at the injection site, and is more likely if the agent is injected into a peripheral vein [324, 325, 327]. The vinca alkaloids are vesicants and extravasation of vincristine or vinblastine is associated with local skin irritation and ulceration. If a local reaction occurs, heat and injection of hyaluronidase may disperse the drug and minimize local irritation and inflammation. Folinic acid may rescue vincristine overdose [330].

Radiation Therapy

Key Points

- Acute radiation dermatitis has a separate pathogenesis from chronic radiation dermatitis.
- Radiation therapy most commonly causes acute radiation dermatitis, which consists of erythema, dry skin, occasional desquamation and ulceration, and alopecia.
- Gentle washing, emollients, and avoiding unnecessary friction to the skin are first-line treatments for acute radiation dermatitis.

Radiation therapy plays a crucial element in many multidisciplinary treatment regimens for a variety of cancers. Pediatric cancers commonly treated with radiation therapy include brain tumors, sarcomas of bone and soft tissues, neuroblastoma, Wilms tumor, and Hodgkin's lymphoma. Since the 1970s, the use of radiation therapy for pediatric cancers has declined, although it is still used to treat over half of children with Wilms tumor, and Hodgkin's lymphoma, and over one-quarter of children with brain cancer, soft-tissue cancer, and neuroblastoma [331].

Historically in dermatology, radiation therapy was used for the treatment of acne, eczema, and tinea capitis. However, given the advent of more successful therapies without the long-term sequelae of radiation, rarely, if ever, do dermatologists today resort to radiation for the treatment of these benign skin conditions [332].

Mechanism of Action

Radiation therapy acts by inducing DNA damage through single- and double-stranded breaks and inducing free radical damage. Tumor cells are thought to be more sensitive to the damaging effects of radiation because they are rapidly dividing and have a decreased capacity for DNA damage repair. This also means that non-cancer cells that rapidly divide, such as cells of the skin and mucosa, are more sensitive to the effects of radiation.

In skin, radiotherapy damages germinative cells of the epidermis, sebaceous glands, and hair matrix, as well as endothelial cells and Langerhans cells [333–335]. Tissue damage occurs immediately and is mediated by free radicals damaging DNA, proteins, lipids, and carbohydrates. Acutely, this direct tissue injury recruits inflammatory cells and may result in epidermal cell apoptosis and necrosis [336]. The tissue damage, in conjunction with inflammation, contributes to impaired barrier function, propensity for bacterial colonization, and superantigen production. Endothelial damage, in turn, activates the coagulation system, which promotes inflammation, cytokine production, and thrombi formation. This communicates with TGF-beta, a fundamental component of wound healing and fibrosis, which is involved with chronic radiation dermatitis.

Radiation most commonly causes atrophy in epithelial tissue, followed by necrosis, atypia of nuclei and/or cytoplasm, and dysplasia (a late finding that usually occurs several years after exposure), ending in neoplasia. Stromal tissue, on the other hand, most commonly presents with fibrosis after radiation exposure, which is a delayed finding [337].

Types of Ionizing Radiation Therapy

Ionizing radiation is the type of radiation used for cancer therapy. It has the ability to form ions and free radicals in the tissues it passes through, causing cell death and genetic alteration. There are two major types of ionizing radiation: photoradiation (consisting of X-rays and gamma rays) and particle radiation (consisting of electrons, protons, neutrons, carbon ions, alpha particles, and beta particles). Each type of ionizing radiation has different levels of energy, which allows different depth of penetration into tissue.

Photon radiation is the most common form of radiation to be used in radiation oncology. It consists of a high-energy photon beam from a radioactive source, such as cobalt, cesium, or a linear accelerator machine. When delivered by a linear accelerator, it is referred to as external beam radiation therapy. Photon beams affect all cells in their path.

Electron or particle beams are also produced by linear accelerators. They have low energy and do not penetrate tissue well. This type of radiation is mostly used for skin- and lymph-node-directed therapy, such as in treatment of mycosis fungoides.

Proton beams release most of their energy only after traveling a certain distance, thus causing little damage to the tissues they pass through. They are thought to deliver more radiation to the cancer (their target) while doing less damage to the nearby normal tissues. This occurs because protons emit little energy early in their course, and then rapidly release energy in the last few millimeters of their path (as they reach their target). This results in a sharply localized peak of energy emission known as the Bragg peak. The penetration depth of the Bragg peak is proportional to the amount of energy initially in the proton [338]. Several studies of proton beam therapy have shown that it is equivalent to photoradiation for the treatment of childhood malignancies. Some studies have suggested that side effects are less, but the significance has yet to be fully delineated [338]. Proton beam therapy is not widely available, as the equipment required is quite specialized, which limits its use currently. Proton

beam treatment can also result in incidental neutron exposure. Neutrons are more damaging to DNA and thus may have more potential for inducing carcinogenesis. Neutron beams and carbon ion radiation have been used for adult malignancies, but their safety has not been established in children [339]. Alpha and beta particles are less commonly used in cancer treatment, and are rarely, if ever, used in children.

Methods of Delivery for Radiation Therapy

In addition to the type of radiation beam, there are also several methods in which the radiation can be delivered to the target tissue with the goal of decreasing radiation exposure to surrounding tissues. Conventional radiation therapy approaches a target from one to two sides, whereas conformal radiation therapy techniques (e.g., 3-D conformal radiation therapy and intensity-modulated radiation therapy (IMRT)) approach a target from several directions, lowering the total dose of radiation that passes through normal tissue, but also expanding the volume of normal tissue exposed [340]. The guiding principle of conformal radiation therapy is to minimize the dose to normal tissues to "as low as reasonably achievable" (ALARA) [340]. Currently, IMRT is mainly used to treat prostate cancers, cancers of the head and neck, and central nervous system cancers.

For treatment of solid tumors, it is imperative that the patient remain perfectly still and in exactly the same position during each and every treatment. This is achieved through immobilization devices, including masks, body molds, and reference points, as well as anesthesia for young children.

Uses

Ionizing radiation may be used to treat primary solid tumors, as total-body irradiation for malignancies without the goal of bone marrow transplantation, as total-body irradiation used in preparation for marrow transplantation of patients with malignant or nonmalignant diseases, and to palliate metastatic disease.

Adverse Effects

The side effects that occur from radiation therapy occur from the radiation beams passing through nearby normal tissues. Radiation-induced changes can be divided into two groups: acute effects that are noted during or shortly after treatment (usually within 90 days, discussed here) and late side effects that develop months to years after the end of radiation therapy (discussed in Chap. 11). Tissues that have rapid turnover are often most acutely affected by radiation. Thus, bone marrow, skin, mucous membranes, and hair follicles manifest the earliest effects of radiation damage. The most common systemic side effect is fatigue, followed by myelosuppression if the radiation treatment area is large enough. In one retrospective study of 48 children treated with proton beam radiation for CNS malignancies, 77% of patients developed grade I or II fatigue, which peaked between the middle to end of radiation therapy, week 3, and beyond [341].

In terms of skin, acute radiation dermatitis is the most common adverse effect. Generalized erythema, sometimes very mild, may occur hours after radiation and fade within hours to days. A second phase of erythema that is more sustained may be seen 10–14 days after irradiation, with pink, blanchable patches. This change is thought to be mediated by cytokines. In the NCI-CTCAE, v4.0, radiation dermatitis is graded on a scale from 0 to 4 [54]. Grade 1 changes as defined by the NCI include faint erythema or dry desquamation [54]. The erythema can be generalized or follicular, and usually occurs within hours to days with radiation doses of 2–20 Gy [342]. The dryness is secondary to injury to sebaceous glands, and occurs with radiation doses of 20–25 Gy [342]. Patients may complain of pruritus, and their skin may also appear scaly, dyspigmented, and epilated. Grade 2 changes include more persistent, tender erythema and/or edema, which may progress to focal denudation of the epidermis

producing moist desquamation confined to skin folds. This occurs after 4–5 weeks of therapy with radiation doses of 40 Gy or greater. Grade 3 dermatitis is defined as moist desquamation outside of skin folds. The moist desquamation is caused by epidermal necrosis with fibrinous exudates and can cause significant pain. Histologically, the arterioles are obstructed by fibrin thrombi and edema is prominent. Radiation dermatitis usually peaks 1–2 weeks after the last treatment, epidermal regeneration occurs 3–5 weeks after radiation has concluded, and complete healing occurs 1–3 months after the last radiation session.

Rarely, the acute dermatitis never completely heals. When acute changes do not resolve, they may result in chronic skin ulceration, fibrosis, or necrosis of underlying structures, termed "consequential" late effects [336]. Separately, chronic radiation dermatitis may develop despite minimal acute radiation dermatitis.

The skin may easily become secondarily infected. It is important to rule out superinfection by pathogens that make superantigens like *Staphylococcus aureus*, as the superantigens may stimulate cytokine production, inflammation, and subsequent skin damage [343].

Radiation to the brain may result in alopecia. With conventional radiation, alopecia usually begins within 3–4 weeks of radiation at 180–200 cGy/day and affects the areas of the scalp where the radiation beams enter and exit the body. Hair loss may be permanent with total doses greater than 4000 cGy. Usually there is hair growth 4–6 months after treatment completion; however the color and texture of the hair may be changed, often with a lighter color (due to destruction of melanocytes) and finer texture [344]. In the NCI-CTCAE, v4.0, alopecia is graded on a scale of 0 to 2 (Table 7.2) [54].

Radiation to the head and neck area may acutely cause mucositis, eyelid dermatitis, and epilation [345, 346]. Mucositis presents as erythema, mucosal atrophy, and ulceration with or without pseudomembranes, and results in a decreased ability to eat and speak. The loss of integrity of the mucosal barrier predisposes the patient to infections with bacteria, yeast, and viruses. Therapy for mucositis is mostly palliative, including oral hygiene, dietary modifications, and mucosal protectants. Antiplaque rinses of isotonic saline or sodium bicarbonate solution and nystatin and/or amphotericin B rinses may be used to decrease pathogenic flora and maintain oral moistness. Analgesic rinses with 2% viscous lidocaine can be used to relieve pain [346].

Another reaction to radiation that may occur acutely or in a delayed fashion is radiation-recall dermatitis. It is an inflammatory rash that develops days after a systemic medication has been introduced in patients who were treated with radiation. The offending medication is usually a cytotoxic agent that was introduced shortly after the cessation of radiation therapy, especially taxanes and anthracyclines, and rarely antibiotics. It has been reported to occur 7 days to 2 years after radiation, and most patients have not had a reaction while receiving radiation. Like radiation dermatitis, radiation-recall dermatitis ranges from dry desquamation and faint erythema to edema, more diffuse desquamation, and necrosis or ulceration. In 1/3 of cases, internal involvement with corresponding mucositis, colitis, pneumonitis, and optic neuritis has been seen. Anecdotally, treatments showing success include withdrawal of the offending medication, NSAIDs, antihistamines, mast cell inhibitors, and topical or systemic corticosteroids [221].

In adults, a "comedo reaction" of open and closed comedones after head and neck radiation has been reported. Additionally, lesions called "pseudorecidives" that appear as keratotic papules and may spontaneously resolve have been reported in the immediate postradiation period [336, 347–349]. Neither of these reactions has been reported in children.

Other side effects are specific to the location that is treated with radiation therapy. For example, radiation to the head and neck may cause difficulty swallowing and dry mouth, whereas radiation to the abdomen may cause abdominal discomfort and cramping.

One retrospective study of pediatric cancer patients who were treated with either proton or particle beam therapy showed that myelosuppression, radiation dermatitis, and mucositis may persist at

2 months posttreatment, but usually resolve by 6 months posttreatment [350]. Acute problems related to total-body irradiation include gastrointestinal symptoms, rash, mucositis, alopecia, decreased salivation and tears, and veno-occlusive disease of the liver [351].

In studies of adult patients, factors that may worsen acute radiation dermatitis include poor nutritional status, smoking, problems with skin integrity, and obesity [352, 353]. Children who have an impaired ability to repair DNA, such as those with ataxia telangiectasia, or those with chromosomal breakage syndromes, such as Fanconi anemia and Bloom syndrome, are known to develop more severe radiation dermatitis and other late sequelae of radiation therapy, such as secondary malignancies or debilitating fibrosis [336, 354–356]. Interestingly, patients with xeroderma pigmentosum (XP), a syndrome with defective DNA repair, may not be hypersensitive to radiation therapy. DNA damage from ionizing radiation is usually repaired by base excision repair and nonhomologous end joining, which are intact in XP, and not by nucleotide excision repair, which is defective in XP [357]. Lastly, in the adult literature, several case reports and case series suggest that patients with collagen vascular disease may be more predisposed to develop severe radiation dermatitis. Thus far, more comprehensive analyses have failed to report a significant association [358–360].

Treatment of Acute Radiation Dermatitis

The first-line therapy for grade 1 radiation dermatitis is gentle skin care. Patients may gently wash their skin with plain water or a mild, low-pH cleanser. Washing is thought to decrease bacterial burden and washing with soap lowers the incidence of desquamation and erythema [361]. Patients may moisturize with a bland, petrolatum-based emollient. They should wear non-chafing, loose clothing and avoid adhesives on their skin as much as possible. Some physicians and reports have suggested that patients should avoid aluminum or magnesium salts found in antiperspirants and talcs when they are actively undergoing therapy, because these metals can increase the radiation dose to the superficial skin; however, meta-analysis data shows that wearing antiperspirant does not influence the development of acute radiation dermatitis [361]. Lastly, patients should engage in strict photo protection with sun avoidance, wide-brimmed hats, long-sleeved clothing, and sunscreen as tolerated.

Further recommendations for the prevention and treatment of radiation dermatitis are largely anecdotal and few comparison trials have been performed with varying and conflicting results. In terms of acute radiation dermatitis prevention, one meta-analysis from 2014 showed that oral proteolytic enzymes containing papain, trypsin, and chymotrypsin may decrease the incidence of acute radiation dermatitis, as well as the severity. Oral pentoxifylline, washing practices, deodorant or antiperspirant use, and nonsteroidal topicals did not show any significant benefits to preventing acute radiation dermatitis [361]. Topical corticosteroids have been controversial for the treatment of radiation dermatitis, as some studies show no significant difference between steroid and placebo, and some studies show decreased severity and incidence of acute radiation dermatitis with their use [336, 361]. Other topical treatments that have been reported as successful in small clinical trials include radioemulsions containing trolamine, hyaluronic acid, RadiCare Gel, Aquaphor ointment, aloe vera gel, dexpanthenol, hydrophobic and hydrophilic ointments, chamomile, almond ointment, gentian violet dressings, and hydrogel dressings [336, 361].

Summary

In summary, recognizing cutaneous reactions to traditional chemotherapeutic agents and radiation therapy is important for both dermatologists and oncologists who are involved in the care of critically ill oncology patients. Determining which reactions are self-limited or reversible vs. life threatening can help to direct care.

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Cutaneous Reactions to Targeted Anticancer Agents

8

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Introduction: The Era of Targeted Anticancer Therapy

Significant advances in understanding oncogenic pathways have led to the development of many molecularly targeted therapies. While targeted therapies have improved responses, prolonged survival, and reduced bone marrow and mucosal toxicity, they are associated with unanticipated characteristic and common dermatologic adverse events (dAEs) [1]. The utilization of these therapies has been rapidly increasing in the adult population, with ongoing trials across targets, malignancies, and in combination regimens. With precision medicine and tumor-specific mutation analyses driving personalized cancer care, investigators and clinicians have begun to explore the efficacy and safety of these agents in the pediatric population. Although these studies remain limited in number, it has been speculated that AEs may be different in children and adolescents due to overlap between developmental and oncogenic pathways and the propensity for long-term effects in childhood cancer survivors [2]. Thus, until there is a greater understanding of mechanisms of toxicity, pediatric oncologists must remain cautious when considering targeted therapies for their patients.

As targeted therapies are increasingly used, it is imperative, particularly in the pediatric population, that research on mechanisms of toxicity continues in parallel. Side effect profiles from targeted therapies are thought to be related to the underlying mechanism of action of the drug, with on-target bystander binding in non-tumor tissues. Further study is required to confirm this hypothesis, and determine the

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Table 8.1 Targeted anticancer agents currently used or in active trials in the pediatric population: cutaneous adverse effects and management options

Targeted anticancer agent	Cutaneous adverse effects	Treatment options
EGFR inhibitors	– Papulopustular eruption – Xerosis – Nail changes (paronychia, pyogenic granulomas) – Hair changes (trichomegaly, hirsutism)	– TCS, oral TCNs – Emollients – TCS or topical antibiotic, silver nitrate – Regular trimming, laser hair reduction
BRAF and MEK inhibitors	– Rash – Photosensitivity – Xerosis – Squamoproliferative lesions – Melanocytic nevi and melanoma	– TCS, antihistamines – Photoprotection – Sensitive skin care, emollients – Routine skin examinations, surgical excision, oral retinoids – Routine skin examinations, photoprotection
mTOR inhibitors	– Edema – Stomatitis – Delayed wound healing	– Compression garments – TCS, topical analgesics – Dressing
Tyrosine kinase inhibitors	– Hypo > hyperpigmentation – Rash	– Self-resolution upon discontinuation – TCS, antihistamines
Antiangiogenesis agents	– Mucosal bleeding – Stomatitis – Thromboembolism – Delayed wound healing – Ulcerations in striae	– TCS, topical analgesics – Dressing

TCNs tetracyclines, *TCS* topical corticosteroids

specificity of binding in non-target tissues and the consequences of this during development. For example, common adverse effect patterns may in fact be due to binding of a common non-target kinase expressed in a keratinocyte or dermal vasculature. In this chapter, cutaneous AEs of targeted anticancer therapies are discussed, focusing on agents currently used or in active trials in the pediatric population (Table 8.1). While data on adverse effects in children is limited, to date the largest study analyzing the dAEs has found that there is considerable overlap between findings in children and adults [3]. As such, management data generated from the adult population is included, with special consideration paid to pediatric specific challenges.

Special Implications in Children

Key Points

- Few targeted anticancer agents have been approved in children.
- Side effects from these agents in children appear to mirror their adult counterparts.
- Malignant cells often hijack key pathways that also control normal development; thus targeted anticancer therapies may have unique adverse effect profiles and long-term implications in developing children.

While more than 60 agents have been approved in adults, very few have been approved for use in children. The mTOR inhibitors (e.g., everolimus) used in tuberous sclerosis complex for subependymal giant cell astrocytoma (SEGA) and c-KIT inhibitors (e.g., imatinib) used for Ph+ chronic myeloid leukemia (CML)/acute lymphoblastic leukemia (ALL) have been recently approved for pediatric use [2]. Currently, the most frequently studied targeted molecules in pediatric oncology trials are inhibitors of EGFR, BRAF, MEK, mTOR, BCR-ABL/KIT, and multikinase and antiangiogenesis agents. Multiple clinical trials with other combinations of these targeted agents are also ongoing in pediatric patients.

While data on dAEs in children is limited, their ubiquitous use in adults is helpful in predicting and developing management strategies in children. In fact, a thorough review of the literature and available clinical trial data on dAEs from targeted therapies in pediatric patients found that to date the side effects in children appear to mirror their adult counterparts [3]. The authors further found that rash was the most common AE encountered during treatment (19%), usually appears in a dose-dependent fashion, tends to vary by tumor type, and may be dose limiting [3]. Like in adults, patients on EGFR inhibitors (EGFRi) appeared to be at highest risk. Interestingly, the incidence and severity of the typical acneiform rash seen with this family of medication have been correlated with a better progression-free survival and overall survival in adults [4]. This has yet to be studied in children.

Importantly, malignant cells often hijack key pathways and the same molecular networks that control normal development. Thus, targeted anticancer therapeutics may have unique adverse effect profiles and long-term implications in developing children [2]. For example, an unanticipated observation in children treated with tyrosine kinase inhibitors (TKIs) for BCR-ABL1+ leukemias is that of growth suppression or growth failure. This is hypothesized to be due to concomitant inhibition of platelet-derived growth factor receptor (PDGFR) in chondrocytes, thus impairing proliferation and linear bone growth [5–7]. Spermatogenesis is also dependent upon PDGFR and c-KIT, and may be affected by exposure to this family of drugs; the long-term effects on fertility remain to be seen [8, 9]. The developing immune system and the potential for immunosuppressive effects of targeted agents should also be considered. Everolimus is associated with an increased risk of infection, and although the degree of immunosuppression is generally manageable, the extent to which immunosuppression persists and the potential for secondary malignancy may ultimately limit its chronic use [10].

EGFR Inhibitors

Key Points

- EGFRi are associated with specific and predictable cutaneous toxicity in 50–90% of cases.
- The most common dAE consists of a papulopustular eruption in a seborrheic distribution. Xerosis, hair changes, mucositis, and paronychia are other commonly reported cutaneous side effects.
- Management is dependent upon severity of involvement, and usually enables continuation of therapy.

EGFRi were among the first targeted therapies and are used in the treatment of several malignancies in adults, including non-small-cell lung, colorectal, head and neck, and breast cancers [11]. EGFRi include monoclonal antibodies that target the extracellular ligand-binding domain of EGFR (cetuximab, panitumumab), small-molecule TKIs that target EGFR intracellularly (erlotinib and gefitinib), dual-kinase inhibitors of EGFR and human EGFR-2 (HER 2) (lapatinib), inhibitors of erbB (canertinib, afatinib), and other less specific multikinase inhibitors such as vandetanib [12]. Given the distribution of EGFR in the epidermis and pilosebaceous unit, it is not surprising that modulation of this receptor evokes skin and hair adverse effects. Interestingly, EGFR

has also been shown to play a putative role in restraining interleukin-1 (IL-1)-dependent inflammatory reactions at the hair follicle level, shedding light on the follicular and papulopustular eruptions seen in conjunction with EGFR blockade [13].

Cutaneous AEs from EGFRi range in incidence from 50 to 90%, and include a spectrum of predictable and specific toxicities. Among these, papulopustular eruptions, xerosis, hair changes, mucositis, and paronychia are the most commonly reported. Data from pediatric patients treated with EGFR inhibitors (erlotinib, vandetanib) were reviewed by Belum et al. and rash was noted in 42/57 (73.7%) patients [3]. More specifically, an "acneiform rash" was noted with vandetanib (3/15) and erlotinib (3/13) [14, 15].

The most common eruption reported in the adult literature (over 80% of patients on cetuximab) consists of follicular papules that evolve into pustules (Fig. 8.1) and that may coalesce into lakes of pus in a seborrheic distribution (scalp, face, and upper torso). This papulopustular eruption typically presents within 2 weeks of initiation, is dose dependent, may improve in some patients with continuation of therapy, and typically resolves after therapy is discontinued [16, 17]. While commonly described as acneiform, the eruption lacks comedones and cystic nodules and is inflammatory in nature. Significant pruritus is also reported in association with this dAE. Sun exposure may exacerbate this specific skin toxicity without necessarily inducing classic sunburn erythema [18]. Grade of severity is based on the body surface area involved and degree of limitation in performing activities of daily living [19].

In general, management of toxicities is dependent upon severity of involvement. However, in adults treated with panitumumab, the use of a preventative regimen reduced the incidence of grade 2 or greater toxicity and resulted in less quality-of-life (QOL) impairment than reactive treatment alone [20]. This regimen consisted of an oral tetracycline (TCN) antibiotic, topical corticosteroids (TCS), sun protection, and emollients. It has not been studied in children, where

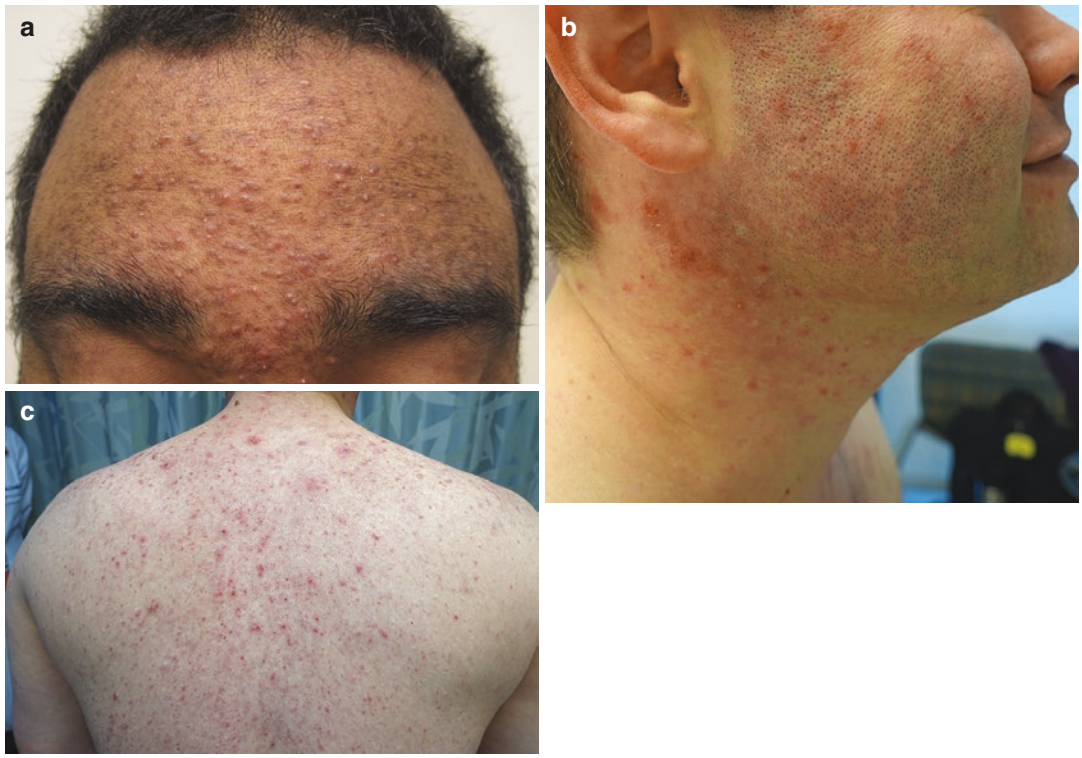

Fig. 8.1 **(a–c)** Papulopustular eruption secondary to EGFR inhibition

TCNs require additional considerations. When taking a reactive approach to grade 1 eruptions, low-potency TCS or topical antibiotics may be sufficient [21]. Given the inflammatory nature of this eruption, TCS are generally indicated. Grade 2 and 3 eruptions are best managed with systemic TCNs, which are considered first-line agents given their anti-inflammatory properties, in addition to TCS [22]. All patients should be counseled on sun protection and emollients. Calcineurin inhibitors, gel-based topical antibiotics, and benzoyl peroxide are avoided due to irritant potential and inability of most patients to tolerate them, supporting the finding that this is not simply drug-induced acne vulgaris.

Xerosis is also reported in 1/3 of patients receiving EGFRi, has a significant impact on QOL, and commonly leads to asteatotic dermatitis (Fig. 8.2) [23]. It is characterized by dry and scaly skin reminiscent of atopic dermatitis, and is thought to be due to loss of the water-retaining function of the epidermis, developing as a result of disturbed keratinization and sebaceous gland function [24]. In addition, effects on the innate immune system lead to reduced defense and overgrowth of *Staphylococcus aureus* [25]. As in atopic dermatitis, gentle skin care, emollients, dilute bleach baths, and antihistamines may be of benefit [26].

Nail and/or nail fold toxicity occurs in approximately 17% of patients, with the first digit being most commonly affected [27]. Nail changes usually appear after 2 months of treatment and can manifest as onycholysis, nail fragility with brittleness, and paronychia, or pyogenic granuloma-like lesions which may first occur after many months of therapy (Fig. 8.3). Culture is recommended in cases of inflammatory paronychia to rule out secondary infection, given disrupted epidermal defense. In addition to antimicrobial soaks (including dilute bleach or dilute vinegar, with explicit reminders to never combine these) and topical antimicrobials depending on the suspected or cultured organism, warm compresses, TCS, and systemic TCNs can be used for management [26]. Silver nitrate-based chemical cautery is helpful when granulation tissue is evident.

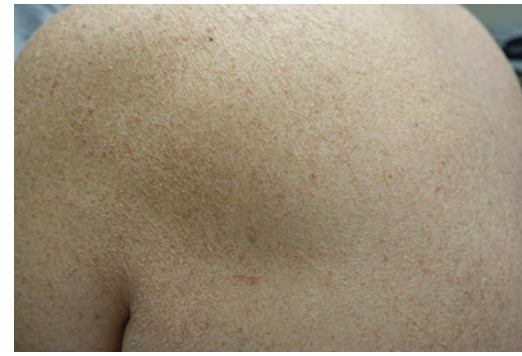

Fig. 8.2 Severe xerosis with asteatotic changes on EGFRi

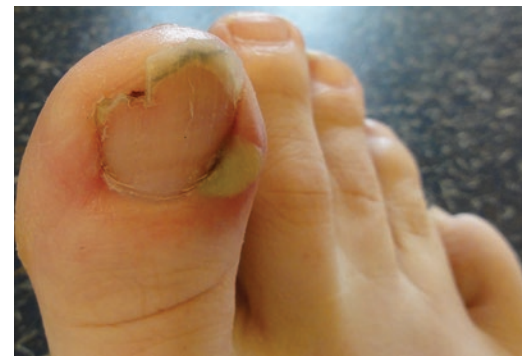

Fig. 8.3 Nail changes associated with EGFR inhibition include paronychia

Changes in hair texture and growth pattern can be seen after 2–3 months of treatment and can be quite significant, particularly if patients have chemotherapy-induced alopecia immediately prior to or at the time of initiating EGFRi. Hair typically grows more slowly, and becomes more fine, brittle, and kinky [28]. Trichomegaly of the eyelashes is also characteristic (Fig. 8.4), and has been reported in 17% of pediatric patients [3, 29]. Management of this dAE is critical, as lashes may curl inward and lead to corneal scarring if they are not trimmed. Mild diffuse alopecia, in a pattern similar to androgenic hair loss, and poliosis have also been reported [30].

Mucositis may develop, manifesting with aphthae, xerostomia, or geographic tongue [31]. Genital involvement is less common. Other reactions to EGFRi include anaphylaxis (1.2–3.5% of patients taking cetuximab), enhancement of radiation dermatitis, ocular complications from

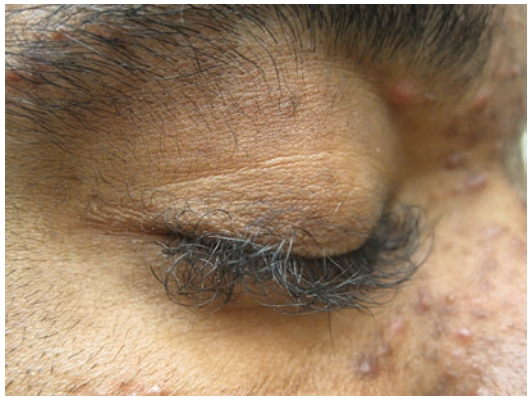

Fig. 8.4 Trichomegaly associated with EGFR inhibition

dryness or trichomegaly as above, vasculitis, necrolytic migratory erythema, and transient acantholytic dermatosis [26, 32–34].

BRAF and MEK Inhibitors

Key Points

- Activating BRAF mutations are found in over 50% of melanomas, but also in other cancers such as hairy cell leukemia and Langerhans cell histiocytosis.
- Dermatologic adverse effects secondary to BRAF inhibitors affect up to 95% of patients, manifesting as nonspecific/morbilliform rash, evolving over time to become more folliculocentric. Photosensitivity, alopecia, pruritus, superficially desquamative hand-foot syndrome, and proliferative lesions of the epidermis have also been reported.
- Dermatologic adverse effects secondary to MEK inhibitors are similar to EGFRi and include papulopustular eruptions favoring the scalp, face, chest, and back as well as xerosis, pruritus, and photosensitivity.
- The combination of BRAF and MEK inhibitors improves survival in metastatic melanoma and induces fewer cutaneous side effects.

The MAP kinase, or RAS-RAF-MEK-ERK, pathway is a sequential enzyme cascade that leads to a multitude of effects on cellular proliferation, differentiation, migration, and apoptosis [35]. BRAF is a serine-threonine protein kinase in this signaling cascade. Activating BRAF mutations are found in more than 50% of malignant melanomas and the majority of these mutations affect a specific amino acid residue (V600) in BRAF. These mutations also occur at lower frequencies in other types of proliferative lesions, including benign nevi, and a subset of head and neck squamous cell, colon, lung, and thyroid cancers as well as hairy cell leukemia and malignant histiocytoses [36]. Vemurafenib and dabrafenib are selective inhibitors that target these kinases and are FDA approved for advanced melanoma (2011, 2013, respectively). They have demonstrated favorable clinical responses in melanoma patients carrying the mutation BRAF V600E and to date are most commonly used in combination with MEK inhibitors (MEKi) in an attempt to overcome BRAF resistance. BRAF inhibitors (BRAFi) present unique and predictable dAEs that are due, at least in part, to molecular events linked to the mechanism of action of these drugs, paradoxical activation of MAPK. The dAEs appear proportional to dose and duration of drug exposure [37].

As with EGFRi, dAEs are the most common adverse effects in patients treated with BRAFi, affecting up to 95% of patients; a nonspecific rash occurs in up to 75% of patients [38]. Patients often present with a mild, transient morbilliform eruption within the first few weeks of therapy that is asymptomatic or mildly pruritic and resolves with time or TCS. Failure to respond should raise suspicion for a delayed-type hypersensitivity reaction. The persistent "rashes" associated with BRAFi are better classified as folliculocentric or papulopustular, sometimes with a keratosis pilaris-like appearance, and occur primarily on the face (Fig. 8.5) and upper torso and arms (Fig. 8.6).

Photosensitivity is common affecting 30–57% of patients (Fig. 8.7); this is UVA induced and patients are advised to wear sunscreen daily to avoid toxicity from incidental

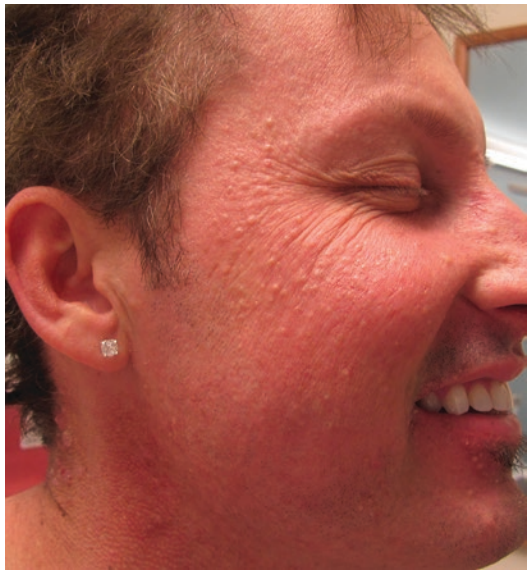

Fig. 8.5 Milia-like folliculocentric papules on the face secondary to BRAF inhibition

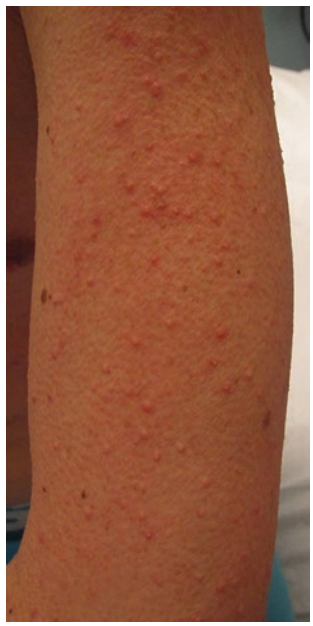

Fig. 8.6 Keratosis pilaris-like papules on the arm secondary to BRAF inhibition

indoor exposure through windows [39]. Alopecia, pruritus, superficially desquamative hand-foot syndrome, and proliferative lesions of the epidermis have also been reported. Proliferative lesions classically develop within

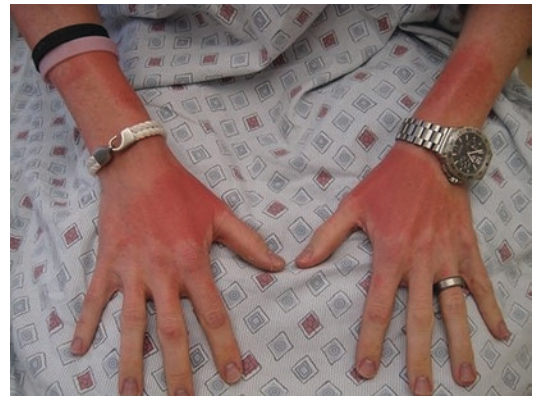

Fig. 8.7 Severe sunburn after minimal sun exposure while on BRAF inhibitor

8–12 weeks of treatment. These lesions represent a continuum and encompass benign papillomas, verrucae, verrucous keratoses, seborrheic keratoses, warty dyskeratomas, palmar/plantar hyperkeratosis, actinic keratoses, and keratinizing skin tumors such as keratoacanthomas and cutaneous squamous cell carcinomas (SCC) [40]. These are treated with skin-directed therapies, reserving surgery for invasive SCC. An additional and occasionally challenging effect of BRAFi is the occurrence of melanocytic changes. Darkening of existing nevi, regression of nevi, eruptive nevi (Fig. 8.8), and development of atypical melanocytic proliferations have all been described [40]. Second primary melanomas have also been reported [41]. Paradoxical MAP kinase pathway activation by wild-type BRAF or RAS mutant cells provides a plausible mechanism for SCC and, potentially, melanocytic tumor development as well [42].

Understanding this paradoxical MEK/MAPK activation in normal cells and tissues contributed to the hypothesis that MEKi may reduce cutaneous tumor formation induced by BRAFi [43]. MEK inhibitors, such as trametinib, target the MAPK pathway further downstream, and in studies combining a MEKi with a BRAFi in patients with metastatic melanoma, there was not only an extension of progression-free survival but also a reduced incidence of treatment-associated SCCs from 19 to 7% [44]. While patients treated with MEKi monotherapy suffer from an array of

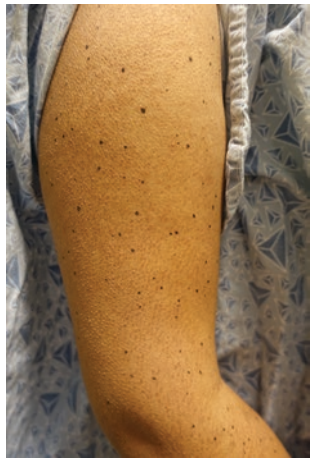

Fig. 8.8 Eruptive dark nevi with a background of keratosis pilaris-like papules secondary to BRAF inhibition

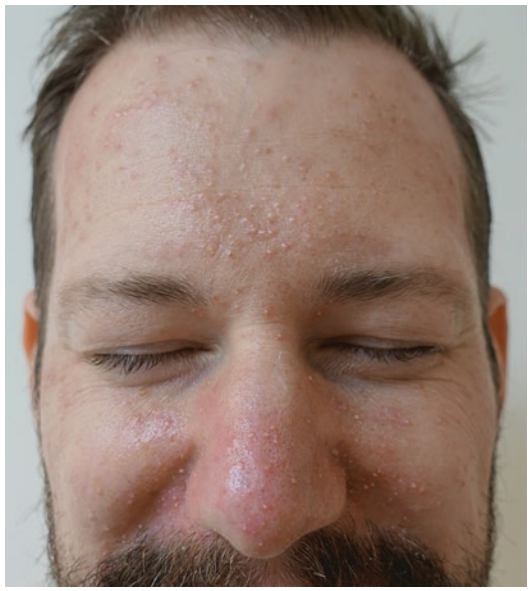

Fig. 8.9 Tiny monomorphic papules and pustules secondary to MEK inhibition

dAEs, patients treated with BRAF/MEK combination therapy have few skin side effects.

While often described as similar to EGFRi toxicities, dAEs seen with MEKi have some morphologic distinctions. Eruptions include an inflammatory papulopustular morphology favoring the scalp, face, chest, and back (52–93% of patients) as well as xerosis, and pruritus [45]. In many patients, the papulopustular eruption differs from that induced by EGFRi in that patients present with tiny, monomorphic follicular papules (Fig. 8.9) and eroded pustules that may extend to the lower trunk and extremities. Additional common AEs from MEKi that can confound the presentation include edema (with resultant erythema and dermatitis), fevers, and photosensitivity.

mTOR Inhibitors

Key Points

- mTOR inhibitors are used increasingly in children, and currently approved for patients with SEGA in the setting of tuberous sclerosis complex.
- Most common adverse effects involve the oral mucosa, manifesting as painful stomatitis and oral ulcers.
- "Rash" is less commonly seen and described as nonspecific in nature.

The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway is critical to cell growth and survival and has been shown to govern normal vascular development and angiogenesis [46]. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, integrates signals from the PI3K/AKT pathway to coordinate proper cell growth and proliferation by regulating ribosomal biogenesis and protein synthesis [47]. Everolimus is similar to sirolimus in that it is an effective antiproliferative and immunosuppressive agent, developed to improve upon the pharmacokinetics of sirolimus [48]. Tuberous sclerosis and lymphangio leiomyomatosis are caused by inactivating mutations in the tuberous sclerosis complex tumor-suppressor proteins TSC1 and TSC2,

leading to increased activation of mTOR [49]. Disorders that lead to inappropriate activation of the PI3K/AKT/mTOR pathway have also been shown to result in tissue overgrowth in association with vascular anomalies. Sirolimus is now approved in children with tuberous sclerosis complex, and increasingly studied in patients with vascular anomalies such as kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon and lymphatic malformations [50]. As mTOR inhibitors (mTORi) have significant antitumor activity, they are increasingly being studied in pediatric cancers, including rhabdomyosarcoma, osteosarcoma, medulloblastoma, and neuroblastoma, alone and in combination with chemotherapy.

Dermatologic AEs seen in pediatric patients treated with mTORi usually consist of a macular or papular exanthema, or papulopustular eruption thought to be due to the inhibition of PI3K-AKT-mTOR signaling, which is one of the downstream effector pathways of the EGFR [51]. However, the most common AEs involve the oral mucosa, with painful stomatitis causing significant QOL impairment in adults and children. A phase 3 trial of everolimus in children with SEGA in the setting of tuberous sclerosis found that most AEs were grade 1 and 2, with mouth ulcers (32%) and stomatitis (31%) being the most frequently reported [52]. Rash was reported in 12% of patients, and one patient developed zoster during treatment. A trial studying the safety of everolimus in patients under 3 years of age found a similar AE profile, with the most common adverse effect being stomatitis (66.7%) [53]. Temsirolimus is a potent and highly specific inhibitor of mTOR, the ester form of sirolimus, and was the first mTORi approved by the US Food and Drug Administration for use in oncology in advanced renal cell carcinoma in the adult population. A study in pediatric patients with recurrent and refractory solid tumors showed similar AEs, including rash (32%) and mucositis (32%) [54]. Cutaneous AEs from PI3K isoform inhibitors are poorly described to date, but have been observed to include eczematous, psoriasiform, and pityriasiform eruptions.

Tyrosine Kinase Inhibitors

Key Points

- TKIs that target BCR-ABL and c-kit such as imatinib have been approved in children with leukemias (CML/ALL).
- Edema, mainly periorbital, is a distinct and specific side effect of imatinib.
- A dose-dependent papular rash can also occur, and is generally follicular or finely keratotic in nature. Reversible pigmentary changes have also been reported in 33–41% of patients.

The development of BCR-ABL/KIT TKIs has greatly improved the outcome of patients with CML and gastrointestinal stromal tumors. Imatinib was the first molecule developed to inhibit the tyrosine kinase BCR-ABL; it also inhibits c-kit and PDGFRs. Because it acts on multiple targets, this class of drug is used and studied in other malignancies [55, 56]. Cutaneous AEs have been reported to occur in 7–88.9% of patients taking imatinib [56, 57]. Edema, mainly periorbital, is a distinct and specific side effect. It can also occur in the extremities and occasionally as central fluid retention. It has been speculated that inhibition of PDGFR leads to an increase in dermal interstitial fluid, as it has a central role in regulating interstitial fluid homeostasis [56]. A dose-dependent papular rash can also occur that is generally follicular or finely keratotic in nature. Reversible pigmentary changes manifesting as localized, patchy, or diffuse hypopigmentation and depigmentation have been reported in 33–41% of patients [58, 59]. These changes are caused by the inhibition of c-kit, which regulates melanocyte development, migration, and survival. Interestingly, hyperpigmentation has been reported in 3.6% of patients, usually occurring in hair, nails, and oral mucosa [57]. Dyspigmentation has been less commonly noted in pediatric patients (13%) [3].

Other uncommon reactions include urticarial, lichenoid, pityriasiform, and psoriasiform eruptions, Stevens-Johnson syndrome, acute and generalized exanthematous pustulosis, Sweet's syndrome, neutrophilic eccrine hidradenitis, and neutrophilic panniculitis. Rarely reported effects include mycosis fungoides-like reactions, follicular mucinosis, Epstein-Barr virus positive B cell lymphoproliferative tumors, hyaline cell syringoma, malpighian epithelioma, porphyria cutanea tarda, and pseudoporphyria [56].

Fewer cutaneous AEs have been reported with second-generation BCR-ABL- and c-kit-inhibiting TKIs, such as nilotinib and dasatinib. These agents were developed to treat resistant CML with acquired BCR-ABL mutations. Dasatinib was initially associated with 15% risk of dAEs in clinical trials [60]. Follow-up reviews report dAEs in up to 35% of treated patients [56]. Skin reactions that commonly occur include pruritus, acneiform papules, xerosis, hyperhidrosis, urticaria, and eczematous dermatitis. Other rare side effects that have been reported are pigmentary changes, skin ulcers, bullous disorders, photosensitivity, nail changes, acute febrile neutrophilic dermatosis, panniculitis, and hand-foot skin reaction (Fig. 8.10) [56]. Rates vary for nilotinib with dAEs affecting between 10 and 28% of patients [56, 61]. The reported cutaneous AEs include xerosis and pruritus. Other less frequent reactions include scalp alopecia, body hair loss, and bullous Sweet's syndrome. Third-generation inhibitors in this class have been reported to induce similar follicular, xerotic, and pityriasiform eruptions [62].

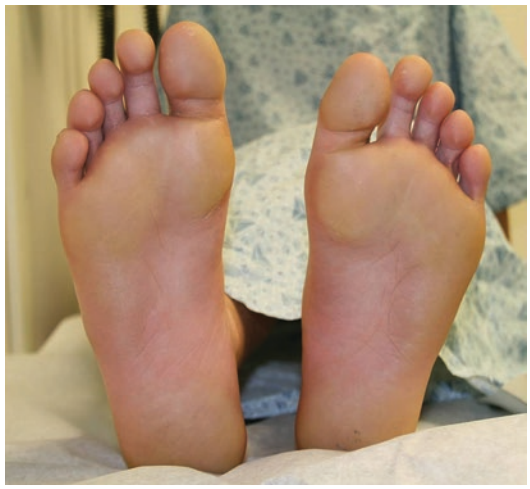

Fig. 8.10 Hand-foot skin reaction secondary to dasatinib

Antiangiogenesis Agents

Key Points

- The most common adverse effects of vascular endothelial growth factor receptor (VEGFR) inhibitors are mucosal bleeding, stomatitis, thromboembolism, and disturbed wound healing. Oral mucositis and rash are the main dAEs reported in children.
- Multikinase inhibitors, such as sorafenib and sunitinib, inhibit angiogenesis and proliferation via VEGFR and PDGFR. Hand-foot skin reaction and stomatitis are the most frequently encountered side effects.

The physiologic process of angiogenesis is tightly regulated at the molecular level and depends on a balance between growth-promoting and -inhibiting factors. Angiogenesis is dysregulated in many pathological conditions including cancer; tumor growth and metastatic potential is highly dependent on competing factors [63]. Vascular endothelial growth factor (VEGF) is a major driver of tumor angiogenesis and is therefore the target of many angiogenesis inhibitors. Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF. By binding to VEGF, bevacizumab leads to a decrease in endothelial cells and the quantity of microcapillaries in tumor tissue. It can also reduce vascular permeability, and thus inhibit tumor progression or migration [64]. It has been approved in adults for the treatment of advanced non-small-cell lung, breast, colorectal, and renal cell carcinoma.

In comparison to other targeted anticancer therapies, bevacizumab causes less frequent and less severe dAEs. VEGFR inhibitors (VEGFRi) are most commonly used in combination with other systemic agents; therefore assessments of dAEs specifically attributable to this class are limited. The most well-documented AEs include mucosal bleeding and hemorrhage, stomatitis, thromboembolism, and disturbed wound healing [65]. As expected given the importance of neovascularization in wound healing, studies have identified treatment with bevacizumab proximate to the time of surgery as leading to a significant risk of postoperative wound healing complications [66]. A few cases of ulcerated striae have also been reported in patients receiving both bevacizumab and corticosteroids [67].

In pediatric patients, oral mucositis has been reported in more than 10% of patients treated with VEGFRi [68]. Rash has also been reported in 46% of treated patients, described as mild and papular [69]. A phase 1 trial of bevacizumab in pediatric patients with refractory solid tumors reported non-dose-limiting grade 1–2 cutaneous toxicities manifesting as rash in 3/19 patients and mucositis in 2/19 patients [68]. No thromboses or hemorrhages were reported.

Sorafenib, sunitinib, and regorafenib are multikinase inhibitors (MKIs) that target VEGFR and PDGFR, among other kinases [70]. They are used and studied alone and in combination across multiple malignancies. Cutaneous reactions are common in adults, occurring in up to 74% of patients taking sorafenib and 81% taking sunitinib [71]. Hand-foot skin reaction (HFSR) and stomatitis are the most frequently encountered side effects (Fig. 8.11). HFSR presents as painful

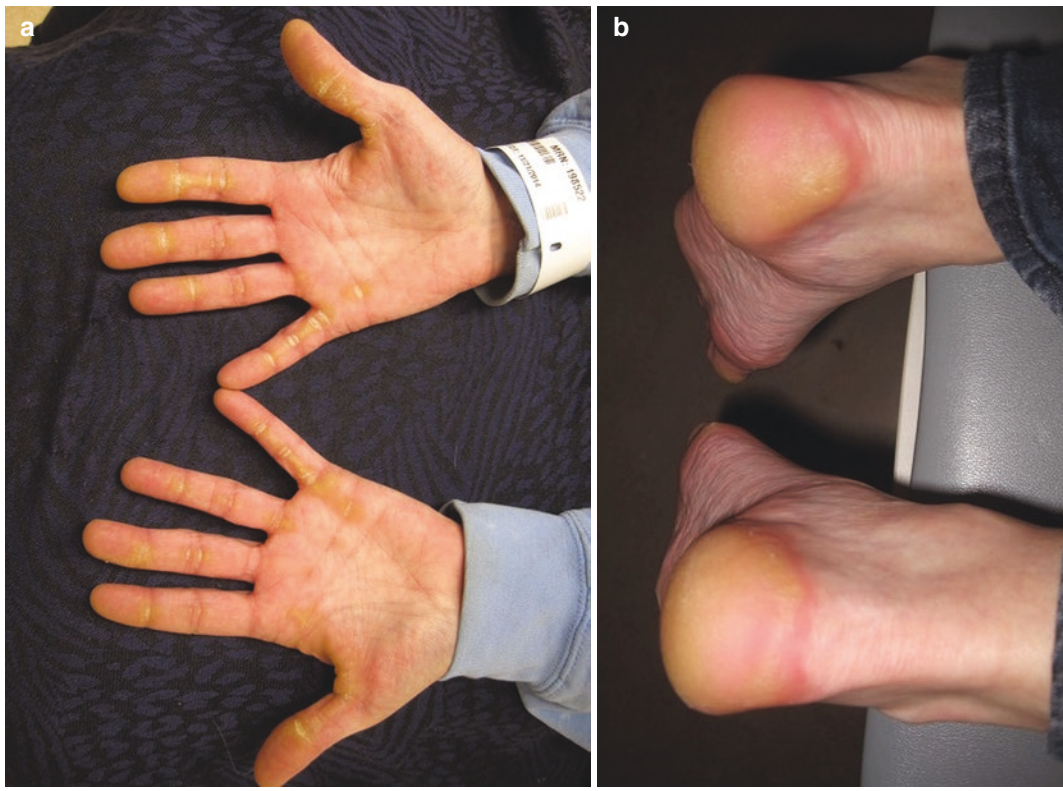

Fig. 8.11 (**a**) Hand-foot skin reaction secondary to multikinase inhibition. (**b**) Hand-foot skin reaction with evident inflammation at the border of the callosities on the heels from multikinase inhibition

localized inflamed callosities that develop on friction and trauma-prone areas, such as the heel, lateral aspects of the soles, beneath the metatarsal heads, and in web spaces. This toxicity first appears after 2–4 weeks of treatment in 10–62% of patients, is often dose limiting, and has a profound impact on QOL [72].

Similar to adults, children with solid tumors and leukemias treated with MKIs as monotherapy also experienced rash, and to a lesser extent HFSR. However when used in combination with other agents, these children experienced grade 2 and 3 HFSR and rashes with much greater incidence (8/12 children with leukemia, 5/19 children with solid tumors) [73]. Patients initiating MKIs are advised to avoid activities involving prolonged heat and friction and to use preventive measures when these are unavoidable. Examples include wearing well-fitting shoes and lubricating the feet with an ointment prior to prolonged walking. In addition, prophylactic urea-based keratolytics can help reduce painful callous formation and topical steroids and nonsteroidal drugs can help when inflammation develops. Local wound care is necessary if bullae or skin breakdown occurs, and dose reduction may be required.

After HFSR, stomatitis is the second most common cutaneous side effect from this drug class (26–36%) and can generally be managed with oral hygiene and use of topical steroids and anesthetics [74]. Other dAEs include alopecia, which may occur 2–28 weeks after the onset of therapy, and manifests as hair loss with eventual hair regrowth. With sorafenib, regrowth is often brittle and curly, while sunitinib induces reversible depigmentation in some patients [70, 75]. Seborrheic dermatitis-like facial erythema has been noted in 63% of patients on sorafenib, and to a lesser extent sunitinib [70, 71]. Scalp dysesthesia has also been observed in half of patients, with spontaneous resolution upon discontinuation of treatment [76]. Subungual splinter hemorrhages develop in more than half of patients on sorafenib. Other cutaneous reactions include yellow skin pigmentation, SCCs, and inflammation of preexisting actinic keratoses, generalized keratosis pilaris-like eruption (21%), body alopecia (19%), nipple hyperkeratosis or pain (19%), and epidermal inclusion cysts (5%) [70, 71, 76]. There have also been single reports of an erythema multiforme-like eruption [77], ultraviolet radiation recall [78], and localized dyskeratotic plaque with milia [79]. Single cases of benign eruptive melanocytic nevi [80] and drug-induced lentigines [70, 71] have been reported secondary to sorafenib and may be related to its inhibition of BRAF.

Summary

Targeted anticancer therapies are now part of the therapeutic arsenal for pediatric oncologic care and are being studied at increasing frequencies across malignancies. The effect of these novel agents on developmental pathways in the tissues and organs of growing children remains unknown. To date, cutaneous AEs seem to mirror those of the adult population; however nuances are likely to emerge as the numbers of patients treated increases. Classification of dAEs beyond "rash" will be required to better understand the targets and population-specific side effects. A better understanding of the pathogenesis, classification, management, and prognostic significance of these toxicities is imperative. Dermatologists can have a significant impact on the care of these patients by recognizing and managing cutaneous reactions, thereby improving patient QOL and allowing for continuation of potentially lifesaving anticancer regimens whenever possible.

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Pediatric Graft-Versus-Host Disease

9

Valerie Carlberg[$], Emily Simons[$], Sophia Delano, and Jennifer T. Huang

Introduction to GVHD

Graft-versus-host disease (GVHD) is an important cause of morbidity and mortality in children receiving hematopoietic stem cell transplantation (HSCT). While children are less likely to develop GVHD than adults, recognizing the pathophysiology, incidence, clinical features, classification, and treatment of acute and chronic variants of this condition is key to optimizing the management of cutaneous and extracutaneous sequelae. Further understanding of pediatric GVHD is needed to improve outcomes for pediatric HSCT recipients.

Pathophysiology and Risk Factors for GVHD

Key Points

- Acute GVHD is an alloimmune reaction in which donor T cells become activated against host antigens and pro-inflammatory cytokines are released, resulting in damage to host tissues [1, 2].
- Chronic GVHD is characterized by non-specific and persistent inflammation, loss of immune tolerance, and aberrant tissue repair leading to fibrosis and irreversible damage.
- The degree of HLA mismatch between donor and recipient is the most significant risk factor for both acute and chronic GVHD.

Understanding the pathophysiology of and risk factors for acute and chronic GVHD is the first step in preventing, diagnosing, and treating these adverse sequelae.

As the name implies, acute GVHD is characterized by an immune reaction in which transplanted donor T cells (the graft) recognize the patient receiving the transplant (the host) as foreign and mount a response against the patient. In 1966, Billingham proposed three requirements for the development of GVHD: histocompatibility

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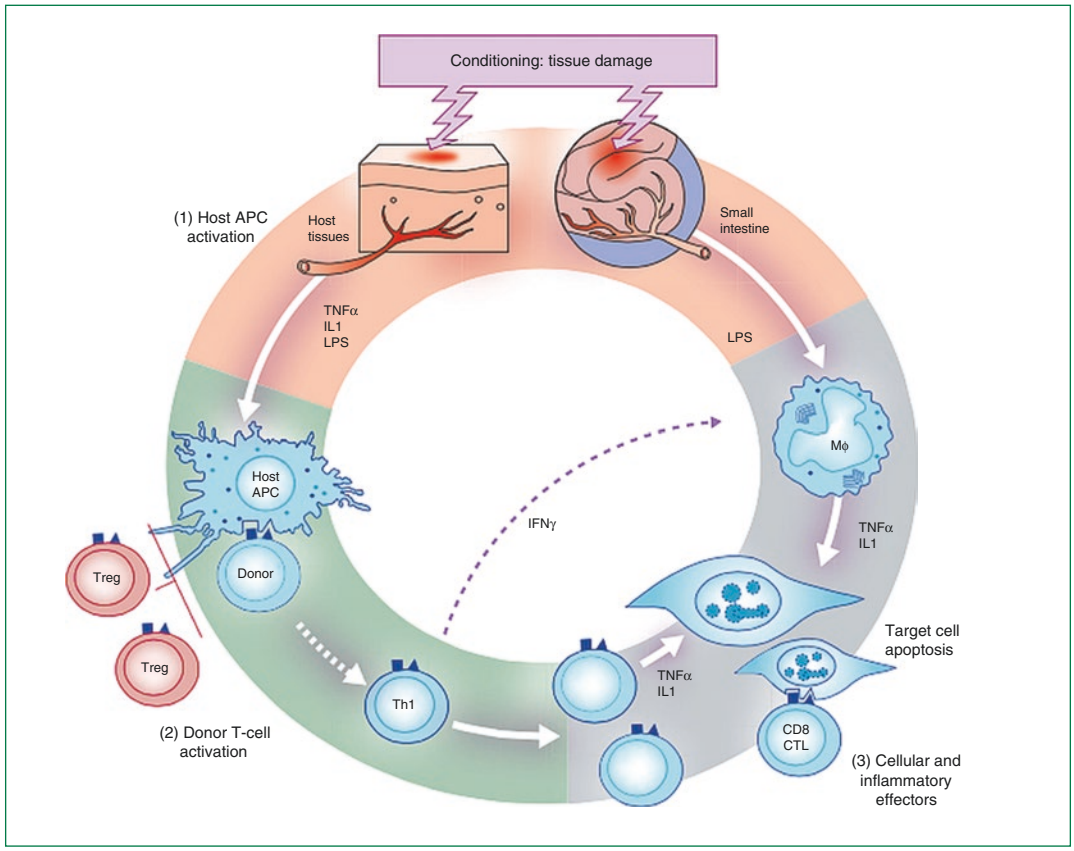
differences between donor and recipient, the presence of immunocompetent cells in the graft, and the inability of the host to mount an effective immunologic reaction against the graft [3]. Additional studies led to our current understanding of a three-phase model for acute GVHD as illustrated by Ferrara et al. (Fig. 9.1) [2]. In the first phase, pretransplant damage (from chemotherapy, radiation, infection, etc.) to recipient tissues results in activation of local dendritic cells and release of cytokines, yielding a proinflammatory state. In the second phase, donor T cells proliferate in response to the cytokine storm. Additionally, these donor T cells become activated by circulating host dendritic cells. In the third and final stage, the activated donor T cells proliferate into cytotoxic T cells that target the originally inflamed host tissues and further propagate tissue damage [1, 4]. The host gastrointestinal system is particularly important in the development of acute GVHD, given its vulnerability to trauma from conditioning treatments, infection, and additional external stimuli as well as the high concentration of dendritic cells and increased antigenicity of the gut [1].

While the pathophysiology of chronic GVHD is not fully understood, the diversity of clinical phenotypes and the discovery of autoantibodies and genetic polymorphisms similar to patients with classic autoimmune disorders suggest a



Pathophysiology of acute GVHD
IL 1=interleukin 1. IFN γ=interferon γ. LPS=lipopolysaccharide. Treg=regulatory T cell. Th1=T-helper 1 cell. CTL=cytotoxic T lymphocyte.

Fig. 9.1 Pathophysiology of acute GVHD. *IL 1* interleukin 1, *IFN γ* interferon γ, *LPS* lipopolysaccharide, *Treg* regulatory T cell, *Th1* T-helper cell, *CTL* cytotoxic T lymphocyte [2]. Reprinted from The Lancet, Vol. 373, number 9674, Ferrara JLM, Levine JE, Reddy P, Holler E, Graft-versus-host disease, pages 1550–1561, © 2009, with permission from Elsevier

more complex immune reaction than that seen in acute GVHD [4]. Chronic GVHD typically follows acute GVHD, yet it may also occur de novo. In the Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease, Cooke et al. propose another three-phase model [5]. Similar to acute GVHD, the first phase is characterized by tissue injury, inflammation, and activation of donor T cells. The second phase involves diffuse, nonspecific inflammation as donor T cells migrate through inflamed, leaky vasculature and lymphatics. Activation of the adaptive immune system also takes place; however, maturation of T cells in a dysfunctional thymus—one that is aging or has been damaged by conditioning or acute GVHD rendering it incapable of negative selection—leads to loss of central tolerance. Peripheral tolerance is also diminished due to an imbalance between regulatory T cells (Tregs) and alloreactive T cells. In the final phase, aberrant tissue repair and fibrosis may occur, leading to irreversible organ damage [5].

Overall, risk profiles for acute and chronic GVHD are similar [6]. GVHD occurs most commonly after allogeneic HSCT, due to inherent HLA disparity between the recipient and donor. Though less common, GVHD may also arise following autologous HSCT (the recipient and donor are the same patient) [7] and also after solid-organ transplant (most commonly in small bowel or liver transplantation) [8–11]. GVHD following autologous HSCT is hypothesized to result from sensitization of the harvested cells during processing and storage prior to reintroduction to the patient. In solid-organ transplant, co-transplantation of alloreactive immune cells residing in the donor tissues initiates the GVHD cascade [9]. In allogeneic HSCT and solid-organ transplants, the most significant risk factor is HLA mismatch between donor and recipient. Risk for GVHD may be higher with HLA mismatch at the HLA-A or -B locus. It is also important to note that acute GVHD increases the risk of chronic GVHD by 11-fold [12]. Additional clinical, genetic, and biomarker-based risk factors are listed in Table 9.1 [13–22].

Table 9.1 Risk factors for acute and chronic GVHD

Host variables
• Recipient age <1 or >10 years [13, 19]
• Malignancy as indication for transplant, as well as features of more advanced disease (WBC >50 × 10^9/L and cytogenetic abnormalities t(4;11), t(9;22), and hypodiploidy) [13–16, 22]
• Prior damage to gut (viral illness, prolonged fasting, chemotherapy) [15]
Donor or graft variables
• HLA mismatch [14]
• Unrelated donor [14]
• ABO blood group mismatch [14]
• Older donor age (>8) [17–19]
• Female multiparous donor to male recipient [17, 19, 22]
• Graft source: allogenic HSCT (PBSC > BM > UCB) > autologous HSCT > solid organ transplant [19, 21, 22]
• Graft with high CD34+ cell dose or low regulatory T-cell content [15]
Other variables
• Conditioning with total body irradiation [14–16, 19, 22]
• Single-agent GVHD prophylaxis [15, 18]
• Genetic polymorphisms within genes encoding for innate immunity, or inflammatory/immunoregulatory proteins in either donor or host [15]
• Prior acute GVHD (increases the risk for chronic GVHD) [20]

BM bone marrow, *GVHD* graft-versus-host disease, *HLA* human leukocyte antigen, *PBSC* peripheral blood stem cell, *UCB* unrelated cord blood, *WBC* white blood cell

Incidence of GVHD

Key Points

- The lowest rates of acute and chronic GVHD are among recipients of HSCT from related donors and from umbilical cord donors.
- The incidence of acute and chronic GVHD in children is approximately half that of adults.

In the United States, over 1500 allogeneic HSCTs are reported annually in patients less than 20 years old [23]. The incidence of GVHD within this population ranges widely depending on risk factors, most notably HLA compatibility and stem cell

graft source (e.g., bone marrow, peripheral blood, or umbilical cord blood). About two-thirds of allogeneic HSCT in children are from unrelated donors and the majority of children receive HSCT derived from the bone marrow or cord blood [23].

In those receiving unrelated donor HSCT, Grade II–IV acute GVHD has been reported in 40% of cord blood and 85% of bone marrow HSCT [12, 16, 21, 24]. There is greater immune tolerance, and thus lower incidence of acute GVHD, associated with cord blood HSCT compared to bone marrow HSCT for similar levels of HLA mismatch. In those receiving related donor HSCT, the incidence of grade II–IV acute GVHD is significantly lower, reported in about 25% of those receiving grafts from HLA-identical siblings, with equivalent rates between bone marrow and peripheral blood cell sources [21].

The incidence of chronic GVHD varies by these same factors. Chronic GVHD has been reported in as few as 6% of recipients of sibling-related umbilical cord blood HSCT and up to 65% of recipients of mismatched peripheral blood stem cell HSCT [19, 25–27]. The onset of chronic GVHD in relation to acute GVHD is progressive in 30–40%, quiescent (e.g., acute GVHD occurred but resolved prior to chronic GVHD onset) in 30–40%, and de novo in 20–30% [28].

In general, the incidence of GVHD in children is about one-half that of adult populations [20, 29, 30]. Decreased incidence may be attributed to more frequent use of cord blood as a stem cell source in children, nonmalignant indications for HSCT, limited history of prior infections, and overall improved state of health in children [14].

Clinical Features of GVHD

Key Points

- Acute GVHD most often occurs within months after HSCT, but may occur at any point and can overlap with chronic GVHD.
- Acute GVHD primarily involves the skin, liver, and gastrointestinal tract.
- Chronic GVHD may have more diffuse, often irreversible, organ involvement.

Although acute GVHD most often occurs within 1–2 months after HSCT [2, 16], the diagnosis can be made at any point after HSCT. Because time-based criteria are currently less emphasized, there is a greater emphasis on clinical features in making the diagnosis of acute GVHD [2, 6, 13].

Acute GVHD most commonly targets the skin, liver, and gastrointestinal tract [4, 31]. The skin is the most frequently affected organ and is often the first involved [2]. The classic rash is pruritic, may be painful, and is characterized by erythematous macules and papules coalescing on the trunk and extremities (often sparing the scalp), resembling the morbilliform rash of measles (Fig. 9.2). Acral involvement is common (Fig. 9.3). In severe GVHD, bullae and desquamation may develop, and with extensive involvement may resemble toxic epidermal necrolysis (Fig. 9.4). Gastrointestinal symptoms include nausea, vomiting, anorexia, abdominal pain, and diarrhea [2].

Children tend to develop symptoms of chronic GVHD at a median of 6 months after HSCT [30]. About 40% of these patients manifest extensive disease; the remainder experience limited involvement of the skin, liver, or both [19]. Again, the skin is the most commonly affected organ, with cutaneous features in 65–80% of children with chronic GVHD, followed by oral lesions in half, liver disease in a third, and gastrointestinal

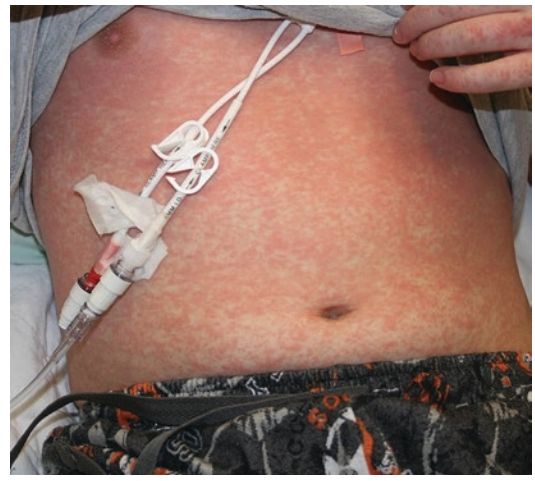


Fig. 9.2 Acute GVHD presenting as a morbilliform skin eruption

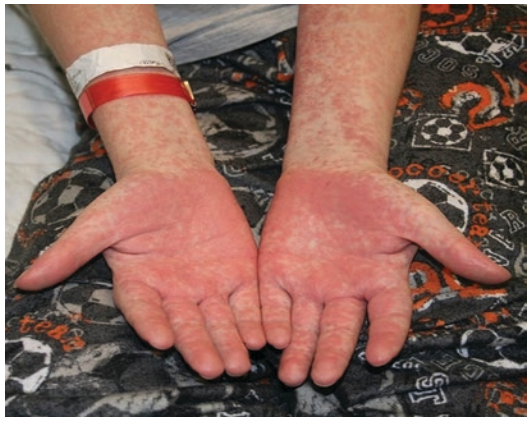


Fig. 9.3 Acral involvement in acute GVHD

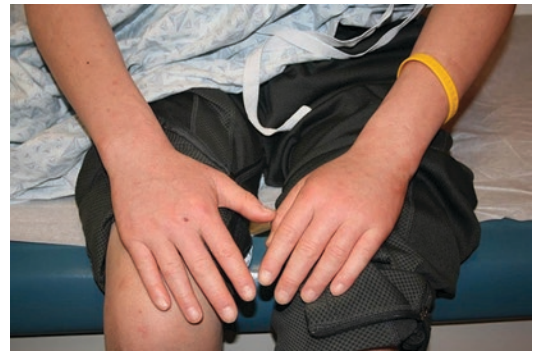


Fig. 9.5 Acral edema as an early sign of sclerotic chronic GVHD

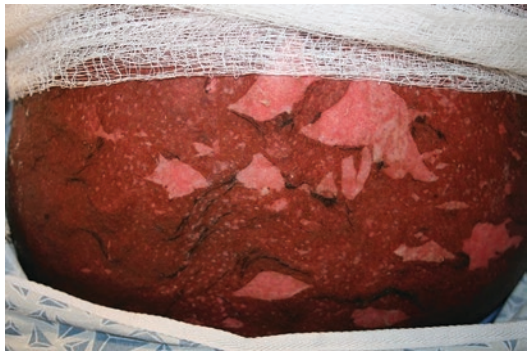


Fig. 9.4 Toxic epidermal necrolysis-like acute GVHD

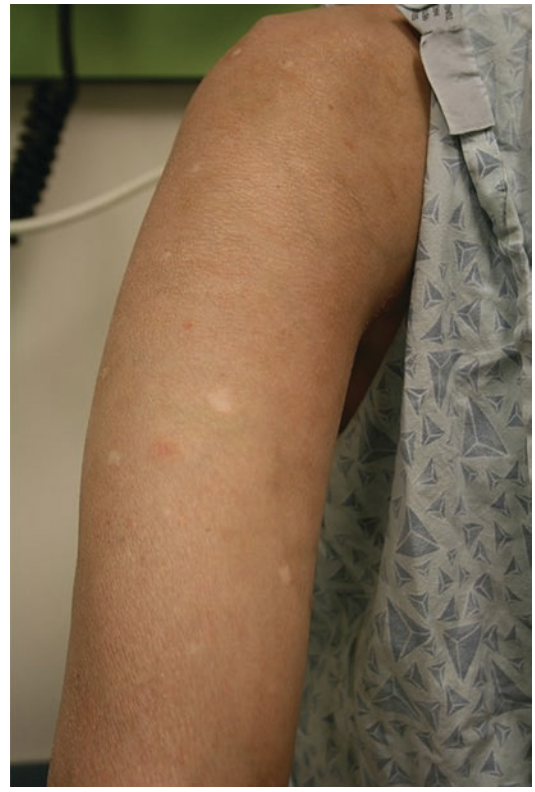


Fig. 9.6 Dyspigmentation (both hyperpigmentation and hypopigmentation) in a child with chronic GVHD

involvement in 25–60% [19, 32]. Involvement of the lungs, eyes, and/or musculoskeletal system is not uncommon [6, 19, 33].

Cutaneous chronic GVHD (particularly sclerotic forms) is often preceded by peripheral edema in children (Fig. 9.5) [34]. Chronic GVHD has a propensity to affect the mouth, nails, and areas of friction such as the waistband, while the face and digits are rarely involved. Affected limbs can become bound-down and restricted in width. Dyspigmentation is almost universal and vitiligo is a known, but less common, presentation (Fig. 9.6) [30, 34]. The depth of sclerotic disease ranges from superficial lichen sclerosus-like lesions to dermal fibrosis and myofascial involvement (Figs. 9.7 and 9.8) [34]. Of note, fasciitis and myositis can arise independent of skin involvement and predispose to permanent contractures [6]. Eczematous and ichthyosiform features can be found in sclerotic and nonsclerotic disease and may be more common in children than adults (Fig. 9.9) [34]. The reported incidence of lichenoid lesions varies widely; they may be more common in steroid-refractory

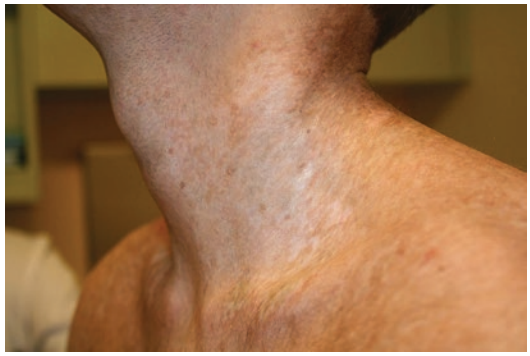


Fig. 9.7 Morpheaform sclerotic chronic GVHD

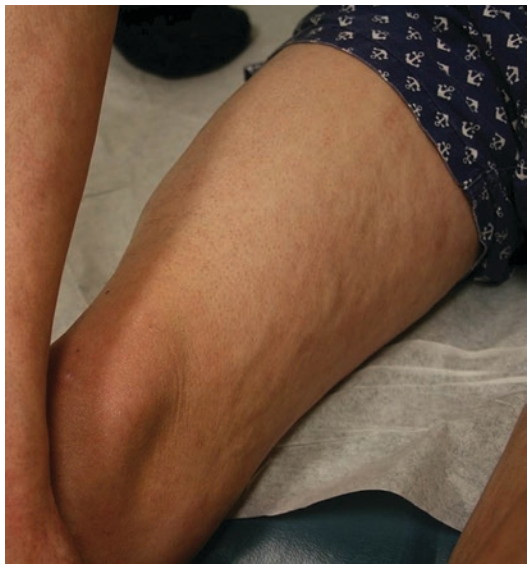


Fig. 9.8 Sclerotic chronic GVHD with myofascial involvement

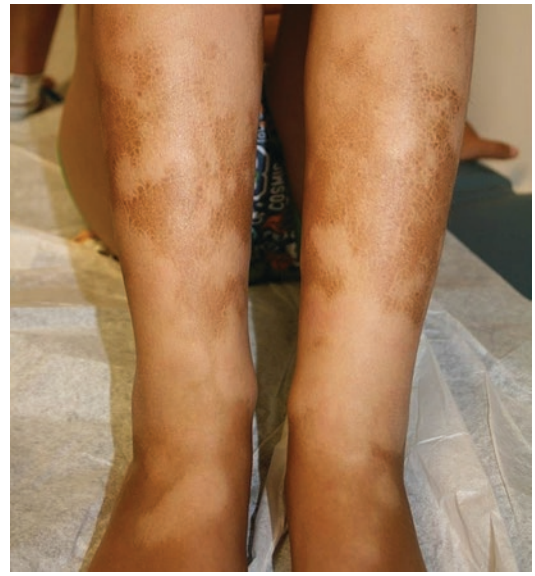


Fig. 9.9 Eczematous or ichthyosiform presentation of chronic GVHD

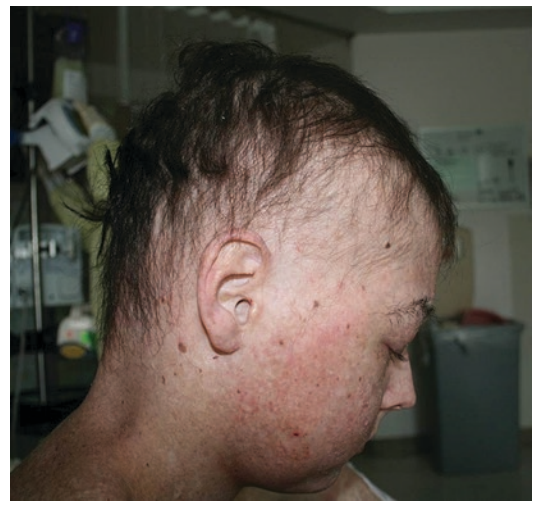


Fig. 9.10 Alopecia is common in children with chronic GVHD

chronic GVHD [33–35]. It is important to recognize that multiple morphologies may be present in an individual patient, and thus a thorough skin examination is imperative.

Mucosal, hair, and nail findings may also be appreciated during dermatologic examination. The eyes may be less commonly affected by chronic GVHD in children than other organs, though one study reports involvement in 50% of patients [19, 33]. In these patients, lacrimal dysfunction leads to conjunctivitis [5, 6]. Oral lesions may be erythematous, reticular, or ulcerative; they are infrequently painful, leading to underreporting [32]. Involvement of the oral mucosa often corresponds to genital findings including lichen planus-like features, lichen sclerosus-like features, clitoral and vaginal scarring in females, and phimosis and urethral stricture in males [6]. Focal or diffuse alopecia may occur in up to 50% of children and can be scarring or nonscarring (Fig. 9.10) [30]. Nails are affected in up to 45% of children, with

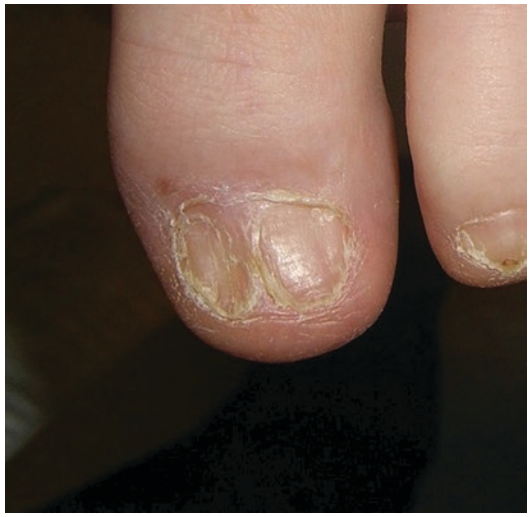


Fig. 9.11 Pterygium nail deformity may be a harbinger of severe lung involvement in children with chronic GVHD

periungual erythema and/or dystrophy [30, 34]. Pterygium inversum unguis, in which the distal nail bed adheres to the nail plate, is common in severe chronic GVHD and is associated with a higher risk of lung involvement in children (Fig. 9.11) [34].

Though outside of the spectrum of dermatologic care, physicians should be aware of other organ systems involved in chronic GVHD. Chronic pulmonary inflammation can lead to bronchiolitis obliterans syndrome [6]. Multifactorial gastrointestinal changes (e.g., scarring, altered motility) can result in decreased intake, poor absorption, and failure to thrive. As in acute GVHD, nonspecific hyperbilirubinemia and transaminitis may also manifest in chronic GVHD [6].

Differential Diagnosis for GVHD

Given the comorbidities of patients at risk for GVHD and the various morphologies of GVHD in its acute and chronic forms, the differential diagnosis for GVHD is broad and includes infectious and inflammatory etiologies.

Bacterial and viral exanthems occur more commonly in children, and solid-organ transplant and HSCT recipients are at increased risk for HHV6 and HHV7 reactivation [36], making infectious etiologies important to consider in patients with acute GVHD. Signs and symptoms of infection typically accompany the classic childhood exanthems and the distribution and evolution of the rash may be helpful in differentiating these from acute GVHD. The viral exanthem of HHV6 is characterized by erythematous macules and papules surrounded by white halos, which begin on the trunk and spread to neck and proximal extremities [36]. It is accompanied by high fever (101–106 °F) and resolves over several days. Atopic dermatitis and allergic contact dermatitis may present with similar pruritic, papular eruptions, though typically without associated systemic signs and symptoms.

Engraftment syndrome is an early complication of HSCT, occurring within 96 h of granulocyte recovery (absolute neutrophil count of ≥500μL for 2 consecutive days) and characterized by fever >38.3 °C without source of infection, rash >25% body surface area (BSA) that is not attributable to medication, weight gain of ≥2.5% of baseline and albumin drop to 90% of pretransplant levels, and non-cardiogenic pulmonary edema [37, 38]. Additional features such as hepatic dysfunction with total bilirubin ≥2 mg/dL or transaminase ≥2 times normal, renal insufficiency with serum creatinine ≥2 times baseline, and transient idiopathic encephalopathy have also been described in adults, though these are less common in children [38]. Given that granulocyte recovery typically takes place 8–27 days following HSCT [39], it can be difficult to distinguish engraftment syndrome from hyperacute GVHD if distinguishing features are not present.

Clinical features of acute GVHD may mimic the range of drug reactions, including morbilliform drug eruptions, drug reaction with eosinophilia and systemic symptoms, radiation-recall dermatitis, toxic erythema of chemotherapy (TEC), and Stevens-Johnson syndrome/toxic epidermal necrolysis [4, 14]. TEC is a spectrum of cutaneous reactions to chemotherapeutic agents most commonly presenting with erythema and tenderness of the palms, soles, and flexural regions including the axillae and groin [40]. There may be an increased incidence of TEC

with conditioning regimens including busulfan and fludarabine, with a median onset of 22 days after dose administration [41]. See Chap. 7 for a more detailed discussion of TEC. Drug hypersensitivity reactions to non-chemotherapeutic agents should also be considered, yet they tend to occur more in adults. Drug reactions typically occur between 1 and 14 days of initiating a drug, manifesting as a morbilliform rash on the trunk, which spreads to the extremities, and less commonly involves the face, palms, or soles. Comparatively, GVHD is more likely to have acral and facial involvement, follicular prominence, and concurrent diarrhea and hyperbilirubinemia. Radiation-recall dermatitis should also be considered in the setting of total-body irradiation or prior sunburn followed by methotrexate for GVHD prophylaxis.

Lichenoid papules of chronic GVHD may appear similar to lichen planus or lichenoid drug eruption. Voriconazole-induced phototoxicity may present as a macular erythematous rash suggestive of chronic GVHD (Fig. 9.12) [42]. Morphea, scleroderma, lichen sclerosus, eosinophilic fasciitis, atrophoderma of Pasini and Pierini, discoid lupus erythematosus, and vitiligo are all within the differential for sclerotic or dyspigmented GVHD lesions. Alopecia areata, telogen effluvium, and anagen effluvium may produce hair loss in patients also at risk for GVHD.

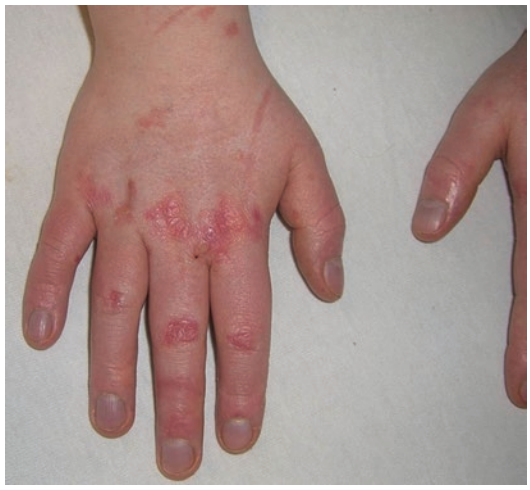


Fig. 9.12 Erythematous, scaly papules in photodistributed locations as a result of voriconazole phototoxicity

Histopathology and Laboratory Evaluation of GVHD

Key Points

- Histopathologic features of acute and chronic GVHD are nonspecific.
- Biopsy may be helpful for children with distinctive but not clinically diagnostic features of chronic GVHD.

Biopsy is often not necessary to diagnose GHVD. Though skin biopsies may confirm a diagnosis of acute GVHD if clinical suspicion is high, the histologic findings are nonspecific and many of the differential diagnoses show similar features. Histologic findings include sparse lymphocytic interface and perivascular inflammation with variable degrees of adnexal extension. Dyskeratosis, spongiosis, lymphocytic exocytosis, and satellitosis may also be present. In addition to lymphocytic infiltration, eosinophils may be noted, making it difficult to distinguish acute GVHD from drug hypersensitivity reaction. In more severe acute GVHD, subepidermal clefting and full-thickness epidermal necrosis may be seen, mimicking toxic epidermal necrolysis [43, 44]. Thus, biopsy can be unhelpful or misleading if wrongly interpreted and clinical observation with close attention to time course, evolution of disease, and response to withdrawal of a potential offending agent is key in making an accurate diagnosis [45–50]. Histopathology of chronic GVHD is only required for diagnosis of chronic GVHD if features are distinctive but not diagnostic [6]. Features of chronic GVHD vary by clinical manifestation, including epidermal orthohyperkeratosis, hypergranulosis, and acanthosis for lichen-planus-like disease; thickening and homogenization of collagen bundles or pandermal sclerosis with overlying interface changes for morphea-like disease; and homogenization

with overlying interface changes for lichen sclerosis-like disease [51].

Additional lab testing is nonspecific for GVHD. Patients with acute GHVD may have hyperbilirubinemia and/or transaminitis [2]. Peripheral eosinophilia has been noted in about half of children with chronic GVHD prior to disease onset [52]. Eosinophilia can be present in patients without chronic GVHD, however, particularly in association with eczema or drug hypersensitivity [35].

Classification of GVHD

Key Points

- Staging of acute GVHD relies on the extent of skin, liver, and gut involvement.
- The global severity score for chronic GVHD includes the evaluation of eight organ systems.
- Proper staging is necessary for prognosis and therapeutic decision making.

Proper classification of acute GVHD is important, as this largely directs therapy. In 1974, Glucksberg devised the original staging system for acute GVHD, which was later modified during the Keystone Conference in 1994 [53]. The Keystone staging attempted to classify acute GVHD based upon the extent of skin, liver, and gut involvement, but the staging of pediatric gut GVHD was not discussed during the Keystone Conference, and stool output varies considerably between children and adults. The current proposal set forth by the University of Michigan and now utilized by the Mount Sinai Acute GVHD International Consortium redefines the Keystone criteria based on volume of diarrhea per kilogram of body weight, rather than absolute volume (Table 9.2) [54]. An additional consideration when staging pediatric acute GVHD is the difference in the distribution of body surface area between adults and children, as children have relatively larger heads and smaller extremities than adults.

Scoring the severity of chronic GVHD is challenging due to the diversity of phenotypes and current lack of biomarkers [6]. Originally proposed in 2005 and revised in 2014, the NIH Consensus Conference outlined organ-specific criteria for diagnosing and scoring the severity of chronic GVHD [6]. The skin, mouth, eyes, gastrointestinal system, liver, lungs, joints, and genitalia are independently evaluated. A global severity score (mild, moderate, or severe) is then assigned [6]. While still complex, this system more accurately describes the burden of disease and may aid our understanding of the pathophysiology of chronic GVHD.

Treatment of GVHD

Key Points

- Immunosuppressive agents are often used for GVHD prophylaxis.
- Topical steroids and/or topical calcineurin inhibitors are recommended for mild skin-limited acute and chronic GVHD, or as adjuvant therapy for more extensive disease.
- Systemic corticosteroids are the first-line treatment for moderate-to-severe (grade II–IV) acute GVHD and extensive cutaneous chronic GVHD; however, many cases are refractory to these agents.
- There is no consensus for treatment of steroid-refractory acute or chronic GVHD.

Because of the difficulty in treating acute GVHD, there is a significant emphasis on prevention. Prophylactic regimens typically consist of one or a combination of the following agents: prednisone, cyclosporine, tacrolimus, sirolimus, methotrexate (MTX), mycophenolate mofetil (MMF), antithymocyte globulin, or alemtuzumab [14].

Table 9.2 Staging and grading of acute GVHD in children [54]

Stage	Skin	Liver (bilirubin)	Upper GI	Lower GI (stool output per day)
0	No GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	<10 mL/kg/day or < 4 episodes/day
1	Rash <25% BSA	2–3 mg/dL	Persistent nausea, vomiting, or anorexia	10–19.9 mL/kg/day or 4–6 episodes/day
2	Rash 25–50% BSA	3.1–6 mg/dL		20–30 mL/kg/day or 7–10 episodes/day
3	Rash >50% BSA	6.1–15 mg/dL		>30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma + bullae	>15 mg/dL		Severe abdominal pain ± ileus or grossly bloody stool (regardless of stool volume)
Grade[a]				
0	None	None	None	None
I	Stages 1–2	None	None	None
II	Stage 3	Stage 1	Stage 1	Stage 1
III	Stage 0–3	Stage 2–3	Stage 0–1	Stages 2–3
IV	Stage 4	Stage 4	Stage 0–1	Stage 4

BSA body surface area, *GI* gastrointestinal

[a]Grade is based on most severe target organ, regardless of presence/absence of other organ involvement

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Once acute GVHD occurs, the prophylactic regimen can be adjusted and additional treatment may be considered, based on the grade of disease. Grade I acute GVHD, which is limited to the skin, usually has a favorable course and can be treated with topical corticosteroids and calcineurin inhibitors or narrow-band ultraviolet B phototherapy (nbUVB). For moderate-to-severe (grade II–IV) acute GVHD, high-dose systemic corticosteroids are employed as the first-line treatment [14, 55–57]. Unfortunately, only about half of patients are responsive to systemic corticosteroids [2, 58]. If there is no response to systemic corticosteroids after 2–7 days, or if there is rapid progression within 48–72 h, second-line therapies should be considered. Treatment agents which have been trialed in children include antithymocyte globulin (ATG), daclizumab, extracorporeal photopheresis (ECP), etanercept, infliximab, mesenchymal stem cells (MSC), MMF, MTX, and pentostatin [58–71]. Additional agents, such as cyclophosphamide and thalidomide, have been discussed in case reports and small case series [72, 73], but their efficacy and safety have yet to be demonstrated in larger studies.

First-line therapy for chronic GVHD in children, based on data from adults, consists of topical immunosuppressive agents (corticosteroids, calcineurin inhibitors) for limited cutaneous chronic GVHD and systemic corticosteroids for extensive cutaneous (>20% BSA or sclerotic features) or visceral involvement in children, which can be used in conjunction with other systemic immunosuppressants and/or topical calcineurin inhibitors [6, 74]. Photoprotection and topical moisturizers are also important aspects of care. Limited data is available on treatment practices, such as duration of therapy and frequency of first-line versus other agents, among pediatric patients.

There is no consensus of treatment for steroid-refractory chronic GVHD. A wide range of therapies have been investigated for chronic GVHD in children with cutaneous features, including ECP,

nbUVB, imatinib, pentostatin, MMF, thalidomide, and hydroxychloroquine. Unfortunately, these treatments have demonstrated inconsistent or inconclusive outcomes [33, 35, 75–83]. ECP may be promising, with over half of patients experiencing improvement in cutaneous features in a retrospective study [62, 63]. However, ECP units are designed for adult blood volumes, resulting in higher risk for fluid and electrolyte complications in children. Long-term central access and long duration of ECP sessions can also be difficult for small children [75].

Outcomes of GVHD

Key Points

- GVHD correlates with increased engraftment and graft-versus-tumor effect, but is associated with increased mortality in pediatric HSCT recipients.
- Mortality from acute GVHD ranges from <10% for mild disease to slightly >50% for severe disease.
- Children can experience numerous long-term sequelae of GVHD due to persistent skin and fascial involvement.

GVHD is the most common cause of non-relapse mortality in HSCT recipients. While presence of acute GVHD correlates with increased engraftment and graft-versus-tumor effect, it is associated with increased mortality in pediatric HSCT recipients, particularly in those with steroid-refractory disease [12]. Mortality from acute GVHD ranges from 8% for mild acute GVHD to 55% for severe acute GVHD, and is usually due to infection, hepatic failure, or malnutrition [15, 36, 84]. No therapies have been shown to decrease mortality or prevent progression to chronic GVHD [15].

Chronic GVHD may follow acute GVHD or may occur independently. As in acute GVHD, chronic GVHD has also been shown to be protective against relapse, with the strongest protective effect observed in acute lymphoblastic leukemia [19, 21, 85]. However, severe chronic GHVD is associated with a lower chance of remission compared to mild or moderate disease (20% versus 65% remission by 10–15 years after HSCT, respectively), as well as longer disease course and lower likelihood of responding to systemic corticosteroids [85]. In at least one cohort, 70% of survivors had resolution of chronic GVHD at a median duration of 5 months with treatment [19]. Other studies show that chronic GVHD is associated with an overall 5-year mortality rate of 30–50%, with higher mortality for severe compared to mild or moderate chronic GVHD [19, 85, 86]. Causes of death in patients with chronic GVHD are most often HSCT related (typically infection), but they also include respiratory failure directly attributable to GVHD and/or relapse.

Long-term sequelae of GVHD include lower Karnofsky performance scores due to persisting skin, eye, and fascial involvement, as well as generalized sicca, mucositis, malabsorption, and generalized wasting [29, 85]. Many children will have other coexisting long-term sequelae associated with HSCT, such as osteopenia, hypothyroidism, cataracts, hypogonadism, growth hormone deficiency, chronic renal insufficiency, academic difficulty, and attention-deficit hyperactivity disorder (ADHD) [87].

Summary

GVHD contributes significantly to the morbidity and mortality associated with HSCT in children. However, much existing research on GVHD has focused on adult patients. Compared to adults, children may present with unique considerations when managing this condition. Given the great strides that have been made in treating childhood malignancies, immunodeficiencies, and other conditions with HSCT, future research is greatly needed to improve our care of GVHD in pediatric HSCT recipients in order to improve outcomes in this special population.

Acknowledgment Photographs are courtesy of Jennifer T. Huang, M.D.

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Opportunistic Skin Infections in Immunosuppressed Children

10

James Treat and Elizabeth Heller

Introduction

Immunosuppressed children are at high risk of infection. There are many described primary immunodeficiencies involving production and signaling of the various parts of the immune system. Anti-inflammatory and antineoplastic medications function by inhibiting components of the immune system and thus can cause secondary immunodeficiency. Neonates who are extremely premature should also be considered immunosuppressed, because their immune systems are not fully functional [1]. Infections that do not typically present in the absence of an immunodeficiency or that present differently in immunodeficient patients are termed "opportunistic." These infections can either originate in the skin or can appear in the skin after hematogenous spread. For instance, 5–10% of infections in neutropenic patients start in the skin [2]. Therefore, it is vital to recognize cutaneous manifestations of opportunistic infections.

In addition to the underlying immunosuppression, children who are treated with chronic antibiotics can have altered gut microbiomes [3]. The cutaneous microbiota is also likely altered by antibiotics [4]. The skin is normally colonized with bacteria such as *Staphylococcus epidermidis* and diphtheroids such as *Corynebacterium* species that are nonpathogenic in the normal host. These normal flora can help outcompete more pathogenic bacteria and other harmful microorganisms. When children are immunosuppressed, normal skin flora can cause infection and pathogenic bacteria can lead to more severe infections.

Some infections are more prevalent in certain types of immunodeficiency, but since there can be significant overlap, clinicians must consider a broad infectious differential diagnosis in immunosuppressed patients. For instance, patients with secondary immunodeficiency due to induction chemotherapy prior to bone marrow transplantation typically have more severe immunosuppression and can present with nearly any type of opportunistic infection. Meanwhile, children with specific primary immunodeficiencies may have more specific types of opportunistic infections. For instance, children with Papillon-Lefevre syndrome (PLS) are missing a serine protease that is necessary to make the innate

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immunity molecule LL-37 [5]. LL-37 helps to kill specific mouth flora that cause gingivitis; consequently, PLS patients often have severe gingivitis due to these bacteria [5].

Recognizing cutaneous signs and symptoms of opportunistic infections can facilitate early diagnosis and therapy and thus be lifesaving. This chapter discusses bacterial, viral, fungal, and mycobacterial infections, and then organizes them based on clinical presentation. Clinical presentation will often dictate the most effective and expedient way to diagnose and treat infectious pathogens. Therapy is often driven by local resistant patterns and practices. Given the potential severity of infections in immunocompromised hosts, strong consideration of involving an infectious disease expert in therapeutic decisions is recommended. As such, this chapter concentrates on the clinical manifestations and diagnosis of opportunistic infections, as well as unusual presentations of typical infectious agents seen in immunosuppressed patients.

Bacterial Infections

Key Points

- Immunosuppressed patients can present with deeper and more exuberant bacterial infections.
- Cutaneous *Pseudomonas aeruginosa* infection can be an initial presentation of immunodeficiency.
- Anaerobic bacteria can be pathogenic in immunosuppressed patients.

Many bacteria can infect the skin of immunosuppressed patients and these can be divided into those bacteria that normally cause infection but are more exuberant (such as *Staphylococcus aureus*) and those that typically do not cause skin infection unless the patient is immunosuppressed (such as *Corynebacterium*). Infections in immunosuppressed patients may also be polymicrobial or caused by rare bacteria. Treatment can be challenging, due to the potential for increased antimicrobial resistance as a result of patients' frequent exposures to systemic and topical antibiotics.

Aerobic Gram-Positive Bacteria

Staphylococcus aureus, a gram-positive rod, is a common cause of cutaneous infections in children. Widespread use of antibiotics has led to resistant strains of *S. aureus* [6]. *S. aureus* infection has been associated with certain primary immunodeficiencies such as defects in IL1R and TLR pathways due to defects in MYD88 or IRAK4 signaling [7]. In addition, defects in the TH17 pathway associated with hyper-IgE syndrome can result in severe *S. aureus* infections [8, 9].

S. aureus can present with more invasive and more widespread disease in immunosuppressed hosts (Fig. 10.1) [10]. For example, the incidence of *S. aureus* sepsis has been reported to be higher

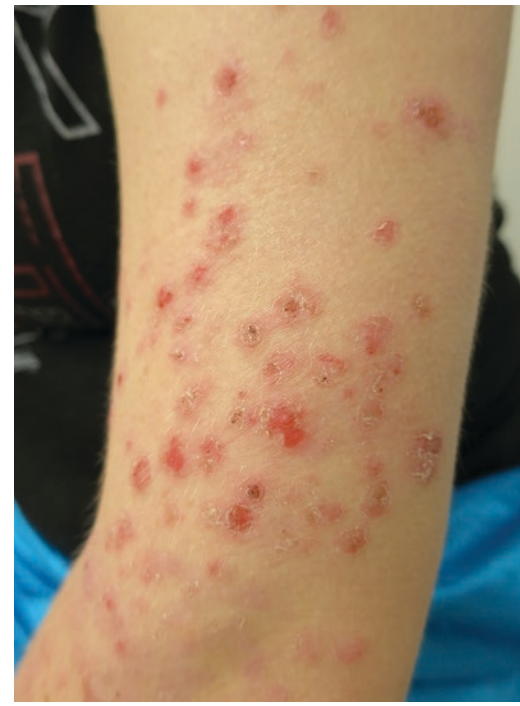

Fig. 10.1 Widespread cutaneous methicillin-sensitive *Staphylococcus aureus* infection in a renal transplant recipient (image courtesy of Carrie C. Coughlin, MD)

in patients with acute lymphoblastic leukemia [11]. Scheduled chlorhexidine gluconate (CHG) washes have been used in some pediatric centers for prevention of infection from indwelling lines [12]. This has led to a higher prevalence of CHG-resistant strains of *S. aureus* in pediatric oncology patients, showing the complexity of managing these infections [10].

Cellulitis is a superficial infection of the dermis and/or subcutaneous tissue typically from a bacterial infection. Necrotizing fasciitis and muscle infection (myonecrosis) are deeper infections that can be especially severe in immunosuppressed patients. Although *S. aureus* and group A *Streptococcus* (GAS) are more common causes of these deep bacterial infections, necrotizing fasciitis and myonecrosis in immunosuppressed patients are often polymicrobial, including gastrointestinal flora and anaerobic causes [13]. Due to the lack of a typical immune response in immunosuppressed patients, the clinical findings of erythema and induration may be missing or subtle in these deeper infections, thus complicating diagnosis [13]. Severe neutropenia after induction chemotherapy is a significant risk factor for these bacterial infections [14]. Therapy is similar to treating immunocompetent hosts except that the initial empiric antibiotic therapy should be broad and include gram-positive, gram-negative, and anaerobic bacterial coverage.

Coagulase-negative staphylococci such as *Staphylococcus epidermidis* are part of the normal bacterial microbiome of the skin and not typically pathogens. In fact, *S. epidermidis* plays an important role in cutaneous immunity by secreting antimicrobial peptides, in addition to activating Toll-like receptor 2, helping augment the innate immune system [15]. *S. epidermidis* is an important cause of bloodstream infections in very low-birth-weight neonates and immunosuppressed patients, though it does not usually cause primary cutaneous infection [16].

Aerobic Gram-Negative Bacteria

Ecthyma is a necrotic infection of the skin and soft tissue due to vascular compromise in the infected area. The term "ecthyma gangrenosum" is typically reserved for ecthyma caused by the oxidase-positive, gram-negative rod *Pseudomonas aeruginosa.* In immunosuppressed patients, the clinician should have a broad differential diagnosis for a purple eschar including infection by bacteria such as *Escherichia coli*, *Aeromonas,* GAS and *Serratia*, as well as invasive molds such as *Aspergillus* and *Zygomycetes* [17]. Lesions of ecthyma gangrenosum can occur due to direct inoculation of bacteria into the skin or from hematogenous spread. *P. aeruginosa* often colonizes stool; therefore, especially in diapered infants, primary lesions may be in the perineum [18, 19]. The primary lesion is a purple macule or patch that upon palpation often has underlying induration. The initial lesion rapidly progresses to a hemorrhagic bulla or ulcer with an indurated margin. If the cutaneous infection was caused by hematogenous spread to the skin, the child will typically have fever. However, if the lesion was inoculated into the skin from an outside source, the patient may initially be afebrile. *Pseudomonas* rarely infects normal hosts, so the presence of ecthyma gangrenosum should alert a clinician to evaluate for immunodeficiency such as neutropenia or a newly presenting hematopoietic malignancy [20]. A biopsy with frozen section (if possible) as well as culture can help rapidly determine if the cause is bacterial (gram negative or positive) or fungal, helping to guide empiric therapy. Choosing empiric coverage for *Pseudomonas* is challenging due to geographically different resistance patterns [21]. Some experts advocate for initial empiric therapy with two antipseudomonal antibiotics that have different mechanisms to increase the likelihood of successful treatment for this life-threatening infection until susceptibility testing can help narrow the coverage [18, 21, 22].

Anaerobic Infections

Corynebacterium and other diphtheroids are common colonizers of the skin that are difficult to differentiate from contaminant in cultures. Anaerobic bacteria can cause coinfection of

surgical sites [23]. They can also be present as a coinfection in abscesses and deeper infections such as myonecrosis and necrotizing fasciitis [13]. Culturing anaerobes is more challenging because the collection requires anaerobic conditions and the laboratory must be aware to consider any growth, and not assume that anaerobes are contaminants.

Viral Infections

Key Points

- Herpesviruses establish latency following primary infection, allowing for recurrence in select hosts.
- HSV may present at multiple or atypical sites, or manifest as hyperkeratotic or verrucous lesions.
- VZV infection may result in chronic or disseminated disease.
- EBV may cause lymphoproliferative disease with rare cutaneous manifestations.
- Kaposi sarcoma can be confused with benign vascular tumors, and may have additional systemic signs.
- HPV and molluscum contagiosum lesions can be extensive, atypical appearing, and refractory to treatment.

Herpesviridae

The herpesvirus family, consisting of HSV1/2, VZV/HHV-3, EBV/HHV-4, CMV/HHV-5, HHV-6, HHV-7, and KSHV/HHV-8, are relatively ubiquitous, double-stranded DNA viruses. They are further divided into subfamilies (alpha-, beta-, and gamma-herpesviruses) based primarily on the length of their reproductive cycles and the cell types in which they establish latency. While herpesvirus infection in the immunocompetent host is rarely severe, these viruses can cause atypical or disseminated infections in immunocompromised patients, leading to significant morbidity and mortality.

Herpes Simplex Virus (HSV)

HSV-1 and HSV-2 are alpha herpesviruses. Primary infection and replication occur within mucocutaneous sites, followed by retrograde axonal flow extending to the dorsal root ganglion. The virus can remain latent for long periods within the dorsal root ganglia, thus avoiding detection by the host immune system. HSV-1 is the dominant serotype among young children [24]. It is typically acquired between the ages of 2 and 10 through contact with contaminated oral secretions [24]. In contrast, primary infection with HSV-2 more commonly occurs after puberty through anogenital contact, and remains the leading serotype associated with genital herpes worldwide [24]. Many factors can trigger reactivation, including immunosuppression. Viral culture, Tzanck smear, and direct fluorescence antibodies (DFA) have classically been used as initial diagnostic tests; however polymerase chain reaction (PCR) is now the gold standard for diagnosis due to its high sensitivity and specificity, in addition to its rapid turnaround time [25].

HSV classically presents as tender, grouped, erythematous vesicles that can become infiltrated with inflammatory cells leading to a pustular appearance. Tingling or burning may precede lesions in both primary and recurrent infections. In immunosuppressed children, the immune system may have difficulty clearing the virus from the skin. Reactivation occurs more frequently when there is impaired cell-mediated immunity, and exhibits both more prolonged symptom duration and viral shedding [24].

In immunosuppressed patients, lesions are more likely to affect multiple sites. Large, hyperkeratotic, verrucous, ulcerated, and exophytic plaques have been reported in adults, but can present in children as well [26]. Lesion location also differs in immunosuppressed hosts; there is more frequent intraoral involvement, most notably affecting the gingiva, palate, or buccal mucosa [27]. Deep, linear fissuring ("knife-cut sign") can occur in intertriginous areas, as well as on the tongue dorsum (herpetic geometric glossitis) [28]. HSV can disseminate to the lungs, liver, GI tract, and central nervous system, although this is

rare. Lesions may be preceded by fever, lymphadenopathy, and malaise. In primary HSV gingivostomatitis of an immunosuppressed host, there can be severe involvement of the oral cavity. Pharyngitis is more common in older children and adolescents.

Intravenous (IV) acyclovir is the mainstay of treatment for severe and disseminated infections, as well as for patients with systemic complications [29]. Unlike in immunocompetent hosts, oral and IV antivirals should be continued until lesions are completely healed. Acyclovir-resistant strains of HSV may occur, particularly among immunosuppressed patients. Degree of immunosuppression and prolonged or erratic acyclovir use are risk factors in developing resistant strains [30]. Persistent lesions without appreciable decrease in size after more than 1 week of treatment, development of atypical lesions, or appearance of new satellite lesions after 3–4 days of therapy suggest resistance, and treatment with foscarnet or systemic cidofovir may be considered [29].

Varicella Zoster Virus (VZV)

VZV is the third member of the alpha-herpesvirus subfamily. It is transmissible through contact with respiratory secretions or fluid from skin lesions. The incubation period lasts from 14 to 20 days, and an individual is infectious from 1 to 2 days prior to development of skin lesions until all lesions have crusted [31]. As with HSV, VZV can be diagnosed via multiple tests, but PCR from a swab of a lesion is now commonly used.

Primary infection with VZV manifests as varicella (chickenpox), which presents with scattered vesicles on an erythematous base, resembling "dewdrops on rose petals." Fever and influenza-like symptoms may occur. The cutaneous eruption and any systemic symptoms typically will self-resolve in immunocompetent hosts. Reactivation of the virus causes herpes zoster (shingles), presenting as a tender vesicular eruption in a dermatomal distribution (localized disease) (Fig. 10.2). A prodrome of itching, tingling, or burning is frequently reported in the involved dermatome. If the initial dermatomal VZV then disseminates, a workup for immunosuppression should be initiated, as intact immune systems generally contain the infection to one dermatome [26]. VZV is considered disseminated if cutaneous lesions cross three contiguous dermatomes, or 20 or more vesicles appear beyond the affected dermatome. Systemic involvement, including pneumonitis, meningoencephalitis, and hepatitis, as well as gastrointestinal tract and ocular involvement, can also develop following the cutaneous eruption. Recurrent primary varicella, defined as one or more episodes of disseminated VZV without an initial zosteriform distribution, has been reported in patients with HIV, leukemia, and lymphoma [32]. VZV may present atypically as hyperkeratotic, pustular, purpuric, or even ulcerated and necrotic lesions in immunosuppressed patients. Finally, chronic herpes zoster, lasting longer than 1 month, has been reported with advanced HIV, but less frequently in patients undergoing cancer chemotherapy or in posttransplant patients on immunosuppressive therapy [33]. These forms of zoster cause significant morbidity and even mortality in these populations.

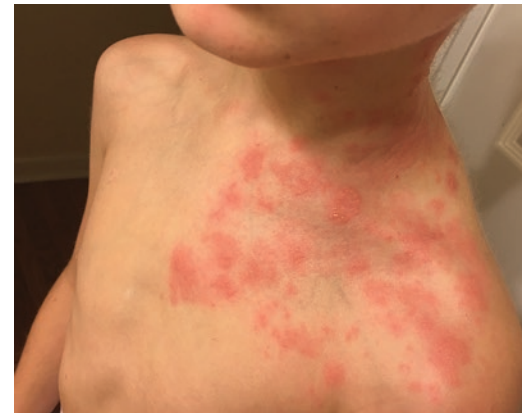

Fig. 10.2 Herpes zoster in a hematopoietic stem cell transplant recipient (image courtesy of Marissa J. Perman, MD)

Parenteral antiviral therapy should be initiated in immunosuppressed patients diagnosed with VZV infection. First-line treatment is IV acyclovir, with the goal of preventing progression to disseminated disease. Acyclovir resistance is less common in VZV than in HSV; however foscarnet

can be used as a second-line agent when resistance is suspected [34].

Epstein-Barr Virus (EBV/HHV-4)

EBV is transmissible via contact with infected body fluid, including saliva, breast milk, and genital secretions. Incidence of primary EBV infection peaks from 1–6 to 14–20 years of age, and reactivation can occur with immunosuppression. EBV may be causative in multiple malignancies, including B-cell lymphoma and nasopharyngeal carcinoma. Natural killer/T-cell lymphoma (NKTL) is an aggressive lymphoma linked to EBV that classically presents with ulceration and necrosis involving the nose. It is more common in East Asian and Latin American patients. Immunosuppression is rarely reported to be an associated risk factor, and can result in atypical or severe disease [35].

EBV is also implicated in lymphoproliferative disorders such as posttransplant lymphoproliferative disorder (PTLD). PTLD typically occurs 1–2 years following organ transplant with incidence varying based on organ type and immunosuppressive regimen [36]. Approximately 5% of cases will have cutaneous manifestations [36]. The cutaneous presentation of PTLD classically is that of indurated, violaceous papules and plaques; however, its appearance can range from a localized erythematous eruption to diffuse subcutaneous plaques, nodules, or masses [37]. See Chap. 11 for further discussion of PTLD.

EBV can also present as chronic ulceration of the cutaneous or mucous surfaces in immunosuppressed patients (mostly described in adults). PCR from an active lesion can demonstrate the virus, and withdrawal of immunosuppression can lead to spontaneous regression [38, 39]. Chronic ulcerations can be caused by many agents, but when considering EBV as an etiology, CMV should be in the differential diagnosis.

Human Herpesvirus 8

HHV-8, a DNA gamma-herpesvirus, is causative in Kaposi sarcoma (KS), as well as lymphoproliferative disorders like multicentric Castleman's disease and hemophagocytic lymphohistiocytosis (HLH). The virus can infect several different cell types, including monocytes, B lymphocytes, and oral epithelial cells [40]. It is important to note that the incidence of KS rose dramatically with the HIV epidemic, suggesting that the retrovirus may provide a cofactor necessary for the progression of HHV-8 to KS. This association remains even among individuals with well-controlled HIV on retroviral therapy [40].

The diagnosis of KS should be histologically confirmed; thus skin biopsy is the gold standard when this virally mediated disease is suspected; serology for HHV-8 is not required.

KS is classified into one of four types, based primarily on host characteristics and disease course. The classical and endemic (African) types largely occur in immunocompetent hosts. The remaining categories occur in special populations: iatrogenic/transplant patients and individuals with HIV/AIDS (epidemic KS).

The clinical presentation of HHV-8 varies depending on the immunologic status of the host at the time of infection. Primary infection may be mild and nonspecific, or even asymptomatic, in immunocompetent children. On the other hand, severe disease characterized by fever, bone marrow failure with plasmacytosis, and rapid dissemination has been reported in children with HIV and posttransplant patients [41].

In children, epidemic KS is an aggressive disease with significant lymphatic involvement, as well as classic pink-purple cutaneous papules and plaques. Lesions can be painful or pruritic and may koebnerize. They may initially be mistaken for hematoma, purpura, bacillary angiomatosis, or even hemangioma when localized. Extracutaneous spread is common, with involvement of the oral mucosa, gastrointestinal tract, and lungs. Gastrointestinal involvement may present as melena, hematemesis, or hematochezia, while dyspnea, nonproductive cough, or hemoptysis signals pulmonary disease.

The clinical spectrum of KS in the transplant population is not well elucidated; both primary

infection from HHV-8-infected donor grafts and viral reactivation may occur. Cases have been reported in both solid-organ- and bone marrow-transplant patients. Manifestations are similar to that of epidemic KS, although prognosis may be poorer; severity is likely related to baseline HHV-8 immunity, degree of immunosuppression, and, in solid-organ-transplant patients, organ type [42].

No established guidelines exist for the treatment of KS and therapy should be guided by an infectious disease expert, especially someone with experience treating children. For primary HHV-8 infection, supportive care is recommended in immunocompetent patients, while antivirals such as ganciclovir or valganciclovir are recommended for immunosuppressed populations [40]. In localized epidemic KS, treatment typically consists of therapy for underlying HIV, intralesional vincristine, or topical alitretinoin. For patients with systemic or refractory disease, systemic chemotherapy protocols are considered [43]. In immunosuppressed patients, including transplant patients, a typical treatment approach includes reduction and modification of the immunosuppressive regimen, such as including tacrolimus or sirolimus, agents with antitumorigenic properties [40].

Human Papilloma Virus (HPV)

HPV is the most common viral skin infection, and is the etiologic agent of both common and genital verrucae (warts) [44]. There are more than 120 subtypes of HPV, many of which carry an anatomic predilection. Transmission occurs through skin-to-skin contact or via contaminated surfaces or objects. HPV infections occur in both immunocompetent and immunocompromised patients; however prevalence is increased in patients with impaired cell-mediated immunity [45]. Diagnosis is typically made clinically, or histologically with an HPV immunostain.

HPV lesions can be chronic, extensive, or atypical in appearance in immunosuppressed patients. Additionally, they may be refractory to multiple treatment modalities in this population [46]. Predisposition to HPV infection has also been associated with several syndromes. Epidermodysplasia verruciformis, a genetic disease due to mutations in EVER1/EVER2, predisposes to HPV 5 and 8. The typical lesions are flat-topped verrucae that are skin colored or tan brown and are recalcitrant to therapy. These lesions must be closely monitored over time due to risk of development of squamous cell carcinoma in the field. Other genetic syndromes presenting with verrucae include warts, hypogammaglobulinemia, infections and myelokathexis syndrome (WHIM), warts, immunodeficiency, lymphedema, dysplasia (WILD) syndrome, and GATA-2 mutations [47].

In immunocompetent patients, lesions can self-resolve over years, but therapy can be much more challenging in the setting of immunodeficiency. Many therapies work in whole or part via immunomodulatory mechanisms (i.e., cryotherapy, salicylic acid, podophyllin, imiquimod) and so may not be successful in the immunocompromised host. Additional options for recalcitrant warts include topical cidofovir or 5-flurouracil, systemic agents such as oral cimetidine or retinoids, and photodynamic therapy [48, 49].

Molluscum Contagiosum

Molluscum contagiosum virus is a DNA poxvirus. Infection occurs commonly via skin-to-skin contact or through contact with contaminated surfaces or objects in children and as a sexually transmitted infection in adults. It has increased prevalence in immunocompromised patients, particularly those with HIV/AIDS [50]. Diagnosis is made clinically or histopathologically.

Clinically, molluscum contagiosum lesions appear as firm, skin-colored, pearly papules with central umbilication. In children, they have a predilection for the trunk, thighs, buttock, and face. Similar to HPV, molluscum can cause significant morbidity in immunocompromised hosts as lesions can become widespread and extensive, and can be refractory to treatment. In immunocompromised

hosts, the differential diagnosis of molluscoid lesions includes cryptococcal infection, histoplasmosis, and penicilliosis [51]. Options for therapy include manual expression (such as curettage or extraction), cryotherapy, and topical agents including cantharidin and cidofovir, in addition to photodynamic therapy [49, 52].

Human Polyomavirus

The human polyomaviruses include six small DNA viruses that appear to be ubiquitous in the environment; however these only cause significant disease in immunocompromised hosts; other identified human polyoma viruses have not been identified in human disease to date. JC and BK are polyoma viruses that can cause rapidly progressive neurologic decline and nephropathy in immunosuppressed patients, such as those treated with TNF alpha-blocking agents [53, 54].

Two polyomaviruses have been associated with cutaneous tumors. Merkel cell polyomavirus is implicated in some Merkel cell carcinomas (MCC), a rare but aggressive tumor most common in white males over the age of 50. This classically presents as a rapidly expanding pink to violaceous papule or nodule on sun-exposed skin. HIV, organ transplant, and CLL have been identified as major risk factors [55, 56]. There are rare reports of this malignancy in the pediatric population [57].

The trichodysplasia-spinulosa polyomavirus (TSPyV) has recently been identified as the cause of trichodysplasia spinulosa [58–60]. This rare eruption appears as numerous folliculocentric papules and keratin spines referred to as spicules, most prominently over the nose, eyebrows, and ears, but can be found on other areas of the body as well. There may be associated thickening of the skin and alopecia of the eyebrows and scalp, resulting in leonine facies [61]. This appears to occur exclusively among immunocompromised hosts, and can become of significant cosmetic concern. Topical cidofovir has been shown to be an effective therapy [62].

Fungal Infections

Key Points

- Invasive mold infections can start in the skin and spread rapidly.
- Disseminated yeast infections may first present in the skin with widespread papules.

Fungal spores are ubiquitous in our environment. Some fungi colonize the skin (such as Malassezia yeasts), some are pathogens in normal hosts (dermatophytes and Candida species), and some are opportunistic fungi that are not typically pathogens in normal hosts. Cutaneous fungal infections can occur due to primary inoculation, dissemination, or infection of a preexisting wound.

Dermatophyte Infections

Dermatophyte infections such as those caused by *Trichophyton* and *Microsporum* may be more common in immunosuppressed patients such as those with AIDS [63]. They do not typically cause invasive, life-threatening disease, but can invade into the dermis leading to more exuberant papulopustular eruptions. Therapy is typically with systemic agents such as azole or allyl amine antifungals or griseofulvin [64].

Opportunistic Yeast Infections

Malassezia yeasts are colonizers of normal skin, but in immunosuppressed patients they can lead to cutaneous infections. Overgrowth of *Malassezia* can cause severe seborrheic dermatitis and folliculitis, especially in immunosuppressed patients. More rarely, *Malassezia* infections of indwelling catheters, especially in neonates and those receiving parenteral nutrition, can lead to septicemia [65, 66]. Diagnosis can be challenging, as the yeast

needs to be grown on lipid-containing media [67]. Therapy can be initiated with amphotericin or systemic azole antifungals. Interestingly, the fungemia has been shown to spontaneously resolve with removal of the catheter and discontinuation of the lipid-containing nutrition in adults [68].

Colonization with Candida species is common in the gastrointestinal tract, as well as the perineum and oral cavity, and overgrowth can lead to infection [67]. Localized candidal infection in the mouth (thrush) can be a presenting sign for immunosuppression in children [69].

Candidemia is a very important cause of sepsis in immunosuppressed patients. Many different Candida species, including *Candida albicans* and *C. glabrata*, can cause infection in immunosuppressed patients [67, 70]. Cutaneous candidal infections usually manifest as red patches with scaling and peripheral pustules, especially in moist areas such as neck, axillary, and inguinal folds. Topical therapy with an azole antifungal or nystatin is usually sufficient for localized disease. Disseminated candidiasis in an immunocompromised host requires systemic treatment. Fever is common; disseminated candidiasis can also be associated with muscle pain, presumably due to yeast infection into the muscles [71].

Disseminated yeast infections also can occur due to *Aspergillus*, *Trichosporon*, *Fusarium*, and other yeasts [67]. These typically present in the skin with widespread, red-purple macules, and papules [72]. In addition, they can lead to pulmonary, renal, and hepatic disease [67]. While blood cultures may grow the fungus, a biopsy with direct histopathologic visualization, as well as culture, may yield a faster result. A frozen section performed on a biopsy of a suspicious site aids in even more rapid diagnosis. Tissue stains such as periodic acid-Schiff (PAS) and Grocott methenamine-silver (GMS) can help visualize the fungi on histopathologic slide preparations.

Invasive Mold Disease

Mold will not typically live in the skin unless a patient is immunosuppressed. Mold infections can be rapidly fatal in immunosuppressed patients. The skin is a common portal of entry for fungal spores. Spores of fungi such as *Aspergillus* and *Zygomyces* are frequently in the air and take advantage of breaks in the skin or occlusion with tape or bandages. If an opportunistic fungal infection appears first in the skin and is recognized early, it may be cured before it disseminates. Disseminated disease that starts elsewhere in the body, such as in the lungs, may also appear in the skin early in its course. Proper evaluation of skin lesions can again lead to early diagnosis.

Aspergillus infection is a common cause of serious morbidity and mortality in immunosuppressed patients [73]. After the lungs, the skin is the second most common site for *Aspergillus* infection [73]. *Aspergillus* can present with papules, eschars, ulcerations (especially at sites of trauma), or pustules and plaques due to infiltration of the hair follicles. In one study, over half of patients' skin disease was localized [74]. In addition to patients undergoing chemotherapy or bone marrow transplantation, extremely low-birth-weight infants are at risk for *Aspergillus* infection [75]. Tape or other occlusion can cause the fungus to proliferate (Fig. 10.3). Diagnosis of invasive *Aspergillosis* can be aided by the galactomannan blood test [76].

Presentation with individual papules and nodules raises the suspicion for direct inoculation of opportunistic mold infections. Many different types of mold can infect the skin of severely immunosuppressed patients through direct inoculation, including *Zygomyectes* (*Rhizopus* and *Mucormycosis*), *Alternaria*, *Aspergillus*, *Curvilaria*, and *Fusarium* (Fig. 10.4), among others [77]. Risk factors for primary cutaneous fungal infections include long-standing immunosuppression, tape or dressing occlusion of the skin, and breaks in the skin (such as a peripheral IV, a central line, or other laceration or abrasion). Diagnosis is based on culture and tissue culture is the gold standard. A surface swab is

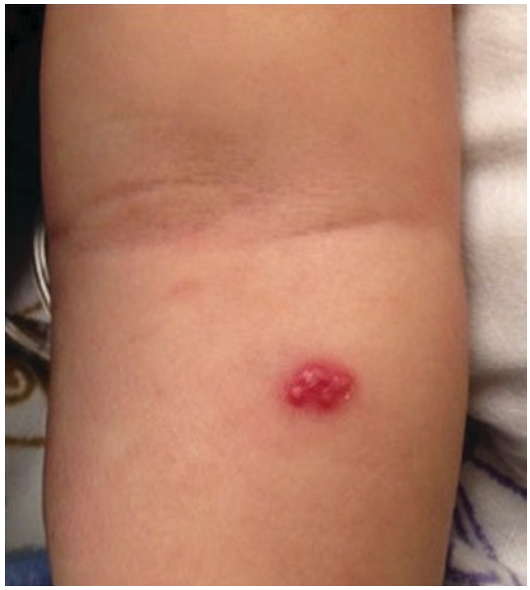

Fig. 10.3 *Aspergillus* on the forearm at a site of occlusion by tape for a peripheral IV (image couresy of Marissa J. Perman, MD)

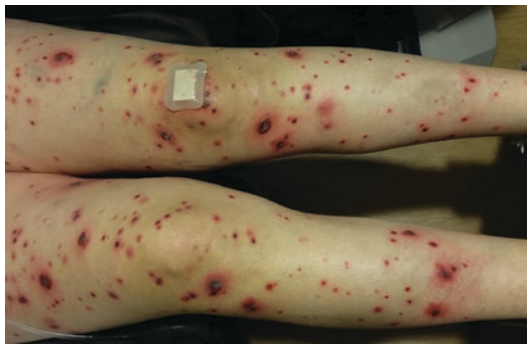

Fig. 10.4 Disseminated *Fusarium* infection (image courtesy of Jennifer T. Huang, MD)

insufficient, as it may grow a contaminant sitting on top of the skin, and not the cause of the tissue infection.

Therapy for fungal infections is targeted toward the most likely pathogen. While awaiting cultures, empiric therapy should be started in immunosuppressed patients. Amphotericin is often a first-line agent due to its broader fungal coverage. Azoles such as voriconazole and posaconazole are often used for *Fusarium* infections, but the choice of antifungals should be guided by an infectious disease expert [78].

Some practitioners advocate surgical excision of primary cutaneous mold disease [79]. If there is a single lesion that occurs due to primary inoculation into the skin, it is possible that early debridement may mitigate the risk of hematogenous spread. Frozen-section examination of a specimen can help determine the margins and ensure that the entire lesion is removed. In the setting of immunosuppression and thus paucity of inflammatory reaction, the actual size of the infected tissue may be much larger than what is seen clinically. In addition, since growth within the tissue can be rapid, a frozen-section biopsy of the skin can help make the initial diagnosis as soon as possible to allow for rapid therapy. There are no large studies to demonstrate the efficacy of surgical intervention.

Cryptococcus is a fungus that is commonly found in soil and pigeon stool. *Cryptococcus* is a very rare cause of cutaneous lesions. Immunosuppression, especially from HIV infection, can cause cryptococcal infection that manifests as umbilicated papules resembling molluscum lesions. The virus can also infect the central nervous system, lungs, and other tissues [80]. Workup of a new infection should include evaluation for the cause of immunosuppression (such as HIV testing) and consideration for systemic workup of disseminated cryptococcal disease. Therapy should be directed by an infectious disease specialist.

Mycobacterial Infections

Key Points

- Latent mycobacterial infections can reactivate in immunosuppressed patients.
- Non-tuberculosis mycobacterial infections can occur in various specific immunodeficiencies.

Tuberculosis (TB) can cause primary infection in immunosuppressed patients, but latent TB can also reactivate when patients are iatrogenically immunosuppressed. Non-tuberculosis mycobacterial (NTM) infections can also cause primary inoculation disease and spread more rapidly in immunosuppressed patients. In adults, cutaneous NTM infections account for 70% of NTM infection in hematopoietic stem cell transplant patients, 35% in solid-organ-transplant patients, and patients treated with immunosuppressing therapy for inflammatory diseases [81]. Although data is limited in children, *Mycobacterium abscessus*, *M. fortuitum*, and *M. chelonae* may more commonly cause cutaneous disease [81]. Children with hypohidrotic ectodermal dysplasia with immunodeficiency caused by mutations in the IKBKG gene that encodes the NF Kappa-B essential modulator NEMO protein are at especially high risk for mycobacterial infections such as *Mycobacterium avium complex* (MAC). In these patients, the papules, plaques, and nodules of MAC infection can be widespread [82]. An eruption of cutaneous MAC has also been reported presenting with a purulent ulcer during immune reconstitution syndrome in a patient with AIDS starting antiviral therapy [83]. Interestingly, multiple types of immunodeficiency such as cartilage hair hypoplasia and ataxia telangiectasia can be associated with granulomatous plaques that can be mistaken for mycobacterial infections [84, 85]. Cultures are important to help diagnose these granulomatous reactive phenomenon and rule out infection.

Bacillus Calmette-Guerin (BCG) is a mycobacterium that, in its live attenuated form, is used as a vaccination against TB in many countries [86]. Disseminated cutaneous infection from latent BCG that reactivates with immunosuppression can be the presenting sign of primary immunodeficiency or liquid malignancy [87]. Live vaccines are contraindicated in immunosuppressed patients. In addition to dissemination of the attenuated pathogen used in the vaccine, there are reports of chronic granulomatous lesions that have vaccine strain rubella in them potentially caused by the inability to create a productive immune response [88].

Clinical Presentation

Clinical presentation of cutaneous infections can overlap, especially in immunosuppressed children. The immune response (or lack thereof) to an infection often helps determine how it presents clinically. For instance, the true infectious borders of an invasive mold infection may not be clinically apparent if the immune system does not recognize the infection and thus does not create erythema. Recognizing opportunistic infections based on their clinical presentation (Table 10.1) is helpful so that the clinician can favor a certain type of infection and choose empiric therapy appropriately. A cutaneous infection can go through multiple stages of evolution, so the same infection may be listed below in multiple categories. Some non-opportunistic infections are listed in the differential diagnosis for completeness.

Vesicles and Bullae

The vesicles of HSV and VZV tend to be a few millimeters and clustered (Fig. 10.2). Group A *Streptococcus* can also cause relatively small vesicles. *Staphylococcus aureus* causes bullae that are larger (bullous impetigo). The initial stage of ecthyma gangrenosum or other severe deep bacterial infection such as myonecrosis or necrotizing fasciitis can present with vesiculation of the epidermis due to edema and devascularization. Swabs for bacterial culture and viral PCR can diagnose superficial infections, but a biopsy with tissue culture is necessary for deeper infections.

Pustular Eruptions

A pustule is typically caused by a collection of neutrophils within the epidermis and/or dermis. There are many noninfectious causes of pustules including pustular psoriasis, neutrophilic dermatoses, miliaria, erythema toxicum, neonatal pustular melanosis, and more. When infection is

Table 10.1. Morphology of infections in immunosuppressed hosts and suggested diagnostic workup

Cutaneous lesion	Infectious differential diagnosis	Workup
Vesicle	HSV VZV Enteroviral infection *Staphylococcus aureus* Group A *Streptococcus*	PCR for HSV, VZV, enterovirus Bacterial swab
Pustule	*Staphylococcus aureus* Group A *Streptococcus* Molluscum (the shiny appearance can simulate a pustule) *Cryptococcus* *Pseudomonas* *Candida* Invasive fungi Dermatophyte	PCR for HSV, VZV, enterovirus Bacterial swab Biopsy or extraction for exam under a light microscope if molluscum is suspected Biopsy (and tissue culture) if *Cryptococcus* is suspected Fungal swab for dermatophyte If invasive disease is suspected, biopsy for histopathology and tissue culture
Umbilicated papule	Molluscum *Cryptococcus* *Penicillium marneffei* *Histoplasma*	Biopsy for histopathology and tissue culture If molluscum is high on the differential, consider extraction to view under light microscopy
Verrucous papule	HPV HSV *Cryptococcus* Mycobacteria	If considering more than HPV on the differential, biopsy for histopathology and tissue culture
Nodule	Bacterial abscess Invasive mold	Biopsy for histopathology and tissue culture
Eschar/ulcer	Ecthyma Ecthyma gangrenosum Invasive fungus Mycobacteria EBV/CMV HSV VZV	Biopsy for histopathology and tissue culture Consider a surface swab for bacteria PCR for HSV and VZV, as well as EBV and CMV if possible

PCR polymerase chain reaction, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *HPV* human papillomavirus, *CMV,* cytomegalovirus, *EBV* Epstein-Barr virus

suspected, the most common cause of a pustular eruption is a pyogenic bacteria such as *S. aureus* and Group A *Streptococcus*.

Vesicular infections such as HSV and VZV infections can also become pustular if neutrophils collect in the sterile fluid. Clinically, the vesicles or pustules of HSV are grouped or clustered. When the top of the vesicle or pustule comes off, it will leave an erosion, so grouped erosions or cribriform ulcers are also suggestive of HSV.

Fungal infections can be pustular, as well. In immunosuppressed patients, spores from the environment can be occluded under tape and proliferate. This often yields a pustular look when the tape is removed. Candida is also classically pustular with areas of erythema and peeling. Mycobacterial infections can also look purulent.

Pustular eruptions may be unroofed and swabbed for bacterial culture, viral PCR, and fungal culture. A tissue culture with histopathology is beneficial to detect cutaneous mold as a surface culture positive for mold could be interpreted as a contaminant.

Eschars and Ulcerations

An eschar or crust is caused when the epidermis or epidermis and dermis are damaged leading to a layer of devitalized skin. An eschar is the end stage of a bulla/vesicle and thus the differential diagnosis includes all of the infections under the vesicles/bullae category. An ulceration is the result of necrosis of the epidermis into the dermis or subcutaneous tissue (Fig. 10.4). Identifying

the original lesion that then ulcerated (such as a vesicle, bulla, pustule, or primary ulceration) can guide presumptive diagnosis.

While swab culture of an ulcer will likely yield the pathogens growing on top of the open wound, the surface swab may not detect an underlying pathogen. HSV can reliably be detected from swabbing the base of the ulcer. Therefore, biopsy with tissue culture and histopathology is warranted.

Papules and Nodules

A papule or nodule is caused by the buildup of some material in the dermis or subcutaneous tissue. Bacterial abscesses, molluscum, *Cryptococcus*, deep invasive fungal infections (Fig. 10.2), and mycobacterial infections are infectious causes of papules and nodules. Therefore, a tissue biopsy sent for both culture and histopathologic evaluation is necessary.

Summary

Recognizing and treating opportunistic infections is extremely important to the care of immunosuppressed patients. While many cutaneous infections can be detected with swabs, histopathologic evaluation should also be highly considered in these patients. A direct look at sectioned tissue with appropriate stains can rapidly identify a pathogen or category of infection (fungal, mycobacterial, etc.) prior to microbiologic detection. Understanding how opportunistic infections present in the skin can guide rapid workup and empiric therapy, thus improving treatment.

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Skin Cancer and Other Late Effects of Cancer Therapy

11

Carrie C. Coughlin

Introduction

Skin cancer is rare in children, but it is more common in certain groups of children than others. Survivors of childhood cancers, certain immunosuppressed patients, and patients with genetic predispositions are at increased risk to develop skin cancer at a younger age than the general population. Non-melanoma skin cancer, posttransplant lymphoproliferative disease, and Kaposi's sarcoma are addressed in this chapter; melanoma (Chap. 1) and other lymphoproliferative disorders (Chap. 3) are addressed elsewhere in the book. There are several nonmalignant, long-term side effects of cancer therapy, as well. Development of nevi, lentigines, and hyperpigmentation is discussed in Chaps. 7 and 8 as sequelae of traditional and targeted therapies. Their development after voriconazole is reviewed in this chapter. Permanent alopecia, cutaneous autoimmune disorders, scarring, and long-term care recommendations are covered in this chapter, showing the range of potential cutaneous late effects of cancer therapies.

Much of the work on late effects and long-term risks in survivors of childhood cancer in the United States centers on the Childhood Cancer Survivor Study (CCSS). This cohort study includes patients diagnosed with pediatric cancer and initially treated between 1970 and 1986 (approximately 14,000), and the original methods are described by Robison et al. [1]. The dates of diagnosis and treatment of this cohort thus do not include those treated with newer agents and evolved regimens, so an "expansion cohort" of patients treated from 1987 to 1999 (approximately 10,000 patients) is now included. Given the rapidly changing landscape of treatment, targeted therapies that are being used more currently are not yet represented substantially in the CCSS.

Skin Cancer

Key Points

- Basal cell and squamous cell skin cancers are rare in children, but more common in immunosuppressed populations and can appear at an earlier age than in patients without immunosuppression.
- Voriconazole can cause marked sun sensitivity, leading to pigmented lesions and predisposing to development of squamous cell cancer.
- Posttransplant lymphoproliferative disease is common as visceral disease after solid organ transplant, but less commonly appears in the skin.

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Non-Melanoma Skin Cancer

Skin cancer incidence is low in children, but risk is higher in survivors of childhood cancer, as well as other groups: solid organ transplant recipients, hematopoietic stem cell-transplant (HSCT) recipients (including indications other than cancer for transplant), patients with genetic cancer predisposition syndromes (see Chap. 5), children with genetic disorders with photosensitivity (see Chap. 5), indoor tanning users, and patients with increased risk due to medication side effects (see below).

Childhood cancer survivors have several risk factors for skin cancer development, including radiation exposure, chemotherapy, and antifungal therapy, in addition to the typical risk factors of fair skin, sun exposure, and family history (when applicable). In a study comparing 10,397 adult survivors of childhood cancer with sibling controls from the original CCSS cohort, 1.3% of survivors had basal cell carcinoma (BCC), whereas only 0.1% of control patients were diagnosed with BCC [2]. Of this group, 3.78% of patients with a history of Hodgkin's disease developed BCC; radiation therapy may be a large contributor to this risk. In a 2012 analysis of original cohort CCSS participants, radiation therapy with or without chemotherapy increased patients' risk for BCC, with an excess odds ratio of 1.09 with each Gray (Gy) of radiation exposure [3]. In a 2002 study, significant risk factors for non-melanoma skin cancer (NMSC) identified on multivariate analysis included Hodgkin's disease, white race, older age at diagnosis, longer time since diagnosis, radiation therapy, and positive family history of skin cancer [4]. Chemotherapy history was not related to skin cancer risk.

Childhood cancer survivors with NMSC are likely to have multiple skin cancer diagnoses in their lifetime. They are also likely to present at a younger age than those without a history of childhood cancer. In the CCSS cohort, NMSC was seen in 213 of 13,132 survivors, with 46.5% (99/213) patients having multiple NMSC [4]. In these patients, skin cancer was found to occur among childhood cancer survivors at a mean age of 31 years (range 7–46 years), a much younger age than that seen in adults without a history of childhood cancer [4]. This study found a median of 15 years from original cancer to skin cancer diagnosis.

Pediatric solid organ transplant recipients (POTRs) also are at risk for developing NMSC. In non-renal pediatric transplant patients, NMSC is the most frequent posttransplant malignancy (Fig. 11.1) [5]. The lip is a common site, and the tumors can be aggressive [5, 6]. Additionally, POTRs are at risk for anogenital carcinomas. Posttransplant NMSC can occur in childhood, but often occurs 10–20 years after transplant [5].

Voriconazole, a triazole antifungal, is effective at treating several infections, often those caused by *Aspergillus* spp., but it is also active against *Scedosporium*, *Fusarium*, and *Candida* spp. [7, 8]. The Food and Drug Administration approved voriconazole in 2002, and since then many reports of photosensitivity and phototoxic reactions have surfaced. In 2010, a review of eight patients with 51 SCC after initiation of voriconazole therapy included two pediatric patients who each had a history of cord blood hematopoietic cell transplant and developed AK, SCC in situ, and SCC [9]. Voriconazole phototoxicity has several clinical appearances. The acute phase can include erythema (Fig. 11.2), blistering, erosions, scaling/desquamation, cheilitis, hyperpigmentation, and lentigines [9–12]. Long-term sequelae include lentigines, ephelides, atrophy, actinic keratoses (Fig. 11.3), and skin cancers, most often SCC [13]. Additionally, voriconazole

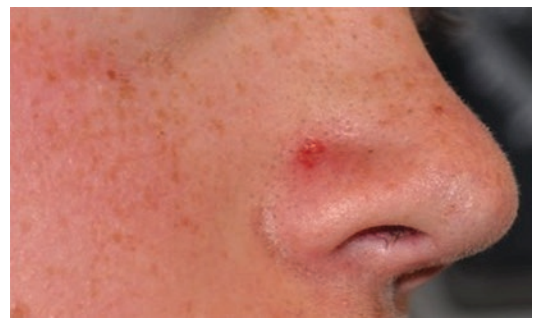

Fig. 11.1 Basal cell carcinoma on the nose of a teenage heart transplant recipient (image courtesy of Susan J. Bayliss, MD)

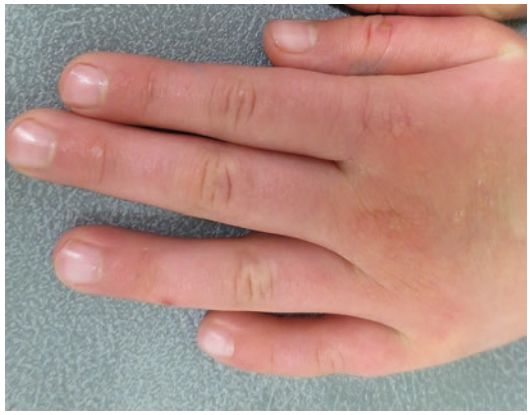

Fig. 11.2 Erythema and scale of the hand with voriconazole phototoxicity

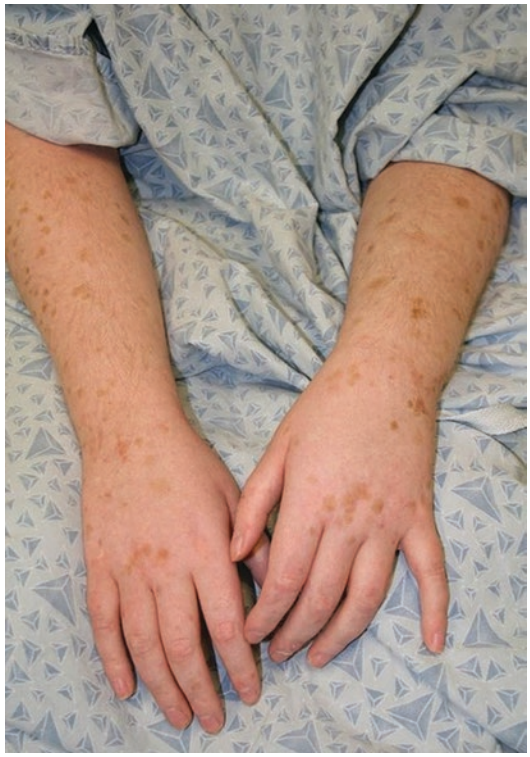

Fig. 11.3 Solar lentigines and actinic keratoses in a child after long-term use of voriconazole (image courtesy of Jennifer T. Huang, MD)

phototoxicity can mimic a flare of GvHD [10]. SCC has been reported in pediatric cancer patients and HSCT recipients [9, 13–15], POTRs [13, 16], and immunosuppressed pediatric patients [13, 17]. The mechanism leading to voriconazole-associated SCC is unclear. Recent work proposes an increased risk for voriconazole-associated SCC in patients with ultrarapid metabolism of the drug, seen in the *CYP2C19*17/*17* genotype [18].

Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) is the most common malignancy following renal transplant in children [5]. Its presentation in the skin, however, is rare. In a review including 16,130 patients with solid organ transplants from 1987 to 2008 who were <20 years old, the risk for both T- and B-cell lymphomas was elevated posttransplant [19]. The number of skin lymphomas in children captured in this study was very small, but cases of primary cutaneous anaplastic large-cell lymphoma (ALCL) and mycosis fungoides/Sezary syndrome were reported. With <3 cases of each, it is difficult to interpret significance, but given the rarity of primary cutaneous ALCL in children (see Chap. 3), the reports are notable. The B-cell diseases of Burkitt lymphoma/leukemia (24 cases; standardized incidence ratio [SIR] 123) and diffuse large B-cell lymphoma (138 cases; SIR 379) were much more common. This study did not comment on the frequency of cutaneous presentations of the diffuse large B-cell lymphomas, but skin involvement in this lymphoma has been reported in an infant (two reports of the same case) [20, 21]. Follicular mucinosis was reported in a 17-year-old patient with a history of acute myeloid leukemia, HSCT, and quiescent cutaneous GvHD [22]. At the time of the report there was no transformation to PTLD. The folliculotropic subtype of mycosis fungoides as PTLD has been seen [23]. Time from transplant to presentation varies, but many cases of PTLD (regardless of subtype) occur in the first year after transplant [19, 24]. Posttransplant B-cell disorders are often related to Epstein-Barr virus infection, which many attribute to the high incidence in children.

Kaposi's Sarcoma

In children, Kaposi's sarcoma (KS) typically presents in those who are immunocompromised, including POTRs and patients infected with the human immunodeficiency virus (HIV). It is associated with human herpesvirus-8 infection (HHV8; also known as Kaposi sarcoma herpesvirus), but HHV8 infection alone does not cause disease. Impaired T-cell immunity in HHV8-infected individuals has been implicated in the disease pathogenesis [25]. Its incidence is markedly elevated in patients in or from sub-Saharan Africa infected with HIV [26]. Cutaneous involvement (such as patches, plaques, and nodules) is variable, but can occur in all types (epidemic, endemic, iatrogenic, and classic) of KS [25]. Classic KS in pediatric patients is uncommon [27]. POTRs may develop KS, but it is not common [5, 28]. See Chap. 9 for more details on HHV8.

Permanent Alopecia

Key Points

- Permanent alopecia is common after cancer therapy.
- Patients with higher cranial radiation doses are at increased risk to develop permanent alopecia.
- Both traditional and targeted medical cancer therapies can predispose to the development of long-term alopecia.

Permanent alopecia can be a distressing long-term side effect of cancer therapy, occurring secondary to radiation or medical therapies. Alopecia is considered permanent in this setting if it lasts for more than 6 months following the completion of therapy (Fig. 11.4). It can be diffuse or patchy. It is a commonly reported long-term side effect, though Casagranda et al. note that alopecia, along with other late effects, may be underreported by patients [29].

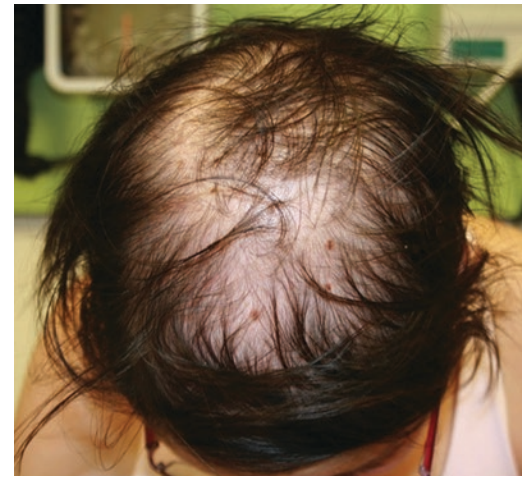

Fig. 11.4 Permanent alopecia present more than 20 years after radiation therapy as a child (image courtesy of Jennifer T. Huang, MD)

Radiation with traditional photon beam treatment, as well as proton beam, can cause permanent alopecia. In a study of adult patients, increasing mean follicle dose (dose calculated to contact the hair follicles) was associated with higher risk for permanent alopecia [30]. In this population (26 patients) treated with traditional photon beam cranial irradiation, the dose at which 50% of patients developed permanent alopecia was 43 Gy, and was not affected by chemotherapy agents the patients also received. In a Dutch cohort, childhood cancer survivors who received cranial radiation therapy more commonly experienced alopecia than those who did not [31]. Other work has shown alopecia incidence to be related both to radiation and chemotherapy. Specifically, in a group of 12 pediatric patients treated with proton beam radiation, patients who received standard-dose chemotherapy and 30 Gy of proton beam craniospinal radiation were at risk for permanent alopecia, while patients who received high-dose chemotherapy were at risk after receiving 21 Gy of proton beam therapy [32].

Traditional chemotherapy, especially high-dose regimens followed by HSCT, can cause permanent alopecia. In adults, busulfan-containing regimens have long been implicated [33, 34], though regimens without busulfan can also

trigger alopecia [35, 36]. Busulfan has also been identified as a risk factor for permanent alopecia in pediatric patients [37–39]. ThioTEPA has been associated with permanent alopecia in some reports, both in children [40] and in adults [36] undergoing HSCT. In HSCT patients, GvHD is another significant risk factor for permanent alopecia [38].

Permanent alopecia, generally scarring, as a consequence of a pustular eruption with EGFR inhibitors has been reported in adults, particularly women [41]. Data about permanent alopecia in children taking EGFR inhibitors is lacking.

Alopecia is an unwanted and stress-inducing side effect for many patients and parents [38, 42]. Permanent alopecia has been associated with depressive symptoms in females [43]. Interestingly, it was associated with impairments in physical function, bodily pain, and general health, in addition to social function, vitality, role function, and emotional health on Short-Form 36 (SF-36) subscales [43]. Further work is needed to more completely describe the effects of permanent alopecia on cancer survivors' long-term physical and emotional health.

Unfortunately, treatment options for patients with permanent alopecia are limited. Surgical procedures are complicated and invasive, but can provide some patients with good results [44]. Preventing alopecia would be a more ideal solution. Recent investigations into preventing acute alopecia in adults undergoing chemotherapy have utilized scalp-cooling devices, as well as pharmacologic agents [45, 46]. Long-term data, and data in children, has not been published yet.

Autoimmune Disorders

Key Points

- Vitiligo and alopecia areata are the more commonly reported cutaneous autoimmune diseases following HSCT.
- Many patients with autoimmune sequelae after HSCT also have GvHD.

Autoimmune sequelae of cancer therapies are not well described. Recently there have been several reports of cutaneous autoimmune disorders after HSCT. These can occur with or without a known donor history of the autoimmune disorder. This section focuses on vitiligo and alopecia areata after transplantation.

Vitiligo after HSCT occurs in both children and adults, presenting months to years after transplant. Both pediatric [47] and adult [48–50] patients have developed vitiligo after transplant from donors with a known history of vitiligo, but many reports of vitiligo after HSCT do not include this history. Children with history of cancer, primary immunodeficiency, and hemoglobinopathy have developed vitiligo, both after manifesting GvHD and without GvHD [51–55]. Interestingly, in a series of pediatric and adult patients with vitiligo and GvHD, three patients had disease after an autograft [54]; other series report patients with allografts. Some adult patients have had donor lymphocyte infusions prior to onset of vitiligo [56]. The convergence of total leukoderma and leukotrichia in patients with a history of HSCT is striking, and several cases of affected children have been reported [57–59].

Alopecia areata is less commonly reported as a consequence of cancer therapy. It has been seen as adoptive from the HSCT donor in adult cancer survivors [60, 61]. It has also been reported de novo in a handful of patients with GvHD, including in a 19-year-old male with history of HSCT for chronic myelogenous leukemia [62].

Patients with both vitiligo and alopecia areata in the setting of HSCT have also been reported [63]. In a series by Zuo et al. of patients with chronic GvHD and vitiligo and/or alopecia areata, 3/15 were under 18 years of age. Interestingly, though all had GvHD, not all had cutaneous GvHD [64]. Čeović et al. reported 10/50 patients with GvHD also developing vitiligo or alopecia areata, but did not specify which patients were children [65].

Several authors have debated the mechanism for autoimmune sequelae after HSCT, outside of adoptive transfer from donors, including donor recipient mismatch in female-to-male

transplants, effect of conditioning regimens, genetic predisposition, and environment [64, 66]. More studies are needed to investigate these theories.

Scars

Key Points

- Scarring is very common in childhood cancer survivors.
- Scarring can affect mental health and quality of life in cancer survivors.
- Treatment of scars in pediatric dermatology is evolving.

In the course of cancer treatment, patients have many exposures that can lead to the development of scars. Intravenous access can lead to scarring; peripheral and central lines, as well as ports, have associated scars. Additionally, complications of these access points, such as extravasation injury, can predispose to further scarring. Procedures such as biopsies (particularly skin and bone marrow) and resections are more obvious causes. Also, radiation therapy is a risk factor for scarring. In a review of 14,358 survivors of childhood cancer through the CCSS, scarring or disfigurement was reported by 25% of patients on the head or neck, 18% on the arms or legs, and 38% on the chest or abdomen [43]. On follow-up questionnaires, patients were queried on quality-of-life measures. Increased depressive symptoms were reported by patients with head or neck and arm or leg scarring or disfigurement. These patients also reported impairment in SF-36 subscales of general health and vitality, with mental health being affected in patients with head or neck scarring or disfigurement. Patients with arm or leg changes also reported impaired physical function, bodily pain, and social function. Thus, scarring is present long-term, and is associated with impairment of quality of life.

This data shows an opportunity for providers to be thoughtful in approaches to care and prevent or hide scars when possible. To this end, Braam et al. investigated prophylactic use of silicone sheeting for patients after removal of venous access devices (ports) [67]. The investigators showed nonsignificant improvement in patients' scars after 2 months of use, but wider scars after 6 months of use. Thus, longer term use of the sheets cannot be recommended at this point, though short-term use could potentially be helpful. Scar treatment in pediatric patients has been evolving. In addition to the traditional options of surgical scar revision and, for thick scars, intralesional steroid injections, laser treatment with full ablative, fractional ablative, and pulsed-dye technology has been advancing. Laser-assisted delivery of medications to augment scar treatments is also progressing [68]. Thus, patients will have more options going forward for scar revision/treatment. Currently there are multiple validated instruments for patient-reported scar outcomes, developed through work with different patient populations such as dermatology, burn, and postsurgical patients, though each has drawbacks [69, 70].

Education and Anticipatory Guidance

Education about skin cancer risk and photoprotection is important for pediatric cancer survivors and other patients at risk for photosensitivity and skin cancers. There are several tools and websites that can help with this education (see Table 11.1). Of note, given the increased risk for skin cancer in users of indoor tanning beds [71–73], these devices should be strictly avoided in children [74, 75], especially in cancer survivors and other children more at risk for developing skin cancer. Childhood cancer survivors have incomplete adherence to photoprotection [76, 77] and skin surveillance [78] recommendations. Both children and their caregivers must be educated about skin cancer risk and photoprotection. Studies in both childhood cancer survivors and POTRs have shown improvement in short-term (1–6 months) photoprotection behaviors after education interventions [79, 80]. Importantly, education about these topics often needs to be repeated for patients and parents. In a study of POTRs and their

Table 11.1 Resources for pediatric photoprotection and skin cancer information and handouts for patient education

Organizations	Tool	Description	Source
AAD: American Academy of Dermatology	General skin cancer education	Information about skin cancer and its prevention, as well as consequences of tanning bed use	https://www.aad.org/public/spot-skin-cancer/learn-about-skin-cancer/types-of-skin-cancer
CDC: Centers for Disease Control and Prevention	Skin cancer and sun education	General skin cancer and sun education, with a link to handouts for families and students	https://www.cdc.gov/cancer/skin/basic_info/sun-safety.htm
COG: Children's Oncology Group	Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers	General guidelines for pediatric cancer survivors, with a section dedicated to skin	http://www.survivorshipguidelines.org
PeDRA: Pediatric Dermatology Research Alliance	Pediatric skin cancer handout	2-page handout detailing risk, detection, prevention, and treatment of pediatric skin cancer	https://pedsderm.net/for-patients-families/patient-handouts/#PediatricSkinCancer
SPD: Society for Pediatric Dermatology			
AAP: American Academy of Pediatrics			
US EPA: United States Environmental Protection Agency	Pediatric sun safety handouts	Activities, fact sheets, handouts reviewing sun safety	https://www.epa.gov/sunsafety/sun-safety-fact-sheets-and-handouts

parents, more than half of participants desired at least yearly reminders [81].

The Children's Oncology Group (COG) publishes guidelines for long-term follow-up in survivors of childhood cancer. These are updated periodically, and the COG *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* can be accessed at http://www.survivorshipguidelines.org. Separately, COG has published an update of late effects monitoring guidelines for patients with a history of HSCT [82]. In these late effects guidelines, annual (at least) skin examinations are recommended for all patients with a history of total-body irradiation and chronic GvHD.

To improve prompt recognition and treatment (when possible) of late cutaneous side effects of cancer therapies, it is helpful to educate patients and parents about presenting signs and symptoms. For example, discussing the time course of acute versus permanent alopecia and reviewing risk factors patients have accrued during their therapy can inform patients' and parents' expectations for outcomes. Moreover, given the distress and negative effects on quality of life associated with some of these sequelae [43], anticipatory guidance could improve screening and management of psychological late effects, as well.

As care for these complicated patients is often provided in teams, education of team members is also helpful. Transplant nurses and coordinators, oncologists, pharmacists, infectious disease specialists, and primary care physicians, in addition to dermatologists, all interact with oncology patients and can contribute to photoprotection messaging, as long as they are informed of patients' risks and know the contributions to risk of their portions of the patients' treatments.

Summary

In sum, many patients experience cutaneous late effects of their cancer therapies. By working with patients and their caregivers, we can improve late-effect monitoring and treatment.

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Index

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