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REVIEW ARTICLE

Pediatric Mastocytosis: Recognition and Management

Julie V. Schaffer[1]

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Abstract
Mastocytosis is a heterogeneous group of disorders characterized by the accumulation of clonal mast cells in organs such as the skin and bone marrow. In contrast to adults, most affected children have only cutaneous involvement. This article reviews the molecular pathogenesis, skin findings, mast cell mediator-related symptoms, evaluation, and management of childhood-onset mastocytosis, noting differences from adult-onset disease. Current classification of cutaneous mastocytosis and the natural histories of different variants in pediatric patients are highlighted, with a focus on clinical manifestations with prognostic implications. A practical algorithm is provided to guide clinical assessment, laboratory and other investigations, and longitudinal monitoring, including recognition of hepatosplenomegaly as a marker of systemic disease and utilization of allele-specific quantitative PCR (ASqPCR) to detect *KIT* mutations in the peripheral blood. Updated information and consensus-based recommendations regarding possible triggers of mast-cell degranulation (e.g., physical, medications) are discussed, with an emphasis on patient-specific factors and avoiding excessive parental concern. Lastly, an individualized, stepwise approach to treatment of symptoms, skin-directed therapy, and potential use of kinase inhibitors for severe systemic disease is outlined.

Key Points

The clinical features of pediatric mastocytosis help to predict the disease course, with earlier onset and shorter duration in children with large/polymorphic maculopapular skin lesions, diffuse cutaneous mastocytosis, and mastocytomas.

Extensive skin disease and an elevated serum tryptase level indicate increased risk of severe mast cell mediator-related symptoms, while hepatosplenomegaly and *KIT* mutations detectable in the peripheral blood represent markers of systemic disease.

An individualized approach to management includes recognition of pertinent triggers and treatment tailored to the frequency, severity, and type of symptoms.

1 Introduction

Mastocytosis is a heterogeneous group of disorders characterized by accumulation of clonal mast cells in organs such as the skin and bone marrow. It is traditionally divided into cutaneous and systemic forms, with the latter characterized by mast cell infiltrates in the bone marrow or extracutaneous tissues (Table 1) [1, 2]. Skin involvement occurs in > 80% of all mastocytosis patients [3]. Most children are suspected to have purely cutaneous disease, while most adults have systemic involvement [4].

This article reviews the pathogenesis, cutaneous and extracutaneous findings, evaluation, and management of childhood-onset mastocytosis. Current classification of cutaneous mastocytosis (CM) and the natural histories of different clinical variants in pediatric patients are highlighted, with an emphasis on clinical findings with prognostic implications.

2 Classification

Classification of CM is based upon the number of skin lesions and some morphological features as well as whether disease onset is during adulthood or childhood, with the

✉ Julie V. Schaffer
julie.schaffer@hmhn.org

[1] Division of Pediatric Dermatology, Hackensack Meridian School of Medicine at Seton Hall University, 155 Polifly Road, Suite 101, Hackensack, NJ 07601, USA

Table 1 WHO 2016 classification of mastocytosis and criteria for diagnosis

Cutaneous mastocytosis (CM)	
Subtypes of CM	Maculopapular CM (urticaria pigmentosa) Diffuse CM Cutaneous mastocytoma
Criteria for cutaneous involvement (mastocytosis in the skin)	Major: Typical skin lesions of mastocytosis associated with the Darier sign Minor: Increased numbers of mast cells in lesional skin Activating *KIT* mutation in lesional skin *1 major + 1 minor* required[a]
Systemic mastocytosis (SM)	
Subtypes of SM	Indolent SM[b] Smoldering SM[b] SM with associated hematologic neoplasm[c] Aggressive SM Mast cell leukemia
Criteria for SM	Major: Multifocal, dense infiltrates of MCs (≥15 MCs in aggregates) in BM or EC organ Minor: > 25% of MCs are atypical on BM smears or spindle-shaped in EC organs *KIT* codon 816 mutation in BM or EC organ MCs in BM, blood, or EC organ exhibit CD2 and/or CD25 Baseline serum tryptase >20 ng/mL[d] *1 major + 1 minor* or *3 minor* required
Mast cell sarcoma	

BM bone marrow, *EC* extracutaneous, *MC* mast cell

[a]In children, cutaneous mastocytosis is often diagnosed clinically without a skin biopsy and thus would not meet minor diagnostic criteria

[b]Frequently have cutaneous involvement and (by definition) lack organ impairment; smoldering SM is associated with 'B' findings (e.g., hepatosplenomegaly, lymphadenopathy, serum tryptase >200 ng/mL + MC infiltration in BM > 30%, hypercellular BM)

[c]Previously SM with clonal hematologic non-mast cell-lineage disease

[d]Not valid as an SM criterion in the case of an unrelated myeloid neoplasm

latter variably defined as < 15–17 years of age [5, 6]. In addition to more diversity in the underlying *KIT* mutations, childhood-onset mastocytosis is usually limited to the skin and often has spontaneous regression before puberty. However, the clinical features of the skin lesions that develop in pediatric patients help to predict the prognosis and disease course. Skin involvement in CM is categorized into three main groups, which are discussed below; (i) maculopapular CM, also referred to as urticaria pigmentosa; (ii) diffuse CM; and (iii) cutaneous mastocytoma [4, 7]. Table 2 summarizes

Table 2 Clinical variants of childhood-onset mastocytosis

	Maculopapular		Diffuse	Mastocytoma
	Small/monomorphic[a]	Larger/polymorphic		
Proportion of patients in 10 pediatric series ($n = 1076$) [6–15]	70% (all maculopapular variants) 12%	58%	5%	25%[b]
Typical age of onset	> 2 years	Birth to 6 months	Birth to 6 months	Birth to 6 months
Typical duration	> 10–14 years	≤ 7–10 years	≤ 7–10 years[c]	≤ 7–10 years
Tryptase level	Sometimes elevated	Rarely elevated	Typically highly elevated	Normal

[a]This variant is similar to typical adult-onset maculopapular mastocytosis

[b]Likely underrepresented in the literature, since affected children are less frequently referred to a pediatric dermatologist or mastocytosis center

[c]Longer duration in a rare subset of patients with familial disease

the features of different clinical variants of childhood-onset CM [6, 8–16].

3 Pathogenesis

Somatic activating mutations in the *KIT* gene, which encodes a tyrosine kinase receptor that induces mast cell growth and maturation, play a central role in the pathogenesis of mastocytosis. A particular *KIT* mutation affecting the second catalytic domain in exon 17, D816V, underlies > 80% of adult-onset cases. In contrast, a wider variety of *KIT* mutations occur in patients with childhood-onset mastocytosis: codon 816 in ~ 35–40%; exons 8–11 in ~ 35–40%; and no detectable mutation in ~ 15–20% of those with complete *KIT* sequencing of a lesional skin sample [15, 17–20]. In one recent study of childhood-onset CM, having a codon 816 mutation or congenital disease was significantly associated with spontaneous regression [21]. A significant correlation between the mutational status of skin lesions and the subtype, severity, or time course of pediatric mastocytosis has not been observed in other studies, although the results of some have suggested less spontaneous improvement in those with no detectable *KIT* mutation [6, 15, 18, 19]. In addition, rare *germline KIT* mutations have been reported in familial forms of mastocytosis [22, 23].

4 Clinical Types

4.1 Maculopapular Cutaneous Mastocytosis

This type of CM presents with multiple yellow-tan or pink-tan to brown or red-brown lesions, ranging from < 10 to > 100 in number. Two variants of maculopapular mastocytosis are currently recognized based on the morphology of the lesions: *small/monomorphic* and *large/polymorphic*. A telangiectatic variant (formerly referred to as telangiectasia macularis eruptiva perstans) thought to occur primarily in adults was excluded from the current classification [4].

Small, monomorphic macules and thin papules resemble the classic urticaria pigmentosa type of mastocytosis lesions commonly seen in adults. This variant tends to develop in older children or adolescents and to persist for a longer period of time. Lesions usually have a round shape and favor the trunk and proximal extremities (Fig. 1). They may

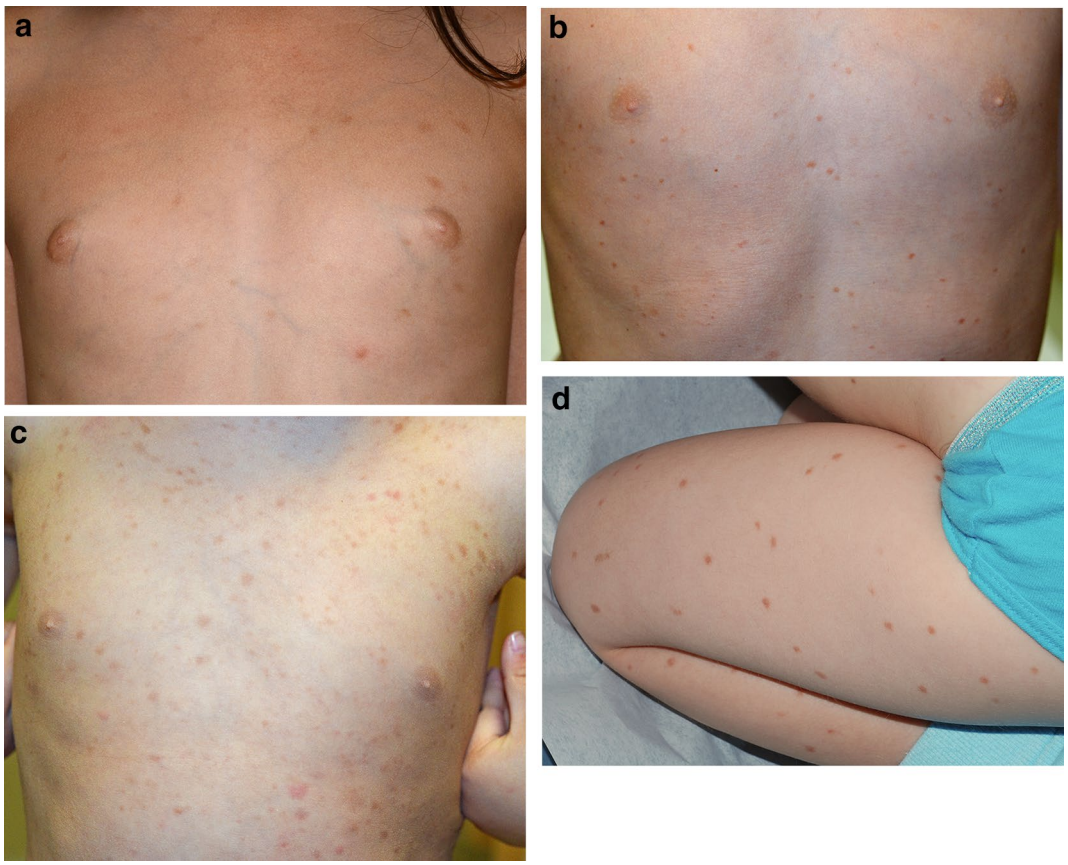

Fig. 1 Maculopapular cutaneous mastocytosis in school-aged children with variable numbers of small, monomorphic, pink-tan to brown macules or thin papules on the chest (**a**–**c**) and thigh (**d**). These 'urticaria pigmentosa' lesions could be mistaken for melanocytic nevi or lentigines

have an appearance similar to lentigines and melanocytic nevi, with elicitation of the Darier sign helping to confirm the diagnosis (see Sect. 5); in patients with Fitzpatrick skin phototype I, the lesions can be pink to red in color.

Larger, polymorphic papules, plaques, and/or nodules of variable sizes usually arise during infancy and often regress spontaneously by the second decade of life [8, 24, 25]. Lesions in this variant are heterogeneous in shape (round, oval, or irregular), margination (sharp or indistinct), and degree of confluence as well as size (with some lesions ≥ 1 cm in diameter) and elevation (Fig. 2) [4, 6, 15]; it encompasses types of CM previously referred to as 'plaque' and 'nodular' [4, 8, 26]. In some patients, there is progression over the years from nodules to plaques to macules [4, 6]. The distribution is often widespread on the trunk, extremities, head, and neck, classically sparing the palms, soles, and central face.

In patients with childhood-onset maculopapular CM followed at a German mastocytosis clinic [6], the mean age of onset was 7.3 years (> 2 years in 58%) in individuals with small/monomorphic lesions ($n = 19$), but only 4.7 months (≤ 6 months in 84%) in those with large/polymorphic lesions ($n = 89$). Patients with the small/monomorphic variant had a significantly higher mean tryptase level than those with the large/polymorphic variant (44 and 7 ng/mL, respectively), and the mean tryptase level was also higher in those with confluent compared with nonconfluent lesions (34 and 8 ng/mL, respectively). The mean disease duration was 24.7 years (≤ 7 years in 5%, > 14 years in 58%) in individuals with small/monomorphic lesions, compared with 5.9 years (≤7 years in 69%, > 14 years in 6%) in those with large/polymorphic lesions.

A long-term follow-up study of 53 pediatric mastocytosis patients with a mean disease duration of 12 years found

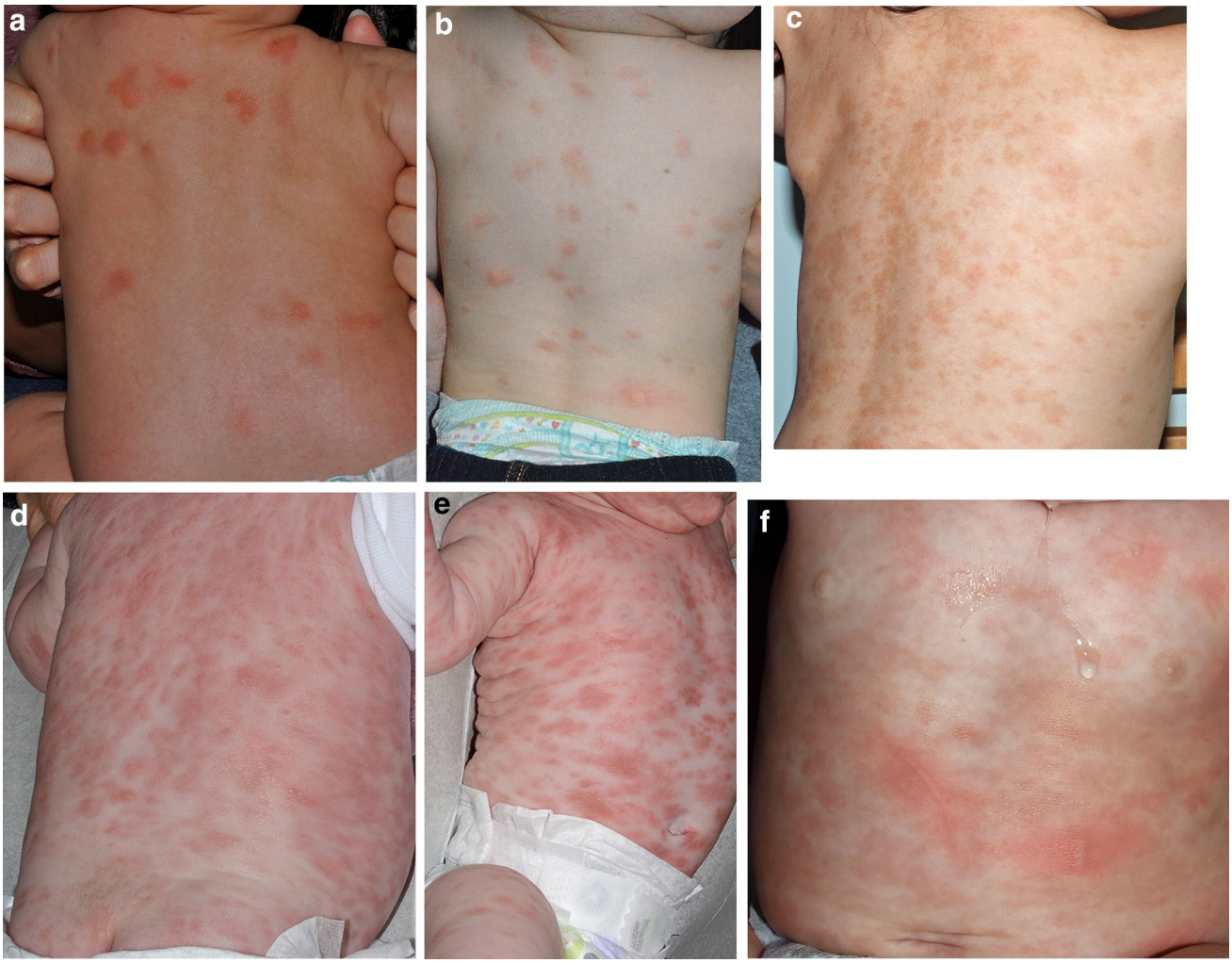

Fig. 2 Maculopapular cutaneous mastocytosis in infants presenting with a few to numerous polymorphic macules, papules, plaques, and papulonodules on the trunk and proximal extremities (**a**–**f**). Note the variation in color, elevation, shape, margination, and degree of confluence. Photo **a** courtesy of Mercedes Gonzalez, MD

that disease onset before 2 years of age was associated with a higher likelihood of skin improvement (79%) than onset after 2 years of age (36%) [15]. Another series of pediatric patients with maculopapular CM ($n = 227$) found that those with onset at < 2 years of age had significantly lower serum tryptase levels [27]. A fourth study of 43 pediatric maculopapular CM patients followed at a pediatric dermatology center for a median of 8 years found that earlier disease onset, less extensive skin involvement, and (in contrast to Wiechers et al. [6]) smaller lesions were associated with resolution prior to 12 years of age [28].

Considering that childhood-onset mastocytosis persists until adulthood in some patients (estimated as ~ 20–30%) [15, 29, 30], this group accounts for a proportion of adults with mastocytosis. For example, a prospective study in France found that 20% of adults with mastocytosis (28/142) had disease onset at age ≤ 15 years; most of these individuals had maculopapular skin lesions (86%) and systemic disease (75%) [31]. Some authors have suggested that such patients, who tend to have small/monomorphic lesions, could be characterized as having an early-onset form of 'adult' mastocytosis [6].

4.2 Diffuse Cutaneous Mastocytosis

Diffuse CM is defined as a generalized distribution of thickened skin that has a leathery or 'peau d'orange' texture, with variable hyperpigmentation and erythema (Fig. 3). This category of CM does *not* include patients with extensive individual maculopapular lesions that have become confluent [4, 32]. Diffuse CM presents within the first few months of life, and prominent blistering may lead to initial suspicion of conditions such as epidermolysis bullosa or staphylococcal scalded skin syndrome (see Fig. 3) [32–36]. Some affected infants develop hemorrhagic bullae, likely related to local heparin release from mast cells [4, 34]. Flushing and gastrointestinal symptoms secondary to mast cell mediator release (see below) are also common and often severe during the first 2 years of life [34, 35]. Potentially fatal complications such as anaphylactic shock, electrolyte imbalances, and gastrointestinal bleeding occasionally develop [35, 37, 38].

Tryptase levels in patients with diffuse CM are usually elevated (sometimes > 100 µg/L) but tend to decrease over time [6, 32]. Like large/polymorphic maculopapular CM, diffuse CM typically regresses by puberty, sometimes leaving a cutis laxa-like appearance [32]. However, a rare familial variant with autosomal dominant inheritance of germline *KIT* mutations in exon 8 or 9 is characterized by mast cell infiltrates in other organs and a chronic course [6, 22, 23]. More persistent diffuse CM may also evolve to a pseudoxanthomatous appearance with doughy papules superimposed on yellowish skin [34].

4.3 Cutaneous Mastocytoma

A mastocytoma presents as a yellow-tan to brown papule, nodule, or plaque, which often has a leathery texture that represents a clue to the diagnosis (Fig. 4) [39]. The current CM classification removed the 'solitary' designation, utilizing the term mastocytoma for patients with up to three lesions [4]. Mastocytomas usually develop within the first 6 months of life, with approximately half apparent at birth, and regress by puberty [6, 32, 39]. They may be found anywhere on the skin, favoring the extremities in some series [40]. Lesions may blister during the first 2–3 years of life, especially when in a location that is subjected to friction or pressure (see below). The diagnosis of mastocytoma should

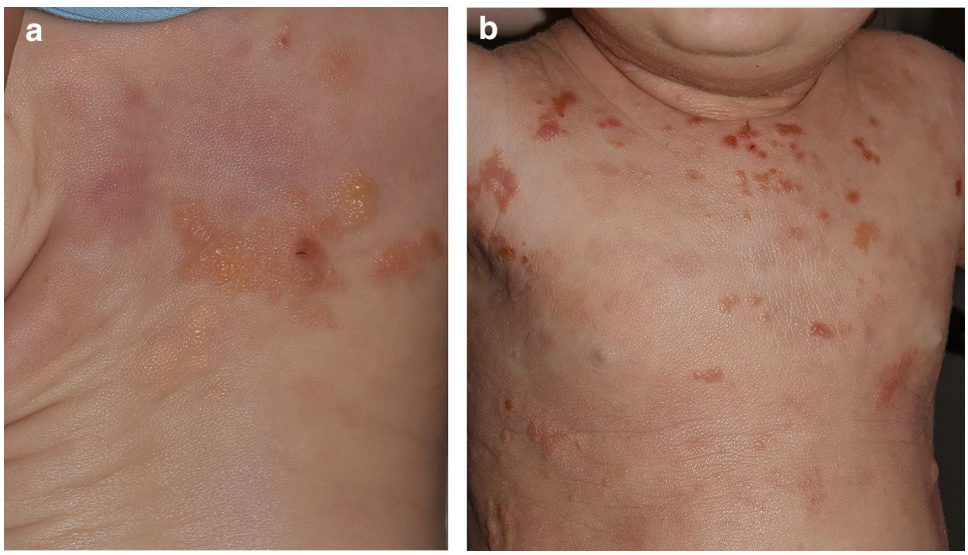

Fig. 3 Diffuse cutaneous mastocytosis in infants producing a leathery, pigskin-like texture on the back (**a**) and chest (**b**). Note the blistering and erosions. Photos courtesy of Helen Shin, MD

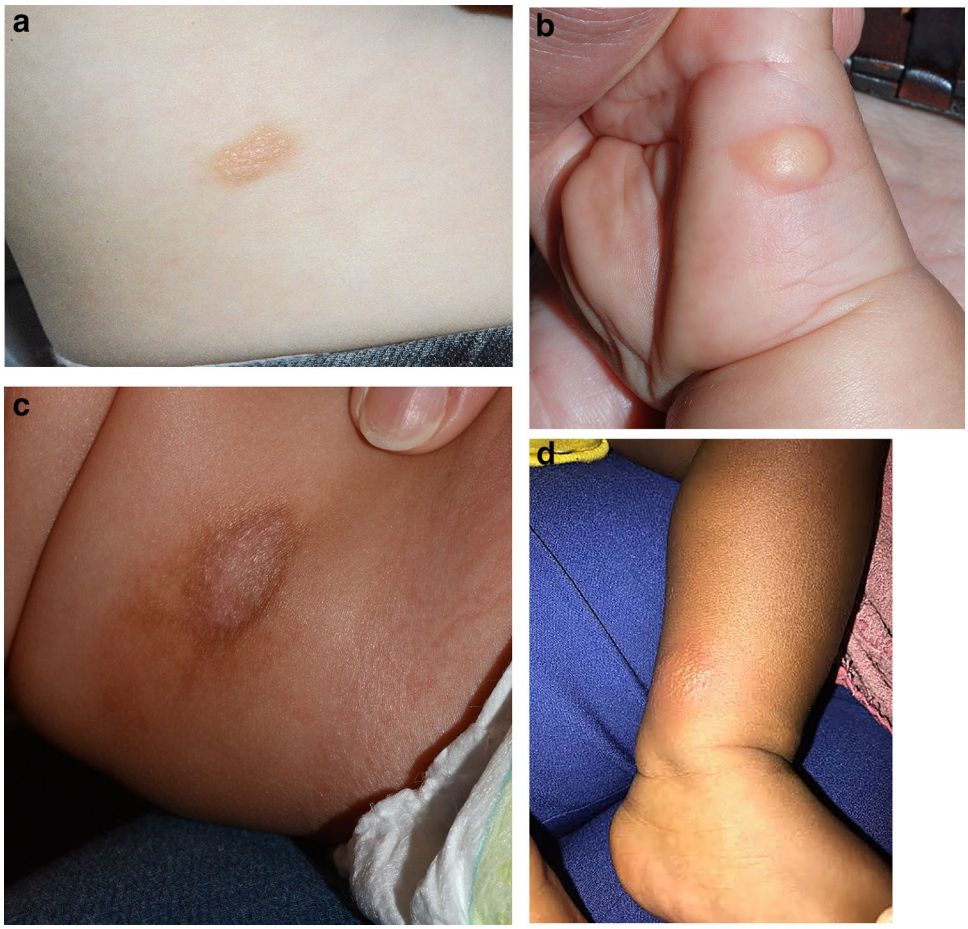

Fig. 4 Mastocytomas in infants and young children appearing as a yellow-tan plaque with a leathery texture (**a**), yellow nodule with swelling and a pink rim due to urtication (**b**), brown plaque with central pink color due to prior erosion (**c**), and vesiculating plaque (**d**). Photo **d** courtesy of Mercedes Gonzalez, MD

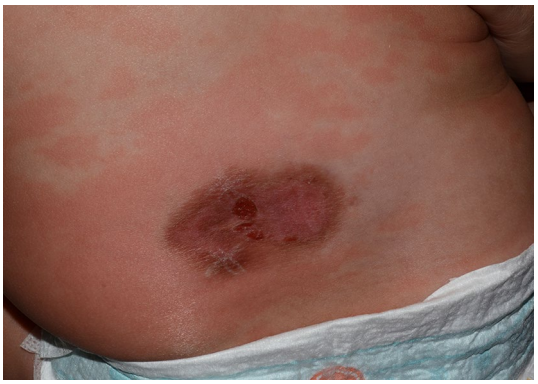

Fig. 5 Large, thick, focally eroded mastocytoma on the back of an infant, with urtication due to rubbing leading to widespread hiving and flushing

be considered for a lesion or site with recurrent blistering in an infant. Mastocytomas may also be mistaken for melanocytic nevi, connective tissue nevi, xanthogranulomas, persistent arthropod bite reactions, dermatitis, pseudolymphomas, or (with blistering) child abuse. Larger, thicker mastocytomas can contain a high density of mast cells, and their degranulation occasionally results in flushing or, rarely, hypotension (Fig. 5) [41].

4.4 Segmental Cutaneous Mastocytosis

Occasionally, patients present with mastocytosis lesions confined to a segment or region of the body. Referred to as 'nevoid urticaria pigmentosa,' this has been proposed to reflect a mosaic manifestation of the disease, although not yet confirmed on a molecular level [42, 43]. Such lesion may mimic a nevus spilus or telangiectatic vascular anomaly [44, 45].

5 Other Cutaneous Findings

The *Darier sign* is a useful tool in the diagnosis of CM, and the refined major criterion for CM is typical skin lesions associated with a Darier sign [4]. An urticaria-like wheal is elicited by stroking skin lesions using moderate pressure (e.g., with the wooden end of a cotton-tip applicator) (Fig. 6); when done in nonlesional skin, the reaction should be absent or (if dermographism is present) less prominent.

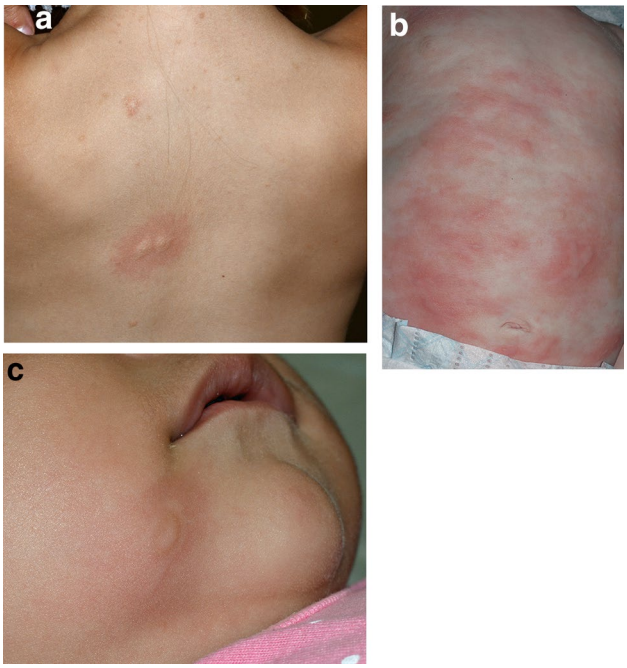

Fig. 6 Darier sign in pediatric mastocytosis patients with small/monomorphic maculopapular lesions (**a**), coalescing large/polymorphic lesions (**b**), and a mastocytoma (**c**)

The Darier sign is usually positive in pediatric patients with mastocytosis. In young children with a large mastocytoma or nodular lesions, testing for the Darier sign should be avoided or performed very gently, as it can potentially provoke flushing or even hypotension [4, 32].

Dermoscopic findings in cutaneous mastocytosis include diffuse light brown blot (most common), ill-defined yellow-orange blot (especially in mastocytomas and nodular lesions), pigment network, and reticular vascular patterns [46].

Blistering following urtication is a common occurrence in infants with large, thick lesions or diffuse CM (Fig. 7), and it most frequently affects the head and sites subjected to friction or pressure [4, 32]. Bullous lesions were described in a third of pediatric mastocytosis cases analyzed in a recent systematic review [18]. The tendency to blister is thought to be related to release of serine proteases from mast cells [33], and it usually ceases by 2–4 years of age [4, 9, 24, 34, 47].

6 Mast Cell Mediator-Related Symptoms

Symptoms in pediatric mastocytosis typically result from the release of mast cell mediators such as histamine, eicosanoids, and cytokines from skin lesions. In a systematic

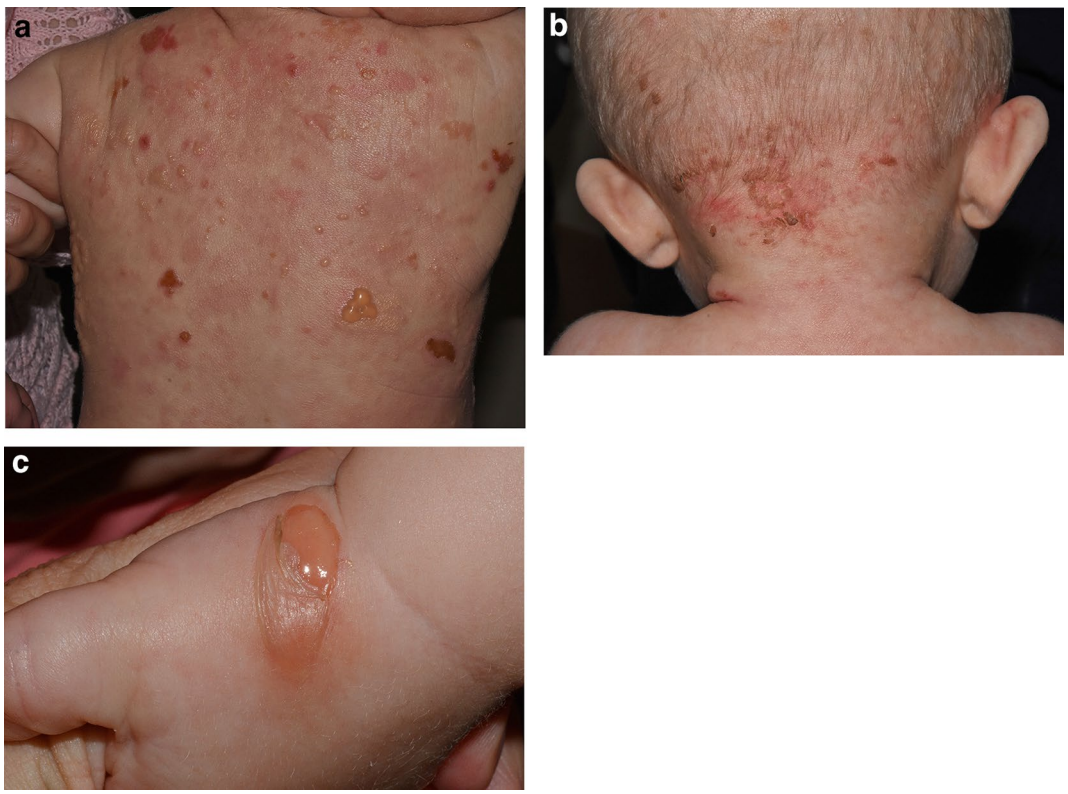

Fig. 7 Blistering and erosions in infants with diffuse cutaneous mastocytosis (**a**, **b**) and a mastocytoma (**c**). Photos **a** and **b** courtesy of Helen Shin, MD

review of the literature on pediatric mastocytosis, the approximate proportion of patients with mast cell mediator-related manifestations were as follows: flushing in 25%; gastrointestinal symptoms (e.g., abdominal pain, diarrhea, nausea/vomiting) in 20%; bone pain in 15%; and anaphylaxis in 5% [18]. Systemic symptoms are most common in patients with extensive or diffuse skin disease, and their frequency correlates with the number of skin lesions and skin symptoms in children with maculopapular CM [4, 27, 32, 48].

In a recent series from five pediatric dermatology centers [49], anaphylaxis occurred in 4% (9/227) of patients with maculopapular CM and was associated with having a greater number of systemic and cutaneous symptoms. Heinze et al. [28] observed no anaphylaxis in 43 pediatric patients with maculopapular CM followed for a median of 8 years. In contrast to the overall anaphylaxis rate of ≤ 5% in pediatric mastocytosis [18], adult mastocytosis patients have a substantially higher risk of anaphylaxis, ranging from 20 to 50% in different studies [50]. Anaphylaxis in pediatric mastocytosis is idiopathic in ~ 60–70% of cases [51, 52], whereas hymenoptera stings represent the most common cause in adult mastocytosis (see below) [53]. Other causes of anaphylaxis in pediatric mastocytosis series include foods (~10–20%), drugs (< 10%), and hymenoptera stings (< 10%) [51, 52].

Previous reports suggested that pediatric mastocytosis may be associated with an increased risk of autism spectrum disorders and learning disabilities [54, 55]. However, Gurnee et al. [49] found that 10.5% (9/86) of maculopapular CM patients aged 3–18 years had a neurodevelopmental disorder, similar to the ~14% prevalence in the same age group within the general US population. Interestingly, an association of CM with a neurodevelopmental disorder caused by mutations in the *GNB1* gene, which encodes a G protein β subunit, has been reported [56].

7 Evaluation

7.1 Cutaneous Histopathology

Diagnosis of mastocytosis in the skin officially requires the aforementioned major criterion of typical skin lesions associated with a Darier sign plus at least one of two minor criteria: (1) histologic evidence of increased numbers of mast cells in lesional skin; and (2) detection of an activating *KIT* mutation in lesional skin [2, 4]. However, in clinical practice, mastocytomas and maculopapular CM in children are often diagnosed based on their clinical features without a skin biopsy for histologic confirmation [27, 28, 32, 48, 49].

The density of mast cells is typically high in mastocytomas and diffuse CM. Although few studies have focused on the histopathologic features of childhood CM, some authors have observed that large/polymorphic maculopapular CM tends to have a high density of mast cells with a round or cuboidal shape, whereas small/monomorphic CM typically has a lower density of mast cells with a spindle shape [4, 32, 57, 58]. Staining with toluidine blue, Giemsa, and antibodies that recognize CD117 (KIT) or tryptase can help to identify less prominent mast cell infiltrates in the skin and other tissues. Of note, staining for CD2 and CD25, which represent markers of bone marrow mast cells in systemic mastocytosis, is often negative in cutaneous mast cells [4]. Recent series have found that CD30 staining is frequently positive in lesional mast cells of childhood-onset CM (~ 85–95% of cases, maculopapular CM and mastocytomas) as well as various forms of systemic mastocytosis (≥80% of cases), but not in mast cells from normal skin or urticaria lesions [58–61]. Lesional expression of CD2, CD25, and/or CD30 in childhood-onset CM has not been shown to correlate with the clinical subtype or disease course [59, 60]. Some studies have found that expression of CD2 and/or CD25 in maculopapular skin lesions is more frequent in adults with systemic than skin-limited mastocytosis [62, 63]. In a recent study, expression of CD30 in maculopapular skin lesions of adults with systemic mastocytosis was associated with involvement of skin folds and sheet-like infiltration of dermal mast cells, but not disease course [64].

7.2 Laboratory Testing, Imaging, and Bone Marrow Biopsy

Tryptase, a serum protease, represents the most abundant mediator stored in mast cell granules. The baseline serum tryptase level can serve as a marker for the extent of mast cell disease and an indicator of risk for anaphylaxis and other severe reactions in children with mastocytosis [13, 27, 52, 65, 66]. In patients with elevated serum tryptase levels, periodic assessment (e.g., every 6–12 months) can be used to monitor the disease course, with decreasing levels typically observed as symptoms improve over time [65]. Although a serum tryptase level of > 20 ng/mL represents a WHO minor criterion for the diagnosis of systemic mastocytosis (normal range < 11.5 ng/mL) [2], pediatric mastocytosis patients with elevated tryptase levels do not necessarily have systemic disease. Likewise, systemic symptoms due to mast cell mediator release are not indicative of systemic disease and can occur in patients with normal serum tryptase levels [67].

In a National Institutes of Health (NIH) study, 53 pediatric mastocytosis patients with serum tryptase levels > 20 ng/mL and/or severe mast cell mediator-related symptoms underwent bone marrow biopsy. All 19 of those with hepatosplenomegaly had systemic disease, whereas none of the 34 patients without hepatosplenomegaly had systemic disease, representing 100% sensitivity and specificity [65]. A subsequent NIH study assessed the utility of allele-specific

quantitative PCR (ASqPCR) for *KIT* D816V mutation detection in the peripheral blood to assess for systemic disease in 65 pediatric mastocytosis patients. The ASqPCR was negative in all 37 children with only cutaneous disease and positive in 21/28 of those with systemic disease, corresponding to specificity and sensitivity of 100% and 75%, respectively [68]. In a recent study of 32 Polish children with diffuse CM or maculopapular CM involving > 50% of the body surface area (87.5% with elevated serum tryptase levels and 19% with hepatosplenomegaly), a *KIT* D816V mutation was detected in the peripheral blood in 11 (34%); a subsequent bone marrow biopsy was positive in 4/5 of these patients who had persistently elevated or rising tryptase levels, one of whom also had hepatomegaly [69].

Evaluation of pediatric patients with a new diagnosis of diffuse CM or maculopapular CM with severe symptoms or extensive disease typically includes a complete blood count with differential and hepatic function panel as well as a baseline serum tryptase level [70] (Fig. 8). Some studies have also noted hypogammaglobulinemia in 15–20% of infants and toddlers with CM [71, 72]. However, costs should be considered and unnecessary laboratory evaluation avoided in patients with milder disease. Assessment for hepatomegaly should be performed via clinical examination and (in high-risk patients) abdominal ultrasound. In patients with hepatosplenomegaly and/or elevated tryptase levels, *KIT* D816V mutation detection in the peripheral blood can help to identify individuals at increased risk of systemic mastocytosis, decide whether a bone marrow biopsy should be considered, and follow disease progression over time [68, 69] (see Fig. 8).

It is recommended that complete staging including a bone marrow biopsy be offered to all *adult* CM patients, who have a high likelihood of systemic involvement. This can also be considered in teenage patients with new-onset mastocytosis (especially if severe or extensive) or progressive disease. In contrast, bone marrow biopsy is rarely needed in childhood CM, as the results do not typically affect prognosis or management [4, 73].

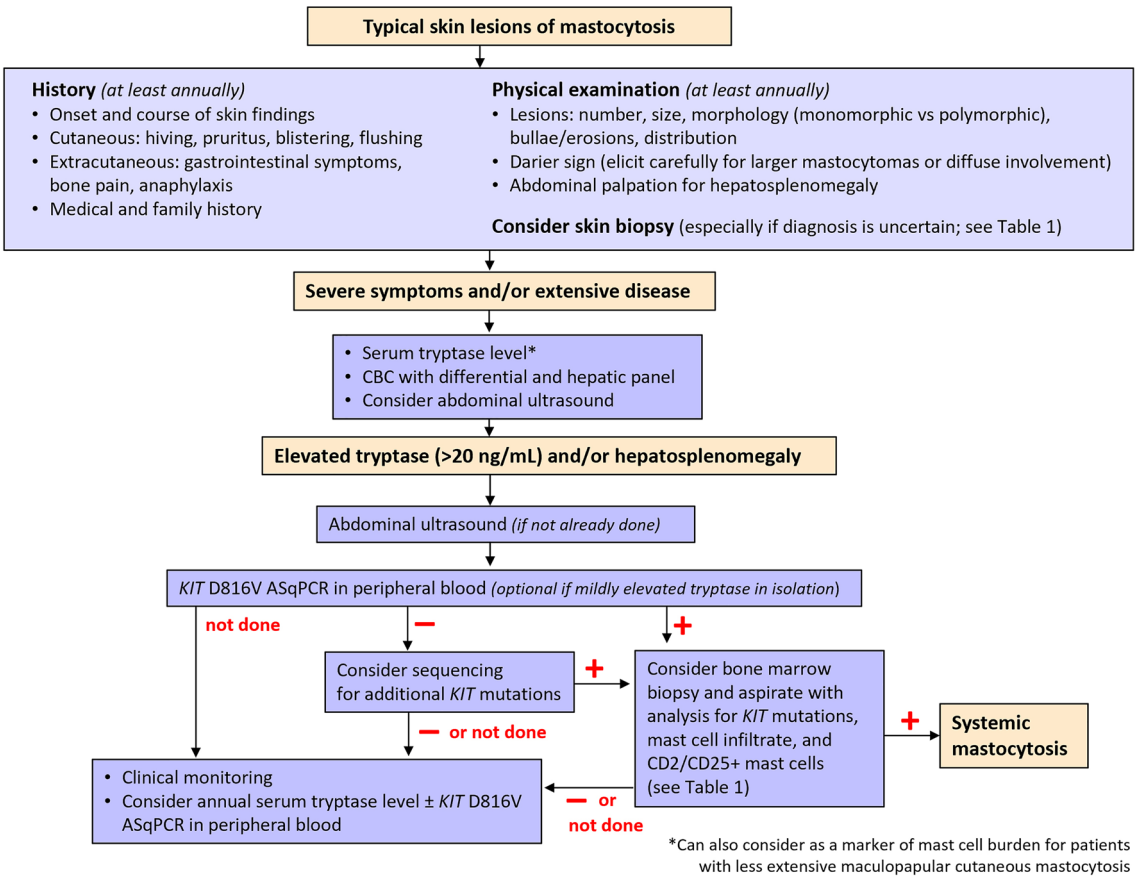

Fig. 8 Approach to the evaluation of pediatric patients with cutaneous mastocytosis. For patients with milder disease, only clinical monitoring (described in the top box of the algorithm) is necessary. *ASqPCR* allele-specific quantitative PCR

8 Management

8.1 Avoidance of Triggers

Mastocytosis patients and their caregivers should be provided with information on factors that can induce symptoms via mast cell mediator release [74]. The triggers vary greatly in different individuals and may include environmental (e.g., friction, heat) and dietary (hot beverages, spicy foods) stimuli as well as mast cell-degranulating medications (Table 3) [30, 41, 74, 75]. Simple measures such as preventing lesions from being rubbed and avoiding heat exposure or abrupt temperature changes can have substantial impact in reducing flares [74].

A variety of medications have been implicated as potential triggers of mast cell degranulation (Table 3). These include nonsteroidal anti-inflammatory drugs (NSAIDs), dextromethorphan, opioids (e.g., morphine, codeine), and muscle relaxants. Extensive lists available on the internet designate many agents as mast cell degranulators, often based on data that is not reliable or relevant [76]. This can lead to excessive concern in parents of children with mastocytosis [77]. However, significant reactions to such agents are uncommon. For example, in a recent series, none of 37 children with maculopapular CM who received ibuprofen experienced a reaction [28]. In another study, only 2% (2/96) of pediatric mastocytosis patients who received an NSAID had a reaction [78]. A recent Work Group Report from the Mast Cell Disorder Committee of the American Academy of Allergy, Asthma and

Table 3 Management of pediatric mastocytosis

Potential environmental and dietary triggers	Friction, pressure Heat, cold, sudden temperature changes Alcohol Hot beverages, spicy foods
Drugs with potential to trigger mast cell degranulation	Opioids: codeine, morphine Muscle relaxants: atracurium, mivacurium, rocuronium Aspirin, NSAIDs Dextromethorphan Dextran (in IV solutions)
Lower risk alternatives	Opioids: fentanyl, sufentanil, remifentanil Muscle relaxants: pancuronium, vecuronium, cisatracurium Hypnotics: midazolam, propofol, etomidate, ketamine Inhaled anesthetics: sevoflurane, desflurane
Treatment of mast cell mediator-related symptoms	
First-line	Second-generation H1 antihistamines (up to 4× standard dose and/or multiple agents)
For anaphylaxis	Epinephrine autoinjector
Other options	Sedating H1 antihistamines H2 antihistamines (adjunctive or for GI) Leukotriene antagonist Cromolyn sodium: oral for GI, topical for skin Omalizumab Oral corticosteroid (short course)
Skin-directed treatment	
First-line	Topical corticosteroids, class 1–3 (2–6 week cycles ± occlusion)
Other options	Pimecrolimus Intralesional corticosteroid Hydrocolloid dressing (for mastocytoma) Excision (for mastocytoma) Narrowband UVB or PUVA
Treatment for severe systemic disease	
FDA-approved for aggressive systemic mastocytosis in adults	Midostaurin (D816V or wild type *KIT*) Imatinib (non-exon 17 *KIT* mutation)
Other options	Masitinib (under investigation) Avapritinib (under investigation) Interferon-α-2b Cladribine

GI gastrointestinal, *IV* intravenous, *NSAID* nonsteroidal anti-inflammatory drug, *PUVA* psoralen plus UVA

Immunology (AAAAI) concluded that avoiding NSAIDs in mastocytosis patients might be unwarranted and should be approached on an individual basis, considering patients' previous experiences with these medications [76]. Mastocytosis patients (adults > children) may also develop hypersensitivity reactions to the same drugs (e.g., β-lactam antibiotics, radiocontrast media) as the general population, and there is no need to withhold such medications if there is no history of sensitivity [76].

Because medications commonly used in anesthesia can degranulate mast cells, parents and medical providers of pediatric mastocytosis patients are often anxious about procedures requiring conscious sedation or general anesthesia [77, 78–81]. Local anesthesia (e.g., with lidocaine injection) is considered to be safe in individuals with mastocytosis [81]. In four series of pediatric mastocytosis patients who underwent general anesthesia (total $n = 84$), only one patient had a severe reaction [77, 79, 82, 83]. Children with more extensive CM and elevated serum tryptase levels generally have a higher risk of anaphylaxis [13, 52, 76], although perioperative anaphylaxis has been reported in a child with a large cutaneous mastocytoma [41]. Risk factors for perioperative anaphylaxis in adult mastocytosis patients include general anesthesia, major surgery, lack of premedication, and a history of anaphylaxis [81, 83]. Friction, pressure (e.g., from a tourniquet), infusion of cold solutions, other temperature changes, and emotional stress may also contribute to perioperative mast cell activation [81, 84].

In addition to choosing anesthetic agents with a low capacity to elicit mast cell degranulation and avoiding environmental triggers (Table 3), some authors recommend premedication for high-risk procedures/patients with H1– ± H2-antihistamines (1–2 h prior to procedure) and potentially prednisone (12–24 and 1–2 h prior to procedure) and/or a benzodiazepine [41, 50, 81]. Others recommend maintaining regularly scheduled antihistamine treatment before and after procedures [77, 79, 84]. The recent AAAAI Work Group Report found insufficient evidence to recommend routine prophylactic administration of antimediator medications prior to anesthetic procedures in patients with mastocytosis [76]. It is helpful for the patient's mastocytosis specialist, provider performing the procedure, and anesthesiologist to develop a plan ahead of time [80, 81].

The rate of vaccine reactions may be slightly higher in pediatric mastocytosis patients than the approximately 3–6% incidence in the general population [76]. In a recent study [85], 4 of 75 children with mastocytosis (6%) had a reaction following their first dose of hexavalent vaccination (urticaria within 1–4 h, bullae, mild bronchospasm); none had reactions with subsequent vaccinations, including boosters of the same vaccine. In general, vaccines should be administered on the recommended schedule in children with mastocytosis, although postvaccination observation for 1–2 h is recommended and single-vaccine regimens can be considered in those with extensive CM [76].

Although it has been suggested that dietary intake of histamine/biogenic amines and 'histamine-releasing foods' may potentially exacerbate mastocytosis symptoms, no studies have shown benefit from a 'low histamine' diet [86]. Long lists of histamine-containing (e.g., cured meats, smoked fish, aged cheeses, fermented foods, eggplant, spinach) and histamine-releasing (e.g., citrus fruits, strawberries, pineapple, tomatoes, nuts, shellfish, chocolate, additives) foods can be found on the internet, but there is little scientific evidence behind these designations [87]. Despite this, a recent survey from The Mastocytosis Society support group found that 25% (94/382) and 35% (132/382) of patients (including adults and children) had tried a 'low histamine' or 'elimination' diet, respectively, with only 50–60% of these individuals feeling that they had adequate nutrition [88].

The prevalences of food allergies and other atopic conditions in children with mastocytosis are similar to those in the general pediatric population [50–53]. Although foods are the most common cause of allergy reported by history in pediatric mastocytosis patients, only a small minority of these patients have specific IgE antibodies to the suspected allergen [53]. It should be emphasized to families that mastocytosis does not cause food or drug allergies, although children with a high total mast cell burden who do have an allergy may potentially have a more severe reaction [76]. Avoidance of particular foods is not recommended for mastocytosis patients without a history of food sensitivity [89].

Hymenoptera stings are an infrequent cause of anaphylaxis in children with mastocytosis but represent the most common trigger of anaphylaxis in *adults* with mastocytosis, typically men without CM lesions who develop hypotension and syncope in the absence of urticaria or angioedema [90]. Conversely, up to 7% of adults with Hymenoptera venom allergy have an underlying clonal mast cell disease [91, 92]. The overall prevalence and severity of hymenoptera allergy is greater in boys and men than in girls and women [53]. In general, higher serum tryptase levels are associated with an increased risk of severe reactions in children with insect venom hypersensitivity [93]. Venom immunotherapy should be utilized for patients with systemic reactions, and lifetime treatment is required for adults with systemic mastocytosis [91].

8.2 Epinephrine Autoinjectors

Although the exact indications have been the subject of debate, prescription of an epinephrine autoinjector [EAI] is often recommended for pediatric mastocytosis patients with extensive skin involvement, a history of anaphylaxis or other severe symptoms, and/or elevated serum tryptase levels [50, 53, 70, 75, 76]. In a series of children with maculopapular

CM at two pediatric dermatology centers, 69% (92/133) were prescribed an EAI but no patients experienced anaphylaxis, with one patient using it following intake of a known food allergen [94]. Although epinephrine represents the first-line treatment for anaphylaxis, it is underutilized in pediatric patients [41, 53]. When prescribed, patients should be given the appropriate epinephrine dose for their body weight (0.1 mg for 7.5–15 kg, 0.15 mg for 15–30 kg, 0.3 for >35 kg). There is expert consensus that epinephrine is safe for infants and, if there is no alternative, administration of a 0.15 mg or 0.1 mg dose to a child weighing <15 kg or <7.5 kg, respectively, poses little risk [95]. Parents, teachers, and other caregivers should receive an emergency action plan and be instructed regarding why, when, and how to use the EAI.

8.3 Treatment of Symptoms

The main goal of CM treatment is control of symptoms caused by the release of mast cell mediators [50, 70, 74]. The approach to therapy is stepwise and should consider the severity, frequency, and type of manifestations [74]. The first-line medications for patients with frequent and/or problematic symptoms are second-generation, low-/non-sedating H1-antihistamines administered on a continuous basis [50, 75]. Use of higher antihistamine doses (up to 4 times the standard dose) or multiple agents may be required [50, 75]; this mirrors the approach that is utilized for chronic urticaria [96, 97]. On-demand treatment can be used for individuals with less frequent flares.

Addition of an H2 antihistamine (especially for patients with gastric acid hypersecretion) or leukotriene antagonist (e.g., montelukast) may provide further benefit in patients with persistent symptoms [98]. Oral cromolyn sodium (disodium cromoglycate; 15–20 mg/kg/day in children, maximum 800 mg/day), a mast cell stabilizer with poor oral absorption, may lessen gastrointestinal symptoms. Topical cromolyn sodium 4% lotion or cream also has potential utility and can be compounded by a pharmacy or families [74, 99, 100].

Omalizumab is a monoclonal antibody against IgE that has the potential to reduce mast cell expression of the FcεRI and release of mediators, although its mechanism of action in mastocytosis remains to be determined [101, 102]. It is approved for chronic idiopathic urticaria (ages ≥ 12 years) and asthma (ages ≥ 6 years), with administration via subcutaneous injection. Treatment of severe diffuse CM in children as young as 2 years of age with omalizumab has been reported, with 150–300 mg every 2–4 weeks resulting in a dramatic reduction in mast cell mediator-related symptoms but stable tryptase levels [103]. A systematic review of studies in adults with systemic ($n = 56$) or cutaneous ($n = 13$) mastocytosis treated with omalizumab (typically 300 mg every 2–4 weeks) found that complete resolution of anaphylaxis episodes, cutaneous symptoms, and gastrointestinal manifestations were observed in 84%, 29%, and 27% of patients, respectively, with a mean of 2 months until the first response [102]. A recent randomized controlled trial in 16 adults with systemic mastocytosis found a 50% reduction in the median AFIRMM severity score (from 52 to 26) in patients treated with omalizumab 150–300 mg every 4 weeks for 6 months, but the difference from placebo (104–102) was not statistically significant [104].

Although systemic corticosteroids are not generally recommended as a CM treatment due to their problematic side effects, short-term administration is occasionally beneficial in children with extensive CM associated with extremely severe mediator-related symptoms and recalcitrant blistering [50, 105]. A 2-to 4-day course of prednisone may also be employed to prevent recurrent reactions following anaphylaxis.

8.4 Skin-Directed Therapy

To date, there have been no randomized controlled studies showing faster resolution of cutaneous mastocytosis from topical treatments or photo(chemo)therapy.

Pimecrolimus has been shown to induce mast cell apoptosis and prevent mediator production in a mouse model of mastocytosis [106]. Mashiah et al. [107] recently reported the treatment of mastocytomas or maculopapular CM in 18 children (mean age 16 months, range 3–42 months) with pimecrolimus 1% cream twice daily for a mean of 8 months (range 3–16 months). They observed disappearance of 27% (39/146) and fading of 67% (98/146) of the lesions; 47% (56/119) of raised lesions became macular, and Darier sign became negative in 82% (14/17) of patients. Untreated areas in three patients with numerous lesions were unchanged. Controlled studies are needed to determine the efficacy of topical calcineurin inhibitor therapy for CM.

A retrospective study followed mastocytomas in 130 children for a mean of 56 months. The end results were similar in those treated with a topical corticosteroid (class 1 or 3) in 7- to 10-day cycles (33/62 [53%] completely healed) and in those not treated (28/68 [41%] completely healed), but the healing time was shorter in the treated patients (16.4 vs 34.7 months; $p = 0.001$) [108]. Application of class 1–3 topical corticosteroids in 2- to 6-week cycles (± occlusion) or intralesional triamcinolone injection may help to flatten CM lesions, eliminate the Darier sign, and reduce lesional mast cells, with cutaneous atrophy as a possible side effect [109, 110].

For larger mastocytomas with frequent blistering and/or associated flushing during infancy, covering with a hydrocolloid dressing can prevent flares due to friction [111]. Topical corticosteroids (applied in cycles) or pimecrolimus could potentially be used in conjunction with the dressing.

Surgical excision could also be considered for a mastocytoma that causes severe symptoms or anaphylaxis [50].

In a study of 20 adults with maculopapular CM [112], narrowband UVB (NBUVB) phototherapy and psoralen plus UVA (PUVA) photochemotherapy were shown to reduce pruritus and cutaneous manifestations, with fewer treatments required for symptomatic control using PUVA (mean 20.7) than NBUVB (mean 40.9); 35% of patients relapsed within 4–6 months of discontinuing treatment. Photochemotherapy has also been utilized in infants with diffuse cutaneous mastocytosis [113]. However, PUVA has a less favorable risk–benefit profile and there has been little investigation of NBUVB for pediatric mastocytosis.

8.5 Kinase Inhibitors for Severe Systemic Disease

The use of kinase inhibitors with activity against mast cells carrying D816V and other *KIT* mutations has been a game changer in the treatment of systemic mastocytosis [114]. The multi-kinase inhibitor midostaurin is FDA-approved for treatment of aggressive systemic mastocytosis, with response rates of ≥60% in patients with D816V or wild type *KIT* [115]. Side effects include nausea, vomiting, diarrhea, and cytopenias. Midostaurin therapy was successfully used in an infant with indolent systemic mastocytosis associated with severe, recalcitrant blistering who previously failed conventional treatments including methylprednisolone; tryptase levels normalized and blistering resolved within 3 months of starting midostaurin [116]. Avapritinib also targets D816V-expressing mast cells and is currently under investigation for the treatment of systemic mastocytosis.

In contrast, the tyrosine kinase inhibitor imatinib is FDA approved for systemic mastocytosis in patients with *KIT* mutations outside of exon 17, and it is generally not effective for D816V-associated disease. Imatinib has been used to treat children with extensive CM accompanied by severe systemic symptoms and blistering with underlying KIT mutations in exon 8 [117, 118]. Side effects include gastrointestinal symptoms and peripheral edema.

9 Conclusions

Pediatric mastocytosis typically involves only the skin and often undergoes spontaneous regression by puberty, with the clinical features of the cutaneous lesions helping to predict disease course. Large/polymorphic maculopapular lesions, diffuse CM, and mastocytomas usually develop during infancy and resolve by the second decade of life, whereas small/monomorphic maculopapular lesions similar to adult urticaria pigmentosa tend to arise in older children and persist for a longer period of time. Mast cell mediator-related symptoms are most common in patients with extensive or diffuse skin disease, and the serum tryptase level can serve as an indicator of mast cell burden and risk for anaphylaxis/other severe reactions. In general, small/monomorphic maculopapular CM and diffuse CM are associated with higher tryptase levels, while diffuse CM and larger mastocytomas are frequently complicated by blistering early in life. Recently recognized markers of systemic disease in pediatric mastocytosis patients include hepatosplenomegaly and *KIT* mutations in the peripheral blood detected with ASqPCR. An individualized approach to management enables recognition and avoidance of pertinent triggers of mast cell degranulation and prevention of unnecessary parental worry as well as a stepwise treatment tailored to the type, frequency, and severity of symptoms.

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