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PEDIATRIC ALLERGY AND IMMUNOLOGY (W DOLEN, SECTION EDITOR)

Mastocytosis in Children

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Abstract
Purpose of Review In this review, we examine the current understanding of the pathogenesis, clinical presentations, diagnostic tools, and treatment options of pediatric mastocytosis as well as the natural history of the disease.
Recent Findings We discuss the emerging concept of mast cell activation syndrome.
Summary Mastocytosis in children presents most commonly as isolated cutaneous lesions and is a relatively rare occurrence with excellent prognosis and spontaneous regression often occurring by adolescence. Systemic mastocytosis with organ system involvement is a more serious condition and is likely to persist into adulthood.

Keywords Mastocytosis · Pediatric mastocytosis · Pediatric mastocytosis prognosis · Mast cell activation · Mast cell · Tryptase

Introduction

Mastocytosis refers to a group of disorders characterized by an increase in mast cell numbers in the tissues involved, as well as abnormal morphology with aberrant surface receptor expression of tissue mast cells. These disorders are usually a result of various gain of function mutations affecting the tyrosine kinase KIT receptor, leading to increased accumulation and survival of tissue mast cells [1]. Pediatric mastocytosis is a relatively rare occurrence presenting most commonly as isolated cutaneous lesions. Clinical manifestations of mastocytosis are usually due to the release of mast cell mediators, including histamine and other vasoactive substances. The diagnosis involves measurement of mast cell mediator release in the serum and/or urine as well as characteristic histopathological findings in biopsies of involved tissue. Treatment is primarily directed at preventing mast cell mediator release by avoidance of triggers as well as pharmacologic interventions to suppress the clinical effects of mast cell mediators. In this review, we describe the various clinical presentations of mastocytosis in children, as well as the epidemiology, pathogenesis, treatment, and natural history of the disease. We examine the relatively newly described mast cell activation syndrome with clinical manifestations of acute or chronic release of mast cell mediators without demonstrable evidence of mastocytosis.

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Epidemiology and Natural History

The estimated prevalence of mastocytosis is 1 per 10,000 persons in the USA, while its incidence is estimated at 5 to 10 new cases per million persons annually [2]. Overall, approximately two thirds of all mastocytosis diagnoses are made in children. A majority of pediatric cases are diagnosed within the first year of life, and > 80% of these patients have limited cutaneous disease [3]. There is a bimodal age distribution in pediatric mastocytosis with a dramatic drop in incidence during early adolescence followed by a rise in diagnoses after the age of 15 years. Later age of diagnosis is correlated with an increased risk of systemic disease. An isolated case report of a pediatric patient with a solitary mastocytoma diagnosed at age 15 years, who subsequently presented as an adult with mast cell leukemia after

having an anaphylactic event is notable, but nonetheless represents the exception to an overwhelmingly positive prognostic outlook for pediatric patients with cutaneous mastocytosis [4]. One study of 15 pediatric mastocytosis patients over a 20-year period noted a complete resolution rate of 67% [5]. On the opposing end of the age spectrum, cases of congenital aggressive systemic mastocytosis have been reported in neonates, but are exceedingly rare [6]. Conflicting evidences on gender discrepancies within the pediatric mastocytosis patient population exist, with some studies noting no difference in male or female prevalence and others observing a male predominance during adolescence, with a reversal of this trend following puberty, leaving more females affected in the older age group [7].

By far, the most prevalent form of mastocytosis in children is urticaria pigmentosa (UP), also known as maculopapular cutaneous mastocytosis (MPCM) [8]. MPCM can be classified based on lesion morphology into one of two categories [9••]. Patients with multiple small maculopapular lesions of similar size and shape have the monomorphic variant of MPCM (Fig. 1a), while those with irregular, larger lesions with considerable variability in shape and size are labeled as having polymorphic MPCM (Fig. 1b). Of the two subclasses, pediatric patients more frequently display lesions consistent with polymorphic MPCM. This division also has prognostic implications. Within the group with MPCM, lesional size has been inversely correlated with tryptase levels [10]. In addition, larger lesions were observed in patients with earlier onset, shorter total course, and generally less severe disease. It has also been noted that children with the monomorphic variant may have a higher rate of symptom persistence into adulthood, although only a minority of these individuals possess the canonical D816V mutation [11].

Familial cases of mastocytosis are well documented, with most mutations localized within the *c-kit* gene [12]. One series of 180 pediatric patients with cutaneous mastocytosis noted approximately 11% of the group had what could be characterized as familial disease [13]. No ethnic, socioeconomic, or environmental influences on the incidence of pediatric mastocytosis are currently noted in the literature. No data is available on the incidence or prevalence of mast cell activation syndrome, though multiple case reports exist of the disease in pediatric patients [14].

Pathophysiology

The *c-kit* gene encodes for Kit (CD117), a transmembrane receptor with intrinsic tyrosine kinase activity and pleotropic effects on multiple cell types. The majority of hematopoietic cells stop expressing Kit following differentiation, whereas mast cells retain a dependency upon this pathway throughout their life span. Upon binding to stem cell factor (SCF), dimerization of Kit results in intracellular tyrosine kinase activation.

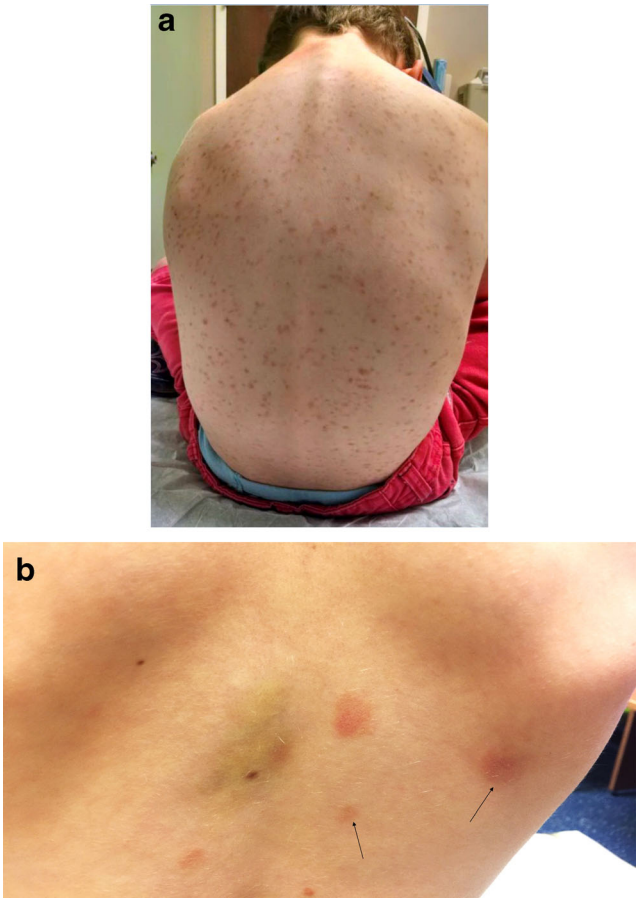

Fig. 1 Maculopapular cutaneous mastocytosis. **a** Monomorphic. **b** Polymorphic. Arrows indicate different size lesions

Kit and its cognate ligand, SCF, are necessary to promote the maturation, survival, and function of mast cells [15].

In adults, greater than 90% of patients with systemic mastocytosis have a somatic mutation of the *c-kit* gene where valine is substituted for aspartic acid in exon 17, resulting in D816V Kit [16]. In contrast, multiple mutations to *c-kit* are found in several exons in children with mastocytosis [1]. Indeed, approximately 40% of mutations were reported to be outside of exon 17 [17], consistent with other genetic studies of mutational diversity in pediatric mastocytosis. Despite the overall lower prevalence of the D816V mutation in pediatric patients, it is still the most frequently detected variation, reported in approximately 30% of pediatric mastocytosis patients. Evidence from small studies indicates that pediatric patients who harbor the D816V mutation may be more likely to have systemic rather than cutaneous mastocytosis at the time of diagnosis compared to patients with non-D816V mutations [18].

Mutations to the *c-kit* gene can be grouped broadly on the basis of impacting either the catalytic or regulatory domains of the receptor. The classic D816V mutation affects the catalytic site and produces constitutive receptor activation and downstream signaling in the absence of dimerizing ligand [18]. The

D816V mutation is not by itself sufficient to actuate malignant transformation, and it is considered only mildly oncogenic. Mutations in the regulatory domain of the *c-kit* gene, including in exons 8 and 9, have been detected in aggressive clonal mast cell diseases, gastrointestinal stromal tumors, acute myeloid leukemia, mucosal melanoma, rare cases of T cell lymphomas, and germ cell tumors [19, 20]. Multiple different deletion mutations within exon 7 of the *c-kit* gene have been detected in pediatric patients, and many of these same deletions have also been identified in gastrointestinal stromal tumors. These mutations also reside in precancerous lesions, sometimes concurrently with mutations to SRFS2, ASXL1, and RUNX1 in advanced cases of systemic mastocytosis such as mast cell leukemia [21]. These aggressive mast cell diseases have been described in the pediatric population but are extremely rare [6, 22].

In addition to influencing disease stratification, the mutational status of patients can also affect clinical treatment algorithms. D816V Kit tyrosine kinase activity is not inhibited by imatinib at pharmacologic concentrations [23]. Patients with mutations outside of exon 17 are likely to respond favorably to imatinib therapy, while those with the D816V mutation exhibit much less improvement on this targeted therapy [24]. In contrast, midostaurin, a promiscuous kinase inhibitor, does inhibit D816V Kit tyrosine kinase activity and reduces disease burden in most patients with advanced systemic mastocytosis and D816V Kit [25].

Overall, Kit activity promotes mast cell differentiation, survival, and activation, facilitating the increased mast cell burden and pathology underlying mastocytosis. Symptoms of mastocytosis are due to both acute and chronic release of inflammatory mediators by mast cells, including histamine, tryptase, leukotrienes, prostaglandins, and cytokines. In addition, signs and symptoms of organ system dysfunction can be caused by the physical infiltration of mast cells into the bone marrow and peripheral organs. In cutaneous lesions, pain and pruritus occur with degranulation of mast cells in response to both mechanical and biologic stimuli. Along with increased capillary permeability causing tissue edema, nociceptors are activated via substance P, NK-1, and histamine, leading to increased patient discomfort [26].

Clinical Manifestations

Cutaneous Mastocytosis

Most children present with isolated cutaneous findings with minimal to no systemic symptoms. Itching can be present in up to 50% of patients. Dermographism is common with monomorphic UP and with diffuse cutaneous mastocytosis (DCM). Flushing can occur with trauma to a mastocytoma lesion.

The skin exam usually reveals one or more small reddish brown macular lesions which develop a wheal and flare reaction with slight scratching, whereas non-lesional skin does not exhibit dermographism. This phenomenon is known as the Darier's sign (Fig. 2). Occasionally, the skin lesions can develop blisters, especially in the very young children under 3 years of age (Fig. 3).

The classification of cutaneous mastocytosis is based on the extent and appearance of the skin lesions [9••].

1. UP, also known as maculopapular cutaneous mastocytosis, is the most common form seen in childhood. In this variant, the children exhibit individualized skin lesions. Two subtypes are recognized:

   Polymorphic UP where lesions vary in shape, size, and distribution over time and usually affect the head, neck, and extremities. These lesions are typically larger than those found in adult patients. Blistering may occur in children < 3 years old. Serum tryptase levels are usually in the normal range. Some children have extensive and sometimes confluent skin lesions. They may initially have increased serum tryptase levels that decrease over time. This UP type carries an excellent prognosis with resolution of the skin lesions in the vast majority of patients [5].

   Monomorphic UP where lesions are similar in size and shape, small, round, and are typical of lesions observed in adult UP. This type is found in a minority of pediatric patients who present with elevated serum tryptase levels that persist over time and may show systemic involvement outside of the skin. This type carries a poorer prognosis with respect to persistence into adulthood and development of systemic mastocytosis (SM) [27••].

2. DCM exhibits generalized erythematous papules, with thickened and darker skin. Children often exhibit marked dermographism as well as blistering of the lesions in

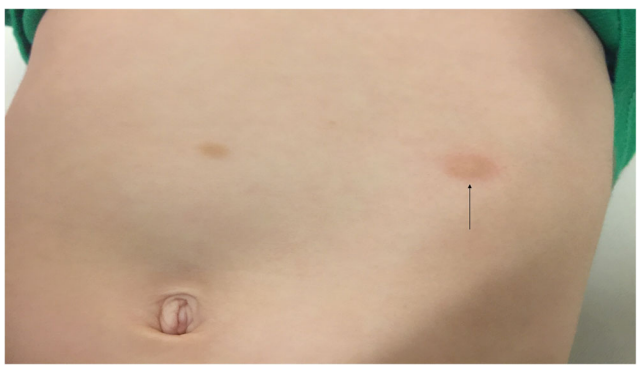

Fig. 2 Darier's sign. Arrow indicates wheal and flare of one of the two maculopapular cutaneous mastocytosis lesions after light scratching

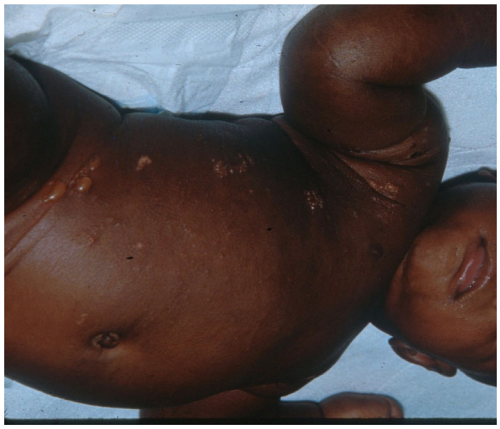

Fig. 3 Blistering maculopapular cutaneous mastocytosis lesions in a 5-month-old infant

response to minor trauma, especially in the first few years of life. Serum tryptase levels are usually elevated at presentation despite lack of systemic organ involvement. Occasionally, children demonstrate hepatomegaly, splenomegaly, and bone marrow involvement indicating progression toward systemic mastocytosis. DCM skin lesions often resolve by adolescence. In contrast, a small minority of patients with DCM and familial mastocytosis due to germline mutations in c-kit exhibit a chronic course with persistently elevated serum tryptase levels and extracutaneous mast cell infiltrates [28–30].

3. Mastocytoma usually presents as an isolated elevated cutaneous lesion with brown or yellow discoloration. Slight mechanical trauma may result in blistering and regional or generalized flushing. Serum tryptase levels are usually normal without organ system involvement. Mastocytomas usually resolve spontaneously in childhood. In rare instances where a child has more than three mastocytoma skin lesions, the current consensus recommendations is to consider this a case of MPCM [9••].

Systemic Mastocytosis

Early-onset systemic mastocytosis is rarely found in children and may present as indolent SM, well-differentiated systemic mastocytosis (WDSM), or advanced SM with multi-organ involvement. Symptoms of explosive diarrhea, syncope, and dyspnea as well as a history of recurrent acute anaphylactic reactions, flushing, unexplained itching, or anaphylaxis with hymenoptera stings, general anesthesia, or certain medications including morphine and vancomycin should raise the suspicion for systemic mastocytosis.

The diagnosis of SM in children follows the WHO criteria established in 2001, largely based on adult presentation (Table 1). However, some children with SM may not fulfill these criteria. Future studies should allow for the development of specific diagnostic criteria for pediatric SM.

Mast Cell Activation Syndrome

Mast cell activation syndrome is characterized by intermittent episodes of release of inflammatory mediators such as tryptase, histamine, prostaglandins, and leukotrienes without any identified antigenic stimulus [32•, 33]. It manifests itself with acute episodes of anaphylaxis, including flushing, urticarial rash, pruritus, signs and/or symptoms of hypotension, acute gastrointestinal distress, and angioedema. Although baseline serum tryptase levels are not usually elevated, exacerbations are accompanied by an acute rise in the serum tryptase level within 30 min to 2 h of symptom onset. To be considered clinically significant, this rise should be greater than or equal to 1.2 times the patient's baseline level plus 2 (ng/ml) to support a diagnosis of mast cell activation syndrome. Urine collected over 24 h may also show elevation in N-methylhistamine, 11 beta-prostaglandin F2 alpha or leukotriene E4, metabolites of histamine, PGD2, and LTC4, respectively.

Mutations to *c-kit* may be present in clonal (also referred to as monoclonal mast cell activation syndrome or MMAS) or absent in non-clonal variants of mast cell activation syndrome. Bone marrow biopsy may be performed to rule out isolated bone marrow mastocytosis (BMM). Patients often associate mast cell activation events with exposure to a foreign substance immediately prior to or during the onset of symptoms, leading to the false perception of multiple allergic sensitivities. Care should be taken to identify true allergenic sensitivities as opposed to coincidental exposure to potential allergens [14].

A recent variant of mast cell activation syndrome was described in patients with autosomal dominant hereditary alpha-tryptasemia, due to a copy number gain in the alpha-tryptase gene (TPSAB1). These patients have elevated basal tryptase levels (> 11.3 ng/ml), as well as signs and symptoms of multi-organ involvement, including vibratory Urticaria, connective tissue disease, and dysautonomia. As alpha-tryptase homotetramer is not proteolytically active, how this mutation causes symptomatology remains to be clarified [34•].

Diagnostic Testing

Physical Exam: Darier's Sign This refers to the development of a wheal and flare reaction within 5–15 min of scratching a skin lesion and is due to the release of preformed mediators including histamine from cutaneous mast cells (Fig. 3). It is important to ascertain that the child does not have dermographism by demonstrating lack of a wheal and flare reaction when scratching the normal surrounding skin. The Darier's sign is almost always positive in pediatric patients and is diagnostic of cutaneous

Table 1 WHO diagnostic criteria for systemic mastocytosis

Major	Minor
Multifocal clusters of ≥ 15 mast cells in bone marrow and/or other extracutaneous organ	Baseline serum tryptase level > 20 ng/ml
	Expression of CD25 or CD2 on mast cells
	Presence of a codon 816 mutation in peripheral blood or lesional tissue
	Morphologic abnormalities affecting > 25% of bone marrow mast cells (spindle shape, hypogranulation, bilobed, or multilobed nuclei)

The diagnosis of systemic mastocytosis requires the presence of one major and one minor, or three minor criteria. Adapted from Valent et al. [31]

mastocytosis. The Darier's sign should not be elicited in case of a large mastocytoma, as it may result in flushing and hypotension.

Skin Biopsy A biopsy of a skin lesion allows identification of the number, morphology, and surface markers of cutaneous mast cells. Mast cells are usually visualized with a Giemsa stain due to their metachromatic cytoplasmic granules. A more sensitive immunohistochemical technique employs anti-tryptase antibodies or anti-CD 117 (Kit). Although mast cells are normally found in the dermis and express surface Kit, their numbers are markedly increased in lesions of cutaneous mastocytosis where they often appear in aggregates, display a spindle-shaped appearance, and express additional aberrant surface markers such as CD2 or CD25 [9••]. When performing a skin biopsy, it is crucial to exercise great care to prevent mast cell degranulation which may interfere with visualization of the cells. Thus, local anesthetic injections should not be used directly on the lesions but rather around the biopsy site [35].

Laboratory Tests (Table 2)

a. Serum tryptase levels reflect the total burden of mast cells and are usually within normal limits (≤ 11.3 ng/ml) in children with cutaneous mastocytosis. As a tetrameric serine protease, tryptase represents the quantitatively dominant protein constituent of the mast cell secretory granule. An elevated serum tryptase level suggests the diagnosis of systemic mastocytosis but can also be found in children with either monomorphic UP or DCM as stated above. An acute increase in total serum tryptase levels over baseline provides objective evidence of mast cell activation in the context of acute symptoms. On the other hand, increases in serum tryptase levels over time are helpful in monitoring patients for systemic progression [36]. In a study of 111 children with cutaneous mastocytosis, Alvarez-Twose et al. reported that baseline serum tryptase levels over 6.6 ng/ml predicted the need for daily antimediator therapy, while levels over 15.5 and 31 ng/ml predicted hospitalization and intensive care management, respectively [36]. Due to other potential causes of increased serum tryptase levels, including hematologic malignancies, a complete blood count with differential should also be obtained. Liver enzymes are indicated if the physical exam demonstrates hepatomegaly or splenomegaly.

b. *c-Kit* mutation: Pediatric cutaneous mastocytosis was traditionally thought to be a non-clonal disease, but evidence is accumulating for the presence of clonality due to a gain of function mutation in *c-kit*, the gene that encodes for a tyrosine kinase receptor expressed by mast cells. The most common *c-kit* mutation is D816V on chromosome 17. Other mutations have been described on exons 8 and 9. *c-Kit* mutation analysis can be performed on biologic samples obtained from either peripheral blood, skin biopsy, or bone marrow biopsy. If performed by DNA sequencing, clonal mast cells need to account for > 10% of the cells being analyzed, which typically requires purification of the mast cells. When looking for the D816V mutation, an allele-specific qPCR can be performed, detecting this mutation if ≥ 1 in 10,000 cells are affected. Since mature mast cells are not usually detected in the peripheral circulation, the assay is most sensitive when performed on a bone marrow biopsy when the mutation affects only the mast cell lineage.

Table 2 Indications for additional work-up in pediatric cutaneous mastocytosis

Classification	Serum tryptase	c-KIT mutation	Bone marrow biopsy
UP polymorphic	If systemic symptoms	If tryptase > 20 ng/ml	If tryptase > 20 ng/ml
UP monomorphic	Yes	Yes	If tryptase > 20 ng/ml
DCM	Yes	Yes	If tryptase > 20 ng/ml
Mastocytoma	> 3 mastocytomas	If tryptase > 20 ng/ml	If tryptase > 20 ng/ml

c. A bone marrow biopsy is not usually indicated in pediatric cutaneous mastocytosis, regardless of whether the serum tryptase level is elevated. It may be considered in children with systemic symptoms and/or a rising baseline serum tryptase level where SM is suspected [27••].

Management

Most pediatric patients with cutaneous mastocytosis will not require any treatment. Given an excellent long-term prognosis, management is conservative and aimed at counteracting the symptoms due to mast cell mediator release. Given the lack of double-blind placebo controlled studies or various therapeutic agents in this field, many of the recommendations below are derived from personal experience and/or expert opinions.

Non-pharmacologic Interventions

Measures to prevent mast cell degranulation include avoidance of various triggers including skin friction at sites of lesions, exposure to hot temperatures, such as a hot bath or shower, and extreme physical exertion as well as less common triggers such as fever, irritability, and teething. Of note, other reported triggers such as food, vaccinations, and certain medications such as NSAID, vancomycin, and opioids are rarely involved except in children with DCM [37]. Parents are often instructed to avoid these triggers at all cost. However, these are relative contraindications. Therefore, a child who has previously tolerated medications such as ibuprofen does not need to discontinue its use. Similarly, a child who tolerates playing sports or a specific exercise regimen may continue to do so.

Medical alert bracelets should be prescribed if there is concern about the possibility of anaphylactic episodes, such as in children with an elevated serum tryptase level or with diffuse cutaneous involvement or a large mastocytoma. An often overlooked but very effective maneuver is to teach the patient and their caretakers the importance of the child adopting the supine position in case of dizziness and/or hypotension.

Education of the child's caretakers at home, school, daycare, and after school programs is advised, including recognition of the signs and symptoms of anaphylaxis, avoidance of specific triggers relevant to the patient, and appropriate and timely management of flare ups. A written, individualized action plan should be developed for every child. Children with DCM may suffer psychological stress related to their skin appearance and may benefit from counseling.

Antihistamines

In children with symptoms of pruritus and/or flushing, treatment with antihistamine agents is often beneficial. This is also recommended as prophylactic therapy in patients with extensive skin involvement and/or increased baseline serum tryptase levels of > 11.3 ng/ml to attenuate signs and symptoms of mast cell degranulation events. Second-generation H1 antihistamine agents are preferred due to their non-sedating properties which allow the use of higher doses without interfering with school performance. Dosage can be increased based on clinical response to as much as four times the normal dose for age. Addition of an H2 antihistamine agent such as famotidine, ranitidine, or cimetidine will provide additional benefit in children with a partial response to H1 antihistamine therapy alone or with significant gastrointestinal symptoms.

Oral Cromolyn Sodium

Oral cromolyn sodium has been used to treat gastrointestinal symptoms such as abdominal pain and diarrhea, although there are no clear studies to demonstrate its efficacy. This therapy is approved by the FDA for the treatment of mastocytosis in children > 2 years of age. Dosage should not exceed > 40 mg/kg/day to a maximum of 800 mg/day.

Topical aqueous sodium cromoglycate 0.21% (prepared from cromolyn sodium inhalation solution mixed into a water-based emollient cream) can be used an adjunct treatment for symptomatic lesions to lessen pruritus [38]. Evidence for its effectiveness derives mostly from case reports [39].

Topical corticosteroids are used in children with frequent blistering lesions to prevent recurrence.

Topical antibiotics like mupirocin should be used on open skin lesions to prevent secondary infections.

Epinephrine autoinjectors should be prescribed for children with increased risk factors for anaphylaxis, including an elevated baseline serum tryptase level, DCM, or a large mastocytoma.

Management of Other Atopic Conditions

Effective management of other atopic conditions which may lead to increased severity of anaphylactic reactions is particularly important in children with pediatric mastocytosis.

Bee venom immunotherapy should be instituted for children > 12 years of age with a previous history of anaphylaxis to bee venom and elevated baseline serum tryptase levels. Once maintenance dosing is achieved, bee venom immunotherapy is very effective in reducing systemic reactions to subsequent stings [40].

IgE-mediated food allergy should be properly diagnosed and measures instituted to prevent exposure to food allergens. Epinephrine autoinjectors should be available for prompt use

at all times during the school day as well as at home and in other settings.

Poorly controlled asthma is a significant risk factor for increased severity of anaphylactic reactions due to any cause. Appropriate management and close follow-up to ensure compliance with and response to therapy are essential.

Preparation for Anesthesia and Surgical Procedures

A multidisciplinary team discussion involving the surgical team, the anesthesia team, and the treating physician prior to surgery is essential to educate the providers about the signs and symptoms of mast cell degranulation events and put in place appropriate intervention measures to prevent and/or treat intraoperative anaphylaxis. Prophylaxis with a regimen of H1 and H2 antihistamine agents is recommended [41•]. Fentanyl is the anesthetic agent of choice. If other opioid medications are required, oral administration with lower peak concentrations is safer than intravenous administration. It is important to keep in mind that naloxone would not reverse the mast cell degranulation properties of opioids that are mediated via a different MAS-related G-protein-coupled receptor-X2 than the classic opioid receptor.

Conclusions

Pediatric mastocytosis is largely a benign condition with excellent prognosis and frequent spontaneous resolution. Although considered rare, the availability of serum tryptase determination has facilitated the recognition of mastocytosis in children with and without presenting skin lesions. A minority of children with mastocytosis develop systemic symptoms and persistence into adulthood. Accurate prognostic criteria are still lacking; however, the increased availability of molecular diagnostic techniques, specifically the ability to detect *c-kit* mutations in involved tissues, may allow for improved understanding of the underlying pathogenesis as well as the development of new therapeutic modalities. At present, it is important to increase the awareness of pediatric mastocytosis among general practitioners and specialists alike in order to tailor the diagnostic work-up and therapies to the appropriate patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Irani reports receiving royalty payments from ThermoFisher for the tryptase assay and from Millipore, Santa Cruz, BioLegend, Hycult, and BioTech for antibodies used to identify mast cells and basophils. Drs. Klaiber and Kumar declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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