

Primary Mast Cell Disorders in Children

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Abstract Mastocytosis arises from clonal mast cell expansion and the resultant accumulation of mast cells in cutaneous and sometimes extracutaneous tissues. Recent studies have demonstrated that *c-kit* mutations seem to be more prevalent in pediatric mastocytosis than previously assumed, but what determines disease evolution and severity in the individual patient remains elusive. For the large majority of children, mastocytosis is a self-limited cutaneous disease that spontaneously regresses before they reach adult age. Rarely, children develop systemic disease progression that is the hallmark of adult-onset disease. Therefore, invasive diagnostic testing, including performing a bone marrow biopsy, is not routinely recommended and usually reserved for children that present with signs of systemic involvement and persistently elevated serum tryptase levels. Despite its often-transient nature and limited skin involvement, some children experience challenging disease-associated symptoms due to spontaneous or trigger-induced mast cell degranulation. Anticipation of and preparation for potential complications can in many instances avoid symptomatic exacerbations. Proper symptomatic treatment and supportive care can often improve the child's quality of life. Cyto-reductive therapy is usually not indicated given the natural history of spontaneous disease resolution.

Keywords Mastocytosis · Mast cell disorders · Children · Pediatric · Cutaneous mastocytosis · Urticaria pigmentosa ·

Pediatric mastocytosis · Kit · Mast cell-mediator symptoms · Pathogenesis · Classification · Solitary mastocytoma · Diffuse cutaneous mastocytosis · Diagnosis · Treatment

Introduction

Clinical signs and symptoms of deranged mast cell activation can be seen in a broad spectrum of disorders that involve aberrant mast cell degranulation, including IgE-mediated allergies, chronic non-allergic urticaria and angioedema, idiopathic anaphylaxis, as well as in some neoplastic disorders, and in patients meeting defined clinical and laboratory criteria of mast cell activation syndrome (MCAS) [1]. The presence of an intrinsic molecular defect in mast cells and/or their progenitors distinguishes primary mast cell disorders from these entities. The defect leads to clonal mast cell expansion, with abnormal growth and accumulation of mast cells in cutaneous and/or extracutaneous tissues, including bone marrow, gastrointestinal tract, liver, spleen and lymph nodes. Mastocytosis is the prototypic and the only well-described primary mast cell disorder in children. However, our knowledge, particularly of its childhood variant, is still limited. Childhood-onset mastocytosis generally appears to have a biologic behavior and associated clinical course different from adult-onset mastocytosis, for reasons largely unknown. In contrast to adult-onset mastocytosis, which is invariably associated with bone marrow (systemic) disease, childhood-onset mastocytosis most often manifests as a self-limited skin disease without other organ involvement and with spontaneous involution after puberty. However, the natural course of the disease is variable, and an estimated less than 10 % of children develop a more persistent phenotype resembling adult-onset mastocytosis. Also, rare subtypes with a less indolent clinical course exist and can have a poor outcome if not managed properly. Here we will review primary mast cell

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disorders in childhood and recent advances in our understanding of the disease, diagnosis and management.

Pathogenesis

Human mast cells originate in the bone marrow from pluripotent hematopoietic precursor cells. They acquire maturation in peripheral tissues and proliferate through interaction of their surface receptor Kit (or CD117) with its ligand stem cell factor (SCF), which is considered the essential mast cell growth factor produced by stromal tissue cells. Kit is a transmembrane receptor made up of an extracellular ligand-binding domain with an immunoglobulin-like structure, a transmembrane domain, a juxtamembrane intracellular domain and a cytoplasmic tyrosine kinase domain interrupted by an insert [2]. Ligand-induced activation of Kit causes autophosphorylation of tyrosine residues at its intracytoplasmic portion, initiating a cascade of downstream signaling events that results in activation of transcription factors critical for cell growth. The majority of cases of mastocytosis are associated with somatic gain of function mutations in c-kit, the gene encoding Kit. By far the most common mutation encountered in adults is the substitution of valine for aspartate in codon 816 (Asp816Val or D816V) of exon 17, located within the tyrosine kinase domain [3, 4]. The mutated Kit receptor is constitutively activated, independent of SCF ligation, which provides the basis for the pathologic expansion and accumulation of mast cells in tissues [5]. Very rare familial cases of cutaneous mastocytosis due to germline c-kit mutations have been reported in association with gastrointestinal stromal tumors (GIST) [6]. Interestingly, a few other familial cases were described carrying somatic instead of germline c-kit mutations, which suggested that the predisposition to acquire somatic mutations was inherited [7, 8]. There is emerging evidence that somatic c-kit mutations may be found in most cases of childhood-onset mastocytosis, similar to adult-onset disease. While earlier studies that evaluated small numbers of patients with pediatric mastocytosis did not find c-kit mutations in the majority of patients [4, 9], more recent studies using higher sensitivity assays found codon 816 mutations in 25–83 % of pediatric mastocytosis patients [10, 11, 12•]. A multicenter study by Bodemer et al. examined 50 children with cutaneous mastocytosis for the presence of a c-Kit mutation in lesional skin and demonstrated that while 44 % of the children had codon 816 mutations, 42 % had mutations in other KIT regions, most clustering around two mutational hotspots in the extracellular domain, encoded by exons 8 and 9 [12•]. In this study of patients with cutaneous disease, the type of c-kit mutation did not predict disease extent or severity. The authors concluded that there may not be a strict genotype-phenotype correlation, consistent with previous observations [13].

While it has been speculated whether the presence of the D816V Kit mutation influences a predilection for cutaneous versus rare systemic childhood disease, this has not been systematically studied. Recent studies of adult-onset mastocytosis have suggested that multilineage involvement by Kit mutations, with presence of mutated clones outside of the mast cell compartment, and possibly additional molecular aberrations in other genes may influence the phenotype and overall prognosis [14, 15]. It is not known if these or other factors could also be relevant in childhood disease. How a presumably clonal disease with sometimes extensive skin involvement in children spontaneously regresses by puberty or adulthood is still puzzling and remains unexplained. Potential explanations affecting persistent or transient disease include multilineage involvement extending beyond the immediate mast cell progenitor, additional genetic alterations other than c-kit and involvement of different pools of tissue progenitor cells.

Classification and Presentation of Childhood Mastocytosis

Cutaneous mastocytosis was first described in 1869 by Nettleship and Tay as a form of urticaria [16]. Unna identified mast cells in the skin lesions of patients in 1887 [17], and the skin disease was descriptively named ‘urticaria pigmentosa’ (UP) by Sangster [18]. Systemic involvement of mastocytosis was demonstrated when Ellis in 1949 described a fatal case of mastocytosis in a 1-year-old child with UP, with evidence of mast cell infiltration of multiple organs from the child’s autopsy [19].

Skin involvement with the presence of typical cutaneous lesions due to dermal mast cell infiltration is considered the *sine qua non* of childhood mastocytosis, in contrast to adult-onset disease, which can present without skin lesions. The variants of childhood-onset cutaneous mastocytosis are included in the WHO-recognized classification of mastocytosis (Table 1) [20]. Telangiectasia macularis eruptiva perstans is a rare adult form that is not reviewed here.

Solitary Mastocytoma

A solitary lesion of mastocytoma is often present at birth or develops during early infancy, rarely later in childhood. Some children may have several mastocytomas. These are typically 5–60 mm in diameter, yellowish, tan or brown colored plaques with a nodular center. These have a tendency for vesicle or bulla formation (30–90 % frequency reported), which is often most prominent early in the course (usually within the first 3 years), with decreasing frequency thereafter [21, 22]. Prognosis for this variant is excellent as most lesions will involute spontaneously or markedly diminish by adolescence. However, rare persistence into adulthood and adult-onset solitary lesions has been described [21, 23]. Physical irritation,

Table 1 WHO classification for cutaneous mastocytosis

Criteria:
Typical skin lesion(s)
AND
Positive histology and criteria for diagnosis of SM not fulfilled
Subtypes:
Urticaria pigmentosa (UP) or maculopapular cutaneous mastocytosis (MPCM)
a) Typical UP
b) Plaque form
c) Nodular
Solitary mastocytoma of the skin
Diffuse cutaneous mastocytosis (DCM)

Adapted from Valent et al. [20]

rubbing or scratching of the mastocytomas may cause generalized flushing, hives and wheezing.

Maculopapular Cutaneous Mastocytosis/Urticaria Pigmentosa

Urticaria pigmentosa (UP) or maculopapular cutaneous mastocytosis (MPCM) is the most common manifestation of cutaneous mastocytosis in children, making up about 50–80 % of cases. Urticaria pigmentosa can be considered a misnomer, as neither urtication nor hyperpigmentation is uniformly present. Lesions are quite variable in appearance, distribution and number. The childhood variant often appears as small, 2–30-mm-diameter, symmetrically distributed macules and papules of reddish-brown or light tan color [21, 23]. Lesions can sometimes be barely discernible and can remain unrecognized. A plaque variant is distinguished by some authors from classic UP and usually only seen in children, presenting as slightly larger, 1–5-cm-diameter, flat or slightly elevated, lightly and homogeneously pigmented, light brown or orange to yellowish plaques, which can coalesce [24]. Another subvariant with the presence of multiple nodular, sharply demarcated lesions has been described [24]. UP lesions can be few or several hundred in number. These typically involve trunk and extremities, but sometimes present with generalized distribution. There often is centripetal accentuation of lesions, and there appears to be a predilection for the groin and gluteal area. Scalp involvement is not uncommon in children. In an early series of 112 patients with childhood-onset UP, Caplan reported that lesions developed from birth to 42 months, with a median age of onset of 2.5 months. By the age of 6 months 80 % of children had developed skin lesions [21]. Most series have reported a disease onset prior to the age of 2 in about 80–90 % of children. Erythema, edema, pruritus and vesiculation of the lesions often occur. In the majority of cases lesions will develop wheals and flares upon rubbing or stroking (positive Darier's sign). Reactivity of the lesions tends to decrease over

time, and many patients will eventually lose the positive Darier's sign. Similarly, vesicle formation tends to gradually decline [21, 25]. Lesions that appear after the age of 10 years tend to persist and resemble adult-onset cutaneous mastocytosis, and can be associated with systemic mastocytosis [23]. The 'adult-type' lesions are generally smaller (only a few millimeters in diameter), flatter, more numerous, have a darker pink to brown color, and are rarely associated with blistering [21, 26]. However, 'adult-type mastocytosis' cannot be reliably distinguished from the more benign classic childhood variant by morphologic criteria only. A single case of transformation of childhood onset UP to mast cell sarcoma was reported [27].

Diffuse Cutaneous Mastocytosis

Diffuse cutaneous mastocytosis (DCM) is a rare form of CM that can involve the entire skin and presents usually at birth or early infancy [23]. Manifestations are heterogeneous. Patients can present with thickened skin with a yellowish tint without individual lesions or widespread yellow- to brown/red-colored nodular cutaneous and subcutaneous infiltrates [28, 29]. Very rare extreme forms with pachydermia and extensive skin folding have been reported [30]. Uniformly, there is evidence of diffuse band-like mast cell infiltration under the epidermis in involved and uninvolved skin [28]. Extensive bullae formation is often observed, and the condition can be confused for other bullous dermatoses, delaying diagnosis and proper management [26]. Bullous lesions tend to predominate during infancy, whereas nodular or diffuse infiltrative lesions may develop later in the course [29]. The extensive cutaneous mast cell infiltration is often accompanied by measurably increased markers of mast cell burden (serum tryptase, urine N-methylhistamine), which decrease gradually as skin lesions resolve [28]. Cases with associated systemic involvement and persistent disease are reported, but are not thought to represent the typical outcome of DCM [29, 31].

Systemic Mastocytosis of Childhood

Rare patients with early onset systemic involvement have been described, with either an indolent course or advanced systemic disease with early multiorgan involvement [19, 31, 32, 33••]. Children with systemic disease are diagnosed (Table 2) and classified according to the WHO criteria, and management usually follows guidelines for adult-onset disease. That said, some childhood-onset systemic cases may not be well represented by the current WHO criteria. An example is well-differentiated systemic mastocytosis (WDSM), a more recently described subtype of systemic mastocytosis, characterized by the presence of excessive numbers of round, mature-appearing mast cells in the bone marrow and often associated with childhood onset cutaneous mastocytosis [34]. Aberrant mast cell surface markers that are classically seen in

Table 2 Diagnostic criteria for systemic mastocytosis

Major criterion:

Multifocal clusters of ≥ 15 mast cells in bone marrow and/or other extracutaneous tissue

Minor criteria:

Baseline serum tryptase >20 ng/ml (not valid if another clonal hematologic disease is present)

Aberrant expression of CD25 and/or CD2 on mast cells

Presence of a codon 816 mutation (most commonly D816V) in peripheral blood or a lesional tissue

Morphologic abnormalities found in more than 25 % of bone marrow mast cells (spindle shapes, hypogranulation, bilobated or multilobated nuclei)

One major and one minor, or three minor criteria are needed for the diagnosis of systemic mastocytosis

Adapted from Valent et al. [20]

SM (CD2, CD25) and are part of the WHO classification are usually missing (Table 2). Also, childhood onset systemic mastocytosis may lack the presence of dense bone marrow aggregates (>15 mast cells), which is the major criterion used to classify adult disease. As more cases of pediatric-onset systemic disease are reported and their molecular defects unraveled, our understanding of this entity should grow and allow for better classification and management.

Clinical Symptoms

Symptoms of childhood mastocytosis are largely due to mast cell degranulation with local and systemic effects from released mast cell mediators. Despite being an asymptomatic disease in many pediatric patients, all variants of CM can cause localized symptoms confined to the skin or, less frequently, symptoms in other organ sites such as the gastrointestinal tract. These may arise from degranulation of abundant cutaneous mast cells and release of mediators into the circulation, but the exact mechanism for this phenomenon has not been studied in this population. Symptoms commonly include blistering, flushing, erythema, edema, pruritus, dermatographism, sometimes gastrointestinal symptoms (abdominal pain, diarrhea, dyspepsia, nausea, vomiting, gastrointestinal hemorrhage) and less frequently hypotension, bronchospasm, syncope, anaphylaxis or anaphylactoid reactions [21, 23]. Symptoms are often elicited by certain triggers, which tend to vary from patient to patient, but include physical stimuli (temperature changes, pressure, rubbing, sunlight exposure), drugs (opioids, anesthetic agents, muscle relaxants, NSAIDs, antibiotics), surgical or endoscopic procedures, vaccinations, contrast dyes, febrile illness, hymenoptera venom, foods and emotional stress, excitement or irritability [33•, 35].

In DCM the extensive skin infiltration predisposes to severe systemic reactions in addition to cutaneous symptoms

due to potential massive mast cell mediator release from affected skin. Complications include hypotension, hypovolemic shock, dyspnea, gastrointestinal hemorrhage, skin superinfection after blistering and diarrhea with wasting. Fatalities secondary to these complications have been reported [29, 36]. One study reported a strong association of life-threatening mast cell mediator events with extensive skin disease not only for DCM variants, but also for widespread UP with skin lesions that involved most of the body surface [33••].

In rare cases of SM with extensive extracutaneous mast cell involvement, symptoms secondary to organ infiltration (bone marrow, liver, spleen, lymph nodes, GI tract) can arise similar to those seen in systemic mastocytosis of adulthood. Aggressive systemic mastocytosis, mast cell leukemia and mastocytosis associated with another hematologic disorder are rare in children, but should be suspected in those with cytopenias or other unexplained peripheral blood abnormalities, unexplained persistent lymphadenopathy, liver or spleen enlargement, failure to thrive and a rapid clinical decline.

Natural Course and Systemic Versus Non-Systemic Involvement

The natural history of childhood onset CM has been reviewed both retrospectively and prospectively in a few series [21, 22, 37, 38]. These studies showed similar results that were largely based on longitudinal skin examinations. The large majority of reported patients with early-childhood onset CM experienced spontaneous regression or a significant decrease in skin findings and associated symptoms. If lesions did not clear completely by adolescence, many patients had only residual quiescent, lightly pigmented remnants when they reached adulthood. In the largest published retrospective review, Ben-Amitai et al. described 180 children with CM monitored over a 20-year period [22]. Solitary mastocytomas completely resolved in 74 % and partially resolved in 18.5 % of patients; 54.2 % of patients with childhood-onset UP had complete resolution of lesions at follow-up and 24.2 % had partial resolution. Despite the often-dramatic presentation of DCM and potential life-threatening complications related to excessive mast cell mediator release, the overall prognosis is good. Many patients will experience spontaneous disease regression, however, likely overall to a lesser degree compared to the other CM variants [28, 29, 31].

Among the UP and DCM forms, however, there are affected children that can develop persistent disease, which usually goes along with bone marrow involvement of mastocytosis [28, 29, 32]. Identifying those patients remains a challenge. Brockow et al. demonstrated that the extent of cutaneous disease in children does not predict the presence of systemic disease [26].

Uzzaman et al. reported long-term follow-up of 15/17 patients with early childhood-onset UP or DCM 20 years after

their original evaluation, which had included a bone marrow assessment [32]; 10/15 or 67 % of patients had complete regression of skin and associated constitutional symptoms. Of the remaining five patients, three had major disease regression, and two had persistent disease that had not further progressed compared to the initial study. Three patients who had persistent symptomatic disease underwent repeat bone marrow biopsies. The one single patient who met criteria for indolent systemic mastocytosis (ISM) at follow-up already had findings consistent with ISM at initial evaluation. Furthermore, he was the only of the three patients tested at follow-up who was identified to carry the *c-kit* mutation D816V in the bone marrow [32]. Of note, bone marrow examinations of the other two patients, while not meeting the criteria for systemic mastocytosis, revealed some degree of aberrant mast cell presence in the bone marrow, with unknown clinical significance and prognostic implications. This report is supportive of the previously described natural history of disease resolution in the majority of patients, but leaves the question whether there is a reliable identifier for persistence of disease.

Diagnosis

An examiner who is familiar with the disease will readily recognize the skin stigmata of cutaneous mastocytosis, but not uncommonly these may be initially missed or misdiagnosed. A thorough history and physical exam are essential (Table 3). The history should include an allergic reaction history, and the patient/family should be questioned as to the presence or absence of mast cell mediator events. The physical exam should assess for potential organomegaly, followed up by imaging if there is a clinical suspicion. Darier's sign (urtication upon vigorous rubbing or stroking of lesional skin) is diagnostic for CM, but may not be elicited in all cases. Larger mastocytoma lesions should not be manipulated for diagnostic purposes as this may provoke a degranulation episode with potential systemic symptoms. A skin biopsy will provide clarity as to the diagnosis and is recommended unless the exam is unambiguous. Special staining should be obtained, if possible including staining for tryptase and Kit (CD117). Mutational analysis for the D816V *c-kit* mutation is commercially available and could be considered depending on the clinical context. It should be emphasized that analysis of peripheral blood may yield a negative result for the presence of the D816V *c-kit* mutation while the mutation may still be detectable in lesional skin or bone marrow.

There is no consensus as to the minimal laboratory workup recommended for uncomplicated childhood mastocytosis. Some authors recommend a complete blood count, liver function tests and basal serum tryptase level analysis at initial diagnosis [35].

High basal serum tryptase levels correlate with mast cell burden and disease severity and sometimes, but not always,

Table 3 Diagnostic approach to childhood mastocytosis

History and physical exam

- Evaluate for morphologic appearance of skin lesions, Darier's sign, symptoms and triggers of mast cell mediator release

Skin biopsy

- Include immunohistochemical stains for tryptase and Kit (CD117)

Screening laboratory tests^a

- Baseline serum tryptase level
- Complete peripheral blood count with differential
- Liver function tests

Additional imaging or specific testing^a

- E.g., abdominal ultrasound if hepatosplenomegaly is suspected

Bone marrow biopsy and aspirate^{a,b}

- Include immunohistochemical stains of the core specimen for tryptase, Kit (CD117) and CD25
- Examination of the bone marrow aspirate for morphologically abnormal mast cells
- Flow cytometric assessment of the bone marrow aspirate for CD2/CD25/CD117 coexpressing cells
- Analysis for Kit mutations (exon 17, or other exon mutations)

^a Only indicated if there is a clinical suspicion for extensive or systemic disease

^b Only indicated if one or more of the following: persistent high serum tryptase level, organomegaly or lymphadenopathy, persistent and unexplained abnormality in CBCs with differential, disease progression/persistence of disease into adulthood

with presence of systemic disease [26, 33••]. A tryptase level >20 ng/ml is included as a minor criterion for systemic mastocytosis in adults according to the WHO classification. Baseline tryptase levels in children are comparable to those of adults [39]. However, the exact threshold for normal versus elevated basal serum tryptase levels has not been well established in children. Basal tryptase elevations >10 ng/ml in a child with mastocytosis was proposed as a threshold to warrant at least alertness for potential systemic disease and timely follow-up. Alavrez-Twose et al. investigated the utility of the basal serum tryptase level as a predictor for occurrence and severity of mast cell mediator symptoms and associated complications in 111 children with mastocytosis followed at a tertiary care referral center in Spain [33••]. The authors found significantly higher median basal serum tryptase levels in children with extensive skin involvement (>90 % of BSA affected) compared to children with less extensive skin disease (46 vs. 5.2 ng/ml; $p < 0.001$). Furthermore, they found a strong positive correlation of elevated basal serum tryptase levels with the development of severe mast cell mediator symptoms, requiring hospitalization with treatment in an intensive care setting. Three children with severe, near-fatal disease-associated symptoms and high basal serum tryptase levels (>20 ng/ml) and very high peak total serum tryptase levels during degranulation episodes (>200 ng/ml) had a bone marrow biopsy done, with confirmation of systemic

mastocytosis in two of those patients. Receiver-operating characteristic curve analysis of the data showed that optimal cutoff basal serum tryptase levels to predict the need for daily anti-mediator therapy, hospitalization and ICU management were 6.6, 15.5 and 30.8 ng/ml, respectively [33•]. However, while this demonstrates the utility of measuring serum tryptase levels in the evaluation of pediatric mastocytosis, one has to keep in mind that basal serum tryptase levels <20 ng/ml have been found in adult patients with SM and therefore do not rule out systemic disease [14]. High tryptase levels >20 ng/ml on the other hand can be seen in some cases of childhood-onset extensive cutaneous mastocytosis without systemic involvement.

In contrast to the evaluation of adults, which always includes a bone marrow biopsy as part of the initial workup, this is not routinely required for the diagnosis of childhood mastocytosis (Table 3) [35, 40]. In view of the generally benign clinical course with spontaneous resolution of disease, invasive testing is reserved for children with an unusual presentation. A bone marrow biopsy is indicated if the child presents with clinical features of persistent systemic disease, which include unexplained and persistent peripheral blood abnormalities, hepatomegaly, splenomegaly, lymphadenopathy, persistently elevated or rising basal serum tryptase levels >20 ng/ml in the context of a clinical presentation that suggests extracutaneous mast cell disease, and/or recurrent severe systemic mast cell mediator symptoms (anaphylaxis or anaphylaxis-like reactions) without a clearly identified cause (e.g., identified IgE-mediated allergies). For a child with a slightly elevated basal serum tryptase level of 10–20 ng/ml, but without other signs or symptoms that warrant invasive testing, we recommend clinical follow-up and monitoring of tryptase levels every 6 months.

If a bone marrow biopsy is indicated, it should preferably be done at a center with expertise in the examination of bone marrow specimens for mastocytosis, as subtle abnormal findings may be easily missed, particularly in children who may not have the classic bone marrow phenotype of adult mastocytosis. In addition to metachromatic stains, immunohistochemical stains for tryptase and/or Kit (CD117) as well as CD25 staining should be obtained from the core biopsy. Flow cytometric analysis of the bone marrow aspirate for CD117+ cells coexpressing CD25 and CD2 should be considered [41] and genetic analysis for a Kit mutation should be performed from the bone marrow specimen (Table 3).

Treatment

In consideration of the most often benign clinical course and tendency to regress spontaneously, treatment of childhood mastocytosis is mainly symptomatic, with the exception of rare aggressive variants. Symptomatic treatment focuses on prevention of mast cell degranulation symptoms, which can range

from mild to severe/life-threatening. In addition to avoidance of triggers that have been identified to cause mast cell degranulation for the individual patient, therapeutic options for cutaneous disease include use of systemically active medications that target mast cell mediator effects and use of topical medications/skin-targeted therapy for local control of symptoms in selected cases [42]. The use of topical medications in the treatment of cutaneous mastocytosis has not been formally studied, but topical glucocorticoid preparations and topical water-soluble cromolyn sodium at 0.21–0.4 % strengths have been anecdotally used to treat skin inflammation/blistering and to alleviate skin pruritus respectively. Non-sedating H1 antihistamines can be considered first-line therapy to control mast cell mediator symptoms and are routinely used in children with symptomatic mastocytosis. Additional medications commonly used include first-generation H1 antihistamines, H2 antihistamines, antileukotrienes and oral disodium cromoglycate for gastrointestinal complaints.

Rarely, solitary mastocytomas are surgically excised in cases with associated uncontrollable mast cell mediator symptoms. Skin complications such as severe blistering or bullae formation and skin superinfection need to be treated according to general guidelines for these conditions. Phototherapy including application of UVA light plus oral psoralen (PUVA) has been reported to cause reduction of skin lesions in addition to decreasing pruritus and urtication and has been used in a few pediatric patients with DCM and extensive blistering [42, 43]. Potential treatment-associated adverse effects, including an increased risk of development of skin cancers, make this therapy a rare choice in children [44].

Epinephrine is the treatment of choice for anaphylaxis or anaphylaxis-like acute systemic mast cell mediator release episodes. Therefore, if a child has extensive disease or a history of systemic reactions, an epinephrine autoinjector based on the child's weight for intramuscular administration should be readily available and the family/caregiver be properly trained in its use.

Childhood-onset mastocytosis only very rarely presents with an aggressive phenotype that meets the criteria of advanced systemic mastocytosis according to the WHO classification. Only in exceptional cases of persistent and progressive childhood multiorgan disease may cytoreductive therapy be indicated. There is no broadly accepted first-line treatment of childhood advanced systemic mastocytosis. Treatment follows adult management guidelines and is determined based on individual disease characteristics, a molecular defect if established, and drug-adverse effect profile and projected treatment tolerability. Complete response to imatinib including regression of skin lesions has been reported in a child with well-differentiated systemic mastocytosis [45]. However, this treatment is not recommended in children with typical and uncomplicated cutaneous mastocytosis because of potential long-term complications of imatinib and the transient nature of disease in most children.

Perioperative Care

Mastocytosis may confer an increased risk of mast cell mediator symptoms in the perioperative period. While anesthesia-associated cardiovascular collapse with profound hypotension has been reported in adults with mastocytosis [46], severe anesthesia-related complications are only rarely observed in pediatric mastocytosis [47, 48]. There is a single report of a pediatric patient with bullous cutaneous mastocytosis who developed cardiac arrest during general anesthesia, attributed to acute mast cell degranulation with resulting gastrointestinal hemorrhage [49]. However, published data as to the potential risk of complications in the pediatric population are scarce. Carter et al. reported their experience in a retrospective series of 22 children with various subtypes of mastocytosis including systemic mastocytosis undergoing general anesthesia and found only a few documented events of milder symptoms attributed to mast cell degranulation (flushing, gastrointestinal symptoms), but no serious adverse events [47]. Patients did not receive additional prophylactic premedication, but did continue regular maintenance medications for their mastocytosis, which included scheduled H1 antihistamines. Similarly, a series of six patients and review of the literature by Ahmad et al. did not reveal life-threatening complications in children with mastocytosis using conventional anesthetic management [48].

As with other potential triggers for mast cell mediator events in patients with mastocytosis, heightened awareness for possible symptoms associated with medications is also warranted in the perioperative period, particularly with muscle relaxants, opioids and NSAIDs, but should not routinely preclude use of these if medically indicated unless there is a history of allergy or intolerance to these medications. Known trigger factors for the individual patient need to be identified and avoided, requiring a detailed history of previous reactions. If available, drugs with less known mast cell degranulation potential are preferred, and higher risk medications may be given in incremental doses instead of single boluses [47, 48]. Other known triggers for local and/or systemic mast cell mediator release should be avoided and/or addressed if possible (e.g., preoperative agitation/anxiety, temperature changes, mechanical pressure to the skin during the procedure). Most important is meticulous preparation and anticipation of potential complications to ensure prompt treatment if these were to occur. This may be done best by establishing a perioperative treatment plan in advance that is reviewed by all health care personnel involved in the case.

Conclusions

Childhood mastocytosis is a rare and usually benign and self-limited condition. Nonetheless, even transient disease can sometimes be clinically challenging and can be associated with

life-threatening complications. Some variants of pediatric mastocytosis can mimic adult-onset disease and can persist. Awareness of mastocytosis, required for recognizing, correctly diagnosing and referring patients if needed, is critical and may still be underdeveloped in parts of the medical community. Different subspecialties involved in the diagnosis and management of mastocytosis need to work closely together to optimize care of children and to avoid inconsistency in the management approach. If symptoms occur, proper treatment and supportive care can often significantly improve the child's quality of life. Preparedness for potential complications can in most instances avoid or lessen the severity of symptomatic exacerbations.

Many features of the pathogenesis of childhood mastocytosis remain poorly understood. Both clinical and basic science research is needed to answer the remaining questions: What determines the extent of disease and its natural course? Are there genetic lesions other than mutations in *c-kit* that determine outcome, and, if so, can these be targeted therapeutically? Are there certain phenotypic characteristics or surrogate markers that could be used for diagnostic and treatment purposes? When we have an improved understanding of the disease pathogenesis progresses, does the WHO classification for mastocytosis need to be updated to include more childhood disease-relevant criteria? If a child has unusual early onset systemic disease or disease that persists into adulthood, how is the condition best monitored and treated? It will take time and continued effort to try to answer these questions. In the meantime, awareness of childhood mastocytosis needs to be raised and the current knowledge applied for optimum care.

Compliance with Ethics Guidelines

Conflict of Interest Ari J. Fried - None. Cem Akin has a consultancy agreement with Novartis.

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 importance
- Of major importance

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