

Pediatric Expression of Mast Cell Activation Disorders



Sigurd Broesby-Olsen, MD^{a,b,*}, Melody Carter, MD^c,
Henrik Fomsgaard Kjaer, MD, PhD^{a,b}, Charlotte Gotthard Mortz, MD, PhD^{a,b},
Michael Boe Møller, MD, DMSc^{a,d}, Thomas Kielsgaard Kristensen, PhD^{a,d},
Carsten Bindselev-Jensen, MD, PhD, DMSc^{a,b}, Lone Agertoft, MD, PhD^{a,e}

KEYWORDS

• Mastocytosis • Mast cell activation • Mast cell activation disorders • *KIT* mutations
• Urticaria pigmentosa • Tryptase • Anaphylaxis

KEY POINTS

- Symptoms in pediatric mastocytosis are often limited to the skin, and presence of skin lesions (urticaria pigmentosa) is the key feature for diagnosis.
- In most affected children, a somatic mutation in the *KIT* gene can be found; however, the *KIT* D816V mutation is only detected in one-third of pediatric patients.
- Extracutaneous symptoms, including anaphylaxis, are rare as opposed to in adult disease and mainly reported in children with very extensive skin involvement, bullous lesions, and high mast cell burden.
- Frequent triggers for exacerbations include friction, heat, fever, and insect stings; however, counseling in regard to avoidance of other potential mast cell activation triggers should be individualized after careful evaluation.
- In approximately 70% to 80% of children, the disease resolves by adulthood and risk for persistent disease may be related to the presence of small, monomorphic skin lesions; disease onset after 3 years of age; detection the *KIT* D816V mutation; high mast cell burden; and systemic disease. Further research is, however, needed including long-term follow-up studies.

Conflicts of Interest: Authors declare no relevant conflicts of interest in relation to this article.
Funding: M. Carter is supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

^a Mastocytosis Centre Odense University Hospital (MastOUH), Søndre Boulevard 29, 5000 Odense C, Denmark; ^b Department of Dermatology and Allergy Centre, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital, Søndre Boulevard 29, 5000 Odense C, Denmark; ^c Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA; ^d Department of Pathology, Odense University Hospital, J.B. Winsløvs Vej 15, 5000 Odense C, Denmark; ^e Hans Christian Andersen Children's Hospital, Odense University Hospital, Klørværnget 23C, 5000 Odense C, Denmark

* Corresponding author. Department of Dermatology and Allergy Centre, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital, Søndre Boulevard 29, 5000 Odense C, Denmark.

E-mail address: sigurd.broesby-olsen@rsyd.dk

Immunol Allergy Clin N Am 38 (2018) 365–377

<https://doi.org/10.1016/j.iac.2018.04.009>

0889-8561/18/© 2018 Elsevier Inc. All rights reserved.

immunology.theclinics.com

INTRODUCTION

Mast cell activation disorders (MCADs) is a term proposed to cover diseases and conditions related to activation of mast cells (MCs) and effects of released MC mediators. In its broadest sense, the term, therefore, encompasses a wide range of diseases from allergic asthma to rhinoconjunctivitis, urticaria, food allergy, and anaphylaxis, among many other conditions where MC activation (MCA) may contribute to the pathogenesis.¹

This article focuses on mastocytosis and gives an overview of its presentations, challenges, and controversies from a pediatric perspective. Mastocytosis is an unusual, heterogeneous group of diseases characterized by the proliferation and accumulation of MCs in body tissues.^{2,3} Clinical manifestations depend on the localization of MC infiltration and effects of mediators released from activated MCs, that is, MCA.

The World Health Organization (WHO) classifies mastocytosis into 7 subcategories, including cutaneous mastocytosis (CM)—where MC accumulation is limited to the skin—and systemic mastocytosis (SM)—where internal organs are involved.^{3–5} Although most adults (>95%) with mastocytosis are diagnosed with SM when fully investigated, with diverse clinical manifestations ranging from mild to very severe or potentially life-threatening, the disease manifestations in pediatric mastocytosis are typically limited to the skin, that is, CM, and symptoms are often mild (Table 1), although gastrointestinal (GI) symptoms are encountered.⁶

Several areas of pediatric mastocytosis are in need of research, including the elucidation of mechanisms involved in the peculiar spontaneous disease resolution observed in approximately 70% to 80% of affected children during adolescence as opposed to adult-onset mastocytosis, which is a chronic disease.^{7,8}

EPIDEMIOLOGY

Epidemiologic aspects of pediatric mastocytosis have not been studied in detail. In a population-based study, the prevalence of adult mastocytosis was found to be 10 in 100.000 with a slight female predominance.⁹ The incidence and prevalence of pediatric mastocytosis are estimated to be overall similar to or higher than adult mastocytosis.¹⁰ In the adult population, the disease is likely highly underdiagnosed due to a lack

Table 1 Comparison of adult mastocytosis and pediatric mastocytosis		
	Pediatric Mastocytosis	Adult Mastocytosis
Most frequent disease category	CM	SM
<i>KIT</i> D816V mutation	20%–30%. Other <i>KIT</i> mutations (exons 8, 9, 11) frequent. ¹⁴	>90%–95%
Skin lesions	Always present	May be absent
Typical tryptase level (ng/mL)	<11.4 (normal)	>20, but may be normal
Typical course of the disease	Resolution in 70%–80% before adulthood	Chronic
Symptoms	Often limited to the skin and controllable by anti-MC mediator therapy	Very heterogeneous, may be severe and difficult to control
Extracutaneous manifestations	Rare, but GI symptoms may be encountered	Frequent, including osteoporosis
Risk for anaphylaxis	Low (1%–9%)	High (35%–50%)
Advanced/aggressive disease	Exceedingly rare	5%–10% of patients

of awareness and the very heterogeneous clinical presentations. Although symptoms in pediatric mastocytosis are more homogeneous and often limited to skin and GI tract, the pediatric population is also facing a lack of awareness and experience with the disease among medical care providers and likely a similar under-recognition.

A majority of children (60%–90%) present with mastocytosis skin lesions within the first 2 years of life¹¹ and in approximately 10% to 20% the skin lesions are already present at birth.¹² When presenting later than the age of 15 years, the disease is likely to represent early-onset adult SM. In pediatric mastocytosis, a slight male predominance has been reported by some groups,^{8,11} whereas others have not found any clear gender discrepancies in pediatric mastocytosis.¹²

Although adult disease is almost always equal to SM, invasive tests (ie, bone marrow examinations) to rule out systemic involvement are not routinely performed in pediatric mastocytosis and, thus, the exact frequency of SM in affected children is largely unknown.³ Among those children who are diagnosed with systemic disease, virtually all have indolent SM (ISM) and advanced disease categories are exceedingly rare in the pediatric population.^{11,13}

In general, mastocytosis is a sporadic-appearing disease; however, familial cases of mastocytosis are well documented, most often related to germline *KIT* mutations,¹⁴ although cases of familial mastocytosis related to somatic *KIT* D816V mutations have been reported.^{15,16}

PATHOGENESIS

In contrast to earlier assumptions, it has been shown that in a majority (approximately 80%) of children with mastocytosis, a somatic gain-of-function point mutation in the *KIT* gene can be found, at least in lesional skin MCs,¹⁴ leading to a stem cell factor-independent constitutive activation and autophosphorylation of *KIT* with subsequent clonal accumulation of MCs through up-regulated recruitment from progenitor cells and defective apoptosis.

By far, the most frequent *KIT* mutation in adult-onset disease (ie, SM) involves codon 816, resulting in the replacement of an aspartic acid by a valine residue (D816V) in exon 17 involved in the kinase activity of *KIT*. The *KIT* D816V mutation can be detected in more than 90% of adult mastocytosis patients, not only in MCs in lesional skin and bone marrow but also in peripheral blood.^{17–20} In pediatric mastocytosis, the *KIT* D816V mutation is only detected in approximately 25% to 35% of affected children,⁸ and *KIT* mutations in exons 8, 9, and 11 are much more prevalent in the pediatric population compared with adult SM (**Fig. 1**).^{8,14,21}

Thus, overall there is increasing evidence that pediatric mastocytosis is a clonal disease in line with adult-onset mastocytosis; however, the mechanisms involved in the apparent spontaneous resolution observed in approximately 70% to 80% of children before adulthood have not yet been elucidated.

The symptoms in mastocytosis are caused by the localization of MCs and effects of mediators released from activated MCs. MCs may excrete numerous preformed as well as de novo synthesized mediators, including histamine, tryptase, platelet-activating factor, leukotrienes, prostaglandins, and cytokines, with a wide range of potential effects and related symptoms.²² Although the classic allergic IgE-mediated MC degranulation is a well described cellular reaction, MCA may also occur by non-IgE-mediated mechanisms and be induced by several different immunologic as well as nonimmunologic triggering factors. In childhood disease, MC accumulation and symptoms are often limited to the skin. The mechanisms involved in the hyperpigmentation of skin lesions in mastocytosis are not known in detail but involve the interaction

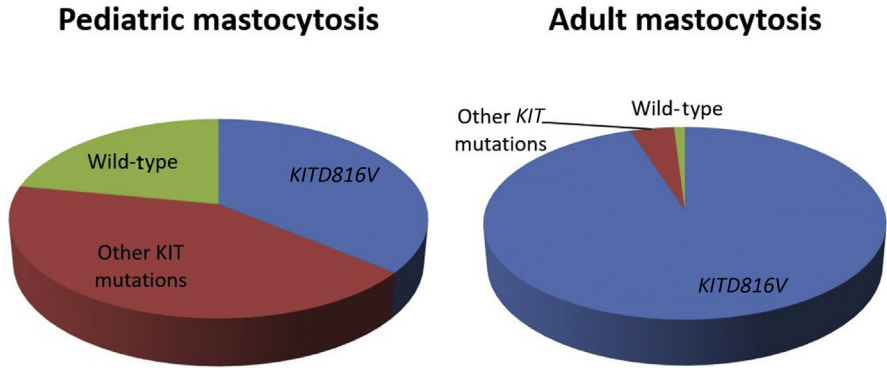


Fig. 1. Mutational profiles in pediatric mastocytosis (*left*) and adult mastocytosis (*right*). (Data from Bibi S, Langenfeld F, Jeanningros S, et al. Molecular defects in mastocytosis: *KIT* and beyond *KIT*. *Immunol Allergy Clin North Am* 2014;34(2):239–62.)

between clonal MCs in the skin and adjacent melanocytes, resulting in increased melanogenesis and melanin deposition in epidermis.²³ In adult SM, cytoreductive therapies have been shown to be able to reduce or clear skin lesions but so far no mediator-targeted therapy has been able to do so, although, for example, histamine has been shown to stimulate melanocytes.²⁴ Further studies are needed to clarify how the MC accumulation results in pigmented spots and furthermore why the clinical appearance of these skin lesions in pediatric mastocytosis is often more polymorphic compared with adult disease.

CLINICAL FEATURES

Skin Manifestations

The classic presentation of mastocytosis in children is the gradual onset of skin lesions within the first 2 years of life.^{8,12} These demarcated, reddish-brown, maculopapular skin lesions have traditionally been named urticaria pigmentosa (UP); however, in recent literature the term, *maculopapular CM*, is applied.⁴ Symptoms from the skin include pruritus, flushing, and whealing, which may be triggered by physical stimuli, such as heat, cold, sunlight, and friction as well as infections/fever. The number of skin lesions may vary from few to widespread skin involvement. Some children exhibit classic, small (up to 5 mm in diameter) monomorphic UP skin lesions as in adults (**Fig. 2**), whereas others have larger, polymorphic lesions (**Fig. 3**).^{25,26} These skin lesions typically exhibit a wheal-and-flare reaction on friction—called the Darier sign. In clinical practice, a useful approach to elicit this sign is to apply 5 strokes with a wooden tongue spatula with a moderate pressure over the skin lesions—and wait 3 minutes to 5 minutes (up to 15 minutes) to evaluate response. False-negative results may be encountered due to intake of H₁-receptor blockers and individual thresholds. Dermographism (stripes of whealing in the normal skin on scratching) may be seen in mastocytosis but are also seen in inducible urticaria and should not be confused with the Darier sign.

A common type of CM almost exclusively seen in the pediatric population is mastocytoma of the skin, presenting as a solitary, itchy, and swollen or sometimes bullous pigmented lesion, with a diameter of typically 1 cm to 2 cm. In the vast majority of children with a mastocytoma, symptoms are limited to the affected skin area; however, generalized flushing and hypotensive episodes may rarely occur in relation to physical provocation of the mastocytoma.¹²

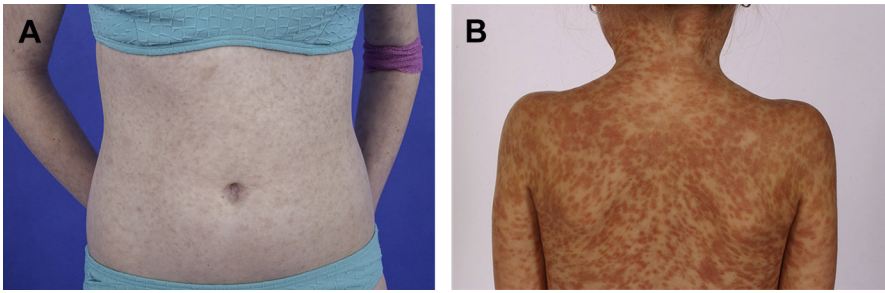


Fig. 2. (A) Monomorphic UP in cutaneous disease (CM). (B) Monomorphic UP in systemic disease (ISM).

Another special pediatric subtype is diffuse CM (DCM), in which the entire skin integument is infiltrated by MCs. Thus, children with DCM do not present with individual skin lesions but instead exhibit generalized erythema, usually with thickened, pachydermatous, darker skin and an often extensive, dermographism with bullous reactions. The clinical presentation may be dramatic with severe blistering and hypotensive episodes, requiring hospitalization; however, the overall prognosis is good. Even though serum tryptase levels are often increased in DCM at presentation, evidence of systemic involvement is usually not found and clinical improvement or resolution over time is the rule.^{11,26,27}

Cosmetic complaints may be a major issue in adolescents and younger adults and also an important aspect to address in children—and their worried parents. The challenge of treating the skin lesions is, as discussed previously, that the reduction of skin lesions demands reduction of the MC infiltration. The use of potentially toxic drugs in pediatric CM, however, is not warranted for cosmetic indication. The most important aspect in a majority of younger children and their parents is, therefore, reassurance of the benign nature of the disease and providing tools for the child to cope with their disease and accept their skin lesions. In younger adults, treatment options targeting the cosmetic burden of skin lesions are currently limited to UV therapy and short-term high-potency topical steroid. These treatments should be used cautiously due to potential cutaneous side effects but can make skin lesions less visible in addition to reducing pruritus and whealing.

Anaphylaxis

In adult SM, there is a 7-fold to 8-fold increased risk of anaphylaxis compared with the background population,²⁸ with a reported cumulative prevalence from specialized



Fig. 3. Polymorphic UP in cutaneous disease (CM).

centers of 35% to 50%.^{29–31} In comparison, the reported prevalence of anaphylaxis in pediatric mastocytosis is in the range of 1% to 9%, including mild episodes without cardiovascular compromise,^{30,32} which seem higher than rates reported in the general pediatric population,³³ however, much lower than in adult SM, and overall severe anaphylaxis in pediatric mastocytosis is uncommon.

Patterns of elicitors of anaphylaxis in pediatric mastocytosis differ somewhat from those in adult SM. Here, cases of idiopathic anaphylaxis or unknown triggers are the most frequently reported, followed by foods and drugs, whereas Hymenoptera stings are not a frequent trigger of anaphylaxis in pediatric mastocytosis as opposed to inadult disease, where this is the most frequently reported trigger.^{29,30,32}

In general, the incidence of IgE-mediated allergic rhinitis, asthma, and food allergies is not more frequent in mastocytosis,³⁰ but symptoms may be more difficult to control when the conditions coexist.

Currently, no clear predictors or surrogate markers have been identified to allow for an individual risk assessment for anaphylaxis in mastocytosis and further studies on this are needed. Suggested predictors for increased risk of anaphylaxis in pediatric mastocytosis include proved systemic disease, very extensive skin involvement, bullous skin reactions, persistently high serum tryptase levels, and previous anaphylaxis (**Box 1**).^{32,34,35} In pediatric mastocytosis, the risk thus seems to correlate with the severity and character of skin lesions as well as MC burden/level of serum tryptase. By contrast, the risk of anaphylaxis in adult SM does not correlate to MC burden or may even correlate inversely—and adult patients without skin lesions (bone marrow mastocytosis [BMM]) may even be more prone to anaphylaxis than patients with typical ISM, which is an apparent paradox. Currently, even though firm evidence is lacking, most centers recommend that all adults patients are equipped with an adrenaline autoinjector for use in case of anaphylaxis, whereas this in general only is provided to pediatric patients in the presence of risk factors, as described previously (see **Box 1**). In addition, patients/families should be informed about potential MC triggers and risk situations individually, as described previously, and a thorough evaluation and allergological work-up is recommended in case of anaphylaxis.

Other Symptoms and Disease Manifestations

In general, extracutaneous symptoms occur less often in pediatric mastocytosis compared with adult SM. GI symptoms, such as reflux, abdominal cramping, and loose stools, may be encountered in pediatric patients, especially with flushing events. This may be caused by an increase in intestinal MCs and/or MC mediator effects in the GI tract; however, in children with such GI symptoms, a thorough evaluation for differential diagnoses is mandatory. Similarly, other symptoms that are frequent in adult

Box 1
Suggested risk factors for anaphylaxis in pediatric mastocytosis

Very extensive skin involvement

Severe blistering disease

Significantly elevated basal serum tryptase

Systemic disease

KIT D816V mutation

Previous anaphylaxis

SM, such as fatigue, moods, lack of concentration, depression, and musculoskeletal pain, are rare in pediatric mastocytosis—and should prompt a search for other causes when present. At present, little is known about the bone metabolism in pediatric mastocytosis compared with adult SM, where osteoporosis is prevalent; however, from clinical experience, this does not constitute a problem in children.

MAST CELL ACTIVATION SYNDROME

MCA syndrome (MCAS) is a term proposed to describe a severe constellation of episodic multisystem symptoms resulting from MCA.^{1,36} MCAS and its diagnostic criteria were primarily introduced in the adult population, and little has been published about MCAS in children.

To meet criteria for MCAS a patient must fulfill all of the following 3 criteria:

1. Episodic symptoms consistent with MCA involving 2 or more organ systems (skin [flushing, urticaria, and angioedema], GI tract [diarrhea, abdominal cramping, nausea, and vomiting], airways/naso-ocular [wheezing, conjunctival injection, and nasal stuffiness], or cardiovascular system [hypotensive syncope, and tachycardia])
2. Appropriate response to medications targeting MCA
3. A documented increase in a validated marker of MCA during a symptomatic episode compared with the patient's baseline value. The most commonly used marker is serum tryptase and an increase of 20% from baseline plus 2 ng/mL is suggested as a meaningful indicator of MCA³⁷

By this definition, anaphylaxis is 1 category of MCAS, and, when clinical diagnostic criteria for anaphylaxis are met,³⁸ it is more appropriate to use this designation, whereas patients with chronic MCAS typically present with milder systemic symptoms from MCA.

Currently, MCAS is applied in patients with mastocytosis or with evidence of clonal MC disease not fulfilling WHO criteria for SM (MMAS), that is, clonal or primary MCAS, as well as in patients without identifiable cause for MCA, that is, idiopathic or nonclonal MCAS.³⁹

The current literature on MCAS does not address the pediatric population and there is a need for studies to better understand and classify this in children.

In a child referred for suspected MCAS, it is currently advised to apply the criteria discussed previously, after ruling out mastocytosis (ie, presence of UP skin lesions) as well as other etiologies with similar clinical manifestations. A final diagnosis of nonclonal MCAS should not be assigned unless all these 3 criteria are fulfilled.

In clinical practice, an increasing number of referrals for investigation of MCAS are seen—also in the pediatric population—due to more diffuse, nonspecific symptoms without an identifiable cause. These symptoms often present on a chronic basis without well-defined episodes of MCA and include intolerance to environmental factors, foods, and drugs; chronic fatigue; headaches; and memory problems. Currently, there is no evidence to suggest that an abnormal MC phenotype or a continuous state of MCA with chronic MC mediator release is the cause for these symptoms.³⁶ In some of these patients, a slightly elevated baseline serum tryptase level might have led to the suspicion of MCAS. Familial alpha-tryptasemia resulting from duplication or triplication of the alpha-tryptase gene (TPSAB1) may be the cause and is reported in 4% to 6% of the general population.⁴⁰ Alpha-tryptase is enzymatically inactive (as opposed to beta-tryptase) and there are currently no data to suggest that patients with an elevated tryptase level caused by familial alpha-tryptasemia have an activated MC phenotype.

DIAGNOSIS

In children, a diagnosis of mastocytosis is largely clinical and based on the typical appearance of skin lesions associated with the Darier sign, which is also accepted as the major diagnostic criterion for cutaneous involvement in mastocytosis in general. Minor diagnostic criteria are increased numbers of MCs in biopsy sections of lesional skin and/or the detection of a *KIT* mutation in lesional skin tissue.²⁶

In contrast to adult SM, children with mastocytosis always present with skin lesions, that is, so far no cases of pediatric BMM or clonal MCAD without skin lesions have been reported.

Baseline serum tryptase is most often in the normal range or only slightly elevated in pediatric mastocytosis, except for in children with DCM or ISM who in a majority of cases have a value greater than 20 ng/mL.^{11,41}

Typically serum tryptase values decrease over time in all children with mastocytosis in conjunction with improvement of clinical symptoms.^{11,41}

The application of sensitive, allele-specific quantitative polymerase chain reaction *KIT* D816V mutation analysis in peripheral blood has become a standard diagnostic screening tool in adult mastocytosis; however, experiences in pediatric patients are limited.⁴² For diagnostic purposes, this approach may be less valuable in pediatric mastocytosis for 3 reasons; first, children present with UP skin lesions on objective examination; second, only approximately one-third of children carry this specific mutation; and, finally, the mutation analysis may be negative in blood even though the *KIT* D816V mutation is detected in lesional skin (personal communication, Broesby-Olsen S, 2017). Therefore, a negative result of a *KIT* D816V mutation analysis in peripheral blood should be interpreted cautiously in pediatric mastocytosis and further studies are needed on this topic.

A recent study has shown that the most reliable predictor for systemic disease in children with mastocytosis is organomegaly and even in children with serum tryptase greater than 20 ng/mL and severe MC mediator symptoms, but no organomegaly, evidence of SM was not detected on bone marrow examination.¹¹ When making a decision whether to perform a bone marrow examination in pediatric mastocytosis, it must be considered whether bone marrow findings will alter disease management in the child. In general, a bone marrow examination is only warranted in severely affected children with a failure to thrive and where there is a significant concern for the health of the child, in combination with organomegaly and a persistently elevated serum tryptase indicating systemic disease.¹¹ On the other hand, CM is usually accepted as the final diagnosis for polymorphic lesions without the other variables.

DIFFERENTIAL DIAGNOSIS

Usually UP skin lesions have distinct features, as described previously, including the Darier sign, which is close to pathognomonic for mastocytosis. Localized smooth muscle hamartoma, an uncommon benign skin tumor in children, appearing typically as a slightly hyperpigmented 1-cm to 2-cm skin lesion, may also feature redness and a slight swelling (ie, pseudo-Darier sign) after rubbing and thus be taken for a solitary mastocytoma.

Other differential diagnoses in cases of multiple pigmented skin lesions include melanocytic nevi, café au lait spots and neurofibromatosis, tuberous sclerosis, postinflammatory pigmentation, juvenile xanthogranulomas, and lentigines among others. Bullous eruptions in mastocytosis may be taken for bullous impetigo, phytophotodermatitis, or autoimmune bullous skin diseases.

TREATMENT AND MANAGEMENT

Children with mastocytosis are generally best handled by comprehensive care centers with experience in managing the disease, using a coordinated, multidisciplinary approach. Treatment and follow-up should focus on the individual child and be tailored to symptoms, disease manifestations, and clinical course.

Treatment options in mastocytosis is divided into antimediator therapy, aiming at reducing release or effects of MC mediators, and cytoreductive therapies, aiming to reduce the MC burden. Due to potential side effects, currently available cytoreductive drugs are not relevant in the vast majority of pediatric patients and reserved for very rare cases of advanced SM.

Antimediator treatment should be symptom-directed and is not mandatory in all pediatric patients. Information on common triggers for MCA, such as friction, heat, and cold, should be given but should be individualized and, apart from physical stimuli to the skin most other theoretic triggers, do not have clinical relevance in childhood mastocytosis. It must be stressed that it is not helpful to provide a long list of potential MC triggers to avoid in pediatric mastocytosis. To that end, counseling and thorough information for often worried parents are often helpful, because information found on the Internet on this heterogeneous disease may vary greatly in quality and lead to unnecessary concerns and misinformation.

Antihistamines are most often sufficient to control skin symptoms. Second-generation, nonsedating H₁-antihistamines are generally recommended and may be updosed,⁴³ whereas sedating H₁-receptor blockers should be used cautiously and only for short periods for sleep-disturbing symptoms but should not be applied for long-term use. Emollients may be helpful to decrease the sensitivity to physical stimuli. Topical corticosteroids may relieve skin symptoms and increase threshold for MCA but should only be prescribed for short-term use due to potential side effects in the skin.¹²

Risk of anaphylaxis in pediatric mastocytosis is much lower than in adult mastocytosis, as discussed previously, and most expert mastocytosis centers only prescribe an adrenaline pen as emergency medication to selected children (see **Box 1**).^{32,34,35}

PROGNOSIS

A yet unsolved enigma is the spontaneous resolution observed in a majority of children, as discussed previously.⁷ This is in contrast to the increasing evidence that pediatric mastocytosis is a clonal disease in the great majority of children. One possible explanation is differences in mutational profiles compared with adults, with the *KIT* D816V mutation only detectable in approximately 25% to 35% of children as opposed to 80% to 95% of adult patients. In addition, children have more mutations in the transmembrane and extracellular domains of *KIT*.²¹ Mechanisms involved in the resolution of an apparent clonal disease, however, are yet to be elucidated. From a clinical perspective, recent data have suggested that children presenting with monomorphic small-sized lesions similar to adult patients may have a higher risk of having persistent mastocytosis, whereas in those with polymorphic larger lesions, the disease more often resolves before or at puberty.^{26,44} Similarly a late onset in childhood, evidence of systemic disease at diagnosis, and persistently elevated levels of serum tryptase have been proposed to predict persistency (**Box 2**); however, further studies, including long-term studies, are needed for clarification.

CURRENT CONTROVERSIES

In general, knowledge about pediatric mastocytosis is limited, because invasive tests, such as bone marrow biopsies, are not routinely performed in children and, thus, the

Box 2**Suggested predictors for persistent disease**

Small, monomorphic skin lesions (adult-type UP)

Systemic disease (often related to monomorphic UP)

KIT D816V mutation

Persistently elevated basal serum tryptase

Onset after 3 years of age

Skin lesions present after 12 years of age

true prevalence of systemic disease in pediatric patients is not known. Given that systemic involvement most likely is equal to persistent disease as well as associated with an increased risk for anaphylaxis, osteoporosis, and other comorbidities in adulthood, this lack of knowledge limits the possibility of properly counseling and treating the pediatric patients. It is possible that development of improved diagnostic methods, such as highly sensitive methods for detection of non-*KIT* D816V mutations and highly sensitive flow cytometry, may in the future provide a better understanding and guide a personalized approach to affected children.

So far, no children with mastocytosis without skin lesions, that is, BMM/monoclonal MCAD, have been reported. This is, however, a frequently encountered entity in the adult population, often only recognized by diagnostic screening using a highly sensitive *KIT* D816V mutation analysis in peripheral blood⁴⁵ or by performing a bone marrow examination in, for example, anaphylaxis patients based on proposed scoring systems.^{46–48} Although evidence of a similar high prevalence of underlying mastocytosis in pediatric venom anaphylaxis patients is lacking,⁴⁹ further research is needed to understand to what extent clonal MC disease without skin lesions may be found in the pediatric population when systematically applying diagnostic screening methods with very high analytical sensitivity, which in the future may be able to detect even lower levels of mutated cells and non-*KIT* D816V mutations.

Similarly, future studies on idiopathic MCAS are of paramount importance to better classify this newly introduced entity in the pediatric population and to understand to what extent the current knowledge from adult patients can be transferred to children. To that end, there is a need for further studies to clarify if a chronic, nonepisodic form of MCAS may exist with multiple symptoms caused by but not specific to MC mediators and if a continuous state of MCA is possible in such patients, which for now remains speculative.

SUMMARY AND FUTURE CONSIDERATIONS

This article focuses on pediatric mastocytosis, which in a broader perspective may be grouped among MCADs. Although symptoms in pediatric mastocytosis are typically mild and often limited to the skin,^{6,12,50} several aspects of the disease are in need of further research, such as the pathogenesis, disease course and prognostication, risk of persistent disease, and extracutaneous manifestations. It is, therefore, generally recommended that children with mastocytosis are offered an evaluation by specialized multidisciplinary mastocytosis centers.

REFERENCES

1. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126(6):1099–104.e4.

2. Metcalfe DD. Mast cells and mastocytosis. *Blood* 2008;112(4):946–56.
3. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37(6):435–53.
4. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25(7):603–25.
5. Horny HP, Akin C, Metcalfe DD, et al. Mastocytosis (mast cell disease). In: Swerdlow CD, Campo E, Harris NL, et al, editors. World Health Organization (WHO) classification of tumours of the haematopoietic and lymphoid tissues, vol. 2. Lyon (France): IARC Press; 2008. p. 54–63.
6. Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002;86(5):315–9.
7. Uzzaman A, Maric I, Noel P, et al. Pediatric-onset mastocytosis: a long term clinical follow-up and correlation with bone marrow histopathology. *Pediatr Blood Cancer* 2009;53(4):629–34.
8. Meni C, Bruneau J, Georgin-Lavialle S, et al. Paediatric mastocytosis: a systematic review of 1747 cases. *Br J Dermatol* 2015;172(3):642–51.
9. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol* 2014;166(4):521–8.
10. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am* 2014;34(2):283–95.
11. Carter MC, Clayton ST, Komarow HD, et al. Assessment of clinical findings, tryptase levels, and bone marrow histopathology in the management of pediatric mastocytosis. *J Allergy Clin Immunol* 2015;136(6):1673–9.e3.
12. Hartmann K, Metcalfe DD. Pediatric mastocytosis. *Hematol Oncol Clin North Am* 2000;14(3):625–40.
13. Lange M, Niedoszytko M, Renke J, et al. Clinical aspects of paediatric mastocytosis: a review of 101 cases. *J Eur Acad Dermatol Venereol* 2013;27(1):97–102.
14. Bibi S, Langenfeld F, Jeanningros S, et al. Molecular defects in mastocytosis: KIT and beyond KIT. *Immunol Allergy Clin North Am* 2014;34(2):239–62.
15. Broesby-Olsen S, Kristensen TK, Moller MB, et al. Adult-onset systemic mastocytosis in monozygotic twins with KIT D816V and JAK2 V617F mutations. *J Allergy Clin Immunol* 2012;130(3):806–8.
16. Zanotti R, Simioni L, Garcia-Montero AC, et al. Somatic D816V KIT mutation in a case of adult-onset familial mastocytosis. *J Allergy Clin Immunol* 2013;131(2):605–7.
17. Kristensen T, Broesby-Olsen S, Vestergaard H, et al. KIT D816V mutation-positive cell fractions in lesional skin biopsies from adults with systemic mastocytosis. *Dermatology* 2013;226(3):233–7.
18. Kristensen T, Broesby-Olsen S, Vestergaard H, et al. Mastocytosis Centre Odense University Hospital (MastOUH). Circulating KIT D816V mutation-positive non-mast cells in peripheral blood are characteristic of indolent systemic mastocytosis. *Eur J Haematol* 2012;89(1):42–6.
19. Kristensen T, Vestergaard H, Bindslev-Jensen C, et al. Mastocytosis Centre, Odense University Hospital (MastOUH). Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol* 2014;89(5):493–8.
20. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. *J Mol Diagn* 2011;13(2):180–8.
21. Bodemer C, Hermine O, Palmerini F, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. *J Invest Dermatol* 2010;130(3):804–15.

22. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med* 2015;373(19):1885–6.
23. Pec M, Plank L, Szepe P, et al. A case of systemic mastocytosis—an ultrastructural and immunohistochemical study of the dermal mast cells in relation to activation of the epidermal melanin unit. *J Eur Acad Dermatol Venereol* 1998;11(3):258–61.
24. Tomita Y, Maeda K, Tagami H. Histamine stimulates normal human melanocytes in vitro: one of the possible inducers of hyperpigmentation in urticaria pigmentosa. *J Dermatol Sci* 1993;6(2):146–54.
25. Hartmann K, Henz BM. Cutaneous mastocytosis – clinical heterogeneity. *Int Arch Allergy Immunol* 2002;127(2):143–6.
26. Hartmann K, Escribano L, Grattan C, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol* 2016;137(1):35–45.
27. Carter MC, Metcalfe DD, Clark AS, et al. Abnormal bone marrow histopathology in paediatric mastocytosis. *Br J Haematol* 2015;168(6):865–73.
28. Broesby-Olsen S, Farkas DK, Vestergaard H, et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: a nationwide population-based study. *Am J Hematol* 2016; 91(11):1069–75.
29. Gulen T, Hagglund H, Dahlen B, et al. High prevalence of anaphylaxis in patients with systemic mastocytosis - a single-centre experience. *Clin Exp Allergy* 2014; 44(1):121–9.
30. Gonzalez de Olano D, de la Hoz Caballer B, Nunez Lopez R, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007;37(10):1547–55.
31. Broesby-Olsen S, Kristensen T, Vestergaard H, et al. KIT D816V mutation burden does not correlate to clinical manifestations of indolent systemic mastocytosis. *J Allergy Clin Immunol* 2013;132(3):723–8.
32. Brockow K, Jofer C, Behrendt H, et al. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008; 63(2):226–32.
33. Huang F, Chawla K, Jarvinen KM, et al. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. *J Allergy Clin Immunol* 2012;129(1):162–8.e1–e3.
34. Alvarez-Twose I, Vano-Galvan S, Sanchez-Munoz L, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67(6): 813–21.
35. Brockow K, Ring J, Alvarez-Twose I, et al. Extensive blistering is a predictor for severe complications in children with mastocytosis. *Allergy* 2012;67(10):1323–4.
36. Akin C. Mast cell activation syndromes. *J Allergy Clin Immunol* 2017;140(2):349–55.
37. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26(3):451–63.
38. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; 115(3):584–91.

39. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157(3):215–25.
40. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multi-system disorder associated with increased TPSAB1 copy number. *Nat Genet* 2016;48(12):1564–9.
41. Lange M, Zawadzka A, Schrors S, et al. The role of serum tryptase in the diagnosis and monitoring of pediatric mastocytosis: a single-center experience. *Postepy Dermatol Alergol* 2017;34(4):306–12.
42. Kristensen T, Vestergaard H, Bindslev-Jensen C, et al. Prospective evaluation of the diagnostic value of sensitive KIT D816V mutation analysis of blood in adults with suspected systemic mastocytosis. *Allergy* 2017;72(11):1737–43.
43. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69(7):868–87.
44. Wiechers T, Rabenhorst A, Schick T, et al. Large maculopapular cutaneous lesions are associated with favorable outcome in childhood-onset mastocytosis. *J Allergy Clin Immunol* 2015;136(6):1581–90.e3.
45. Broesby-Olsen S, Oropeza AR, Bindslev-Jensen C, et al. Recognizing mastocytosis in patients with anaphylaxis: value of KIT D816V mutation analysis of peripheral blood. *J Allergy Clin Immunol* 2015;135(1):262–4.
46. Carter MC, Desai A, Komarow HD, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 2018;141(1):180–8.e3.
47. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz L, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012;157(3):275–80.
48. Zanotti R, Lombardo C, Passalacqua G, et al. Clonal mast cell disorders in patients with severe hymenoptera venom allergy and normal serum tryptase levels. *J Allergy Clin Immunol* 2015;136(1):135–9.
49. Yavuz ST, Sackesen C, Sahiner UM, et al. Importance of serum basal tryptase levels in children with insect venom allergy. *Allergy* 2013;68(3):386–91.
50. Torrelo A, Alvarez-Twose I, Escribano L. Childhood mastocytosis. *Curr Opin Pediatr* 2012;24(4):480–6.