Pediatric Mastocytosis

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The onset of mastocytosis occurs between birth and 2 years of age in approximately 55% of all cases; an additional 10% develop the disease before the age of 15 years. Mastocytosis in these age groups differs in many respects from mastocytosis that has its onset in adulthood. The typical presentation of pediatric-onset mastocytosis consists of cutaneous manifestations: either a solitary mastocytoma, urticaria pigmentosa, or, less commonly, diffuse cutaneous mastocytosis. Particularly in infants, bullous eruptions may occur. Mastocytosis in infants and children may involve internal organs, including the bone marrow and the gastrointestinal tract, although such manifestations appear to be less common in children than in adults. Plasma histamine levels may be elevated in pediatric-onset mastocytosis. Treatment usually involves the use of H1 and H2 antihistamines to control itching and to control the hypersecretion of gastric acid that may occur. The prognosis for children with mast cell disease is variable; approximately half of the children with urticaria pigmentosa may experience resolution of lesions and symptoms by adolescence. J Invest Dermatol 96:15S–18S, 1991

M astocytosis may present during infancy, childhood, or adulthood. The disease is characterized by an increased number of tissue mast cells and symptoms caused by the release of mast cell mediators. The organ system most frequently involved is the skin (cutaneous mastocytosis); however, mastocytosis may involve the lymphoreticular (liver, spleen, lymph nodes), gastrointestinal, bone marrow, and skeletal systems (systemic mastocytosis) [1]. The symptoms are both isolated to the organ system involved and systemic, due to local or generalized release, respectively, of histamine and other mast cell mediators, i.e., leukotrienes, prostaglandins, and platelet-activating factor. In addition to the age of onset, adult and pediatric forms of mastocytosis differ in their clinical course and pathophysiology. This article will review pediatric-onset mastocytosis, providing information for counseling parents of children with mastocytosis and a starting point for study and treatment of this unusual and protean disorder.

CLINICAL MANIFESTATIONS

The onset of mastocytosis occurs in approximately 55% of patients between birth and 2 years of age; another 10% develop symptoms between the ages of 2 years and 15 years (pediatric onset). The remaining 35% of patients develop symptoms after 15 years of age (adult onset) [2]. In the pediatric population evaluated at the National Institutes of Health, 16 of the 17 children had onset of their disease before 2 years of age, with 14 manifesting the disease by 6 months of age [3]. Two patients, one with urticaria pigmentosa and a second with diffuse cutaneous mastocytosis, presented at birth with skin lesions (congenital mastocytosis). In children there appears to be an equal sex distribution, and although individuals from varied ethnic groups have been affected mastocytosis appears to be more common in caucasians [4]. The occurrence of mastocytosis appears to be sporadic, yet 47 cases of familial mastocytosis have been reported [4], with dominance in 14 families [5]. In the pediatric-mastocytosis study population at NIH, we have not yet identified a family in which mastocytosis could be shown to be familial.

The typical presentation of pediatric-onset mastocytosis consists of cutaneous manifestations of either a solitary mastocytoma, urticaria pigmentosa, or, less commonly, diffuse cutaneous mastocytosis [6]. In addition, adults may present with telangiectasia macularis eruptiva perstans (discussed by Dr. Soter, page 32S), but that lesion is rarely if ever observed in pediatric patients [2]. The nodular form of mastocytosis that has been reported [7] most likely reflects a localized collection of mast cells, which may be associated with either urticaria pigmentosa or diffuse cutaneous mastocytosis, as we observed in one child with diffuse cutaneous mastocytosis followed at the NIH. Although some children manifest one form of skin lesion, overlap of classifications can occur. Lesions of urticaria pigmentosa may continue to increase in number after diagnosis, but children who present with a mastocytoma rarely demonstrated additional lesions more than 2 months subsequent to the initial lesion [8]. Stroking or trauma of affected skin results in a wheal with flare (Darier’s sign) or (less commonly than with large lesions, i.e., mastocytomas) flushing and hypotension. Infrequently, an infant will exhibit hepatosplenomegaly or skeletal lesions in addition to other clinical findings due to mast cell hyperplasia in these organ systems [9]. Rarely, an infant with cutaneous mastocytosis will initially present with an extensive bullous eruption that must be differentiated from other bullous diseases of infancy [10,11].

Pruritus is the primary presenting symptom in children with mastocytosis. The pruritus may be intermittent or unremitting, with itching leading to extensive excoriation of the skin. Additional symptoms include flushing, gastrointestinal complaints (i.e., vomiting, colicky pain, diarrhea), headaches, and, in children less than 2

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Abbreviation:
IgE: immunoglobulin E

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years of age, bullae. In the NIH patient population of 17 children with pediatric-onset mastocytosis, 88% manifested pruritus, 65% flushing, 53% vesicles/bullae, 41% abdominal pain, 18% bone pain, and 12% headache [12]. Asthma was an infrequent symptom and was seen in only one of 17 pediatric mastocytosis patients.

Prolonged bleeding, usually in the skin or gastrointestinal tract, has been observed in pediatric mastocytosis, especially in infants with diffuse cutaneous mastocytosis. In some cases, abnormal coagulation studies with reversal of abnormal thrombin clotting time in vitro with protamine (a heparin antagonist) have been documented, although circulating heparin has yet to be established as the cause of the bleeding diathesis. In vivo reversal of the abnormal coagulation with protamine has been considered but has yet to be employed [13]. Perhaps the bleeding tendency in skin may result when heparin contained in mast cells acts as a local anticoagulant, permitting prolonged bleeding from wound sites. Gastrointestinal hemorrhage appears to be associated with peptic ulcer formation due to high levels of circulating histamine.

Children with mastocytosis appear to be at no greater risk than other children for the development of allergies. In the NIH study, the patient group demonstrated no increase in atopy and their serum IgE levels were within normal limits [14]. Those observations suggest that the etiology of pediatric mastocytosis is not related to the development of allergic diseases.

Adult patients with mastocytosis have been reported to experience systemic anaphylaxis after insect stings. This does not appear necessarily to relate to an immunoglobulin E (IgE)-mediated allergy to insect venom, but may in some cases be secondary to direct activation of mast cells by the insect venom itself [15]. The possibility of an adverse reaction to an insect sting suggests that epinephrine (Epi-Pen, ANA-Kit) might be prescribed for selected children.

Mastocytosis is often instructed to avoid mast cell degranulating agents to minimize the potential of systemic mast cell mediator release [16,17]. Information supporting that recommendation is deficient. Only one study of five patients (two adults, one child, and two infants) has reported systemic symptoms to codeine (three of five patients) and polymyxin B (three of five challenges) given subcutaneously and intramuscularly, respectively [18]. During our study of pediatric mastocytosis, the synthetic narcotic meperidine was a constituent of a sedative used prior to diagnostic and investigational procedures. This synthetic narcotic has been reported to be safely used in patients with mastocytosis [18]. One child with urticaria pigmentosa who received the medication developed extensive bullae without other symptoms of mast cell degranulation 2 h after receiving the meperidine-containing sedative. As we could not rule out an adverse reaction to the synthetic narcotic, we no longer routinely use it but now use intravenously administered lorazepam, a short-acting benzodiazepine. This sedative has not resulted in any adverse reactions to date in our patient population. We believe that routine use of narcotics should be avoided if possible in this patient population. If they must be used, caution and close observation are essential.

The use of any potential mast cell secretagogue is of concern. However, one review of general anesthesia in 12 children with cutaneous mastocytosis revealed no significant adverse reactions [19].

DIAGNOSIS AND LABORATORY EVALUATION

Typically the diagnosis of pediatric-onset mastocytosis is based on the recognition of the clinical appearance of the cutaneous lesions. Because other pediatric skin lesions, i.e., xanthomas, juvenile xanthogranulomas, and pigmented nevi, may have a similar appearance [20], diagnosis should be confirmed by documentation of significant mast cell hyperplasia on biopsy, employing toluidine or Giemsa staining techniques [21]. Bullous lesions may precede the typical skin lesions of urticaria pigmentosa or diffuse cutaneous mastocytosis in infants with mastocytosis and may resemble other bullous skin diseases of infancy, such as bullous erythema multiforme or scalded skin syndrome [10]. Thus biopsy of bullous lesions is essential for diagnosis. Examination of bullous fluid from one patient revealed a predominance of neutrophils without mast cells. The skin biopsies from pediatric mastocytosis patients may exhibit extensive mast cell infiltration around blood vessels and within skin appendages, in some cases resulting in the disruption of normal skin architecture. Despite the gross differences in the cutaneous lesions in children with urticaria pigmentosa and diffuse cutaneous mastocytosis, skin mast cell numbers and dermopathology were similar in four children with urticaria pigmentosa and one child with diffuse cutaneous mastocytosis [22].

Plasma histamine levels have been elevated in the majority of pediatric mastocytosis patients studied [14]. In children with urticaria pigmentosa the histamine levels vary from normal to several times normal. In those with diffuse cutaneous mastocytosis, plasma histamine levels can reach remarkably high levels, even exceeding values reported in adults with systemic mastocytosis [23]. High levels of plasma histamine in children with diffuse cutaneous mastocytosis may reflect the extreme hyperplasia of their dermal mast cells. One child in our study, who had markedly elevated plasma histamine levels (more that 100 times normal), developed esophageal ulcerations with hemorrhage, with no other systemic histamine effects observed [14]. Thus, plasma histamine levels may be useful in following the clinical course of pediatric-onset mastocytosis and may identify those children who are at risk for the development of gastrointestinal ulcerations.

Further diagnostic evaluations, such as gastrointestinal radiography/endoscopy, skeletal surveys/bone scans, and bone marrow examinations, should be reserved for those children who exhibit evidence of organ-system involvement (e.g., anemia, leukopenia, thrombocytopenia, hemochromatosis, melena, severe bone pain). In our study, bone marrow examinations in 17 children with mastocytosis revealed narrow pathology [3]. Bone marrow aspirates identified five children with increased mast cell numbers and 10 children with eosinophilia. Trephine core bone marrow biopsies in 17 children demonstrated focal areas of mast cell hyperplasia in 10 children. Those lesions consisted of focal perivascular and paratrabecular aggregates of mast cells, eosinophils, and early myeloid cells; they differ markedly from the typical lesions observed in the bone marrow of patients with adult-onset mastocytosis. Such adult lesions consist of nodular collections of fusiform mast cells associated with lymphocytes and eosinophils. Despite the presence of mast cell hyperplasia in the marrow of 10 of 15 children, such lesions were not pathognomonic for pediatric-onset mastocytosis, as these were observed in three of 16 control pediatric patients with other hematologic diseases. The significance of such lesions is unknown, but may reflect an abnormality of mast cell proliferation [3].

The usefulness of skeletal surveys in pediatric mastocytosis is limited. A review of 95 patients who underwent skeletal surveys revealed no skeletal lesions attributable to mastocytosis in 81 patients. Although 14 patients demonstrated significant bone lesions thought to be due to systemic mast cell involvement, none developed a malignant course. A follow-up of three patients revealed resolution of their skeletal abnormalities [9]. The significance of these skeletal lesions remains unclear and does not appear to predict systemic progression.

TREATMENT

The treatment of pediatric onset mastocytosis is currently limited to the palliation of symptoms, usually pruritus. The treatment of choice is a classical H1 antihistamine, such as hydroxyzine. In a recent study of hydroxyzine versus ketotifen, hydroxyzine provided substantial relief of pruritus, bullae, flushing, and abdominal pain without significant side effects from the hydroxyzine [11]. In the child who exhibits gastrointestinal symptoms of hyperacidity or ulceration, the addition of an H2 antihistamine may be warranted. The use of oral sodium cromolyn in adult-onset mastocytosis, although having shown no effect on urine histamine and N-methylimidazole acetic acid excretion [24], has ameliorated gastrointestinal symptoms of diarrhea, abdominal pain, nausea, and vomiting. No improvement in symptoms of flushing, urticaria, headache, or bone pain was observed [25]. That study and the known pathophysiology
of gastrointestinal-system involvement in mastocytosis suggests that the use of oral sodium cromolyn in pediatric patients with gastrointestinal symptoms is reasonable, but documentation of efficacy requires a formal study utilizing a double-blind placebo-controlled design with crossover. A previous study of three children with pediatric-onset mastocytosis suggested improvement in both gastrointestinal symptoms (100%) and non-gastrointestinal symptoms (pruritus, 66%; wealing, 33%), but the protocol of that study did not control for maturational improvement [26].

Rarely, infants with pediatric-onset mastocytosis may develop a shock-like illness accompanied by bullous eruptions and gastrointestinal hemorrhage [27,28]. These infants require intensive care support with treatment with both H1 and H2 antihistamines as well as corticosteroids to correct the systemic effects of the massive mast cell mediator release [29]. In patients with adult-onset disease, epinephrine has been useful in reversing severe hypotension unresponsive to antihistamines and fluid administration [30]. This treatment appears to be reasonable for children with severe hypotension unresponsive to standard therapy.

The use of topical corticosteroids to aid the resolution of skin lesions has shown some efficacy [31], although widespread and long-term use of potent topical corticosteroids may cause hypothalamic-adrenal suppression in young infants. This treatment should only be undertaken in severely affected children and in conjunction with a physician experienced in high potency topical steroid use in children.

Treatment of the bullae that may occur in children less than 2 years of age is similar to that of a scald injury: local care and prevention of infection [10]. Bullae heal without scarring but may leave an area of hyperpigmentation [22]. Intravenous steroids have been reported to be useful in the treatment of severe and progressive bullae of infantile urticaria pigmentosa [8]. In the child with isolated mastocytosis with resultant severe systemic symptoms from mast cell mediators, surgical excision of the mastocytoma may be the treatment of choice, although the majority of mastocytomas spontaneously resolve after several years [32].

PROGNOSIS

The prognosis for children with mast cell disease is variable. Children with mastocytomas have not been reported to develop systemic involvement, and their lesions typically exhibit involution during childhood [32]. Retrospective studies report that approximately half of the children with urticaria pigmentosa will experience resolution of lesions and symptoms by adolescence, with the remainder exhibiting marked reduction in symptomatic cutaneous lesions and dermatographism [8]. One report of 47 adults and 122 children with urticaria pigmentosa disclosed that 27 of the adults experienced onset of their mastocytosis in childhood [33]. Children whose mastocytosis persists into adult life typically exhibit a course similar to adult-onset mastocytosis, in which 15–30% of patients develop systemic involvement [8].

Rarely a child will develop aggressive mastocytosis, most often with bone marrow involvement, although any organ system may be involved [6]. This systemic involvement may be infiltrative (not unlike reticulonodularis, such as histiocytosis) [34] or may exhibit circulating mast cells, resembling a leukemia. Importantly, the observation of circulating mast cells does not always imply an aggressive malignant condition; it has been reported in children with urticaria pigmentosa who have been otherwise healthy. In a reported case of “mast cell leukemia” [35], circulating mast cells were found at one hospitalization, but in a subsequent hospitalization (during which the child died) there was no evidence of circulating mast cells despite extensive organ-system involvement [36]. Several reports of the occurrence of acute lymphocytic leukemia raise the possibility of hematologic malignancy in children with rapid or late-onset urticaria pigmentosa [37], although the association has yet to be firmly established.

The prognosis for infants with diffuse cutaneous mastocytosis appears to depend on whether they exhibit bullae early in the neonatal period or if such bullae are delayed relative to the appearance of their skin lesions [35]. Eight infants who manifested bullae as their initial symptoms of mastocytosis all exhibited systemic involvement, and two died of their disease [16]. Children who manifest diffuse cutaneous mastocytosis prior to bullous eruptions appear to have a better chance of a gradual improvement in their disease.

The development of systemic disease appears to be more common in adult mastocytosis than in pediatric mastocytosis. A report of 71 patients with systemic disease revealed a ratio of pediatric to adult patients of 1:2.8. The association or development of malignancy appears to be less frequent in children. Of 20 mastocytosis patients with an associated malignancy, only four were children (pediatric to adult ratio of 1:4) [20]. Death in children with mastocytosis has been reported to be secondary to hemorrhage [36,38], leukemia [39], and cachexia [40].

REFERENCES


ROUNDTABLE

DR. AUSTEN: You said a lot about prognosis in urticaria pigmentosa being very favorable for a younger. What about the diffuse form of the disease? Is the prognosis less favorable?

DR. KETTELHUT: Most reports in the literature give a guarded prognosis for this group. Without having any figures on hand, I believe that although they may have improvement of their generalized skin manifestations, the disease does not usually resolve and often persists into adulthood.

DR. ROBERTS: Why do only children develop bullous lesions, as opposed to adults?

DR. KETTELHUT: No one really knows the answers. In our experience, if the patient has bullae only and does not have gastrointestinal bleeding, the bullae clear with minimal treatment as if they were a scald injury. Bullae do not leave scars, but they may leave an area of hyperpigmentation.

DR. AUSTEN: Dr. Kettelhut, is the appearance of bullous lesions and the appearance of nodular lesions unique characteristics of childhood disease, as opposed to adult disease?

DR. KETTELHUT: In general, yes. Occasionally some adults have bullous lesions, but that’s very unusual. Bullae are most common in children who are less than two years of age.

DR. AUSTEN: And the other fact we can carry away is that the prognosis of urticaria pigmentosa is clearly different in the child versus the adult.

DR. SOTER: I have one 25-year-old woman who has one solitary mastocytoma on her back that appeared when she was 20. I also have a comment about bullous disorders. Dermatologists have the impression that a variety of skin conditions are associated with bullae in children but not in adults. A classic example is staphylococcal disease; children develop bullous impetigo and adults seldom do.

DR. METCALFE: Would you comment on the statement that mastocytosis may be hereditary?

DR. KETTELHUT: In the literature there are reported cases of familial occurrence of mastocytosis in first- or second-degree relatives. There have been instances where one twin has mastocytosis and the other one doesn’t. You may see a possible familial component but, for the most part, when you’re counseling parents, I think it’s appropriate to tell them that the likelihood that a subsequent child is going to have urticaria pigmentosa or mastocytosis is virtually non-existent.

DR. METCALFE: I don’t think mastocytosis is a hereditary disease. We don’t see familial patterns. I will concede that, just as you can find an adult with mastocytoma, there may be rare instances where it is familial.

DR. SOTER: I recently looked into this, and I would agree it’s not a hereditary disorder, but there are 30 to 40 families in which more than one person has had urticaria pigmentosa. There are eight sets of identical twins and one set of triplets where all have urticaria pigmentosa, so that’s very intriguing.

DR. AUSTEN: And your conclusion?

DR. SOTER: It’s still not a hereditary disease.
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