Paediatric mastocytosis

M C Carter, D D Metcalfe

An unusual disease in infants and children

Mastocytosis in infants and children is an unusual disease characterised by an excess of mast cells in body tissues. The phenotypic expression of the disease is dependent on the pattern of localisation of the mast cells to specific organs and the release of mast cell mediators. The skin is the most common organ involved in children and may be the only manifestation of the disease. Mastocytosis can present from birth¹ to adulthood, with adult onset disease generally being more severe. The cutaneous form was recognised over 100 years ago, but the term mastocytosis, based on the offending cell, was initiated in 1936 by Sezary and Chauvillon.²

AETIOLOGY AND PATHOGENESIS

Mast cells are most abundant in connective tissues, with a predilection for peripheral nerves, and blood and lymphatic vessels. It is at these sites, under the influence of cytokines (interleukins

3, 4, 5, 6, 9, 10, and 15)³⁻⁹ and the principal mast cell growth factor, stem cell factor (SCF), that mast cells differentiate from a CD34+ pluripotent haematopoietic stem cell.¹⁰ This pluripotential cell expresses the receptor for SCF, KIT (CD117), but does not yet express the high affinity IgE receptor, FcεRI.¹¹ SCF is present in a soluble and membrane bound form and is produced by fibroblasts, endothelial cells, and bone marrow stromal cells. This growth factor orchestrates the complete cycle of the mast cell from proliferation to differentiation.¹² Mastocytosis in some instances appears to be the clinical expression of dysregulation of the production and function of mast cells caused by distinct activating somatic mutations in c-KIT (table 1).¹³ KIT is a type III transmembrane tyrosine kinase with an extracellular domain that binds mast cell growth factor, also known as SCF. Additionally, KIT is expressed by

and is essential for the development of melanocytes, haematopoietic stem cells, and the interstitial cell of Cajal.¹⁴

Other phenotypic expressions of KIT abnormalities are illustrated in the following situations: (1) autosomal dominant piebaldism in which a mutation decreasing KIT function results in a permanent localised absence of melanocytes and melanosomes; (2) c-KIT mutations have been found in neoplastic mast cell lines^{15 16}; (3) c-KIT somatic activating mutations have been found in human gastrointestinal stromal tumours^{17 18}; and (4) KIT protein expression is found in the neoplastic cells of approximately 63% of those with acute myelogenous leukaemia.^{19 20} However, paediatric expression of these abnormalities is seen predominately in piebaldism and in paediatric onset mastocytosis with extracutaneous disease. There has been no identified c-KIT abnormality reported to date in familial mastocytosis.¹³

The sequelae of aberrant mast cell numbers and mediator release are linked to three categories of products: preformed mediators, lipid metabolites, and chemokines/cytokines. Symptoms of mastocytosis are to a great extent a direct result of spontaneous mediator release, or mediator release in response to immunological and non-immunological stimuli. Table 2 lists mast cell derived mediators and their contributions to disease manifestations.²¹

CLINICAL PRESENTATIONS

Approximately 65% of individuals with mastocytosis present with disease in childhood; 55% of these patients have manifestations of disease by the age of 2 years.¹ The remaining 35% of those that develop their disease after puberty are classified as adult onset.²² Although the occurrence of mastocytosis appears to be sporadic, there are reports of familial mastocytosis with dominance in several families.²³ Mastocytosis is classified based on prognosis and clinical presentation (table 3).²⁴

Cutaneous mastocytosis

Children with cutaneous mastocytosis typically present with a spectrum of findings from solitary or multiple mastocytomas to urticaria pigmentosa (UP), or diffuse cutaneous mastocytosis (DCM). Blistering may occur in younger individuals, particularly with UP or DCM.²⁵ Some children may exhibit features typical of more than one distinct category, each category of which is discussed below. Children with more extensive skin involvement are more likely to exhibit systemic symptoms. Telangiectasia muscularis eruptiva persitans is a variant of UP, is associated with adult onset disease, and presents with diffuse telangiectasias.²⁶

Table 1 KIT mutations in children with sporadic disease

Mutation	Phenotype
Asp-816→Val Asp-816→Phe	Urticaria pigmentosa, with or without extensive disease
Asp-816→Tyr	Urticaria pigmentosa, with or without systemic disease
Glu-839→Lys	Urticaria pigmentosa

Table 2 Selected mast cell mediators and their effects

Preformed secretory granule mediators	
Histamine	Pruritis, increased vascular permeability, gastric hypersecretion, bronchoconstriction
Heparin	Local anticoagulation
Tryptase, other proteases	Degradation of local connective tissues, bone lesions
Lipid derived	
Sulphidopeptide leukotrienes	Increased vascular permeability, bronchoconstriction, vasoconstriction, vasodilatation
Prostaglandin D ₂	Vasodilatation, bronchoconstriction
Platelet activating factor	Increased vascular permeability, vasodilatation, bronchoconstriction
Cytokines	
TNF-α	Activation of vascular endothelial cells, cachexia, fatigue
TGF-β	Fibrosis
IL-3	Stimulation of haematopoiesis
IL-5	Eosinophilia
IL-16	Lymphocyte accumulation

IL, interleukin; TGF, tumour growth factor; TNF, tumour necrosis factor.

Table 3 Mastocytosis classification**Cutaneous mastocytosis**

1. Urticaria pigmentosa
2. Diffuse cutaneous mastocytosis
3. Mastocytoma of the skin

Systemic mastocytosis (without AHNMD or leukaemic mast cell disease)

1. Systemic indolent mastocytosis
2. Systemic smouldering mastocytosis

Systemic mastocytosis with an AHNMD

1. Myeloproliferative syndrome
2. Myelodysplastic syndrome
3. Acute myeloid leukaemia
4. Non-Hodgkin's lymphoma

**Systemic aggressive mastocytosis
Mast cell leukaemia****Mast cell sarcoma
Extracutaneous mastocytoma**

Classification adopted from WHO classification.²⁴
AHNMD, associated haematological non-mast cell disorder.

UP is the most frequent form of cutaneous mastocytosis. A subvariant consists of non-pigmented, plaque forming lesions that occur most often in infants. The lesions of UP appear as red-brown macules, papules, or plaques. These lesions are of varying size with the highest concentration usually on the trunk (fig 1). Darier's sign, present in the majority of patients with cutaneous mastocytosis, is the development of an urticarial wheal when a lesion is stroked and where the oedema is usually confined to the border of the lesion. In contrast, dermatographism is the development of a wheal formation after stroking or scratching normal appearing skin. The triple response of Lewis is classically

Figure 1 Child with urticaria pigmentosa. Both large and small pigmented lesions are visible.

described as the sequential development of a flush, a flare, and a wheal that may last for several hours. The most common associated symptom of UP is pruritis which varies in degree of intensity and chronicity. Flushing has been reported in association with bathing in hot or cold water, friction of the lesions, and exercise.²⁷ Bullae and blistering may appear in the first few years of life and must be distinguished from other bullous diseases of childhood, such as pemphigoid (fig 2). Blister formation tends to be tense and may become haemorrhagic. Blistered areas usually heal without scar formation, unless the lesions become secondarily infected.²⁸ When the lesions of UP are not associated with systemic disease, there is a tendency for such lesions to fade during

adolescence.²⁹ Skin lesions of UP histologically show an accumulation of mast cells within the papillary dermis with variable extension throughout the reticular dermis and into the subcutaneous fat. Of interest, the incidence of atopic disease in patients with UP approximates that observed in the general population.³⁰

Mastocytomas occur as brownish solitary or multiple nodules, which when traumatised may cause systemic symptoms, such as flushing and hypotension (fig 3). It is unusual for a child who presents with a solitary mastocytoma to develop further skin lesions more than two months after the presentation of the initial lesion.³¹ Histologically, sheets of mast cells without cytologic atypia fill the papillary and reticular dermis with variable extension into the subcutaneous tissues.

DCM is seen initially almost exclusively in infants, although it may persist into adult life.²⁵ The skin may be thickened with a peau d'orange appearance and/or a reddish-brown discoloration.¹ Lesions characteristic of UP may also be present. Dermographism with the formation of haemorrhagic blisters is common. There is a distinct pattern of mast cell infiltration around blood vessels, in skin appendages, and throughout the dermis. Patients with DCM appear to be at increased risk for flushing, hypotension, shock, and death.²⁹ Diarrhoea and other gastrointestinal manifestations are common.³²

Extracutaneous manifestations

Patients with mastocytosis may have other associated findings based on the concentration of mast cells in other organ systems or systemic production of mediators. Thus, mastocytosis may affect the gastrointestinal tract, cardiovascular,

Figure 2 Bullous eruption in a child with mastocytosis. Note the generalised erythematous, crusted lesions and plaques, with a sterile bulla.

Figure 3 Mastocytoma on the sole of a 3 year old child. It usually occurs as a solitary nodule, but rarely on the palms and soles.

haematological, hepatic, and lymphoid tissues. Abnormal mast cell mediator release may also alter the function of the central nervous system and cardiovascular system. Patients with a non-physiological increase in mast cells found in the bone marrow³³ or in an organ system other than the skin are said to have systemic disease.³⁴

Paediatric disease is less frequently associated with bone marrow pathology typical of systemic mastocytosis. Abnormalities in the bone marrow have, however, been shown in some children. These patients may have a substitution of valine for aspartate in codon 816

(V816D).^{35, 36} A number of case reports have documented an association between UP and haematological malignancies. The most frequent association appears to be with acute myeloid leukaemia and acute lymphoblastic leukaemia.³⁷ Systemic mast cell disease as defined by the presence of the classic bone marrow lesion associated with systemic mastocytosis was not observed in these cases. In one instance, the Philadelphia translocation 46, XY,t(9;22)(q34;q11)³⁸ was observed.

In one survey of children with cutaneous mastocytosis, small perivascular and paratrabeular aggregates of mast cells, early myeloid cells, and eosinophils were observed in occasional individuals.³⁹ Associated symptoms in such patients included pruritus (88%), flushing (65%), vesicles/bullae (53%), abdominal pain (41%), bone pain (18%), and headache (12%).⁴⁰ The results were microscopically distinct from mast cell aggregates observed in the bone marrow of those with adult onset disease, although rare children with mastocytosis may have more severe bone marrow involvement.^{41–43} A bone scan reflects skeletal involvement and is sometimes used as an adjunct to other positive tests.

Haematological abnormalities are thus rare in children with mastocytosis and in patients who have mastocytosis otherwise limited to the skin.^{44, 45} Mild normochromic normocytic anaemia is the most common abnormality, although there have been reports of prolonged bleeding time caused by abnormal thrombin clotting times. Infants with DCM may be at greater risk for this complication.³² Hepatosplenomegaly is associated with systemic disease in the paediatric population.

Studies of various subpopulations of patients with mastocytosis have concluded that between 35% and 80% of adult patients with systemic mastocytosis have gastrointestinal involvement.^{33, 34, 46} However, gastrointestinal involvement is much less common in children.⁴⁷ Gastrointestinal bleeding is a potential complication with severe disease. It is believed to be provoked by high concentrations of circulating plasma histamine, which drives gastric hypersecretion.¹ Abdominal cramping and diarrhoea have also been reported.

Patients with mastocytosis may react adversely to mast cell degranulating agents, such as narcotic analgesics^{48, 49} or polymixin B.³⁰ Patients with mastocytosis may also be more sensitive to venoms of stinging insects. There are a number of activators of mast cell secretion, which work through immunological and non-immunological mechanisms, which are summarised in table 4. Children with cutaneous mastocytosis do not appear to have any unique behavioural patterns other than those which would be expected from the intense pruritus which

may occur, from the side effects of antihistamines used to control itching and from problems in socialisation associated with the visible skin lesions. There is no clear psychopathology that exists in children with mastocytosis.⁵¹

DIAGNOSIS

Mastocytosis is diagnosed on the basis of history and clinical presentation, with confirmation of cutaneous involvement by biopsy. Stains such as toluidine blue or Giemsa, and the demonstration of mast cell tryptase by immunohistochemistry have been used to identify mast cells within cutaneous tissues.⁵² In some unusual circumstances degranulation of mast cells by a local anaesthetic may complicate the identification of mast cells.

Mast cell mediator concentrations may be increased in the plasma of patients with mastocytosis, but may also be increased in patients undergoing anaphylaxis.⁵² Plasma tryptase⁵³ and histamine concentrations⁵⁴ along with urine prostaglandin D₂⁵⁵ and histamine metabolite concentrations⁵⁶ are reflective of the increase in tissue mast cells and/or their activation.

Plasma histamine concentrations are known to be increased in the majority of the patients with paediatric onset mastocytosis.⁵⁷ Another study showed high concentrations of N-methylhistamine in the urine of children with mastocytosis, with the highest concentrations suggestive of more severe and extensive disease, although there was some overlap with a normal control group.⁵⁸ A commercially available enzyme linked immunosorbent assay (ELISA) can determine amounts of plasma tryptase using a monoclonal antibody with a sensitivity of about 0.2 ng/ml. Median total plasma tryptase in healthy controls was 5.0 ng/ml.⁵² A total tryptase ≥ 20 ng/ml in association with a total tryptase to β tryptase ratio of ≥ 20 identifies patients more likely to have systemic mastocytosis.⁵³

A bone marrow biopsy in those with paediatric onset cutaneous disease is not recommended unless there is evidence of systemic disease. Such evidence includes unexplained peripheral blood abnormalities, hepatosplenomegaly, and lymphadenopathy.⁵⁷

TREATMENT

Therapy for mastocytosis is focused on providing symptomatic relief. Patients and parents should be counselled on avoidance of key triggers of mast cell degranulation such as extremes of temperature, certain medications, and Hymenoptera exposure. Fortunately, the symptoms of paediatric onset cutaneous disease are usually less severe than those observed in patients with adult onset

Table 4 Pharmacological agents and physical stimuli that may exacerbate mast cell mediator release in patients with mastocytosis

Immunological stimuli

Venoms (IgE mediated bee venom)
Complement derived anaphylatoxins
Biological peptides (substance P, somatostatin)
Polymers (dextran)

Non-immunological stimuli

Physical stimuli (extreme temperature, friction, sunlight)

Drugs

Acetylsalicylic acid and related non-steroidal analgesics*
Thiamine
Ketorolac tromethamine
Alcohol
Narcotics (codeine, morphine)*
Radiographic dyes (iodine containing)

*Appears to be a problem in less than 10% of patients.

mastocytosis. Pruritus, the most common symptom, is usually controllable to some degree with antihistamines and skin care in the majority of children. It does not usually reach the intensity that is associated with other pruritic diseases such as atopic dermatitis.

The treatment of choice is an antihistamine to block the H_1 effects of histamine and control pruritus, flushing, and urticaria. Hydroxyzine, and more recently cetirizine or loratidine for less sedating properties, can be administered. In a double blind, placebo controlled, crossover trial, hydroxyzine was superior in children in reducing symptoms scores compared to ketotifen and had a similar side effect profile.⁴⁰ The addition of an H_2 antagonist may be useful to alleviate the symptoms associated with hypersecretion of gastric acid. Doxepin, with H_1 and H_2 properties, can be administered to children over 12 years. Orally administered disodium cromoglycate, although poorly absorbed, has been shown to relieve diarrhoea and abdominal cramping in some individuals.⁵⁹ Disodium cromoglycate has also been reported to relieve musculoskeletal pain, headache, central nervous system complaints, and skin symptoms in some patients.⁶⁰⁻⁶⁴

Mastocytosis with bullous lesions in infancy sometimes presents with a shock like syndrome.⁶⁵ As shown in one case study where the patient died of massive hypotension secondary to mast cell degranulation,⁶⁵ it is prudent to administer adrenaline and other therapy as indicated including fluids, glucocorticoids, and H_1 and H_2 antihistamines. Bullae present in children less than 2 years of age can be managed in a similar fashion to scald injury with blistering.¹ Care should be focused on prevention of infection and general skin health. Intravenous glucocorticoids have been used successfully to treat progressive severe bullae in infantile UP.³¹

Interferon α -2b has been used to treat several adult patients with mastocytosis, but overall findings are inconclusive.⁶⁶ Interferon α -2b has shown some efficacy in controlling mast cell mediated symptoms, but appears less effective in decreasing the number and extent of UP and the extent of mast cell infiltration in the bone marrow.⁶⁷⁻⁶⁹ This drug has not been adequately studied in a paediatric population.

PROGNOSIS

The course of disease in paediatric onset cases is often benign in that there is no progression to systemic disease. In a review of 67 patients with UP, 83.7% developed lesions in the first year of life. In this same group the average duration of disease was 9.4 years. Approximately one third had improvement without

clearing at an average of 6.1 years follow up.²⁷ The skin lesions resolve in approximately half of the patients by adolescence. Notable improvement was expected in the remainder.³¹ Children whose mastocytosis persists into adulthood may experience a similar progression (15–30%) to systemic involvement.³¹

The prognosis for infants with cutaneous mastocytosis in part appears to depend on whether they exhibit bullae early in the neonatal period or if bullae are delayed relative to the appearance of their skin lesions.⁷⁰ Children who manifest diffuse cutaneous mastocytosis prior to bullous eruptions appear to have a better chance at gradual improvement in their disease. Several reports of the occurrence of acute lymphocytic leukaemia in rapidly progressive and late onset paediatric onset mastocytosis suggest the possibility of a predilection for the development of a haematological malignancy in these patients.⁷¹

In summary, paediatric onset mastocytosis is an unusual disease with an often benign course. The disease in children is less likely to have a systemic component. Review of the literature suggests that those at potential risk for experiencing shock or sudden death include children with extensive bullous cutaneous involvement, those with symptoms of vasodilatation, flushing, and hypotension, and those with early onset of disease.⁶⁵

Arch Dis Child 2002;**86**:315–319

Authors' affiliations

M C Carter, D D Metcalfe, NIAID/NIH, Bethesda, MD, USA

Correspondence to: Dr M C Carter, NIH/NIAID/LAD, Building 10, Room 11-C206, 10 Center Dr. MSC 1881, Bethesda, MD 20892-1881, USA; mcarter@niaid.nih.gov

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