Paediatric Mastocytosis

Mastocytosis refers to a set of well-described diseases, all of which involve inappropriate activation of mast cells. Mastocytosis can occur in children or adults, and the classification of disease seen in children includes some types not seen in adults. Most families with one child who has mastocytosis will not experience the disease in other children. Classifications of mastocytosis include cutaneous mastocytosis and systemic mastocytosis, with subtypes for each classification. The remainder of this discussion is a brief overview related specifically to pediatric mastocytosis.

**Forms of pediatric mastocytosis**

**Cutaneous mastocytosis:**

Urticaria pigmentosa is the most frequently seen form of pediatric cutaneous mastocytosis. It is also known in medical literature as “maculopapular cutaneous mastocytosis” and presents as a long-lasting (months to years) yellow to brown rash with characteristic features. The rash may occur on any part of the body and may involve only a few lesions (or “spots”), or much of the skin may be involved. Children with pediatric mastocytosis may also have red spots that appear when their symptom level increases; these spots then clear within a few hours or days of symptoms returning to the usual, or baseline, level.

Urticaria pigmentosa may be present at birth or may appear at any time during childhood. Very young children may also have blisters on their skin in addition to the rash. Rarely, pediatric urticaria pigmentosa is associated with systemic mastocytosis, so children with severe symptoms that don’t respond well to appropriate treatment may need to be examined for the presence of systemic disease.

Urticaria pigmentosa that appears in infancy has a high chance of spontaneously clearing. With increasing age of the child at the time urticaria pigmentosa lesions appear, there is increasing chance that the disease will continue through adulthood. We do not yet understand how to predict which children will outgrow their disease or which children whose disease continues into adulthood will progress to systemic mastocytosis. In general, though, if these children develop systemic mastocytosis in adulthood, their disease will probably be mild and their symptoms reasonably well controlled with proper medication and management.

Nodular cutaneous mastocytosis, or mastocytoma consists of one or a few lesions that may be slightly elevated above the surface of the skin. They have a brownish or yellow-orange color and often may blister if they are stimulated by rubbing. Rubbing also causes redness and swelling of the mastocytoma. The mastocytoma lesions may be present at birth or may develop in early infancy. Only rarely does a lesion develop after the child is 3 months of age. A mastocytoma may occur on any part of the body. This type of skin lesion has not been reported to progress to systemic mastocytosis; indeed, the lesions almost always disappear late in childhood.

Diffuse cutaneous mastocytosis is an extremely rare form of pediatric cutaneous mastocytosis that involves almost the entire skin surface. They have a brownish or yellow-orange color and often may blister if they are stimulated by rubbing. These children usually develop many blisters on much of their skin. Children with diffuse cutaneous mastocytosis may have severe symptoms even in the absence of systemic disease mastocytosis, because of the high mast cell burden in their skin. Most of these children, from the low numbers that have been reported, do not develop systemic mastocytosis, and their disease clears in young childhood, mostly by 3 to 5 years of age.

**Pediatric systemic mastocytosis**

Systemic mastocytosis refers to a proliferation of mastocytosis mast cells in internal organs, involving bone marrow, spleen, and/or other organs.

Rarely, a child will be seen who has systemic mastocytosis. The vast majority of children with mastocytosis, though, will not develop systemic disease and should not be tested for systemic mastocytosis because of the invasive nature of testing and the very low likelihood of finding systemic involvement. Systemic involvement
may be suspected if the child has ongoing severe symptoms in spite of appropriate medication and management of their cutaneous mastocytosis, and/or if they have enlarged spleen and/or lymph nodes that remain large for an extended time (months), in addition to their cutaneous mastocytosis. Systemic mastocytosis has not been reported in children who do not have cutaneous mastocytosis.

The aggressive forms of systemic mastocytosis that are seen occasionally in adults occur in an extremely small number of children, and some might not occur at all. No reports of pediatric aggressive systemic mastocytosis or pediatric mast cell leukemia were found in a literature search.

Symptoms

Symptoms in pediatric mastocytosis are related to the release of mediators, or chemicals, from overactive mast cells. Release of the chemicals found in mast cell granules, notably histamine, tryptase, and heparin, and molecules that communicate with other immune system cells, is referred to as “degranulation”. Factors that cause mast cell degranulation vary from child to child, but common factors include ingestion of alcohol (often used in pediatric preparations of medications); drugs such as codeine, morphine, dextromethorphan (a cough suppressant), and a number of drugs used in anesthesia; preservatives in drugs or foods; vigorous exercise, heat, cold (or a rapid transition from one to the other), and excessive sun exposure. Also, emotional stress, and infections of all types increase mast cell activity and can precipitate symptoms.

There is wide variation in symptoms in different children with mastocytosis. Many children have no symptoms and others experience itching, flushing (temporarily red skin), light-headedness and possibly fainting, vomiting, abdominal pain, diarrhea, fatigue, mood swings, or bone pain.

Anemia is seen in some children, in both cutaneous and systemic mastocytosis. This is usually mild and responds to treatment with iron supplementation.

Children with diffuse cutaneous mastocytosis are at increased risk of severe gastro-intestinal bleeding and their symptoms should especially be well-controlled.

Diagnosis

Cutaneous mastocytosis is often diagnosed based on appearance of the skin lesions, the history of their development, and symptoms. Darier’s sign, the formation of a wheal, or hive, when a skin lesion is stroked or rubbed, is seen in most forms of pediatric mastocytosis.

If there is any doubt about the diagnosis, and especially if a newborn or very young infant develops skin blisters, biopsy of a lesion is the method of making a definite diagnosis. This can eliminate the diagnosis of more sinister diseases that cause skin blisters in very young infants.

Diagnosis of systemic mastocytosis in children is made through measurement of blood serum level of tryptase, which is persistently elevated in systemic mastocytosis; and bone marrow biopsy and aspirate, which require proper staining and examination by a pathologist experienced in pediatric mastocytosis. This testing is not recommended in most children with mastocytosis and if it is done, it should be carried out in consultation with a specialist center that has extensive experience in mastocytosis. In other situations, the results may be equivocal and difficult to interpret.

Treatment

Treatment of the symptoms occurring in pediatric mastocytosis consists of the prevention of exposure to agents that are known to cause symptoms in that child, and the use of medications if necessary. “Management” is at least as important as “medication”.

When symptoms are present in children with mastocytosis, it is often beneficial to treat them with medications at the time of symptoms, or with routine doses of medication if symptoms are frequent.
H1 antihistamines, such as are normally associated with relief of allergic symptoms, are the first treatment used, and can relieve most of the symptoms present in pediatric mastocytosis. It may be necessary to try several different H1 antihistamines, using each for several weeks before evaluating its effect.

H2 antihistamines, such as Pepcid (famotidine) and Zantac (ranitidine) may relieve skin symptoms that continue in spite of adequate treatment with H1 antihistamine. They also relieve symptoms from excessive stomach acid or gastric reflux.

If a child is taking both H1 and H2 antihistamines in adequate doses and still experiences frequent symptoms, there are several other medications used, depending on the symptoms.

Cromolyn (disodium cromoglycate) reduces mast cell activity. It can be used orally for GI symptoms, by inhalation for respiratory symptoms, as a nasal spray to reduce congestion, as eye drops to relieve itching and swelling of eyes, and as a topical cream to relieve skin symptoms. Cromolyn is absorbed into the system through both oral and inhalational use and, although absorption is minimal, children often experience a reduction in many of their symptoms.

Children with severe and symptomatic skin involvement (such as those with extensive urticaria pigmentosa and those with diffuse cutaneous mastocytosis) may be helped with light treatments in conjunction with taking a medication called psoralen. This treatment is referred to as PUVA, and reduces substantially the number of mast cells in the skin.

Leukotriene receptor blocking agent montelukast (Singulair) may be helpful when respiratory symptoms remain in spite of all of the above treatment, especially in children who have asthma along with their mastocytosis.

Other drugs are available for various symptoms and may be tried in consultation with a mastocytosis-experienced specialist. Aspirin and other non-steroidal anti-inflammatory drugs can cause sudden onset of severe symptoms in people with mastocytosis and are especially contraindicated in children with diffuse cutaneous mastocytosis because of their ability to cause gastrointestinal bleeding.

The emergency use of epinephrine (adrenaline) injection is controversial in very small children, for whom the available single-dose injectors would result in overdose. In children whose body weight is adequate for the use of EpiPen Jr., having one on hand and instructing the parent or caregiver in its use is an important safeguard if severe symptoms, such as loss of consciousness and shock, occur. These severe symptoms are possible in all forms of pediatric mastocytosis, and consultation with an experienced physician as to the use of EpiPen should be undertaken as soon as a child is diagnosed with mastocytosis.

**Conclusion:**

A diagnosis of pediatric mastocytosis may present challenges for the child and the family involved. Children with “spots” need to be reassured about social contacts, and children who experience obvious symptoms need the protection of having the adults around them educated in how to manage and treat these symptoms. Organizations such as Mastokids.Org (www.mastokids.org) can help families and affected children select useful techniques for coping with the disease while helping the child live as normal a life as possible.

**References:**

Pediatric mastocytosis; Karin Hartmann MD and Dean D Metcalfe MD; Hematology/Oncology Clinics of North America 14(3):625-640 (June 2000)

Diagnostic criteria and classification of mastocytosis: a consensus proposal; P Valent, H-P Horny, et al; Leukemia Research 25(7):603-626 (July 2001)

Clinical and histopathological aspects of cutaneous mastocytosis; K Wolff, M Komar, and P Petzelbauer; Leukemia Research 25(7):519-528 (July 2001)
The discovery of cromolyn and its effect on research and practice in allergy and immunology; A M Edwards; The Journal of Allergy and Clinical Immunology;115(4):885-888;(April 2005)

Diffuse cutaneous mastocytosis. Treatment with oral psoralen plus UV-A.; S Mackey, HB Pride, and WB Tyler; Archives of Dermatology 132(12):1429-1430 (December 1996)