

Indolent Systemic Mastocytosis

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KEY WORDS: mastocytosis, urticaria pigmentosa, indolent, systemic mastocytosis, mast cell, Darier sign, tryptase, flushing, anaphylaxis

IMAJ 2010; 12: 185–187

Mastocytosis is a rare disease. Because of this, general practitioners have limited exposure to its clinical manifestations and management. Mastocytosis is characterized by an accumulation of mast cells in the skin and/or other tissues. The most frequent form of mastocytosis is cutaneous, followed by indolent systemic mastocytosis. Depending on the extent of the disease, it may present with symptoms resulting from mast cell degranulation, including flushing, diarrhea, vomiting, syncope, or anaphylaxis. We present the case of a young man with this rare disease, and review the literature on the more interesting aspects of the disorder for general practitioners.

PATIENT DESCRIPTION

A 22 year old man was referred to the mastocytosis unit of our hospital because of a 2 year history of itchy cutaneous lesions on his trunk and extremities. His medical history revealed multiple allergic reactions to several drugs, including betalactamics, diclophenac and aminoglucoisides. The patient complained of recurrent symptoms related to hot temperatures (climate or overheated room) consisting of headache, flushing and even syncope. Physical examination revealed multiple brownish

circular macules, less than 1 cm in diameter, located on his trunk and extremities [Figure A]. Wheals and surrounding erythema developed in the lesions after rubbing (positive Darier sign).

Laboratory analyses showed mild eosinophilia with an increased total tryptase level of 40 ng/ml. Densitometry was normal. With the strong clinical suspicion of cutaneous mastocytosis, a skin biopsy was performed. Histological examination [Figure B] using immu-

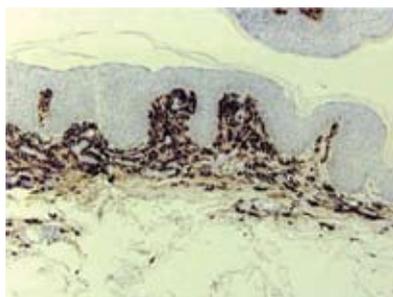
nochemistry revealed an intense mast cell infiltrate in the papillary dermis around the blood vessels with positivity of tryptase, confirming the diagnosis of mastocytosis. The bone marrow biopsy demonstrated multifocal dense infiltrates of mast cells, expressing CD25 and tryptase, which led us to the diagnosis of indolent systemic mastocytosis.

Counseling and information on the disease was provided to the patient. Treatment with oral antihistamines (desloratadine and dexchlorpheniramine) and oral disodium-cromoglycate was started, with adequate control of symptoms after 4 weeks.

[A] Clinical image of the patient's back showing multiple brownish circular macules < 1 cm in diameter



[B] Histological image of the skin biopsy, showing the positivity of tryptase by immunochemistry in the dense infiltrate in papillary dermis



COMMENT

Mastocytosis is a heterogeneous disease characterized by an accumulation of mast cells in the skin and/or other tissues [1]. The World Health Organization classification of mastocytosis defines seven disease variants: cutaneous mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with an associated (clonal) hematologic non-mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma [2].

Since mastocytosis is a rare disease, general practitioners have limited exposure to its clinical manifestations, diagnosis, classification and management [3]. Its incidence is estimated to be around 1/50–100.000 per year. There is no gender predilection. Most patients with mastocytosis are children. Incidence peaks again at age 30–50 years. Most cases of urticaria pigmentosa in

children resolve spontaneously [4], although acute extensive degranulation rarely causes life-threatening episodes of shock. Patients with adult- or adolescent-onset urticaria pigmentosa are more likely to have persistent disease and are at greater risk for systemic involvement.

Patients may present with cutaneous lesions, systemic symptoms of an acute nature, and/or chronic systemic symptoms. The predominant presentation is a pruritic lesion or lesions, especially after rubbing or a hot bath. Less frequently, there is flushing, headache, or fatigue. The range of symptoms depends on the extent of the mast cell disease and the mediators released, as well as the organs involved [5].

Patients may also have chronic systemic symptoms involving various organ systems, such as the skeletal system (bone pain or pathologic fractures due to osteoporosis), central nervous system (neuropsychiatric symptoms), gastrointestinal involvement (diarrhea, nausea, vomiting, malabsorption), and cardiovascular symptoms (shock, syncope, flushing). Anaphylactic reactions to drugs or hymenoptera stings are common and may be the first sign of mastocytosis. General anesthesia is a high risk procedure, since severe reactions – such as systemic hypotension and coagulopathy even resulting in death – have been reported. A close communication between anesthesiologists, surgeons and intensivists must be established prior to surgery [3].

Cutaneous lesions of mastocytosis are observed in most patients. The most frequent form of mastocytosis, urticaria pigmentosa, manifests as a maculopapular symmetric eruption of yellow-tan to red-brown lesions, predominantly affecting trunk and extremities and sparing the face, scalp, palms and soles. Other cutaneous forms include solitary mastocytoma, diffuse cutaneous mastocytosis and a bullous form. Darier's sign is diagnostic of cutaneous mastocytosis, and it is detected in

about 75% of patients. It refers to the change observed in a skin lesion after it is rubbed, becoming swollen, itchy and erythematous. It reflects the mast cell degranulation induced by the rubbing. In contrast to dermatographism, the Darier sign implies the swelling of a preexisting cutaneous lesion (in dermatographism the previously healthy skin becomes erythematous and swollen, without a preexisting skin lesion).

A suspected diagnosis of cutaneous mastocytosis can be made on the basis of anamnesis and the typical pruriginous skin lesions that demonstrate the Darier sign. Confirming the diagnosis requires the histological demonstration of an increased number of mast cells by a skin biopsy. The term systemic mastocytosis implies bone marrow affection, and a bone marrow biopsy is required to diagnose this form of mastocytosis.

The WHO criteria for diagnosis of systemic mast cell disease mandate the presence of one major criterion and two minor criteria, or three minor criteria:

- **Major:** multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous organs (> 15 mast cells aggregating)
- **Minor:** a) mast cells in bone marrow, or other extracutaneous organs show abnormal (spindling) morphology (> 25%); b) codon 816 c-kit mutation D816V in extracutaneous organs; c) mast cells in bone marrow express CD2, CD25, or both; and d) serum tryptase values greater than 20 ng/ml

Bone marrow biopsy is not recommended in children, since systemic involvement is rare. In adults, it is usually performed due to the frequent systemic involvement, especially if the patient has severe symptoms or anaphylactic reactions.

Laboratory analyses may be abnormal; in systemic mastocytosis, complete blood cell counts can reveal anemia, thrombocytopenia, thrombocytosis, leukocytosis, and eosinophilia. Hypocholesterolemia or hypoproteinemia may be the present-

ing signs of subclinical malabsorption. The measurement of total tryptase level can be helpful in the diagnosis of mastocytosis. Tryptase is a marker of mast cell degranulation released in parallel with histamine. Total tryptase levels in plasma correlate with the density of mast cells in urticaria pigmentosa lesions in adults with systemic mastocytosis.

In the doctor's clinic, mastocytosis should be suspected when a patient (usually a child or an adolescent) presents with itchy cutaneous lesions and a flushing, anaphylactic reaction to drugs or hymenoptera sting, or malabsorption. A skin biopsy should be performed and serum total tryptase measured.

Management of patients irrespective of the mastocytosis category includes counseling of patients (parents in pediatric cases) and care providers, avoidance of factors triggering acute mediator release (heat, cold, friction of skin lesions, pressure, exercise, stress, anxiety, radiographic dyes, drugs), and treatment of acute mast cell mediator release as well as chronic mast cell mediator release [3].

Therapy is conservative and aimed at symptom relief since the prognosis for most patients with mastocytosis is excellent. None of the currently available therapeutic measures induces permanent involution of cutaneous or visceral lesions. Patients should be advised to avoid drugs that precipitate mediator release, such as aspirin, non-steroidal anti-inflammatory drugs, codeine, morphine, thiamine and opiates. The traditional use of antihistamines, H1 with or without H2, is the mainstay of symptomatic treatment to allay pruritus, flushing, and wheal formation. Oral disodium cromoglycate may ameliorate cutaneous symptoms, such as pruritus, whealing and flushing, as well as systemic symptoms such as diarrhea, abdominal pain, bone pain, and disorders of cognitive function. Other modalities of treatment include topical cromolyn, leukotriene antagonists, corticosteroids, phototherapy, interferon, and cyclosporine [3]. Potent corticosteroids used topically with occlusion may help

in controlling pruritus and decreasing the number of mast cells [5].

In conclusion, general practitioners usually have limited exposure to patients diagnosed with mastocytosis. They should be alert to the possibility of this entity particularly in patients presenting with chronic and itching skin lesions accompanied by a history of several allergic reactions to drugs, bites/stings, or anesthetic procedures. It is crucial

that physicians advise patients affected with mastocytosis about the risks of anesthesia and some medications.

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