



CASE REPORT

Systemic mastocytosis in childhood: report of 3 cases

Evódie I. Fernandes,¹ Beatriz C. de Faria,² André Cartell,³
Boaventura A. dos Santos,⁴ Tania F. Cestari⁵

Abstract

Objective: mastocytosis comprises a group of diseases characterized by accumulation of mast cells on the skin, with the possibility of affecting other systems. Symptoms can be exclusively cutaneous, associated with symptoms of the organs involved or even systemic, due to the release of chemical mediators. Three cases of systemic mastocytosis are described, each case presenting different manifestations of the disorder.

Description: the first report is about a patient with urticaria pigmentosa that presented persistent lesions until puberty when systemic manifestations initiated with lymphoreticular involvement, splenomegaly and bone marrow infiltration. In the second case, the child had bullous mastocytosis associated with gastrointestinal symptoms, whose investigation showed mast cell infiltration in the intestinal wall. The third patient presented an early and extensive cutaneous manifestation of mastocytosis, with a dramatic evolution to shock and posterior death.

Discussion: clinical aspects, treatment and prognosis of such forms of the disease are discussed.

J Pediatr (Rio J) 2002; 78 (2): 176-80: mastocytosis, urticaria pigmentosa.

Introduction

Mastocytosis is a disease characterized by disorderly accumulation of mast cells in several organs, with a wide spectrum of clinical signs and symptoms. Its prevalence in the population at large is not easily determined, since many cases are self-limited and/or not diagnosed. In children, the prevalence is estimated at approximately 5.4 cases per 1,000 children treated in dermatological clinics.¹

Systemic mastocytosis occurs when the amount of mast cells is abnormally high in regions other than the skin. In children, the disease is usually considered to be benign,²⁻⁵ characteristically involving the skin: mastocytoma, urticaria pigmentosa and diffuse cutaneous mastocytosis.⁶ The excoriation of lesions causes hives and perilesional erythema, which characterizes Darier's sign. Although systemic symptoms are rare, there is evidence of multiple involvement in up to 50% of the cases.² Mastocytosis may involve internal organs, including bone marrow, gastrointestinal tract, skeletal and the lymphoreticular system (spleen, liver and lymph nodes).⁶ The symptoms may restrict themselves to the affected organ or be systemic, due to the local or generalized release of histamine or other mediators.

Three cases of systemic mastocytosis with unexpected presentation or evolution are reported. This illustrates the complex manifestations and prognosis of this disease.

-
1. Dermatologist, Brazilian Society of Dermatology; graduate student, Universidade Federal do Rio Grande do Sul (UFRGS).
 2. Undergraduate student, School of Medicine, UFRGS.
 3. Assistant professor, Department of Pathology, UFRGS; dermatopathologist, Hospital de Clínicas de Porto Alegre.
 4. Associate professor, Department of Pediatrics, UFRGS.
 5. Associate professor, Division of Dermatology, UFRGS. Postgraduate course in Pediatrics, School of Medicine, UFRGS, Division of Dermatology, Hospital de Clínicas de Porto Alegre.

Manuscript received Sept 03 2001. Accepted for publication Jan 30 2002.

Case reports

Case 1

White, male patient, 14 years old, followed up at the Department of Dermatology, Hospital de Clínicas de Porto Alegre (HCPA), since the age of 12, diagnosed with urticaria pigmentosa, which started off as skin lesions in the sixth month of life. On dermatological examination, the patient had several papules and erythematous, brown plaques with Darier's sign, distributed on the face, neck and trunk (Figure 1). The anatomopathological skin biopsy revealed perivascular mast cell infiltrate, with an average count greater than 30 cells/high-power field, compatible with mastocytosis. The assessment of the bone marrow two years ago made by myelogram and biopsy did not show involvement, and lab exams (blood and liver function tests) were always normal. The patient was intermittently treated with topical corticosteroids and used anti-histamines continuously. In the last few months, a new systemic evaluation was made, since papulous and infiltrated lesions persisted. Abdominal echography revealed splenomegaly and the bone marrow aspirate presented discreet eosinophilia and a 5% presence of mast cells. The bone marrow biopsy showed normal cells. The use of anti-histamines was maintained, alleviating itching. The patient is regularly submitted to blood testing with clinical and laboratory reassessments every three months.

Case 2

White, female patient, one year and two months old, living in the countryside, was referred to Hospital de Clínicas de Porto Alegre for hospitalization and investigation of bullous skin lesions since the age of four months, accompanied by intermittent diarrhea and fever. The patient had undergone several treatments for intestinal parasites and pyoderma. The child had flaccid or ruptured bullae with hives at the base, located especially on the trunk, with some lesions on the upper and lower limbs (Figure 2). Blood test, ESR, liver function tests, and bone x-rays yielded normal results; abdominal echography showed normal-size liver and spleen. The skin biopsies of the abdomen, posterior thorax, and thigh confirmed the suspicion of bullous mastocytosis, with mast cell count greater than 30 cells/high-power field. The myelogram and bone marrow biopsy did not show any involvement, and no mast cells were identified by toluidine blue and Giemsa staining. Colonoscopy and intestinal biopsy (transverse and descending colon) revealed mucous membrane with increased mast cell count on lamina propria with 15 to 20 cells 20/high-power field. Treatment with H1 and H2 blockers was implemented; after some days, disodium chromoglycate was added and maintained for approximately 10 months. Treatment response was slow, but satisfactory, with no bullae or digestive symptoms in the last six months. The child is using hydroxyzine (1 mg/kg/day) and is under dermatological follow-up, with reassessment every four months.



Figure 1 - Case 1: urticaria pigmentosa - papules and erythematous, brown plaques with presence of Darier's sign, distributed on the face, neck and trunk

Case 3

White, female patient, six months old, referred to pediatric emergency room of Hospital de Clínicas de Porto Alegre due to wheezing and difficult breathing, along with recurrent erythematous and pruriginous spots on the face and extremities since the 15th day of life; at the beginning, the lesions were vesiculous. On examination, the patient presented with erythematous papules with positive Darier's sign (distributed on the face, upper and lower limbs), bilateral cervical lymphadenopathy and hepatosplenomegaly (Figure 3). The patient was admitted to hospital and her respiratory disorders were treated with antibiotics and bronchodilators. She was also submitted to an in-depth investigation, which showed anemia, reduced platelet count, high ESR and altered liver enzymes. Abdominal echography confirmed hepatosplenomegaly. The myelogram revealed erythroid hyperplasia and megaloblastosis, while bone marrow biopsy showed predominance of erythroid series. The biopsy and the anatomopathological exam of one skin lesion revealed mononuclear infiltrate, with predominance of perivascular lymphocytes and mast cells (10 to 15 cells/high-power field). Bone x-rays and scintigraphs were normal. During hospital stay, the child was treated with H1 and H2 anti-histaminic drugs, chromoglycate, systemic corticoids, and cyclosporine. Despite treatment, the patient did not



Figure 2 - Case 2: bullous mastocytosis - flaccid or ruptured bullae with hives at the base, located on the trunk, with some lesions on the upper and lower limbs

respond satisfactorily. Her respiratory problem worsened and developed into respiratory insufficiency. The patient died from irreversible shock.

Discussion

Mast cells are capable of generating a great number of mediators responsible for effects on target organs in the short and long run.³ The set of clinical symptoms associated with mastocytosis results from an increase in the production or release of these mediators, which act at their production site and in remote regions, regardless of the etiology of mast cell increase or of disease category. These mediators may circulate through blood or lymphoid vessels to produce the biological effects observed in patients with mastocytosis.³

The onset of mastocytosis symptoms may occur at any age; however, in more than 50% of the patients, these symptoms appear between birth and the second year of life,^{3,7} as with the cases described herein. Although several organs may be involved, skin is more commonly affected.⁸⁻¹¹ The clinical symptoms of mastocytosis on the skin are: telangiectasia macularis eruptiva perstans, mastocytoma, diffuse cutaneous mastocytosis and urticaria pigmentosa (UP).⁸ These four categories have clinical characteristics related to the excessive production of mast cell-derived mediators, although some aspects of the disease may predominate in a specific type.

The diagnosis of the disease is clinically suspected and confirmed by histology.³ Currently, the observation of an increased number of mast cells in characteristic skin lesions is regarded as gold standard for the diagnosis of mastocytosis. In certain patients with suspected systemic mastocytosis, but whose characteristic signs and symptoms of the disease are not present, tests such as serum or urinary levels of mast cell mediators or their metabolites may be useful (histamine, prostaglandin D2, tryptase and N-methyl-histamine, among others).^{8,12} Subsidiary studies are determined by symptoms or by the findings during routine assessment.¹³

Cutaneous mastocytosis is called telangiectasia macularis eruptiva perstans when telangiectasia is the predominant characteristic, with little pigmentation and edema. It does not usually occur in childhood; in adults, it is persistent and less responsive to treatment.

Isolated lesions called mastocytomas are characteristic symptoms in children.⁶ They represent 15% of the cases and, most of the times, the lesions resolve spontaneously. Mastocytomas are red, pink or yellowish nodules (sometimes multiple), 3 to 4 cm in diameter. In children, these lesions are asymptomatic and present edema when rubbed, possibly causing flushing and low blood pressure.⁶

Diffuse cutaneous mastocytosis is rare and consists of diffuse infiltration of the skin with mast cells, with possibly isolated lesions. Usually, the whole tegument is involved, with diffuse thickening and pasty consistency, similar to that of leather, with normal or yellowish brown color and intense itching. The most affected regions are the armpits and inguinal region; however, the symptoms may be systemic, with hepatosplenomegaly.^{2,3}

The most frequent skin disorder caused by mastocytosis in children is urticaria pigmentosa. It is observed in more than 90% of patients with mild disease and in less than 50% of those patients with mastocytosis associated with blood disorders or with lymphadenopathy and eosinophilia.²



Figure 3 - Case 3: systemic mastocytosis - erythematous papules with positive Darier's signs on the face, upper and lower limbs

Lesions of urticaria pigmentosa are characterized by erythematous, brown macules or slightly elevated and sparse papules with poorly defined borders. The palms, sole of the feet, face and scalp may be lesion-free. Mild trauma, including excoriation or rubbing, usually cause hives and perilesional erythema, known as Darier's sign. Urticaria pigmentosa is associated with a variable itching intensity that may be exacerbated by climatic changes, rubbing of the skin, intake of hot drinks or spicy foods, alcohol, and certain drugs, all these mechanisms favor mast cell degranulation with the release of chemical mediators.^{8,9,11}

In most cases, UP has spontaneous remission before or during puberty. However, when this does not happen, as with case 1 described here, or in patients who have peripheral blood disorders, lymphadenopathy, hepatomegaly or splenomegaly, an in-depth systemic investigation should be carried out, since manifestations or clinical signs are only evident when the involvement is already extensive. Samples of lymphoid tissues, spleen, liver, and gastrointestinal mucous membrane help to define the extension of the disease.³

Bullous skin lesions may appear and be present in all forms of mastocytosis; however, when this kind of lesion predominates, it is called bullous mastocytosis (BM).¹⁴ This rare type of mastocytosis affects children and is associated with systemic involvement⁴ and more reserved prognosis,⁹ including case reports in which death occurred.¹⁴ According to Murphy, patients at a higher risk for shock or sudden death are those with extensive bullous lesions, symptoms of vasodilation symptoms, flushing, or low blood pressure, and those with early onset of the disease, in the neonatal period.¹⁴ These children should be carefully followed up and parents should be informed of potential mast cell degranulators. The systemic finding in the patient with BM herein reported, based on the symptoms and on a thorough investigation, showed intestinal involvement. The involvement of the gastrointestinal tract by mastocytosis is described in literature as a less common event.⁹ The main manifestations in children include gastrointestinal symptoms related to peptic ulcer and malabsorption with villous atrophy. Gastric hypersecretion due to the increase in serum histamine resulting in gastritis and peptic ulcer are the most frequent problems, in addition to diarrhea and abdominal pain, associated with malabsorption in up to one third of the cases.^{3,6} It is important to underscore that intestinal symptoms in the present case report were repeatedly interpreted as secondary to intestinal infection, usually observed during childhood, in children who live in the countryside, especially when associated with skin lesions that resemble those of pyoderma.

In addition to the involvement of the gastrointestinal tract, mastocytosis may affect other organs, such as the lymphoreticular system, skeletal system and bone marrow. Hepatosplenomegaly may be detected in 40%, bone involvement in 57%¹⁵ and blood disorders such as anemia, leukocytosis and eosinophilia in over 50% of the cases.³

Hepatic and splenic manifestations, including portal hypertension and ascites due to liver fibrosis are more frequent in patients with mastocytosis associated with blood disorders or in those with aggressive mastocytosis.

Bone marrow infiltration with mast cells may include bone disorders whose lesions can be detected, in most cases, by radiography, through lytic or condensed lesions.⁵

Proximal long bones are more commonly affected, followed by pelvis, ribs and skull. Bone scintigraphy is the most sensitive exam for the detection and location of active lesions.

Bone pain affects between 19 and 28% of patients and, those patients with more severe or advanced disease may have pathological fractures.³

Bone marrow disorders consist of paratrabeular aggregates of spindle-shaped mast cells, usually mixed with eosinophils, lymphocytes and, occasionally, plasmocytes, histiocytes and fibroblasts. These disorders are rarely observed in children. Anemia, leukopenia, leukocytosis, thrombocytopenia or eosinophilia may, however, occur along with systemic disease.⁵ Prolonged bleeding of the skin or of the gastrointestinal tract have been observed in pediatric patients with mastocytosis, especially in those with diffuse cutaneous mastocytosis.⁶ In addition to these blood disorders, dysplasia or neoplasia of myeloid cells with systemic mastocytosis have been reported, especially in adult patients.^{10,16} There are only two reports of malignant blood disease in children, both with systemic mastocytosis, and there is no report of isolated urticaria pigmentosa combined with malignant lymphoproliferative disease in children.¹⁷

Patients with mastocytosis often have cardiovascular disorders, such as flushing, low blood pressure, tachycardia, syncope and shock.^{2,4,8} Such reactions are secondary to the effects of mediators released by mast cells by agents that stimulate its degranulation. Among the most relevant degranulators, we have bacterial toxins, physical stimuli (heat, cold, sunlight, friction), venoms (snakes, *Hymenoptera*), biological polypeptides (from *Ascaris*, jellyfish, lobster, wasp and bee venoms), polymers (dextran) and medications (acetyl salicylic acid, codeine, morphine, polymixin B, quinine, contrast media, scopolamine, gallamine, decamethonium, reserpine).^{2,4,8,18}

One of the probable causes of death of the patient in case 3 might have been low blood pressure secondary to massive degranulation of mast cells, precipitated by some agent. Among these agents, we may find bacterial toxins, since the patient was being kept at an intensive care unit and was under mechanical ventilation. Another hypothesis for her death, associated or not with mast cell degranulation, is sepsis with multiple organ failure.

The major objective of treating all types of mastocytosis is to control the signs and symptoms determined or provoked by the release of mast cell mediators. Patients should always avoid the use of mast cell degranulators. Either in adults or

in children, H1-receptor antagonists are useful to reduce itching, flushing, Darier's sign and tachycardia. If that is not enough, the addition of H2 antagonist may be beneficial. In spite of this, symptoms still persist, partly because this antagonist cannot block the effects of high histamine levels and the presence of other mediators.³

Disodium chromoglycate inhibits mast cell degranulation and may be effective in alleviating gastrointestinal symptoms, but it does not reduce the serum and urinary levels of histamine.³

Other treatments cited in most case reports or case series include: ketotifen, as mast cell membrane stabilizer, with anti-histaminic properties;^{3,5} adrenalin, used in episodes of vascular collapse;² photochemotherapy with psoralen and ultraviolet A, which induces a temporary reduction in dermal mast cells;⁵ interferon associated or not with systemic corticoids for patients with systemic mastocytosis.¹⁹ Topical glucocorticoids may be used in extensive UP or in diffuse cutaneous mastocytosis. The amount of mast cells decreases as lesions become clearer; these lesions may occasionally recur after treatment completion, but recovery may take more than one year. In children, topical corticoids should be used in small areas and very carefully due to the risk of adrenal suppression caused by chronic use.⁶

In general, patients with UP or mastocytoma have an excellent prognosis. The number of lesions in UP may continually increase after its onset, first quickly and then gradually until it reaches a plateau. Approximately 50% of UP lesions and symptoms in children resolve during adolescence, and the remaining cases have a remarkable reduction in symptoms related to skin lesions. Nevertheless, the evolution into systemic involvement occurs in 10% of the children with UP, whose first symptoms appear after the age of five years.⁷ Children with bullous lesions as the first sign of mastocytosis seem to have a worse prognosis than those children with diffuse cutaneous mastocytosis with later development of bullae.^{9,14} It is important to emphasize that the association or the development of malignant diseases, such as mast cell leukemia, is rare in children with mastocytosis, but very common in adults.^{8,11}

Although mastocytosis is relatively rare, its diagnosis is important because of the multiple skin disorders it causes and due to the risk associated with the symptoms that derive from it. This illustrates the clinical complexity that may accompany the disease and the necessity for a combined pediatrician-dermatologist work in order to treat and guide patients.

References

1. Fernández AT, Campoamor LN, Mora LE, Zambrano AZ. Diagnóstico, tratamiento y clasificación de la mastocitosis pediátrica. Estudio de 172 casos. *Actas Dermosifiliogr* 1998;89:461-76.
2. Greaves MW. Mastocytosis. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. *Textbook of Dermatology*. 6th ed. Oxford: Blackwell Science; 1998. p.2337-46.
3. Metcalfe DD. The mastocytosis syndrome. In: Ffredberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, et al., eds. *Dermatology in general medicine*. 5th ed. Austen: McGraw-Hill; 1999. p.1902-08.
4. Longley J, Duffy TP, Kohn S. The mast cell and mast cell disease. *J Am Acad Dermatol* 1995;32:546-61.
5. Katsambas AD, Karpouziz AJ, Koumantaki-Mathioudaki E, Jorizzo JL. Mastocytosis with skin manifestations: current status. *J Eur Acad Dermatol Venereol* 1999;13:155-65.
6. Kettelhut BV, Metcalfe DD. Pediatric mastocytosis. *J Invest Dermatol* 1991;96:15S-18S.
7. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991;96:2S-4S.
8. Van Gysel D, Oranje AP. Mastocytosis. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*. 1st ed. Blackwell Science; 2000. p.600-9.
9. DiBacco RS, De Leo VA. Mastocytosis and the mast cell. *J Am Acad Dermatol* 1982;7:709-92.
10. Travis WD, Li CH, Bergstralh EJ, Yam LT, Swee RG. Systemic mast cell disease: analysis of 58 cases and literature review. *Medicine* 1988;67:345-68.
11. Stein DH. Mastocytosis: a review. *Pediatric Dermatol* 1986;3:365-75.
12. Tharp MD. Mast cell disease and its diagnosis. *J Invest Dermatol* 1995;104(6):885-6.
13. Setcalfe DD. Conclusions. *J Invest Dermatol* 1991;96:64S-65S.
14. Murphy M, Walsh D, Drumm B, Watson R. Bullous mastocytosis: a fatal outcome. *Pediatric Dermatol* 1999;16:452-5.
15. Horan RF, Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. *J Invest Dermatol* 1991;96:5S-14S.
16. Horny HP, Ruck M, Wehrmann M, Kaiserling E. Blood findings in generalized mastocytosis: evidence of frequent simultaneous occurrence of myeloproliferative disorders. *Br J Hematol* 1990;76:186-93.
17. Güler E, Emir S, Kutluk T, Varan A, Büyükpamukçu. Urticaria pigmentosa associated with Wilms tumor. *Pediatr Dermatol* 2001;18:313-5.
18. Leaf FA, Jaecks EP, Rodriguez DR. Bullous urticaria pigmentosa. *Cutis* 1996;58:358-60.
19. Delaporte E, Piérard E, Wolthers BG, Desreumaux P, Janin A, Cartot A, et al. Interferon- α in combination with corticosteroids improves systemic mast cell disease. *Br J Dermatol* 1995;132:479-94.

Correspondence:

Dra. Tania F. Cestari

Rua Florencio Ygartua, 150 - ap. 401
90430-010 – Porto Alegre, RS, Brazil

Fax: + 55 51 3346.2773

E-mail: tcestari@terra.com.br