

## CASE REPORT

# Type Ib indolent mastocytosis with systemic involvement: cutaneous mastocytosis and gastrointestinal involvement at young girl

E. F. GEORGESCU<sup>1)</sup>, LIGIA STĂNESCU<sup>2)</sup>,  
CLAUDIA VALENTINA GEORGESCU<sup>3)</sup>,  
IULIANA GEORGESCU<sup>4)</sup>

<sup>1)</sup>Department of Internal Medicine

<sup>2)</sup>Department of Pediatrics

"Filantropia" University Hospital of Craiova

<sup>3)</sup>Department of Morphopathology,  
Emergency County Hospital of Craiova

<sup>4)</sup>Department of Dermatology,  
Mediplus Diagnostica Gastroenterology Center, Craiova

### Abstract

A 21-year-old young girl presents with intense abdominal pain, nausea, diarrhea in the context of a cutaneous eruption formed by erythematous and papulous elements with brown violet aspect, very pruriginous, occasioned by the preparation of some fishmeal. Similar eruption debuted from childhood from the age of 4 year became rare with age. Since 3 years, the patient presents more intense digestive manifestation. The therapy with H2 antagonist (loratadine) and a mast cell stabilizer is beneficial over the digestive symptoms and in the same time cancel the pruritus and the erythema of the cutaneous lesions that remain hyperpigmented. The histopathological examination of a cutaneous lesion confirms the diagnosis of mastocytosis and the endoscopic examination discovers a duodenal ulcer and an erosive gastritis. The systemic mastocytosis is a rare disease, often associated with an urticaria pigmentosa, with difficult diagnosis in his absence. That's why, in patients with macular or nodular pigmented cutaneous lesions appeared in infancy and early childhood and which urticate in a characteristic manner when the skin is firmly rubbed, a cutaneous biopsy is necessary.

**Keywords:** mastocytosis, gastrointestinal involvement.

### Introduction

The mastocytosis are a group of disorders characterized by the accumulation of mast cells, particularly in the skin. These mast cells release histamine and other mediators of inflammation, often in large quantities. Thus, such patients may complain of itching and flushing of the skin [1].

Mastocytosis may present in any age groups. However, approximately 55% of mastocytosis patients develop their disease by 2 years of age, and in another 10%, disease onset occurs between the ages of 2 and 15 years [2, 3]. Thus, most patients are infants or children and there is a general tendency for the diseases to regress with age. There is a slight male predominance (1.5/10) [4].

The prevalence of the disease is unknown. Familial occurrence is unusual. Not all familial cases of mastocytosis reported have been documented by histopathology, and most patients with mastocytosis have no familial association.

We present a patient path had from childhood cutaneous mastocytosis and, present after years a digestive involvement.

### Patient, Methods and Results

A 21-year-old young girl comes to our clinic for intense abdominal pains, nausea and diarrhea. Concomitantly, she presents a very pruriginous and cutaneous eruption localized on thorax and flank, upper extremities, but spares the face and palms.

From history, the 4-year-old patient present repeatedly erythematous and papulous cutaneous eruption, apparently correlated with alimentation (oranges, bananas, tomatoes, moonshine, fermented cheese or fish, etc.), the disease had been considerate as urticaria. With ketotifen as treatment, the erythema of the cutaneous lesions ameliorated but remained hyperpigmented. During the next 14 years the disease had been observed by the pediatrician, evolving with period of apparent silence with some occasional exacerbations generated by some aliments, sudden temperature variation or emotional distress. In the last 5 years, the observation of the patient has been interrupted, the person leaving abroad. The patient came back now for the symptoms early mentioned. From her affirmations result that the digestive symptomatology appeared about at age of 18, first with nausea and

vomiting, diarrhea then with intensified abdominal pains, associated always with very pruriginous cutaneous eruption. Generally, using treatment with loratadine and ranitidine, the digestive symptoms disappeared, the pruritus ameliorated and the cutaneous lesions became less erythematous but hyperpigmented.

### Clinical and paraclinical evaluation

The clinical examination had been not decelerated significant modifications. It notes diffuse pains on the palpation of the abdomen in epigastric region. We not discovered lymphadenopathy or splenomegaly.

The dermatological examination; the patient had an eruption formed by pointed out, smooth maculae, without squamae, about one cm diameter and papulous and papulonodular erythematous lesions with brownish aspect, on the thorax, abdomen, upper extremities but spare the face and palms (Figure 1).

After the treatment we remark the disappearing of the erythema and the persistence of papulonodular lesions that appear brown violet and hyperpigmented, the rubbing of one of the lesion determines the its turgescence and the appearance of a erythema around, the Darier's sign (Figure 2).

The common laboratory values were normal with the exception of a relative hypochrome anemia associated with mild eosinophilia and with a no significant augmentation of phosphatase alkaline.

The osseous radiography of the proximal limbs and pelvis presented normal imagines.

The endoscopy examination initially effected, discovered alteration of erosive gastritis with large severity (Figure 3).

A pyloric spasm not permitted penetration of endoscope to duoden. Three weeks later another superior endoscopy imposes by the existence and worsening of digestive symptomatology discovers a duodenal ulcer on the anterior face of the bulb (Figure 4).

The histopathological assessment of the cutaneous lesions shows in the dermis (papillar and middle) a proliferation of prolonged cells, with imprecise cellular limits, and acidophil cytoplasm; these replace complete the normal structure of the dermis (Figure 5).

A detailed observation of previous image (some with nucleous), but the cellular limits are imprecise (Figure 6).

With Giemsa stain we observes that the cytoplasm of the proliferated cells contain numerous metachromatic granule that is in the favor the diagnosis of mastocytosis (Figure 7).

The detailed observation remarks big metachromatic granulation in cytoplasm (Figure 8).

### Diagnosis

The suspicion of the diagnosis of mastocytosis evoked by the clinical aspect is confirmed by histopathological examination. The association of the digestive pathology with evident endoscopic alterations is in the favor for the diagnosis of indolent mastocytosis type Ib with systemic involvement. The association of H2 antagonist (ranitidine, nizatidine, loratadine) with

mast cell stabilizer (ketotifen) had been beneficial over both the cutaneous manifestation and over the digestive manifestation.

### Discussion

The mastocytosis are a group of disease characterized by accumulation of mast cells in tissues. The cutaneous implication is the most frequent, often isolated, sometimes associated with a systemic involvement, which exceptional can be the only clinical expression of the disease. The digestive involvement is exceptional and represents one of the components of systemic mastocytosis.

The pathogeny of mastocytosis is not clear. A well-established concept is that mast cells originate from pluripotent bone marrow stem cells and migrate through the blood stream and lymphatics to specific sites. Mast cells number and differentiation are regulated by factors produced both in the hematopoietic marrow and by cells in the tissues in which mast cells finally reside. Early mast cells differentiation depend on the colony stimulating factor interleukin-3 (IL-3) and is inhibited by granulocyte-macrophage colony stimulating factor (GM-CSF). Final maturation depends on the production of specific growth factors by fibroblasts and stromal cells such as c-kit ligand, or stem cells factor (SCF) [4].

The c-kit receptor encodes for the tyrosine kinase KIT, which is structurally related to receptor for platelets derived growth factor and melanocyte colony stimulating factor. Under normal circumstances, KIT is activated after dimerization with its ligand stem cell factor. Alterations in SCF and KIT are important in the pathogenesis of mastocytosis. Two c-kit mutations at the 560 and 816 loci have been demonstrated to result in KIT autoactivation and are believed to be responsible for increase mast cells arising originally from the bone marrow [5].

Mast cells circulate in the peripheral blood as agranular, monocytic-appearing cells. After migrating into tissues, these immature mast cells assume their typical granular morphology [6–8].

The targeting of mast cells to defined locations is determined by sequential expression of cell surface adhesion molecules. Mast cells are often found along endothelial and epithelial basement membrane, along nerves and around glandular structures. Tissues and interfaces between the external and internal environment, including the skin, respiratory and gastrointestinal tract, are particularly rich in mast cells. The skin is the organ the most rich in mast cells ( $7\,225\text{ cells/mm}^3$ ). Parenchymatous organs, such as the heart, brain, liver, spleen, lymph nodes, and genitourinary tract, possess fewer mast cells, the number of which increase in patients with mastocytosis [9].

Mast cells are rarely found in peripheral blood, and their recognition in tissues is facilitated by their content of methachromatic granules and dye staining properties as well as by their content of proteolytic (chymotryptic) enzymes [10, 11].

Mast cells mediators are of three categories:

secretory granules (histamine, proteases, chymase, carboxypeptidase A, proteoglycans); membrane-derived lipid mediators (prostaglandin: prostaglandin D<sub>2</sub>; leukotrienes: leukotriene B<sub>4</sub> and leukotriene C<sub>4</sub>;

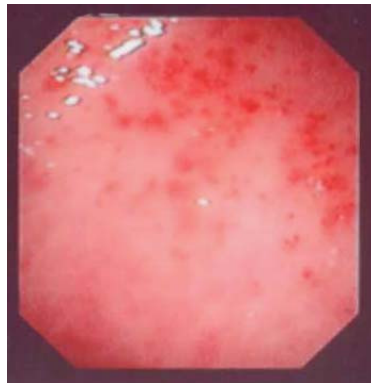
platelet-activation factor); chemokines and cytokines (proinflammatory mediators: TNF- $\alpha$ , TGF- $\beta$ ; immunomodulatory mediators: IL4, IL5, IL6, IL13; chemokines: chemotactic cytokines) [9].



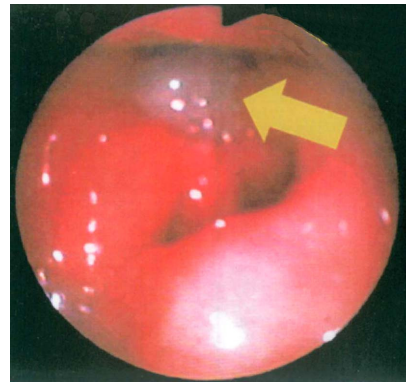
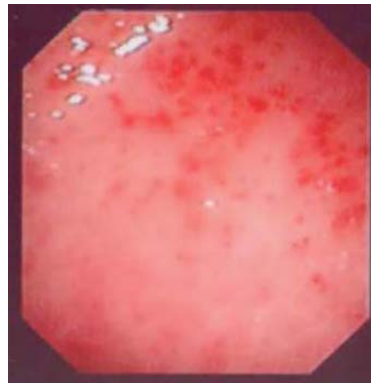
**Figure 1** – Cutaneous lesions in the shape of reddish brown macules and papules about one centimeter or less in diameter involved the skin



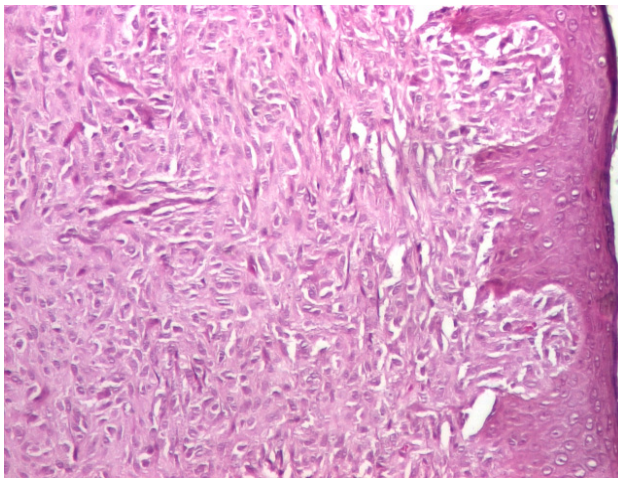
**Figure 2** – The rubbing of one of the cutaneous lesions determines the its turgescens and appearance of erythema around, compatible aspect of the Darier's sign



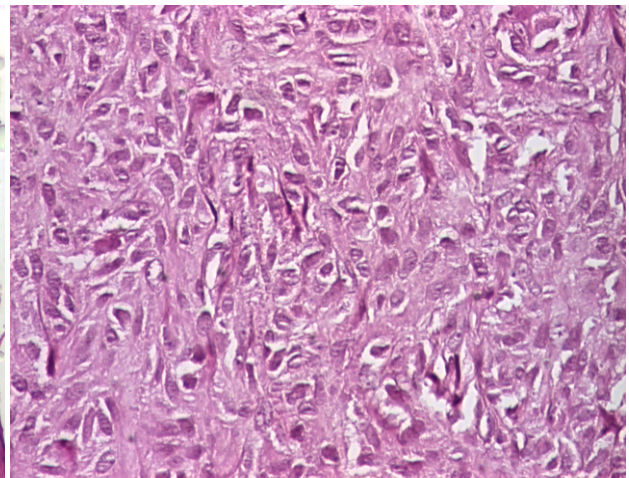
**Figure 3** – Superior endoscopy discover lesion of erosive gastritis with large severity



**Figure 4** – Another endoscopy showed duodenal ulcer on the anterior face of the bulb

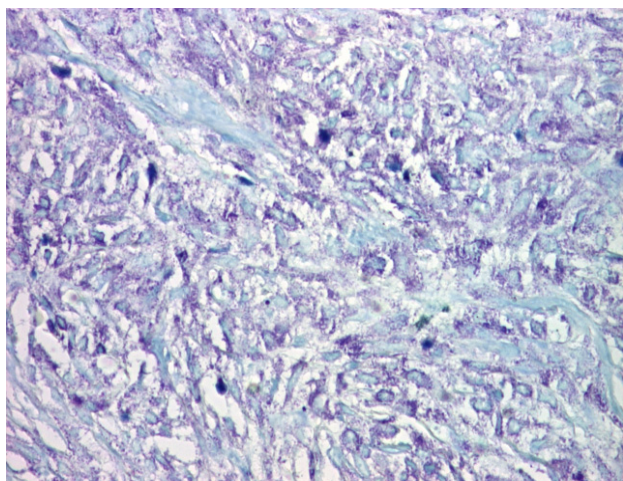


**Figure 5** – In the dermis (papillar and middle) is present a proliferation of prolonged cells, with imprecise cellular limits, and acidophil cytoplasm; these replace complete the normal structure of the dermis

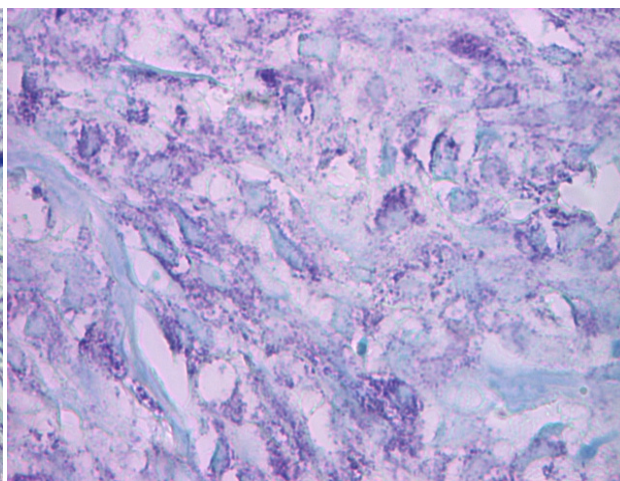


**Figure 6** – A detailed observation of previous image, with good remark of the nuclei of cells (some with nucleolus), but the cellular limits are imprecise





**Figure 7 – With Giemsa stain we observe that the cytoplasm of the proliferated cells, contain numerous metachromatic granule, that is in the favor of the diagnosis of mastocytosis**



**Figure 8 – The detailed observation remarks big metachromatic granulation in cytoplasm**

Some of these mediators, such as histamine, are stored and released from mast cells after cross-linking of high-affinity IgE receptors or activation by complement [1, 3]. Other compounds, such as  $\alpha$ -tryptase, are constitutively produced and constitutively secreted by mast cells. Therefore, baseline total tryptase levels can be used as a marker of mast cells (roughly indicating the total mast cells mast) in normal subjects and in patients with mastocytosis [12–14].

Regardless of the cause of the increased burden of mast cells, the pathogenesis of the disease is largely the result of the increased production of mast cells mediators, which have effects both of the site of their production and at remote sites.

After clinical features, mastocytosis patients have been classified into four major types: type Ia, indolent mastocytosis without systemic involvement; type Ib, indolent mastocytosis with systemic involvement; type II – mastocytosis associated with a myeloproliferative or myelodysplastic disease; type III – lymphadenopathic mastocytosis with eosinophilia; type IV – mast cell leukemia [15, 16].

Traditionally, mastocytosis can be divided into cutaneous mastocytosis and systemic mastocytosis.

Cutaneous mastocytosis is usually diagnosed in early childhood [13]. By contrast, most adult patients have systemic mastocytosis. In adults, the diagnosis is usually established by a bone marrow examination, whereas in most children, a bone marrow examination is not required. Apart from the bone marrow, other organs such as gastrointestinal tract or the liver may be affected in systemic mastocytosis. In contrast to systemic mastocytosis, cutaneous mastocytosis shows spontaneous regression in a significant number of cases, mostly during or shortly before or after puberty [17].

The most common manifestation of mastocytosis is urticaria pigmentosa. It is seen in >90% of patients with indolent mastocytosis and in <50% of patients with mastocytosis with an associated hematologic disorder or those with aggressive mastocytosis. The lesion of urticaria pigmentosa appears as scattered

small reddish-brown macules or slightly raised papules. Scratching or rubbing the lesions usually causes urtication and erythema around the macules; this is known as Darier's sign.

Urticaria pigmentosa is associated with pruritus, which may be exacerbated by changes in climatic temperature, skin friction, ingesting hot beverages or spicy food, ethanol and certain drugs. The disease does not appear or disappear suddenly. There may be an initial period of approximately six months before pigmentation develops and a final period of some years when urtication is absent, and only macular pigmentation remains. In most cases, the lesions disappear entirely by adolescence or early life [1]. The diagnosis is confirmed by characteristic skin histopathology. Diffuse cutaneous mastocytosis or xanthelasmoidal mastocytosis consists of diffuse mast cell infiltration of the skin.

Solitary lesions calls mastocytomas occur but are quite rare, and telangiectasia macularis eruptiva is a variant of urticaria pigmentosa more often seen in adults. Young children with urticaria pigmentosa or diffuse cutaneous mastocytosis may have bullous eruptions.

Gastrointestinal disease often develops in patients with mastocytosis. Patients with systemic disease may have some of gastrointestinal complaints, including abdominal pain, diarrhea, nausea, and vomiting [4]. The most common problem is gastric hypersecretion due to elevated plasma histamine with resultant gastritis and peptic ulcer disease. Two types of abdominal pain, dyspeptic and cramping, have been described in patients with mastocytosis. Dyspeptic pain usually lasts from minutes to hours, whereas cramping pain occurs in waves and persists for several hours to days [18].

Alcohol, certain foods, stress and increased mast cell mediator release exacerbate dyspeptic and cramping abdominal pain. Diarrhea in patients with mastocytosis is usually episodic and can result from malabsorption, increased motility, hypersecretion of acid, or released of mast cell derived histamine and prostaglandins.

Gastrointestinal hemorrhage has been reported in some patients with systemic mastocytosis and is often caused by gastritis, duodenitis, or peptic ulcer disease. Roentgenographic abnormalities fall into three major categories: peptic ulcers, abnormal mucosal patterns such as mucosal edema, multiple nodular lesions and motility disturbance. Histopathology of jejunal biopsies has shown moderate blunting of the villi; significant mast cell hyperplasia is uncommon.

Hepatic and splenic involvement in indolent systemic mastocytosis is relatively common, although liver function test are usually normal. Bone marrow lesions consist of focal aggregates of spindle-shaped mast cells, often mixed with eosinophils, lymphocytes, and occasional plasma cell, histiocytes and fibroblasts [20]. Bone changes may be induced from bone marrow infiltration with mast cell. Radiographically detectable lesions appear in up to 70% of patients. Demineralization is the most common change in patients with diffuse skeletal disease, followed of osteosclerosis and mixed lesions of osteosclerosis and osteoporosis [21].

Lymph node enlargement is uncommon in patients with indolent systemic mastocytosis but occurs frequently in patients with type II–IV disease [22]. The diagnosis of mastocytosis rests on histology supported by clinical, biochemical and radiographic data.

The diagnosis of cutaneous mastocytosis is established by demonstrating characteristic mast cell infiltrates in one or more organs. For patients with type I disease who usually have cutaneous lesions, mast cell infiltrates can be demonstrated in a biopsy of lesional skin. The most useful stains for mast cells include metachromatic stains, such as toluidine blue and Giemsa, and enzymatic stains such as chloroacetate esterase and aminocaproate esterase. These procedures highlight the granules in the cytoplasm of the mast cell. In cases of adult-onset mastocytosis with cutaneous lesions that contain only borderline number of mast cell, molecular diagnostic studies for c-kit codon 816 mutations may help confirm or established a diagnosis [23].

The biopsy of gastrointestinal tract lesions may be indicated for patients in whom the diagnosis of mastocytosis is expected but who lack cutaneous lesions [16]. Unfortunately, to date, mast cell quantification methodology similar to that used in skin biopsies has not been applied to gastrointestinal tissue. Because anaphylactic reactions have been reported with endoscopy, it is recommended that mastocytosis patients be treated with combined H1 and H2, antihistamines before the procedure.

Immunophenotyping of bone marrow mast cells may be necessary to identify atypical mast cells that are sometimes present in patients with more aggressive disease. Monoclonal antibodies against CD117 (KIT) and tryptase may be particularly helpful in confirming the presence of this atypical mast cell infiltrates [24].

The presence of circulating mast cell mediators or their metabolites offers indirect evidence of a

proliferative mast cell disorder. Two forms of tryptase (alpha and beta) have been identified using the monoclonal antibodies G5 and B12.

The G5 monoclonal antibody primarily detects beta tryptase, whereas the B12 monoclonal antibody measures both alpha and beta (total) tryptase [21].

Elevated urinary histamine levels also have been reported in mastocytosis patients. In many instances unmetabolized urinary histamine levels may be normal in patients with asymptomatic systemic mastocytosis, whereas 1,4-methylimidazole acetic acid Melm AA levels one from metabolites of histamine, are often persistently elevated. Patients with only cutaneous disease had normal or only slightly elevated Melm AA.

Increased urinary excretion of major urinary metabolite of prostaglandin D (PGD<sub>2</sub>) also has been reported in some patients with systemic mastocytosis.

Hematological analysis may be normal in patients with indolent mastocytosis, whereas anemia, leukocytosis or leucopenia, eosinophilia or thrombocytosis or thrombocytopenia may occur in patients with types II–IV disease.

The treatment with H1 or combined H1 and H2 antagonists can be beneficial for controlling many of the symptoms associated with mastocytosis. Ketotifen, which has both antihistamine and mast cell stabilizing properties, has been reported effective in combination with ranitidine in patients with indolent mastocytosis [25].

Treatment of gastrointestinal disease is directed at controlling peptic symptoms, diarrhea, and malabsorption. Gastric acid hypersecretion leading to peptic symptoms and ulcerations is controlled with H2 antagonists. Diarrhea is difficult to manage, and H2 antagonists are generally not effective. Anticholinergic may give partial relief. In patient with severe malabsorption, systemic steroids have been to be effective.

Our patient has from childhood a cutaneous mastocytosis. At this, after puberty has adding a digestive disease, endoscopic had been uncovered erythemato-edematous alterations and ulcerative erosions of the gastric and duodenal mucosae. The good evolution under the treatment with H2 antagonists associated with mast cell stabilizer – of the digestive symptomatology and the cutaneous one, suggest the involvement of a common factor in the etiology of both type of clinical manifestation. The absence of the lymphadenopathy and the hepatosplenomegaly sustain the diagnosis of indolent mastocytosis type I with systemic involvement.

## Conclusions

The systemic mastocytosis is a rare disease, often associated with an urticaria pigmentosa, with difficult diagnosis in his absence. That is why in patients with macular or nodular-pigmented cutaneous lesions appeared in infancy and early childhood and which urticate in a characteristic manner when the skin is firmly rubbed, a cutaneous biopsy is necessary.

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## Corresponding author

Eugen Florin Georgescu, Professor, MD, PhD, Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200 349 Craiova, Romania; Phone +40744–782 136, Fax +40251–420 896, E-mail: efg@usa.net

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