CASE REPORT

Systemic mastocytosis presenting with gastrointestinal, bone and skin involvement

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Abstract Ultrasonography (US) is often the first imaging study performed in patient with abdominal pain or vague symptoms related to the gastrointestinal tract. To this end, it has been demonstrated that transabdominal sonography achieves good to excellent results in potential bowel disorders; especially, if ultrasonography findings are framed in the context of clinical information. Systemic mastocytosis is not a common disease and it usually involves skin, gastrointestinal tract and bone. It results from a clonal neoplastic proliferation of abnormal mast cells and clinically it can range from ‘asymptomatic’ with normal life expectancy to ‘highly aggressive’. Symptoms are caused by the release of mast cell mediators, such as histamine, and by the increase bulk of mast cells in the tissue. We present herein a case of systemic mastocytosis presenting with abdominal symptomatology due to thickened colonic involvement showed by US associated with bone and skin involvement.

Keywords Cutaneous mastocytosis · Bowel involvement · Ultrasound

Riassunto L’ecografia è spesso considerata l’indagine di primo livello nei pazienti con dolore addominale o con altra sintomatologia aspecifica del tratto gastrointestinale. A tal proposito, è stato dimostrato che l’ecografia transaddominale è in grado di raggiungere anche eccellenti risultati nello studio dei disturbi intestinali, soprattutto se inquadrata nel contesto di specifiche informazioni cliniche. La mastocitosi sistemica è una rara patologia che generalmente coinvolge cute, tratto gastrointestinale e osso. Si tratta di proliferazione neoplastica di tipo clonale di mastociti, che clinicamente può variare da una sintomatologia lieve con normale aspettativa di vita fino ad un quadro altamente aggressivo. I sintomi sono causati dal rilascio dei mediatori contenuti nei mastociti, tra i quali l’istamina, e dall’incremento dei mastociti nei tessuti. Presentiamo qui un caso di mastocitosi sistemica caratterizzato dalla comparsa di sintomatologia addominale dovuta a ispessimento del grosso intestino identificato all’esame ecografico, associato a interessamento osseo e cutaneo della patologia.

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Introduction

Mastocytosis results from a clonal neoplastic proliferation of abnormal mast cells (MCs) in different tissues, including lymph nodes, spleen, liver, bone, bone marrow, gastrointestinal (GI) tract and lungs. The clinical course ranges from ‘asymptomatic’ with normal life expectancy to ‘highly aggressive’ due to the release of MCs mediators. The skin is the most commonly affected organ in mastocytosis and urticaria pigmentosa is the most common

cutaneous manifestation, but several other rashes have been described [1]. Gastrointestinal and bone involvement, otherwise, are less common than skin lesions, getting poorer quality of life. In this report, we describe a challenging case of woman with systemic mastocytosis (SM), who at onset manifested with gastrointestinal and skin involvement.

Case report

A 73-year-old white female was referred to the dermatological outpatient department of our hospital with 2-year history of violaceous, maculopapular rash over the trunk, which was often pruritic and aggravated by stress, friction and specific food. Moreover, she suffered of several intermittent constipation and diarrhea. Physical examination was remarkable for brownish-red widespread maculopapular rash, sized 3–6 mm, localized over the patient anterior and posterior trunk (Fig. 1). On abdominal examination, there was no organomegaly, masses, tenderness, or inguinal lymphadenopathy. Her past medical history was unremarkable. She denied the use of alcohol and had no history of smoking. Her family history was non-contributory for inflammatory bowel disease and cutaneous disease. The results of routine laboratory examinations were within normal limits, except for an increased of serum tryptase: 31.5 mcg/L (4.3–11.4 mcg/L). Ultrasound examination of the abdomen performed with a 5-MHz curvilinear transducer, initially showed the presence of a diffuse thickening of the bowel wall and the presence of small hypoechoic nodules, size 9–10 mm, with adjacent periintestinal lymph nodes, without increasing blood flow in the area of inflamed fat examined with Color-Doppler imaging yet (Fig. 2). According to these findings, colonic involvement was suspected. Moreover, an ultrasound examination of the skin was also performed with a 7.5-MHz linear transducer before and after physical stimulation of maculopapular lesions (Darier's sign). The ultrasonography images both before and after stimulation were negative, without increasing blood flow in the area at Color-Doppler. Therefore, due to the increased of serum tryptase and positive skin lesions Darier's sign (Fig. 3), an incisional biopsy of a skin lesion and bowel wall endoscopic biopsy were performed. Histopathological examination revealed an unremarkable epidermis with round or spindle cells shaped with abundant eosinophilic cytoplasm; especially, in the papillary dermis and around blood vessels in hematoxylin and eosin stain. The histological mast cells lesion consists of focal typical and atypical MC aggregates infiltrating tissues. Giemsa or toluidine blue stains can reveal metachromatic granules, allowing discriminating between spindle mastocytes and fibroblasts. In our patient,

examination with Giemsa and toluidine blue stains revealed that the spindle cells were mast cells (Fig. 4). To rule out the presence of a bone involvement, a column radiography was also performed revealing several vertebral fractures (T12, L4), defined as loss of vertebral high of more than 30 % at the anterior edge, and granular irregularity throughout the axial skeleton surrounded by sclerotic halo. A magnetic resonance examination of the vertebral column was performed and it confirmed the presence of this lesions. According to the current guidelines [2–5], she underwent a bone marrow aspirate and sacral bone biopsy to differentiate bone metastases from mastocytosis involvement. Immunohistochemical stains showed marked fibrotic replacement of the bone marrow with a slight increase in the number of eosinophils and CD117, CD25 and CD2-positive mast cells as well as increased perivascular and perisinusoidal mast cells. Cytogenetic analysis showed a normal karyotype, and molecular studies showed the presence of *JAK2V617F* mutation. After bone biopsy, she suffered of sacral fracture that forced the patient to be at rest for 40 days. SM was finally diagnosed on the basis of one major criteria and two minor criteria, according to WHO classification [2]: multifocal dense infiltrates of mast cells in the bone marrow, increased serum tryptase (31.5 mcg/L) and mast cells co-expressed both CD25 and CD2. The patient was treated with 250 mg sodium cromoglycate per day (Nalcrom) and with 5 mg levocetirizine per day (Xyzal) for cutaneous mastocytosis and with 26 drops colecalciferol per week (Dibase 10000 UI/M) for osteoporosis. She was also referred to a hematologist for regular evaluation and follow-up.

Discussion

SM is characterized by MCs proliferation in several organs of the reticulo-endothelial system and it is often associated with clinical features attributable to the release of MCs mediators. The autonomous growth and expansion of neoplastic MCs may be explained by somatic mutations in the gene encoding kit [6]. In our patient, molecular studies revealed the absence of c-KIT gene mutation, although in different study, *JAK2V617F* mutation was present. MCs are secretory specialized cells characterized by prominent cytoplasmic granules that contain pro-inflammatory and vasoactive mediators as histamine, leukotrienes, prostaglandins and platelet activating factor, along with cytokines intrinsically linked to the body's inflammatory response. The release of mediators causes a wide variety of symptoms, ranging from episodic flushing, pruritus, hypotension, headaches, nausea, vomiting and diarrhea. Other symptoms of the disease are caused by the increase bulk of MCs in the tissue, especially skin, bone and GI

Fig. 1 A 73-year-old white female with widespread violaceous, maculopapular rash over the anterior and posterior trunk, sized 3–6 mm

Fig. 2 Bowel ultrasound performed with a linear high-frequency transducer (7.5–13 MHz), axial and longitudinal scan. **a** Colonic involvement, with the presence of small hypoechoic nodules (size

9–10 mm), without increasing blood flow in the surrounding fat, examined with Color-Doppler technique; **b** an adjacent periintestinal hyperplastic lymph node, size 7 × 3 mm

tract. Systemic involvement can precede, but more frequently follows, the development of skin lesions, which is a feature in 85 % of patients with SM. Commonly skin lesions consists of tan to red-brown macules that rapidly spread symmetrically and usually spared palms, soles, face and scalp. The lesions may remain small and freckle-like or may evolve into papules, nodules or plaques. Exposure to

physical stimuli, such as heat, cold or pressure is typically followed by the onset of Darier's sign consisting in reactive redness of the skin. The histopathological substrate of all lesions of cutaneous mastocytosis is an infiltrate by MCs that can be visualized using basic dyes, such as Giemsa, toluidine blue and Astra blue. Proliferation of MCs in bone can produces osteoporosis possible associated with

Fig. 3 **a** Red-brown maculopapular rash that appear on the abdomen and spread symmetrically, **b** positive Darier's sign: after stroking the skin, it becomes swollen, itchy and reddish. This is the result of mast cells friction that release inflammatory granules

Fig. 4 **a** Hematoxylin and eosin stain revealing dermal mast cell infiltrates; especially, in the papillary dermis around blood vessels (Hematoxylin and eosin $\times 100$). **b** Giemsa staining reveals metachromatic granules within mast cells (Giemsa $\times 100$). **c** Demonstration of

mast cell granules using toluidine blue stain (toluidine blue $\times 100$). **d** Close-up of dermal mast cell infiltrates showing that mast cell nuclei are round with surrounding ample cytoplasm producing a "fried-egg" appearance (toluidine blue $\times 400$)

pathological fractures, causing pain [7]. The GI manifestations are numerous, occurring in 50–80 % of patients. Splenomegaly, abdominal pain, diarrhea, hepatomegaly,

nausea and vomiting, GI bleeding and liver function test abnormalities can be seen in patients with SM [8]. The differential diagnosis in this category is short even

although it includes the greatest proportion of patients with malabsorption. Ultrasonography, being a widely available investigation is often the first morphologic study performed on patients with suspected bowel involvement. Examination of the intestinal tract usually begins with a systematic standardized study using a curvilinear (3.5–5 MHz) transducer. Otherwise, detailed evaluation of intestinal wall thickening is performed with a linear high-frequency (7.5–13 MHz) transducer. Because of different clinical presentation, abdominal mastocytosis can mimic different type of medical conditions, as inflammatory bowel disease (IBD), Zollinger–Ellison syndrome, lymphoma, vasculitis, amyloidosis, intestinal tuberculosis and neoplastic processes [9–11]. It has been shown that transabdominal sonography achieves good to excellent results as a directed technique for evaluating potential bowel disorders. In fact, careful examination of the thickened bowel segment in context with the clinical information often leads to a limited differential diagnosis or to the correct diagnosis [12]. However, ultrasonography pattern in all of these entities can vary from normal to thickened folds to nodular tumefaction. In particular, in our patient bowel ultrasound showed small hypoechoic nodules and adjacent periintestinal hyperplastic lymph node. However, this US feature is not specific only for mastocytosis, but could be encountered in case of lymphoma; in fact in the past mastocytosis was called mastzellen lymphoma. Therefore, biopsy and laboratory studies are required. Our patient firstly presented with some localized violaceous papules that gradually extended over the trunk and with symptoms of gastrointestinal involvement such as intermittent constipation and

diarrhea. Although she did not present bone pain, despite the multiple nontraumatic bone fractures. The results of laboratory tests were normal except for elevated serum tryptase. Because of clinical suspicion, sacral bone biopsy was performed leading to a diagnosis of SM; that is, defined by major and minor SM criteria (Table 1) [2].

Systemic mastocytosis is a not common disease and more often it is overlook. We present this case because when thickened bowel wall, skin lesions and bone fractures, SM may be included in the differential diagnosis. Even if there is no known cure for SM and therapy is directed towards symptomatic reliefs, an early diagnosis of this rare clinical–pathological entity is essential for a correct management of the patients.

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Conflict of interest Maria Rosignuolo, Marta Muscianese, Guglielmo Pranteda declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). All patients provided written informed consent to enrolment in the study and to the inclusion in this article of information that could potentially lead to their identification.

Human & Animal Studies The study was conducted in accordance with all institutional and national guidelines for the care and use of laboratory animals.

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Table 1 Diagnostic WHO criteria for systemic mastocytosis

Diagnostic WHO criteria for systemic mastocytosis

Major

Multifocal dense infiltrates of MCs in the bone marrow or other extracutaneous organs, confirmed by special stains, such as MCs tryptase (>15 MCs aggregating)

Minor

In MCs infiltrates on the bone marrow or other extracutaneous organs, >25 % of MCs are spindle-shaped or otherwise atypical; or in bone marrow smears, >25 % of MCs are spindle-shaped or otherwise atypical

Activating point mutation of KIT in codon 816 is present in extracutaneous organ(s)

MCs in extracutaneous organs (CD117) co-express either CD2 or CD25, or both, as determined by flow cytometry

Serum tryptase is persistently >20 ng/ml (does not count in patients, who have an associated clonal hematological non-MCs lineage disease = AHNMD)

If at least one major and one minor criteria or three minor criteria are fulfilled, the diagnosis SM can be established [2]

MCs mast cells

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