

Adult mastocytosis: a review of the Santo António Hospital's experience and an evaluation of World Health Organization criteria for the diagnosis of systemic disease*

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Abstract: **BACKGROUND:** Mastocytosis is a clonal disorder characterized by the accumulation of abnormal mast cells in the skin and/or in extracutaneous organs. **OBJECTIVES:** To present all cases of mastocytosis seen in the Porto Hospital Center and evaluate the performance of World Health Organization diagnostic criteria for systemic disease. **METHODS:** The cases of twenty-four adult patients with mastocytosis were reviewed. Their clinical and laboratorial characteristics were assessed, and the properties of the criteria used to diagnose systemic mastocytosis were evaluated. **RESULTS:** The age of disease onset ranged from 2 to 75 years. Twenty-three patients had cutaneous involvement and 75% were referred by dermatologists. Urticaria pigmentosa was the most common manifestation of the disease. One patient with severe systemic mast cell mediator-related symptoms showed the activating V560G KIT mutation. The bone marrow was examined in 79% of patients, and mast cell immunophenotyping was performed in 67% of the participants. Systemic disease was detected in 84% of cases, and 81% of the sample had elevated serum tryptase levels. All the diagnostic criteria for systemic mastocytosis had high specificity and positive predictive value. Bone marrow biopsy had the lowest sensitivity, negative predictive value and efficiency, while the highest such values were observed for mast cell immunophenotyping. Patients were treated with regimens including antihistamines, sodium cromoglycate, alpha-interferon, hydroxyurea and phototherapy. **CONCLUSIONS:** Cutaneous involvement is often seen in adult mastocytosis patients, with most individuals presenting with indolent systemic disease. Although serum tryptase levels are a good indicator of mast cell burden, bone marrow biopsy should also be performed in patients with normal serum tryptase, with flow cytometry being the most adequate method to diagnose systemic disease.

Keywords: Flow cytometry; Mast cells; Mastocytosis, cutaneous; Mastocytosis, systemic; Tryptases

INTRODUCTION

The term 'mastocytosis' designates a heterogeneous group of disorders characterized by the abnormal clonal proliferation and accumulation of mast cells (MC) in one or multiple organs and/or tissues including the skin, bone marrow (BM), liver, spleen, and lymph nodes.¹

Its clinical presentation is variable, ranging from skin-limited disease, especially in pediatric cases which spontaneously resolve over time, to a more aggressive condition involving extracutaneous sites and associated with multiple organ dysfunction/failure and shortened survival.^{2,3,4} Diseases involving the pathologic proliferation of MC are classified based on their clinical presentation, pathologic findings, and prognosis. The 2008 World Health Organization

(WHO) classification divided tumors into the following categories (Chart 1): **1**) Cutaneous mastocytosis (limited to the skin); **2**) Extracutaneous mastocytosis (unifocal MC tumor with low-grade cellular atypia and non-destructive features); **3**) Mast cell sarcoma (unifocal mast cell tumor with destructive features and poorly differentiated MC); **4**) Systemic mastocytosis (SM), which almost invariably involves the BM, frequently presents with skin lesions and is the most commonly diagnosed MC disorder in adults.^{5,6,7} The diagnostic criteria for SM were also established by the same 2008 WHO document (Chart 2).^{5,8} Patients are diagnosed with SM upon fulfilling one major and one minor or three minor criteria.

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CHART 1: Mastocytosis variants and subvariants according to the 2008 World Health Organization classification⁵

Variants and subvariants
Cutaneous mastocytosis (CM)
Urticaria pigmentosa (UP)
Maculopapular CM (MPCM)
Diffuse CM (DCM)
Mastocytoma of skin
Indolent systemic mastocytosis (ISM)
Smoldering SM
Isolated bone marrow mastocytosis
Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease (SM-AHMD)
Acute myeloblastic leukemia (SM-AML)
Myelodysplastic syndrome (SM-MDS)
Myeloproliferative disorder (SM-MPD)
Chronic myelomonocytic leukemia (SM-CMML)
Non-hodgkin lymphoma (SM-NHL)
Aggressive systemic mastocytosis (ASM)
Mast cell leukemia (MCL)
Aleukemic MCL
Mast cell sarcoma
Extracutaneous mastocytoma

SM has been associated with somatic mutations in the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*), which codes for a transmembrane receptor with kinase activity (*KIT* receptor, CD117) whose ligand is the stem cell factor (*SCF*).⁹ *KIT* mutations that induce ligand independent phosphorylation of the *SCF* receptor and consequently lead to constitutive activation seem to play a critical role in the pathogenesis of SM by inducing autonomous MC growth. As such, these mutations may be potential diagnostic markers and therapeutic targets. Two activating point mutations leading to the amino acid substitutions Asp-816(r)Val and Val-560(r)Gly in the proto-oncogene *C-KIT* have been reported in the human mast cell leukemia cell line HMC-1, and also in adult-onset mastocytosis, although with very different frequencies.¹⁰ The D816V mutation has also been found to be common in adult mastocytosis patients, and its frequency in adult individuals with SM is estimated to be higher than 80%, although its presence does not necessarily imply associated hematologic disease and is not a reliable prognostic indicator, as was initially suggested.^{11,12,13} In contrast, the V560G mutation has been reported in only a small number of patients.^{14,15} Patients with CM have the best prognosis, followed by those with indolent systemic mastocytosis (ISM). Patients with SM associated with clonal hematologic non-mast cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), or mast cell leukemia (MCL) experience a more rapid and complex clinical course.

The purpose of the present study was to review all cases of mastocytosis seen in a university hospital, and to evaluate the use of WHO diagnostic criteria for systemic disease.

CHART 2: World Health Organization criteria for the diagnosis of systemic mastocytosis^{5*}

Major criteria:
Multifocal dense infiltrates of mast cell (MC) detected in bone marrow (BM) and/or other extracutaneous organs.
Minor criteria:
In MC infiltrates detected in BM or other extracutaneous organs, >25% of MC are spindle shaped or in BM smears, atypical MC comprise >25 of all MC.
Detection of codon 816 C-Kit point mutation in BM, blood or other extracutaneous organs.
BM, blood or other extracutaneous organs MC are CD2+ and/or CD25+.
Serum total tryptase persistently >20µg/L

Footnotes: * The diagnosis is made when individuals meet 1 major and 1 minor or 3 minor criteria

MATERIAL AND METHODS

Between January 2003 and March 2011, 24 adult patients with mastocytosis were assessed at the multidisciplinary center for cutaneous lymphoma in the Porto Hospital Center. Patient charts were retrospectively reviewed for information on their disease, treatment and outcome.

The initial evaluation included a physical examination, full blood count, biochemical survey, and the assessment of serum immunoglobulin, vitamin B12, folate, ferritin and total tryptase serum levels (range: 2-13 µg/L). Suspected cutaneous lesions were biopsied, and all patients underwent BM biopsy and aspirate in order to confirm the diagnosis and detect systemic disease. Biopsy specimens were routinely processed and stained with hematoxylin and eosin. When necessary, CD117 expression was assessed by immunohistochemical staining. BM aspirate smears were stained with Leishman's and toluidine blue stains. Additionally, BM MC were immunophenotyped by flow cytometry. MC were quantified and phenotyped by four-color staining using fluorochrome-conjugated monoclonal antibodies directed against CD2, CD25, CD45 and CD117. All patients with SM underwent bone mineral density testing and abdominal ultrasound at diagnosis.

The diagnostic properties of each WHO criterion were evaluated by calculating sensitivity, specificity, predictive values and efficiency, using the WHO requirements for the diagnosis of SM (1 major and 1 minor or 3 minor criterion) as the gold standard. Spearman's rank order correlations were run to determine the relationship between serum tryptase levels and percentage of MC in the BM. The Mann-Whitney test was applied to compare serum tryptase levels between patients with SM and individuals with CM.

RESULTS

Twenty-four adult patients with mastocytosis were studied, and 14 (58%) of these individuals were women. The median age of disease onset was 34 years, and ranged from 2 to 75 years, while the median age at first clinic visit was 45 years, and ranged from 18 to 75 years. Most patients (75%) were referred by Dermatology, followed by Hematology (12.5%), Internal Medicine (8.3%) and other services (4%). The median time of follow-up was 10 years (range: 1 to 27 years) from the first manifestation of the disease, 9 years (range: 6 months to 26 years) from the diagnosis of mastocytosis and 42 months (range: 3 to 108 months) from the first visit to the multidisciplinary clinic for cutaneous lymphomas.

Cutaneous manifestations were observed in 23 (96%) patients (Table 1). Urticaria pigmentosa (UP) was seen in 21 patients (88%) (Figure 1). One patient pre-

sented with telangiectasia macularis eruptiva perstans (TMEP), and another had multiple cutaneous anetoderma lesions (Figure 2). Pruritus, which was usually moderate and typically described as itching of the lesions, was the most frequent symptom, being present in 15 patients (63%). Gastrointestinal and neuropsychiatric manifestations were seen in 6 (25%) and 5 (21%) patients, respectively. One patient had severe systemic MC mediator-related symptoms, consisting of episodes of flushing, hypotension and syncope (Table 1).

Skin biopsies were performed in all patients with cutaneous manifestations (96%), and in all cases, skin involvement was confirmed. Pathological findings included multifocal aggregates of MC in the upper dermis and perivascular areas (Figure 3). Whenever necessary, CD117 immunostaining was used to identify MC in biopsy specimens (skin and BM). Elevated total serum tryptase levels (range: 2 to 194 µg/L) were found in 14 cases (58%) at the first clinical assessment. BM examinations were performed in 19 (79%) patients, all of whom were biopsied. Aspirate smears were examined for 18 (75%) patients, and 16 (67%) individuals underwent MC immunophenotyping by flow cytometry.



FIGURE 1: Urticaria pigmentosa lesions: multiple hyperpigmented red-brown maculae and papules



FIGURE 2: Anetodermic lesions: multiple small, circumscribed, skin-colored, wrinkled patches that may bulge slightly and herniate into the skin

TABLE 1: Description of patients' cutaneous manifestations and symptoms

Condition	Manifestation	Number (percentage)
Cutaneous manifestations	urticaria pigmentosa	21 (88%)
	Telangiectasia macularis eruptiva perstans	1 (4.2%)
	Anetoderma	1 (4.2%)
	Total	23 (96%)
Symptoms*	Pruritus	15 (63%)
	Gastrointestinal	6 (25%)
	Neuropsychiatric	5 (21%)
	Flushing, hypotensions and syncope	1 (4.2%)

Footnotes: * Each patient could show more than one symptom

In order to evaluate the properties of each WHO criteria for the diagnosis of SM, their sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and efficiency were calculated (Table 2). BM biopsy confirmed systemic involvement in 11 (58%) of the 19 patients. Of the eight patients with no apparent BM abnormalities, 3 had CM and 5 had SM (false negatives), as later confirmed by other diagnostic methods (Table 2). Of the 18 patients who underwent BM aspirate examination, 12 (67%) showed systemic involvement. Features of neoplastic MC included the presence of cytoplasmic processes, atypical nuclei and spindled, degranulated and hypogranulated forms (Figure 4). Atypical MC morphology was not observed in the remaining six patients. Three of these patients were true negatives (patients with CM), while the other three were diagnosed with SM (Table 2). Twelve (92%) of the 13 SM patients whose BM MC were analyzed by flow cytometry were found to have BM involvement, as detected by the presence of phenotypically abnormal CD25+ and/or CD2+ MC (Figure 5). In the remaining case, flow cytometry was inconclusive (unrepresentative BM aspirate). Flow cytometry analysis was able to detect an aberrant MC population as low as 0.004%. In 3 patients, the BM MC showed a normal phenotype, confirming that mastocytosis was limited to the skin (Table 2).

Systemic involvement was confirmed in 16 patients, of whom 15 were diagnosed with ISM and one with SM-AHNMD (myeloproliferative syndrome, MPS), and CM was diagnosed in 3 patients. In 5 cases, a definitive differential diagnosis between MC and MS could not be established, since BM involvement was not evaluated. Eleven (69%) of the 16 SM patients who met the major criterion (multifocal dense infiltrates of MCs detected in the BM and/or in other

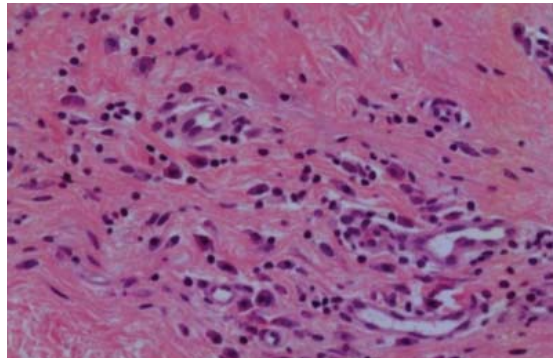


FIGURE 3: Histopathological findings in a skin specimen from a patient with urticaria pigmentosa lesions showing multifocal mast cell aggregates in the dermis (hematoxylin-eosin staining, 200x magnification)

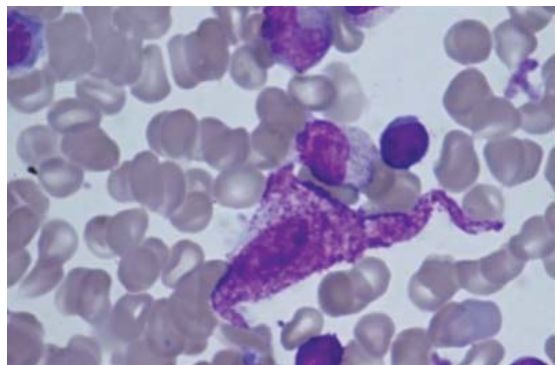


FIGURE 4: Bone marrow aspirate smear from a patient with systemic mastocytosis, revealing a morphologically atypical mast cell with fusiform shape, polar cytoplasmic processes, hypogranularity and atypical nuclei (Leishman's staining, 400x magnification)

TABLE 2: Title: Sensitivity, specificity, predictive values and efficiency of each World Health Organization criterion used in this study for the diagnosis of systemic mastocytosis

Who criteria	Organ (sample)	Laboratorial finding	Sensitivity	Specificity	Negative predictive value	Positive predictive value	Efficiency
Major	Bonemarrow (biopsy) (i)	Multifocal dense infiltrates of mast cells	11/16(69%)	3/3(100%)	3/8(38%)	11/11(100%)	14/19(74%)
Minor	Bone marrow (smcar)	Atypical mast cell morphology	12/15(80%)	3/3(100%)	3/6(50%)	12/12(100%)	15/18(83)
Minor	Bone marrow (aspirate)(ii)	Aberrant phenotype	12/13(92%) (iii)	3/3(100%)	3/4(75%) (iv)	12/12(100%)	15/16(94%)
Minor	Peripheral Blood (iv)	Elevated serum tryptase (>20µg/L)	12/16(75%) (vii)	3/3(100%)	3/7(43%) (viii)	12/12(100%)	15/19(79%) (ix)

Footnotes: (i) Bone marrow analysis was not performed in 5 patients, one of whom had increased serum tryptase levels; (ii) One of these cases had an unrepresentative BM aspirate; if this case is not included in the analysis, the following values are obtained: (iii) 12/12 (100%), (iv) 3/3 (100%) and (v) 15/15 (100%); (vi) One of these cases was SM-AHNMD (MPD); if serum tryptase levels are not used as diagnostic criteria in this case, the following values are obtained: (vii) 12/15 (80%); (viii) 3/6 (50%) and (ix) 15/18 (83%)

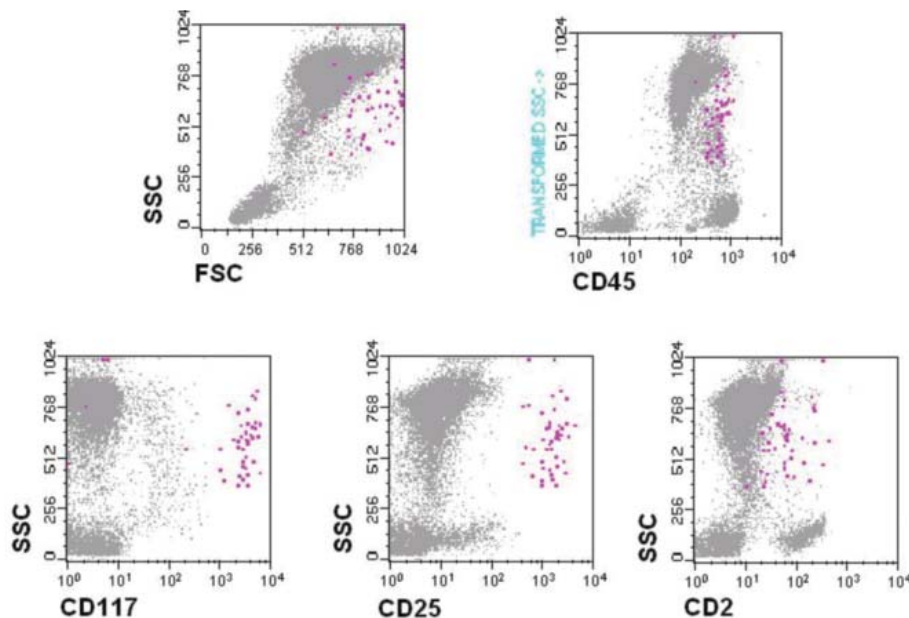


FIGURE 5: Typical dot-plots showing phenotypically abnormal CD117+, CD25+, CD2+ neoplastic mast cells (pink dots) identified by flow cytometry in the bone marrow aspirate from a patient with systemic mastocytosis

extracutaneous organs) also met ≥ 2 minor criteria. The remaining 5 (31%) patients were diagnosed with SM based on the presence of ≥ 3 minor criteria.

Hematologic abnormalities were present in 38% of SM patients and included anemia, leucopenia, leukocytosis and thrombocytopenia. Bone densitometry revealed signs of osteoporosis in three patients, and two patients were found to have hepatosplenomegaly.

Associated diseases were present in five patients. Two of these individuals had autoimmune cytopenias (anemia and thrombocytopenia in one patient; thrombocytopenia in another), one had *BCR-ABL* negative myeloproliferative disorder, another had anetoderma, while the remaining participant was diagnosed with colon carcinoma. One patient evolved from ISM to ASM 13 years after disease onset. Years before any evidence of disease progression was

detected, this patient was found to carry the activating D816V mutation of the *C-KIT* gene in both MC and myeloid non-mast BM cells, while the patient diagnosed with systemic MC-mediator related symptoms was found to carry the activating V560G in BM MCs only. The other cases were not investigated for the presence of C-KIT mutations, since molecular analyses are not routinely performed in the hospital.

All patients were treated with antihistamines with some clinical response. Sodium cromoglycate (200 mg orally 5 times per day) was used by 22 (92%) patients with variable clinical benefit. One patient was treated with alpha-interferon (3MU, 3 times a week, subcutaneously) over 8 weeks without clinical response. The patient who progressed to ASM received corticosteroids and hydroxyurea for 6 months with limited clinical benefit and refused further treatment. A transient response was observed in patients with associated autoimmune cytopenias, all of whom were treated with oral corticosteroids and intravenous high-dose immunoglobulins.

DISCUSSION

Mastocytosis has been found to involve the skin in approximately 80% of cases. In agreement with other studies, the present results showed that UP was the most common skin manifestation of mastocytosis.¹³ Only one patient was found to have atypical cutaneous alterations in the form of secondary anetoderma. Anetodermic lesions are an unusual clinical presentation of mastocytosis.^{16,17} MCs play an important role in the development of anetodermic lesions, as they release different mediators which interfere with collagen synthesis and increase the fragmentation of elastic fibers. Moreover, the chemotactic substances released during mastocyte degranulation induce the accumulation of eosinophils, neutrophils and macrophages, which might promote elastase activity.¹⁸

Cases of suspected CM should be investigated by skin biopsy. In the present study, cutaneous biopsies were performed in all patients with skin lesions. Typically, MC are more abundant in UP lesions than in normal skin. However, small increases in MC numbers have also been reported in patients with other conditions, such as unexplained flushing, chronic urticaria, and atopic dermatitis.^{19,20}

The diagnostic approach to SM usually starts with BM analysis, since this site is almost universally involved in adult mastocytosis, and its examination allows for the detection of second hematologic neoplasms.^{8,21,22} In the vast majority of cases (90%), SM can be diagnosed by BM examination alone (major criterion). However, the fact that multifocal and dense MC infiltrates (major criterion for SM according to the WHO classification) were only observed in 69% of our

patients suggested that this criterion has a low NPV (38%) and low efficiency (74%) for diagnosing SM (Table 2). This can be explained in part by the intrinsic subjectivity of this analysis, and also by the fact that, in some cases, it can be especially difficult to identify the typical features of mastocytosis in the BM, especially when MC are significantly hypogranulated or when significant reticulin fibrosis is present.⁸ Tryptase appears to be the most sensitive immunohistochemical marker of the disease. However, tryptase testing was not available in the hospital studied, so that in some cases, CD117 immunostaining was performed to identify MC in biopsy specimens.

Atypical MC morphology in BM smears was observed in 80% of patients. This criterion had higher sensitivity, NPV and efficiency in diagnosing SM than the presence of dense infiltrates of MC in BM specimens (Table 2).

MC immunophenotyping by flow cytometry proved to be an excellent method for screening for SM (sensitivity, NPV and efficiency of 92%, 75% and 94%, respectively; all values increased to 100% when only cases with representative BM aspirates were considered) (Table 2). Currently, CD117 is considered to be the best immunological marker of mature MC.²³ It can also be found in normal and pathological MC, as well as in several other cells such as CD34+ hematopoietic stem and progenitor cells, myeloid precursors, CD56^{bright} NK cells, and neoplastic cells from patients with various hematological and non-hematologic malignancies.²⁴ However, MC usually express much higher levels of CD117 than other CD45+ hematopoietic cells, and the combined analysis of CD117 expression and light scatter properties allows for the identification of MC by flow cytometry (Figure 5).^{1,23} Neoplastic MC are usually CD2 and/or CD25 positive, and the abnormal expression of at least one of these two antigens is considered a minor criterion according to the 2008 WHO classification. In the present study, CD25 positivity appeared to be the most sensitive and specific method to identify neoplastic MC, a finding which is in accordance with the literature.²³ All CM patients in the present sample had normal serum tryptase levels, and 13 (81%) of the 16 patients with confirmed SM showed elevated tryptase levels, leaving a total of three patients with systemic involvement but normal levels of serum tryptase. Although the present data confirm previous reports suggesting that the measurement of serum tryptase levels is a reliable noninvasive diagnostic approach to monitor MC burden in patients with mastocytosis, it is important to emphasize that this test has limited diagnostic utility for SM screening due to its relatively low sensitivity, NPV and efficiency (75%, 43% and 79%, respectively; these values increased to 80%, 50%

and 83% when the patient with SM-AHNMD was excluded from the analysis) (Table 2).²⁵ Moreover, it is known that serum tryptase levels can be temporarily elevated during severe allergic reactions, and in a significant proportion of cases of acute myeloid leukemia (AML), myeloproliferative and myelodysplastic syndromes, which limits the diagnostic utility of this test in individuals with a second SM-associated myeloid neoplasm.^{1,12,26} One study has reported that approximately 5% of AML patients have serum tryptase levels > 200 µg/L, possibly due to the presence of associated SM.²⁷ Myeloid disorders account for 80-90% of cases of SM-AHNMD. For these reasons, the WHO classification states that this criterion cannot be used reliably in patients with an associated myeloid disorder. Plasma cell myeloma is the most frequent lymphoid malignancy associated with SM.²⁸ It is not completely clear whether elevated serum tryptase levels are diagnostically effective in cases of SM associated with lymphoid neoplasms.²⁵ According to the literature, the proportion of ASM and SM-AHNMD patients who exhibit markedly elevated serum tryptase levels (> 200 µg/L) is significantly higher than that proportion among ISM patients.^{4,8} In the present study, the patient with SM-AHNMD (MPD) had normal serum tryptase levels.

Despite their variable sensitivity and NPV, all WHO criteria proved to have high specificity and PPV for diagnosing SM (100% in our series) (Table 2). Despite the sample limitations, the present results suggested that patients who met these criteria had a significantly higher probability of systemic disease.

Of the 16 patients diagnosed with SM, 11 (69%) met both the major criterion and ≥ 2 minor criteria. The remaining 5 (31%) patients were diagnosed based only on the presence of ≥ 3 minor criteria. These findings are similar to other reports. A study of 53 patients with SM reported the presence of the major criterion in 68% of the sample.²⁵ Atypical MC morphology was observed in 100% of patients, an aberrant immunophenotype was identified in 96% of individuals, and elevated serum tryptase (>20 µg/L) levels were detected in 85% of the sample.²⁵ Spearman's rank order correlation was used to determine the relationship between serum tryptase levels and the percentage of MC in the BM. A positive correlation was found between the two variables ($r = 0.340$, $P < 0.05$). The Mann-Whitney test was applied to compare serum tryptase levels between patients with SM and those with CM, and it was found that patients with CM had significantly lower levels of serum tryptase than SM patients ($P=0.014$).

The conclusions of the present study regarding genetic aberrations are limited by the fact that the molecular analysis of MC is not routinely performed in our hospital, and only two cases were evaluated using this procedure. The patient who presented the D816V mutation, which is common in patients with adult onset SM, showed disease progression from indolent to aggressive SM 13 years after the first disease manifestation.²⁹ This is in accordance with the fact that individuals who carry this mutation in BM MC, CD34+ hematopoietic precursors and mature non-mast myeloid cells tend to have a poorer prognosis.¹³ In contrast, the patient whose BM MC displayed the Val-560(r)Gly mutation, which is rare in both children and adult patients with mastocytosis, had an atypical presentation of SM, displayed associated CM and showed no evidence for disease progression for 19 years after the initial diagnosis.¹³ It is unclear whether these mutations play a causal or permissive role, where additional factors are necessary to develop ISM and/or ASM, and whether they may influence the response to different tyrosine kinase inhibitors, as suggested by *in vitro* studies with mast cell leukemia cell lines.³⁰

CONCLUSION

When considered individually, the WHO criteria have different degrees of diagnostic utility for SM. Although all criteria have high specificity and PPV for the diagnosis, their sensitivity, NPV and efficiency is highly variable. The present results suggested that flow cytometry based immunophenotypic analysis of BM MC was the most adequate test for SM screening due to its high sensitivity and NPV. Serum tryptase analysis also has relatively good sensitivity for diagnosing SM, and may provide an indirect measure of MC mass. However, normal serum tryptase levels cannot be used to exclude systemic involvement due to their low NPV. Thus, when serum tryptase levels are found to be normal, the BM should be evaluated and MC phenotypes should be analyzed by flow cytometry. Other conventional methods, such as BM smears and biopsy, in that order, could also be used for a correct evaluation of systemic disease. Further studies are necessary to explain the differences between ISM and ASM, disease progression and the association between SM and other hematologic disorders in some patients. To help with this process, new algorithms are being proposed for a better diagnostic definition and prognostic classification of these disorders.³¹ □

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