



Letter

Diagnostic challenge in a patient with severe pruritic rash

Mastocytosis is a rare and highly heterogeneous disorder characterized by the clonal proliferation of morphologically and immunophenotypically abnormal mast cells in at least 1 organ.¹ Clinical signs and symptoms are related to the mast cell burden in different organs and the subsequent release of mediators.²

The World Health Organization recognizes several variants of cutaneous mastocytosis (CM) and systemic mastocytosis (SM). Diagnosis follows strict criteria (Table 1).³

Despite recent advances in molecular and genetic diagnoses, in some cases of early or low-burden disease, the full diagnostic criteria for mastocytosis are not fulfilled. Also, when associated with hematologic non–mast cell lineage disease, the differential diagnosis might prove a difficult task for the clinician.

We describe the case of a 58-year-old white man with a history of partial nephrectomy for clear-cell renal carcinoma who was referred by the urology team to the allergology unit for a generalized pruritic skin rash of 1-year duration and evidence of persistent peripheral eosinophilia.

The skin complaint manifested as intermittent pruritus exacerbated by heat and rash, which initially appeared on the trunk and gradually spread to the extremities and the face. This presentation was previously interpreted as chronic urticaria. At the time of presentation, the pruritus had become constant and severe.

The patient's medical history disclosed that the onset of skin complaints was shortly after a systemic immediate hypersensitivity reaction to Hymenoptera venom (Mueller grade IV or Ring and Messmer grade III anaphylaxis to wasp sting). He had no further investigations or follow-up for the suspected anaphylactic reaction.

The patient did not report any flushing, wheezing, and gastrointestinal manifestations.

Clinical examination showed fixed erythematous maculopapular lesions distributed symmetrically on the lower extremities and upper body with the Darier sign (Fig 1).

Moderate hepatomegaly was noted. There was no palpable lymphadenopathy.

The full blood cell count showed a total normal white blood cell count ($6.05 \times 10^3/\mu\text{L}$), an absolute eosinophil count of $1.4 \times 10^3/\mu\text{L}$ (23.1%), and an elevated total serum IgE level (1,226.9 IU/mL).

Neoplastic and non-neoplastic causes of hypereosinophilia and end-organ damage were investigated and excluded.

Atopy was investigated and documented. The patient was sensitized to house dust mites (*Dermatophagoides farinae*), noted by skin testing and in vitro specific IgE testing, without evidence of clinical relevance.

The diagnostic protocol of a Hymenoptera sting reaction, performed according to the European Academy of Allergy and Clinical Immunology Interest Group on Insect Venom Hypersensitivity,⁴

identified sensitization to bee and wasp venom and a persistent elevated level of serum tryptase (57,000 ng/L).

Skin biopsy showed histopathology compatible with mastocytosis. Bone marrow (BM) biopsy showed hypercellularity (60%) in the eosinophil lineage. A small number of mast cells of atypical morphology (<5%) were identified. Testing for KITD816V in peripheral blood showed a negative result. The peripheral hypereosinophilia prompted screening for the FIP1-like-1/platelet-derived growth factor receptor- α (FIP1L1-PDGRFA) rearrangement, which showed a positive result.

Based on clinical and hematologic findings, we reached a diagnostic dilemma of whether the patient had an atypical association of CM with chronic eosinophilic leukemia (CEL) or pre-existing SM with superimposed hematologic clonal non–mast cell disease (SM-CEL).

This patient lacked the major diagnostic criterion of mast cell clusters in the BM and met 2 minor criteria: (1) the persistent elevated level of serum tryptase and (2) atypical mast cells in BM aspirate smears for diagnosis. However, the diagnostic relevance of the serum tryptase criterion was invalidated by the associated clonal myeloid eosinophilic disorder.

Owing to financial constraints, the level of expression of CD117 and CD2 and/or CD25 was not checked. If positive, there still would have been insufficient criteria for an SM diagnosis.

The histopathologic picture of the skin biopsy confirmed the diagnosis of CM. The current medical literature describes that only a minority of adult patients has skin-limited disease. According to recent data, 50% of adults with apparent cutaneous-limited mastocytosis have a clonal BM mast cell infiltrate that does not meet the threshold for SM, which may suggest a prediagnostic or early stage of indolent SM.⁵

Idiopathic hypereosinophilic syndrome was excluded by identifying the FIP1L1-PDGFRA fusion gene mutation. As reported previously, clonal neoplastic eosinophil proliferation, secondary end-organ dysfunction, and SM characterize FIP1L1-PDGFRA–positive disorders.⁶

Table 1

Diagnosis of systemic mastocytosis according to the World Health Organization^a

Major criterion	multifocal dense aggregates of >15 tryptase-positive mast cells in bone marrow and/or other extracutaneous tissues
Minor criteria	>25% of mast cells (in bone marrow or other extracutaneous organs) are atypical or display a spindle-shape morphology - detection of the codon 816 c-KIT mutation in the blood, bone marrow, or extracutaneous tissue - mast cells in the blood, bone marrow, or extracutaneous tissue express CD2 and/or CD25 - a persistent elevated level of serum tryptase (>20 ng/mL) in the absence of an associated clonal myeloid disorder

^aDiagnosis requires the major criterion and 1 minor criterion or at least 3 minor criteria.

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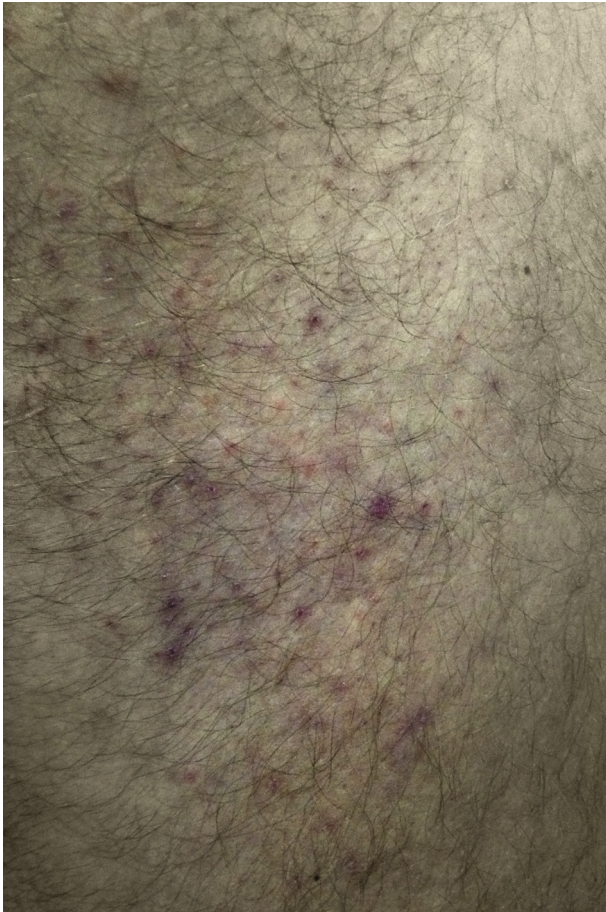


Figure 1. Skin rash consisting of fixed erythematous maculopapular lesions distributed symmetrically on the lower extremities in addition to numerous excoriations.

The CEL and SM present with peripheral hypereosinophilia and raised levels of serum tryptase. Also, patients with CEL commonly present with atypical BM mast cells. It is known that eosinophils and mast cells coexist in various clonal and nonclonal disorders.⁷ The complex interplay between these immune cell types represents the piece of a puzzle that has not been solved.

Nevertheless, patients with positive FIP1L1-PDGFRα genetic testing results might have a spectacular response to the tyrosine kinase inhibitor, imatinib mesylate. Because of the risk of cardiac complications of eosinophilic infiltration, cytoreductive treatment with imatinib should be prompted in these patients.¹

Cutaneous mastocytosis and SM have been associated with the c-KIT codon 816 mutation, which leads to spontaneous activation of the Kit protein (a type III receptor tyrosine kinase) and malignant proliferation of mast cells. The present patient had a negative result for the blood c-KIT mutation. However, a c-KIT negative testing result does not exclude the diagnosis of mastocytosis.¹

The therapeutic approach toward this patient covered the following aspects: education on avoidance of triggers of mast cell degranulation, anti-mediator agents for symptom control, and an epinephrine auto-injector for self-medication for acute events. We also initiated cytoreductive treatment. Disease regression using imatinib at a dose of 100 mg/d was favorable, the eosinophil count decreased significantly to $0.34 \times 10^3 \mu\text{L}$ (2.9%), and the patient reported notable relief from pruritus 1 month after initiating therapy.

All the data gathered support the following conclusions:

- In some cases of early or low-burden disease, the full diagnostic criteria for mastocytosis cannot always be fulfilled.
- In a small percentage of patients with mastocytosis, the c-KIT mutation cannot be detected.
- Mastocytosis can hide under the clinical umbrella of chronic urticaria. In the present case, an early diagnosis was established based on the European Academy of Allergy and Clinical Immunology Insect Venom Hypersensitivity protocol. Early diagnosis is essential for a favorable outcome of the patient.
- Despite recent advances in genetic and molecular diagnoses of myeloproliferative disorders, in patients with overlapping features of myeloproliferative disease and persistent eosinophilia, areas of controversy remain. In such cases, the differential diagnosis might prove a difficult task for the clinician.

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References

- [1] Magliacane D, Parente R, Triggiani M. Current concepts on diagnosis and treatment of mastocytosis. *Transl Med UniSa*. 2014;8:65–74.
- [2] Metcalfe DD. Mastocytosis. In: Akdis CA, Agache I, eds. *Atlas of Allergy*. Zurich: European Academy of Allergy and Clinical Immunology; 2014:242–244.
- [3] Horny HP, Metcalfe DD, Bennett JM, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. 4th ed. Lyon: International Agency for Research and Cancer; 2008:54–63.
- [4] Biló BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN; EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60:1339–1349.
- [5] Sánchez-Muñoz L, Alvarez-Twose I, García-Montero AC, et al. Evaluation of the WHO criteria for the classification of patients with mastocytosis. *Mod Pathol*. 2011;24:1157–1168.
- [6] Yamada Y, Cancelas JA. FIP1L1/PDGFRα-associated systemic mastocytosis. *Int Arch Allergy Immunol*. 2010;152(suppl 1):101–105.
- [7] Gotlib J, Akin C. Mast cells and eosinophils in mastocytosis, chronic eosinophilic leukemia, and non-clonal disorders. *Semin Hematol*. 2012;49:128–137.