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Case Report

Delayed Diagnosis of Indolent Systemic Mastocytosis as the Cause of Unexplained Skin Rash: A Case Report

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Keywords
Mastocytosis · Indolent systemic mastocytosis · Skin rash · Urticaria pigmentosa

Abstract
Mastocytosis is a heterogeneous group of disorders in which mast cells exhibit clonal proliferation that infiltrates one or more organs. In cutaneous mastocytosis, the mast cells infiltrate the skin only, whereas systemic mastocytosis is diagnosed when at least one extra-cutaneous site is involved, with or without the skin being affected. Given the rarity of mastocytosis and the fact that skin rash can be a manifestation of different conditions and many clinicians are not familiar with this disorder, an accurate diagnosis may be delayed. We report a delayed diagnosis of indolent systemic mastocytosis in a 40-year-old gentleman who had been complaining of an unexplained skin rash for 6 years.

Introduction

Mastocytosis is a heterogeneous group of disorders in which mast cells exhibit clonal proliferation that infiltrates one or more organs. Mastocytosis can be classified into cutaneous, systemic, and mast cell sarcomas [1, 2]. It is a rare disease; the prevalence has been estimated to be around 10 cases per 100,000 people [3].

Mastocytosis manifestations range from spontaneously regressing skin rash to highly aggressive cancer, which may lead to multi-organ failure and poor outcomes [4, 5]. Given the

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rarity of mastocytosis and the fact that skin rash can be a manifestation of different conditions and many doctors are not familiar with this disorder, an accurate diagnosis may be delayed, which may lead to serious consequences, including disease progression and life-threatening anaphylactoid reactions [6–8].

Herein, we report a delayed diagnosis of indolent systemic mastocytosis in a 40-year-old gentleman who had been suffering from chronic itchy skin lesions for 6 years. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529347).

Case Report

A 40-year-old man with no past medical history of note presented with itchy skin lesions for 6 years. Skin lesions were distributed over the trunk and extremities and became itchier after a hot shower or touching the lesion; otherwise, he denied any reaction to food or drugs. He denied fever, flushing, abdominal pain, shortness of breath, palpable lumps, or weight loss. There was no history of anaphylaxis.

Physical examination showed a well-built gentleman with multiple brown maculopapular skin rashes, measuring 5–10 mm in diameter and present on the trunk and extremities (Fig. 1). There were no palpable lymph nodes or hepatosplenomegaly.

The patient sought medical advice from different doctors, who prescribed topical creams for him without establishing a clear diagnosis until a skin biopsy was done. A 4-mm skin punch biopsy revealed aggregates of neoplastic mast cells in the papillary dermis (>15 mast cells in the aggregates) (Fig. 2). The mast cells were positive for CD117 and negative for melanocytic markers (Fig. 3). The histological appearances were in keeping with cutaneous involvement by mastocytosis.

The patient was referred to a hematology clinic for further investigation and management. Peripheral blood tests revealed normal hemoglobin, leukocyte, and platelet counts and a normal peripheral smear. Renal and liver function tests were within normal limits. Serum tryptase level was 14.5 μg/L (negative <11 μg/L).

A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan showed moderately increased diffuse bone marrow uptake, which may represent disease involvement; however, reactive bone marrow hyperplasia presents with a similar pattern. Otherwise, the study demonstrated no abnormal uptake to suggest high-grade malignancy.

Bone marrow aspiration and biopsy were performed. Bone marrow aspirate was cellular with trilineage hemopoiesis with few dysplastic forms and approximately 1% blasts. There were approximately 1% mast cells, and the majority show abnormal morphology including a kidney-shaped nucleus, irregular granules distribution, hypogranulation, and spindle forms (Fig. 4). Flow cytometry on the bone marrow revealed approximately 1% of myeloid blasts and less than 0.1% of mast cells aberrantly expressing CD25 and partial CD2. BM biopsy reflected fair cellularity (~30–45% cellularity) with trilineage hemopoiesis and shows few aggregates of phenotypically abnormal mast cells, which were well highlighted by immunohistochemistry, mostly perivascular; morphologically, many look abnormal with elongated/kidney-shaped nucleus and/or spindle-shaped. The mast cells were positive for CD117, mast cell tryptase, and aberrantly positive for CD25.

Based on these findings (Fig. 5), bone marrow involvement by systemic mastocytosis was concluded. In the absence of hepatosplenomegaly and lymphadenopathy, these findings would be compatible with indolent systemic mastocytosis.

The case was discussed in a multidisciplinary team meeting, and the panel recommended managing his symptoms with an oral antihistamine with symptom-trigger avoidance. Also, the

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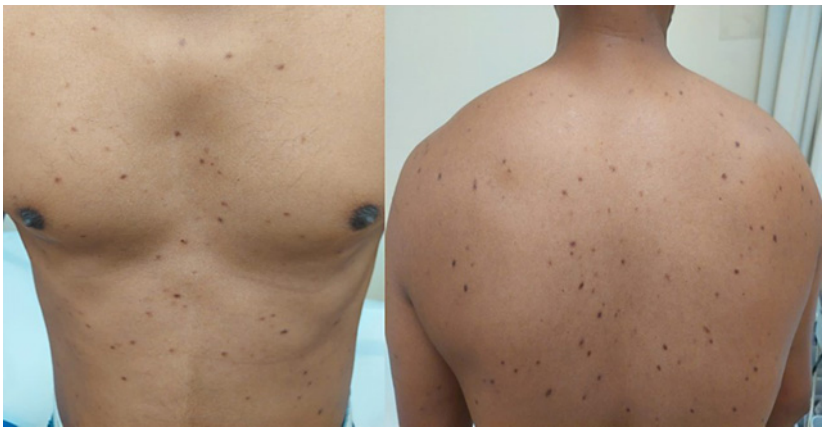

Fig. 1. Multiple brown maculopapular skin rashes distributed over the trunk and extremities.

panel recommends monitoring for osteopenia and osteoporosis as patients with all forms of systemic mastocytosis are at risk of bone disease ranging from mild osteopenia to severe osteoporosis.

Discussion

According to the World Health Organization (WHO) classification, mastocytosis is classified into cutaneous, systemic, and mast cell sarcomas based on clinical presentation, disease distribution, and pathology work-up [9]. In cutaneous mastocytosis, the mast cells infiltrate the skin only, whereas systemic mastocytosis is diagnosed when at least one extra-cutaneous site is involved, with or without the skin being affected. Cutaneous mastocytosis has three variants: urticarial pigmentosa/maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, and mastocytoma of the skin [4, 10].

The diagnosis of systemic mastocytosis can be made if the major criterion and one minor criterion or three minor criteria are present, as outlined by the WHO classification. The major criterion is the detection of multifocal dense mast cell infiltrates (>15 in aggregates) in the bone marrow and/or extra-cutaneous site, while minor criteria are as follows: >25% of mast cell infiltrates are spindle-shaped or have atypical morphology, expression of CD25 in addition to mast cell markers with or without CD2 expression, presence of the c-KIT D816V mutation, and the serum tryptase level is persistently >20 ng/mL in the absence of associated hematological malignancy. Systemic mastocytosis has five variants: indolent systemic mastocytosis, bone marrow mastocytosis, smoldering mastocytosis, systemic mastocytosis with associated hematological malignancy, aggressive systemic mastocytosis, and mast cell leukemia [1, 4, 11].

We diagnose our case as indolent systemic mastocytosis based on the following: (1) the presence of general criteria for systemic mastocytosis of bone marrow involvement by mast cell aggregates, CD25 and CD2 expression, and the presence of >25% spindle shape cells and atypical morphology in mast cells infiltrates; (2) the presence of characteristic skin lesion; (3) low mast cell burden; and (4) no features requiring cytoreductive therapy like bone marrow dysfunction, skeletal involvement, or organomegaly, and there was no evidence of concomitant hematological neoplasm. The serum tryptase level did not meet the WHO diagnostic minor criterion (>20 ng/mL) for systemic mastocytosis; however, the diagnosis was already made based on other criteria.

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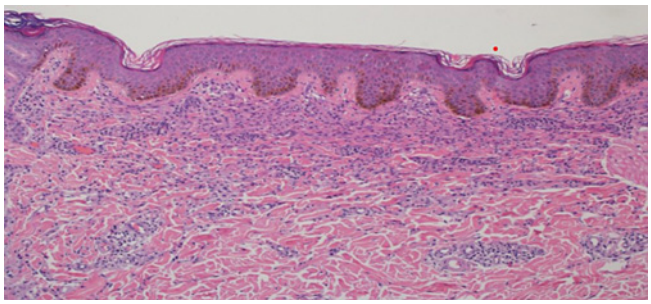

Fig. 2. Skin punch biopsy showing neoplastic mast cells in the papillary dermis (H&E, ×100).

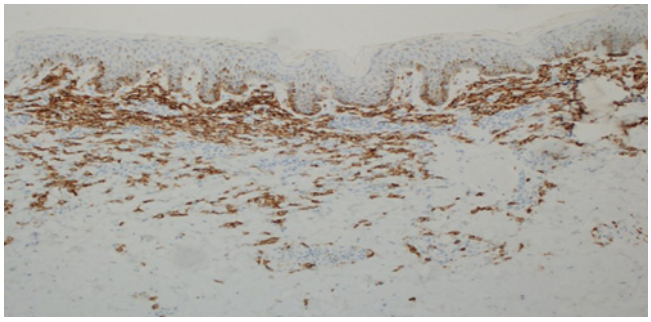

Fig. 3. CD117 highlights the neoplastic mast cells.

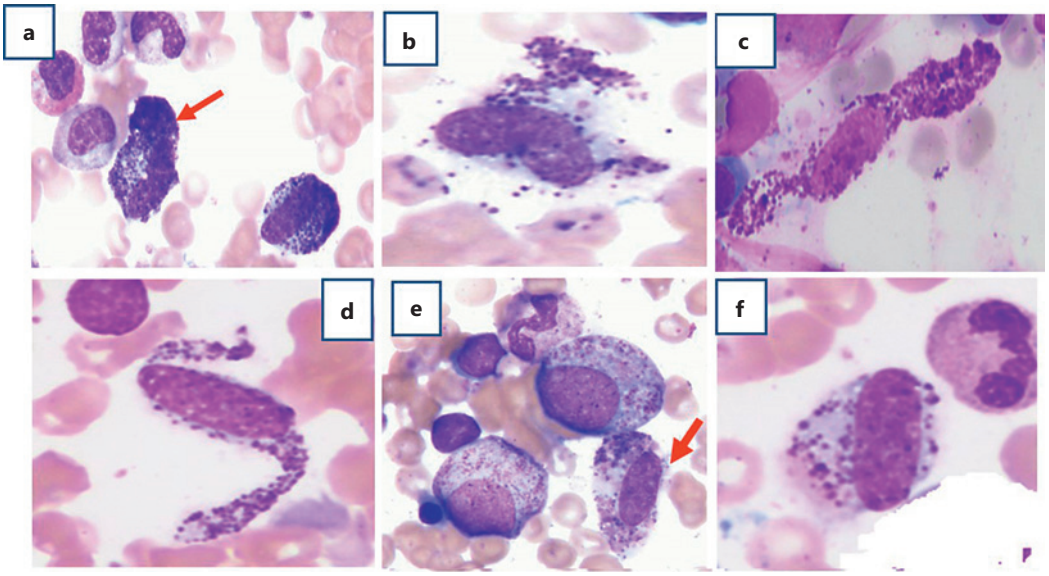

Fig. 4. Mast cells from bone marrow aspirate smear: arrowed cells (**a**) and atypical mast cell (**b**) with kidney-shaped nucleus with mature chromatin, atypical spindle-shaped mast cell (**c**, **d**), and arrowed cells (**e**) and atypical mast cell (**f**) with hypogranular cytoplasm (Wright stain, original magnification ×1,000).

The value of FDG-PET in lymphoid malignancies has been validated for staging and treatment monitoring [12, 13]. However, the data about the usefulness of the FDG-PET/CT scan in mastocytosis are limited [14, 15]. In a French multicenter study, 19 patients with systemic mastocytosis who underwent PET scanning were retrospectively reviewed. Results showed that there was no significant FDG uptake in most mastocytosis variants. Moreover,

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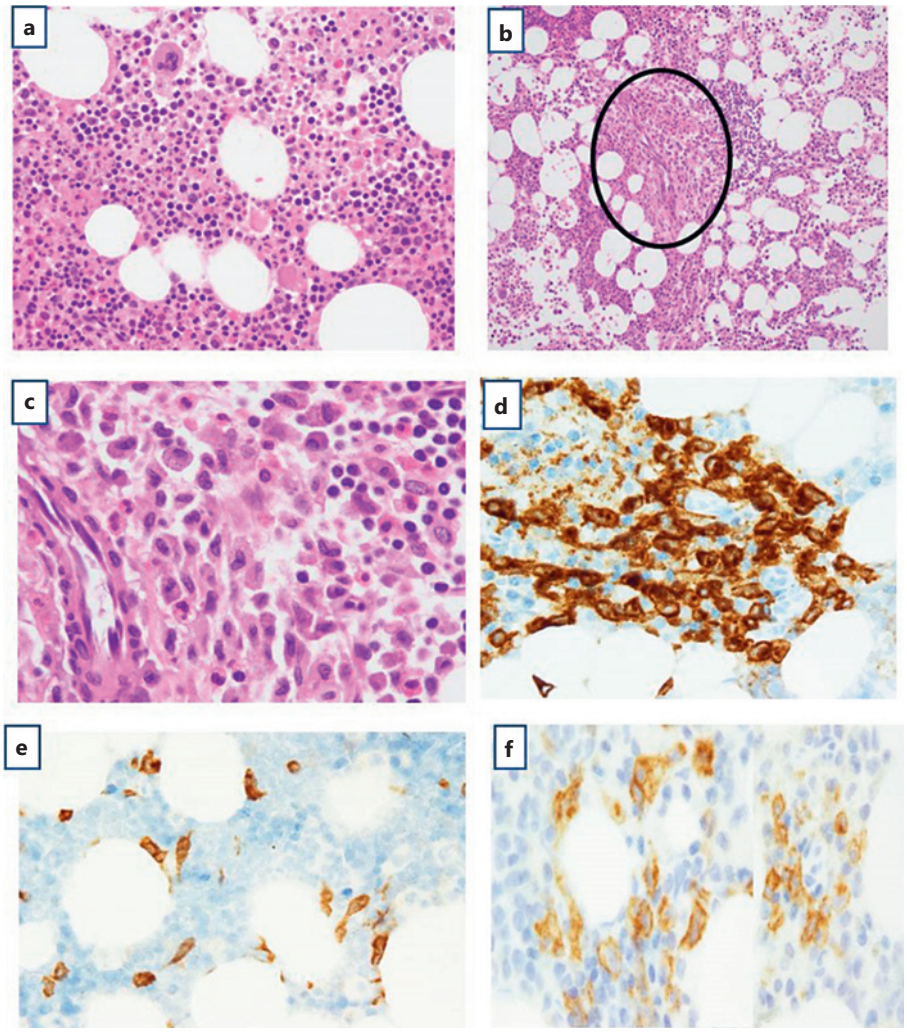

Fig. 5. a Bone marrow biopsy shows cellular marrow with trilineage hemopoiesis, H&E, ×200. **b** Focal aggregate of mast cells, H&E, ×100. **c** Focal aggregate of mast cells, many with abnormal morphology with kidney-shaped nucleus, H&E, ×1,000. **d** CD117 highlights the mast cell aggregate, ×1,000. **e** Many of the mast cells are spindle-shaped, as highlighted by CD117, ×1,000. **f** CD25 shows aberrantly positive mast cells ×1,000.

there was no correlation found between the FDG-PET result and tryptase level, bone marrow involvement, and mast cell expression of CD2 and CD30, concluding that FDG uptake does not seem to be a sensitive marker of mast cell proliferation [14].

In conclusion, we report a delayed diagnosis of indolent systemic mastocytosis in a patient who was suffering from an unexplained skin rash for 6 years. Given that skin rash has a wide differential diagnosis, this case highlights the importance of keeping mastocytosis in mind to avoid such diagnostic delay.

Statement of Ethics

The case was approved by the Hamad Medical Corporation Medical Research Center (MRC-04-22-323), and the patient signed a written informed consent to publish their case

(including publication of images). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of Interest.

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Author Contributions

Conception and design of the study and approval of the version of the manuscript to be published: Dr. A. Alshurafa and Dr. M. Yasin. Acquisition of data and drafting the manuscript: Dr. A. Alshurafa, Dr. M. Abu-Tineh, Dr. M. Petkar, and Dr. F. Ibrahim. Revising the manuscript for intellectual content: Dr. A. Alshurafa, Dr. M. Abu-Tineh, and M. Yassin.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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