

CASE REPORT

Hyperpigmented cutaneous lesions that flare-up with scratching: Darier's sign

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Abstract

We present the case of a 40-year-old male with a past medical history of urticaria pigmentosa (UP) who presented for consultation to the Allergy clinic for an opinion of systemic mastocytosis. Previous workups included elevated serum tryptase level, UP on skin biopsy and an increased number of CD117-positive/CD25-positive mast cells on bone marrow biopsy. This case emphasizes the importance of physical findings such as Darier's sign in patients with hyperpigmented lesions, which virtually supports the diagnosis UP, raises the suspicion for systemic mastocytosis and guides further diagnostic evaluation. This case also outlines the management of systemic mastocytosis.

INTRODUCTION

Mastocytosis describes a group of disorders characterized by clonal proliferation of mast cells (MCs) and infiltration to tissues, with the skin the most frequently affected organ. This condition is divided into cutaneous and systemic forms. Cutaneous forms are limited to the skin and include: urticaria pigmentosa (UP), solitary mastocytoma, diffuse cutaneous mastocytosis and telangiectasia macularis eruptive perstans [1]. Contrary to the cutaneous forms of the disease, which present with localized lesions, systemic forms manifest with symptoms secondary to MC infiltration or release of MC mediators. This case emphasizes the importance of performing a thorough history and physical evaluation to accurately classify patients with different forms of mastocytosis. We present a patient with systemic mastocytosis who was found to have on physical examination Darier's sign,

a typical dermatological sign indicative of degranulation of MCs with release of inflammatory mediators in response to rubbing or scratching of the skin lesion that occur in patients with this condition [2]. We report the symptoms of MC degranulation that affected the patient, like pruritus after trigger exposure to exercise or heat as well as described the workup that allowed a diagnosis of a most severe form of disease and the propose management.

CASE REPORT

A 40-year-old male was evaluated in the Allergy clinic as a self-referral for systemic mastocytosis. The patient reported a 13-year history of generalized hyperpigmented cutaneous lesions with a wheal-and-flare reaction after scratching, and with

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exposures to warm and hot baths, and to exercise. His face was spared from cutaneous lesions. He had associated lightheadedness after exposure to hot baths and exercise without need for emergency room visits. He denied other symptoms such as angioedema, hives, shortness of breath/wheezing or anaphylaxis. He also denied previous adverse reactions to hymenoptera stings. Previous workup included an elevated serum tryptase level of 49 (range 2–10 ng/ml) and a bone marrow biopsy with 30% of aggregates of spindle CD117-positive/CD25-positive MCs, consistent with a diagnosis of systemic mastocytosis. Skin biopsy report showed an increase number of MCs around dilated blood vessels within the superficial dermis. Leder stain confirmed an increased quantity of MCs (Fig. 1). The patient had been started on loratadine 10 mg every other day and diphenhydramine 25 mg as needed for acute exacerbations with no further workup follow-up.

During his initial evaluation at our clinic, he was found to have generalized hyperpigmented lesions (Fig. 2a) that flared upon scratching (Fig. 2c) with a tongue depressor (Fig. 2b) and hepatomegaly. We requested bone marrow biopsy slides for further review by our Pathology Department, and our pathology review was that immunohistochemical stains demonstrated

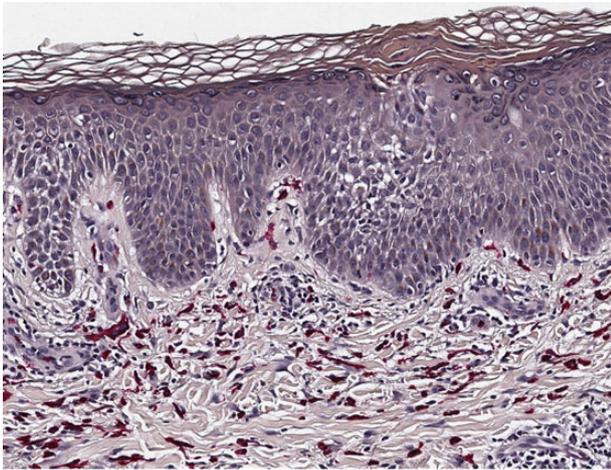


Figure 1: Skin biopsy with Leder stain ($\times 15$) highlights increased MCs in the superficial dermis. Epidermis exhibits spongiosis and focal areas of parakeratosis.

lymphoid aggregates to contain numerous CD3-positive cells admixed with slightly fewer CD20-positive cells (Fig. 3a). The atypical spindled MCs were positive for CD117 (Fig. 3b). A bone scan showed no lytic osseous lesions. A c-kit gene analysis reported no known pathogenic mutations in exons 8, 9, 11, 13 or 17 of the kit gene. CT of the chest and abdomen showed no liver, spleen or lymph node enlargement. The patient received a diagnosis of indolent systemic mastocytosis. He was instructed to decrease sport activities, such as participating in marathons, since this type of exercise could exacerbate his condition. Medical therapy was recommended and this included self-injectable epinephrine prescription, fexofenadine 180 mg twice a day and ranitidine 150 mg twice a day. After 4 months, when the patient was seen again in follow-up, the patient was asymptomatic on medical therapy.

DISCUSSION

In 2008, the World Health Organization (WHO) presented an updated in mastocytosis categories, dividing mastocytosis in two categories: cutaneous and systemic [3]. UP is the most common form of the disease. UP has been described in 33–99% of the cases in patients with systemic mastocytosis [4]. Darier's sign has been associated with this disorder as well with other conditions that increase the number of MCs in the dermis like UP, insect bite reactions, neurofibromas, juvenile xanthogranulomas and acute neonatal lymphoblastic leukemia [5]. Although Darier's sign is virtually diagnostic of UP, failure to elicit this sign does not exclude the diagnosis. The pathophysiology behind it involves the degranulation of MCs with the release of inflammatory mediators including histamine, which is responsible for the response. On our evaluation, the patient had evidence of skin involvement as well as symptoms suggestive of extracutaneous involvement like the triggering of his rash by sun exposure, hot weather and exercise and palpable splenomegaly. These findings suggested a systemic form of the disease. Workup included an elevated serum tryptase level and a bone marrow biopsy showing aggregates of spindles and CD117-positive/CD25-positive MCs, providing additional evidence for a diagnosis of systemic mastocytosis.

The diagnosis of systemic mastocytosis requires as per WHO the presence of one major criterion defined as the presence of multifocal dense infiltrates of MCs (< 15 MCs in aggregates in

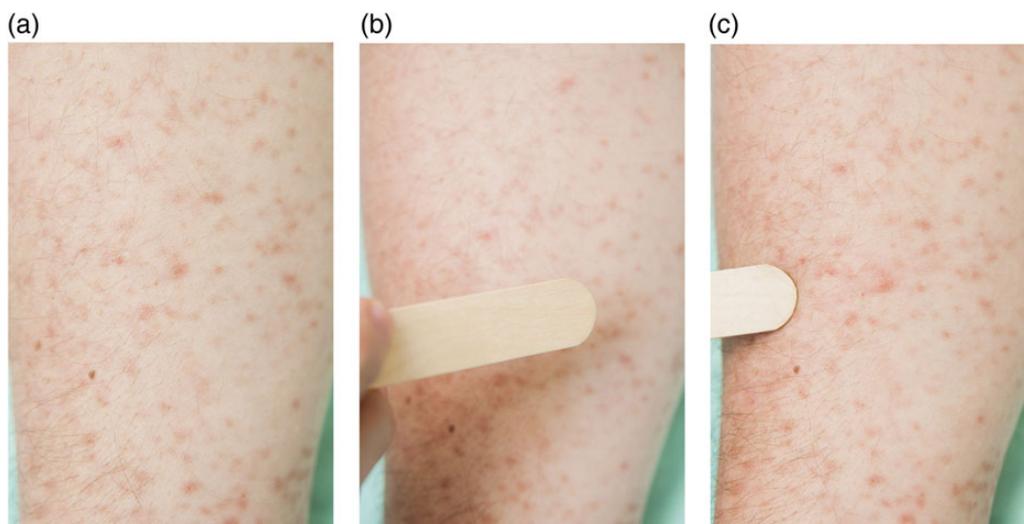


Figure 2: (a) Generalized hyperchromic lesions at presentation. (b) Tongue depressor. (c) Flare reaction after scratching with a tongue depressor.

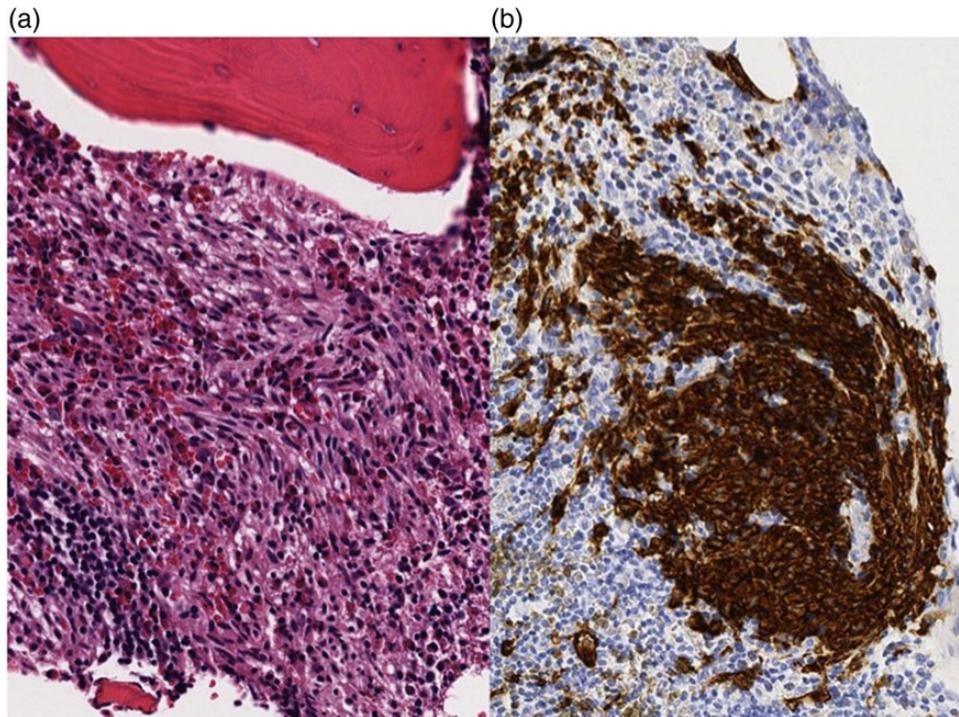


Figure 3: (a) Bone marrow biopsy with hematoxylin and eosin $\times 20$: a compact aggregate of atypical spindled MCs admixed with eosinophils, occasional histiocytes and plasma cells. (b) Bone marrow biopsy ($\times 20$): CD117 (c-kit) immunohistochemical stain highlights the MC aggregate.

the bone marrow or other extracutaneous organs with one minor criterion), or three minor criteria: (i) MC infiltrates $>25\%$ spindle-shaped cells, (ii) c-kit D816V mutation, (iii) expression of CD2 and/or CD25 on CD117-positive MCs and (iv) serum tryptase levels >20 ng/ml [6]. Indolent systemic mastocytosis is the most common form of systemic mastocytosis. This form of the disease has a stable and slowly progressive clinical course and appeared to be the situation for our patient; however, there is 1–5% chance of progression of more severe systemic forms of mastocytosis.

Treatment of this condition begins by avoidance of triggers of MC degranulation, preparation for treating possible anaphylactic episodes with self-injectable epinephrine and relief of MC mediator-related symptoms. First-line medications include antihistamines (both H1 and H2 blockers). Oral Cromolyn sodium is used to control gastrointestinal symptoms. Cyto-reductive therapy is reserved for invasive forms of the disease, such as systemic mastocytosis with hepatosplenomegaly [4].

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Vano-Galvan S, Alvarez-Towse I, De las Heras E, Morgado JM, Matito A, Sanchez-Munoz L, et al. Dermatoscopic features of skin lesions in patients with mastocytosis. *Arch Dermatol* 2011;**147**:932.
2. Kiorpelidou D, Gaitanis G, Bassukas ID. Darier's sign: a model for studying dermatographism. *Indian J Dermatol Venereol Leprol* 2008;**74**:271–72.
3. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statement on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;**37**:435–53.
4. Bains SN, Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. *Ann Allergy Asthma Immunol* 2010;**104**:1–10.
5. Patel LM, Lambert PJ, Gagna CE, Maghari A. Cutaneous signs of systemic disease. *Clin Dermatol* 2011;**29**:511–22.
6. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;**25**:603–25.