Telangiectasic mastocytosis with systemic sclerosis

Mastocytose télangiectasique associée à une sclérodermie systémique

Cutaneous mastocytosis is characterized by increased number of mast-cells in skin that release mediators causing pruritus, urticaria, and flushing [1]. Most cases of mastocytosis involve the skin, whereas systemic mastocytosis is less frequent. Systemic mastocytosis has been reported in association with other diseases such as haematological malignancies and solid tumours [2]. Systemic sclerosis (SSc) is a connective tissue disorder characterized by excessive collagen deposition in the dermis and internal organs and by vascular hyperreactivity and obliteration phenomena [3]. Although interleukin 4 (IL-4) level is of major importance in the pathophysiologic features of both mastocytosis and SSc, we know of only one case of an association of cutaneous mastocytosis and SSc [4]. Here we report on two patients with SSc who showed skin lesions associated with mast-cell infiltrates compatible with a diagnosis of cutaneous mastocytosis.

**Case Reports**

**Case 1**

A 32-year-old white woman of North African origin presented a 5-year history of Raynaud’s phenomenon, dysphagia, and sclerosis, as well as thickening of the skin on the face, trunk, and legs. The modified Rodnan skin score was 14/51 and mouth opening was reduced, with interincisor distance 25 mm. The patient complained of dysphagia and gastroesophageal reflux. She was positive for antinuclear antibodies (ANA), at 1:320 titers, with anti-Scl70 specificity. Capillaroscopy revealed giant capillaries, together with avascular areas. Results of electrocardiography and Doppler echocardiography, CT of the chest, and tests of systolic pulmonary arterial pressure and pulmonary function were normal. The diagnosis was diffuse SSc [5]. The treatment was calcium channel blockers and proton pump inhibitor. Digital ulcers were recurrent and were treated with several intravenous infusions of iloprost and finally oral bosentan. Six years later, the patient presented pigmented macules on her back that became red, swollen and pruritic when mechanically rubbed or when exposed to hot water. There was no evidence of dermographism. Over the next 3 years, new macules and turgid papules continued to appear on the skin of other areas, including the arms and thighs. At the 6-year visit, the Rodnan skin score was 16/51 and the interincisor distance 23 mm. The skin was thick, tight, and bound to underlying structures, and the patient had severe hand involvement and disability. Bony prominences of the hands had crusted ulcers. Well-delimited telangiectatic macules 0.5 to 1 cm in diameter were present on the trunk, back (figure 1a) and arms. The remainder of the physical examination was unremarkable. Blood tests gave normal results for haemoglobin (12.8 g/dl), leukocyte count (6.5 x 10^9/l), platelet count (335 x 10^9/l), glucose level (99 mg/dl), urea level (87 mg/dl), calcium level (2.35 mmol/l), and serum levels of albumin (38 g/l) and creatinine, as did urinalysis and liver function test. Values were increased for erythrocyte sedimentation rate (35 mm/h) and C-reactive protein (12 mg/l). Test results were positive for ANA, at 1:320 titers, with anti-Scl70 specificity and no anti-centromere pattern. Results were negative for anti–double-stranded DNA, -Sm, -La, -Ro, and -ribonucleic protein (RNP) antibodies. Contents of CH50, C3, and C4 complement components and immunoglobulin A, M, G and E were within normal ranges. Electrocardiography, chest X-ray and CT results were normal. Hematoxylin and eosin (H&E) staining for histology of a telangiectatic macule revealed a mild increase in number of mast-cells as confirmed by positive CD117 staining, which suggested cutaneous mastocytosis. Total tryptase level was 12.5 µg/l (normally < 15) and bone marrow biopsy results were normal. Treatment with oral antihistamines was started, with partial control of symptoms.

**Case 2**

A 64-year-old Caucasian man presented Raynaud’s phenomenon, polyarthritis, swollen fingers, dysphagia and telangiectasia of the face. ANA titers were > 1:1280 with an anticientromere pattern, and capillaroscopy revealed multiple giant capillaries. Results of electrocardiography, cardiac echocardiography, CT scan of the chest, and pulmonary function tests were normal. Thirty years later, the patient presented a 6-month history of pruriginous cutaneous lesions on his trunk. Physical examination revealed acrosclerosis and multiple brownish and telangiectatic circular macules < 1 cm in diameter on the trunk, shoulder and upper limbs (Fig. 1b). There was no evidence of dermographism. The remainder of the physical examination was unremarkable. Values for erythrocyte sedimentation rate and C-reactive protein level, full blood count, and serum creatinine level, and results of urinalysis and liver function test were all within normal ranges. Test results were positive for ANA, at 1:640 titers,
with an anticentromere pattern. Results were negative for antidouble-stranded DNA, -Sm, -Scl70, -La, -Ro and anti-RNP antibodies. Contents of CH50, C3, and C4 complement components and immunoglobulin A, M, G and E were within normal ranges. Results of electrocardiography, chest X-ray and CT scan of the chest were normal. Immunohistochemistry of a skin biopsy from a trunk lesion revealed increased number of mast-cells in the papillary dermis around blood vessels that expressed CD117 and thus suggested cutaneous mastocytosis (figure 2). Total tryptase level was 9.3 μg/l and bone marrow biopsy results were normal. Treatment with oral antihistamines was started, with adequate control of symptoms after 4 weeks.

Discussion
We present two cases of skin lesions associated with mast-cell infiltrates compatible with the diagnosis of cutaneous

Figure 1
Skin lesions compatible with the diagnosis of cutaneous mastocytosis
A. Well-delimited telangiectasic macules 0.5 to 1 cm in diameter on the back of a 38-year-old woman with systemic sclerosis (SSc) (case 1). B. Multiple brownish and telangiectasic circular macules < 1 cm in diameter on the shoulder and upper arm of a 64-year-old man with SSc (case 2).

Figure 2
Histology of skin biopsies compatible with the diagnosis of cutaneous mastocytosis
A. Hematoxylin and eosin staining of a lesion from the trunk of case 2 showing increased staining for mast-cells in the papillary dermis around blood vessels (magnification × 20). B. Mild increase in mast-cell staining confirmed by positive staining for CD117 (magnification × 20).
mastocytosis at 30 and 6 years after the onset of SSc. The diagnosis of cutaneous mastocytosis was suspected because both cases presented erythematous and telangiectatic macules associated with pruritus despite low evidence of telangiectasia, which is classically associated with SSc. Telangiectatic macules were located in non-sclerotic skin areas in an unusual location for scleroderma associated telangiectasia. The presence of excess number of mast-cells on biopsies reinforced an association of mastocytosis with SSc. We know of only one case of cutaneous mastocytosis associated with SSc [4], in a 48-year-old white woman who presented urticaria pigmentosa at least 15 years before the onset of SSc symptoms [4]; the authors suggested the coincidental occurrence of two rare skin diseases because of the lack of historical or theoretical basis to explain such an association at that time.

Although the pathogenesis of SSc remains unclear, attention has been drawn to the potential role of mast-cells [4,6] – bone-marrow-derived cells found primarily in the skin, gastrointestinal tract, and upper and lower respiratory tract [7] – in the disease. The cells exhibit numerous metachromatic granules containing preformed products such as histamine, heparin, chemotactic factors, and proteases [7]. Several lines of evidence support the involvement of mast-cells in the pathogenesis of SSc [8]: an increased number of mast-cells in the dermis of patients with SSc and mast-cell degranulation preceding dermal fibrosis in early diffuse SSc, as well as reduced degranulation with ameliorated skin thickening in late generalized disease [6]. Likewise, use of mast-cell stabilizers [9,10] or activators [11] in animal models of SSc ameliorated disease or reduced disease induction.

Calman integrated mast-cells in the three mechanisms of the well-accepted model of the pathogenesis of scleroderma: immunologic abnormalities, vascular alteration, and increased collagen synthesis by fibroblasts [12]. Increased mast-cell number in sclerodermatous skin may be secondary to IL-3 and/or IL-4 released by activated T-helper cells that are present in increased numbers in early inflammatory SSc. Endothelial-cell damage may then be mediated by mast-cell products, including histamine, proteases, and tumor necrosis factor-like factors. Fibroblast proliferation and enhanced synthetic activity may then be promoted by mediators such as growth factors released by platelets at sites of endothelial-cell injury, mast-cell mediators, and fibroblast growth factors released by endothelial cells, which when bound to heparin are protected against deactivation [12].

Because telangiectasia is common in patients with SSc and because the presence of mast-cells in telangectasic lesions has never been systematically investigated, we cannot rule out that the clinical presentation of our patients mimicked mastocytosis but was not really mastocytosis. Our cases may suggest a rare but possible association between SSc and mastocytosis that deserves further investigation of mast-cells in skin telangiectasia of patients with SSc and controls.

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References


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