

Cutaneous Mastocytosis in a Patient with Primary Sjögren's Syndrome

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ABSTRACT. Mast cells have been linked to rheumatoid arthritis (RA) and are essential to the pathogenesis of RA-like disease in a mouse model. We describe a 34-year-old woman who developed Sjögren's syndrome concurrently with telangiectasia macularis eruptiva perstans (TMEP), a rare form of cutaneous mastocytosis. The patient had sicca symptoms with an abnormal minor salivary gland biopsy and decreased salivary flow, peripheral neuropathy, an 80 pound weight loss, and a macular erythematous rash that exhibited superficial perivascular mast cell infiltrates on biopsy of lesional skin. This case further underscores the link between mast cells and the development of autoimmunity. (J Rheumatol 2006;33:1697-700)

Key Indexing Terms:

CUTANEOUS MASTOCYTOSIS
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MAST CELLS
AUTOIMMUNITY

Mast cells participate in innate immunity by virtue of their localization near portals of pathogen entry in mucosal membranes, serosal cavities, the dermis, and around blood vessels¹. They are enriched in rheumatoid pannus, and a pathogenic role has been suggested^{2,3}. It is unknown whether increased numbers of mast cells increase the risk of other autoimmune diseases. We describe a patient with telangiectasia macularis eruptiva perstans (TMEP), a rare form of cutaneous mastocytosis, who concurrently developed Sjögren's syndrome (SS), further underscoring a link between mast cells and autoimmunity.

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CASE REPORT

A 34-year-old female teacher was evaluated for sicca symptoms, rash, polyneuropathy, and weight loss. In August 2003 she developed paresthesias of the feet and hands. A nerve conduction study revealed an upper and lower extremity peripheral sensory neuropathy. In September 2003, she developed a macular erythematous rash exacerbated by stress or temperature changes. She also complained of nausea, early satiety, postprandial abdominal pain, and watery diarrhea 2-4 times per day and lost 80 pounds from June 2003 to April 2004. A D-xylose breath test, computed tomography (CT) scan with contrast of the chest, abdomen, and pelvis, endoscopy, and colonoscopy were normal. Serological tests for HIV and hepatitis B and C were negative.

In January 2004 she developed progressive fatigue, dry eyes, and dry mouth. Physical examination revealed dry oral mucosa, diffuse alopecia, an erythematous/violaceous macular rash of the extremities and trunk in a reticular pattern, and telangiectasias in sun-exposed areas of the chest and extremities (Figure 1). Darier's sign was absent. There was no lymphadenopathy, splenomegaly, or salivary gland enlargement. She had decreased sensation to light touch in a stocking-glove distribution.

Her blood count and chemistry were normal. Sedimentation rate was 49 and rheumatoid factor was weakly positive (1:2). Antinuclear antibodies were initially positive (1:160) but were later negative. Anti-Ro60 (SS-A) antibody ELISA (Varelixa, Scimedex, Denville, New Jersey, USA) was positive and anti-Ro60 antibodies also were detected by radioimmunoprecipitation⁴. Schirmer test was normal (right eye 8 mm, left eye 20 mm). A minor salivary gland biopsy revealed collections of ≥ 50 lymphocytes and plasma cells per 4 mm² of salivary gland tissue and yielded a focus score of 4 (Figure 2A-D). At high power, the infiltrate was predominantly lymphocytic, although plasma cells were present (Figure 2E). Occasional mast cells also were scattered within the inflammatory infiltrate. The glandular tissue exhibited relatively normal acinar architecture, and small scattered areas of mild fibrosis were seen. This was consistent with SS. On unstimulated whole sialometry she produced 0.08 ml/minute (< 0.1 ml/min is considered hyposalivation).

Biopsy of affected skin showed mild hyperkeratosis and dermal telangiectasias with a sparse superficial perivascular lymphocytic infiltrate on hematoxylin and eosin staining (Figure 3A-B). Tryptase staining showed increased numbers of mast cells (> 15 tryptase cells per high power field) consistent with a diagnosis of TMEP (Figure 3C). Tryptase staining of salivary



Figure 1. Appearance of the rash. Reticular violaceous/erythematous skin lesions on the arms.

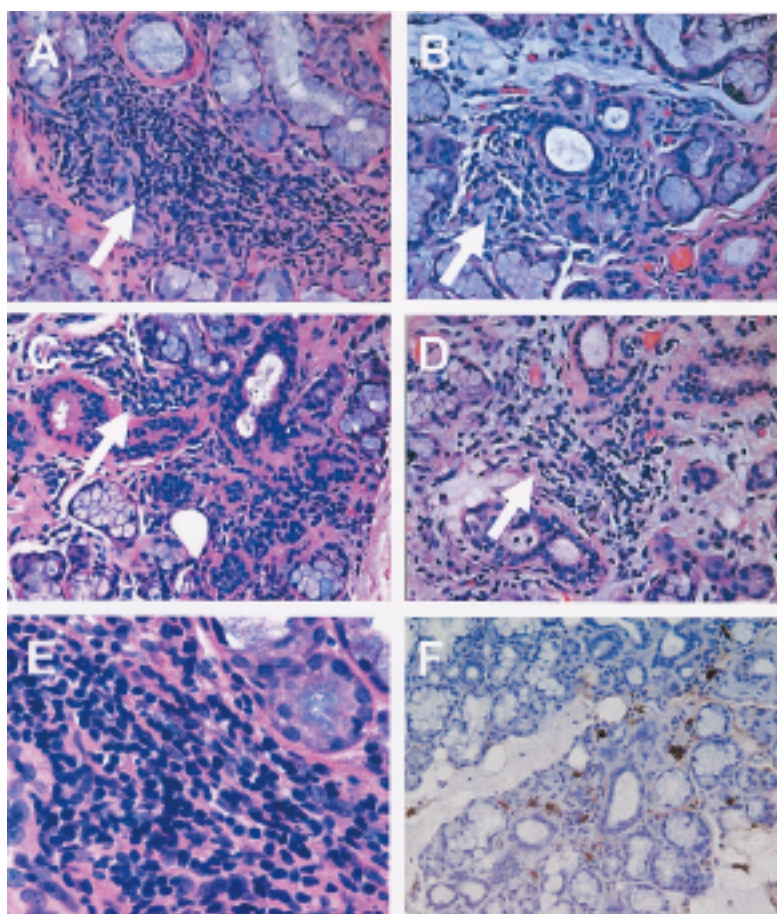


Figure 2. Minor salivary gland biopsy. A-D: hematoxylin and eosin staining showing lymphocytic/plasmacytic foci containing > 50 lymphocytes (arrows), focus score 4 ($\times 400$). E: high power (final magnification $\times 630$) showing predominantly lymphocytic infiltrate with occasional plasma cells. F: Tryptase staining of minor salivary gland tissue showing mast cells (brown).

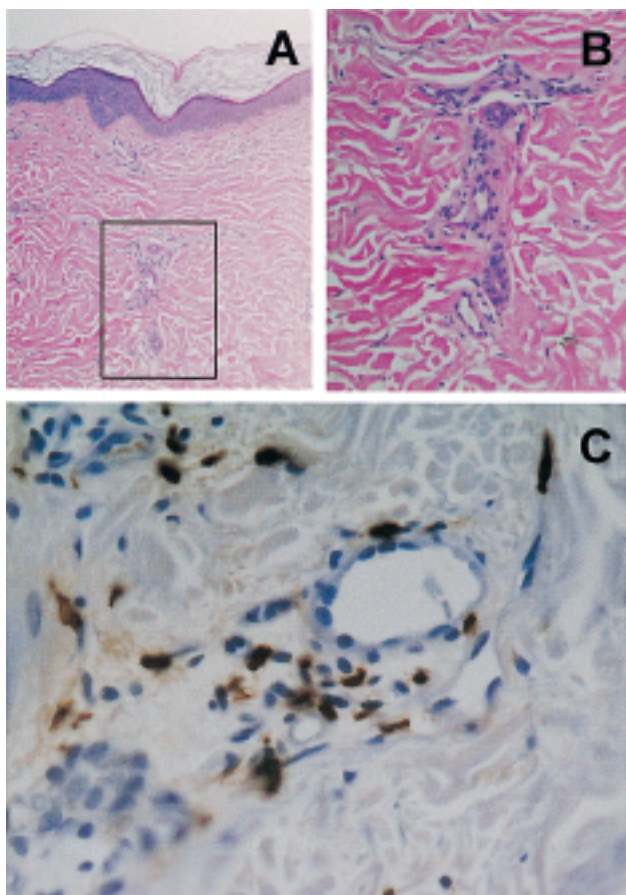


Figure 3. Skin biopsy. A: hematoxylin and eosin staining. B: enlargement of boxed region (Panel A) showing a dermal perivascular lymphocytic and mast cell infiltrate. C: Tryptase staining showing a collection of > 15 perivascular mast cells.

gland tissue also showed mast cells (Figure 2F), but these were fewer in number and salivary gland biopsies from other patients with SS or chronic sialoadenitis exhibited similar findings (not shown).

Bone marrow aspirate and core biopsy did not show atypia, increased numbers of mast cells, or blasts. Immunochemical staining for c-Kit (CD117) did not reveal mast cell infiltration. Flow cytometry did not reveal increased numbers of c-Kit-positive mast cells and the mast cells were CD2⁺/CD25⁻. She was treated with loratidine 10 mg daily and ranitidine 150 mg twice a day with a reduction in the frequency of her diarrhea and an 8 pound weight gain.

DISCUSSION

We describe a patient with the unusual association of primary SS with TMEP, a form of cutaneous mastocytosis. A variety of mast cell disorders are recognized^{5,6}. When limited to the skin, it is classified as cutaneous mastocytosis; with extracutaneous involvement, it is termed systemic mastocytosis. Cutaneous mastocytosis includes nodular cutaneous mastocytosis, maculopapular cutaneous mastocytosis, and diffuse cutaneous mastocytosis⁶. TMEP is a rare variant of maculopapular cutaneous mastocytosis restricted to adults and characterized by generalized, irregular, red to brown telangiectatic macules and increased numbers of mast cells around capillaries and venules of the superficial vascular plexus⁶.

Our patient's macular rash was consistent with TMEP (Figures 1 and 3). Although mast cells are normal residents of dermis, > 15 mast cells per high power field is abnormal⁵. Although usually thought to be purely cutaneous, systemic involvement of TMEP is not infrequent⁶. The 80-pound weight loss, diarrhea, early satiety, nausea, abdominal discomfort, and paresthesias are suggestive of systemic (gastrointestinal, nervous system) involvement, but confirmatory biopsies were unavailable.

The close temporal relationship between the onset of TMEP and SS is unique. Our patient meets criteria for primary Sjogren's syndrome (oral and ocular symptoms, minor salivary gland biopsy showing > 1 focus per 4 mm², decreased salivary flow, anti-Ro60 autoantibodies)⁷. There is a previous case report linking systemic mastocytosis with SS⁸, but an association with TMEP has not previously been reported. In SS, increased numbers of mast cells have been noted in the salivary glands^{9,10} and this has been suggested to correlate with progression to fibrosis and fatty infiltration¹¹. Mast cells are present in the extraosseous pannus and intraosseous invasive tissue of rheumatoid arthritis (RA) and higher mast cell counts are associated with more severe synovitis^{2,3}. Mast cells also are essential for the pathogenesis of joint disease in the K/BxN antibody-mediated mouse model of RA and it has been suggested that they are activated by articular immune complexes in an Arthus-like reaction, causing release of tumor necrosis factor- α (TNF- α) and other mediators from mast cell granules¹².

It is unclear whether similar mechanisms are involved in Sjogren's syndrome. There is little evidence that TNF- α mediates SS¹³, but activated mast cells also release interleukin (IL)-6, which is produced at high levels in SS¹⁴. IL-6 production by atrial myxomas and in Castleman's disease is associated with autoantibody production^{15,16}. In view of the role of IL-6 in B cell differentiation and immunoglobulin secretion, it is tempting to speculate IL-6 produced by mast cells might have played a role in the onset of autoantibody production and SS in this patient.

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