Mastocytosis and Sjögren's syndrome

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Abstract

A 61 year old man with dryness of the eyes and mouth, constitutional and musculoskeletal symptoms is described. A diagnosis of fibromyalgia with Sjögren's syndrome was made elsewhere. Further examination, however, disclosed diffuse mast cell infiltration in several organs, including the labial accessory salivary glands.

Sjögren's syndrome commonly results from diminished lachrymal and salivary gland function due to autoimmune exocrinopathy. Additionally, this syndrome may also be secondary to other diseases affecting the salivary glands, such as haemosiderosis, sarcoidosis, AL amyloidosis, and large granulated T cell lymphocytosis.¹⁻⁴

Case report

A 61 year old man was admitted for observation of a broad range of complaints and recently diagnosed paraproteinaemia. He had been well until five years before admission when yellow-brownish papules started to appear, mainly on his trunk and upper legs. From that time he progressively experienced constitutional symptoms with diffuse symmetrical bone and muscle pains, accompanied by dryness of mouth, throat, and eyes. Additionally, he had periodic diarrhoea and postprandial vomiting. Elsewhere a diagnosis of fibromyalgia was made and keratoconjunctivitis sicca was confirmed by an ophthalmologist, who prescribed methylcellulose eye drops.

On examination there were facial telangiectasias and yellow-brownish maculae, and maculopapular skin lesions predominantly on his back and upper legs. Darier's sign (urtication and itching on rubbing) was positive. Palmar erythema was noted without spider naevi. The mouth and pharynx were dry and reddish. The wrists metacarpus, and ankles were painful on palpation but did not show other abnormalities. A Schirmer test confirmed decreased tear production.

Laboratory investigation showed blood count, urea, electrolytes, and results of liver function tests were normal. Protein electrophoresis indicated an IgG λ monoclonal component of 9 g/l. A test for Bence Jones proteinuria was negative. Thyroid function, vitamin B-12, folic acid, serum iron, ferritin, and immunoglobulins IgA, IgM, β_2 microglobulin, and cryoglobulin were normal. Antinuclear antibodies, rheumatoid factors, antibodies to SS-A, SS-B, double stranded DNA, and to salivary

glands, thyroid globulin, and microsomes were all negative.

Skeletal x ray examination showed osteoporosis and a circumscribed lesion in the left radius with thinning of the cortex and endosteal scalping. A bone marrow aspirate and biopsy showed normal haematopoiesis and a slight increase in plasma cells (5%), which seemed to be monoclonal (cytoplasmatic IgG λ) on immunophenotyping. There was a massive mast cell infiltration, however, especially of the peritrabecular and perivascular areas. Biopsy specimens taken from the hypopharynx, stomach mucosa, and labial glands all demonstrated an increased number of mast cells. Skin biopsy specimens of the brownish papules showed the typical pattern of urticaria pigmentosa with mast cell infiltration. A 24 hour urine collection showed an increase of histamine metabolites. *N*-Methylhistamine was 0.27 mmol/mol creatinine (normal 0.03-0.16 mmol/mol creatinine) and *N*-methylimidazoleacetic acid was 3.4 mmol/mol creatinine (normal 0.40-2.4 mmol/mol creatinine).

A diagnosis of systemic mastocytosis was made based on tissue infiltration of mast cells in various organs and increased values of histamine metabolites in the urine.

Discussion

Systemic mast cell disease is rare, and is characterised by abnormal proliferation of mast cells that infiltrate the bone marrow, skin, liver, gastrointestinal tract, and lymph nodes.⁵ Most patients have typical skin lesions called urticaria pigmentosa. The symptoms are often vague and affect several organic functions. Often, patients also have psychiatric complaints.⁷ Most patients have constitutional symptoms, such as tiredness, weight loss, moderately raised temperature, and night sweats. Abdominal pains, diarrhoea, nausea, and vomiting are commonly described.⁵ Additionally, there may be flushes, syncope, palpitations, and hypertension. Most symptoms are due to mediator release from the increased number of mast cells; other symptoms might arise from direct tissue infiltration by mast cells. Degranulation releases granule associated mediators, including eosinophil and neutrophil chemotactic factors, heparin, and a number of enzymes such as tryptase, aryl sulphatase A, glucuronidase, and peroxidase. Other mediators, such as prostaglandin D₂ and leukotrienes, are derived from the arachidonic acid metabolism.

Remarkable in most patients with systemic mast cell disease are the bone disorders. Severe osteoporosis is most common and is often the

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first manifestation of the disease.⁸⁻¹⁰ Radiographic abnormalities are found in more than 50% of all patients with systemic mast cell disease, showing diffuse demineralisation, osteosclerosis, or circumscribed lucent areas.⁵ Often these bone lesions are misdiagnosed as metastatic carcinoma, multiple myeloma, or Paget's disease of bone. Scintigraphic bone scans can be useful in detecting osseous lesions of systemic mast cell disease.¹¹ The cause of the bone disorders remains unclear. Release of heparin from the mast cells, which can cause bone resorption, may play a part.

The clinical picture of systemic mast cell disease can easily be mistaken for fibromyalgia. Chronic generalised aches, chronic fatigue, sleep disturbances, abdominal complaints with a lack of physical symptoms, and laboratory abnormalities may easily mislead the rheumatologist. Sicca symptoms with a positive Schirmer's test are not uncommon in patients with fibromyalgia.^{12 13}

As far as we know Sjögren's syndrome in association with systemic mast cell disease has not yet been described. Direct infiltration of tear and salivary glands by mast cells probably causes the decreased glandular secretion, although an effect from the mediators released by mast cells cannot be completely excluded. In our patient extensive mast cell tissue infiltration was demonstrated with a toluidine blue stain of labial glands and hypopharynx biopsy specimens.

The case described here indicates that Sjögren's syndrome can be associated with systemic mast cell disease. Lack of clinical awareness and the absence of well defined histopathological features of the disease can delay its diagnosis. When systemic mast cell disease is suspected a bone marrow aspiration and biopsy specimen should be examined for

increased mast cell infiltration. Increased excretion of histamine metabolites in the urine helps to confirm the diagnosis.^{14 15}

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