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 lacrimal 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 macules, 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 IgGκ 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, β₂microglobulin, 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 circumscript lesion in the left radius with thinning of the cortex and endosteal scalping. A bone marrow aspirate and biopsy showed normal haemopoiesis and a slight increase in plasma cells (5%), which seemed to be monoclonal (cytoplastic IgGκ) on immunophenotyping. There was a massive mast cell infiltration, however, especially of the peri trabecular 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 6 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 6 Additionally, there may be flushing, 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...
first manifestation of the disease.\textsuperscript{4,10} Radiographi
cal abnormalities are found in more than
50\% of all patients with systemic mast cell
disease, showing diffuse demineralisation,
osteosclerosis, or circumscribed lucent areas.\textsuperscript{4,11} 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.\textsuperscript{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 rheuma-
tologist. Sjogren’s syndrome is a common
manifestation of the disease.\textsuperscript{12,13}

As far as we know Sjogren’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
Sjogren’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.\textsuperscript{14,15}

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