Systemic mastocytosis: a rare cause of osteoporosis and its response to bisphosphonate treatment

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Mastocytosis comprises a heterogeneous group of disorders of mast cell proliferation. Infiltration of multiple organs by mast cells may occur, including skin and bone, with cutaneous and systemic variants being well described. There are few reports of the treatment of osteoporosis, a secondary manifestation of systemic mastocytosis (SM).[1–3] We undertook a retrospective analysis of six patients with osteoporosis associated with SM treated with bisphosphonates.

CASE REPORTS

The mean age of the patients was 58 years (range 40–70) and the mean duration of SM was 8 years (range 3–13). All patients had a past history of urticaria pigmentosa and had presented to their general practitioner with back pain. Four patients had vertebral crush fractures on plain radiography. Isotope bone scans in the remaining two patients showed diffuse skeletal uptake consistent with marrow infiltration. Bone marrow biopsy in all patients confirmed mast cell infiltration. All patients had mast cell mediator related symptoms (flushing, wheezing, diarrhoea with abdominal pain, pruritus, bone pain) and raised total serum tryptase levels persistently >20 ng/ml. This fulfilled the diagnostic criteria for SM, defined by multifocal histological lesions in the bone marrow or other extracutaneous organs (major criteria) together with cytological and biochemical signs (minor criteria) of systemic disease.[4] Tryptase levels correlate with the clinical severity of SM,[5] and we used this to monitor disease activity.

Treatment was started with bisphosphonates (annual intravenous pamidronate followed by alendronate in five patients, alendronate only in the sixth patient). No further fractures developed despite absence of specific treatment for mast cell proliferation. All patients had a subjective improvement in pain after bisphosphonate treatment. Hologic bone mineral density (BMD) measurements were assessed at baseline and at 1–2 yearly intervals thereafter. BMD in the lumbar spine rose in all patients from baseline; two patients (Nos 1 and 2) were excluded owing to multiple lumbar vertebral fractures. Total hip BMD rose in three patients and stabilised in the other three (table 1).

DISCUSSION

Disorders of mast cells, derived from the multipotent haematopoietic stem cell are rare. Cutaneous mastocytosis without systemic involvement manifests in childhood as urticaria pigmentosa and spontaneous regression occurs during puberty. Symptoms of SM are related to the release of mast cell mediators, including histamine, prostaglandins, leucotrienes, and proteases, with bone pain occurring frequently. The radiological findings in SM include diffuse osteoporosis with vertebral fractures and/or a combination of osteosclerotic and osteolytic lesions, primarily affecting the axial skeleton and ends of long bones. Solitary lesions (mastocytomas) may cause localised pain.

The cellular and pathophysiological mechanisms leading to osteoporosis in SM are poorly understood. Mast cells infiltrating bone marrow may have an inhibitory effect on the coupling of bone formation and resorption, with the balance in favour of the latter. It is unlikely that bone resorption is caused directly by mast cell release of heparin, prostaglandin D_2, and tryptase.[1 6]

SM has been reported to account for a greater than expected cause of osteoporosis in the younger population.[7] Indeed, back pain secondary to osteoporotic vertebral fractures may be the major presenting symptom of SM. BMD stabilised without the occurrence of further fractures in our patients. Fracture reduction is due not only to inhibition of osteoclasts by bisphosphonates but their ability to reduce the activation frequency and birth rates of new bone remodelling units and to enhance osteon mineralisation.[8] Musculoskeletal pain in mastocytosis may be present in up to 28% of patients and is difficult to manage.[9] Interestingly, our patients reported improvement in bone pain after bisphosphonate treatment.

In conclusion, SM, although rare, should be included in the differential diagnosis of idiopathic osteoporosis because of its

Table 1 Demographics

	Patient No					
	1	2	3	4	5	6
Age	70	67	54	58	40	61
Sex	F	F	M	F	F	F
BM biopsy	Mast cell infiltration	10% Mast cell infiltration	Focal clusters of mast cells	Mast cell infiltration	Mast cell infiltration	20% Mast cell infiltration
Treatment duration with IV pamidronate	1992–2000 annual doses	1990–2000 annual doses	1994–1998 annual doses	2000 single dose	Not treated	2001–2003 three doses
Cumulative dose of pamidronate (mg)	555	915	360	90	Not treated	270
Year alendronate started	2000 until current	2001 until current	1998 until current	2001 until current	2001 until current	2001 for 6 months
L1-4 spine T score before treatment	−1.49	−4.05	−4.54	−4.07	−2.8	−0.76
L1-4 spine T score in 2003	−2.0	−3.27	−3.34	−3.29	−3.0	−0.45
Total hip T score before treatment	−1.7	−3.5	−3.29	−1.16	−1.8	+0.23
Total hip T score in 2003	−1.4	−3.07	−2.36	−1.17	−1.8	+0.23

significant morbidity. Bisphosphonates are effective in SM for osteoporosis and have a role in the associated refractory bone pain.

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Frostbite arthritis

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A 46 year old black woman, born in Haiti, was admitted in 1999 owing to bilateral and symmetric arthritis of the hands. Her past history was unremarkable. She had lived in New York in the 1970s, where she sustained an episode of severe frostbite in 1977 while staying outside for 1 hour at a temperature of −20°C without protection. Frostbite affected all fingers but not the thumbs, requiring admission to hospital for 11 days (amputation of some fingers was discussed at this time).

She had complained about arthritis affecting the interphalangeal (IP) joints since 1994, without extra-articular involvement or fever. Progressive joint deformations appeared at this time. Clinical examination was normal except for proximal IP joint deformation.

Routine laboratory tests, immunological tests (antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, complement), seric tests (HIV, HTLV-1, TPHA-VDRL), proteins, and haemoglobin electrophoresis were normal or negative.

Plain radiographs of the hands showed an erosive arthritis with subchondral osteosclerosis and large punched-out cystic defects affecting all proximal and some of the distal IP joints and metacarpophalangeal joints (fig 1). A technetium-99m scintigraphy showed early and massive increased uptake of the radiologically affected joints. A radiographic survey of the skeleton and pulmonary *x* ray findings were normal. A synovial biopsy and a bone biopsy of a lytic lesion of the second phalange of the third left finger were non-conclusive.

Treatment with non-steroidal anti-inflammatory (NSAIDs) drugs was unsuccessful. Significant clinical improvement was obtained with clodronic acid, 800 mg twice a day. In 2004, radiographs of hands showed a moderate extension of punched-out cystic defects, without progression of joint deformations. Immunological tests remain negative.

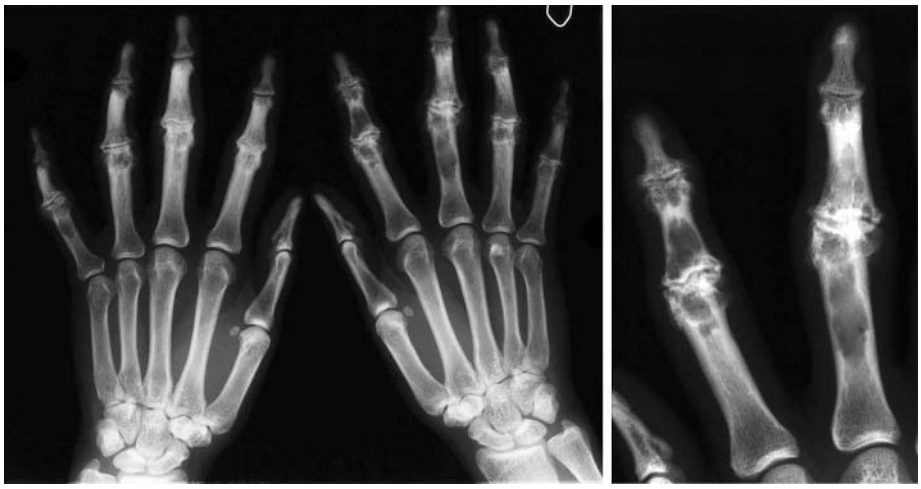

Figure 1 Erosive arthritis with subchondral osteosclerosis and large punched-out cystic defects affecting all proximal and some of the distal IP joints.