Osteoporosis with vertebral fractures in young males, due to bone marrow mastocytosis: a report of two cases

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ABSTRACT

Male osteoporosis in young patients is an unusual condition, always worth investigating as a possible manifestation of secondary osteoporosis. Mastocytosis is a clonal disorder of mast cells with heterogeneous presentations; when pathologic cells accumulate only in the bone marrow, vertebral fractures and systemic osteoporosis may represent the sole clinical presentation at the onset of the disease. We report on two young male patients who came to our attention because of multiple dorsal and lumbar vertebral fractures, with no other signs of systemic mastocytosis (SM). Lumbar and femoral dual x-ray absorptiometry showed reduced bone mineral density values; biochemical investigations did not report significant anomalies, suggestive of secondary osteoporosis. One of the patients underwent iliac crest bone biopsy, which was not diagnostic. A vertebral intralesional CT-guided bone biopsy was performed in both patients, which allowed the diagnosis of SM. Our experience pointed out that bone biopsy still remains the gold standard for the diagnosis of SM. However, iliac crest biopsy can be not significant because of circumscribed bone marrow involvement: in these cases only intralesional bone biopsy could be diagnostic.

Introduction

Male osteoporosis in young patients is an unusual condition, always worth investigating as a possible manifestation of secondary osteoporosis. Mastocytosis is a clonal disorder characterised by abnormal proliferation of pathologic mast cells which accumulate in various tissues, including the bone marrow, resulting in systemic osteoporosis; vertebral fractures may represent the sole onset presentation of this disease. Here we report on two young male patients who came to our attention because of secondary osteoporosis due to systemic mastocytosis (SM).

Case reports

Case one

This 36-year-old white man was referred to our Centre because of persistent back pain. He had a 10-year history of multiple vertebral non-traumatic fractures. He had been evaluated at another hospital; screening for secondary osteoporosis related to endocrinopathies, malabsorption, epathopaty, drugs assumption or inherited diseases was reported to be negative as was bone metabolism blood chemistry. Bone mineral density (BMD) of the lumbar spine, measured by dual x-ray absorptiometry (DXA) (QDR 4500; Hologic), was markedly reduced (T-score -4.46, BMD 0.625 g/cm^2), but total femoral BMD was within normal range for age and sex (T-score -0.74, BMD 0.975 g/cm^2).

On admission, both history and physical exam were not clearly suggestive of SM: no episodes of diarrhea, tachycardia, flushing or syncope were reported and no skin abnormalities, lymphadenopathy or hepatosplenomegaly were observed. Blood chemistry was unrelevant with blood count and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum electrophoresis, renal, liver, thyroid and gonadal function all within the reference range as were parameters of calcium and bone metabolism: serum calcium, 8.9 mg/dl (normal, 8.4–10.2); phosphate, 2.6 mg/dl (2.5–4.6); urinary calcium excretion, 100 mg/24h; ALP, 48 U/l (32-92); PTH, 4.1 pmol/l (1.3–7.6); 25-hydroxyvitamin D, 40 mmol/l (25–125). Serum triptase levels were slightly elevated (9.5 ng/ml with normal values of 0.0–5.0).

On plain radiographs of the spine, all lumbar vertebrae appeared severely deformed while multiple dorsal vertebrae – severe T11, T9 and T7 and moderate T3 – middle fractures were observed.

BMD of the lumbar spine, measured by DXA (QDR 4500; Hologic), was significantly reduced (T-score -3.1, BMD 0.775 g/cm^2) despite being overestimated for the presence of vertebral deformities in all lumbar vertebrae, but the total femoral (T-score -0.9, BMD 0.903 g/cm^2) and femoral neck BMD (T-score -0.6, BMD 0.851 g/cm^2) were normal.

A CT-guided L3 intralesional bone biopsy was performed which showed a decrease in bone volume, trabecular number and thickness. A bone marrow core biopsy revealed multiple foci of mast cells, accompanied by lymphocytes, histiocytes and eosinophils,

with a normal haematopoietic cell count; mast cells showed an atypical spindle shape morphology and the immunophenotypical analysis revealed a pattern (c-kit +, CD25 +, tryptase +, CD45 -) diagnostic for mastocytosis (1) (Figs. 1-3).

Osteoporosis was managed with oral administration of alendronate (70 mg/ week) and calcium and 25-hydroxyvitamin D supplementation; at a 12-month follow-up no further fractures were recorded nor a worsening of pre-existing fractures was observed on plain radiographs of the spine.

Case two

This 39-year-old white man presented to our hospital with a 3-year history of low back pain and the finding of multiple spontaneous vertebral fractures. His previous history was uneventful.

He did not report episodes of flushing, syncope, diarrhea or tachycardia; skin abnormalities, lymphadenopathy and/ or hepatosplenomegaly were not detected on physical examination. Blood chemistry (complete blood cell counts, ERS, CRP, serum electrophoresis, renal, liver, thyroid and gonadal function) were all within normal range as were alkaline phosphatase, calcium and phosphate metabolism and PTH; serum 25-hydroxyvitamin D values were only slightly reduced (22 mmol/l; normal range, 25-125).

Plain radiographs of the spine showed multiple severe vertebral fractures: T7, T8, T10, T12, L3, L4 and L5. BMD, measured by DXA (QDR 4500; Hologic), yielded conflicting results due to the presence of L3 and L4 fractures: it was only slightly reduced at the total lumbar spine (T-score -2.2, BMD 0.871 g/cm^2), but markedly reduced when L2 only was measured (T-score -3.3, BMD 0.732 g/cm^2); total femoral (T-score -2.4, BMD 0.671 g/cm^2) and femoral neck BMD (T-score -2.2, BMD 0.627 g/cm^2) were also reduced.

Bone marrow examination (iliac crest biopsy and aspirate) showed a non-specific pattern of moderate mast cell infiltrate and diffuse osteopenia. The patient then underwent L5 vertebral biopsy which was diagnostic for SM: multiple paratrabecular and perivascular aggregates of spindle-shaped mast cells, which stained positive for triptase, CD117 and CD25, were observed (1).

The patient was started on alendronate 70 mg/ week per os plus calcium and 25-hydroxyvitamin D supplementation, with significant improvement both in back pain and DXA findings:

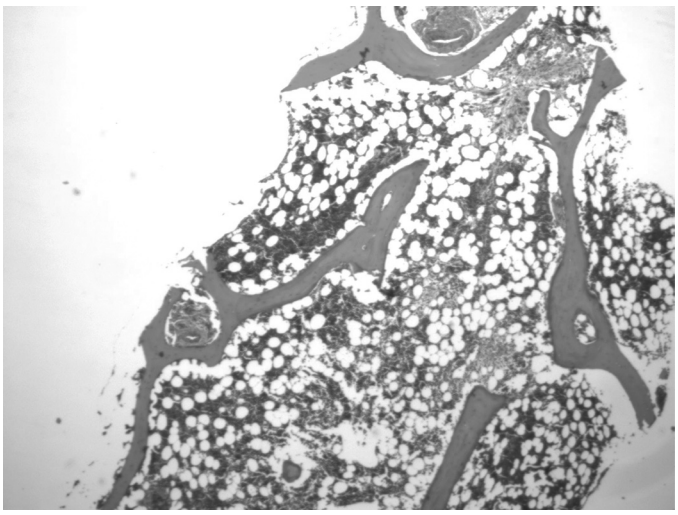

Fig. 1. A bone marrow core biopsy showing smalls multiple, well demarcated foci of mast cells with a tendency to paratrabecular and perivascular locations. Mast cells are accompanied by lymphocytes, histiocytes and eosinophils.

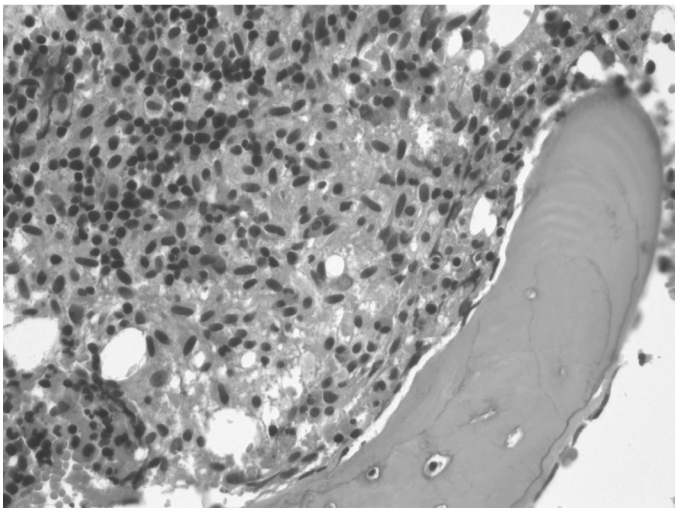

Fig. 2. Large sheets of atypical, predominantly spindle cells with pale and clear cytoplasm.

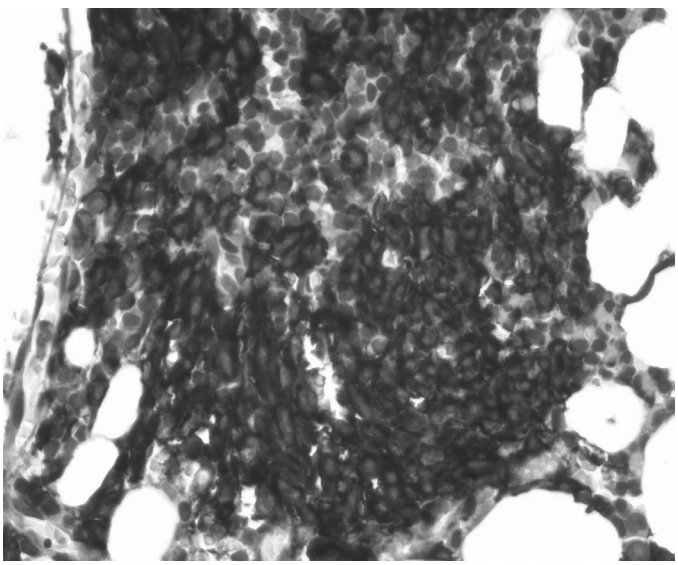

Fig. 3. Inset: mast cells are strongly positive for CD117 (c-Kit) and for tryptase.

total femoral BMD increased by 7.4% at one-year follow-up (from a BMD of 0.671 to 0.721 g/cm^2). No further vertebral fractures developed as showed by a further x-ray evaluation.

Discussion

Mastocytosis is a clonal disorder of bone marrow origin, characterised by abnormal growth and proliferation of mast cells and their CD34+ progenitors; its heterogeneous presentation is related to the infiltration of clonal mast cells in one or more organs and the release of different biological mediators (1). The diagnosis of SM is most commonly established by histologic and immunohistochemical examination of a standard bone marrow specimen (iliac crest aspirate and biopsy), since the bone marrow is easily accessible for biopsy and often involved in adult SM (2). Diagnostic WHO criteria for mastocytosis include one major criterion (multifocal compact tissue or bone marrow infiltration by mast cells) and four minor criteria: prominent spindling of mast cells, atypical immunophenotype of mast cells with coexpression of CD2 and/or CD25, point mutations of the c-kit proto-oncogene, and persistently elevated serum tryptase level (>20 ng/ml). To establish the diagnosis of SM, at least one major and one minor criterion, or at least three minor criteria, have to be fulfilled (1).

Up to 80% of patients show radiological signs of bone involvement which is classified into two main categories, diffuse and circumscribed; both may take the form of either osteosclerotic lesions of the axial skeleton – or, less commonly, of the long bones – or porotic lesions, with vertebral fractures occurring in approximately 16% of patients (3, 4).

Diffuse osteoporosis is frequently observed in SM: a low bone mass has been found in over a third of cases (5), with an incidence observed of 33% (6), and a high prevalence of osteopenia is described in bone biopsies from patients diagnosed with SM (7). Osteoporosis may be the sole presenting sign of abnormal mast cells proliferation in the bone marrow, in which case diagnosis relies on histological examination of a bone marrow biopsy (5, 8).

The role of mast cells in osteoporosis has been extensively studied. An increased number of mast cells around endosteal surfaces of bone in rats with experimentally induced secondary hyperparathyroidism and rickets was first described by Urist and Mc Lean in 1957 (9). A bone marrow containing an excessive number of mast cells was observed in patients with osteoporosis of aging (10), in primary (11) and secondary hyperparathyroidism due to malabsorption or chronic renal failure (12), and in postmenopausal osteoporosis (13). Different assumptions about the mechanism of bone loss related to mast cells proliferation have been proposed; the role of biologic products derived from mast cells – like histamine, heparine and cytokines like IL-6 – on osteoblasts and osteoclasts proliferation and activity has been documented and is continuously investigated (14-16).

The presence of end-organ dysfunction distinguishes indolent from aggressive SM (17). First-line treatment with either cladribine or interferon-alfa is the currently available therapy for patients with aggressive SM, with response rates in the range of 50% (17). However, due to the sole bone involvement, our patients were considered as having the indolent form of SM and therefore were not considered eligible to these treatments. They underwent standard treatment for osteoporosis with bisphosphonates, whose efficacy on relief of pain, BMD parameters and recurrence of fractures is well documented in this setting (3, 18-21).

Despite its low incidence in the general population, Delling describes an overall prevalence of SM of 1.25% in bone biopsies of patients diagnosed with osteoporosis, but a prevalence of 2.25% in osteoporotic patients younger than 45 (7). Therefore, the presence of SM should always be suspected, and ruled out, in patients with unexplained osteoporosis, even in absence of clinical signs or symptoms typical of this disease. Male osteoporosis, especially in young people, is a rare condition that always needs to be investigated for the presence of secondary causes (22). Unfortunately, common laboratory tests for first and second level screening of secondary osteoporosis are not efficient in identifying SM for the lack of serological markers usually available in medical practice and specific for this disease; dosage of serum tryptase or urinary excretion of N-methylhistamine, even if proved to be efficient non-invasive tests for the diagnosis of SM, have limited laboratory availability (5, 23). Bone marrow aspirate and biopsy still remain the gold standard for the diagnosis of SM and they must be performed every time other investigations have failed to identify an adequate cause for osteoporosis. Our experience pointed out that, in cases of SM limited to the bone, iliac crest biopsy can be not significant because of circumscribed bone marrow involvement: in these circumstances only intralesional bone biopsy could be diagnostic, so that it becomes mandatory.

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