Netherlands
The Journal of Medicine

CASE REPORT

Mast cell leukaemia presenting with multiple osteoporotic fractures in an elderly woman

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ABSTRACT

Osteoporotic fractures in elderly women are mainly due to postmenopausal bone loss but can sometimes be caused by a disabling haematological disease. We describe an 84-year-old woman suffering from multiple osteoporotic fractures as a manifestation of mast cell leukaemia. Mast cell leukaemia is a rare form of systemic mastocytosis with a poor prognosis and very few therapeutic options. Osteoporotic fractures have seldom been reported as its initial manifestation.

KEYWORDS

Secondary osteoporosis, vertebral fractures, mastocytosis, mast cell leukaemia

What was known about this topic?
Systemic mastocytosis is a rare disease of which a mast cell leukaemia is seldom seen. It results from a clonal proliferation and an accumulation of pathological mast cells in bone marrow and / or other extracutaneous tissues. Systemic mastocytosis frequently leads to osteoporosis because of the devastating effects that the mast cell mediators, such as histamine, heparin and cytokines (TNF, IL-6, TGF-beta), exert on bone turnover.

What does this add?
This is the first recorded case in which progressive vertebral fractures were the presenting symptom of mast cell leukaemia in a postmenopausal woman; the diagnosis could have been made earlier if many characteristic symptoms of mast cell disease had been recognised. Recognition of these symptoms is essential for specific diagnostic testing as these are not part of the general screening for secondary causes of osteoporosis.

INTRODUCTION

Osteoporosis is a common disease in postmenopausal women affecting approximately one-fifth of elderly women. It is characterised by a low bone mass and skeletal fragility, coupled with an increased fracture risk.[1] Osteoporotic fractures directly impair mobility and quality of life. In the majority of ageing women osteoporotic bone loss is related to oestrogen deficiency and advanced age, denoted as primary osteoporosis. In contrast, secondary osteoporosis may arise at any age and equally affects both men and women. This form results from several well-identified chronic predisposing disorders such as hypogonadism, gastrointestinal, haematological and rheumatological diseases, or prolonged use of medications such as glucocorticoids.[2] A secondary cause of osteoporosis can be identified in about 20-30% of postmenopausal women and 50% of men. In this report we describe a rare cause of secondary osteoporosis in an elderly woman with multiple osteoporotic fractures.

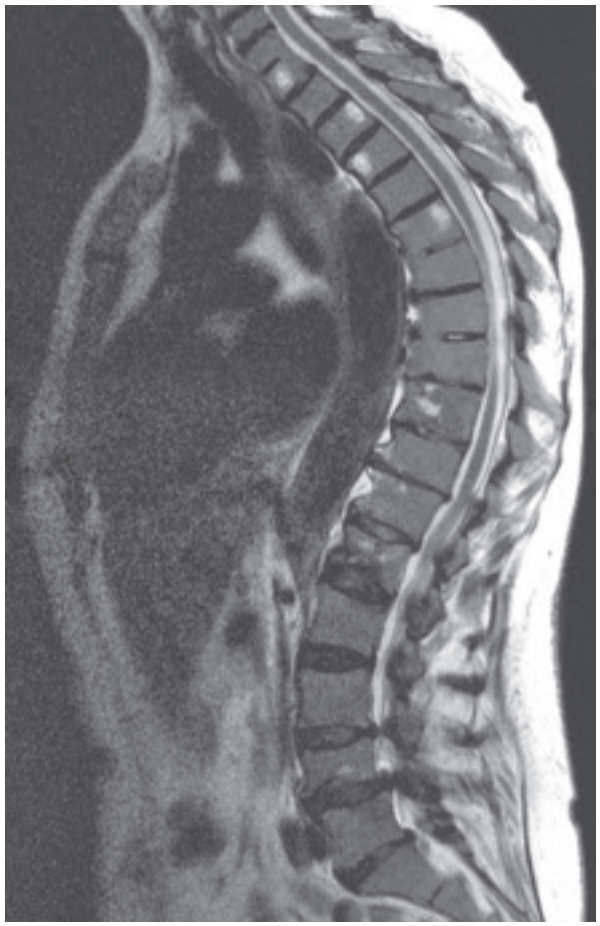
CASE REPORT

An 84-year-old woman with a vertebral fracture, caused six months earlier, which had been attributed to postmenopausal osteoporosis, was referred because

of disabling back pain after passing over a speed bump during a car ride. She had been feeling ill for quite some time, complaining of weight loss, loss of appetite, and clamminess at night. Her medication consisted of alendronate 70 mg once weekly, calcium-cholecalciferol 1.25 g/800 IU once daily and salmeterol/fluticasone inhalations. Her medical history revealed an urticarial rash to diclofenac. She had also been hospitalised recently as a result of hypotension attributed to systemic inflammatory response syndrome (SIRS), caused by a urinary tract infection. That admission was complicated by an episode of wheezing and dyspnoea ascribed to a COPD attack and an urticarial rash that was considered to be a reaction to antibiotics.

Upon physical examination, there were no overt abnormalities. Notably, the liver and the spleen were not enlarged and skin lesions were absent. Laboratory testing showed a normocytic anaemia (haemoglobin level of 6.8 mmol/l), leucocytes of 12.9 x 10^9/l with 10% large atypical cells, 1% erythroblasts and thrombocytes of 181 x 10^9/l.

Figure 1. *T2 weighted lateral MRI imaging showing compression fractures of the T10, L1 and L4 vertebrae with oedema around Th. 10 and L1, indicating that these are recent fractures*

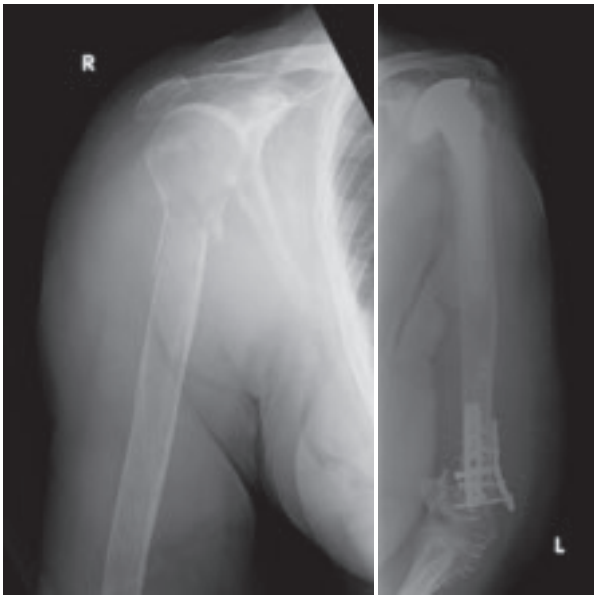


The erythrocyte sedimentation rate was 44 mm in the first hour, and the C-reactive protein was 6 mg/l. Kidney, liver and thyroid function, vitamins (cholecalciferol, folic acid and cobalamin), ferritin, iron parameters, calcium and albumin were all within normal ranges. A lumbar X-ray showed fractures of L1, L4 and Th10. An MRI performed later showed that the L1 and Th10 fractures were recent (*figure 1*).

A diagnostic procedure was started to search for secondary causes of osteoporosis, such as metastatic bone, or a primary haematological disease. A bone scintigraphy showed abnormalities of the lumbar spine, the right iliac crest and several ribs. These lesions were suspicious of metastatic bone disease on a CT scan. The diagnostic process was complicated by two consecutive pathological fractures of the right and left humerus (*figure 2*) that developed during nursing and for which she was operated. Both operations were complicated by hypotension which was ascribed to SIRS for which she was treated with antibiotics.

A bone marrow aspirate and biopsy were taken from the right ileac crest, of which the aspirate was hypercellular with an increase in megakaryocytes with dysplastic maturation features, and a decrease in the erythroid, lymphoid and myeloid lineage cells without distinct dysplasia. There was a diffuse infiltration of more than 50% large polymorphic cells. The bone marrow biopsy showed similar abnormalities with the presence of many atypical cells. In addition the biopsy showed thin, broken

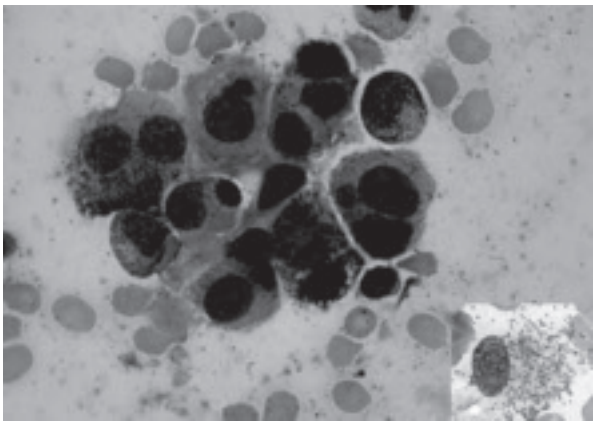
Figure 2. *Subcapital right humerus fracture (left panel) and supracondylar left humerus fracture after osteosynthesis (right panel) in the patient developed during daily nursing*



trabeculae and focal bone formation. Immunohistological staining showed that the atypical cells were CD117 positive. They were recognised as atypical mast cells (*figure 3*). A later serum tryptase level was extremely high: 1040 µg/l (normal values < 11.4 µg/l). A genetic D816V mutation could not be detected. The diagnosis was established to be a systemic aggressive mastocytosis and because of the number of mast cells, mast cell leukaemia. These cells were also seen in the peripheral blood smear.

The patient was given symptomatic treatment through sodium cromoglycate and high-dose H1 and H2 antagonists. She was also put on teriparitide injections and mast-cell eradication therapy through imatinib. Despite these treatments her disease continued to cause complications. Over the next few weeks, she was hospitalised four times for hypotension associated with dyspnoea, wheezing and pulmonary oedema. Initially, each time her symptoms were attributed to SIRS. Later, they were correctly denoted to be anaphylactic reactions through massive mast cell degranulation, caused by her mast cell leukaemia. At the last admission her hypotensive shock was refractory and respecting the policy of no resuscitation, she died one day later.

Figure 3. *Bone-marrow smear (May-Grunwald Giemsa stained, x100) of the patient showing that 50% of the cells are mast cells ranging from mature mast cells to immature promastocytes and blasts. The mast cells show cytological abnormalities, such as cell enlargement, the presence of multilobulated nuclei and focal granule accumulations. Immunohistological evaluation of the biopsy showed that the cells were CD117 positive. A normal mast cell is shown on the bottom right*



DISCUSSION

Mastocytosis comprises a rare group of disorders which are characterised by a clonal proliferation and an accumulation of pathological mast cells. Mastocytosis can be either limited to the skin (cutaneous mastocytosis), or it can involve bone marrow and other extracutaneous tissues such as the spleen, lymph nodes, liver and gastrointestinal tract (systemic mastocytosis).[3,4] The systemic findings and symptoms are due to mediator release by the mast cells (of which histamine is the most important) and organ infiltration. These can lead to angioedema, flushing, nausea, vomiting, abdominal pain, diarrhoea, unexplained syncope and pulmonary oedema (anaphylactic attacks), hypersplenism, osseous pain, or pathological fractures.[3,4] Most of these symptoms were prominent in our patient.

Systemic mastocytosis can be classified as indolent, aggressive, associated with a clonal non-mast cell lineage disease, and mast cell leukaemia. The classification depends on the results of the bone marrow biopsy and associated findings.[4] In mast cell leukaemia, the percentage of mast cells is ≥ 20% in bone marrow aspirate.[4,5] It was remarkable that the massive bone marrow infiltration did not result in a pancytopenia in our patient.

A number of clinical conditions may lead to the suspicion of systemic mastocytosis, such as unexplained anaphylaxis (as in our patient), severe osteoporosis of unknown aetiology (as in our patient), unexplained neurological or constitutional symptoms, unexplained ulcerative intestinal disease or chronic diarrhoea.[3,4] Many of these conditions were present in our patient, although they were initially not recognised as the histamine effects on H1 and H2 receptors resulting in vasodilatation and increased vascular permeability. Instead, the symptoms were several times mistakenly interpreted as SIRS, even after the patient had been diagnosed with mast cell leukaemia.

Mast cell leukaemia is a very rare form of aggressive systemic mastocytosis accounting for < 1% of all mastocytosis. It may appear de novo or secondary to previous mastocytosis.[5] Cytotoxic therapy with cladribine, interferon-α and imatinib have been used with poor results with a median survival of seven months, with patients dying between 2-29 months from progression or multiorgan failure.[5] Current therapy in systemic mastocytosis is largely palliative and directed at diminishing the symptoms of mast cell degranulation and/or organ dysfunction from mast cell tissue infiltration.[4]

Half of all adult patients with systemic mastocytosis have bone involvement with osteoporosis as the most common manifestation. An osteoporotic fracture is the presenting symptom in only a small minority of patients.[6] Osteoporosis in systemic mastocytosis is due to the direct effects on bone turnover of the mast cell mediators histamine, heparin and the cytokines TNF, IL-6, and TGF-beta.[7] In our patient, it was initially justified to attribute her vertebral fractures to primary osteoporosis. Osteoporosis guidelines recommend searching for secondary causes by measuring erythrocyte sedimentation rate, calcium, albumin, creatinine, thyroid-stimulating

hormone, 25(OH)D and alkaline phosphatase. Serum protein electrophoresis, coeliac serology and parathyroid hormone need to be done on indication.[8] However, none of these investigations would have led to the diagnosis of systemic mastocytosis in our patient. It was the two new vertebral fractures that eventually led to the diagnosis of a mast cell leukaemia.

Most patients in whom an osteoporotic fracture led to diagnosis of systemic mastocytosis were younger and the majority were male.[9-14] There are three cases in which systemic mastocytosis was diagnosed during the primary evaluation of an osteoporosis.[9,11,14] There is also one case of an elderly woman with a previous osteoporotic fracture in whom systemic mastocytosis was established after a wasp sting induced an anaphylactic shock.[12] Hence, an osteoporotic fracture as a leading symptom to the recognition and diagnosis of systemic mastocytosis is rare. In case of the rarity of a mast cell leukaemia; there are only two cases reported in which pathological vertebral fractures revealed the diagnosis.[15,16]

In conclusion, we report a rare cause of secondary osteoporosis: mast cell leukaemia. A diagnosis that, retrospectively, could have been recognised earlier because of the many characteristic manifestations of mast cell disease. This is the first recorded case in which progressive vertebral fractures were the presenting symptom of mast cell leukaemia in a postmenopausal woman who had previously been diagnosed with primary osteoporosis. Despite its low prevalence, mastocytosis should be included in the differential diagnosis of severe osteoporosis, especially when associated with symptoms of mast cell mediator release.

ACKNOWLEDGEMENTS

We would like to thank J.D.J Steinberg for reviewing the radiology.

DISCLOSURE

The authors declare no conflict of interest. No funding or financial support was received.

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