

CASE REPORT

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Two patients with osteoporosis: initial presentation of systemic mastocytosis

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Abstract In two patients with osteoporosis, systemic mastocytosis ultimately turned out to be the underlying disease. Both patients had a history of anaphylactic reactions caused by wasp stings but did not have any skin or other symptoms. This observation reflects the need for careful history taking and physical examination in patients with osteoporosis to identify possible underlying diseases, such as systemic mastocytosis.

Key words osteoporosis · systemic mastocytosis · tryptase

Introduction

Primary or idiopathic osteoporosis frequently presents in postmenopausal women and people of 65 years of age and older. In such cases, no underlying cause or contributory factor other than age or the postmenopausal state can be found. Secondary osteoporosis, which is much more frequently observed in premenopausal women (30%) and men (50%–80%), refers to those types of osteoporosis in which an underlying cause is present [1].

Causes for secondary osteoporosis, apart from nutritional deficiencies and lifestyle factors such as excessive smoking or alcohol abuse, include hypogonadism, hypopituitarism, glucocorticoid excess, immunosuppressive agents, and hematological malignancies, including multiple myeloma and systemic mastocytosis (SM). We here describe two patients presenting with persistent low back pain probably caused by osteoporosis. Although not initially diagnosed, SM turned out to be the underlying disease.

Patient 1

A 54-year-old man visited our outpatient department in July 2005 with severe low back pain after a minor trauma refractory to 6 weeks of physical therapy. Radiographs revealed a vertebral fracture at T12, which was attributed to osteoporosis after bone densitometry (Table 1). Other than an anaphylactic reaction to a wasp sting in 1978, there was no relevant medical history, and the man had no known risk factors for the development of osteoporosis. On physical examination we saw a healthy man with no abnormalities (e.g., acroosteolysis) other than restricted spinal movements.

Laboratory evaluation revealed elevated levels of serum tryptase [29.0 µg/l; normal <11.4 µg/l, minor WHO criteria for systemic mastocytosis >20 µg/l [2], and an elevated urinary excretion of methylhistamine (227 µmol/mol creatinine; normal <150 µmol/mol creatinine)]. Tryptase levels were determined using the B₁₂ assay [3]. The measurements were performed using Pharmacia UniCAP Tryptase reagents and the Pharmacia Unicap100 analysis device (Pharmacia and Upjohn, Uppsala, Sweden). Levels of MH were determined by an isotope-dilution mass fragmentographic method [4].

Laboratory tests for other causes of osteoporosis, including cortisol, parathyroid hormone, 25-hydroxyvitamin D₃, 1,25-dihydroxyvitamin D₃, phosphate, creatinine, serum and urine calcium, and thyroid-stimulating hormone (TSH) were within normal ranges (see Table 1). Consecutively, a diagnostic bone marrow biopsy specimen was taken from the posterior iliac crest, after which tryptase immunohistochemistry (anti-CD117) confirmed the presence of mast cell infiltrates. Within these infiltrates of >15 mast cells (major SM criterion for systemic mastocytosis [2]), >25% of the mast cells showed prominent spindling (minor criterion for systemic mastocytosis [2]), thereby confirming the diagnosis (Fig. 1). There was no evidence for an associated nonmast cell lineage hematological malignancy. No organopathy or other signs of another form than indolent systemic mastocytosis were observed. According to the WHO classification

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Fig. 1. Formalin-fixed bone marrow material with collections of spindled mast cells stained by anti-CD117. **A** $\times 20$; **B** $\times 60$

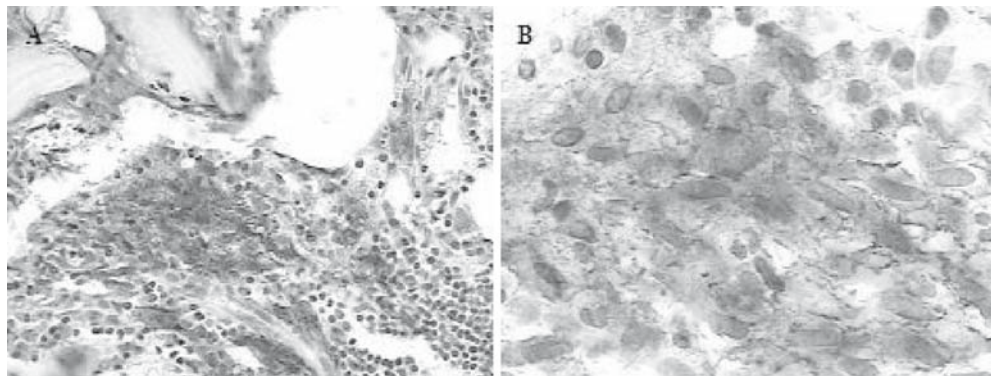


Table 1. Patient characteristics

	Patient 1	Patient 2
Age (years)	53	62
Gender	Male	Female
Bone densitometry		
T-score (lumbar)	-3.1	-3.1
Z-score (lumbar)	-2.7	-1.5
T-score (hip)	-1.0	-1.2
Z-score (hip)	-0.6	-0.1
Serum tryptase ($\mu\text{g/l}$)		
N ≤ 11.4	29	23
Urinary excretion methylhistamine ($\mu\text{mol/mol creatinine}$)		
N ≤ 150	227	288
Calcium (mmol/l)		
N = 2.20–2.60	2.44	2.33
Parathyroid hormone (pmol/l)		
N = 0.60–4.20	2.3	2.0
Alkaline phosphatase (U/l)		
N = 40–120	84	75

N, normal values

[2], the patient was classified as indolent SM and was treated with vitamin D preparations and the oral biphosphonate alendronate. In addition, an Epipen (DEY, Napa, CA, USA) was provided for the occurrence of an anaphylactic shock, and careful follow-up was initiated.

Patient 2

A 63-year-old woman visited our outpatient department in June 2004 to evaluate her osteoporosis, which was detected after a routine screening. Radiographs revealed no vertebral or other fractures, but she suffered from persistent low back pain. Medical history revealed rachitis at childhood, hysterectomy and single ovariectomy at the age of 32, and a relatively early menopause at the age of 45. There were no indications for the Hajdu–Cheney syndrome. Because laboratory screening for cortisol, parathyroid hormone, 25-hydroxyvitamin D₃, 1,25-dihydroxyvitamin D₃, phosphate, creatinine, serum and urine calcium, and TSH was within normal ranges, her osteoporosis was regarded as primary

or possibly partly the result of her early menopause (see Table 1).

In January 2005, however, she suffered from a grade IV systemic reaction after a wasp sting and was admitted to the intensive care unit. Because of the suspicion of SM, serum tryptase and urinary excretion of methylhistamine were evaluated, which were both elevated (tryptase 23 $\mu\text{g/l}$, and methylhistamine 288 $\mu\text{mol/mol creatinine}$, respectively). Consequently, a diagnostic bone marrow biopsy specimen was taken from the posterior iliac crest, after which immunohistochemistry (anti-CD117) confirmed the presence of mast cell infiltrates. Within these infiltrates (major criterion for systemic mastocytosis [2]), >25% of the mast cells showed prominent spindling (minor criterion for systemic mastocytosis [2]), thereby confirming the diagnosis. There was no evidence for an associated nonmast cell lineage hematological malignancy. No organopathy or other signs of an other form than indolent SM were observed. According to the WHO classification, the patient was classified as indolent SM and was treated with vitamin D preparations and the oral biphosphonate alendronate. In addition, an Epipen (DEY, Napa, CA, USA) was provided for the occurrence of an anaphylactic shock, and careful follow-up was initiated.

Discussion

The incidence of mastocytosis is still largely unknown. Despite recent advantages in the understanding of the disease, the diagnostic process is often hampered by the heterogeneous presentation.

Mastocytosis, or mast cell disease, is characterized by the abnormal growth and accumulation of neoplastic mast cells in one or more organ systems. Cutaneous mastocytosis (CM), in which the skin is the only organ involved, is most often diagnosed in childhood, and might regress spontaneously. By contrast, systemic mastocytosis (SM) is more frequently diagnosed in adults. SM is a persistent clonal disorder of mast cells and its progenitors in which at least one other organ than the skin is involved, almost invariably the bone marrow [5].

Mastocytosis is classified and diagnosed according to WHO criteria. The diagnosis of SM is established when either one major and one minor criterion, or three minor criteria, are satisfied [2]. Biochemical markers that correlate with mast cell burden, such as serum tryptase and the urinary histamine metabolites *N*-methylhistamine (MH) and *N*-methylimidazole acetic acid (MIMA), can be helpful in the diagnostic workup of patients in whom the diagnosis SM is considered. Serum tryptase is elevated in the large majority of SM patients [>20 ng/ml (minor WHO criterion)], and correlates with the mast cell burden, but an elevated serum tryptase is not exclusive for SM [6]. The most important step in the diagnosis of adult patients is a histological bone marrow examination because multifocal, dense infiltrates of >15 mast cells (major WHO criterion) and spindle-shaped or atypical mast cell morphology (minor WHO criterion) can be detected in this way. In addition, other diagnostic tests can be performed to confirm the diagnosis, such as defining the cell-surface phenotype and mutational analysis of the c-KIT receptor (both minor WHO criteria) [2], as activating mutations in the c-KIT receptor underlie the aberrant cell signaling and mast cell growth in a majority of patients.

SM is further subclassified into indolent SM (little or no evidence of impaired organ function), aggressive SM (presence of impaired organ function), SM with an associated clonal hematological nonmast cell lineage disease (SM-AHNMD), mast cell leukemia (MCL; $>20\%$ mast cells in bone marrow), and mast cell sarcoma [2].

Clinical heterogeneity is a hallmark of mastocytosis. Symptoms and signs of systemic mastocytosis are related to the release of mast cell mediators and may occur with all subtypes of SM, which can cause a range of symptoms including flushing, itching, headache, gastrointestinal symptoms, fatigue, osteoporosis, syncope, and anaphylactic attacks. In addition, infiltration of neoplastic mast cells can cause organomegaly, organopathy, skin lesions (urticaria pigmentosa), and pancytopenia. These symptoms and signs are typically related to the tissue mast cell burden, to the response of the release of mast cell mediators, or to the presence or absence of an associated nonmast cell hematological disorder [7].

In SM, diffuse osteoporosis with a combination of osteosclerotic and osteolytic lesions can be observed in which the axial skeleton and ends of long bones are primarily affected. Back pain secondary to osteoporotic vertebral fractures may be the major presenting symptom of SM [8]. The incidence of mastocytosis in osteoporotic patients varies from 1% to 2.5%, depending on patient age and gender [9]. The pathophysiological mechanisms leading to osteoporosis in SM are only poorly understood in humans. However, mast cells appear to be relevant in the pathogenesis of bone turnover. Mast cell deficiency demonstrates delayed osteoclastic recruitment and a delayed osteoblastic formation phase. Histamine deficiencies lead to a decrease in osteoclast number. Osteoblasts stimulated by parathyroid hormone synthesize abundant stem cell factor, which contributes to enhanced osteoclastogenesis. Mast cell deficiency has been associated with low remodeling states, whereas

their excess is associated with accelerated bone loss. Even their by-products, such as histamines, are responsible for increased bone resorption [10,11].

Currently, there is no curative treatment for mastocytosis. Bisphosphonates are effective in SM for osteoporosis and have a role in the associated refractory bone pain [8]. Furthermore, patients with systemic mastocytosis associated osteoporosis might benefit from interferon-alpha (IFN- α) therapy [6,9]. Novel strategies designed to inhibit the growth of mast cells containing the c-KIT D816V mutations have shown success in vitro and may provide effective targeted therapy [12].

In a patient with unexplained osteoporosis and associated back pain, careful history taking and thorough physical examination are important because a secondary cause is very likely in these patients. This possibility is especially true for systemic mastocytosis as these patients may have a history of flushes, allergic reactions and other symptoms, as exemplified by patient 1, who suffered from an anaphylactic reaction after a wasp sting some 20 years ago. Although our patients did not have skin abnormalities, careful inspection of the skin may also be very helpful because the majority of patients with indolent systemic mastocytosis have skin lesions of urticaria pigmentosa.

When frequent causes of osteoporosis have been excluded by laboratory studies, serum tryptase and urine histamine metabolites should always be measured to make the diagnosis systemic mastocytosis more or less plausible. If laboratory studies or clinical signs and symptoms point to systemic mastocytosis, a bone marrow biopsy should at least be considered.

In conclusion, these cases should trigger the awareness that in patients with unexplained osteoporosis, even in postmenopausal women and people over 65 years of age, one should always think of a manifestation of systemic mastocytosis, a relatively rare cause of osteoporosis that should not be unrecognized because of its significant morbidity and good treatment options.

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