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# Multimodal Therapy for Vertebral Involvement of Systemic Mastocytosis

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**Study Design.** Case report and clinical discussion.

**Objective.** To describe a rare case of vertebral involvement of systemic mastocytosis and its multimodal therapy.

**Summary of Background Data.** Vertebral fractures in young men are rare events. A thorough diagnostic work-up that unravels the underlying cause of osteoporosis and appropriate therapy are crucial to prevent further fractures.

**Methods.** A 36-year-old man was evaluated for severe back pain and was found to suffer from progressive osteoporosis and multiple vertebral fractures. Bone biopsy analysis revealed tryptase-positive mast cells that were positive for c-*KIT*, thus confirming the diagnosis of systemic mastocytosis.

**Results.** In addition to zoledronic acid (4 mg per month) and prednisolone (50 mg per day) treatment, the patient underwent kyphoplasty. The procedure was associated with arterial hypotension which was most likely because of pressure-induced mast cell degranulation. Follow-up visits demonstrated stable bone mineral density and tolerable back pain while on zoledronic acid.

**Conclusion.** Systemic mastocytosis is a rare cause of vertebral fractures in young men. Because of the potential risk of pressure-induced release of the allergy mediator histamine, kyphoplasty for vertebral involvement of systemic mastocytosis should be conducted with appropriate precautions.

**Key words:** histamine, kyphoplasty, male osteoporosis, mastocytosis, zoledronic acid. **Spine 2009;34:E626–E628**

Vertebral fractures in young men are rare events and frequently the consequence of an unrecognized underlying disease.[1] A thorough diagnostic work-up that unravels the underlying cause of osteoporosis and appropriate therapy are crucial to prevent further fractures. We report the case of a young man with vertebral fractures due to systemic mastocytosis and emphasize the need for an interdisciplinary therapeutic approach.

## Case Report

We report on a 36-year-old man who presented in November 2006 with an AO type A3.1 fracture of the 12th thoracic vertebra after lifting a 20 kg case (Figure 1A), which was treated with internal fixation (Figure 1B). He had no other signs or symptoms, and did not take drugs. In February 2007, the patient presented with lower back pain, and the magnetic resonance imaging demonstrated multiple vertebral compression fractures (Figure 1C). The internal fixation had loosened. He was evaluated for secondary osteoporosis. His routine laboratory assessment was unremarkable. Serum levels of 25-OH-cholecalciferol were decreased to 5.9 $\mu$g/L (normal 10–50). Serum levels of intact parathyroid hormone were normal, whereas total alkaline phosphatase activity was elevated to 151 U/L (normal 38–126). All endocrine parameters were within normal age-adjusted limits. Bone mineral density measurement by dual-energy radiograph absorptiometry (DXA) revealed a *Z* score at the lumbar spine of −4.8 and at the proximal femur of −2.8, consistent with osteoporosis.

To identify the underlying cause, an iliac bone biopsy was performed and revealed nests of spindle-shaped, tryptase-positive mast cells which were located at perivascular sites (Figure 2A) and accounted for 10% to 20% of the bone marrow cells. High-turnover osteoporosis without defects of bone mineralization was also noted. The c-KIT proto-oncogene (CD117) was abundantly expressed by mast cells (Figure 2B). Mast cells partially stained positive for CD2 and were strongly positive for CD25. A somatic mutation in exon 17 of the c-KIT gene was shown in mast cells, resulting in an amino acid substitution of aspartic acid for valine at amino acid 816 (D816V).[2] Serum tryptase concentration (45 ng/mL, normal: <13.5) and urinary excretion of histamine (78 $\mu$g/24 hours, normal 5–30) were elevated. Based on the presence of 3 minor criteria according to the World Health Organization definition,[3] (I) expression of surface markers CD2, CD25, or both in tissue mast cells; (II) increased markers of mast cell activation (serum tryptase levels greater than 20 ng/mL); and (III) mutational analysis of c-*KIT* showing D816V in extracutane-

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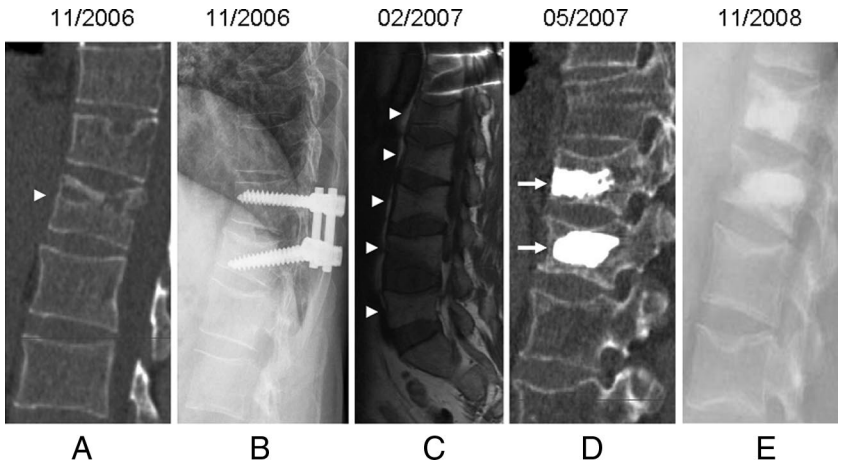


Figure 1. Management of osteoporotic fractures secondary to systemic mastocytosis. **A**, Computed tomography demonstrating vertebral compression fracture (arrow head) at the 12th thoracic vertebra. **B**, Lateral spine radiograph after internal fixation. **C**, Magnetic resonance imaging demonstrating extensive spinal compression fractures (arrow heads). **D**, Lateral spine computed tomography after kyphoplasty of the 12th thoracic and the first lumbar vertebra using calcium phosphate cement (arrows). **E**, Lateral spine radiograph 19 months after kyphoplasty.

ous organs, a diagnosis of systemic mastocytosis was made. No extraskeletal involvement was noted.

The patient was discussed at the tumor board which recommended prednisolone (50 mg per day with slow tapering), 1,25-$(OH)_2$-cholecalciferol (5.000 IU per day), and zoledronic acid (4 mg every 4 weeks intravenously), which were initiated in April 2007. This regimen rapidly improved his symptoms. Two weeks later, he was referred for evaluation for kyphoplasty for persistent and localized back pain and implant removal. The procedure was conducted under antihistamine coverage. Kyphoplasty of the 12th thoracic and the first lumbar vertebra was performed using resorbable KyphOs-FS-R bone cement (radiopaque calcium phosphate) (Figure 1D). During the procedure the patient experienced arterial hypotension after balloon inflation which was thought to be due to pressure-induced mast cell degranulation and transiently required vasopressor support. The patient was discharged with tolerable back pain and a physical therapy plan.

In August 2007, he presented with fatigue and malaise on 10 mg of prednisolone, but had no fever or night sweats. His back pain had worsened and was permanent. Serum tryptase levels had increased to 51 ng/mL and DXA measurements revealed $Z$ scores of $-5.1$ at the lumbar spine and $-3.0$ at the proximal femur, indicating progressive bone loss. Glucocorticoid therapy was stopped, and subcutaneous treatment with interferon-$\alpha$ at $3 \times 10^6$ U 3 times per week was initiated. When seen in December 2007, he was free of pain without analgesics. Although serum tryptase levels had increased to 66 ng/mL, DXA measurement showed no further bone loss ($Z$ scores of $-5.2$ at the lumbar spine and of $-2.7$ at the proximal femur). On a visit in November 2008, he was free of pain and his radiograph showed the calcium phosphate bone cement in place and no new fractures (Figure 1E).

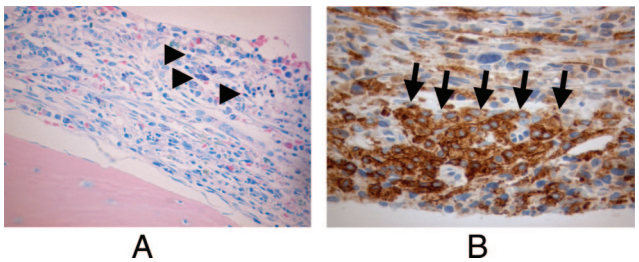


Figure 2. Findings in systemic mastocytosis. **A**, Microscopic analysis of an iliac bone biopsy revealed nests of spindle-shaped, tryptase-positive mast cells (arrow heads), ×400. **B**, Immunohistochemical analysis demonstrated strong expression of c-*KIT* (CD117) by mast cells (arrows), ×400.

## Discussion

Osteoimmunology is a term that describes interactions between immune and bone cells through cytokines, chemokines, and signaling pathways.[4] Our case of a young man with progressive bone loss secondary to systemic mastocytosis is a clinical example of osteoimmunology demonstrating the skeletal sequelae of uncontrolled mast cell proliferation and degranulation, resulting in an altered chemokine milieu. This case is instructive for 2 reasons.

First, it shows the dilemma to diagnose osteoporosis in a health-appearing young man with a negative history and no signs or symptoms. The spectrum includes unrecognized hereditary, gastrointestinal, infiltrative, and neoplastic diseases. Second, our case highlights the need to obtain a bone biopsy early in the work-up of male osteoporosis. A recent study of 99 consecutive middle-aged patients, mostly men, reported an increased number of mast cells in 5 patients and definitive mastocytosis in 1 patient.[5] Despite the low prevalence of systemic mastocytosis, histopathology revealed abnormalities that affected therapy in the majority of patients, and the procedure was safe and well tolerated.[5] Once the histologic diagnosis of systemic mastocytosis has been established, molecular analysis of the gene encoding c-KIT is mandatory. Most adult patients with systemic mastocytosis carry an activating D816V mutation in exon 17 of the c-KIT gene[6] which confers imatinib resistance. Interestingly, mice which overexpress the human D816V mutant KIT proto-oncogene in mast cells spontaneously develop a disease similar to human mastocytosis.[7]

Initially, surgery with short-segment posterior stabilization was performed based on the diagnosis of a traumatic AO type A3.1 fracture. This form of treatment is

consistent with the recent data from a prospective European study.[8] In view of the bone histology and the rapid bone loss of the spine, the therapeutic strategies called for a concerted action. We discussed therapeutic options based on limited evidence at the institutional tumor board. Because of persistent pain due to vertebral fractures, we elected to perform kyphoplasty of the 12th thoracic and the first lumbar vertebrae. Given the patient's young age, we elected to use resorbable KyphOs-FS-R bone cement. Calcium phosphate cement augmentation may be preferable to PMMA because it is resorbable in the long-term, nontoxic, and has similar biomechanical and structural properties compared with PMMA.[9]

A prospective nonrandomized controlled study of 60 patients reported increased vertebral height, reduced pain, and improved mobility in a predominantly female cohort with postmenopausal osteoporosis after kyphoplasty.[10] However, the long-term efficacy and safety of kyphoplasty remain to be determined. Despite appropriate premedication, the procedure was complicated by a systemic reaction after balloon inflation, which most likely resulted from pressure-induced release of histamine and other chemokines from mast cells which required brief catecholamine support and circulatory monitoring. Thus, particular precautions are required before performing kyphoplasty in systemic mastocytosis. This acute allergic reaction points toward a potential mediator of rapid bone loss in systemic mastocytosis, the abundance of histamine. Histamine, the major product released after mast cell degranulation activates osteoclasts and mediates bone loss in ovariectomized rats.[11] Other causes for an acute circulatory impairment during kyphoplasty include cement emboli, fat emboli, or latex allergy.

Because of progressive disease, treatment was switched to interferon-$\alpha$[12] which was combined with zoledronic acid. A regimen of interferon-$\alpha$ and pamidronate increased bone mineral density by 16% in the spine and prevented vertebral fractures in a small study of 4 adults with systemic mastocytosis.[13] At present, there is no cure for systemic mastocytosis with the activating D816V mutation, and the effects and safety of rapamycin, the NF-$\kappa$B inhibitor IMD-0354, and the tyrosine kinase inhibitor dasatinib are currently being evaluated.

In conclusion, kyphoplasty combined with multimodal medical therapy may be required to treat painful vertebral fractures in systemic mastocytosis. Precautions should be taken to minimize the effects of pressure-induced histamine release.

### ■ Key Points

- Systemic mastocytosis represents a rare cause of vertebral fractures in young adults.
- Kyphoplasty along with medical therapy may be required to control symptoms of vertebral involvement in systemic mastocytosis.
- During kyphoplasty in patients with systemic mastocytosis, balloon inflation may cause pressure-induced release of allergy mediators, including histamine.

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