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Clinical Communications

Vertebral fracture in a 7-year-old boy with indolent systemic mastocytosis

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Clinical Implications

A vertebral fracture after a minimal trauma has not been described previously in a child with indolent systemic mastocytosis. Children with mastocytosis are probably susceptible to osteoporotic manifestations and fractures, especially of the spine, as are adults.

Mastocytosis is a clonal disorder, characterized by the accumulation of pathological mast cells.[1] This accumulation may only be present in the skin (cutaneous mastocytosis [CM]) but may involve other organs as well, specifically bone marrow (systemic mastocytosis [SM]). The prevalence and incidence of mastocytosis in children are not exactly known.[1] CM is the typical presentation of mastocytosis in children; however, SM may also occur, mostly in its indolent form (ISM).[1] Aggressive forms of SM are extremely rare in children.[1]

In adults, fragility fractures (FFxs), also known as low-energy trauma fractures, especially of the spine, as well as densitometric osteoporosis, are frequent manifestations of ISM, influencing the quality of life in a relatively young and frequently male patient population.[2,3] The reported lifetime prevalence of FFxs is 41% (mean age 51 years).[2] The observed prevalence of densitometric osteoporosis varies from 18% to 31%.[2,3]

Although the pathophysiology is not fully understood, bone loss in ISM has been attributed to local mast cell infiltration and local release of mediator (eg, histamine), enhancing bone resorption. Recently, the process has also been related to the release of extracellular vesicles (EVs) by neoplastic mast cells in ISM.[4] These EVs block osteoblast differentiation and mineralization, thus negatively influencing bone formation.[4]

In adults, bone resorption−inhibiting drugs (bisphosphonates, denosumab) are efficient in improving lumbar spine bone mineral density (BMD) and decreasing serum collagen C telopeptide (sCTx) Z-scores in ISM-related osteoporotic manifestations. However, FFxs still occur frequently, especially in patients who previously already had FFxs.[5]

For children, in whom ISM is rare, osteoporotic manifestations have not been investigated. To our knowledge, only one group reported a 3% prevalence of osteoporosis, in a group of 100 children with CM, not systematically evaluated for ISM. Children with localized bone pain and/or high tryptase levels were evaluated, but the criteria for osteoporosis were not mentioned.[6] Also, the occurrence of FFxs was not mentioned.

We present a case that clearly highlights bone-related sequelae of ISM in a school-aged child. Our (male) 7-year-old patient was diagnosed with maculopapular CM at age 6 months; basal tryptase levels were regularly checked and were high (30-50 μg/L, normal range <11 μg/L).

At the age of 5 years, our patient suffered from a life-threatening anaphylaxis requiring resuscitation, after a viral infection (polymerase chain reaction [PCR]: rhinovirus). Within the first day after resuscitation, he subsequently suffered from multiple anaphylactic reactions related to drugs (morphine and fentanyl), with severe hypotension, spontaneous bleeding, and tryptase >200 μg/L measured within hours after the anaphylaxis to fentanyl and was subsequently referred to our hospital. The number of cutaneous lesions the patient had was around 15 in total. The SCORing MAstocytosis Index (SCORMA) was, however, 44, mainly due to subjective symptoms. A bone marrow biopsy confirmed ISM based on 3 minor criteria according to the following World Health Organization criteria: tryptase >20 μg/L, D816V *KIT* point mutation in the bone marrow aspirate, and >25% of the mast cells were spindle shaped.[1] No B or C symptoms were present. Main complaints were fatigue, recurrent abdominal pain followed by diarrhea. The patient suffered from failure to thrive as well (FTT, height −1.6 standard deviation [SD], target height was +0.3 SD, weight for height −3.0 SD).

Antimediator treatment was started with H1 and H2 antihistamines and oral cromoglicate after which the diarrhea resolved and the patient grew significantly better (height SD increased to −1.3 and weight for height SD to −1.3). Despite extensive investigations into the cause of the FTT, we found none other.

Our patient however still suffered from frequent attacks of mediator release symptoms triggered by viral infections (up to 6 episodes per year), characterized by severe abdominal cramping followed by excessive diarrhea, sweating, hypotension, collapse, and drop in oxygen saturation for which epinephrine intramuscular was needed and resulting in quick recovery (2 times a polymerase chain reaction was done: positive for sapovirus and influenza A, respectively). Urinary histamine metabolites methylimidazole acetic acid and methylhistamine were constantly elevated (Figure 1) and higher after anaphylaxis. Other urinary metabolites originating from mast cell mediators were not measured.

Therefore, omalizumab was started at 150 mg/2 weeks and optimized at 300 mg/3 weeks in order to modulate the response to viral infections.[7] The number of anaphylactic episodes declined significantly, occurring only twice in the next 24 months, likewise linked to viral infections but with a much milder course than before omalizumab treatment.

At the age of 7 years, he complained of back pain after a fall on his back from of a hanging position at 1 m height. An X-ray of the spine showed a fracture of his fifth lumbar vertebra (L5) (Figure 2).

BMD was measured by dual energy X-ray absorptiometry (Hologic, Marlborough, MA). The BMD Z-score of the lumbar spine (except affected L5) was −2.4, that of the total body (minus the head) −2.9 and that of the femur −1.8. 25-Hydroxyvitamin D and parathormone levels, as well as renal function, were all within the normal range. Because of the vertebral fracture after a

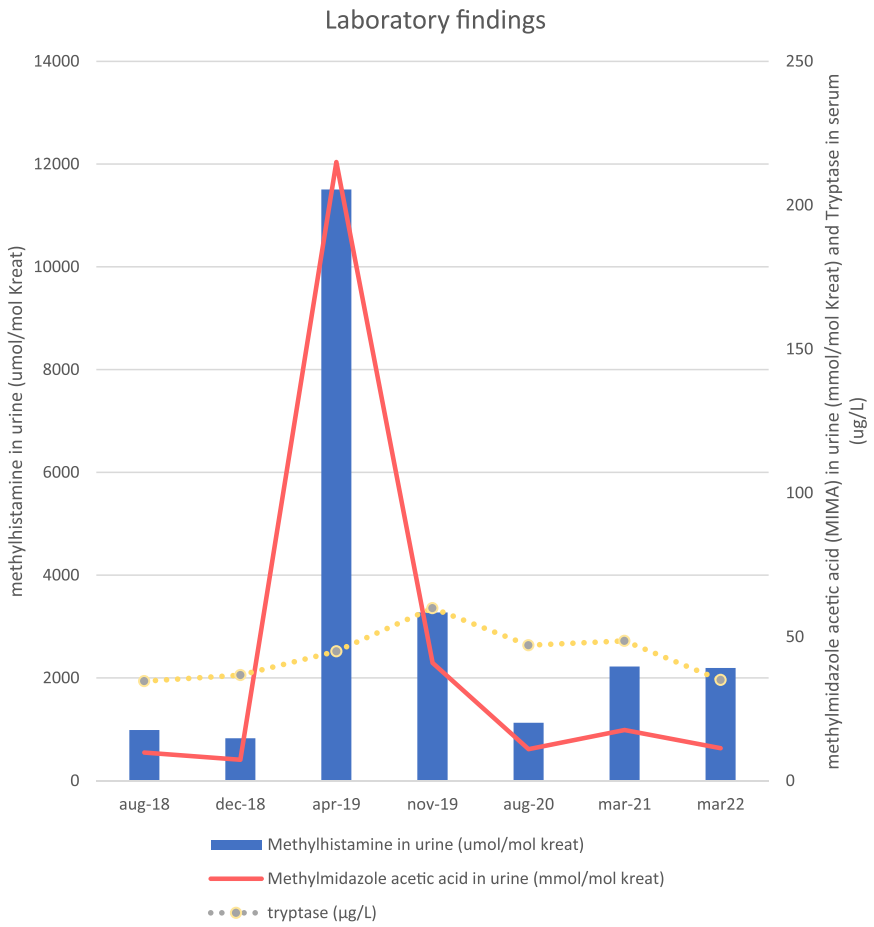

FIGURE 1. Laboratory findings in our patient: levels of methylhistamine (normal value for adults <150 µmol/mol kreat and for children dependent of age, eg, <300 µmol/mol kreat at age 7 years) and methylimidazole acetic acid (normal value for adults <2.0 mmol/mol kreat and for children dependent of age, eg, <3.0 mmol/mol kreat at age 7 years) in urine, as well as tryptase (normal value <11 µg/L) in serum. April 19 marks an anaphylaxis, as does November 19. The other measurements are baseline. In June 20, he had the vertebral fracture.

low impact trauma with a vertebral BMD <−2.0 SD, osteoporosis was diagnosed. Intravenous administration of the bisphosphonate zoledronic acid was started, resulting in an increase of BMD Z-scores of the lumbar spine +0.8 and total body (minus the head) +0.8 after 2 years, without new FFxs.

To our knowledge, a vertebral fracture after minimal trauma has not previously been described in a child with ISM. Data on BMD measurements and (fragility) fractures in children with CM or ISM are lacking. As in adults, children with systemic mastocytosis are probably susceptible to osteoporotic manifestations. Hence, the possibility of fractures, especially of the spine, should be considered in pediatric ISM patients. When there is pain in the back, lateral spine imaging should be performed. It may be helpful to identify those patients at highest risk for osteoporosis and fractures. In adults, a screening tool has been described.[8] The MastFx score distinguishes patients with ISM at high, intermediate, and low risk of new FFxs[8] based on the risk factors male sex, high sCTX levels, low hip BMD, absence of urticaria pigmentosa, and alcohol intake. There is a need for a similar screening tool for children in order to timely take preventive and therapeutic measures.

The nutritional requirements for a growing child are to be met with adequate calcium intake. If 25-hydroxyvitamin D levels are suboptimal, supplementation should be started. Intravenous bisphosphonate treatment in children with secondary osteoporosis has a positive effect on BMD and may reshape vertebras with a compression fracture.[9] Our patient responded with a BMD increase as well. As the pathogenesis of bone involvement and its sequelae become clearer, further research should aim at the possibilities of improved and targeted therapy. Future studies may also focus on the risk of osteoporosis in children with ISM.

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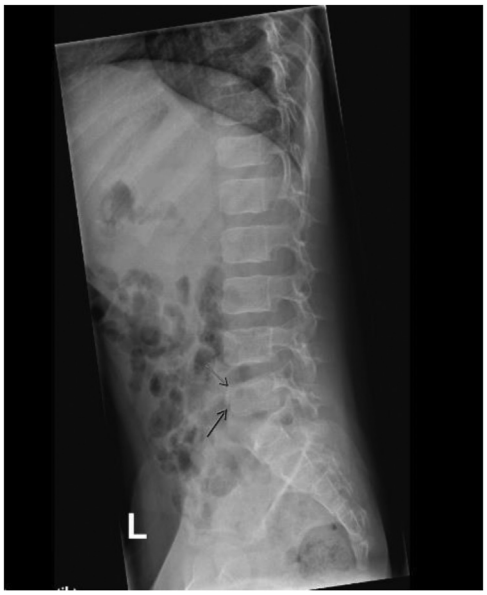

FIGURE 2. X-ray of the spine showing the fracture of L5.

Conflicts of interest: H. N. G. Oude Elberink has received fees for delivering lectures from ALK-Abelló, Mylan, Sanofi Genzyme, and Novartis; consultancy fees from ALK-Abello, Novartis, Blueprint, Viatris, and Sanofi Genzyme; research support from Novartis, ALK-Abello, Aimmune, Takeda, and Blueprint; and payment for developing educational presentations from ALK-Abello and Mylan. The rest of the authors declare that they have no relevant conflicts of interest.

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