Osteoporosis International (2019) 30:1121–1124
https://doi.org/10.1007/s00198-019-04897-9

CASE REPORT

Multiple vertebral fractures as the first manifestation of systemic mastocytosis

Á. Acosta-Mérida[1] · S. Ojeda-Bruno[2]

Received: 19 September 2018 / Accepted: 8 February 2019 / Published online: 15 February 2019

Abstract
Systemic mastocytosis is a clonal disease of the mast cell progenitors of the bone marrow. The clinical picture varies from asymptomatic (indolent) to highly aggressive (mast cell leukemia). Up to one-third of patients with SM have osteoporosis and fractures. The following is an analysis of the case of a young patient with multiple fractures as the first manifestation of SM.

Keywords Mastocytosis · Osteoporosis · Tryptase · Vertebral fractures

Introduction

Mastocytosis is a disease that originates in the bone marrow and is characterized by an abnormal growth and proliferation of mast cells and their CD34 + progenitors. Its heterogeneous presentation is due to the infiltration of mast cells in one or more organs and the production of different biochemical mediators such as histamine or prostaglandins [1]. There are several diagnostic criteria for mastocytosis [2]. The diagnosis of systemic mastocytosis (SM) requires the identification of one major and one minor criterion, or at least three minor criteria. Once the diagnosis has been made, the percentage of mast cell infiltration in the bone marrow will allow us to know whether it is mast cell leukemia (≥ 20% infiltration). When the infiltration percentage is less than 20%, and as long as there are no B or C findings, we are then dealing with a case of indolent mastocytosis; if only B findings were found, SM would be considered, but when only C findings are present, they are indicative of aggressive SM. The B findings are criteria defining the spread of disease (hypercellular bone marrow but insufficient criteria for the diagnosis of a hematopoietic neoplasm, absence of cytopenias, and organomegalies without evidence of functional impairment). The C findings define the aggressiveness of the mast cell infiltrate (bone marrow organ dysfunction with cytopenias, organomegaly with organ failure, severe malabsorption with hypoalbuminemia and weight loss, and large-sized osteolysis with local mast cell infiltration) [2, 3]. The infiltration of mast cells into the bone marrow induces osteoporosis and fractures, and they could be the only manifestation of the disease. Here, we present the case of a young patient with fractures related to osteoporosis secondary to indolent SM.

Clinical CASE

The patient was a 42-year-old woman with no relevant past medical history. Her past surgical history included a cholecystectomy, a tonsillectomy, a cesarean section, and an acromioplasty for rotator cuff tendinopathy secondary to subacromial syndrome on her left shoulder. Her pregnancy had no complications, she had no abortions, and her menstruations were regular at the time. She was a former smoker who had quit smoking 12 years before her admission. Due to the several fractures, she had sustained over the past 15 years; she was being monitored for osteoporosis in another medical center. Some of her fractures included the following: a fracture of T12 and L2 in 2002 while skating, a fractured left wrist in 2005 after she tripped while walking down the street, and a fracture of the greater tuberosity of her left shoulder in 2007 after suffering another fall. For this reason, she was treated

✉ Á. Acosta-Mérida
angyacostamerida@gmail.com

S. Ojeda-Bruno
soas@medicoslaspalmas.es

[1] Rheumatology, Hospitales San Roque Las Palmas De Gran Canaria, Las Palmas, Spain

[2] Rheumatology, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas, Spain

with intravenous zoledronic acid for 5 years (last in 2015), and later, in March 2016, she began treatment with subcutaneous denosumab. A total of three injections of denosumab were administered (the last one being in March 2017). At the time of admission, she was being treated with calcium and vitamin D supplements and practiced sports regularly (Pilates and walking).

In May 2017, the patient was referred to the Neurosurgery Department for follow up, as she had begun experiencing acute disabling low-back pain after falling from her own height. A magnetic resonance study was requested, which showed a depressed fracture of L3 with minimal trabecular edema with no displacement of the posterior wall, a superior vertebral end-plate depression of L2 and L4 and a chronic T12 fracture (Fig. 1). A transpedicular arthrodesis from L1 to L4 was performed by the neurosurgery team, who were able to cannulate the pedicles of the fractured vertebrae and apply skin graft sheets transversely using Malibu screws and rods. A vertebral bone biopsy was also performed during the same surgical procedure, and no mast cells were found. The patient provided a 2016 densitometry study using a dual X-ray absorptiometry (DXA) scan with a − 1.5 Z-score of the lumbar spine and a − 1.3 Z-score of the femoral neck. A DXA scan was performed upon admission which showed a − 1.4 Z-score of the lumbar spine and − 1.2 Z-score of the femoral neck. Blood tests were then requested to rule out the causes of secondary osteoporosis. The results showed normal levels of calcium (Ca) (8.3 mg/dl), albumin, serum phosphorus (P) (2.4 mg/dl), and 25OHvitD (34 ng/ml), while parathormone (PTH) levels were slightly high (92.1 pg/ml) (reference range 14.5–87.1). The measures for procollagen type I N-terminal propeptide and bone alkaline phosphatase were 20.18 ng/ml (reference range 15.1–58.6) and 79 U/l (reference range < 104) respectively. A complete blood count revealed no cytopenias. She showed no alterations in liver function tests, had a normal lipid profile, normal proteinogram, normal sexual hormonal profile, and negative anti-transglutaminase antibodies. A 24-h urine test showed the following levels: Ca 98.7 mg, (reference range 100–300 mg), P 0.07 g (reference range 0.4–1.3 g), and proteins 112.5 mg (reference range <100 mg). Although the patient did not show any mastocytosis-associated symptoms (no skin rash, no tachycardia, no syncope, or diarrhea), and no relevant findings on physical examination were found (adenopathies, hepatomegalies, or splenomegalies), a serum tryptase test was requested, which showed levels of 25.8 mcg/l (the limit is up to 11 mcg). In view of this result, the medical team decided then to refer the patient to the hematology unit of a reference center to detect C-KIT mutations in the peripheral blood and bone marrow aspirates. A normocellular bone marrow aspiration was performed, in which all three series were present, with 0.4% mast cells (fusiform 50%). The flow cytometry revealed 0.008% of mast cells (CD117++, CD34-, CD45++, FcRI+); 85% of them (0.007% of total cellularity) had an aberrant phenotype (CD25+, C2+). Said mast cell phenotype was compatible with systemic mastocytosis. The KIT mutations study detected the presence of D816V (A7176T) KIT mutation in mast cells using the PNA-PCR technique and in CD34+cells, granulocytic series, and T lymphocytes using the ASO-qPCR technique. Once the diagnosis of indolent systemic mastocytosis with D816V mutation and osteoporosis with fractures was reached, treatment with cromolyn sodium 200 mg was started, while also maintaining treatment with denosumab and the calcium and vitamin D supplements.

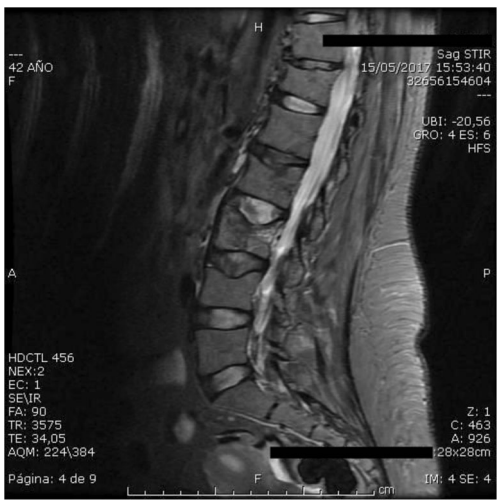

Fig. 1 MRI of the patient

Discussion

Bone manifestations are one of the most frequent symptoms of SM, particularly in adults [4]. According to the traditional WHO criteria (bone mineral density,

BMD, T-score < − 2.5) [5], the reported prevalence of osteoporosis in patients with SM ranges from 18 to 31% [6]. The prevalence of osteoporotic manifestations in men with SM (46% < 50 years; 73% > 50 years) is much higher than in women (18% < 50 years; 58% > 50 years) [7]. Despite the low incidence of SM in the general population, a prevalence of 1.25% has been reported in bone biopsies of patients with osteoporosis and a prevalence of 2.25% in patients with osteoporosis under 45 years of age [8]. Up to 28% of fragility fractures have been reported [6]. The risk of osteoporotic fractures is high, especially at the spine and in men [4]. The most frequent site of involvement is the lumbar spine, even more frequent than the hip, reflecting a greater loss of trabecular bone than cortical bone. This is also confirmed by the fact that the majority of fractures occur at the vertebral bodies [7]. The most common risk factors for fragility fractures found in patients with SM are as follows: a low T-score in the femoral

neck, age at diagnosis, male sex, alcohol consumption, and high bone marrow tryptase levels [6, 9].

The exact mechanism of fracture production in patients with mast cell infiltration of the bone marrow is unknown. Osteoporosis in SM has been attributed either to neoplastic infiltration or more likely to the local release of mediators (histamine, heparin, tryptase, lipid mediators, and cytokines). In particular, cytokines such as tumor necrosis factor alpha, IL-1, IL-6, and IL-17 have been suggested to play a role both in promoting osteoclast activity and in inhibiting osteoblast function. Osteoclast activity is also directly stimulated by the local release of other mediators such as histamine, heparin, tryptase, and RANKL. Also, WNT/β-catenin pathway with its inhibitors (DKK1 and sclerostin) might be affected in patients with SM, with consequent inadequate osteoblast bone formation [10–15]. SM is characterized by bone structure deterioration (decrease in bone trabeculae) and increased osteoid and bone cell (both osteoclasts and osteoblasts) numbers [16].

In SM with bone involvement, there is a prevalence of bone resorption; therefore, antiresorptive drugs are the rational treatment of bone manifestation in SM. The central role of osteoclasts makes bisphosphonates, a type of antiresorptive drug, the most rational treatment for bone involvement in systemic mastocytosis [7]. Currently, mastocytosis-related osteoporosis is treated orally or intravenously with bisphosphonates, with evidence of efficacy on BMD and BTM [17]. The use of teriparatide should not be proposed as an alternative approach in the management of mastocytosis-related osteoporosis as this treatment might further enhance the growth and proliferation of abnormal MCs and induce more aggressive forms of SM [7].

The presence of idiopathic osteoporosis or unexplained fragility fractures, in the absence of trigger factors for anaphylaxis, might be the only sign of a latent SM. The diagnosis of SM can remain hidden for years due to the absence of concordant symptoms. Consideration of causes of secondary osteoporosis, particularly in young people with severe osteoporosis, is recommended [18]. Serum-tryptase is the recommended biomarker of choice to screen patients with unexplained osteoporosis and/or suspected mastocytosis because it is a specific mediator of mast cells and is widely available. If serum tryptase levels are > 25 ng/ml, the diagnosis consists in the histological examination of the bone marrow biopsy [19].

Conclusion

Osteoporosis in premenopausal women, especially in young women, is a rare condition that should always be investigated to look for the presence of secondary causes. Therefore, in a young patient with osteoporosis and fractures where other causes of secondary osteoporosis have already been excluded, we need to rule out SM by determining serum tryptase levels, even in the absence of typical clinical signs or symptoms of this disease. Elevated serum tryptase levels will allow us to select patients who need a bone marrow study and to support the definitive diagnosis earlier.

Compliance with ethical standards

Conflict of interest None.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Horny HP, Sotlar K, Valent P (2007) Mastocytosis: state of the art. Pathobiology 74:121–132
2. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluin-Nelemans HC, Hamdy NAT, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M, Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP, Metcalfe DD (2007) Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Investig 37:435–453
3. Gülen T, Hägglun H, Dahlen B, Nilsson G (2015) Mastocytosis: the puzzling clinical spectrum and challenging diagnostic aspects of an enigmatic disease (review). J Intern Med 279(3):211–228
4. Rossini M, Zanotti R, Viapiana O, Tripi G, Orsolini G, Idolazzi L, Bonadonna P, Schena D, Escribano L, Adami S, Gatti D (2014) Bone involvement and osteoporosis in mastocytosis. Immunol Allergy Clin N Am 34(2):383–396
5. Kanis JA (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO study group. Osteoporos Int 4:368–381
6. Degboé Y, Eischen M, Nigon D, Apoil PA, Mailhol C, Tournier E, Laurent C, Hanssens K, Hermine O, Paul C, Laroche M, Bulai-Livideanu C (2017) Prevalence and risk factors for fragility fracture in systemic mastocytosis. Bone 105:219–225
7. Van der Goot W, de Monchy JG, Kluin-Nelemans HC, van Doormaal JJ (2012) High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. Allergy 67(3):431–438
8. Delling G, Ritzel H, Werner M (2001) Histological characteristic and prevalence of secondary osteoporosis in systemic mastocytosis. A retrospective analysis of 158 cases. Pathologe 22:132–140
9. Van der Veer E, Arends S, Van der Hoek S et al (2014) Predictors of new fragility fractures after diagnosis of indolent systemic mastocytosis. J Allergy Clin Immunol 134(6):1413–1421
10. Metcalfe DD (2008) Mast cells and mastocytosis. Blood 112:946–955
11. Schwartz LB (1987) Mediators of human mast cells and human mast cell subsets. Ann Allergy 58:226–235
12. Macpherson JL, Kemp A, Rogers M et al (1989) Occurrence of plateletactivating factor (PAF) and an endogenous inhibitor of platelet aggregation in diffuse cutaneous mastocytosis. Clin Exp Immunol 77:391–396
13. Theoharides TC, Boucher W, Spear K (2002) Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int Arch Allergy Immunol 128:344–350
14. Brockow K, Akin C, Huber M, Metcalfe DD (2005) IL-6 levels predict disease variant and extent of organ involvement in patients with mastocytosis. Clin Immunol 115:216–223

15. Chiappetta N, Gruber B (2006) The role of mast cells in osteoporosis. Semin Arthritis Rheum 36:32–36
16. Seitz S, Barvencik F, Koehne T, Priemel M, Pogoda P, Semler J, Minne H, Pfeiffer M, Zustin J, Püschel K, Eulenburg C, Schinke T, Amling M (2013) Increased osteoblast and osteoclast indices in individuals with systemic mastocytosis. Osteoporos Int 24:2325–2334
17. Rossini M, Zanotti R, Viapiana O et al (2014) Zoledronic acid in osteoporosis secondary to mastocytosis. Am J Med 127(1127): e1121–e1124
18. Zhu JJ, Mahendran D, Lee MH, Seah J, Fourlanos S, Varadarajan S, Ghasem-Zadeh A, MacIsaac RJ, Seeman E (2018) Systemic mastocytosis identified in two women developing fragility fractures during lactation. Osteoporos Int 29(7):1671–1674
19. Rossini M, Zanotti R, Orsolini G, Tripi G, Viapiana O, Idolazzi L, Zamò A, Bonadonna P, Kunnathully V, Adami S, Gatti D (2016) Prevalence, pathogenesis, and treatment options for mastocytosis-related osteoporosis. Osteoporos Int 27:2411–2421