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Case Report

A 48-Year-Old Man With a Hip Fracture and Skin Rash: A Case Report

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ABSTRACT

Background/Objective: Patients with systemic mastocytosis are at high risk of developing osteoporosis and fractures. Herein, we report a case of hip fragility fracture in a patient with indolent systemic mastocytosis and normal bone density.

Case Report: A 48-year-old man experienced a left femoral neck fracture after a fall. After a dose of oxycodone/hydromorphone postoperatively, he developed an anaphylactic reaction. Previously, he experienced a few other episodes of flushing, dizziness, and syncope precipitated by stress and alcohol. His examination was notable for pink and brown macules on his chest, back, arms, and legs. His laboratory test revealed a markedly elevated tryptase level of 171 ng/mL (<11 ng/mL). Treatment including cetirizine, montelukast, and ranitidine controlled his symptoms. His bone density test result was normal. Ten months after hip surgery, his c-terminal telopeptide of collagen type 1 and bone-specific alkaline phosphatase levels significantly increased. The bone scan demonstrated diffusely increased radiotracer uptake throughout the osseous structures. Given high bone turnover and the prior hip fracture, he received zoledronic acid yearly for 3 years, and no further fractures have occurred.

Discussion: The case is unusual as the fracture occurred despite normal bone density and significant osteosclerosis, which was previously considered protective against fractures. Additionally, rather than the spine, the fracture occurred in the hip, which is an uncommon site for mastocytosis-induced fractures.

Conclusion: Mastocytosis is a rare cause of osteoporosis, and it is important to keep this condition in the differential diagnosis of osteoporosis, particularly when the fracture presentation is atypical.

Introduction

Mastocytosis is a rare cause of secondary osteoporosis with an incidence of approximately 0.5%.[1] In this population, older age, male sex, and an increased N-methylhistamine level are independent risk factors for osteoporotic fractures.[2] Osteoporosis in systemic mastocytosis (SM) can be attributed to neoplastic mast cell involvement or as a result of cytokine, histamine, tryptase, and heparin activating osteoclast directly or indirectly through the activation of the RANK-RANKL system.[3,4]

Herein, we report a case of hip fragility fracture in a patient with indolent SM and normal bone density.

Case Report

A 48-year-old man experienced a left femoral neck fracture after slipping and falling on ice. He underwent open reduction and internal fixation of the fracture. A few hours after surgery, after receiving a dose of oxycodone/hydromorphone, he developed diffuse redness, diaphoresis, pounding heartbeats, acute onset of shortness of breath, and vomiting, and became unresponsive. His blood pressure, heart rate, and oxygen saturation level were 60/40 mm Hg, 143 beats/minute, and 93%, respectively. He was intubated and briefly placed on intravenous phenylephrine and epinephrine drip. A similar episode occurred the following day after he took the same medication. Over the past 3 years, he experienced a persistent, pruritic rash characterized by constant pink and brown

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, c-terminal telopeptide of collagen type 1; SM, systemic mastocytosis.

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macules that gradually expanded on his torso. The rash had been previously evaluated, and a dermatologist clinically diagnosed it as Grover disease, even though a biopsy was not performed at that time. Additionally, he had intermittent episodes of flushing, dizziness, and syncope during this period. Initially, these episodes were attributed to anemia and iron deficiency, despite normal endoscopy and colonoscopy results. Notably, both the rash and syncope episodes were exacerbated or triggered by factors such as stress, alcohol, chocolates, tomatoes, cheese, aged steak, and other fermented foods. Upon examination, he exhibited prominent pink and brown macules on his chest, back, arms, and legs.

His laboratory tests revealed a markedly elevated tryptase level of 171 ng/mL (<11 ng/mL). Additionally, his 24-hour urine N-methylhistamine level significantly increased at 1418 mcg/g creatinine (30-200 mcg/g creatinine). His symptoms were controlled by cetirizine, montelukast, and ranitidine. His skin biopsy showed telangiectasia macularis eruptive perstans, an uncommon skin presentation of mastocytosis (Fig. 1 *A* and *B*). Subsequent bone marrow biopsy revealed the presence of 20% to 30% discrete medium to large aggregates of abnormal spindle-shaped mast cell involvement with D816V-KIT mutation (c. 2447A >T) (Fig. 1 *C* through *F*). His bone density was within the normal range for his age, with lumbar spine, right total hip, and right femoral neck z-scores of −1.7, −0.9, and −1.0, respectively. His vertebral fracture analysis also confirmed the absence of any occult spine fractures. Six months after his initial presentation, his c-terminal telopeptide of collagen type 1 (CTX) and alkaline phosphatase levels significantly increased at 813 pg/mL (60-700 pg/mL) and 484 IU/L (40-130 IU/L), respectively. Ten months after hip surgery, his CTX level was still elevated at 756 pg/mL along with an increased alkaline phosphatase level at 269 IU/L and bone-specific alkaline phosphatase (BSAP) level of 68.9 mcg/L (7.6-14.9 mcg/L). The calcium and albumin levels were both within the normal ranges. Other laboratory test results showed normal vitamin D and parathyroid hormone levels of 38 ng/mL (30-60 ng/mL) and 41 pg/mL (15-65 pg/mL), respectively. A bone scan was obtained to investigate the presence of other potential causes of the increased BSAP level, including the possibility of metastasis. It demonstrated diffusely increased radiotracer uptake throughout the osseous structures (Fig. 2), consistent with a superscan. A superscan detected on bone scintigraphy typically indicates either metabolic bone disease or diffuse metastases. In this case, the symmetric radiotracer distribution strongly supported the diagnosis of metabolic bone disease. His skeletal survey showed a diffusely mottled appearance with punctate areas of increase sclerosis (Fig. 3). He was diagnosed with indolent SM, and observation was advised by his oncologist.

Because of high bone turnover and a prior hip fracture, he received 5 mg of zoledronic acid. His alkaline phosphatase level quickly returned to the normal range 6 months after the therapy. After the zoledronic acid infusion, his BSAP level gradually reduced to 27.7 and 21.8 mcg/L (7.6-14.9 mcg/L) at 6 and 12 months, respectively. His CTX level decreased to 463 pg/mL at 6 months and then slightly increased to 570 pg/mL (60-700 pg/mL) at 12 months after therapy. Subsequently, he received 2 more doses of zoledronic acid, resulting in a further reduction in the BSAP level to 15.2 mcg/L (7.6-14.9 mcg/L) and CTX level to 383 pg/mL (60-700 pg/mL). His follow-up bone density test, conducted 1 year after treatment, showed a 15.8% increase in spine bone density and 13% increase in hip bone density. The lumbar spine z-score improved to −1.4, the right total hip z-score increased to −0.1, and the right femoral neck z-score improved to −0.1. He has not experienced another fracture over the following 3 years. Although his tryptase level remains elevated, it has stabilized at 174 ng/mL (<11 ng/mL).

Highlights

- Hip fracture is uncommon in mastocytosis-induced fractures
- Mastocytosis-induced fracture can occur with normal bone mineral density and osteosclerosis
- Bisphosphonates are effective for mastocytosis-induced osteoporosis and fractures

Clinical Relevance

We describe the presentation and treatment of a man who developed a hip fragility fracture in the setting of indolent systemic mastocytosis. This case serves as a reminder of the importance of considering mastocytosis in the differential diagnosis of secondary osteoporosis and highlights that fractures can occur even in individuals with normal bone density.

Discussion

Indolent SM is diagnosed using criteria similar to those for SM but is characterized by its indolent course and favorable prognosis. It lacks hematologic malignancy, splenomegaly, hepatomegaly, or other aggressive features. Despite its indolent nature, the skeletal system is frequently affected, with manifestations including osteoporosis, diffuse osteosclerosis, and the presence of focal osteolytic or focal osteosclerotic lesions. Previous studies have reported the osteoporosis rate ranging from 18% to 31% in patients with indolent SM, using traditional diagnostic criteria.[5] Rossini et al,[6] using a z-score cutoff of less than −2 for diagnosis, reported an overall prevalence of 20%, with men exhibiting a higher likelihood (28%) than women (9%). Although vertebral fractures accounted for 62% and other non−vertebral fractures accounted for 36% of osteoporotic fractures, hip fractures were less common, constituting only 1% of cases, as per a study.[2]

The bone manifestations of SM are diverse, encompassing osteopenia and osteoporosis with or without fragility fractures, osteosclerosis with increased bone density, as well as isolated lytic lesions or mixed sclerotic and lytic lesions.[7] Risk factors for fractures in this context include male sex, older age, higher levels of bone resorption markers, lower hip bone mineral density, lower DKK1 level, absence of urticaria pigmentosa, and alcohol intake.[7,8] In individuals with osteoporosis and mastocytosis, the bone marker levels can be elevated, normal, or reduced, independent of the tryptase level. However, patients with osteosclerosis and mastocytosis tend to exhibit increased levels of both CTX and tryptase,[6] which is consistent with the findings observed in this case. Because bone density is not always correlated with bone fragility,[7] it is possible for patients with mastocytosis to experience fractures despite having normal bone density, as observed in our patient.

A high prevalence of vertebral fracture is observed in individuals with SM, with a study reporting an overall fracture rate of 28.1% and a vertebral fracture rate of 22.5%, often involving multiple vertebrae.[9] This phenomenon is speculated to be attributed to clonal mast cell infiltration of the bone marrow or a preferential involvement of highly metabolically active bone tissues, such as the trabecular bone.[6] It is noteworthy that our patient did not present with vertebral fractures. A prior study suggests that individuals with increased methylhistamine levels are more likely to exhibit osteosclerosis and increased bone density in the trabecular bone while experiencing a reduction in cortical bone density. This may explain why our patient did not experience spine fractures, as is observed in the majority of other patients.[10] It is postulated that

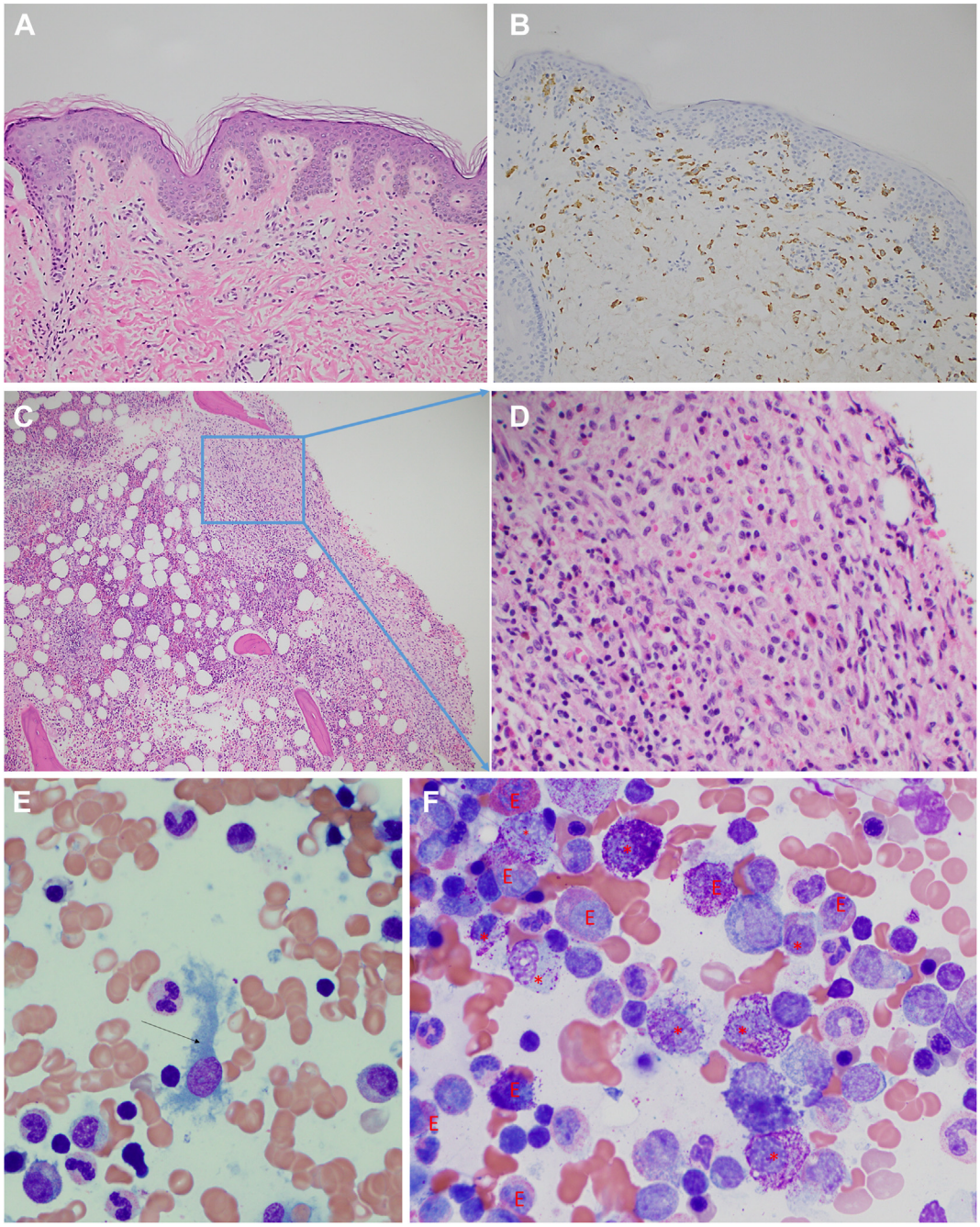

Fig. 1. The skin biopsy specimen showed loosely clustered mast cells in the superficial/papillary dermis, accompanied by mild vascular ectasia (hematoxylin and eosin [H&E] staining, 50×; panel *A*). Immunohistochemical staining confirmed linage-specific tryptase expression (50×, panel *B*). The bone marrow aspirates showed aggregates of spindly mast cells located adjacent to bone trabeculae (H&E, 20× [panel *C*]; H&E, 50× [panel *D*]). The pale mast cells had oval nuclei and abundant cytoplasm (Giemsa-Wright staining, 100×; panel *E*) and were admixed with eosinophils and eosinophil precursors (Giemsa-Wright staining, 100×; panel *F*).

patients with diffuse osteosclerosis are protected from fractures because of increased bone density; however, it is possible that our patient had patchy osteosclerosis and the hip was not a protected site.[5,10]

Mast cells release a number of vasoactive substances. Among them, histamine stimulates osteoblasts for bone formation, whereas substances such as heparin and prostaglandin D2 induce bone resorption by activating osteoclasts.[10] Because of the absolute or relative predominance of bone resorption process, bisphosphonates are often considered first-line therapy.[5] The extent of bone involvement depends on the number and distribution of mast cells, rather than the cutaneous involvement.[5] In terms of treatment, a prior study suggested that a single dose of zoledronic acid reduced the bone alkaline phosphatase levels by 34% and 35% and c-terminal telopeptide levels by 68% and 56% at 6 and 12 months, respectively.[11] In our patient, 1 dose of zoledronic acid reduced the bone alkaline phosphatase levels by 60% and 68% and c-terminal telopeptide levels by 39% and 24% at 6 and 12 months, respectively. The reduction in the BSAP levels appeared to be more significant than the changes in the CTX levels, which is opposite to what was previously reported.[11] We suspect that this phenomenon is likely due to a more dominant osteosclerosis process in this case.

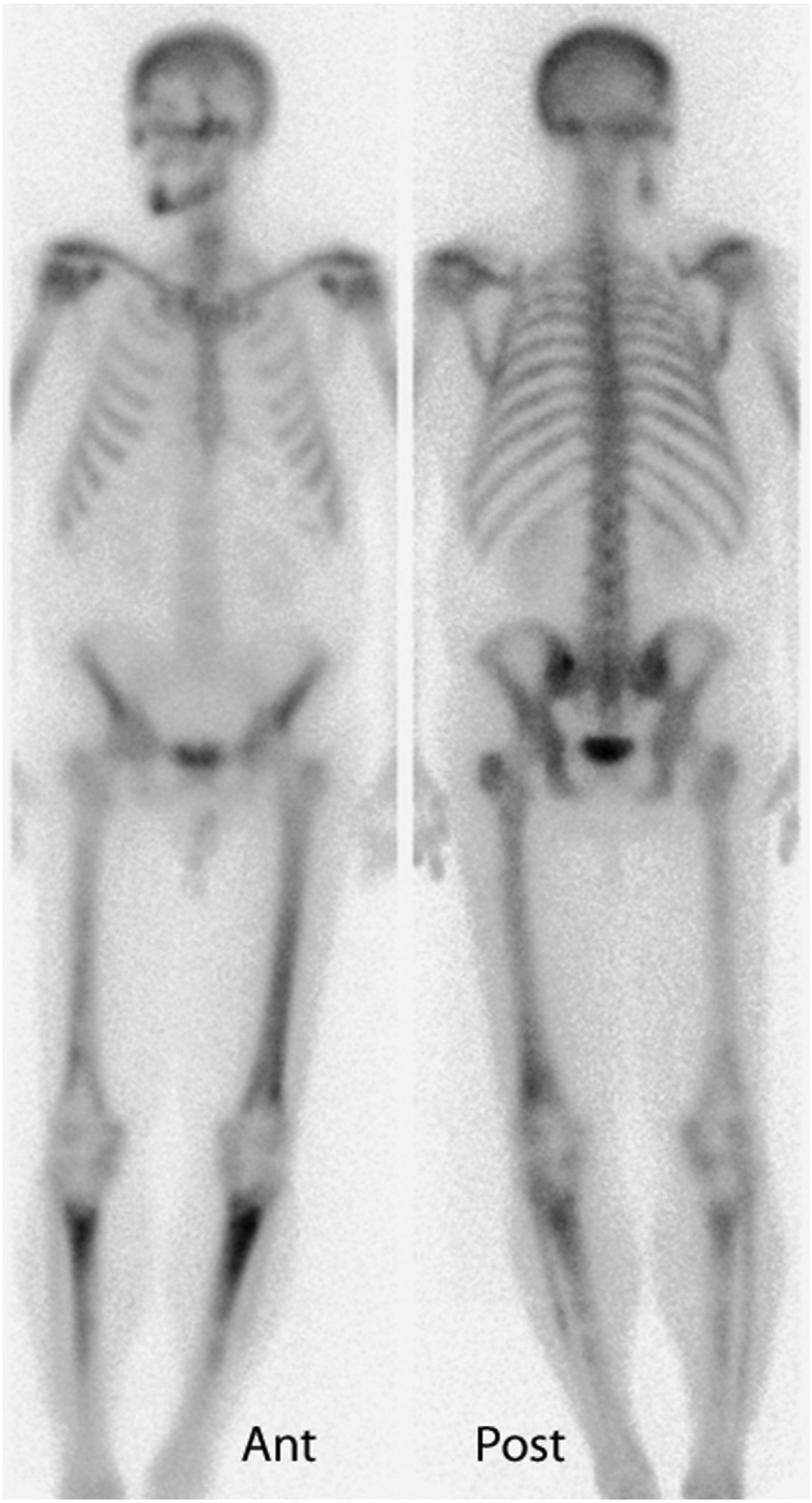

Fig. 2. Bone scan consistent with a super scan.

Our patient did well with zoledronic acid treatment. Nevertheless, the lingering question is how long these patients should be treated with bisphosphonates, given the underlying etiology has not been addressed, variable bone pathologies, and some cases with mixed osteosclerotic and osteolytic changes. We agree with others that clearly, more research is needed in this area.[7]

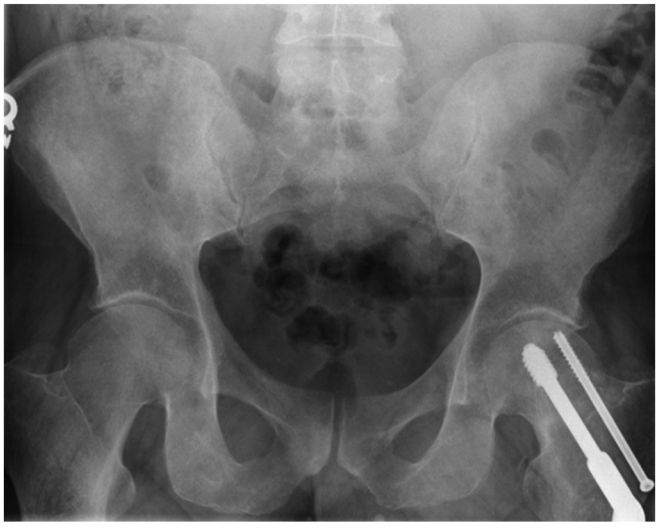

Fig. 3. Hip radiography revealed a diffuse mottled appearance with punctate areas of increased sclerosis.

Conclusion

In conclusion, mastocytosis is a rare cause of osteoporosis. It is important to include this disease in the differential diagnosis of osteoporosis. Patients with osteosclerosis can still experience fractures, even with normal bone density. Bisphosphonates are an effective treatment and should be considered for all patients with bone involvement. The lack of guidelines in this area underscores the necessity for individualized treatment approaches.

Disclosure

The authors have no multiplicity of interest to disclose.

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References

1. Gehlen M, Schmidt N, Pfeifer M, et al. Osteoporosis caused by systemic mastocytosis: prevalence in a cohort of 8392 patients with osteoporosis. *Calcif Tissue Int*. 2021;109(6):685–695.
2. van der Veer E, van der Goot W, de Monchy JG, Kluin-Nelemans HC, van Doormaal JJ. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. *Allergy*. 2012;67(3):431–438.
3. Orsolini G, Viapiana O, Rossini M, Bonifacio M, Zanotti R. Bone disease in mastocytosis. *Immunol Allergy Clin North Am*. 2018;38(3):443–454.
4. Rossini M, Zanotti R, Orsolini G, et al. Prevalence, pathogenesis, and treatment options for mastocytosis-related osteoporosis. *Osteoporosis Int*. 2016;27(8):2411–2421.
5. Rossini M, Zanotti R, Viapiana O, Tripi G, Orsolini G, Idolazzi L, Bonadonna P, Schena D, Escribano L, Adami S, Gatti D. Bone involvement and osteoporosis in mastocytosis. *Immunol Allergy Clin N Am*. 2014;34(2):383–396.
6. Rossini M, Zanotti R, Bonadonna P, et al. Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. *Bone*. 2011;49(4):880–885.
7. Greene LW, Asadipooya K, Corradi PF, Akin C. Endocrine manifestations of systemic mastocytosis in bone. *Rev Endocr Metab Disord*. 2016;17(3):419–431.
8. van der Veer E, Arends S, van der Hoek S, et al. Predictors of new fragility fractures after diagnosis of indolent systemic mastocytosis. *J Allergy Clin Immunol*. 2014;134(6):1413–1421.
9. Degboé Y, Eischen M, Apoil PA, et al. Higher prevalence of vertebral fractures in systemic mastocytosis, but not in cutaneous mastocytosis and idiopathic mast cell activation syndrome. *Osteoporos Int*. 2019;30(6):1235–1241.
10. Johansson C, Roupe G, Lindstedt G, Mellstrom D. Bone density, bone markers and bone radiological features in mastocytosis. *Age Ageing*. 1996;25(1):1–7.
11. Rossini M, Zanotti R, Viapiana O, et al. Zoledronic acid in osteoporosis secondary to mastocytosis. *Am J Med*. 2014;127(11):1127.e1–1127.e4.