

Osteoporosis in systemic mastocytosis — current therapeutic options based on a clinical case report

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ABSTRACT

Systemic mastocytosis (SM) is a rare hematologic neoplastic disorder characterized by infiltration of various organs by clonal mast cells. It is characterized by cutaneous and organ involvement (hepatosplenomegaly, osteolytic lesions, pathological fractures) and systemic symptoms related to the release of anaphylaxis mediators. Based on the 5th Edition of the World Health Organization (WHO-5) criteria and the International Consensus Classification (ICC) systems, systemic mastocytosis was diagnosed in a 50-year-old patient. The disease course included fractures of the TH11 and L1 vertebrae, and densitometric tests revealed low bone mineral density (BMD). The patient was treated with risedronate for 3 years, however treatment was discontinued due to side effects such as abdominal pain and nausea. The therapy was switched to intravenous zoledronic acid, resulting in a significant increase in BMD in control tests and relief from pain. No new osteoprotic fractures were observed during the treatment.

Keywords: mastocytosis, osteoporosis, treatment, bisphosphonates

INTRODUCTION

Systemic mastocytosis (SM) is a rare hematologic neoplastic disorder, with an estimated incidence of 5–10 cases per million people per year [1]. SM is most commonly caused by the D816V mutation in the gene encoding the KIT receptor (a transmembrane receptor with tyrosine kinase activity) [2]. The disease is characterized by excessive proliferation and accumulation of abnormal, clonal mast cells [3] in various organs, including bones, spleen, lymph nodes, bone marrow, and the digestive tract [4, 5]. The main symptoms of the disease include skin changes (urticaria pigmentosa, Darier's sign, itching), anaphylaxis symptoms (hypotension, fainting, sudden skin redness), and symptoms related to organ involvement (hepatosplenomegaly, malabsorption syndrome, anemia, osteolytic lesions, and pathological fractures). Osteoporosis is common

in patients with SM, with its occurrence being three times more frequent than in the general population [6]. The risk of fractures is particularly high in men, mainly involving compression fractures of the spine [7]. The mechanism of bone loss has not been fully explained. Treatment primarily involves inhibiting bone resorption using antiresorptive medications.

CASE REPORT

The 50-year-old patient has been experiencing urticaria pigmentosa, itching of the skin, Darier's sign after physical exertion, episodic flushing, and palpitations for several years. In 2015, the patient suffered a compression fracture of the spine in the Th11 and L1 segments (see Figure 1). Abdominal ultrasound revealed hepatic steatosis and enlargement. Trephine biopsy of the bone

Table 1. Criteria for the diagnosis of systemic mastocytosis according to the WHO from 2022 [9]

Major criterion	Does the patient meet the major criterion of the disease?
1. Presence of multifocal dense infiltrates of mast cells (≥ 15 mast cells) in the bone marrow and/or other extracutaneous organs.	Yes
Minor criteria	Does the patient meet the minor criteria of the disease?
1. Presence of $> 25\%$ spindle-shaped/atypical morphology mast cells in a trephine biopsy or other organ (excluding the skin).	Yes
2. Presence of a point mutation in the KIT gene (most commonly D816V) in the bone marrow or other organ (excluding the skin).	Yes
3. Mast cells in the bone marrow, blood, or other organs (excluding the skin) demonstrating expression of CD2 and/or CD25 and/or CD30 (in immunophenotypic or immunohistochemical analysis).	No
4. Demonstration of elevated tryptase levels in blood serum > 20 ng/mL*	Yes

Diagnosis: Fulfillment of one major criterion and one minor criterion or three minor criteria

*Except in cases where the presence of an accompanying hematological malignancy has been identified

Table 2. Results of dual-energy X-ray absorptiometry (DXA) examination of lumbar spine L2–L4 and the femoral neck from 2017 to 2023 (Hologic). L1 has been excluded from analysis due to fracture

Year of examination	Patient's age	Lumbar spine L2–L4			Neck of the femur		
		BMD [g/cm ²]	T-score	% change in BMD compared to the first examination	BMD [g/cm ²]	T-score	% change in BMD compared to the first examination
2017	50	0.693	-3,8	-	0.709	-1.6	-
2019	52	0.836	-2.5	20.6	0.706	-1.6	-0.5
2020	53	0.885	-2.1	27.8	0.711	-1.6	0.3
2021	54	0.936	-1.6	35.1	0.713	-1.6	0.5
2022	55	0.865	-2.3	25.0	0.673	-1.9	-5.1
2023	56	0.959	-1.4	38.4	0.767	-1.2	8.2

marrow showed dense, multifocal infiltrates of mast cells. Repeated measurements of tryptase levels were significantly elevated (44 and 54 ng/mL). Genetic tests confirmed the presence of a mutation in the D816V region of the KIT gene in a blood sample using the allele specific PCR according to Schumacher et al. The variant allele frequency of KIT D816V was found to be approximately 10% cells. Based on the 2022 World Health Organization criteria (see Table 1) the patient was diagnosed with systemic mastocytosis (SM). Our patient's disease is subclassified as Aggressive SM (ASM) due to of C-findings (large osteolytic lesions with pathological fractures). There were no B-findings (mast cell burden) criteria. Furthermore, the patient meets the ICC criteria based on the same features [8].

In response to pathological fractures in the patient, a dual-energy X-ray absorptiometry (DXA) scan of the L2–L4 vertebrae and the femoral neck was conducted, revealing a significant low bone mineral density (BMD) (see Table 2). He was treated with risedronate 35 mg weekly, vitamin D3 and calcium. Despite a 3-year-long therapy, treatment was discontinued due to side effects such as abdominal pain and nausea. Intravenous zoledronic acid (5 mg/5 mL, once a year) was administered, following the recommended protocol for primary osteoporosis treatment. Subsequent DXA scans showed an improvement in BMD, and no new pathological fractures were observed (see Table 2). Patient did not receive any cytoreductive treatment therapy.

DISCUSSION

An essential aspect of SM treatment is the use of individualized therapy, which was applied to the described patient. The goal of ASM treatment is reducing the severity of symptoms associated with mast cell degranulation and decreasing organ infiltration [8]. To assess bone structure, it is recommended that all patients undergo dual-energy X-ray absorptiometry (DXA), as osteopenia and osteoporosis often coexist with SM [10]. In cases of bone infiltration, the primary goal was to protect against the progression of osteolytic lesions with fractures. For SM patients with C-findings, cytoreductive treatment, including KIT-targeting tyrosine kinase inhibitors (KITi) therapy, is recommended. Until 2024, KIT tyrosine kinase inhibitors such as midostaurin and avapritinib were not available for ASM treatment in Poland [8]. The patient received only antiresorptive therapy initially with risendronte, then with zoledronic acid, which resulted in a good effect on bone mineral density, pain, and fractures. In case of bisphosphonate treatment failure or intolerance, cytoreductive drugs or interferon-alpha (IFN-alpha) are introduced [11]. IFN-alpha reduces mast cell infiltrates in the bone marrow and alleviates symptoms triggered by mast cell mediators. Alternatively, denosumab can be used, which is a human monoclonal antibody directed against RANKL (the nuclear factor kappa B ligand) [2]. It inhibits the activation of the RANK (the receptor activator of nuclear factor kappa B)

Table 3. Proposed treatment scheme for osteoporosis in the course of systemic mastocytosis modified based on [11]

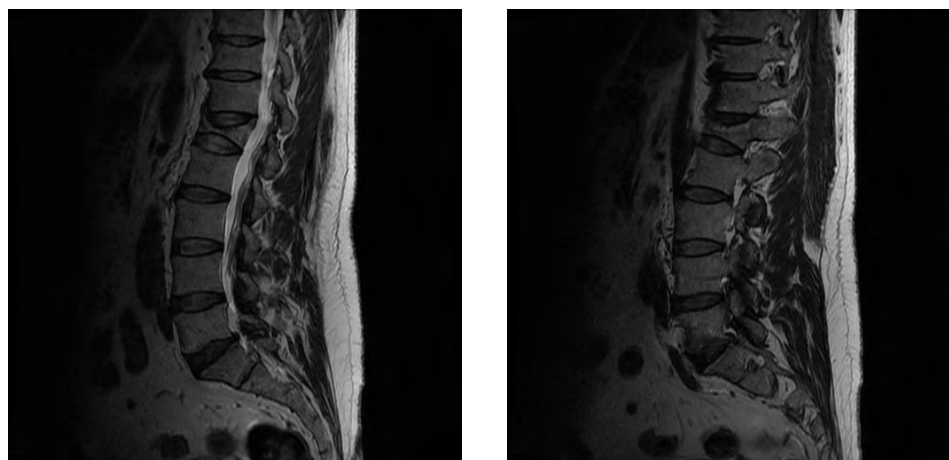
Treatment ladder	Drug class	Specific drugs/dose	Adverse effects
First line	Bisphosphonate	Alendronate 70 mg q week Risedronate 35 mg q week Pamidronic acid 90 mg IV q 4 weeks Zoledronic acid 4 mg IV q 4 weeks	Vomiting, diarrhea, abdominal pain, nausea, hypocalcemia, nephrotoxicity, rash, musculoskeletal pain, headache, osteonecrosis of the jaw (ONJ)
	Monoclonal antibody	Denosumab 60 mg SC q 6 months	Atypical fractures, hypophosphatemia, diarrhea, weakness, ONJ
Second line	Cytokine/ /immunomodulatory drug	Interferon- α Starting dose: 1–3 MU SQ three times per week Target dose: 3–5 MU SQ 3–5 times per week	Flu-like symptoms, headaches, chills, fever, vomiting, abdominal pain, constipation, taste disturbances
Third line	Purine nucleoside analogue	2-Chlorodeoxyadenosine (Cladribine/2-CdA) Dose: 5 mg/m ² IV \times 5 days every 4–8 weeks	Immunosuppression, myelosuppression, severe anemia, fever, rash

Table 4. Factors that can lead to the release of mast cell mediators

Physical factors	Heat, cold, pressure, UV radiation, vibrations, pressure
Emotional factors	Fatigue, anxiety, stress
Medications and drugs	Nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (aspirin), opioids, muscle relaxants used in general anesthesia, local anesthetics, iodine contrasts, alcohol
Other	Insect venoms, invasive procedures, infections, hormones (gastrin, estrogens)

Table 5. The impact of the mast cell activity on bone mineralization

Mast cells	Mechanism of action	Metabolic consequences
Histamine	Activated osteoclast Activated fibroblast	Osteopenia Tissue reemodelling
Tryptase	Activated osteoclastic resorption	Osteoporosis
TNF- α	Epithelial inflammation	Osteoclastic resorption
Chymases	MMP (metalloproteinase)	Vascular remodelling epithelial remodelling

**Figure 1.** Compression fractures of the L1 vertebrae visible in lumbar spine MRI

receptor on the surface of osteoclast precursors and mature osteoclasts. This prevents bone resorption and their survival. 60 mg of denosumab is administered subcutaneously every 6 months. The use of parathyroid hormone analogs (teriparatide) is not recommended due to their proliferative effect on abnormal mast cells resulting from SM. Additionally, it may lead to the induction of more aggressive forms of the disease [7]. The action of teriparatide involves stimulating bone formation and the reabsorption of calcium from the body.

Patients should be educated to avoid stimuli triggering mast cell degranulation (see Table 4) [12]. Elevated histamine levels have been shown to impact the development of SM-associated osteoporosis by enhancing osteoclastogenesis and inhibiting calcitriol synthesis [13]. In mastocytosis, an increased level of RANKL, a positive regulator of osteoclasts, as well as osteoprotegerin (OPG), a RANKL antagonist, is observed. Tryptase can activate osteoblasts and stimulate OPG production, increasing bone turnover and formation (Table 5). These substances identified in

a patient with mastocytosis may serve as specific markers of bone mineral changes [13, 14]. Understanding these mechanisms may enable the implementation of appropriate complementary therapy.

CONCLUSIONS

The treatment of osteoporosis in the course of systemic mastocytosis involves the use of oral or intravenous bisphosphonates (BP). In this case, zoledronic acid therapy has shown a significant increase of BMD and reduced risk of fracture. In severe cases or in patients with BP contraindications, IFN- α and denosumab are used. However, more data is needed to better understand the mechanism of bone involvement and assess the impact of available treatments on systemic mastocytosis. Nowadays there are new therapies like KIT inhibitors; midostaurin and avapritinib. It may be optimal management because it addresses the causal treatment of SM, eliminating all symptoms, including bone-related ones.

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REFERENCES

1. Amon U, Hartmann K, Horny HP, et al. Mastocytosis — an update. *J Dtsch Dermatol Ges*. 2010; 8(9): 695–711; quiz 712, doi: [10.1111/j.1610-0387.2010.07482.x](https://doi.org/10.1111/j.1610-0387.2010.07482.x), indexed in Pubmed: [20678151](https://pubmed.ncbi.nlm.nih.gov/20678151/).
2. Rossini M, Zanotti R, Orsolini G, et al. Prevalence, pathogenesis, and treatment options for mastocytosis-related osteoporosis. *Osteoporos Int*. 2016; 27(8): 2411–2421, doi: [10.1007/s00198-016-3539-1](https://doi.org/10.1007/s00198-016-3539-1), indexed in Pubmed: [26892042](https://pubmed.ncbi.nlm.nih.gov/26892042/).
3. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest*. 2007; 37(6): 435–453, doi: [10.1111/j.1365-2362.2007.01807.x](https://doi.org/10.1111/j.1365-2362.2007.01807.x), indexed in Pubmed: [17537151](https://pubmed.ncbi.nlm.nih.gov/17537151/).
4. Valent P, Akin C, Sperr WR, et al. New insights into the pathogenesis of mastocytosis: emerging concepts in diagnosis and therapy. *Annu Rev Pathol*. 2023; 18: 361–386, doi: [10.1146/annurev-pathmech-dis-031521-042618](https://doi.org/10.1146/annurev-pathmech-dis-031521-042618), indexed in Pubmed: [36270293](https://pubmed.ncbi.nlm.nih.gov/36270293/).
5. Sciumè M, De Magistris C, Galli N, et al. Target therapies for systemic mastocytosis: an update. *Pharmaceuticals (Basel)*. 2022; 15(6): 738, doi: [10.3390/ph15060738](https://doi.org/10.3390/ph15060738), indexed in Pubmed: [35745657](https://pubmed.ncbi.nlm.nih.gov/35745657/).
6. Makovoz A, Wang J, Oshegbo G, et al. Assessment of osteoporosis and fracture risk in mastocytosis within a North American cohort. *J Allergy Clin Immunol Pract*. 2021; 9(12): 4459–4467.e10, doi: [10.1016/j.jaip.2021.08.001](https://doi.org/10.1016/j.jaip.2021.08.001), indexed in Pubmed: [34403839](https://pubmed.ncbi.nlm.nih.gov/34403839/).
7. Gaudio A, Xourafa A, Rapisarda R, et al. Hematological diseases and osteoporosis. *Int J Mol Sci*. 2020; 21(10): 3538, doi: [10.3390/ijms21103538](https://doi.org/10.3390/ijms21103538), indexed in Pubmed: [32429497](https://pubmed.ncbi.nlm.nih.gov/32429497/).
8. Pardanani A, Reichard K, Tefferi A. Advanced systemic mastocytosis — revised classification, new drugs and how we treat. *Br J Haematol*. 2024; 204(2): 402–414, doi: [10.1111/bjh.19245](https://doi.org/10.1111/bjh.19245), indexed in Pubmed: [38054381](https://pubmed.ncbi.nlm.nih.gov/38054381/).
9. El Hussein S, Chifotides HT, Khoury JD, et al. Systemic mastocytosis and other entities involving mast cells: a practical review and update. *Cancers (Basel)*. 2022; 14(14), doi: [10.3390/cancers14143474](https://doi.org/10.3390/cancers14143474), indexed in Pubmed: [35884535](https://pubmed.ncbi.nlm.nih.gov/35884535/).
10. Rossini M, Zanotti R, Viapiana O, et al. Bone involvement and osteoporosis in mastocytosis. *Immunol Allergy Clin North Am*. 2014; 34(2): 383–396, doi: [10.1016/j.jiac.2014.01.011](https://doi.org/10.1016/j.jiac.2014.01.011), indexed in Pubmed: [24745681](https://pubmed.ncbi.nlm.nih.gov/24745681/).
11. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. *Am J Hematol*. 2023; 98(7): 1097–1116, doi: [10.1002/ajh.26962](https://doi.org/10.1002/ajh.26962), indexed in Pubmed: [37309222](https://pubmed.ncbi.nlm.nih.gov/37309222/).
12. Zanotti R, Tanasi I, Crosera L, et al. Systemic mastocytosis: multidisciplinary approach. *Mediterr J Hematol Infect Dis*. 2021; 13(1): e2021068, doi: [10.4084/MJHID.2021.068](https://doi.org/10.4084/MJHID.2021.068), indexed in Pubmed: [34804442](https://pubmed.ncbi.nlm.nih.gov/34804442/).
13. Renke J, Kędzierska-Mieszkowska S, Lange M, et al. Mast cells in mastocytosis and allergy - Important player in metabolic and immunological homeostasis. *Adv Med Sci*. 2019; 64(1): 124–130, doi: [10.1016/j.advms.2018.08.013](https://doi.org/10.1016/j.advms.2018.08.013), indexed in Pubmed: [30641273](https://pubmed.ncbi.nlm.nih.gov/30641273/).
14. Sirufo MM, Suppa M, Ginaldi L, et al. Does allergy break bones? Osteoporosis and its connection to allergy. *Int J Mol Sci*. 2020; 21(3): 712, doi: [10.3390/ijms21030712](https://doi.org/10.3390/ijms21030712), indexed in Pubmed: [31973226](https://pubmed.ncbi.nlm.nih.gov/31973226/).