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Bone fragility in mastocytosis: Clinical insights from a 5-patient retrospective case series

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Abstract

Objective: This retrospective case series aimed to describe 36-month skeletal, biochemical, safety, and patient-reported outcomes in five postmenopausal women with mastocytosis treated with denosumab.

Methods: A technical expert panel (TEP) retrospectively evaluated five consecutive eligible patients with osteoporosis associated with indolent systemic mastocytosis. All subjects underwent physiatric assessment, DXA assessment, and Mini-Osteoporosis Quality of Life (Mini-OQoL) evaluation using the validated Italian version of the questionnaire. Data collected at baseline (T0), 18 months (T1), and 36 months (T2) following initiation of denosumab 60 mg every 6 months, combined with cholecalciferol and calcium supplementation according to individual requirements, were descriptively analyzed.

Results: Over 36 months, femoral and lumbar spine T-scores showed modest improvement/stabilization. Mean femoral T-score improved from -3.9 ± 0.3 at baseline to -3.5 ± 0.3 at 36 months, while lumbar spine T-score improved from -4.3 ± 0.5 SD to -3.9 ± 0.4. Vitamin D levels normalized during follow-up, and Mini-OQoL scores improved from 54.2 ± 9 to 67.3 ± 6. However, BMD remained within the osteoporotic range and one vertebral fracture was documented at 36 months. No severe adverse events were recorded.

Conclusions: In this case series, denosumab was associated with stabilization or modest improvement of BMD and improvement in patient-reported quality of life over 36 months in women with osteoporosis secondary to indolent systemic mastocytosis. These preliminary observations should be interpreted cautiously because of the small sample size, lack of a comparator, and occurrence of one new vertebral fracture during follow-up. Thus, larger multicenter prospective studies are required.

Keywords

Osteoporosis, general medicine, women's health

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1. Introduction

Mastocytosis is a rare pathological condition defined by abnormal mast cell accumulation in one or more tissues, including bone, resulting in heterogeneous clinical outcomes.[1] In nearly 80% of cases, the disorder is driven by an acquired mutation of the *KIT* proto-oncogene, which encodes a transmembrane tyrosine kinase receptor. The D816 V mutation in exon 17 represents the most frequently identified alteration, although other variants have also been described. According to the World Health Organization, mastocytosis is classified into cutaneous and systemic forms.[2]

Systemic mastocytosis represents a chronic condition defined by involvement of at least one extracutaneous organ and is associated with a broad spectrum of clinical manifestations, including skeletal complications.[2,3] Osteoporosis and increased fracture risk affect approximately 20% of patients.

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Bone damage is heterogeneous and may present with both osteolytic and osteosclerotic features, frequently coexisting in the same individual.[3–5]

Several pharmacological approaches are available for managing secondary osteoporosis, including bisphosphonates and denosumab.[4–8] However, a standardized therapeutic approach for osteoporosis in systemic mastocytosis has not yet been established.[8]

Denosumab is a monoclonal antibody targeting RANKL and inhibiting osteoclast differentiation and activation.[6,7] The RANK–RANKL axis plays a central role in mastocytosis-related bone loss because mast cells themselves may express and secrete RANKL.[8] Elevated serum levels of RANKL and osteoprotegerin have also been reported in patients with mastocytosis, further supporting the involvement of the RANKL/RANK/OPG pathway in disease-related bone alterations.[9,10]

Adequate vitamin D status remains an important component of osteoporosis management. Vitamin D contributes to calcium homeostasis and musculoskeletal health,[11–14] and current ESCEO recommendations support supplementation in patients at increased fracture risk and in those receiving antiresorptive therapies.[15,16]

According to ESCEO recommendations, serum 25(OH) D concentrations of at least 50 nmol/L are considered adequate, and daily supplementation with 800–1000 IU of cholecalciferol is advised, particularly in individuals at high fracture risk or receiving anti-osteoporotic therapy.[16]

The present retrospective case series aimed to describe 36-month skeletal, biochemical, safety, and patient-reported outcomes in patients affected by osteoporosis secondary to indolent systemic mastocytosis treated with denosumab. A 36-month follow-up was selected because it corresponds to six scheduled denosumab administrations and permits evaluation of medium-term BMD trends, fracture occurrence, treatment adherence, and adverse events in a rare clinical population.

2. Materials and methods

2.1. Study design

This retrospective case series was conducted by the Technical Expert Panel (TEP) at the Functional Recovery and Rehabilitation Unit (U.O.C.) of the "Paolo Giaccone" University Hospital in Palermo. The TEP retrospectively reviewed records from January 2020 to January 2025 and included all patients who fulfilled the predefined eligibility criteria. Because of the rare condition, the study was designed as a descriptive case series without a comparator group.

The study protocol adhered to the principles outlined in the Declaration of Helsinki and received approval from the Local Ethics Committee Palermo I (Approval No. 2/20245). Data collection and processing were performed in accordance with Good Clinical Practice (GCP) standards. Written informed consent was obtained from all participants for study participation and personal data handling.

2.2. Participants

Clinical information was retrieved from the database of the Regional Reference Center for Osteoporosis (U.O.C. Functional Recovery and Rehabilitation Department) at the University Hospital of Palermo. The dataset included female patients affected by osteoporosis secondary to indolent systemic mastocytosis who had undergone comprehensive physiatric evaluations, including biochemical and instrumental investigations aimed at assessing fragility fractures, bone mineral density variations, and bone metabolism.

All patients had previously undergone DXA examinations at external facilities using the same densitometry device, ensuring consistency of the least significant change (LSC) value. A total of 7524 medical records from January 2020 to January 2025 were screened.

Inclusion criteria were as follows: physiologically postmenopausal women aged between 50 and 60 years; diagnosis of indolent systemic mastocytosis according to World Health Organization criteria established during adolescence; absence of hormone replacement therapy; diagnosis of osteoporosis confirmed by DXA (lumbar spine or femoral T-score ≤ -2.5 SD); ongoing treatment with denosumab 60 mg for a minimum of 36 months, with or without concomitant cholecalciferol and calcium citrate/carbonate supplementation based on individual requirements.

Indolent systemic mastocytosis was confirmed according to World Health Organization diagnostic criteria by the referring hematology/allergy unit, based on clinical history, biochemical assessment, bone marrow evaluation, and/or KIT mutation testing when available. Diagnosis of indolent systemic mastocytosis had been previously established by the referring hematology/allergy unit according to WHO criteria, based on clinical presentation, serum tryptase levels, bone marrow findings, and KIT mutation analysis when available.

Exclusion criteria included: presence of hypocalcemia; recent or planned invasive dental procedures; poor adherence to denosumab therapy; prior treatment with bisphosphonates.

Based on these criteria, five patients were eligible and included in the study. No additional eligible patients meeting the full criteria were excluded. The absence of a control group and the small number of eligible cases should be considered when interpreting the findings.

2.3. Setting

The TEP collected data on previous vertebral fragility fractures using the following assessments:

- Conventional radiographic examination of the thoracolumbar spine in lateral–lateral projection, with morphometric analysis according to Genant's method. Vertebral morphometry was performed by trained clinicians experienced in osteoporosis assessment and reviewed by the TEP. Because of the retrospective study design, assessors were aware of chronological follow-up assessments and treatment status.

Genant's classification categorizes vertebral fractures based on vertebral body shape and the degree of height reduction involving the anterior, middle, and/or posterior portions, as assessed on lateral spinal radiographs. This classification demonstrates high intra-operator (93–99%) and inter-operator (90–99%) agreement. Fractures are graded as follows:

- Grade 0: normal vertebral morphology;
- Grade 1: mild deformity (height reduction <25% or 10–20% reduction in vertebral area);
- Grade 2: moderate fracture (height reduction 25–40% or 20–40% area loss);
- Grade 3: severe fracture (height reduction >40% or area loss >40%).

Anterior height reduction (wedge deformity) was calculated as the ratio between anterior and posterior vertebral height, while posterior height reduction (compression deformity) was assessed as the ratio between posterior and anterior height.

Bone mineral density was evaluated using:

- DXA scans of the lumbar spine and femur.

DXA examinations were performed using the same densitometry device throughout follow-up, ensuring consistency of measurements and least significant change (LSC) interpretation. DXA examinations were performed using a STRATOS DR fan-beam system 2D acquisition; high energy 70 keV and low energy 43 keV).

Dual-energy X-ray absorptiometry (DXA) measures bone mineral density by emitting two X-ray beams at different energy levels. One beam is preferentially absorbed by soft tissues, whereas the other is absorbed by bone. Subtraction of soft tissue absorption allows accurate quantification of bone mineral density. Two indices are derived from DXA:

- **T-score**, representing bone mass relative to a young healthy reference population of the same sex. Values between −1 and −2.5 SD indicate osteopenia, while values below −2.5 SD define osteoporosis;
- **Z-score**, representing bone mass relative to an age- and sex-matched population.

Laboratory evaluations focused on bone metabolism and included:

- **First-level tests:** complete blood count, serum protein electrophoresis, erythrocyte sedimentation rate, serum calcium and phosphate, alkaline phosphatase, creatinine, and 24-h urinary calcium excretion;
- **Second-level tests:** ionized calcium, thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), serum vitamin D, cortisol following overnight dexamethasone suppression test, 24-h urinary cortisol, free testosterone, serum and urinary immunofixation, anti-transglutaminase antibodies, and bone formation markers such as bone-specific alkaline phosphatase and osteocalcin.

Quality of life was assessed using an Italian-language version of the Mini-Osteoporosis Quality of Life (Mini-OQoL) questionnaire.

The Mini-OQoL evaluates five domains—symptoms, emotional status, physical function, daily activities, and social interactions—through 10 items scored on a 7-point Likert scale. Total scores range from 10 to 70, with domain subscores ranging from 2 to 14. A score of 1 indicates severe impairment, whereas a score of 7 reflects optimal functioning without limitations, fear, or anxiety.[26–27]

From a rehabilitation perspective, Mini-OQoL was included to capture patient-centered consequences of bone fragility, including symptoms, daily activities, physical function, emotional status, and social participation. These domains are clinically relevant because vertebral fractures and fear of movement may reduce mobility, independence, and participation even when BMD changes are modest.

In addition to baseline assessment (T0), follow-up evaluations at 18 months (T1) and 36 months (T2) were performed, repeating the same clinical, instrumental, and laboratory assessments after initiation of denosumab 60 mg and cholecalciferol therapy.

Denosumab was administered subcutaneously at a dose of 60 mg every 6 months. Cholecalciferol supplementation was prescribed according to baseline vitamin D status and follow-up serum 25(OH)D levels; Calcium citrate/carbonate supplementation (500–1000 mg elemental calcium daily, according to individual dietary intake and clinical requirements) was provided when dietary calcium intake was considered insufficient. Cholecalciferol supplementation consisted of 25,000 IU every 15 days, administered after meals.

2.4. Statistical analysis

Given the very small sample size (n = 5) and the case-series design, no inferential statistical testing was performed. Data are presented descriptively as individual patient trajectories and, where appropriate, as mean ± standard deviation. The absence of p-values reflects the exploratory nature of the study and avoids overinterpretation of underpowered analyses. Changes over time were interpreted in relation to clinical directionality, fracture occurrence, BMD category, vitamin D normalization, and Mini-OQoL scores.

3. Results

Five postmenopausal women were included, with a mean age of 55.4 years. Patient characteristics at baseline, 18 months, and 36 months are reported in Tables 1, 2, and 3, respectively. Differences in outcome measures across time points (continuous and categorical variables) are summarized in Tables 4 and 5.

Specifically, the following findings were observed:

- Baseline (T0): mean femoral total T-score was −3.9 ± 0.3 SD, while lumbar spine T-score was −4.3 ± 0.5 SD. Five moderate vertebral fractures and one severe fracture were documented. Laboratory values showed PTH levels of 60 ± 5 pg/mL, vitamin D levels of 15 ± 5.7 ng/mL, and a Mini-OQoL score of 54.2 ± 9.
- After 18 months (T1): femoral T-score improved to −3.7 ± 0.2 SD and lumbar T-score to −4.1 ± 0.4 SD. The number of vertebral fractures remained unchanged. Laboratory analysis revealed PTH levels of 43 ± 9 pg/mL, vitamin D levels of 38 ± 9.3 ng/mL, and a Mini-OQoL score of 54.4 ± 10.
- After 36 months (T2): femoral T-score further improved to −3.5 ± 0.3 SD and lumbar T-score to −3.9 ± 0.4 SD. Six moderate fractures and one severe fracture were recorded. Laboratory values showed PTH levels of 39 ± 8.7 pg/mL, vitamin D levels of 45 ± 5.9 ng/mL, and a Mini-OQoL score of 67.3 ± 6.

Across all time points, serum calcium and urinary calcium excretion remained within normal ranges, and no abnormalities were detected in other laboratory parameters. Initial vitamin D deficiency reflected low prior intake, while subsequent supplementation resulted in normalization of serum levels. All patients demonstrated good adherence to the prescribed treatment. Individual patient trajectories are reported in Supplementary Table 1. All patients showed stabilization or improvement in femoral and lumbar spine T-scores throughout follow-up, although bone mineral density values remained within the osteoporotic range. Improvements were more pronounced in patients A and E, whereas patient B maintained the lowest lumbar spine T-scores despite progressive improvement. Vertebral fracture burden remained stable in four patients, while one additional vertebral fracture was documented in patient D at 36 months. Vitamin D status normalized in all patients by the end of follow-up. These individual data highlight the variability of treatment response while confirming the overall trends observed in the descriptive analyses.

4. Discussion

This retrospective case series described 36-month outcomes in five postmenopausal women affected by osteoporosis secondary to indolent systemic mastocytosis and treated with denosumab, focusing on BMD trends, vertebral fracture occurrence, bone metabolism, safety, and quality of life.

Despite inherent limitations, our findings suggest that denosumab therapy over 36 months was associated with stabilization or modest improvement of BMD values and improvement in quality of life. The fracture outcome must be interpreted cautiously because one additional vertebral fracture occurred during follow-up; therefore, these data do not demonstrate fracture prevention or reduced fracture incidence. Alternative therapeutic options for skeletal involvement in systemic mastocytosis include bisphosphonates, zoledronic acid, interferon-alpha therapy, and combined interferon-alpha plus pamidronate regimens.

Antiresorptive agents represent the cornerstone of osteoporosis management in mastocytosis. Several reports support the long-term efficacy of denosumab in preserving skeletal integrity despite ongoing mast cell activity. Denosumab is particularly indicated when bisphosphonates are contraindicated, given the critical involvement of the RANK–RANKL pathway in mastocytosis-related bone loss. Conversely, anabolic agents such as teriparatide are generally discouraged due to their potential to stimulate mast cell proliferation and promote aggressive disease forms, as highlighted by Rossini et al.[16]

Compared with previous reports on denosumab in mastocytosis-related osteoporosis, particularly the case series by Orsolini et al.,[17] the present study provides a longer follow-up period of 36 months and incorporates rehabilitation-oriented patient-reported outcomes through the Mini-OQoL questionnaire. While the small sample size precludes definitive conclusions, our findings contribute additional information regarding the medium-term evolution of quality of life, functional impact, and treatment adherence in patients with mastocytosis-related osteoporosis, complementing the skeletal outcomes assessed by bone mineral density measurements and vertebral fracture monitoring.

Evidence indicates that bisphosphonate-treated patients with prior fractures may remain at elevated fracture risk.[18–19] Zoledronic acid has demonstrated efficacy in

Table 1. Patient-level baseline characteristics (T0).

Patient	Age (years)	Sex	Vitamin D category	PTH category	Femoral T-score	Lumbar T-score	Vertebral fractures, n
A	52	F	Insufficiency (11–30 ng/mL)	Normal (12–70 pg/mL)	−3.6	−3.7	1
B	50	F	Deficiency (<10 ng/mL)	Normal	−4.2	−4.9	2
C	58	F	Deficiency (<10 ng/mL)	Normal	−3.7	−4.0	1
D	60	F	Insufficiency (11–30 ng/mL)	Normal	−4.2	−4.6	1
E	57	F	Deficiency (<10 ng/mL)	Normal	−3.8	−4.3	1

Table 2. Patient-level characteristics after 18 months of treatment (T1).

Patient	Vitamin D category	PTH category	Femoral T-score	Lumbar T-score	Vertebral fractures, n
A	Normal (31–100 ng/mL)	Normal	−3.5	−3.6	1
B	Insufficiency (11–30 ng/mL)	Normal	−4.0	−4.4	2
C	Normal	Normal	−3.7	−3.8	1
D	Normal	Normal	−3.8	−4.5	1
E	Normal	Normal	−3.5	−4.2	1

Table 3. Patient-level characteristics after 36 months of treatment (T2).

Patient	Vitamin D category	PTH category	Femoral T-score	Lumbar T-score	Vertebral fractures, n
A	Normal (31–100 ng/mL)	Normal	−3.3	−3.3	1
B	Normal	Normal	−3.8	−4.2	2
C	Normal	Normal	−3.5	−3.7	1
D	Normal	Normal	−3.7	−4.4	2
E	Normal	Normal	−3.2	−3.9	1

reducing bone turnover markers, although acute-phase reactions are relatively common after the first infusion.[13]

Cytoreductive therapies, such as interferon-α, are primarily reserved for aggressive disease but may be considered in refractory osteoporosis cases. Studies have shown increased bone density and reduced mast cell burden following interferon-α therapy.[20–22]

Emerging therapeutic strategies targeting bone formation pathways, including Wnt signaling modulators such as DKK-1 and sclerostin inhibitors, may offer future benefit, although definitive evidence is lacking.[23] Tyrosine kinase inhibitors represent promising agents for advanced disease but currently lack data regarding skeletal outcomes. Adequate vitamin D and calcium supplementation remains essential across all stages of bone disease.[24]

Vertebral augmentation procedures, particularly kyphoplasty, may be considered for fracture management but require caution due to potential mediator release during intervention.[25] Early diagnosis and timely treatment of osteoporosis in mastocytosis are therefore crucial to improving skeletal outcomes and quality of life.

Patient adherence was excellent, and no severe adverse effects were observed. Mild musculoskeletal pain, paresthesia, and skin rash were the most frequently reported side effects. These findings underscore the importance of compliance in achieving and maintaining therapeutic benefits over time.

No hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, severe infection, or hospitalization related to denosumab was recorded in the available clinical documentation. Because safety assessment was retrospective, minor adverse events may have been underreported.

Limitations include the very small sample size, all-female sample, single-center retrospective design, lack of a control group, and limited ability to control for potential confounders such as dietary calcium intake, sunlight exposure, physical activity, smoking, alcohol consumption, fall risk, comorbidities, and concomitant medications. The selection procedure may also introduce bias, although all eligible patients identified in the institutional database were included. Because only five cases were analyzed, the findings are not generalizable and cannot establish causal treatment efficacy. The descriptive design also limits statistical inference, and fracture outcomes should be interpreted cautiously because one new vertebral fracture occurred at 36 months.

Table 4. Descriptive summary of continuous outcomes at baseline (T0), 18 months (T1), and 36 months (T2).

Outcome	T0	T1	T2
Vitamin D (ng/mL)	15 ± 5.7	38 ± 9.3	45 ± 5.9
PTH (pg/mL)	60 ± 5	43 ± 9	39 ± 8.7
Femoral T-score	−3.9 ± 0.3	−3.7 ± 0.2	−3.5 ± 0.3
Lumbar spine T-score	−4.3 ± 0.5	−4.1 ± 0.4	−3.9 ± 0.4
Vertebral fractures, total n	6	6	7
Mini-OQoL score	54.2 ± 9	54.4 ± 10	67.3 ± 6

Table 5. Categorical distribution of outcomes at T0, T1, and T2.

Variable/category	Definition	T0, n	T1, n	T2, n
Vitamin D normal	31–100 ng/mL	0	4	5
Vitamin D insufficiency	11–30 ng/mL	2	1	0
Vitamin D deficiency	<10 ng/mL	3	0	0
PTH normal	12–70 pg/mL	5	5	5
PTH high	>70 pg/mL	0	0	0
PTH low	<12 pg/mL	0	0	0
DXA normal	T-score > −1 SD	0	0	0
Osteopenia	T-score −1 to −2.5 SD	0	0	0
Osteoporosis	T-score ≤ −2.5 SD	5	5	5
Patients with 1 vertebral fracture	n = 1	4	4	3
Patients with 2 vertebral fractures	n = 2	1	1	2
Patients with 3 vertebral fractures	n = 3	0	0	0
Total vertebral fractures	count of fractures	6	6	7

5. Conclusions

Denosumab therapy was associated with modest improvement or stabilization of bone mineral density and improved Mini-OQoL scores in this 5-patient retrospective case series of osteoporosis secondary to indolent systemic mastocytosis. At baseline, all patients exhibited osteoporotic DXA values, vitamin D deficiency/insufficiency, and vertebral fractures. After 18 months of denosumab and cholecalciferol therapy, vitamin D levels increased, T-scores showed modest improvement, and no new fractures occurred. At 36 months, biochemical improvement and BMD stabilization were maintained, but one patient developed an additional vertebral fracture. Therefore, these preliminary findings suggest potential clinical usefulness but do not prove fracture prevention.

While these results are encouraging, the limited sample size and absence of a control group restrict generalizability. Regular monitoring of bone metabolism from the time of diagnosis remains essential in systemic mastocytosis to ensure early intervention and optimal patient management. Further multicenter prospective studies, ideally including comparator groups and standardized rehabilitation-related outcomes, are required to compare treated and untreated patients and to define the most effective therapeutic strategies.

Ethical approval

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and was approved by the Local Ethics Committee Palermo I (Approval No. 2/20245). Data were handled in compliance with Good Clinical Practice (GCP) guidelines. All patients provided written informed consent for enrollment and the collection of personal data.

Informed consent

All study participants read and signed the informed consent.

Author contributions

Authors' contributions: G.L.M., D.S., conceived the presented idea and were involved in planning and supervised the work. A.d.S., J.A., M.S.M., AD, M.D.S. e S.T. processed the data, performed the analysis and drafted the manuscript. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviation list

-KIT	(gene encoding tyrosine kinase protein)
- CM	(cutaneous mastocytosis)
- UP	(urticaria pigmentosa)
- MPCM	(maculopapular cutaneous mastocytosis)
-DCM	(diffuse cutaneous mastocytosis)
-SM	(systemic mastocytosis)
- SCF	(stem cell factor)
-ISM	(Indolent sistemic mastocytosis)
-SSM	("smoldering" systemic mastocytosis)
- ASM	(aggressive systemic mastocytosis)
- SM-AHNMD	(systemic mastocytosis with associated clonal non-mast cell hematologic disease)
- MCS	(mast cell sarcoma)

- MCL	(mast cell leukemia)
- NSAIDs	(non-steroidal anti-inflammatory drugs)
- TEP	(technical expert panel)
- IFN-alfa	(Interferone alfa)
- BMD	(Bone mineral density)
-MC	(mast cell)
- DXA	(dual-energy X-ray absorptiometry)
- DKK-1	(Dickkopf-1)
- SOST	(sclerostin)
- BTM	(bone turnover marker)
- PAM	(pamidronate)
- RANKL	(nuclear factor kappa-B ligand)
- AdvSM	(Advanced sistemic mastocytosis)
RANK:	receptor activator of nuclear factor-kappa B
RANKL:	receptor activator of nuclear factor-kappa B ligand
OPG:	osteoprotegerin
ESCEO:	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
25(OH)D:	25-hydroxyvitamin D
Mini-OQoL:	Mini-Osteoporosis Quality of Life questionnaire

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