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ORIGINAL ARTICLE

Higher prevalence of vertebral fractures in systemic mastocytosis, but not in cutaneous mastocytosis and idiopathic mast cell activation syndrome

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Abstract

Summary Little is known about osteoporosis in mast cell disorders (MCDs) not related to systemic mastocytosis. We described osteoporosis and fractures in MCDs and showed that systemic mastocytosis was the only studied MCDs associated with osteoporotic vertebral fractures.

Introduction To describe osteoporosis (OP) and fragility fractures in mast cell disorders (MCDs).

Methods We retrospectively analyzed data concerning all successive patients with systemic mastocytosis (SM), cutaneous mastocytosis (CM), and mast cell activation syndromes (MCAS) diagnosed in our mastocytosis expert center between 2004 and 2015. We collected data concerning demographic profiles, clinical signs of MCD, osteoporosis, fractures, densitometry, and biological assessment of MCD. We compared CM and MCAS patients with SM patients with regard to the characteristics of OP and fragility fractures.

Results We assessed 89 SM patients, 20 CM patients, and 20 MCAS patients. Osteoporosis was less frequent in CM (15.0%) and MCAS (10.0%) than in SM (44.9%). Similarly, fractures were less frequent in non-SM MCDs, respectively 5.0%, 5.0%, and 28.1%. SM patients displayed high prevalence of vertebral fractures (22.5%), mostly multiple. Conversely, in non-SM patients, vertebral fractures appeared to be uncommon (5%) and more frequently associated with risk factors for osteoporosis.

Conclusions SM is associated with multiple vertebral osteoporotic fractures, whereas CM and MCAS do not appear to be associated with this phenotype.

Keywords Fracture · Mast cell disorders · Mastocytosis · Osteoporosis

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Introduction

Mast cell disorders (MCDs) are rare conditions associated with mast cell activation, abnormal growth, and/or accumulation in different organs. Among MCDs, SM is known to frequently involve bone with secondary osteoporosis, fragility fractures, and lytic or condensing bone lesions [1–7]. However, little is known about the occurrence of osteoporosis and its mechanisms in other MCDs.

In our study, we aimed to provide data from a monocentric cohort to describe OP and fragility fractures in MCDs.

Patients and methods

Objective

The objective was to compare osteoporosis and fragility fractures in SM and in non-SM MCDs.

Patients

We retrospectively analyzed data concerning all successive patients with SM, CM, and MCAS diagnosed in our mastocytosis expert center at the University Hospital of Toulouse (CHU Toulouse) between 2004 and 2015. These patients were referred to the tertiary mastocytosis center if they had cutaneous involvement, mast cell activation symptoms, severe idiopathic anaphylaxis, osteoporosis, or cytopenia of unknown cause. All SM patients fulfilled the 2001 WHO diagnosis criteria [8] revised in 2016 [9]. CM diagnosis was based on the 2001 WHO criteria [8] refined in 2007 and 2016 [10, 11]. MCAS diagnosis was based on the consensus proposal from Valent et al. [12] and/or Moldering et al. [13].

All patients had enough complementary investigations to classify their MCD, these included bone marrow (BM) biopsy, BM aspirate, and serum analysis.

For this type of study (retrospective), formal consent was not required.

Data collection

We collected the following data at diagnosis:

- Demographic: age at diagnosis, age of disease onset.
- Clinical symptoms/signs of mastocytosis: cutaneous phenotype, mast cell activation symptoms (digestive symptoms, flush, idiopathic anaphylactic shock, allergy to hymenoptera venom).
- Fracture profile: history of osteoporotic fracture, fracture type, number of vertebral fractures, osteoporosis risk factors (smoking, self-reported excessive alcohol intake > 20 g/day for women and > 30 g/day for men, body mass index < 19 kg/m^2, endocrinopathy, early menopause, corticotherapy, history of inflammatory rheumatism).
- Background treatment: mast cell reduction therapy, osteoporosis treatment, glucocorticoids (general and local), hormonal deprivation for breast and prostate cancer.
- MCD classification/diagnosis: results of bone marrow biopsy, results of bone marrow aspirate, results of mast cells phenotyping (CD2, CD25), results of *KIT* point mutation at exon 17, level of serum tryptase, results of skin biopsy (see reference [2] for further details).
- Densitometric assessment: bone mineral density (BMD), T-score and Z-score at the hip and lumbar spine (L1-L4) sites.
- Bone morphologic assessment: plain radiography of the thoracolumbar spine.
- Biological assessment: serum tryptase (ST), bone marrow tryptase (BMT), serum crosslaps (CTX).

Bone assessment

Osteoporotic patients were defined as having a major osteoporotic fracture (the hip, vertebra, humerus) identified by anamnesis or by systematic radiographic assessment, or as having densitometric osteoporosis according to the current definitions [14]. Densitometric osteoporosis was defined as a T-score ≤ -2.5 standard deviations (SD) at the femoral neck or lumbar spine.

BMD was measured using dual X-ray absorptiometry (Lunar Prodigy, GE Healthcare® UK) by a single investigator.

Vertebral fractures were assessed for all patients by a systematic plain radiography of the thoracolumbar spine in order to identify prevalent fractures, using Genant's semi-quantitative method. All radiographies were performed at the time-point of BMD analysis and independently analyzed by two experimented rheumatologists (ME, YD). Disagreements were resolved by a third party (ML).

Statistical analysis

We analyzed all patients. Non-osteoporotic fractures, high kinetic trauma fractures, fatigue fractures, and toe and finger fractures, were excluded from analysis.

Gaussian-distributed variables were described as mean and SD. Non-Gaussian distributed variables were described as median and interquartile range. Dichotomous and ordinal variables were described as numbers and frequencies.

Comparisons between subgroups were performed using the Student *t* test for the normally distributed data, a non-parametric Wilcoxon rank-sum test for non-normally distributed data, and Fisher exact test for dichotomous variables. A p value < 0.05 was considered statistically significant, with a 95% confidence interval (CI).

All analyses were performed using the GraphPad Prism v5.00 (GraphPad Software, Inc., La Jolla, CA, 92037, USA). Figure 1 was created with GraphPad Prism v5.00.

Results

Diagnosis of mast cell disorders

We included 129 patients: 89 had SM, 20 had CM, and 20 had MCAS (see Table 1). SM patients were classified as follows: 78/89 (87.7%) patients had an indolent SM (no B, no C findings), 2/89 (2.2%) had a smoldering SM (2 B findings and no C findings), 9/89 (10.1%) had an aggressive SM (at least a C finding). Six out of 89 patients (6.7%) had SM associated with other hemopathy.

The 20 CM patients (100.0%) were classified as maculopapular cutaneous mastocytosis (MPCM), 12/20 (60.0%) with pigmented lesions and 6/20 (40.0%) with non-pigmented lesions. Data from the six patients classified as CM, but with minor criteria for SM, are provided in Supplementary Table 1.

We classified 20/20 patients (100.0%) as idiopathic MCAS.

Characteristics of patients with mast cell disorders

Clinical and demographic data are provided in Table 2. Demographic data were similar across the three disease groups.

Given our definition of osteoporotic involvement (major osteoporotic fracture and/or densitometric osteoporosis), we excluded isolated minor osteoporotic fractures from the definition. Among the four patients with isolated minor fractures, one also had a history of major fracture and was thus considered osteoporotic. Characteristics of osteoporosis differed between SM, CM, and MCAS. CM patients suffered significantly less from osteoporosis than SM patients. We observed similar findings in MCAS patients. Among patients with osteoporosis, 27/40 SM patients (67.5%), 1/3 CM patients (33.3%), and 0/2 MCAS patient (0.0%) did not have additional risk factors for osteoporosis (see Fig. 1a). Moreover, patients with SM had a higher prevalence of fractures than patients with CM and MCAS. Furthermore, SM patients had higher levels of BMT than CM and MCAS patients.

Exposure to mast cell reduction therapy and bone-modifying agents before or during the assessment of skeletal status is summarized in Supplementary Table 2. Briefly, 11 SM had a history of exposition to mast cell reduction therapies; 14 SM patients, 0 CM patient, and 0 MCAS patient had a history of exposure to bone-modifying agents; four SM patients, three CM patients, and one MCAS patient had a history of bone iatrogeny (corticosteroids, hormonal deprivation).

Osteoporosis and fractures in systemic mastocytosis

We then analyzed the clinical characteristics of SM patients with osteoporosis (see Table 3 and Fig. 1).

The higher prevalence of fractures in SM was related to the occurrence of vertebral fractures. SM patients with vertebral fractures were older at disease onset and at diagnosis (average ages were respectively 50 vs 33 years, $p < 0.0001$; and 55 vs 41 years, $p = 0.0003$). When compared to their non-fractured counterparts, SM patients with vertebral fractures were more likely to have additional risk factors for OP (see Table 3) and had a lower prevalence of degranulation symptoms (30% vs 72.5%, $p = 0.012$). Regarding biological findings, common laboratory findings (ST, CTX) were similar in both subgroups (see Table 3). However, BMT was significantly higher in SM patients with vertebral fractures (see Table 3).

Interestingly, among the 25 SM patients with fractures, only three out of 25 (12.0%) had hip densitometric osteoporosis, seven out of 19 (36.8%; 6/25 with the lumbar spine not eligible for DXA assessment) had lumbar densitometric osteoporosis, and 11 out of 19 had neither hip nor lumbar osteoporosis (57.9%) (see Fig. 1).

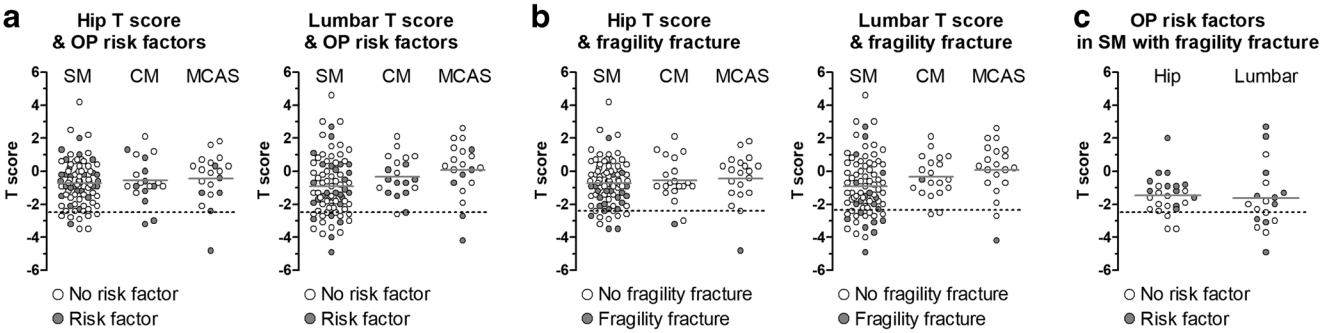

Fig. 1 Individual densitometric data in patients with mast cell disorders. CM cutaneous mastocytosis, MCAS mast cell activation syndromes, OP osteoporosis, SM systemic mastocytosis. **a** Femoral and lumbar T-score in patients with mast cell disorders, according to the presence of osteoporosis risk factors. **b** Femoral and lumbar T-score in patients with mast cell disorders, according to the presence of fragility fracture. **c** Femoral and lumbar T-score in patients with systemic mastocytosis and fragility fracture, according to the presence of risk factors for osteoporosis

Table 1 Criteria for diagnosis of mast cell disorders

	Systemic mastocytosis ($N = 89$)	Cutaneous mastocytosis ($N = 20$)	Mast cell activation syndrome ($N = 20$)
Systemic mastocytosis criteria [8, 9]			
Major-mast cell multifocal dense infiltrate (%)	40/67 (59.7)	0/20 (0.0)	0/20 (0.0)
3 Minor criteria (%)	65/89 (73.0)	0/20 (0.0)	0/20 (0.0)
Minor-> 25% atypical cells (%)	44/81 (54.3)	1/20 (5.0)	0/20 (0.0)
Minor-CD2+/CD25+ mast cells (%)	31/39 (79.5)	0/11 (0.0)	0/17 (0.0)
Minor-KIT mutation (%)	74/85 (87.1)	4/20 (20.0)	0/20 (0.0)
Minor-serum tryptase > 20 ng/mL (%)	66/88 (75.0)	2/20 (10.0)	0/20 (0.0)
Cutaneous mastocytosis criteria [8, 10, 11]			
Major-typical skin lesions*	78/89 (87.6)	20/20 (100.0)	0/20 (0.0)
Minor-mast cell infiltrate in lesional skin	61/83 (73.5)	14/20 (70.0)	3/18 (16.7)
Minor-D816V KIT mutation in skin	72/84 (85.7)	8/20 (40.0)	0/20 (0.0)
No criterion for systemic mastocytosis	–	16/20 (80.0)	20/20 (100.0)
Mast cell activation syndrome criteria [12, 13]			
Degranulation symptoms or anaphylaxis**	56/89 (62.9)	8/20 (40.0)	20/20 (100.0)
Transient increase in serum tryptase/MC mediator	–	–	20/20 (100.0)
Response to anti-mediator drug	–	–	20/20 (100.0)

MC mast cells. *Typical skin lesions include the following: monomorphic maculopapular small lesions of the thigh and trunk and Darier's sign. **Degranulation symptoms include the following: flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, hypotension, and diarrhea

We observed similar findings in the 20/89 SM patients (22.5%) with vertebral fractures: most of them did not have densitometric osteoporosis, notably at the lumbar site. In this subgroup, the average number of fractured vertebrae was 4.4 per patient. We observed 35.8% of grade I, 39.5% of grade II, and 24.7% of grade III vertebral fractures. Concerning the other MCDs, grades of vertebral fractures were the following: 1 grade I and 1 grade III in CM (1 patient); 1 grade I, 1 grade II, and 4 grade III in MCAS (1 patient).

Osteoporosis and fractures in other mast cell disorders

Five out of 40 patients with non-SM MCDs had osteoporosis, and two had a major osteoporotic fracture (see Table 2, Supplementary Table 3 and 4). All three patients (15.0%) with CM and osteoporosis and all two patients (10.0%) with MCAS and osteoporosis had risk factors or etiology for preexisting osteoporosis (smoker, excessive alcohol consumption, menopause, low BMI, bad acquisition of bone capital during childhood). The only CM patient (5.0%) with osteoporotic fractures (2 vertebral fractures), was elderly (90 years old). The only MCAS patient (5.0%) with fractures had multiple vertebral fractures. He also had several risk factors of osteoporosis (smoking, low BMI, maternal hip fracture, transient steroid use for chronic obstructive pulmonary disease) and a history of seizure secondary to a post-traumatic subdural hematoma.

Discussion

In our retrospective study, we described osteoporosis in SM, CM, and MCAS. We showed that SM is associated with an osteoporotic phenotype specifically involving vertebral bone. This osteoporosis differs from osteoporosis observed in CM and MCAS, which is not associated with a higher prevalence of vertebral fractures. Bone marrow tryptase appeared helpful to guide etiological research in OP toward SM.

The main limitations of our study are its retrospective design and the relatively low number of patients diagnosed as CM and MCAS. A case-controlled design with age-matched healthy controls could have been proposed; however, the usefulness to control clinical or biological findings in mastocytosis did not appear relevant. Another limitation concerning osteoporosis assessment was the previous medications prescribed before the inclusion in our study.

OP frequency in SM patients from our cohort was similar to published studies [3, 4, 6, 7]. Mast cell disease-related factors potentially contribute to osteoporosis/fracture risk. Accordingly, osteoporosis in SM is usually attributed to the local release of mediators produced by mast cells [15–17]. Our observation of a lower prevalence of degranulation symptoms in SM patients with vertebral fractures suggests that mediators produced by mast cells in bone may differ from those released in mast cell activation symptoms. Subtypes of SM and mast cell load may account for variability in OP occurrence and in its severity (fractures). Given the low

Table 2 Patients characteristics

	SM ($N = 89$)	CM ($N = 20$)	*P* value (SM vs CM)	MCAS ($N = 20$)	*P* value (SM vs MCAS)
Men (%)	38 (42.7)	11 (55.0)	NS	8 (40.0)	NS
Age at diagnosis (IQR)	46 (34.0;55.0)	38 (32.0;53.3)	NS	45 (37.5;55.3)	NS
Age at 1st symptoms (IQR)	36 (27.0;49.5)	34 (30.3;48.8)	NS	38 (27.0;52.0)	NS
Pigmented maculopapular lesions (%)	70 (78.7)	12 (60.0)	NS (0.0922)	3 (15.0)	< 0.0001
Non-pigmented maculopapular lesions (%)	8 (9.0)	8 (40.0)	0.0017	1 (5.0)	NS
Digestive symptoms (%)	47 (52.8)	8 (40.0)	NS	13 (65.0)	NS
Flush (%)	42 (47.2)	6 (30.0)	NS	13 (65.0)	NS
Idiopathic anaphylactic shock (%)	10 (11.2)	3 (15.0)	NS	13 (65.0)	< 0.0001
Hymenoptera venom allergy (%)	9 (10.1)	1 (5.0)	NS	1 (5.0)	NS
Bone pain	9 (10.1)	0 (0.0)	NS	0 (0.0)	NS
OP (%)	40 (44.9)	3 (15.0)	0.0209	2 (10.0)	0.0043
OP without RF (%)	27 (30.3)	1 (5.0)	0.0218	0 (0.0)	0.0030
≥ 1 RF for OP (%)	30 (33.7)	10 (50.0)	NS (0.1275)	6 (30.0)	NS
Fractures (%)	25 (28.1)	1 (5.0)	0.0392	1 (5.0)	0.0392
Osteosclerosis (%)	4 (4.5)	0 (0.0)	NS	1 (5.0)	NS
BMT, ng/mL (IQR)	300.0 (105.0;930.0)	9.9 (6.5;27.2)	< 0.0001	4.8 (4.0;18.0)	< 0.0001
ST, ng/mL (IQR)	29.5 (20.1;71.5)	6.7 (4.4;12.8)	< 0.0001	4.4 (3.4;7.0)	< 0.0001

BMT bone marrow tryptase, *CM* cutaneous mastocytosis, *IQR* interquartile range, *MCAS* mast cell activation syndrome, *NS* non-significant, *OP* osteoporosis, *RF* risk factor, *SM* systemic mastocytosis, *ST* serum tryptase. *P* value: Student's *t* test for normally distributed variates, Wilcoxon test for non-normally distributed variates, Fisher exact test for proportions

frequency of non-indolent SM patients, subgroup analysis of the differential impact on skeletal status was not performed. Regarding mast cells load, the number of mast cells carrying of *KIT* mutation was not available (we assessed qualitative mutational status of exon 17 including D816V mutation). CD2 and CD25 expression in mast cells from extra-cutaneous tissues (bone marrow) and the result of abnormal mast cells in bone marrow were also collected as qualitative

Table 3 Bone characteristics of SM patients with and without vertebral fractures

	SM ($N = 89$)	SM/VF ($N = 20$)	SM/no VF ($N = 69$)	*P* value (SM/VF vs SM/no VF)
Vertebral fracture (%)	20 (22.5)	20 (100.0)	0 (0.0)	–
Multiple vertebral fractures (%)	15 (16.9)	15 (75.0)	0 (0.0)	–
Peripheral fracture (%)	7 (7.9)	2 (10.0)	5 (7.2)	NS
≥ 1 Risk fact OP (%)	30 (33.7)	11 (55.0)	19 (27.5)	0.0316
Lumbar T-score (IQR)*	− 1.7 (− 2.6; − 0.2)	− 1.8 (− 3.1; − 0.7)	− 1.6 (− 2.6; + 0.7)	NS
Lumbar Z-score (IQR)**	− 0.7 (− 1.8; 0.0)	− 2.4 (− 3.2; + 1.1)	− 0.6 (− 1.7; + 0.0)	NS
Lumbar BMD, g/cm^2 (IQR)	1.047 (0.934;1.230)	0.954 (0.848;1.101)	1.080 (0.956; 1.232)	NS (0.0573)
Lumbar densitometric OP (%)	16 (22.9)	5 (20.0)	13 (18.8)	NS
Hip T-score (IQR)*	− 1.4 (− 2.2;− 0.8)	− 1.9 (− 2.5; − 1.2)	− 1.0 (− 2.0; − 0.4)	0.0227
Hip Z-score (IQR)**	− 0.1 (− 0.8;0.5)	− 0.5 (− 1.4; − 0.1)	0.0 (− 0.8; + 0.5)	NS
Hip BMD, g/cm^2 (IQR)	0.918 (0.819–1.009)	0.822 (0.723; 0.869)	0.957 (0.862; 1.042)	< 0.0001
Hip densitometric OP (%)	6 (7.6)	3 (15.0)	4 (5.8)	NS
BMT, ng/mL (IQR)	300 (105; 930)	1166 (278; 3378)	216 (99; 716)	0.0006
CTX, pg/mL (IQR)	375 (227; 587)	356 (165; 557)	381 (257; 620)	NS

BMD bone mineral density, *BMT* bone marrow tryptase, *CTX* crosslaps, *IQR* interquartile range, *NS* non-significant, *OP* osteoporosis, *SM* systemic mastocytosis, *VF* vertebral fracture. *T-score refers to the population of post-menopausal women and men > 50 years old. **Z-score refers to the population of premenopausal women and men ≤ 50 years old. *P* value: Student's t-test for normally distributed variates, Wilcoxon test for non-normally distributed variates, Fischer exact test for proportions

data (fulfilling marrow criterion, yes/no). Given the low number of patients available for subgroups analysis and the absence of quantitative data for *KIT* mutation, CD2/CD25 phenotyping, and abnormal cytological mast cells, we were not able to draw any conclusion about the impact of mast cells load on skeletal status.

Mast cells burden may account for bone fragility. In line with this statement, it has been hypothesized that mast cell reduction therapies (in addition to IV bisphosphonates) might decrease bone fragility in SM patients. This concept is supported by data from a study of 10 patients showing a higher increase in the spine BMD in SM patients treated interferon + pamidronate than with pamidronate alone [18]. Pathological fractures are considered as an impaired organ function (C-finding) in SM patients [8]. Patients with indolent SM commonly develop OP. A more specific therapeutic approach for OP in these patients would be to use mast cell reduction therapies. However, to date, given the potential adverse effects, an aggressive therapeutic approach in ISM patients with OP is debated but not recommended.

A recurrent issue in dealing with osteoporosis is to identify secondary osteoporosis. Among other possible etiologies, SM represents a rare cause. Our results confirm the previously described pattern of fracturing. SM patients display an osteoporosis manifested as multiple vertebral fractures [1, 4, 6, 7, 19]. Most of the SM patients with OP did not have additional risk factors for OP. However, the subgroup with vertebral fractures was more likely to have at least one additional risk factor for OP. This finding suggests that adaptation of the strategy to prevent vertebral fractures is critical in SM patients with additional risk factors for OP. Moreover, 11/25 SM patients (48.0%) with fractures did not have densitometric OP. This phenotype is shared by a number of secondary causes of OP (glucocorticoid-induced OP, myeloproliferative disorders) [20, 21]. This finding suggests that fracture risk in SM does not fully correlate with BMD as observed in other causes of the secondary OP. A decrease in bone quality (microarchitecture or even mineralization) may also account for bone fragility in SM. Interestingly, the occurrence of vertebral fractures was associated with a lower hip mineral density (in most cases not reaching the threshold for densitometric OP). This observation is consistent with previous publications [2, 7].

To our knowledge, our work is the first to compare osteoporosis in SM with other MCDs. Osteoporosis in CM and MCAS has not yet been thoroughly studied. We observed that osteoporosis in CM differed from the osteoporosis in SM. We cannot formally reject the hypothesis of a CM-related osteoporosis but with a lower impact than in SM. Importantly, CM patients did not display a specific vertebral osteoporosis with multiple vertebral fractures. Six out of 20 CM-classified patients had minor criteria for SM. Since minor criterion, especially marrow criterion, may reflect abnormalities related to SM, we cannot formally exclude a later evolution of these patients toward SM. When compared to SM, MCAS was not associated with the high prevalence of OP and vertebral fractures. These findings could be related to the transient feature of mast cell manifestations in MCAS, and potentially related to differences in the nature of the mediators released in MCAS and SM. Moreover, whether or not MCAS and CM patients with minor criteria for SM (but not fulfilling criteria for this diagnosis) develop a disease-related osteoporosis remains an unanswered question.

Regarding biological findings, our SM patients generally had elevated ST (> 20 ng/mL) and elevated BMT. In the literature (cutoff 20 ng/mL), ST sensitivity and specificity for SM diagnosis were 83.6% and 98%, respectively [22]. We observed similar results. Regarding BMT, we previously showed that this test was valuable for SM diagnosis regardless of bone phenotype [23]. In this work, BMT remains discriminant in SM diagnosis with a "rheumatologic profile" (osteoporosis). Higher BMT was significantly associated with vertebral fractures.

Only a low proportion of our patients had been exposed to steroids (three SM patients, three CM patients, one MCAS patient) hormonal deprivation (one SM patient) prior or at the time of bone assessment. However, this background may have increase bone fragility and induced a favorable environment for fractures.

Our study highlighted that, among mast cell disorders, only SM is associated with a disease-related osteoporosis. In our experience, in case of high suspicion, repeating studies and dosage of BMT are useful to identify SM in the context of vertebral fractures.

Conclusion

SM is associated with vertebral multi-fracture osteoporosis; whereas, CM and MCAS do not appear to be associated with this phenotype.

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Compliance with ethical standards

Conflicts of interest None.

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