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ORIGINAL RESEARCH

Osteoporosis Caused by Systemic Mastocytosis: Prevalence in a Cohort of 8392 Patients with Osteoporosis

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Abstract

Indolent systemic mastocytosis (ISM) is a group of heterogenous diseases characterized by abnormal accumulation of mast cells in at least one organ. ISM can be a cause of osteoporosis. The aim of this study is to determine the prevalence, and the prognosis of ISM in a cohort of patients with osteoporosis. In this monocentric and retrospective study, patients with osteoporosis who did not receive a bone biopsy (cohort 1) and patients that subsequently received a diagnostic bone biopsy for differential diagnosis (cohort 2) are compared with patients who are diagnosed with ISM (cohort 3). A total of 8392 patients are diagnosed with osteoporosis. Out of these patients 1374 underwent a diagnostic bone biopsy resulting in 43 patients with ISM. These figures indicate that ISM is diagnosed in 0.5% of patients with osteoporosis and in 3.1% (men 5.8%) of patients who underwent bone biopsies. Patients with ISM sustained significantly more vertebral fractures in comparison to patients in cohort 2 (4.4 ± 3.6 versus 2.4 ± 2.5 vertebral fractures, $p < 0.001$) and women were significantly younger compared to cohort 2 (57.3 ± 12 versus 63.6 ± 12 years, $p < 0.05$). Only 33% showed an involvement of the skin (urticaria pigmentosa). ISM is a rare cause of osteoporosis (0.5%). However, in a subgroup of rather young male patients with osteoporosis the prevalence is more than 5%. Thus, ISM should be considered in premenopausal women and men presenting with vertebral fractures even if urticaria pigmentosa is not present.

Keywords Osteoporosis · Mastocytosis · Bone biopsy · Vertebral fracture · Zoledronate

Introduction

Systemic mastocytosis (SM) is characterized by abnormal accumulation of mast cells (MC) in one or several organs. The prevalence of SM is estimated to be between 0.5 and 1.0 per 100,000. According to some authors, the incidence is reported to be 0.89 per 100 000 per year [1, 2]. A WHO classification divides SM into two types: the "non-advanced SM" and the "advanced SM". The most frequent subtype is the indolent systemic mastocytosis (ISM) [3].

Skeletal manifestations are frequently observed in SM. This may include bone pain, osteoporosis, osteosclerosis and focal osteolytic bone lesions. Interestingly, osteoporosis is frequently related to ISM, but not to the advanced SM [4, 5]. Osteoporosis caused by ISM is commonly associated with a high number of especially painful vertebral fractures [6–8].

Osteoporosis as a result of ISM seems to be related to the local release of mediators including histamine, heparin, tryptase, RANK-Ligand, osteoprotegerin, respectively. This leads to decreased trabecular bone mass and increase in the numbers of osteoclasts and osteoblasts [6, 9–11]. Activated MC release stored cytokines and synthesize additional pro-inflammatory factors: TNF-alpha, Interleukin 1 (IL-1) and Interleukin 6 (IL-6). These proinflammatory cytokines are known to promote osteoclastic activity [3, 12].

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In patients with osteoporosis caused by ISM a lower bone mineral density (BMD) at the lumbar spine in comparison to the hip has been reported [12, 13], indicating a greater loss of trabecular versus cortical bone. Vertebral fractures seem to be the predominant fracture type [13, 14]. Bone turnover parameters are frequently elevated suggesting a high turnover state [15]. Risk factors for fractures include male sex, high levels of bone resorption, low hip bone mineral density, alcohol and the absence of urticaria pigmentosa [16, 17]. Skin lesions (urticaria pigmentosa) are detected only in less than half of patients with osteoporosis caused by ISM [11, 18].

The prevalence of osteoporosis in a cohort of ISM patients, has been reported to range from 18 to 40% with men being more affected than women [14, 15, 19–22]. However, today little is known about the prevalence of ISM in patients with osteoporosis. Delling et al. described an overall prevalence of ISM in bone biopsy specimens with osteoporosis of 1.25%. In contrast, patients younger than 45 years age of showed a prevalence of 2.25% [23].

For the diagnosis of mastocytosis, bone biopsy is mandatory according to WHO guidelines on mastocytosis. The European Competence Network on Mastocytosis published a diagnostic algorithm that bases on clinical features such as urticaria pigmentosa and the tryptase levels [24–26]. The identification of patients with ISM in patients with osteoporosis is difficult due to the absence of urticaria pigmentosa in nearly half of the patients. Therefore, a large number of patients are identified after performing a bone biopsy for differential diagnosis of osteoporosis.

Therapy recommendations for osteoporosis due to mastocytosis include predominantly an anti-resorptive drug therapy [13, 27]. Rossini et al. report that 25 patients are successfully treated with 5 mg zoledronate per year. In parallel, this group documents a decrease in bone turnover markers and no subsequent fractures after one year [27]. Laroche et al. report about 10 patients who received Pamidronate 90 mg/month in combination with Interferon Alpha (1.5 million Units) three times a week followed by Pamidronate alone in the same dose. This regimen results in an increase of BMD at the lumbar spine but not at the hip. During a follow-up period over an average of 60 months, no further fractures were observed [13]. Since the RANK-RANKL system seems to play an important role in the pathogenesis of osteoporosis caused by ISM, denosumab might be a further therapeutic option [6, 16]. A case series with four patients describe positive results over a time period of one year [28].

In this retrospective study we determine the prevalence of mastocytosis in a large cohort of osteoporosis patients. In addition, in a subgroup of mastocytosis patients we observed the effect of treatment with zoledronate for up to five years.

Methods

Patients and Setting

In this monocentric study 8392 patients with osteoporosis were retrospectively analyzed between 2005 and 2015.

Setting

The patients had been assigned to the clinic because of osteoporosis or vertebral fractures. All patients received inpatient rehabilitation care for three weeks and a comprehensive diagnostic assessment including x-rays of the spine, DXA measurements and evaluation of laboratory parameters.

Bone biopsy was performed as part of the diagnostic assessment if patients fulfilling at least one of the following criterions: subsequent fractures despite drug therapy, unexplained reasons for osteoporosis with rapid disease progression, urticaria pigmentosa, men younger than 60 years, premenopausal women and extremely painful vertebral fractures.

The evaluation of bone histology was performed by the German Reference Pathologist for bone pathology (M. Werner, Berlin, Germany). In the context of typical clinical symptoms, diagnosis was made if WHO criteria for ISM were met [3, 24].

Patients with a main diagnosis other than osteoporosis were excluded.

Selection of Patients

All patients with osteoporosis were selected based on the ICD-10-code documented in the hospital information system. In addition, the clinical documentation of all patients with bone biopsy was reviewed and patients were selected if the WHO-criterions for ISM were met.

Data Retrieved from the Medical Charts

Data were retrieved during the time period from 2016 to 2018. The medical information was obtained from the first documented inpatient rehabilitation of the individual patient. For further analyses of the data we defined three independent cohorts of patients.

Cohort 1: Patients with Osteoporosis Without Bone Biopsy

Based on the medical information system diagnosis (ICD-10), data on age, sex and the time of menopause were

retrieved from the medical charts and compared to the other two cohorts.

Cohort 2: Patients with Osteoporosis who Subsequently Underwent a Bone Biopsy That Showed No ISM

Based on the documentation of receiving a bone biopsy, the resulting data on diagnosis, age, sex, number of vertebral fractures, BMD (lumbar spine and total femur) and the time of menopause were analyzed. All patients received an anterior–posterior and lateral X-ray of the lumbar spine and the thoracic spine.

Cohort 3: Patients with ISM Diagnosed by Bone Biopsy

In the patients with ISM the following parameters were documented: age when ISM was diagnosed, age when osteoporosis was diagnosed, sex, time of menopause, body weight, body height, loss of body height in comparison to the 25th year of life (based on the documentation in the personal identity card), body mass index (BMI), previous diagnoses (other than osteoporosis), premedication (relevant for osteoporosis), history of smoking and the numbers of vertebral fractures. Therefore, all patients with ISM received at baseline an anterior–posterior and lateral X-ray of the lumbar spine and the thoracic spine.

Data from BMD (lumbar spine, total femur, femoral neck) and laboratory findings at baseline of all patients were retrieved from the medical charts. Clinical long-term outcome was observed in 13 patients (5 female and 8 male) by follow-up in the outpatient clinic or as part of inpatient rehabilitations. Follow-up included inquiring about symptoms suggesting new vertebral fractures. Increase in pain or loss of body height were used as criteria to perform X-rays of the thoracic and lumbar spine in order to diagnose new vertebral fractures or further progression of preexisting fractures.

DXA

Delphi W (Hologic) QDR 2000 was used for measurement of BMD at the lumbar spine (L1–L4), the total hip and femoral neck. T-scores were calculated by using the normative values provided by Hologic.

X-Rays

Anterior–posterior and lateral X-rays of the lumbar spine and the thoracic spine were performed as part of the clinical work up. (X-ray generator 501 K&S, Dillingen/ Germany; X-ray tube assembly SV150/40/80, Siemens, Germany). The film focus distance has been kept constant at 115 cm. Fractures were defined according to FDA criteria: decrease in height of 20% or at least 4 mm. The diagnosis was performed by an experienced osteo-radiologist.

Laboratory Findings

Patients received a comprehensive laboratory evaluation. This included but was not limited to testing alkaline phosphatase/AP (Roche, photometry), TSH basal levels (Roche, ECLIA), parathyroid hormone/PTH (Roche, ECLIA), 25-OH-Vitamin D (Roche, ECLIA) in blood and Deoxypyridinoline/DPD (Roche, ELISA) in first morning void urine. Laboratory tests were collected in the morning after an overnight fast and analysed within two hours (Labor Stibbe, Hannover, Germany).

Bone Biopsies

A transiliac biopsy was taken using a manual trocar with 6 mm inner diameter. Any bone specimen was at least 1.5 cm in length. The procedure, including possible complications was explained to every patient in detail and written informed consent was obtained. Bone specimens were placed in a tube with 4% formalin and transported to a specialized bone pathology lab (M. Werner, Vivantes Clinical Center Friedrichshain, Berlin, Germany). It was further processed for undecalcified histology as previously described [29]. Samples underwent a series of increasing ethanol solutions for dehydration, followed by infiltration and methylmethacrylate embedding. Consecutive sections of the polymerized methylmethacrylate (PMMA) blocks were cut at 4-µm thickness with a Leica microtome. Sections were stained with Masson–Goldner trichrome, toluidine blue, Giemsa, prussian blue and acid phosphatase. Additionally immunohistochemical staining with antibodies against CD25, KIT (CD117) and tryptase were performed in any specimen. Staining against KIT (CD117) and tryptase allowed to detect even small mast cell infiltrations, whereas expression of CD25 proved an aberrant immunophenotype.

Histological diagnosis was made using the WHO diagnostic criteria: Major criterion is the presence of a cluster with at least 15 multifocal compact MC. Minor criteria include abnormal MC-morphology, aberrant expressions of CD25 or CD2, mutation of the KIT D816-receptor and elevated serum tryptase levels. WHO criteria for diagnosis are fulfilled if the major criterion plus at least one minor criterion or at least 3 minor criteria are positive [3, 24]. Hence, diagnosis was not solely based on the presence of MC nodules but was also considered in patients with a large number of MC marginalized on the osteoblasts against the bone trabeculae.

Statistical Analyses

Continuous variables were described by mean value, median, range and standard deviation. Significance was calculated by *t* test for independent samples and Mann–Whitney *U* test. Statistical calculations were made by using SPSS version 19 (SPSS Inc., Chicago, IL, USA) and Excel 2013 (MS Office). Data are reported with mean value ± SD.

Results

Characteristics of the Cohorts

A total of 8,392 patients (f: 6864, m: 1,528 [f = female, m = male]) received an inpatient rehabilitation care due to osteoporosis. Of these patients 1374 (f: 959, m: 415) received a diagnostic bone biopsy. 43 patients (f: 19, m: 24) were diagnosed with ISM. Thus, three cohorts of patients were defined and compared.

Cohort 1: Patients with osteoporosis who did not receive a bone biopsy (f: 5905, m: 1113), Cohort 2: Patients with osteoporosis who underwent bone biopsy that showed no ISM (f: 940, m: 391) and Cohort 3: Patients who were then diagnosed with ISM by bone biopsy (f: 19, m: 24).

ISM was diagnosed in 0.51% (f: 0.28%, m: 1.54%) of osteoporosis patients. Hence, ISM was detected in 3.1% (f: 2.0%, m: 5.8%) in patients who received a bone biopsy. The mean age of patients of cohort 1 was 67.2 ± 13 years (f: 67.9 ± 12.6, m: 63.1 ± 13 years). Patients of cohort 2 were significantly younger (total: 61.4 ± 12 years, $p < 0.001$; f: 63.6 ± 12 years, $p < 0.001$; m: 55.9 ± 12 years, $p < 0.001$) due to age being one of the criterions for bone biopsy. Patients with osteoporosis caused by ISM (cohort 3) were significantly younger than patients of cohort 2 at the time when mastocytosis was diagnosed (total: 55.7 ± 12 years, $p < 0.01$). The difference was not significant when data were analyzed according to sex (f: 57.3 ± 12 years, $p < 0.05$; m: 54.4 ± 12 years, p = ns) [ns = not significant]. Cohort 3 was also significantly younger compared to cohort 2 what concerns the first diagnosis of osteoporosis (total: 51.8 ± 12 years, $p < 0.001$; f: 52.9 ± 10 years, $p < 0.001$; m: 51 ± 13 years, $p < 0.01$). Thus, in patients with ISM, osteoporosis was diagnosed approximately four years before ISM was detected (Table 1 and Fig. 1).

Women in cohort 1 were in 8% (478 of 5905) pre- or perimenopausal, whereas women in cohort 2 were so in 12% (114 of 940). In contrast, women in cohort 3 were in 37% (7 of 19) pre- or perimenopausal.

Baseline Characteristics of Patients with ISM (Cohort 3)

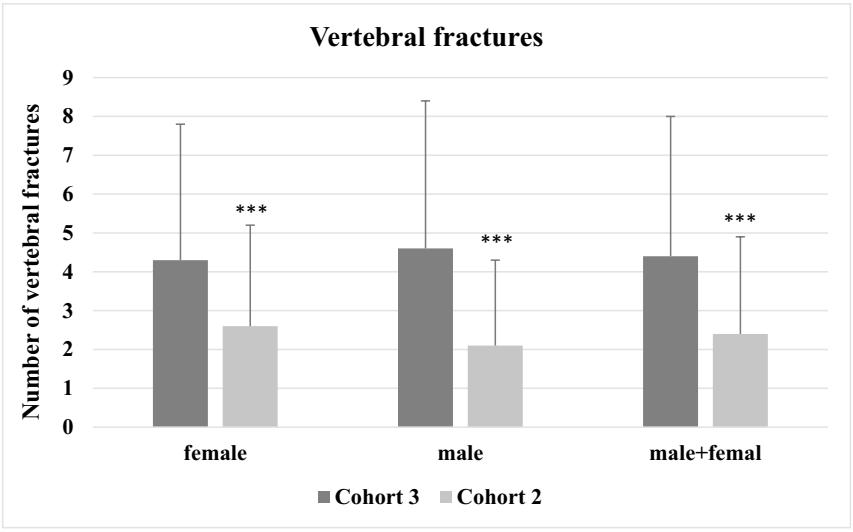
Clinical Features

Patients were slightly overweight (BMI total: 26.9 ± 4.7, f: 25.5 ± 5.2, m: 28.2 ± 4.1 kg/m^2). Mean loss of body height was 4.4 ± 4.8 cm (f: 5.3 ± 4.3, m: 3.7 ± 5.2 cm). 44% of the patients with ISM related osteoporosis were smoker (f: 47%, m: 42%). Urticaria pigmentosa was documented in 33% (f: 16%, m: 46%).

Table 1 Baseline characteristics of the cohorts

	Female	Male	Total
Cohort 1: patients without bone biopsy			
Number	5905	1113	7018
Mean age (yr) ± SD	67.9 ± 12.6	63.1 ± 13	67.2 ± 13
Cohort 2: patients with osteoporosis who subsequently underwent a bone biopsy that showed no ISM			
Number	940	391	1331
Mean age (yr) ± SD	63.6 ± 12	55.9 ± 12	61.4 ± 12
p value (in comparison to 1)	< 0.001	< 0.001	< 0.001
Cohort 3: patients in whom osteoporosis has been caused by ISM			
Number	19	24	43
Percentage of patients with osteoporosis at all	0.28	1.54	0.51
Percentage of the patients that received a bone biopsy at all	2.0	5.8	3.1
Mean age (yr) ± SD when ISM was diagnosed	57.3 ± 12	54.4 ± 12	55.7 ± 12
p value (in comparison to 1)	< 0.001	< 0.01	< 0.001
p value (in comparison to 2)	< 0.05	ns	< 0.01
Mean age (yr) ± SD when osteoporosis was diagnosed	52.9 ± 10	51 ± 13	51.8 ± 12
p value (in comparison to age when mastocytosis was diagnosed)	< 0.001	< 0.01	< 0.001

SD standard deviation, *p* level of significance calculated by *T* Test, *ns* not significant, *yr* years, *ISM* indolent systemic mastocytosis



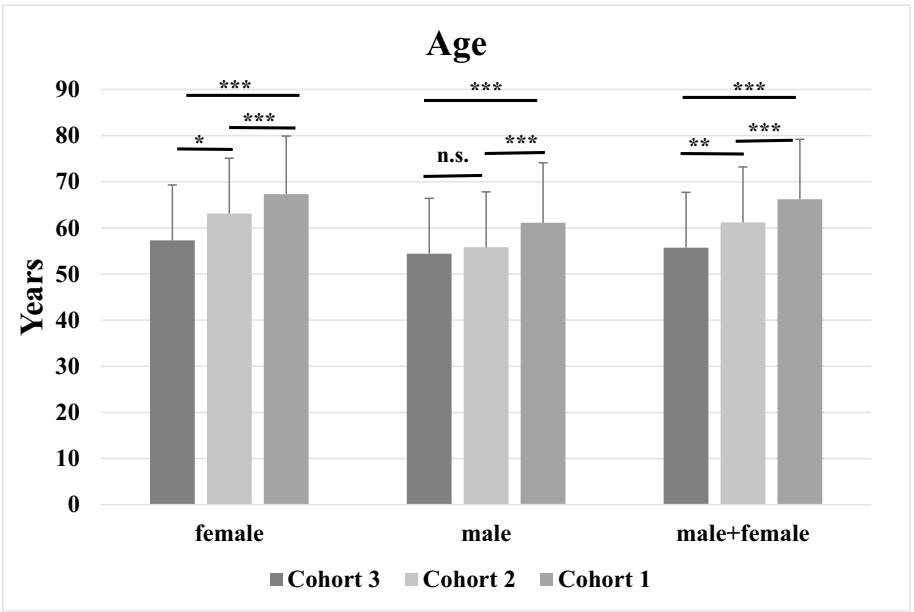


Fig. 1 Comparison between osteoporosis caused by ISM and other forms of osteoporosis. Level of significance: *$p<0.05$, **$p<0.01$, ***$p<0.001$

Level of significance: * p< 0.05, ** p< 0.01, *** p< 0.001

Bone Parameters

At baseline women had on average 4.3 ± 3.5 vertebral fractures and men 4.6 ± 3.8 vertebral fractures. BMD/ SD-T-score was reduced at the lumbar spine (f: − 2.59 ± 1.08, m: − 2.65 ± 1.16 T-score), femoral neck (f: − 1.96 ± 0.8, m: − 2.03 ± 0.86 T-score) and total femur (f: − 1.36 ± 0.76, m: − 1.83 ± 1.13 T-score). BMD at the lumbar spine was significantly lower in comparison to the femoral neck (f: $p<0.05$, m: $p<0.005$) and at the total femur (f: $p<0.05$, m: $p<0.001$). The DPD values in urine per creatinine were elevated (f: 42.7 ± 36.9, m: 23.4 ± 15.6 µg/g creatinine [standard value premenopausal: 11.0–27.0, postmenopausal: 11.0–34.7, men: 8.4–19. 7 µg/g creatinine]). The tryptase level (standard value < 13.5 µg/l) was measured in only four patients (3 men, one woman). In three cases tryptase levels were slightly elevated (17.9 µg/l, 23.3 µg/l and 14.4 µg/l) and in one case within normal range (9.3 µg/l). Other laboratory values were within the normal range (Table 2).

Patients with Osteoporosis Who Received a Bone Biopsy That Showed No ISM (cohort 2)

Patients of cohort 2 suffered from 2.4 ± 2.5 vertebral fractures (f: 2.5 ± 2.5, m: 2.0 ± 2.2 vertebral fractures). This is highly significantly lower than the number of vertebral fractures in patients with ISM ($p<0.001$) (Fig. 1). The BMD at the lumbar spine (f: − 2.2 ± 1.4, m: − 2.5 ± 1.2 SD-T-score)

Table 2 Baseline table of patients with osteoporosis caused by ISM

	Female $n=19$ Mean ± SD	Male $n=24$ Mean ± SD	Total $n=43$ Mean ± SD
Clinical features			
Body height when diagnosis ISM was made (cm)	161.9 ± 8.0	177.4 ± 7.7	170.6 ± 11.0
Loss of body height in comparison to the 25th year of life (cm)	5.3 ± 4.3	3.7 ± 5.2	4.4 ± 4.8
Body weight (kg)	66.6 ± 13.7	87.4 ± 16.5	78.2 ± 18.4
BMI (kg/cm^2)	25.5 ± 5.2	28.2 ± 4.1	26.9 ± 4.7
Smoker (%) [number]	47 [9]	42 [10]	44 [19]
Urticaria pigmentosa (%) [number]	16 [3]	46 [11]	33 [14]
Bone mineral density (BMD)			
DXA-lumbar spine (T-score ± SD)	− 2.59 ± 1.08	− 2.65 ± 1.16	
DXA-femoral neck (T-score ± SD), p value (in comparison to lumbar spine)	− 1.96 ± 0.8 < 0.05	− 2.03 ± 0.86 < 0.005	
DXA-total femur (T-score ± SD), p value (in comparison to lumbar spine)	− 1.36 ± 0.76 < 0.05	− 1.83 ± 1.13 < 0.001	
Fractures			
Vertebral fracture (number)	4.3 ± 3.5	4.6 ± 3.8	4.4 ± 3.6
Laboratory value (unit), [Standard value]			
Calcium (mmol/L) [2.15–2.58]	2.45 ± 0.23	2.33 ± 0.13	
Phosphate (mg/dl) [2.5–5.0]	3.8 ± 0.5	4.5 ± 3.8	
Creatinine (mg/dl) [< 1.2]	0.7 ± 0.2	0.9 ± 0.1	
Glomerular filtration rate/GFR (ml/min) [> 64]	97.4 ± 20.9	99.5 ± 19.5	
Alkaline phosphatase (U/l), [40–129]	96.2 ± 57	82.7 ± 31.6	
Parathyroid hormone/PTH (ng/l) [16–65]	28.7 ± 9.9	31.8 ± 19.2	
25-OH-Vitamin D (nmol/l), [50–100]	66.2 ± 32.3	70.1 ± 31.4	
TSH basal (mU/l) [0.3–4.0]	1.6 ± 0.7	1.7 ± 1	
Deoxypyridinoline/DPD in urinee per creatinine (µg/g creatinine) [female: premenopausal 11.0–27.0, postmenopausal: 11.0–34.7 male: 8,4–19,7]	42.7 ± 36.9	23.4 ± 15.6	

n number of patients, *SD* standard deviation, *BMI* body mass index, *ISM* indolent systemic mastocytosis, *BMD* bone mineral density

and at the total femur (f: 1.8 ± 1, m: 1.3 ± 0.8 T-score) was not significantly different from the BMD in patients with ISM.

Long-Term Outcome in ISM Patients

A total of 13 patients (f: 5, m: 8) were observed over a mean period of 57 ± 23 months (f: 60 ± 21, m: 55 ± 21 months) and clinical outcome was documented. Of these 13 patients, three women were documented over a period of 81 months and five men over a period of 69 months. All patients received 5 mg zoledronate per year. In comparison to baseline, bone turnover markers DPD and AP decreased significantly in women to 33% and 83.7% of basal values (DPD baseline: 62.3 ± 43 µg/g creatinine, DPD month 81: 20.7 ± 2.1 µg/g creatinine, $p < 0.01$ [standard value premenopausal: 11.0–27.0 µg/g creatinine, postmenopausal: 11.0−34.7 µg/g creatinine]; AP baseline: 102 ± 24 U/l, AP month 81: 85.4 ± 11 U/l, $p < 0.01$ [standard value: 40–129 U/l]). In men DPD also showed the efficacy of zoledronate by decreasing values to 55% of baseline values (DPD baseline: 31.4 ± 22 µg/g creatinine, DPD month 69: 17.2 ± 3 µg/g creatinine, $p < 0.01$ [standard value 8.4–19.7 µg/g creatinine]). AP values did not significantly change in men. During the period of follow-up, no patient developed any non-vertebral fracture. In contrast, in 4 patients an overall

of 9 subsequent vertebral fractures occurred in the whole period of observation (f: 2, m: 7 vertebral fractures). Most fractures took place in the first two years (f: 1, m: 4 vertebral fractures). BMD (lumbar spine) increased in both women (T-score baseline: − 2.98 ± 1.5 T-score month 81: − 2.06 ± 2, *p*: ns) and men (T-score baseline: − 2.8 ± 0.5 T-score, month 69: -2.2 ± 0.5 T-score, $p < 0.05$) however, the difference in women was not significant. BMD of total femur and femoral neck showed no significant changes in both sexes although values for women were lower at the total femur (T-score baseline: − 1.97 ± 0.71, T-score month 81: − 2.34 ± 0.8, *p*: ns) and at the femoral neck (T-score baseline: − 1.98 ± 0.1, T-score month 81: − 2.4 ± 0.4, *p*: ns) (Table 3).

Discussion

In this study we retrospectively reviewed data from 8392 patients with osteoporosis and further analyzed the data of 1374 patients with bone biopsy. After performing bone biopsies the diagnosis of ISM was confirmed. We can confirm that ISM was diagnosed in 0.5% of patients with osteoporosis and in 5.8% in the subgroup of young men with osteoporosis. Furthermore, we showed that patients with ISM sustained significantly more vertebral fractures and were significantly younger (4.4 ± 3.6 vertebral fractures, 55.7 ± 12 years of age) compared to patients with other forms of osteoporosis that received a bone biopsy (2.4 ± 2.5 vertebral fractures, 61.4 ± 12 years of age). Zoledronate therapy with 5 mg/year was not sufficient to prevent all subsequent fractures.

In contrast to previous studies in which patients were diagnosed first with ISM and osteoporosis was reported as a secondary complication, in this study we analyzed patients with established osteoporosis diagnosed with ISM during the diagnostic work-up. In patients in whom a bone biopsy was performed ISM was diagnosed in 3.1% (in men 5.8%). A former study published a lower percentage of ISM with 1.25% (2.25% in patients < 45 years) diagnosed by bone biopsies in patients with osteoporosis [23]. The difference might be explained by the different setting. In their institute of pathology Delling et al. received bone specimens from different inpatient and outpatient clinics. It can be speculated, that the indication for bone biopsies and the severity of the osteoporosis varied between the different clinics. In our study the bone biopsies were exclusively gained during an inpatient rehabilitation. The main fracture type of patients with osteoporosis in our clinic are vertebral fractures. Both points can explain the higher number of ISM in our study.

Our patients diagnosed with ISM (cohort 3) were on average ten years younger compared to cohort 1. This may have several reasons. One of the criterions for the indication of bone biopsy in this study was severe osteoporosis in young age (men < 60 years, premenopausal women). This may have caused a certain selection bias in comparing the age of patients with ISM with the reference group of patients with osteoporosis. However, women with ISM were also significantly younger than women in cohort 2. Therefore, the selection bias does not diminish the explanatory power of the conclusion that at least women with ISM associated osteoporosis were younger when osteoporosis firstly occurred than the reference group of patients with osteoporosis.

Our data indicate, that in young male patients with osteoporosis and in women before menopause, ISM should be taken into consideration in the differential diagnosis of osteoporosis with fractures. In the study of Delling the age difference between patients with ISM and patients who received bone biopsy was 3 years. Patient with ISM analyzed for osteoporosis had a mean age of 48 years and therefore were younger than our patients with osteoporosis and bone biopsy [23].

In this study patients with osteoporosis caused by ISM were diagnosed on average four years after the initial diagnosis of osteoporosis with the definitive diagnosis of osteoporosis caused by ISM. As stated before patients were biopsied for differential diagnosis of osteoporosis and not according to guidelines of mastocytosis patients. This is due to the fact that mastocytosis was not diagnosed before the biopsy. Our indication for biopsy was dependent on fractures and young age. In most previous studies ISM was diagnosed first and osteoporosis was described as a complication of ISM. Hence, there are no reports of the delay until the definitive diagnosis was established. However, older age at diagnosis is described as a risk factor for fractures in patients with ISM [7]. It is unclear, whether the higher age when diagnosis was made in the literature might be related to a delay in diagnosis as mentioned above. Given the fact, that osteoporosis caused by ISM is associated with a high recurrence of fractures [6] the gap between first symptoms caused by osteoporosis and the diagnosis of ISM should be as short as possible.

Our data on BMD indicate that trabecular bone represented by spine BMD in ISM is more affected than cortical bone at the hip. BMD at the lumbar spine was significantly lower than at the femur. In addition, vertebral fractures are the dominant fractures. On average, more than four vertebral fractures were found at the time when diagnosis was established. This is significantly higher than the number of vertebral fractures in the reference cohort of patients that received a bone biopsy (cohort 2). The number of vertebral fractures is similar to most previous studies. Laroche reported a mean of 3.5 vertebral fractures [13], van de Veer 389 lifetime fractures in 127 patients with ISM [17]. Additionally, other studies identified the spine as the predominant fracture localization [14, 30]. The reason is unclear, however MC develop from bone marrow which is predominantly localized in the trabecular bone [31]. On the other

Table 3 Long term outcome of patients with osteoporosis caused by ISM

FEMALE	Baseline ($n=5$)	Month 28 ($n=5$)	Month 43 ($n=3$)	Month 67 ($n=3$)	Month 81 ($n=3$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Bone mineral density (BMD)					
DXA-lumbar spine (T-score ± SD), *p*	− 2.98 ± 1.5	− 2.33 ± 1.7 ns	− 2.22 ± 2.3 ns	− 1.99 ± 1.9 ns	− 2.06 ± 2 ns
DXA-femoral neck (T-score ± SD), *p*	− 1.98 ± 0.1	− 1.68 ± 0.9 ns	− 2.79 ± 0.6 ns	− 3.06 ± 0.5 ns	− 2.4 ± 0.4 ns
DXA-total femur (T-score ± SD), *p*	− 1.97 ± 0.71	− 1.28 ± 0.9 ns	− 2.27 ± 0.2 ns	− 2.27 ± 0.2 ns	− 2.34 ± 0.8 ns
New vertebral fractures					
Patient 1		0	0	0	0
Patient 2		0	0	0	0
Patient 3		1	0	0	1
Patient 4		0			
Patient 5		0			
Laboratory value (unit) [Standard value]					
Alkaline phosphatase (U/l) [40–129]	102.7 ± 24	75 ± 9 $p<0.01$	73.3 ± 17 $p<0.01$	80.1 ± 9 $p<0.01$	85.4 ± 11 $p<0.01$
Deoxypyridinoline/DPD in urine per creatinine (µg/g creatinine) [premenopausal: 11.0–27.0] [postmenopausal: 11.0–34.7]	62.3 ± 43	25.2 ± 5.7 $p<0.01$	27.7 ± 6 $p<0.01$	21.6 ± 2 $p<0.01$	20.7 ± 2.1 $p<0.01$
MALE	Baseline ($n=8$)	Month 22 ($n=8$)	Month 33 ($n=6$)	Month 51 ($n=6$)	Month 69 ($n=5$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Bone mineral density (BMD)					
DXA-lumbar spine (T-score ± SD)	− 2.8 ± 0.5	− 2.2 ± 0.8 ns	− 2.3 ± 0.7 ns	− 2.1 ± 0.8 $p<0.05$	− 2.2 ± 0.5 $p<0.05$
DXA-femoral neck (T-score ± SD)	− 2.2 ± 0.8	− 2.1 ± 0.7 ns	− 2.2 ± 0.4 ns	− 2.3 ± 0.8 ns	− 2.1 ± 0.8 ns
DXA-total femur (T-score ± SD)	− 1.5 ± 0.7	− 1.4 ± 0.6 ns	− 1.3 ± 0.3 ns	− 1.2 ± 0.8 ns	− 1.2 ± 0.8 ns
New vertebral fractures					
Patient 6		0	0	2	0
Patient 7		0	0	0	0
Patient 8		0	0	0	0
Patient 9		2	0	1	0
Patient 10		0	0	0	0
Patient 11		0	0	0	
Patient 12		0			
Patient 13		2			
Laboratory value (unit) [Standard value]					
Alkaline phosphatase/AP (U/l) [40–129]	83.5 ± 32	95 ± 31 ns	93.4 ± 31 ns	97.2 ± 39 ns	81.8 ± 33 ns
Deoxypyridinoline/DPD in urine per creatinine (µg/g creatinine) [male: 8,4–19,7]	31.4 ± 22	22.5 ± 7 $p<0.01$	24.4 ± 8 $p<0.01$	36.6 ± 23 ns	17.2 ± 3 $p<0.01$

p level of significance calculated by Witney *U* Test in comparison to Baseline, *SD* standard deviation, *ns* not significant, *ISM* indolent systemic mastocytosis, *BMD* bone mineral density

hand trabecular bone could be more sensitive to the local factors synthesized by MC [12].

The highly elevated bone resorption marker DPD indicate a high bone turnover in our patients. Studies analyzing histomorphometrical data of patients with ISM detected a high turnover state [11]. Bone turnover markers were higher in those patients with fractures [7]. Furthermore, they are associated with a loss of BMD in the future [32]. Another study identified the bone resorption marker serum type I collagen C-telopeptide as one predictor for fragility fractures besides male sex, low hip bone mineral density, absence of urticaria pigmentosa, and alcohol intake at the time of ISM diagnosis [17]. Interestingly, other studies documented a correlation of C-telopeptide and osteoprotegerin to tryptase levels suggesting a correlation to the number of MC [20, 33]. At the time of initial biopsy tryptase levels were not regularly measured for the differential diagnosis of patients in our clinical setting. By now tryptase levels are part of our regular work-up of osteoporosis patients with fractures.

In our study group only a minority of patients showed an involvement of the skin (urticaria pigmentosa). The absence of urticaria pigmentosa is known as a risk factor for vertebral fractures [16, 17]. The prevalence of vertebral fractures in ISM is high, but low in cutaneous mastocytosis [7]. The primary symptoms of patients in our study were osteoporosis and vertebral fractures. Therefore, according to the literature the rate of cutaneous manifestation in our cohort is rather low. However, other authors did not find a difference in the prevalence of mastocytosis-related low BMD and/or vertebral fractures between ISM patients with or without skin involvement [15, 21].

A total of 13 patients were followed up over a mean period of time of 57 ± 23 months and treated with 5 mg zoledronate per year. We showed a significant decrease of bone turnover markers and higher BMD levels at the spine, although not significant due to the low number of patients. However, besides intravenous zoledronate therapy with consequently 100% compliance and adherence we noticed few subsequent vertebral fractures. We did not further analyze the specific reasons for these fractures or the exact time after starting zoledronate, therefore we can only speculate that even zoledronate did not prevent all fractures in our patient group with osteoporosis due to ISM. This is different to the results by other authors. Rossini et al. reported in 25 patients after one year an increase of BMD (lumbar spine) of 6% and no subsequent vertebral fractures. Laroche et al. investigated 10 patients with a median of 3.5 vertebral fractures over a mean period of time of 60 months. These patients received pamidronate and interferon alpha and developed no subsequent vertebral fractures under treatment [13, 27]. Hence, bisphosphonates were recommended by a number of authors [3, 21, 34]. However, in our patients some fractures occurred despite treatment with zoledronate. Due to the application at our center the fractures were not due to missing compliance. We did not find other causes for fracture occurrence in these patients. Our data do not indicate a treatment failure of zoledronate because the number of vertebral fractures is low and there is no control group. Furthermore even in postmenopausal osteoporosis zoledronate is not able to prevent all vertebral fractures [35].

The difference between our data and data of previous studies might be explained by the time of observation (57 ± 23 months in our study versus 12 months in the study of Rossini et al. and Orsolini et al.) and the special setting of our study. The patients were assigned to our inpatient clinic because of osteoporosis or vertebral fractures. Hence, patients with ISM who were observed on the base of an inpatient rehabilitation were much more likely symptomatic in comparison to patients that were not further investigated. This might bias the number of vertebral fractures to be higher in our study.

Meanwhile, additional data of the use of denosumab in this patient group have been published. Orsolini et al. reported in four patients over a period of time of one year no further vertebral fractures [28].

Many authors describe a high recurrence of vertebral fractures in patients with osteoporosis caused by ISM [6, 12]. In spite of some subsequent vertebral fractures, our data support the hypothesis that 5 mg zoledronate annually is a therapeutic option in ISM associated osteoporosis. A treatment with denosumab might be an alternative for patients with fractures using bisphosphonate therapy.

The strength of this study is the high number of patients with osteoporosis and the very high number of diagnostic bone biopsies performed. In contrast to previous studies, this study is based on the analyses of a cohort of patients with osteoporosis in which subsequently ISM has been diagnosed. This might help to gain further information concerning the prevalence of ISM in patients with osteoporosis.

This study has some limitations. The retrospective design and the small number of patients with ISM and follow-up data limit the explanatory power with regard to the long-term prognosis. The measurement of tryptase levels would have added significant information, but was not determined at that time.

Conclusion

We report ISM as a rare reason for osteoporosis in 0.5% of patients. However, in a subgroup of young male patients with osteoporosis, the prevalence is found to be up to 5.8%. Furthermore we showed that patients with ISM sustained significantly more vertebral fractures and were significantly younger than patients with other reasons for osteoporosis who received a bone biopsy. Only a minority of patients present with typical skin lesions. Therefore, ISM should be

considered in premenopausal women and young men presenting with several vertebral fractures. Urticaria pigmentosa is not a prerequisite and bone biopsy is required for diagnosis. Further prospective studies would be of value to evaluate the significance of the tryptase levels in the diagnostic approach in patients with fragility fracture or severe osteoporosis. Especially, clear cut-off values are missing in this respect.

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Author Contributons MG and HS wrote the manuscript. All authors contributed substantial parts to the elaboration of this study. All authors approved the final version of the manuscript.

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Declarations

Conflict of interest Martin Gehlen, Niels Schmidt, Michael Pfeifer, Subathira Balasingam, Michael Schwarz-Eywill, Anna Maier, Mathias Werner and Heide Siggelkow declare that they have no conflict of interest.

Ethical Approval Retrospective study. For this type of study no formal informed consent is required (see above).

Informed Consent According to the ethics committee responsible for our clinic, no formal informed consent is required for this type of retrospective study. Informed consent was obtained from each patient before undergoing a bone biopsy.

Human and Animal Rights This retrospective trial does not include any treatment of humans or animals. Zoledronate was administrated according to the current German guidelines for treatment of osteoporosis.

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