

High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis

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Abstract

Background: Indolent systemic mastocytosis (ISM) is a rare disease characterized by accumulation of abnormal mast cells in various tissues, including bone marrow. Symptoms are usually related to release of mast cell mediators. The aims are to establish the prevalence of osteoporotic fractures in ISM and to investigate the association with serum tryptase and the urinary histamine metabolites, methylhistamine (MH), and methylimidazole acetic acid.

Methods: The fracture prevalence in 157 patients (65 men; 92 women), mean age 54 ± 12 years, was assessed by vertebral morphometry and data from patient records, supplemented by a questionnaire. Bone mineral density (BMD) of lumbar spine and femoral neck was measured, and tryptase and histamine metabolites were analysed.

Results: We registered 235 lifetime fractures in 154 patients, including 140 osteoporotic (low-energy trauma) fractures, of which 62% were vertebral, 1% hip and 36% other nonvertebral fractures. Osteoporotic fractures and osteoporosis were found in 37% and 28% of the patients, respectively. In men, the prevalence of these osteoporotic manifestations (46% <50 years; 73% ≥ 50 years) was much higher compared with women (18% <50 years; 58% ≥ 50 years). Older age, male gender, and higher urinary MH were independently related to the osteoporotic manifestations.

Conclusions: This first publication about prevalence of fractures and osteoporosis in patients with ISM shows that the risk of osteoporotic fractures is high, especially in men. Higher urinary MH levels are associated with a higher risk of osteoporotic manifestations. Routine measurements of BMD and vertebral morphometry are warranted in these patients for early detection of osteoporosis.

Mastocytosis is a rare disorder characterized by a clonal proliferation of abnormal mast cells. Clinical symptoms of mastocytosis are heterogeneous, mainly because of acute and chronic release of mast cell mediators and accumulation of mast cells in various tissues. In cutaneous mastocytosis, mast cell accumulation is by definition limited to the skin. In systemic mastocytosis (SM), extra-cutaneous tissues and organs are involved, notably the bone marrow (1–3). In adults, the vast majority of patients with SM have the indolent form [indolent systemic mastocytosis (ISM)], in which the rate of mast cell proliferation is very low (4). After years, the mast cell amount can stabilize and even decrease (5). In most

patients with ISM, the percentage of mast cells in the bone marrow is below 5% (6).

Patients with SM are prone to develop osteoporosis and osteosclerosis, which is associated with the more severe forms of SM (aggressive SM and SM with associated hematologic non-mast cell lineage disease). The reported percentages of osteoporosis ranged from 18% to 31%, and of osteosclerosis from 8% to 19% in series of patients with various forms of SM (4,7,8).

None of the above studies included the life-long history of fractures with emphasis on osteoporotic (low-energy trauma) vertebral and nonvertebral fractures. Therefore, the aim of

this study was to establish the prevalence of osteoporosis and related fractures in patients with ISM before and after the age of 50. Furthermore, we investigated whether clinical characteristics or higher levels of tryptase in serum and/or the histamine metabolites methylhistamine (MH) and methylimidazole acetic acid (MIMA) in urine were associated with osteoporotic manifestations.

Methods

Patients and methods

Since 1981, ISM was diagnosed in 157 consecutive patients in the referral centre for mastocytosis of the University Medical Center Groningen. The diagnosis was made according to the World Health Organization (WHO) Classification of Mastocytosis (3). Fracture data were collected from the medical records and lateral radiographs of the thoracolumbar spine, combined with a questionnaire sent to all patients. The patients were asked to report in open columns which bone was fractured, at which age or year, and asked to describe the trauma circumstances. Almost all (98%) questionnaires were returned with life-long data of fractures and good recall of trauma circumstances. If it was not possible to discriminate between high- or low-energy trauma circumstances, a telephone call was made to clarify. Fracture data of three patients could not be retrieved. Osteoporotic fractures were defined as fractures because of low-energy trauma. A vertebral fracture was defined according to the Genant classification (9). Bone mineral densities (BMD) of lumbar spine (anterior-posterior projection at L1–L4) and hip (total proximal femur) were measured using DXA (Hologic QDR Discovery, Waltman, MA, USA). Osteoporosis was defined as a T -score ≤ -2.5 SD (10). Patients were categorized by the lowest T -score of the lumbar spine or hip. DXA measurements of lumbar spine ($n = 150$) and hip ($n = 149$) were available from our own hospital. The BMD data analysed in other hospitals were included in the prevalence, but not in the regression analyses; based on these data, four patients had osteoporosis. The maximal accepted interval between BMD measurement and blood/urine analysis was 1 year, only if clinical symptoms had not changed during this period. Biochemical parameters of patients with ISM usually remain rather stable for several years (5). If patients were on osteoporotic drug treatment, the BMD and biochemical data before the start of the treatment were used. Data of medication prescriptions were collected from the medical records. Osteosclerosis was defined as a Z -score above $+2.5$ SD of the BMD of hip, forearm (one-third radius) or lumbar spine. The presence of urticaria pigmentosa (UP) was based on the typical skin lesions of mastocytosis, and was diagnosed by an experienced dermatologist, and confirmed by the histological finding of an increased number of tryptase-positive mast cells in skin biopsies (11). Anaphylaxis was defined as an acute onset and potentially life-threatening systemic reaction caused by any trigger, usually by an insect sting.

Biochemical markers

Tryptase levels were determined using the B12 assay (Pharmacia UniCAP Tryptase; Pharmacia and Upjohn, Uppsala, Sweden) (12). Reference values for healthy individuals were reported by Pharmacia and Upjohn, showing a geometric mean level of $3.8 \mu\text{g/l}$ and an upper 95th percentile of $11.4 \mu\text{g/l}$. To measure MH and MIMA, urine samples were collected after an overnight fast, discarding the first voiding after waking. During 24 h before urine collection, patients were asked to refrain from histamine-rich foods, such as sauerkraut, canned fish, and yoghurt. MH were determined by an isotope-dilution mass fragmentographic method (13). MIMA was determined as described previously (14), with some modifications using isotope dilution mass fragmentography. For MH and MIMA excretion, mean $\pm$ SD values (ranges) of an apparently healthy population were 101 ± 33 (50–154) $\mu\text{mol/mol}$ and 1.3 ± 0.3 (0.9–1.9) mmol/mol creatinine, respectively, in urine collected after an overnight fast (15).

Statistical analysis

Statistical analysis was performed with SPSS 16.0 software (SPSS, Chicago, IL, USA). Results were expressed as mean $\pm$ SD or median (range) for parametric and non-parametric data, respectively. Pearson's and Spearman's correlation coefficients were used as appropriate to analyse the relationship between BMD, and clinical symptoms and laboratory parameters of disease activity. Predictor analysis for osteoporosis was performed using univariate logistic regression and multivariate logistic regression with conditional stepwise backward inclusion of variables that had a P value ≤ 0.3 in univariate analysis. The probability of P for stepwise removal was 0.10. P values < 0.05 were considered statistically significant.

Results

Characteristics of study population

The mean age of 157 patients with ISM (65 men, 92 women) was 54 ± 12 years (Table 1). Median disease duration after the first symptom or sign of ISM was 13 years (range 1.5–40 years). Duration from first symptom to diagnosis was 6.5 (0–37) years. The diagnosis of ISM was made after the first visit to our center in 71% of our patients. Two-thirds of the other 29% patients were diagnosed within 1 year before the first visit. Seven men and five women had osteoporotic fractures or osteoporosis as presenting symptom. Urticaria pigmentosa was present in 110 patients, and 71 patients experienced anaphylactic reactions. One man and five women had osteosclerosis. Analyses of biochemical mediators released by mast cells are outlined in Table 1. Co-morbidity was present in 43 patients. Only one man and one woman had a body mass index (BMI) $< 19 \text{ kg/m}^2$. Eleven women and one man had a weight $< 60 \text{ kg}$, although they had a normal BMI. Current smoking or stopped with smoking within the last 10 years was reported by

Table 1 Characteristics of the indolent systemic mastocytosis study population (*n* = 157)

Characteristic	Deviation, <i>n</i> (%)		
Age (years)	53.5 ± 12.3	Age ≥ 50, <i>n</i> (%)	96 (61)
Gender (male), <i>n</i> (%)	65 (41)		
Urticaria pigmentosa, <i>n</i> (%)	110 (71)		
Anaphylactic shock, <i>n</i> (%)	71 (46)		
Osteosclerosis, <i>n</i> (%)	6 (4)		
Length (cm)	172 ± 10		
Weight (kg)	79 ± 15		
BMI (kg/m ²)	25.8 (18.6–40.5)	BMI < 19.0, <i>n</i> (%)	2 (1.3)
		BMI ≥ 30.0, <i>n</i> (%)	33 (22)
Smoking, <i>n</i> (%)	66 (48)	Current smoker, <i>n</i> (%)	41 (30)
		Stopped within last 10 years, <i>n</i> (%)	25 (18)
Tryptase (µg/l)	33 (2.4–306)	Tryptase > 20, <i>n</i> (%)	122 (78)
MH (µmol/mol creat)	284 (76–2554)	MH > 167, <i>n</i> (%)	139 (89)
MIMA (mmol/mol creat)	3.5 (1.1–21.7)	MIMA > 1.9, <i>n</i> (%)	138 (88)
LS BMD <i>T</i> -score (SD)	−1.10 (−5.2–+2.8)	Osteoporosis LS, <i>n</i> (%)	42 (27)
Hip BMD <i>T</i> -score (SD)	−0.60 (−2.9–+2.7)	Osteoporosis hip, <i>n</i> (%)	2 (1)
Co-morbidity (<i>n</i> , %)			51 (32)
Diabetes mellitus type 2			6
Hyperthyroidism			2
Hypogonadism			3
Hyperparathyroidism			2
Pulmonary disease			15
Epilepsy			1
Malignancy (breast, prostate)			6
Rheumatic diseases			3
Other diseases			8
Drug/alcohol abuse			5
Drug treatment, <i>n</i> (%)	Before first visit	After first visit	
H1 and/or H2 antihistamines	49 (31)	99 (63)	
Oral corticosteroids	9 (6)	12 (8)	
Inhaled corticosteroids	6 (4)	16 (10)	
Cromoglycin	16 (10)	15 (10)	
Interferon	2 (1.3)	2 (1.3)	
Anticonvulsants	1 (0.6)	2 (1.3)	
Proton pump inhibitors	12 (8)	23 (15)	
Bisphosphonates	19 (12)	50 (32)	
Teriparatide	1 (0.6)	1 (0.6)	
HRT (women)	8 (9)	7 (8)	
Calcium	14 (9)	77 (50)	
Vitamin D	9 (6)	74 (48)	
Disease duration (years)			
First symptom to close of study, years		13.7 (1.5–40)	
First symptom to DXA,* years		11.8 (0–38)	
First symptom to diagnosis, years		6.5 (0–37)	
First symptom to first visit, years		6.3 (0–38)	
First visit to close of study, years		5.3 (0–28)	
First visit to DXA,* years		2.3 (−6.7–21)	

Values are mean ± SD or median (range), unless otherwise indicated.

BMI, body mass index; MH, methylhistamine; MIMA, methylimidazole acetic acid; LS, lumbar spine; BMD, bone mineral density; HRT, hormone replacement therapy; SD, standard deviation.

*The last made DXA was used, unless patient received treatment for osteoporosis, then the last DXA before the start of treatment was used; see Methods.

Table 2 Fractures and osteoporosis in patients with indolent systemic mastocytosis (ISM)

Fractures	Total	Men	Women
All fractures, <i>n</i>	235	136	99
Ostp #	140	72	68
Vert #	87	48	39
Other #	51	22	29
Hip #	2	2	0
ISM patients, <i>n</i> (%)			
With fracture(s)	83/154 (54)	43/63 (68)	40/91 (44)
<50 years	26/60 (43)	17/26 (65)	9/34 (26)
≥50 years	57/94 (61)	26/37 (70)	31/57 (54)
With ostp #	57/154 (37)	32/63 (51)	25/91 (27)
<50 years	11/60 (18)	9/26 (35)	2/34 (6)
≥50 years	46/94 (49)	23/37 (62)	23/57 (40)
LS or Hip BMD, <i>n</i> (%)			
<i>T</i> -score < -2.5 SD	43/154 (28)	20/63 (32)	23/91 (25)
<50 years	18/60 (17)	6/26 (23)	4/34 (12)
≥50 years	33/94 (35)	14/37 (38)	19/57 (33)
Combination of osteoporotic fracture and/or osteoporosis, <i>n</i> (%)			
None	76 (49)	24 (38)	52 (57)
Ostp. combination	78 (51)	39 (62)	39 (43)
<50 years	18/60 (30)	12/26 (46)	6/34 (18)
≥50 years	60/94 (64)	27/37 (73)	33/57 (58)

ostp #, osteoporotic fracture(s), because of low-energy trauma; vert #, vertebral fracture; LS, lumbar spine; BMD, bone mineral density.

66/138 patients, with no statistically differences in smoking habits between gender: 54% (30/56) men and 44% (36/82) women. Any use of medication, related to mastocytosis or to bone quality has been listed separately before and after the first visit to our referral center.

Fractures and osteoporosis

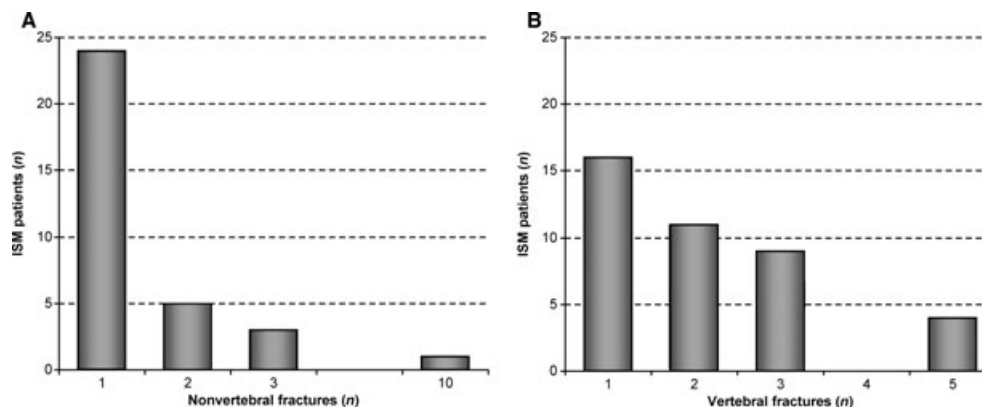
Eighty-three of 154 patients with ISM experienced 235 fractures during lifetime (Table 2). Forty-three percent of the patients <50 years and 61% of the patients ≥50 years had at least one fracture. These include 140 fractures because of

low-energy trauma in 57 patients; of these 87 were vertebral and 53 nonvertebral ones, including two hip fractures. This means for the 57 patients a mean occurrence of 2.4 osteoporotic fractures per patient. Forty-one patients (27%) had one or more vertebral fractures (mean 2.1 per patient), and 33 patients (21%) had nonvertebral, osteoporotic fractures (mean 1.6 per patient). Histograms of low-energy trauma nonvertebral fractures and vertebral fractures are given in Fig. 1. Osteoporotic fractures were reported by 35% of the men and 6% of the women under the age of 50 years, and by 62% of the men and 40% of the women in the older group. High-energy trauma fractures (including the fractures with no information about the circumstances of the trauma) were reported by 32% of the patients (64 fractures in men, 31 fractures in women); of them, 24 patients reported also low-energy trauma osteoporotic fractures at other ages.

The median (range) lumbar spine and hip BMD *T*-scores were -1.10 (-5.2-+2.8) SD and -0.60 (-2.9-+2.7) SD, respectively. Osteoporosis was detected in 23% and 38% of the male patients, younger and older than 50 years, respectively. For women, these percentages were 12% and 33%, respectively (Table 2). Summarizing, we found 37% osteoporotic fractures and 28% osteoporosis in the total group. Patients with co-morbidities (51 found in 43 patients) that might contribute to fractures had 49% osteoporotic fractures and 37% osteoporosis. Excluding this group, the percentages were 32% and 24%, respectively.

A higher prevalence of osteoporotic fractures was detected among ISM patients without UP vs those with UP; 59% vs. 28%, respectively ($P = 0.0002$), while no differences were found in the prevalence of osteoporosis, 33% vs. 25%, respectively ($P = 0.513$).

We used the history of osteoporotic fractures combined with a BMD *T*-score ≤ -2.5 SD for a more refined quantitative assessment of osteoporotic manifestation. Of the male patients, 46% (<50 years) and 73% (≥50 years) had osteoporotic manifestation. For the female patients, these percentages were 18% and 58%, respectively. Only 38% male and 57% female patients with ISM in this cohort did not show manifestations of osteoporosis.

**Figure 1** Histogram of low-energy trauma nonvertebral fractures (A) and vertebral fractures (B) in patients with indolent systemic mastocytosis.

Predictors of osteoporotic manifestations

Predictor analysis was performed to identify parameters related to osteoporotic manifestations. In total, 51% of patients had either an osteoporotic fracture or osteoporosis.

Lumbar spine BMD *T*-score correlated negatively with MH and MIMA. Tryptase correlated positively with disease duration (Table 3). Age and gender were significantly associated with osteoporotic manifestations in univariate regression analysis (Table 4). Multivariate regression analysis showed

Table 3 Correlation assessment in patients with indolent systemic mastocytosis

	Age	Disease duration	Tryptase	MH	MIMA	LS BMD <i>T</i> -score	Hip BMD <i>T</i> -score	Length	Weight
Age (years)									
Disease duration (years)	0.115								
Tryptase (µg/l)	−0.005	0.177*							
MH (µmol/mol creat)	−0.041	0.047	0.609**						
MIMA (mmol/mol creat)	0.082	0.155	0.725**	0.783**					
LS BMD <i>T</i> -score (SD)	−0.296**	−0.118	−0.101	−0.227**	−0.202*				
Hip BMD <i>T</i> -score (SD)	−0.396**	−0.031	−0.053	−0.077	−0.152	0.618**			
Length (cm)	−0.249**	−0.079	−0.035	−0.119	−0.150	0.057	0.144		
Weight (kg)	−0.192*	−0.040	−0.007	−0.171*	−0.200*	0.134	0.340**	0.456**	
BMI (kg/m ²)	0.004	−0.017	0.009	−0.091	−0.097	0.104	0.291**	−0.110	0.804**

**Statistically significant correlation ($P < 0.01$).

*Statistically significant correlation ($P < 0.05$).

See Table 1 for abbreviations.

Table 4 Results of univariate and multivariate regression analysis for osteoporotic manifestations (osteoporotic fracture and/or bone mineral density (BMD) *T*-score < -2.5 SD)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Age (years) [†]	1.071 (1.036–1.107)	0.000	1.079 (1.041–1.118)	0.000
Gender [‡]	1.904 (0.964–3.759)	0.025	2.801 (1.292–6.071)	0.009
Disease duration (years) [†]	1.021 (0.986–1.056)	0.241		*
Urticaria pigmentosa [§]	2.052 (0.957–4.397)	0.065		*
Anaphylactic reaction [¶]	0.861 (0.444–1.669)	0.658		**
Tryptase (µg/l) ^{††}	1.007 (0.999–1.016)	0.096		*
MH (µmol/mol creat) ^{††}	1.001 (1.000–1.003)	0.077	1.002 (1.000–1.003)	0.047
MIMA (mmol/mol creat) ^{††}	1.084 (0.960–1.223)	0.193		*
Length (cm) ^{††}	0.990 (0.956–1.026)	0.594		**
Weight (kg) ^{††}	0.990 (0.967–1.013)	0.374		*
BMI (kg/m ²) ^{††}	0.967 (0.896–1.043)	0.378		*
Smoking ^{‡‡}	0.775 (0.385–1.562)	0.476		**

[†]Per year.

[‡]If gender is male (vs female).

[§]If urticaria pigmentosa (UP) is present (vs absent).

[¶]If anaphylactic reaction is present (vs absent).

^{††}Per 1 point.

^{‡‡}If smoking occurred (vs nonsmoking during the last 10 years).

*The variable was not selected during multivariate regression analysis.

**The variable was not tested in multivariate regression analysis because of a *P* value > 0.3 in univariate regression analysis and absence of significant correlation with lumbar spine or hip BMD *T*-scores.

that older age (odds ratio 1.079, 95% confidence interval: 1.041–1.118) and male gender (OR: 2.801, 1.292–6.071) were independently related to osteoporotic fractures and/or osteoporosis. Higher MH values (OR: 1.002, 1.000–1.003) reached just independent significance ($P = 0.047$). The Nagelkerke R^2 of the multivariate model was 0.263.

Discussion

This study is unique by including the life-time fractures in patients with ISM. A high prevalence of osteoporotic fractures (37%) and of osteoporosis (28%) has been observed. The prevalence especially of osteoporotic manifestations, defined as an osteoporotic fracture and/or a BMD T -score ≤ -2.5 SD, in 62% of the male patients is unexpectedly high.

The prevalence of osteoporotic and nonosteoporotic fractures together is much higher than that found in European population studies (16–20). The nonosteoporotic (high-energy trauma or unknown trauma) fractures in 32% of the patients are in line with these international data. The percentage of osteoporosis is higher in this study than the 18% found in a Spanish ISM group (4), with a median age of 46 years (37 + 9 years follow-up), but in accordance with the 34% (19/56) reported in the ISM subgroup in a French study (8), with median age of 48 years. Also the percentage of osteoporotic fractures we reported is much higher than the 5% reported for the Spanish ISM group. The 27% of fractures in the French study was reported for all types of patients with SM. Even considering that we reported life-time fractures, the differences between the Spanish and our ISM group might be explained in part by age. Although the median ages do not differ much, only 6% of the patients were over 60 years of age in the Spanish ISM group, while in our group, 23% of the patients were over 60 years of age. Furthermore, the ISM patients without UP have a higher percentage of osteoporotic fractures (this study) and osteoporosis [Spanish study (21)] compared with the ISM patients with UP; the larger number of patients without UP in our study (29% vs 10% in the Spanish study) might also have contributed to the found differences.

In order to obtain more knowledge about the pathophysiology of the osteoporotic manifestations in patients with ISM, we investigated the relation between BMD, clinical symptoms, smoking, BMI, and biochemical mast cell parameters. The results demonstrate that older age, male gender, and MH are independent predictors for the osteoporotic manifestations. With regard to age and gender, previous population reports show variances with respect to the age at which fractures occur: life-time fractures are more common in youth for men and at postmenopausal age for women (22–24). Over the age of 35 years, fracture incidence in women climbs steeply, so that the rates become twice those in men (25). In our study, only the premenopausal ISM women seem better protected for the mastocytosis-driven risk of osteoporotic fractures than postmenopausal women or men. The fact that the men with ISM are more prone to get osteoporotic fractures than the ISM-females in both age groups is difficult to explain. Could it be that men are exposed to more traumas during their working life and that this in combination with a

more osteoporotic skeleton because of mastocytosis is so detrimental? Other explanations might be that the release and/or the spectrum of the mast cell mediators are different between the sexes, or that the influence of the mast cell mediators on bone metabolism is gender dependent; mast cells express both estrogen receptors as well as androgen receptors, but it is unknown whether and how sex hormones can influence mast cell activation (26). Furthermore, Brumsen et al. 2002 suggested that mast cells may play a significant role in the pathogenesis of idiopathic osteoporosis in men, and demonstrated that about 9% of men with idiopathic osteoporosis and no evidence for extra skeletal mast cell proliferation have bone marrow infiltration with abnormal mast cells (27). However, only seven men had osteoporosis as a presenting symptom in our study, indicating that osteoporosis as presenting symptom cannot be an argument for the 62% osteoporotic manifestations we found in men.

In the multivariate analysis, MH reached significance ($P = 0.047$) as an independent predictor for osteoporotic manifestations. Moreover, significant negative correlations were found between lumbar spine BMD T -score and MH as well as MIMA. These findings demonstrate an involvement of the pathological mast cells in the process of bone loss, and are in line with earlier suggestions from animal experiments that mast cells may be involved in the events leading to bone resorption [e.g. via histamine release (28)]. In addition, activated mast cells release proinflammatory cytokines IL-1, IL-6, and TNF- α (29), which are important regulators of bone resorption (28,30). Increased plasma levels of IL-6 have been observed in patients with ISM (31). The seemingly contradictory finding that low BMD Z -scores were more common in patients with lower tryptase levels, as reported earlier (32), might be explained by the fact that several variants of mastocytosis were included in that study of only 21 patients with SM. The 14 included patients with ISM had lower BMD outcomes as well as lower tryptase levels than the severe variants of mastocytosis, and the distribution of osteolysis and osteosclerosis among the several SM groups was not reported.

Besides osteolysis also pathological fractures belong to the C-findings indicative of aggressive disease (3). According to the WHO subclassification of mastocytosis, all ISM patients with the C-finding of a pathological fracture should be regarded as an aggressive SM variant. However, osteoporotic fractures in patients with ISM should not be regarded as a C-finding, as the disease process of ISM in our patients have a benign and indolent course with normal life expectancy, which is in agreement with the finding by Lim (33) that patients with ISM have a life expectancy that is not significantly different from the control population. This point of view has previously been discussed (8, 34). Recognition of the high risk of osteoporotic fractures stresses to establish the diagnosis of SM as soon as possible using sensitive and specific methods (35), and stresses that preventive measurements starts with optimizing the peak bone mass in the younger patients, recommending of daily exercise, and ensuring optimal calcium and vitamin D intake and appropriate drug treatment in the older patients with low BMD. More research is needed to investigate whether the use of his-

tamine blockers and cromoglycin influences the prevalence of fractures or the BMD, because we cannot exclude that the high prevalence of fractures and osteoporosis in ISM might be related to the suboptimal antimediator therapy before the referral. Oral bisphosphonates have been shown to be effective in patients with osteoporotic ISM (8).

A limitation of this study is that it is an observational one of daily clinical practice. Co-morbidity was present in 28% of the patients. These various co-morbidities might have contributed to the high prevalence of osteoporosis and fractures. Nonetheless, high percentages were also observed if these patients with co-morbidities were excluded. Our findings are in line with the 21% vertebral fractures and 20% osteoporosis found in 82 ISM patients without concomitant diseases associated with osteoporosis (36). Another limitation was that we could not use the BMD and biochemical data of the last visits of 49 patients (31%), because of osteoporotic drug treatment that was started in the meanwhile (5.13 ± 3.6 years ago).

The main strength is an in-depth analysis of fractures combined with osteoporosis in younger and older age groups. Even though mastocytosis is a rare disease, we could study a large group of patients, representative of the overall ISM population in the Netherlands, due to the fact that we are a referral centre for SM.

In conclusion, the prevalence of osteoporotic fractures and osteoporosis is high in ISM, especially in men. Older age, male gender, and higher MH levels are independently related to osteoporotic fractures and/or osteoporosis. These results

stress the relevance of establishing the diagnosis of SM as soon as possible. Routine BMD measurements and lateral radiographs of the thoracolumbar spine are needed for early detection of osteoporosis and vertebral fractures. Efforts should be made to optimize bone quality by at least ensuring adequate vitamin D and calcium intake in all patients with ISM, especially the younger ones, and by adequate drug treatment in the patients with osteoporosis to reduce the risk of fractures. Prevention of osteoporosis and osteoporotic fractures by early start of antimediator therapy might also be considered, although efficacy data are lacking so far.

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Author contribution

All authors have substantially contributed to concept and design, material contributions to the research, or to the writing and review of this manuscript.

Conflict of interest

The authors state that they have no conflicts of interest. No funding.

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