Bone mineral density in patients with systemic mastocytosis: correlations with clinical and histopathological features

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Abstract

Objective

Systemic mastocytosis (SM) is a heterogeneous haematological entity characterised by proliferation of mast cells. Skeletal abnormalities of SM include osteolysis, osteopenia and osteoporosis but also osteosclerosis. A routinely used modality to assess bone density is dual-energy x-ray absorptiometry (DXA). The present study sought to elucidate possible associations between DXA findings with both clinical and bone marrow biopsy findings in SM.

Methods

Patient records of the local oncology and haematology department from 2007 to 2018 were screened for patients with SM. Overall, 39 patients (18 women and 21 men) with sufficient DXA images and clinical data were identified. We evaluated cKit mutation, tryptase level in serum, alkaline phosphatase, calcium level in serum, haemoglobin level, leucocytes and thrombocytes. Bone marrow biopsies were also evaluated.

Results

There were no significant differences between the different bone marrow patterns and in regard of cKit mutations. Significant lower bone mineral density (BMD) - T-score and Z-score values were identified for the indolent type compared to aggressive type. Correlation analysis revealed an association between BMD and tryptase level ($r=0.35$, $p=0.049$), mast cell proportion in bone marrow biopsy ($r=0.45$, $p=0.01$) and with the years since diagnosis ($r=-0.42$, $p=0.02$). Moreover, the correlations differed between the indolent and aggressive type.

Conclusion

DXA findings are associated with clinical and bone marrow biopsy parameters in SM. A positive association with tryptase level and mast cell amount in bone marrow biopsies was identified. This corroborates the usefulness of DXA in SM beyond the sole assessment of osteopenia and osteoporosis.

Key words

systemic mastocytosis, dual-energy x-ray absorptiometry, bone mineral density

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Introduction

Mastocytosis is one of the subcategories of myeloproliferative neoplasms caused by a neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells that can occur in one or more organ systems (1-3). Mast cells are heterogenous cells, which can release several important proteins when activated (4). Thus, they play a crucial role in allergic inflammation and immunity (4). The clinical presentation is heterogeneous ranging from skin-limited disease, most common in children, to more aggressive variants with systemic involvement manifesting as organ dysfunction, which is more common in adults (1-3).

Indolent systemic mastocytosis (SM) is the most frequent type and is predominantly characterised by symptoms related to mast cell degranulation/mediator release and/or allergies or anaphylaxis, whereas aggressive SM is characterised by specific organ dysfunction associated with mast cells. This entity most commonly affects bone marrow, cortical bone, gastrointestinal tract, and liver (3).

The diagnostic work up of these patients involves anamnestic features indicating mast cell activation, serological parameters, and bone marrow biopsy (3). Most importantly, the total tryptase level is one of the first defining features of SM. Another defining feature is the cKit-mutation, which can be detected in more than 80% of cases (5). Skeletal abnormalities of SM include osteolysis, osteopenia, osteoporosis and even bone destruction but also osteosclerosis (6). In any of the types, a focal or diffuse distribution can be seen (6).

Radiographic methods include radiography, magnetic resonance imaging, nuclear bone scan, and dual energy x-ray absorptiometry (DXA), which have been employed to assess the patterns and severity of skeletal involvement in SM (6).

DXA can assess bone tissue alterations by bone mineral density (BMD) measurement to diagnose osteoporosis in daily clinical routine (7).

It has been shown that bone involvement of SM is a possible risk factor for low BMD resulting in a high amount of osteoporosis in these patients with a prevalence from 18 to 28% (8).

Presumably, DXA can also help stratify patients according to prognosis and might even be related to other serum and histopathology parameters in SM due to its capability to quantify the bone involvement in SM.

Therefore, the present study sought to elucidate possible associations between BMD assessed by DXA and several clinical and histopathology parameters in SM.

Materials and methods

For this retrospective study, the institutional ethics committee waived the need for informed consent (committee of the University of Leipzig, study codes nr. 027/2002 and 162/2004).

Patient records of the local oncology and haematology department and the radiological database from January 2007 to December 2018 were screened for patients with SM. Overall, 282 patients were identified in the patient records and 126 in the radiological database. 88 patients were identified in both. Forty-nine patients were excluded because no DXA imaging was performed. Finally, 39 patients had sufficient DXA images and clinical data and comprised the present study sample. Figure 1 gives an overview of the patient acquisition.

Patients were grouped into indolent, smoldering and aggressive SM according to the proposed WHO classification (9).

Clinical parameters

We retrieved the following serological parameters from the patient records: tryptase level, alkaline phosphatase, calcium level, haemoglobin level, leucocytes and thrombocytes. All blood samples were obtained a week before or after the DXA.

Bone marrow analysis

Bone marrow biopsy was routinely performed in clinical diagnostic work up after informed consent. It was obtained from the iliac crest. Routinely used stainings were used in all cases including Giemsa-stained, Toluidine Blue-stained, and antitryptase-stained tissue sections.

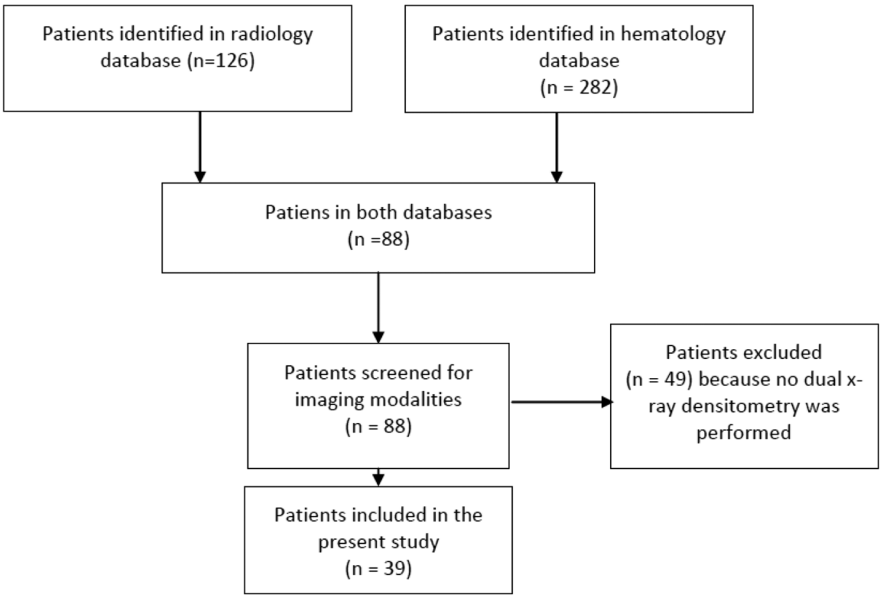


Fig. 1. Flow chart of the data acquisition. The radiology and haematological database were retrospectively screened. Altogether, 39 patients had sufficient radiological and clinical data and comprised the patient sample.

Moreover, the samples were grouped according to the infiltration pattern in aggregate formation, diffuse pattern, and mixed pattern. These patterns were defined by predominant mast cell infiltrate. For aggregate definition more than 15 cells were needed (10). For diffuse pattern no typical aggregates were found. A mixed type is defined by aggregates and diffuse mast cell infiltrates (10). Additionally, immunhistochemical stainings for CD2, CD25 and CD117 were performed.

Bone marrow tissue samples were further analysed for c-kit point mutation D816V using peptide nucleic acid (PNA)-mediated PCR clamping as described previously (5). In brief, a PNA molecule was used to specifically block the c-kit wild-type alleles during PCR, thus exclusively allowing amplification of mutated alleles. The presence of a mutation and its kind was then further determined by melting curve analysis of PCR products with a pair of hybridisation probes.

Dual x-ray absorptiometry

Clinical routinely used DXA (Hologic QDR 1500 Delphie; Hologic, Bedford, Mass., USA) was performed to determine BMD. The areal density measurements (grams per square centimetre), were obtained at the lumbar spine (L1–L4). Each measurement was expressed as the absolute BMD in g/cm^2. The value was compared to a reference database provided by the manufacturer utilising standard conversion into Z- and T-scores. The Z-score is the number of standard deviations (SDs) above or below the average matched individuals in the reference database based on age, gender and ethnicity. The T-score is the number of SDs above or below the mean of peak bone mass in subjects in the reference database matched by gender and ethnicity. Figure 2 shows a patient example of the patient sample.

Statistical analysis

For the statistical analysis Graph Pad Prism 5 (GraphPad Software, La Jolla, CA, USA) was used. Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Categorical variables were expressed as percentages. p-values <0.05 were taken to indicate statistical significance in all instances. Spearman's correlation coefficient was used to analyse the associations between DXA parameters and clinical as well as histopathology parameters after testing for non-normal distribution using Kolmogorow-Smirnow-Test. Mann-Whitney U- and ANOVA-test were used for group comparisons.

Results

There were 18 female (46.2%) patients and 21 male (53.8%) patients with a mean age of 51.2±15.9 years (standard deviation) (range 17–79 years).

Eleven patients (28.2%) had aggressive SM, 23 patients (59.0%) indolent SM, and 5 patients (12.8%) smouldering SM. Table I gives an overview of the patient sample including clinical, histopathology and imaging features.

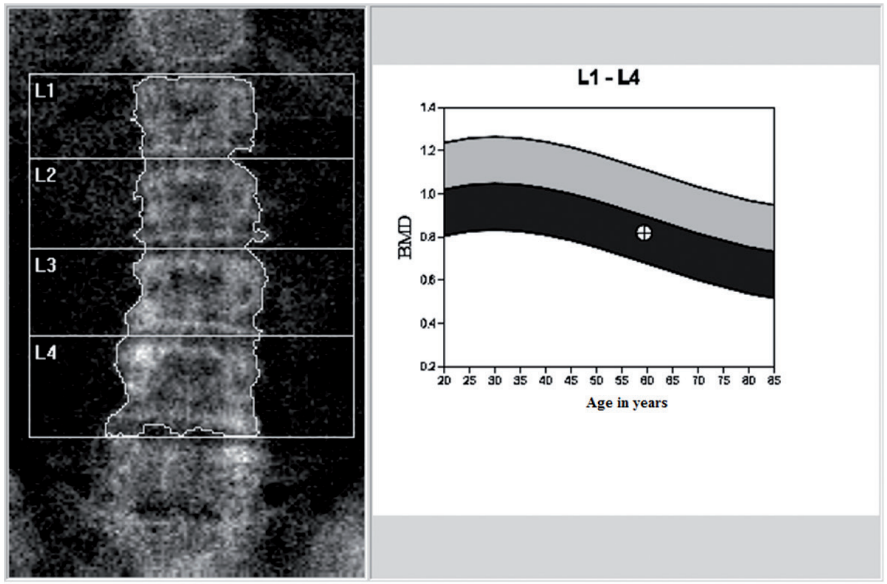
Overall, 7 patients had a negative cKit-Mutation (17.9%) and 32 were positive (82.1%). There were no differences with regard to DXA findings between cKit positive and negative patients.

Regarding bone marrow patterns, there were 19 patients (48.7%) with aggregate formation pattern, 8 (20.5%) with diffuse pattern, 8 (20.5%) with mixed pattern and in 4 patients (10.3%) the information regarding tumour pattern was not available.

There were no significant differences between the different bone marrow patterns regarding DXA parameters (ANOVA test, p=0.49 regarding BMD, p=0.45 regarding T-score, p=0.17 regarding Z-score).

There were significant lower BMD- T-score and Z-score values for the indolent type compared to aggressive type (for BMD: indolent: 0.9 g/cm^2 ± 0.13 *vs*. aggressive: 1.1 g/cm^2 ± 0.2, p=0.016, for T-score: indolent: -1.48±1.16 *vs*. aggressive: 0.5±0.7, p=0.005 and for Z-score: indolent: -0.7±1.4 *vs*. aggressive: 1.1±0.37, p=0.02, respectively).

Table II summarises Spearman's correlation analysis of the whole patient sample. Of note, BMD correlated with tryptase level (r=0.35, p=0.049), with mast cell proportion in bone marrow biopsy (r=0.45, p=0.01) and with the years since diagnosis (r=-0.42, p=0.02). When divided according to indolent and aggressive type, significant different correlations were identified. For the correlations between mast cell proportion in bone marrow biopsy the correlation was stronger in aggressive type (r=0.73, p=0.015 for BMD, r=0.71, p=0.019 for T-score and r=0.72, p=0.017 for Z-score), whereas in the indolent type no correlation was identified (r=0.06, p=0.8 for BMD, r=0.05, p=0.82 for T-score and r=-0.08, p=0.97 for Z-score).



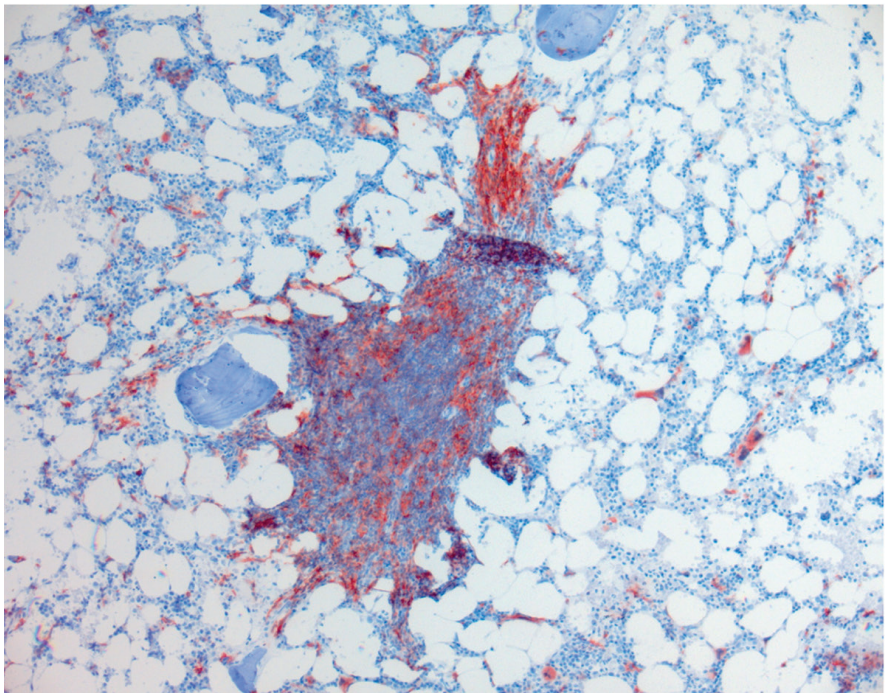


Fig. 2. Patient example of the sample with aggressive systemic mastocytosis.
A: The DXA was performed lumbar and measured the bone mineral density of the vertebral body L1 to L4. The BMD was matched with age for the estimation of T- and Z-scores. The patient had a BMD of 0.94 g/cm².
B: Corresponding histopathologic specimen of this patient with immunhistochemical staining for CD 25 (10-fold magnification). The calculated CD 25 expression is 79%.

Regarding the correlation years since diagnosis, a stronger correlation for the indolent type was identified (r=-0.62, p=0.002), whereas no correlation was identified for the aggressive type (r=-0.36, p=0.27).

Discussion

The present study identified several associations between DXA parameters and clinical and bone marrow findings in SM. Thus, the results corroborate the hypothesis that DXA may aid in disease assessment in SM.

It was previously identified that degree of change in bone density significantly and inversely correlates with bone marrow haematopoietic cellularity in several haematopoietic disorders including SM (9). Thus, DXA can non-invasively predict bone marrow changes. This might indirectly explain the presented results.

Bone involvement of SM is a frequent finding and can lead to osteopenia, osteoporosis and even osteosclerosis (6). This leads to s an overall decrease of bone mineral density, as stated in a recent meta analysis (11).

This results in a high prevalence of osteoporosis in up to 40% of patients with SM and leads consecutively to fragility fractures in 28% of patients (11). Moreover, it was identified that BMD and T-score derived from DXA are capable biomarkers to identify these patients at risk for fragility fractures (12).

Previously, only few reports identified possible imaging findings to be of prognostic and clinical relevance in SM. For example, Avila *et al*. investigated 27 patients with CT und ultrasound of the abdomen (13). In brief, 81% of patients showed pathological findings in these imaging modalities comprising most often hepatosplenomegaly, lymphadenopathy and ascites (13). Therefore, extraosseous, organic findings of SM tend to be of rather unspecific presentation. Yet, in a recent investigation splenomegaly defined by a volume over 1200 ml was a prognostic marker for the overall survival (10).

Previously, no investigations analysed associations between BMD and findings in bone marrow histopathology in SM. We could identify significant lower BMD values for the indolent type compared to the aggressive SM. To the best our knowledge, this is the first description of the phenomenon. These findings are somewhat difficult to ascertain. According to the classification criteria of SM, the amount of mast cell infiltration into bone marrow is not significantly different between the two (14). Furthermore, there are more osteolysis and pathological fractures reported in aggressive forms compared to indolent forms (15), which, presumably, may be caused by lowered BMD in these patients. Moreover, as described previously, there were no significant differences in regard of age between these groups, as a possible confounder (15).

We could not identify differences with regard to bone marrow patterns of SM,

Table I. Descriptive statistics of the patient sample.

Parameter	Mean ± standard deviation	Range
Parameters in blood serum		
Serum-tryptase (µg/L)	203.4 ± 450.6	16-2660
Alkaline phosphatase (µkat/L)	1.8 ± 1.5	0.9-6.7
Calcium (mmol/L)	2.4 ± 0.17	2.0-3.1
Lactate dehydrogenase (µkat/L)	3.5 ± 1.2	2.7-9.3
Haemoglobin (mmol/L)	8.2 ± 1.3	4.5-10.6
Leucocytes (GPt/L)	8.3 ± 4.1	3.4-19.6
Thrombocytes (GPt/L)	274.7 ± 118.7	19-690
Parameters in bone marrow biopsy		
Mast cell proportion (%)	27.1 ± 23.9	5-90
Eosinophil precursor cells	11.0 ± 7.2	2-20
CD2 cells	25.4 ± 23.2	0-79
CD25 cells	12.7 ± 15.8	0-79
CD117 cells	5.1 ± 8.4	0-46
DXA parameters		
Bone mineral density (g/cm^2)	0.9 ± 0.2	0.6-1.5
Z-score	-0.14 ± 1.81	-4.3-6.7
T-score	-0.89 ± 1.69	-4.5-4.5

Table II. Spearman's correlation analysis of the whole patient sample.

Parameter	BMD	T-score	Z-score
Tryptase	**r= 0.35 (*p*=0.049)**	r= 0.26 (*p*=0.16)	r= 0.26 (*p*=0.15)
Alkanine phosphatase	r= 0.14 (*p*=0.44)	r= 0.09 (*p*=0.62)	r= 0.12 (*p*=0.53)
Calcium	r= 0.09 (*p*=0.62)	r= 0.07 (*p*=0.70)	r=0.009 (*p*=0.99)
Lactate dehydrogenase	r=-0.28 (*p*=0.14)	r=-0.28 (*p*=0.13)	r=-0.21 (*p*=0.27)
Mast cell proportion in bone marrow biopsy	**r= 0.45 (*p*=0.01)**	**r= 0.41 (*p*=0.02)**	**r= 0.36 (*p*=0.04)**
Eosinophil precursor cells	r= 0.35 (*p*=0.21)	r= 0.36 (*p*=0.20)	**r= 0.55 (*p*=0.04)**
CD2	r=-0.12 (*p*=0.55)	r=-0.06 (*p*=0.76)	r=-0.19 (*p*=0.36)
CD25	r=-0.24 (*p*=0.23)	r=-0.25 (*p*=0.20)	r=-0.22 (*p*=0.28)
CD117	r= 0.15 (*p*=0.45)	r= 0.12 (*p*=0.55)	r= 0.09 (*p*=0.66)
Haemoglobin	r=-0.02 (*p*=0.91)	r=-0.05 (*p*=0.77)	r=-0.19 (*p*=0.31)
Leucocytes	r=-0.08 (*p*=0.64)	r=-0.09 (*p*=0.66)	r=-0.09 (*p*=0.66)
Thrombocytes	r=-0.06 (*p*=0.73)	r=-0.09 (*p*=0.96)	r= 0.02 (*p*=0.90)
Years since diagnosis	**r=-0.42 (*p*=0.02)**	**r=-0.41 (*p*=0.02)**	r=-0.29 (*p*=0.12)

Statistically significant correlations are highlighted in bold.

even though BMD is associated inversely with bone marrow cellularity (9). The qualitative approach by the pathologist to stratify different patterns is presumably not quantifiably definable by DXA.

There was a moderate correlation between BMD and the amount of mast cells within the bone biopsy. This is in good agreement with the fact that BMD can reflect bone marrow cellularity in several haematological disorders (10).

This is also interesting because in functional imaging applying FDG-PET, there were no correlations between PET findings and mast cell infiltration in bone marrow, serum tryptase level and expression of CD30 and CD2 in 19 patients (16). Therefore, DXA might be more beneficial in SM than the more advanced and more expansive PET.

Interestingly, we identified a moderate inverse correlation between BMD and years since diagnosis of SM in the overall patient sample, which was stronger in the indolent type. Clearly, with an enduring manifestation of SM within the bone the bone density is consecutively lowered due to osteolytic changes. However, this finding is somewhat conflicting with the results of Artuso *et al*., which identified a slight improvement of BMD in a 30 months follow-up under treatment (8). Efficient vitamin D supplementation might, therefore, successfully prevent bone loss in SM patients (8). Moreover, an increase of BMD under bisphosphonate treatment was also reported previously (17).

There was a positive correlation between serum tryptase level and BMD. Overall, serum tryptase levels in SM have been associated with the total body mast cell amount, diffuse bone sclerosis, the extent of bone marrow involvement, and the diagnostic type of SM (14, 18-20). This might be explained by a study identifying a greater amount of diffuse bone sclerosing with increasing tryptase levels (18). This association was also reported by a preliminary study applying DXA (21).

Previously, a preliminary study on 10 patients investigated with MRI could not identify a correlation between percentage of mast cells in bone marrow biopsy and MRI pattern of bone marrow involvement (22). This is surprising, because it is acknowledged that MRI is more sensitive for detection of marrow abnormalities than radiographs and in this way might also better reflect bone marrow involvement (23). Similar findings were reported by a MRI study using an advanced technique to assess trabecular bone microstructure in patients with indolent SM (24). It has been shown that MRI was not significantly different between SM patients and controls (24)

Multiple myeloma is another haematological disease, in which the role of DXA was also evaluated. However, there was no correlation between BMD measurements and osteolytic disease extent in multiple myeloma (25). Moreover, there was no correlation between medullary infiltrations by myeloma cells and bone mineral density (26). Yet, it was shown that that myeloma-induced bone loss improved and may be reversible in patients in sustained remission treatment visualised with DXA (26).

In brief, in SM DXA can assess more specific disease involvement than in multiple myeloma. Another interesting novel serum parameter might be CCL2, which is promoted by the Kit D816V mutation (27). More studies are needed to identify, whether this parameter is also associated with DXA. However, it was stated that the mutation burden of KIT D816V mutation is not associated with clinical manifestation of indolent SM analysed in biopsies and serum (28). This might indicate that a quantification of this parameter is clinically insignificant.

The present study affirms that DXA is not only a useful tool to screen for osteopenia and osteoporosis in SM patients but it is also associated with clinical and histopathology findings. Therefore, DXA might also provide prognostic relevant information, which should be evaluated in further prospective, multi-center trials of SM.

There are several limitations of the present study to address. Firstly, it is a retrospective study with possible known inherent bias. However, due to rare incidence of SM, prospective studies are difficult to perform. Consecutively, this result in a relatively small patient sample of the present single centre study, although it is one of the largest reported yet. Secondly, DXA and bone marrow biopsy are not performed on the same bone location, as the biopsy are most often extracted on the iliac crest, and the DXA measures the bone density of the lumbar spine. Therefore, there might be incongruences between the two, although SM is considered a systemic disease and thus involve the whole skeleton. Thirdly, there might be bias induced by focal osteolysis and osteosclerosis, which can influence DXA findings. To reduce this bias, we excluded prominent focal bone alterations of the measurement.

In conclusion, the present study identified associations between bone mineral density assessed by DXA and clinical and histopathology findings in systemic mastocytosis. A positive association with tryptase level and mast cell amount in bone marrow biopsies was identified. This corroborates the usefulness of DXA in systemic mastocytosis beyond the sole assessment of osteopenia and osteoporosis.

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