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Endocrine manifestations of systemic mastocytosis in bone

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Abstract Systemic Mastocytosis (SM) is characterized by accumulation of clonal, neoplastic proliferations of abnormal mast cells (MC) in one or more organ system other than skin. Presence of these multifocal clusters of abnormal mast cells is an essential feature of SM. Frequently associated with D816V (KIT) mutation, the presence of this mutation and elevated serum tryptase are minor criteria for diagnosis. SM manifestations depend on the degree of mast cell proliferation, activation and degranulation. SM has a variable prognosis and presentation, from indolent to "smoldering" to life-threatening disease. **Bone manifestations of SM** include: osteopenia with or without lytic lesions, osteoporosis with or without atraumatic fracture, osteosclerosis with increased bone density, and isolated lytic lesions. Male sex, older age, higher bone resorption markers, lower DKK1 level, lower BMD, absence of urticaria pigmentosa, and alcohol intake are all associated with increased risk of fracture. Treatment of SM is generally palliative. Most therapy is symptom-directed; and, infrequently, chemotherapy for refractory symptoms is indicated. Antihistamines may alleviate direct bone effects of histamine. Bisphosphonates, including alendronate, clodronate, pamidronate and zoledronic acid are recommended as a first line treatment of SM and osteoporosis. Interferon α may act synergistically with bisphosphonates. As elevation of RANKL and OPG is reported in SM, denosumab could be an effective therapy for bone manifestations of SM.

Keywords Tryptase · Histamine · Osteosclerosis · Mast cells · Systemic mastocytosis · Bone · Fracture · Osteoporosis

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1 Introduction

Mastocytosis is a rare neoplastic disease of the mast cell and its hematopoietic progenitor, occurring in about 1/10,000 individuals, broadly divided into cutaneous and systemic disease [1]. Usually treated by dermatologists, allergists and hematologists, the focus of patient and health care professionals is often the obvious disturbing skin and vascular manifestations of rashes, pruritus, and flushing, related to mast cell degranulation. Although very common, the bone involvement in systemic mastocytosis may be asymptomatic.

2 KIT and the regulation of mast cells

In a normal individual, KIT ligand, also known as stem-cell factor (SCF) present in the hematopoietic microenvironment, binds the CD117 (KIT) transmembrane tyrosine kinase receptor, to form a dimer that activates intrinsic tyrosine kinase activity, and triggers mast cell development. KIT encodes a transmembrane receptor with intrinsic tyrosine kinase activity (*KIT*), which is activated by binding to stem cell factor (SCF or Kit ligand), the major mast-cell growth and differentiation factor.

Upon differentiation of hematopoietic progenitors into mature cells, KIT expression is down-regulated in all lineages, except mast cells, which retain high levels of cell surface KIT expression. The interaction between KIT and its ligand, SCF, plays a key role in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival [2].

Mastocytosis is frequently associated with somatic gain-of-function point mutations within KIT. In a majority of cases of adult systemic mastocytosis (SM) the D816V mutation is found [3]. The somatic point mutation in codon 816 (most commonly Asp816Val) of the proto-oncogene KIT, permits activation and constitutive auto-phosphorylation of Kit, so that Kit does not need to bind to an activating ligand for its function [4]. Mast cell progenitors migrate from the blood into various tissues, including the skin, lungs, and mucosal interfaces, where they acquire tissue-specific phenotypes determined by the local microenvironment [5]. Cytokine signals, epigenetic modifications and other micro-environmental factors can substantially and, in some cases, rapidly and reversibly alter the phenotype of these cells and influence their function [6].

Abnormal clonal mast-cell expansion and accumulation in tissues may be influenced by response to endogenous or exogenous stimuli, in one or more tissues. The distinguishing feature of mastocytosis is the presence of multifocal clusters of abnormal mast cells. In contrast to normal mast cells, the mast cells of mastocytosis are variable in appearance, ranging from round to fusiform variants with long, polar cytoplasmic processes, and may display cytoplasmic hypogranularity with uneven distribution of fine granules, as well as atypical nuclei with monocytoid appearance [7]. Mastocytosis is characterized by varying degrees of mast cell proliferation, accompanied by symptoms of mast cell activation and degranulation in most patients.

3 Clinical disease

Mastocytosis can affect both children and adults. When diagnosed in infancy and children, it usually manifests as cutaneous mastocytosis, without systemic involvement, and with a good prognosis. In general, most children experience resolution or fading of skin lesions by adolescence [8]. Although approximately 60–80 % of patient with cutaneous mastocytosis have gain-of-function KIT mutations, patients with cutaneous mastocytosis usually do not fulfill the criteria for the diagnosis of systemic mastocytosis [9]. Adult-onset systemic mastocytosis patients usually have the activating mutation found in their skin and bone marrow. When mastocytosis is present in any extracutaneous tissue (most often the bone marrow, proven by biopsy) it is termed systemic mastocytosis (SM). Almost half of the individuals with mastocytosis are adults. Furthermore, almost all adults will have systemic disease if one looks closely enough [1]. Adult-onset SM patients usually have the activating mutation found in their skin and bone marrow. Therefore, unlike children, most adults with skin lesions have systemic disease, with bone marrow involvement and a persistent and progressive course [4].

SM is a heterogeneous group of disorders with variable prognosis, varying from indolent to “smoldering” to life-threatening disease [5]. Aggressive SM, which is characterized by specific tissue damage associated with mast cells, is most commonly identified in the bone marrow, liver, gastrointestinal tract, and cortical bone. Some of the most aggressive systemic mastocytosis presentations may occur without any skin manifestations [10].

4 Mastocytosis and the bone

4.1 Clinical manifestations

In adults, skeletal manifestations are one of the frequent findings of SM, occurring in about 50 % of patients, but this may often be asymptomatic [11]. Bone abnormalities reported in systemic mastocytosis include low bone mass or osteopenia, osteopenia with lytic lesions, and osteoporosis by bone density alone, osteoporosis with atraumatic fracture, osteosclerosis, and isolated lytic lesions of bone [10]. Recent studies concur that osteoporosis is the most frequent bone abnormality among patients diagnosed with mastocytosis. To date, the description of bone abnormalities includes not only the clinical manifestations (fractures), but also changes in surrogate markers such as bone mineral density, and biochemical bone turnover markers, such as bone specific alkaline phosphatase (bALP), C-telopeptide, osteocalcin, and osteoprotegerin (OPG) levels (Tables 1 and 2).

Barete et al. evaluated a cohort of 75 patients with SM and found out that, while 40 % of the patients presented with other clinical symptoms of mastocytosis, half already had bone involvement [19]. Clinical presentation may vary. Patients may be asymptomatic and yet have findings on bone density screening including osteopenia (from 33 to 60 %) or diffuse osteoporosis by BMD (10–38 %) or even osteosclerosis (5.3–10 %) (References 11–20; and Table 2). Symptoms include poorly localized bone pain, osteoporosis, pathologic fractures, and skeletal deformities. Sometimes pain due to a lytic lesion is the first presentation, and occasionally lesions may be detected on X-ray, without any history of pain [25]. The prevalence of fracture varies, in part based on sample size, method of selection of patients in study, and other factors. In the larger studies of patients with systemic mastocytosis, the incidence of vertebral fractures was almost 39 % (varies from 21 to 43 %) (References 14, 22; Table 1 and Fig. 1).

Table 1 Studies reporting fracture rate and risk factors in patients with mastocytosis in reverse order of the year of publication

Author/Year	Fracture results	Population	Comments
Alpay Kanıtez N Turk J Haematol. 2015 [12]	No fracture on radiograph	17 adult patients 5 W and 12 M Median age 33 years Age range: 20–64	Patient with severe disease had more sclerotic lesions (besides lytic lesions) 3 patients had lytic and sclerotic lesions in at least 1 site in bone radiographs (1 SSM, 1 ASM, and 1 MCL)
Rossini M Calcif Tissue Int. 2015 [11]	11 patients (23 times fracture)	26 adult ISM 13 men and 13 women Mean age 54 ± 12 Age range: 34–82	Tryptase level was higher in patients with osteosclerosis DKK1 was lower in fractured patient DKK1 and sclerostin were higher in ISM patient (than control)
Van Der Veer E J Allergy Clin Immunol. 2014 [13]	Of 221 patients: 127 patients (389 Fx) 90 patient FFx (264 Fx) 37 patient TFx (125 Fx) 54 patients (139 FFx) Before ISM Dx 56 patients (125 new FFx) After ISM Dx in 5.4 years (range 0.4–15.3 Y) follow up Of 181 patients: LS OP 14 % Hip OP 0.6 % 43 new Fx [normal BMD 12 (28 %), osteopenia 20 (47 %) and osteoporosis 11 (26 %)] 15 % previous FFx	−228 total population (7 missing fracture data) -221 ISM Fx Data: Age range: 19–77 28 OP treatment before ISM Dx 1 Gender change 2 Recent Fx/operation 9 Missing data (BMT and BMD) -181 Predictor analysis for fragility Fx: Mean age 46 ± 13 74 M and 107 W	-New FFxs after ISM Dx happened in patients of older age; male; more frequent anaphylactic reactions; less UP; higher MIMA, osteocalcin and CTX levels; lower hip BMD; and greater alcohol intake. -Independent predictor of FFx: Male sex, high levels of bone resorption (serum type I collagen C-telopeptide), low hip bone mineral density, absence of urticaria pigmentosa, and greater alcohol intake at the time of ISM diagnosis
Seitz S Osteoporos Int. 2013 [14]	118 patients vertebral fracture (39 %) OP Fx (109) higher among ISMs − than ISMs + (44 vs 21 %)	300 ISM M/W ratio 1.2:1 M 51.7 ± 13.3 W 55.8 ± 13.3 2/3 ISMs- (199, M 51.2 ± 11.2; W 56.9 ± 14) 1/3 ISMs + (101, M 48.4 ± 12.4; W 52.9 ± 11.5)	16 (5.3 %) ostoesclerosis (no FFx in osteosclerosis patients) No difference in mean age of ISM-related osteosclerosis and ISM-related bone loss
Guillaume N Am J Med. 2013 [15]	3 fractures (vertebra, vertebra and sacrum, tibia, wrist, and ankle) Osteopenia in 15 (33 %) Osteoporosis 9 (20 %)	45 patient Mean age 51 Age range 17–79 year 69 % female	−38 (84 %) with SM: 29 (64 %) ISM 5 (11 %) ASM 4 (9 %) SM-AHNMD -7 (16 %) cutaneous mastocytosis.
Van Der Veer E Allergy. 2012 [16]	−83/154 (54 %) with Fx (235 Fx) 43/63 (68 %) M with Fx 40/91 (44 %) W with Fx -57/154 (37 %) with OP Fx (140 OP Fx) 32/63 (51 %) M with OP Fx 25/91 (27 %) W with OP Fx	157 ISM (65 M, 92 W) Mean age 54 ± 12 years Median disease duration after the first symptom or sign of ISM was 13 years	1 man and 5 women had osteosclerosis (3.8 %) higher prevalence of osteoporotic fractures was detected among ISM patients without UP OP LS 42 (27 %) OP hip 2 (1 %)

Table 1 (continued)

Author/Year	Fracture results	Population	Comments
	2.4 osteoporotic fractures per patient 62 % vertebral Fx, 1 % hip and 36 % non-vertebral Fx OP Fx 37 % and OP 28 % OP fractures: <50 11/60 (18 %) OP Fx, 35 % of M and 6 % of W ≥ 50 46/94 (49 %) OP Fx 62 % of M and 40 % of W		7 men and 5 women had osteoporotic fractures or osteoporosis as presenting symptom LS or Hip BMD, T-score < -2.5 SD 43/154 (28 %) 20/63 (32 %) M and 23/91 (25 %) W <50 years 18/60 (17 %); 6/26 (23 %) M and 4/34 (12 %) W ≥ 50 years 33/94 (35 %); 14/37 (38 %) M and 19/57 (33 %) W
Laroche M Am J Med. 2011 [17]	All had atraumatic vertebral Fx (mean 3.5, range 1–7). No peripheral fracture.	10 patients 6 M and 4 W Mean age 52.50 Age range 35–77	Treated with interferon alpha (1.5 million U 3 times per week) + monthly pamidronate infusion (1 mg/kg) for 2 years, followed by pamidronate infusion (1 mg/kg) every 3 months.
Rossini M Bone. 2011 [18]	−5 non-vertebral Fx (2 rib, 2 wrist, 1 metatarsus) -17 Vertebral Fx (21.2 %) with moderate or severe vertebral fx (5 postmenopausal women and 12 men); -27 (19 M, median age 43; and 8 W, median age 54) has mastocytosis-related low BMD and/or vertebral Fx	82 ISM Mean age 48 Age range 20–82 79 ISM (3 excluded) 34 W and 45 M (10 postmenopausal)	35 ISMs+ 54 ISM and idiopathic anaphylaxis or severe allergic reactions to hymenoptera sting or drugs OP 16 (20.0 %) (7 W and 9 M) OP spine (18.7 %) than at total hip (2.5 %) The BMD was generally lower at the spine than at the hip
Barete S Ann Rheum Dis. 2010 [19]	-Bone involvement 37/75 (49 %) -OP 23/75 (31 %) of patients -Axial osteosclerosis 6 (8 %) Vertebral Fx 14/75 (19 %) total patient, 13/37 (35 %) of bone involvement, and 10/23 (43 %) of osteoporotic. Peripheral Fx 6/75 (8 %) total patients, 6/37 (16 %) of bone involvement, and 2/23 (9 %) of osteoporotic.	75 SM ISM 47 (62.6 %) SSM 3 (4 %) ASM 22 (30 %) SM-AHNMD 3 (4 %)	-M > W bone involvement (57 vs 26 %) -No correlation between bone involvement and D816 V mutation of KIT -OP more with aggressive form -Osteosclerosis with more aggressive disease -Osteopenia with pre-existing fx 4 (5.3 %) -Mixed patterns 3 (4 %) -Humeral osteolytic with spontaneous fracture (one patient) -Mean lumbar spine T score −3.2 ± 0.73 SD -Mean hip T score was −1.9 ± 0.93 SD
Escribano L J Allergy Clin Immunol. 2009 [20]	OP Fx 4 cases (10 %) had pathological fractures related to severe osteoporosis OP 22 (56 %) Diffuse bone sclerosis 4 (10 %) Patchy bone sclerosis 5 (13 %) patients	145 patients 63 (43 %) M and 82 (57 %) W Median age 37 Age range 16–72	

Table 2 Studies reporting bone density measurement, imaging studies and biochemical markers of bone turnover in patients with mastocytosis in reverse order of the year of publication

Author/Journal and Year	Radiological findings	Bone markers	Population	Comments
Alpay Kanitez N Turk J Haematol. 2015 [12]	9 (52 %) patients had osteopenia at least at one site (lumbar spine L1-L4, the femoral neck, and the distal radius or as calcaneus stiffness). 3 (17 %) patients had OP	-Positive correlation between PyD/Tryptase levels and disease severity and radiologic findings -No correlation between BMD and bone markers (bALP, OC, PyD, DPyD)	17 adult patients 5 W and 12 M Median age 33 years Age range: 20-64 QUS of the calcaneus and DXA for BMD of the lumbar spine (L1-L4), femoral neck, and distal radius.	-Disease severity had positive correlation with osteolytic and osteosclerotic lesions -BMD of the spine and femur was increased in patients with more severe disease -No relationship between DXA and bone lesion severity
Rossini M Calcif Tissue Int. 2015 [11]	Osteopenia 10 (4 M and 6 W) Osteoporosis 10 (5 M and 5 W) Osteosclerosis in 2 patients (2 W)	-DKK1, but not SOST, serum levels was higher in ISM patients with various bone involvements, and correlated with PTH and BTMs, CTX, and bALP	26 adult ISM 13 men and 13 women Mean age 54 ± 12 Age range: 34–82	-Wnt/β-catenin is not primarily involved -Lower DKK1 in patients with one or more vertebral fx
Rossini M Am J Med. 2014 [21]	-Zoledronic acid increased BMD of spine by 6.0 ± 4.4 % and total hip by 2.4 ± 3.2 % -OP of spine (mean T-score of −2.7 ± 0.7) was more than hip mean T-score −1.2 ± 0.7)	Zoledronic acid decreased serum levels of BMTs (bALP -34 % and -35 %, and CTX -68 and -56 %) at 6 and 12 months No significant changes in Ca, Phos, PTH, and Tryptase	25 ISM and OP 13 M and 12 W (postmenopausal) Mean age 58 ± 10	-Single zoledronic acid 5 mg IV in patients with OP and ISM -No reported new fractures after 1 year follow-up - Vertebral deformities in 13 patients
Rabenhorst A J Allergy Clin Immunol. 2013 [22]	Osteosclerosis 6 Osteopenia LS 34 (60.7 %) OP LS 6 (10.7 %) Normal LS BMD 10 -Decrease in LS BMD was more than FN -Most ISM had osteopenia or OP -advanced SM often had normal or increased BMD	-RANKL and OPG were higher in patients with ISM -higher levels of SOST -no change in level of DKK-1	56 patients 20 M and 36 W Mean age 51.2 ± 12.6 Age range 22–80 ISM 48 SSM 6 SM-AHNMD 2	LS T-score -1.2 ± 1.5 (−3.3 to 3.7) FN T-score -0.4 ± 1.4 (−2.7 to 3.8)
Seitz S Osteoporosis Int. 2013 [14]	-Ostoesclerosis 16 (5.3 %): W/M ratio 3/1; no FFx; less ISMs-; No difference in mean age; higher ALP, TBV and trabecular No. (compare to ISM-related bone loss)	-Reduced TBV, TT and trabecular No. –Increased trabecular separation, osteoid volume and thickness –Increased Obl and Ocl parameters	300 ISM -M/W ratio 1.2:1 -M 51.7 ± 13.3 -W 55.8 ± 13.3 -2/3 ISMs- (199, M 51.2 ± 11.2; W 56.9 ± 14) -1/3 ISMs + (101, M 48.4 ± 12.4; W 52.9 ± 11.5)	OP Fx higher among ISMs − than ISMs + (44 vs 21 %) –undecalcified iliac crest biopsies from 105 patients with -ISMs−, 54 patients with ISMs + and 100 control
Guillaume N -Am J Med. 2013 [15]	−24/38 SM (63 %) with BMD alteration: -9 OP (6 W and 3 M) -15 Osteopenia (10 W and 5 M) –16/45 SM (36 %) with radiographic bone lesion (osteolysis, osteocondensation or both) –3/45 fracture –3 BMD abnormalities in CM: -osteoporosis 1 -osteopenia 2	Higher Bone resorption (CTX and DPyD), bone formation (BAP), and bone remodeling (osteoprotegerin) –CTX, DPyD, and OPG were associated with mastocytosis severity -CTX and OPG were higher in advanced SM	45 mastocytosis Mean age 51 Age range 17-79 year 69% female 38 SM: 29 (64 %) ISM 5 (11 %) ASM 4 (9 %) SM-AHNMD -7 CM	38 (84 %) SM and 7 (16 %) CM CTX and OPG levels were correlated with serum Tryptase, a diagnostic marker of mastocytosis.
Van Der Veer E Allergy. 2012 [16]	*Osteoporosis*: *43/154 (28 %)* *M 20/63 (32 %)* *W 23/91 (25 %)* *-Osteosclerosis 6 (4 %)* *-OP Fx related to older age and male sex*	T-score Lumbar spine BMD has negative correlation with MH and MIMA. -Tryptase has positive correlation with disease duration	157 ISM (65 M, 92 W) Mean age 54 ± 12	OP < 50: 18/60 (17 %) M 6/26 (23 %) W 4/24 (12 %) OP ≥ 50:33/94 (35 %) M 14/37 (38 %) W 19/57 (33 %)
Laroche M	7 spine OP		10 patients (6 M and 4 W)	

Table 2 (continued)

Author/Journal and Year	Radiological findings	Bone markers	Population	Comments
Am J Med. 2011 [17]	3 spine osteopenia 1 TH OP 7 TH osteopenia	High Tryptase in all KIT D816V mutation in 8 patients	mean age of 52.50 Age range 35–77	All had atraumatic vertebral Fx (mean 3.5, range 1–7). No peripheral fracture
Rossini M Bone. 2011 [18]	-OP 16 (20.0 %) (7 W and 9 M) -Spine OP (18.7 %) was more than total hip OP (2.5 %) -Spine BMD was lower than hip BMD -MS-related low BMD and/or vertebral Fx in 27 (34 %) (8 W, median age 54, and 19 M, median age 43) -Osteosclerosis 2	No correlation between serum Tryptase levels and T or Z-score BMD Higher BMTx and serum Tryptase levels in osteosclerosis MS-related low BMD and/or vertebral Fx: older, lower serum OC; but no difference in BMI, smoking, and skin involvement	82 ISM Mean age 48 Age range 20–82 79 ISM (3 excluded) 34 W and 45 M (10 postmenopausal)	35 ISMs+ 54 ISM and idiopathic anaphylaxis or severe allergic reactions to hymenoptera sting or drugs Z-score < −2 at spine or hip (mastocytosis-related low BMD) 16 patients (20.0 %), 3 W 13 M
Barete S Ann Rheum Dis. 2010 [19]	37 (49 %) bone involvement: OP 23 (31 %) Axial skeleton Osteosclerosis 6 (8 %) Osteopenia with pre-existing Fx 4 (5.3 %) Mixed patterns 3 (4 %) Humeral osteolytic with spontaneous fracture (one patient) Mean lumbar spine T score −3.2 ± 0.73 SD Mean hip T score was −1.9 ± 0.93 SD	OP was accompanying by ASM, vertebral Fx, and fewer GI symptoms Osteosclerosis with more aggressive disease	75 SM ISM 47 (62.6 %), SSM 3 (4 %) ASM 13 (17.3 %), SM-AHNMD 3 (4 %) WHO categorized: ISM, SSM, ASM and SM-AHNMD	Bone involvement: more in Male (57 vs 26 %); no association with clinical characteristics, and D816V KIT mutation.
Kushnir-Sukhov NM Int Arch Allergy Immunol. 2006 [23]	37 % (7/19) osteopenia 16 % (3/19) OP -1 FN osteopenia (ISM) 3- low BMD at the 1/3 radius (2 ISM and 1 SSM) -Z-scores were lower in the less severe group compared to the more severe group -Patients with more severe disease had higher BMD	Tryptase had positive correlation with FN Z-scores BMD was higher in patients with higher tryptase level Less severe disease associated with lower serum tryptase	21 patients Mean age 51.1 ± 11.3 Age range 13 W and 8 M CM 1 ISM 14 SSM 3 SM-AHNMD 3	Treatment included: Estrogen and alendronate (23.8 %) Calcium/vitamin D (71.4 %) Oral steroid Six patients (28.6 %) -Lack of calcium/vitamin D supplementation, low BMI and smoking were not associated with low BMD
Johansson C Age and Ageing. 1996 Jan [24]	5 vertebral OP Fx 3 severe vertebral Fx 2 osteosclerosis 2 osteopenia BMD in hip was higher in patients with increased histamine metabolite excretion	level of serum ALP was significantly higher in mastocytosis patients with severe osteoporosis	16 patients	Increased mass cell mass was associated with low BMD in hip, OP and vertebral Fx.

ASM aggressive systemic mastocytosis, *bALP* bone-specific alkaline phosphatase, *BMD* bone mineral density, *BMTx* bone turnover marker, *Ca* Calcium, *CM* cutaneous mastocytosis, *CTX* C-telopeptide, *DPyD* deoxypyridinoline, *Dx* Diagnosis, *DXA* dual energy x-ray absorptiometry, *Fx* fracture, *FFx* fragility fracture, *FN* Femoral Neck, *HS* hepatosplenomegaly, *ISM* indolent systemic mastocytosis, *ISMs −* ISM with no evidence of skin lesions, *ISMs +* ISM with skin lesion, *M* Men, histamine metabolites *MH* methyl histamine and *MIMA* methylimidazole acetic acid, *NA* not available, *Obl* osteoblast, *Ocl* osteoclast, *OP* osteoporosis, *OPG* osteoprotegerin, *OC* osteocalcin, *Phos* Phosphorus, *PTH* parathormone, *PyD* pyridinoline, *SM* systemic mastocytosis, *SM-AHNMD* systemic mastocytosis with an associated clonal hematologic non-MC-lineage disease, *SSM* smoldering systemic mastocytosis, *TFx* high-energy trauma fractures, *TH* total hip, *TBV* Trabecular bone volume, *TT* trabecular thickness, *T No*. Trabecular number, *UP* Urticaria Pigmentosa, *W* Women

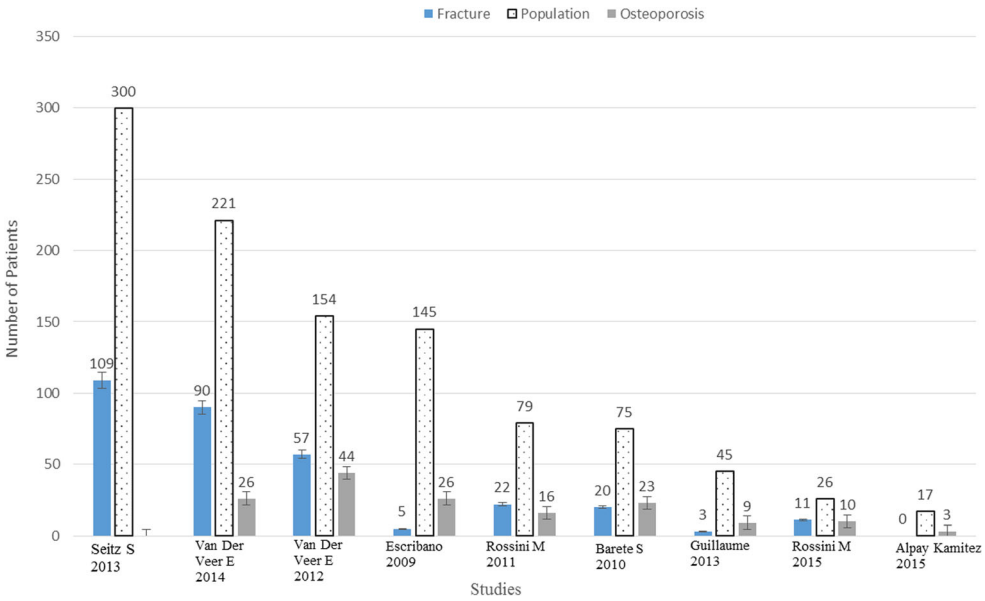

Fig. 1 Number of fractures and osteoporosis diagnosis in the patients with systemic mastocytosis in different studies in order of population size

Some fractures may occur in isolated lytic lesions of mastocytomas (19). Note that in some studies, the reported prevalence of osteoporosis is less than the fracture incidence, demonstrating that the bone fragility of mastocytosis is not always linked to the bone density (References 11, 15, 18, 22; and Fig. 1).

Both focal osteolytic and osteosclerotic bone lesions have been reported and, unlike in most other bone disease, the coexistence of these lesions is not rare [26]. Also fractures are associated with both osteoporosis and osteosclerosis [24].

4.2 Risk factors

In the largest study of fracture prevalence in SM by Seitz et al., the prevalence of osteoporosis is not reported [14]. In Van der Veer's large study of 228 patients with SM, independent risk predictors of future femoral fracture included: male sex, high levels of bone resorption, serum type I collagen C-telopeptide (CTX), low hip bone mineral density, absence of urticaria pigmentosa, and alcohol intake at the time of SM diagnosis [13]. It is also unclear how osteoporosis due to menopause might be separated from effects of mastocytosis on bone. Therefore, low bone density and other parameters in men might demonstrate the effects of mastocytosis on bone better than in women, and therefore might be more predictive. While tryptase level may predict mast cell mass, conversely, it might best relate to higher bone density, though this high bone density in mastocytosis does not protect against fracture [23].

Guillaume et al. have shown that bone turnover is elevated in mastocytosis patients, since markers of both bone resorption and bone formation were elevated, as compared with healthy individuals. This group postulates that the overall increased levels of bone turnover markers may reflect an increase in the number of osteoclasts and osteoblasts, correlated with expansion of mast cell number and activity [15].

5 Histomorphometric analysis

In patients with osteoporosis, the histomorphometric analysis revealed an increased number of both osteoclasts and osteoblasts, together with deterioration of trabecular bone structure [21, 27].

6 Etiology

However, the pathophysiology of bone loss in the context of mastocytosis is not fully understood. Even when there are findings of osteosclerosis by bone density, accelerated bone turnover is found [28].

As both increased bone formation, and increased bone loss have been found, the mediators may be variable in different patients, or act to variable degree. Guillaume found that, not only were biochemical markers significantly higher in mastocytosis patients than in the controls, but these markers were especially high in patients with advanced SM [15].

The level of tryptase, a marker of mast cell burden in SM, may correlate with serum levels of alkaline phosphatase, a marker of bone formation, and is associated with higher bone density [23, 28]. Indeed the highest levels of both tryptase and bone turnover markers are found in SM patients with increased bone density and "osteosclerotic" bone appearance. Guillaime et al. also report that, conversely, tryptase levels correlate significantly with

markers of bone resorption, such as CTX and deoxypyridinoline, and also with osteoprotegerin (OPG) a marker of bone formation. Therefore increased bone turnover occurs [15].

A series of cellular and molecular players coordinate the balance between bone-forming osteoblasts and bone-degrading osteoclasts in bone in a highly complex manner. Both parathyroid hormone (PTH) and the Wnt signaling pathway stimulate osteoblast genesis. The Wnt pathway controls and determines mesenchymal bone cell differentiation into osteoblasts, chondrocytes, and fat cells. It leads to increased production of both RANKL from osteoblasts and bone stromal cells and OPG, from osteoblasts. Next, RANKL binds to its receptor, RANK -the receptor activator of nuclear factor kappa-β, a member of the tumor necrosis factor receptor (TNFR) molecular sub-family-, present on osteoclasts and their precursors, to increase osteoclast differentiation and activation to resorb bone, and, simultaneously, to decrease osteoclast aptosis. Meanwhile, OPG competitively binds to RANKL, blocking RANKL from binding to the RANK receptor, thereby decreasing osteoclast activation and number.

Elevated bone levels of both RANKL and OPG are observed in mastocytosis [11, 22]. Mastocyte products, such as tryptase, may activate osteoblasts, increase OPG production, increasing bone turnover and formation. Supporting this, Laroche postulates that interferon α may reduce inflammation, in turn reducing tryptase secretion, thereby complementing bisphosphonate therapy of osteoporosis in mastocytosis [17].

The Wnt signaling pathway of bone is also regulated by receptor inhibitors such as Dickkopf-1 (DKK1), from several sources, and sclerostin (SOST), produced only by the osteocyte. DKK1 inhibits the Wnt/ β catenin pathway, by tightly binding to LRP6 and preventing it from binding to Fz (frizzled), so the Fz –LRP6 complex cannot form (Reference 29; and Fig. 2).

Rossini found increased levels of serum DKK1 in 46 patients with mastocytosis, compared to controls. While DKK1 serum levels were positively correlated with CTX, correlating to greater bone resorption, yet this marker also correlates with PTH level and bone specific alkaline phosphatase (bALP), a marker of bone formation. However, the level of DKK1 did not relate to extent of osteoporosis or osteosclerosis in these patients, so Rossini concluded that the marker elevation had little clinical import [11]. While Rabenhorst found elevated sclerostin (SOST) levels in patients with mastocytosis and bone disease, Rossini did not find elevated SOST compared to controls and he went on to surmise that SOST had no particular role in the pathogenesis of bone changes in mastocytosis [11, 22]. Although Rossini went on to postulate that the Wnt /β catenin signaling pathway is not important in mastocytosis, he never showed evidence to support this conclusion (11).

Histamine, the most abundant product of mast cells, acts directly on both osteoclasts and their precursors through autocrine/paracrine mechanisms. Histamine increases bone resorption, both indirectly, by increasing the expression of RANKL in osteoblasts, and directly, by stimulating the formation and activation of osteoclasts and their precursors [26]. Histamine might also act through its bone receptor, to decrease osteogenesis. A genetic knock out mouse for histamine production had increased production of active vitamin D (calcitriol), and lower PTH levels, decreased osteoclast number and increased bone density. It was postulated that the increased calcitriol also led to decreased osteoclasts. The authors proposed that anti-histamines might be useful to treat post-menopausal women and patients with SM [30]. In a study of patients with SM, the adequate 25 vitamin D, with low calcitriol levels found also indicated a renal impairment in 1 α hydroxylation activity of the kidney. Treatment with anti-histamines elevated the calcitriol levels and led to increased bone density [31]. While it is known that vitamin D may increase the differentiation of multi-potential stromal cells (MSCs) in bone to osteoblasts, there is *in vitro* evidence that the overexpression of the vitamin D receptor (VDR) in tumor cells, such as osteosarcoma cells, may activate both osteocalcin and the histamine receptor H1 (HRH1). The activated HRH1, negatively feeds back to decrease the osteogenic differentiation of MSCs, thereby minimizing vitamin D effect. Also some anti-histamines are shown to block the HRH1 receptor [32].

The activating D816V mutation of the tyrosine-kinase growth factor receptor KIT, commonly found in systemic mastocytosis, may itself relate to the bone disease, as KIT expression has been found on osteoclasts that resorb bone. Conversely, activated osteoblasts (the cells of bone formation) may increase KIT activation [33]. However, a study by Broesby-Olsen et al. did not find that the level of mutation correlated with the Z score (that represents standard of deviation of bone loss compared to normal age-matched contemporaries without MS) [34]. Furthermore, whether the somatic KIT mutations are also present in osteoclasts or osteoblasts has not been investigated.

Heparin released from mast cells, might also increase PTH-mediated bone resorption, through the Wnt signaling pathway. Also, increased PTH may stimulate osteoblasts to secrete factors activating the KIT pathway, in turn activating mastocytes [27].

The imbalance between bone formation and resorption is likely a result of either neoplastic infiltration or the local release of mediators, including tryptase, histamine, heparin, lipid mediators, and cytokines by mast cells (Fig. 2).

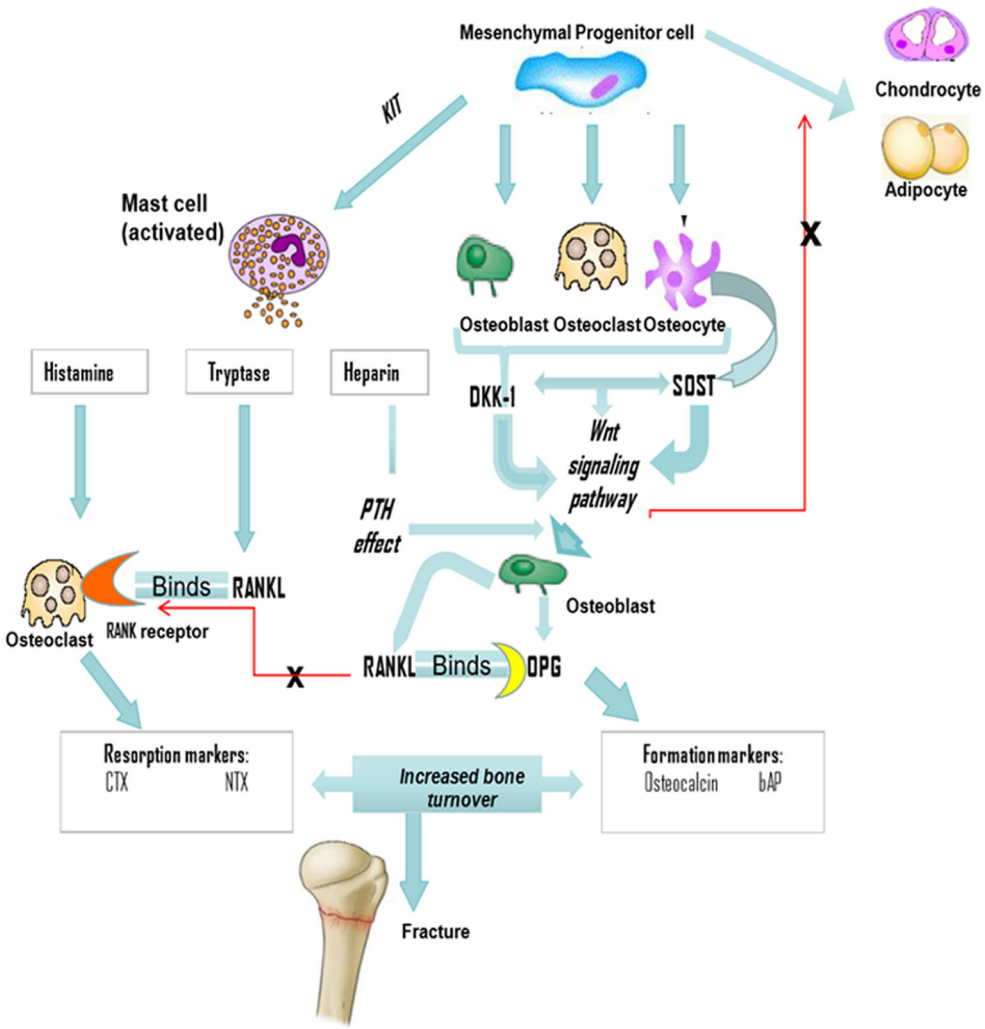

Fig. 2 Mechanism of mastocytosis effects on bone

7 Treatment

In 1990, Graves et al. proposed using a medication to prevent mast cell degranulation, ketotifen, to help decrease bone pain and increase bone density in one case of systemic mastocytosis in a patient with concurrent decrease in 1,25 vitamin D [31]. Past studies of cromolyn, anti-histamines, sodium fluoride showed no effectiveness. Chemotherapeutic agents such as chlorambucil and mithramycin, had variable results [35].

Bisphosphonates, including clodronate, alendronate, pamidronate and zoledronic acid, are the first line agents used in treatment of mastocytosis and osteoporosis [36] and have a role in the associated refractory bone pain [37–39]. Cundy et al. treated a 63 year old woman with a history of urticaria, who had not responded to chlorambucil nor mithramycin, with a successful response to oral clodronate. However, this individual, with a 20 years delay in the appearance of osteopenia, a history of acromegaly and consequent hypogonadotropic hypogonadism, is not likely to be representative [40]. A study by Barete et al. used bisphosphonate therapy in 23 patients with mastocytosis and osteoporosis, with a good response of lumbar spine BMD, but no mean change in hip BMD, though 3 patients had a decline in hip BMD. In addition, no subjects developed new vertebral fractures [19]. In Rossini's study of 25 patients, treatment with intravenous zoledronic acid improved both spine and hip BMD, decreased serum markers of formation (bALP) and resorption (CTX). Also, no patient had a new fracture during the observation period (References 19, 23; and Table 3).

Perhaps reduction of inflammation might link to bone stability or even improvement. When interferon therapy is initiated, mast cells degranulate releasing histamine, but then the mast cells are depleted. In a study of three SM patients with vertebral fractures causing pain, α interferon therapy improved the bone density, as pain abated contemporaneously, permitting analgesic agents to be stopped. One patient in this study had two successful subsequent treatments with interferon α alone, as symptoms recurred off therapy [35]. Interferon may act synergistically with bisphosphonates. In a longer and

Table 3 Reported treatment of osteoporosis in the patients with mastocytosis in reverse order of the years of publication

Author/year	Treatment result	Number of participants	Comments
Rossini M Am J Med. 2014 [21]	Single zoledronic acid 5 mg IV in patients with OP and ISM increased spine BMD by 6.0 ± 4.4 %, and hip BMD by 2.4 ± 3.2 %; decreased serum levels of BMTs (bALP -34 and -35 %, and CTX -68 and -56 %) at 6 and 12 months. No reported new fractures during the year of follow-up.	25 patients	
Laroche M Am J Med. 2011 [17]	3 patients had been received alendronate before Dx and developed new vertebral fractures -No fracture happened during treatment Group 1–8 patients (received INF-α + pamidronate): increase in the mean annual spinal BMD was 12.6 ± 5.6 % and hip BMD 1.93 ± 3 % Group 2-2 patients (received pamidronate alone): increase in the mean annual spinal BMD was 2.4 ± 0.1 % and hip BMD 0 ± 0.1 %. -Decrease in BTMs in group 1 and 2: Serum CTX 66 and 67 % bALP 25 and 36 % Tryptase 22.6 % (only in group 1) Increase in BMD: spine BMD 2.4 ± 0.5 % and hip BMD 0 ± 0.4 %	10 patients Mean age 52.5 Age range 35–77 Atraumatic vertebral Fx in all (mean 3.5, range 1–7) No peripheral Fx 7 UP 2 urticaria only 2 flushes, malaise and palpitations 1 HSP and hyper eosinophilia	−8 pamidronate + INF 2 pamidronate -INF-alpha 1.5 million U 3 times per week -Pamidronate monthly infusions (1 mg/kg) for 2 years, followed by pamidronate infusions every 3 months.
Barete S Ann Rheum Dis. 2010 [19]	23 patient with OP treated with bisphosphonate, calcium and Vitamin D; 9 patients has serial BMD (M/W 6/3, 34–75 yo) Increase in mean lumbar spine BMD from 0.831 ± 0.12 to 0.923 ± 0.13 g/cm2 (+11.07, +2.05 %) without recurrence of vertebral fracture Mean hip BMD values remained stable; 3 patients had a decrease in hip BMD.	75 SM ISM 47 (62.6 %), SSM 3 (4 %) ASM 13 (17.3 %), SM-AHNMD 3 (4 %)	Mean follow-up 65 (26–84) months
Laroche M Clin Rheumatol. 2007 [38]	No new vertebral or peripheral Fx Mean increase in BMD with IFN + Pam was 16.05 ± 6.12 % at the spine, 5 ± 2.24 % at the femoral neck, and 4.12 ± 3.03 % for the whole body Decrease or increase in BMD with Pamidronate alone was +0.2 ± 2.13 % at the spine, −2.25 ± 2.78 % at the femoral neck, and −0.1 ± 3.35 % for the whole body. Reduced BMTs with IFN + Pam: - 49 % for urinary DPyD and -52 % for OC Increase in BMTs with Pam alone: +24 % for DPyD and +41 % for OC.	3 Men and 1 woman Mean age 52 Age range 40–65 Severe osteoporosis and mastocytosis, cutaneous signs,	IFN + Pamidronate: 2 years for 3 patients; and 1 year for 1 patient Then Pamidronate for 2 years.
A Y N Lim Ann Rheum Dis. 2005 [37]	5 annual IV pamidronate followed by alendronate 1 alendronate only No further fractures Improvement in pain	6 SM Mean age 58 Age range 40–70	Mean duration of SM was 8 years (range 3–13) UP, back pain and Tryptase > 20 in all 4 vertebral Fx on X-ray

Table 3 (continued)

Author/year	Treatment result	Number of participants	Comments
	BMD (baseline and at 1–2 yearly intervals) Increase in LS BMD (2 patients had multiple lumbar vertebral fractures were excluded)		
	Hip BMD increased 3 patients and stabilized in the other three		
Marshall A Br J Rheumatol. 1997 [39]	52 yo W:	3 SM	
	Annual pamidronate 90–105 mg for 5 years, reduction of spinal pain, 21 % increase in LS BMD, 2 more vertebral fractures at T6 and T12	52 W, 52 W, 45 M yo	
	52 yo W:		
	Annual pamidronate 90–105 mg for 3 years, improvement in spinal pain, 29 % increase in LS BMD, 3 % reduction fo FN BMD, no further Fx		
	45 yo M:		
	Annual pamidronate 90–105 mg for 2 years, improvement in spinal pain, 16 % increase in LS BMD, 2 % reduction fo FN BMD, no further Fx		

INF interferon

more complicated study, ten patients who had developed fractures while on alendronate, improved their bone density and no longer fractured while on a combination of α-interferon and pamidronate [17].

Theoretically, the anti-histamines used by patients to alleviate flushing and itching might also have a small role in counteracting bone effects of histamines. In general, both H1 and H2 inhibitors increase calcitriol levels, decrease PTH and slow down bone resorption in ovarectomized mice [27, 30]. However, it is not known if H2 blockers might inhibit calcium absorption and, therefore, may have a detrimental effect.

8 Possible future therapies

Although RANKL and osteoprotegerin (OPG) levels have been noted to be elevated in the bone disease of mastocytosis, we could not find any studies using denosumab, a congener of osteoprotegerin. Also, a potential new agent might be sclerostin, though sclerostin levels appear unchanged in one study of bone [11].

As systemic mastocytosis may be a premalignant condition, leading rarely to a leukemic condition, we would not suggest the use of teriparatide as an anabolic agent for patients with mastocytosis.

9 Further questions

As in all forms of bone loss, it is unclear when to initiate therapy. Should a bone drug be started for an isolated low T score (e.g., when T score is less than -2.0 or -2.5), or only when there is a compression fracture regardless of T score? Can response in SM be measured properly with bone density? Response to therapy might be difficult to evaluate, especially in a patient with mixed lytic and sclerotic lesions. Furthermore, it also unknown how long therapy should be continued for maximum benefit.

10 Conclusions

The true incidence and development of bone abnormalities has never been discovered, as most reports are retrospective, in that clinical bone abnormalities are noted first. The study by Laroche et al. of SM patients in Table 1, though not retrospective, is not included in Fig. 1, because prior vertebral fracture was a requisite for inclusion [17].

Rarely, in indolent cases, the bone disease predates the clinical diagnosis of mastocytosis. The variability in presentation of bone disease also is unexplained, as patients may have osteopenia, osteoporosis with or without fracture, isolated islands of dissolution, or even osteopetrosis with or

without fracture. Occasionally, two different bone conditions occur in the same patient. As there is uncertainty in the literature about when to start treatment in common conditions of post-menopausal bone loss, with attempts to provide a risk indicator, such as FRAX, there is even more difficulty when we don't even know or understand the course of bone loss proceeding to fracture in patients with mastocytosis. Appreciating the heterogeneity in pathology and biochemistry, there might be several different solutions too. Clinical research study on the progression and treatment of bone disease is needed. Though mastocytosis is a rare disease, and the bone disease may be silent, there is considerable risk of fracture in this population.

Compliance with ethical standards

Conflict of interest statement Loren Wissner Greene declares that there is no Conflict of Interest.

Kamyar Asadipooya declares that there is no Conflict of Interest.

Patricia Freitas Corradi declares that there is no Conflict of Interest.

Cem Akin declares that there is no Conflict of Interest.

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