Systemic mastocytosis with skeletal involvement: a case report and review of the literature

Maurizio Benucci[a]
Catia Bettazzi[b]
Stefania Bracci[c]
Plinio Fabiani[c]
Laura Monsacchi[c]
Carlo Cappelletti[c]
Mariangela Manfredi[d]
Stefania Ciolli[e]

[a] Section of Rheumatology Department of Internal Medicine, Nuovo Ospedale di S. Giovanni di Dio, Azienda Sanitaria di Firenze, Italy
[b] Day Hospital and Day Service Internal Medicine Unit, Nuovo Ospedale S. Giovanni di Dio, Azienda Sanitaria di Firenze, Italy
[c] Internal Medicine Unit, Nuovo Ospedale S. Giovanni di Dio, Azienda Sanitaria di Firenze, Italy
[d] Laboratory of Immunology and Allergology Laboratory Unit, Nuovo Ospedale S. Giovanni di Dio, Azienda Sanitaria di Firenze, Italy
[e] Haematology Unit, Careggi Hospital, Florence

Address for correspondence:
Maurizio Benucci
Section of Rheumatology, Nuovo Ospedale S. Giovanni di Dio
Via Torregalli, 3 - 50143 Florence, Italy
Ph. +39 055 7192485
Fax +39 055 7192260
E-mail: maubenucci@tiscali.it

Summary

Systemic Mastocytosis (SM) comprises a heterogeneous group of disorders of mast cell proliferation. Infiltration, including skin and bone, of multiple mast cells may occur as cutaneous and systemic variants. A rare form of osteoporosis has been also described as expression of the skeletal involvement.
Here, we describe a case of a 57-years-old woman with SM and, according to the clinical diagnosis, evaluate the possible mechanism underlying osteoporosis. Moreover, a review of the literature, particularly regarding the use of bisphosphonates in this rare disease is also presented.

KEY WORDS: mastocytosis, osteoporosis, bisphosphonates.

Introduction

Systemic Mastocytosis (SM) is an uncommon disorder characterized by an abnormal proliferation of mastocytes which can infiltrate several organs and tissues, such as the skin, bone marrow, spleen, lymph nodes, liver and the gastrointestinal tract (1).
The symptoms of the disease may vary and reflect the involvement of tissues. It is possible to observe fatigue, weight loss, sweats, abdominal pain and diarrhoea, pruritus and urticaria, wheezing, tachycardia, hypotension or hypertension, arthralgia and bone pain (2).
Even if the involvement of the skin in SM, causing urticaria pigmentosa, may represent the only manifestation of the disease, the skeleton is the most frequent localization of SM presenting, according to classical radiography and bone scintigraphy data, in approximately 70% of the affected individuals (2-3). Moreover, in most of cases the bone involvement represents the unique clinical feature of the disease (4), either at the initial stage or during its progression.
The typical radiological aspects of the SM-related bone disease are characterized by the presence of multiple foci of sclerosis alternating with zones with apparently normal or reduced bone density.
Total bone CT-methylendiphosphonate scintigraphy reflects the radiological features with areas of markedly increased uptake alternating with non-uptaking foci.
Due to the possibility of an aggressive progression with haematological involvement, such as myelophthisis, association with lymphoproliferative or myeloproliferative diseases, coagulation disorders or mastocytic leukaemia (5), the recognition of bone involvement at early stages is mandatory for an optimal clinical management.
Here, we describe a recently observed SM clinical case, evaluating its pathogenetic and therapeutical aspects according to recent molecular biological developments.

Case Report

In February 2005 a 57-years-old woman, with a nontraumatic fracture of L1 vertebral body, came to our attention.

Patient's anamnesis

She presented a past history of autoimmune hyperthyroidism diagnosed in 2005 with a swollen throat, weight loss and thyreotossicosis, treated with 5 mg/day of Metimazolo. Moreover, the patient suffered because of four episodes of spontaneous costal fractures since from the age of 45 years. Her risk factors for osteoporosis included menopause at 46 years old and cigarette-smoking (20 per day). According to her general practitioner's prescription, she was taking a calcium carbonate, 1g/day, and colecalciferol, D 800 UI/day, supplementation.

Clinical presentation

Lumbar (LS) and left femoral neck (l-FN) DXA scans, carried out on December 2003, showed a bone mineral density (BMD) 0.660 g/cm^2, T-score -2.83 (-35%), Z-score -2.16 (-29%) and 0.824 g/cm^2, T score -1.0 (-14%), Z-score -0.18 (-0.3%), respectively. Further DXA scans performed during her hospitalization in 2005 showed a worsening of the BMD: LS-BMD: 0.565 mg/cm^2, T-score -4.4 (-46%), Z-score -3.1 (-38%) and l-FN BMD: 0.632 mg/cm^2, T-score -2.0 (-26%), Z-score -0.8 (-12%) (Hologic 4500 QDR).
A Magnetic Resonance Imaging (MRI) of the rachis and pelvis revealed the presence, in all the vertebrae, of multiple roundish

areas ranging from few mm up to 1 cm, hyperintense in the short-tau inversion recovery (STIR) sequences and with a partially confluent aspect within soma of D10-D11-D12 bodies (Fig. 1). Somatic hollows were also observed on D5-D6-D7 bodies.
In order to assess/exclude the possibility of tumoral bone disease, the patient underwent mammography, oesophago-gastroduodenoscopy, recto-colonoscopy, and thoracic abdominal CT, all of which were negative.
All the biochemical tests, including total and fractioned proteins, immunoelectrophoresis, urinary Bence Jones protein and urine free light chains resulted within the normal range. Bone turnover markers were also evaluated: 24 hours collected urinary calcium (colorimetric method with calcium and cresolphthalein in alkaline solution, Roche, Switzerland), urinary phosphate (Phosphorlibdato of ammonium method UV, Roche, Switzerland), urinary creatinine (the Jaffe method modified according to Bartles, complexed with Picric Acid, Roche, Switzerland) tests were performed on a Hitachi 917 instrument; urinary excretion of hydroxyproline (OHPr) (HPLC UV Colorimetric method, BIORAD, USA), urinary excretion of Deoxypiridinoline (DPyr) (ELISA method, DPC Medical System, USA) were calculated on an IMMULITE One device; urinary excretion of N-terminal Collagen (NTX) (ELISA method, Osteomark-Bouty USA), Bone Alkaline Phosphatase (BAP) (immunoenzymatic method, Metra-Quidel, USA), Osteocalcin (OC) (immunoenzymatic chemiluminescence method, DPC Medical System, USA). The measurement of the urinary calcium, phosphate, OHPr, DPyr and NTX were performed in relation to the urinary excretion of creatinine.
We obtained the following abnormal data: BAP 93 UI/L (normal values: 10-22 UI/L), OHPr 0,069 (normal values:<0.020), D-Pyr 12.3 (normal values<7), NTX 63.7 (normal values <47). The Tryptase tests, ImmunoCAP Phadia repeated on two different samples, evidenced values of 24.2 and 29.8 micrograms/L (normal values <13.5 micrograms/L).

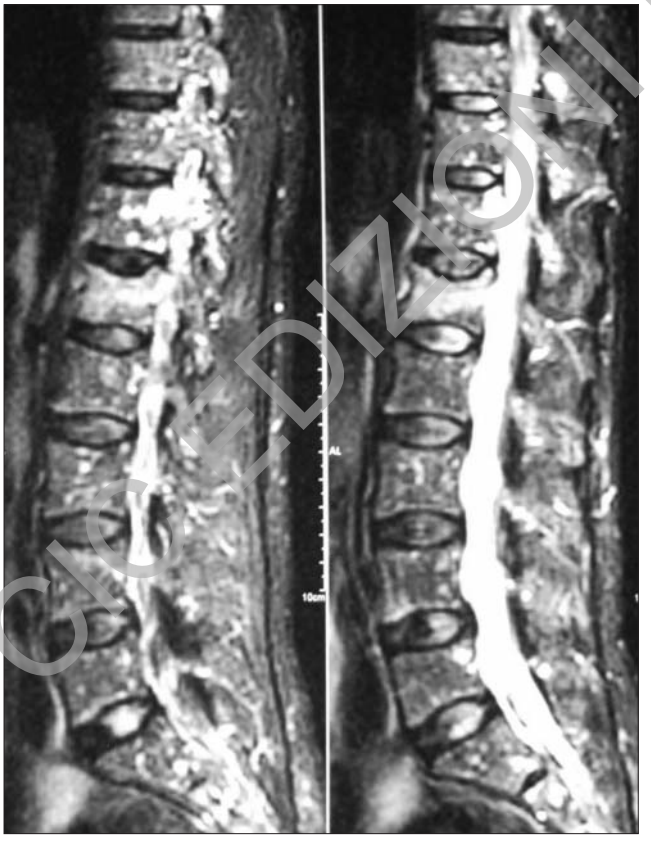


Figure 1 - Presence, in all the vertebrae, of multiple roundish areas from few mm up to 1 cm, hyperintense in the STIR sequences and with a partially confluent aspect within the soma of D10-D11-D12 bodies.

Bone marrow biopsy

In order to define a diagnosis, the patient underwent bone marrow biopsy which showed on histological examination the presence of T and B lymphocyte aggregates in the perisinusoidal and paratrabecular area, together with round and fused cells with cytoplasmic granule aggregates of 15 or more mastocytes (MCT+ CD117+) with an involvement of 20% of the medullary cells suggestive for the diagnosis of SM (Figs. 2-1, 2-2).
In October 10th 2006, she was referred to the haematologist.

Molecular biology investigation

Polymerase chain reaction (PCR)-based DNA sequencing, according to standard method of the EAC program (6), was conducted on BCR/ABL bone marrow cells and Fusion Protein-platelet-derived growth factor receptor-alpha gene (FIP1L1-PDGFRα) rearrangements were absent, whereas a c-*KIT D816V* mutation was detected. SM harbouring a c-*KIT D816V* mutation has been already described accounting for the lack of response to Gleevec (7) therapy, as also to other tyrosine kinase inhibitors used in Phase 2 clinical trials (8).

Therapy

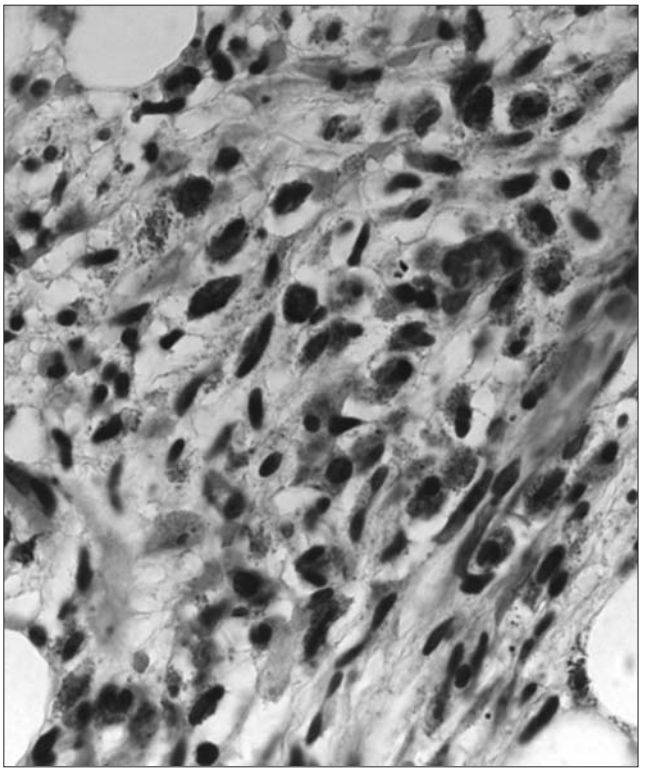
The patient began therapy with Pamidronate 60 mg/month for six months and α2B-Interferon with a dosage of 1 million IU twice a week. At follow-up the patient performed evaluation of circulating Tryptase every three months.

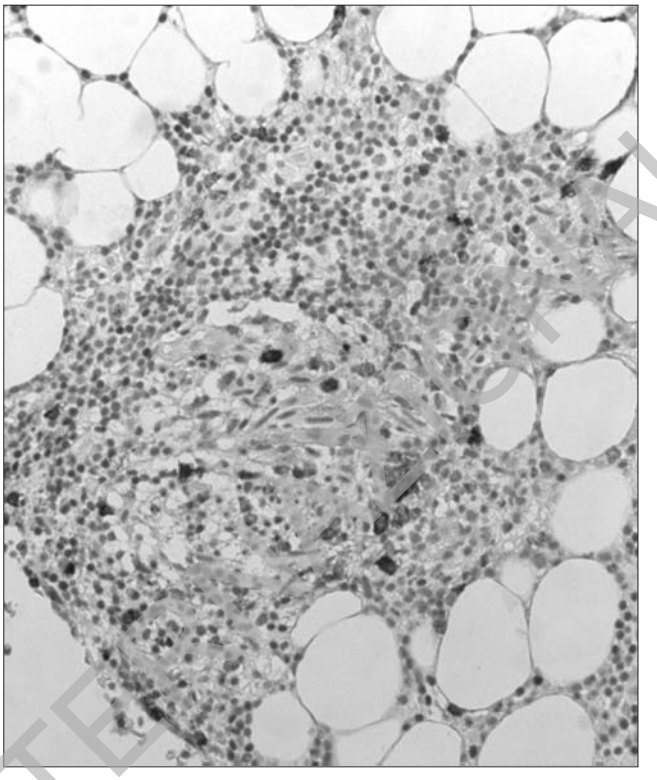
Results

The biochemical results obtained after twelve months of therapy showed: serum Triptase 18.8 micrograms/L, BAP 24 UI/L, OHPr/Cr 0.035, D-Pyr/Cr 9.3, NTX/Cr 52.5. No other vertebral fractures were detected after one year of treatment.

Discussion

Even if the disease is rare, according to the literature the SM-related skeleton involvement occurs in >70% of cases (3, 9).
Considering the interval from 1997 up to August 2006, using mastocytosis/osteoporosis as key words, we found at PubMed (http://www.ncbi.nlm.nih.gov/) 18 SM cases, 6 of which reported within the same manuscript (10). A recent study reviewing the literature from 1957 to 2004 using the same key words quoted 200 articles (11).
Recent data identify in SM an accumulation of mastocytes in the bone marrow in the absence of circulating progenitor cell elements (12). The accumulation of mastocytes is the result of activating mutation of the tyrosin-kinase growth factor receptor c-*KIT*, producing different clinical manifestations (13). Even though the relationship between mastocytes and osteoclasts is still unclear, c-*KIT* expression and its response to binding have been observed on osteoclasts (14).
However, in a mastocytes-deficient mouse model, a reduction of the recruitment of osteoclasts at the bone remodelling sites,





Figures 2-1 and 2-2. Bone marrow biopsy which showed on histological examination the presence in the perisinusoidal and paratrabecular area of T and B lymphocyte aggregates and round and fused cells with the presence of cytoplasmic granules aggregates of 15 or more mastocytes (MCT+ CD117+) and with an involvement of 20% of the medullary cells compatible with the diagnosis of systemic mastocytosis.

of the duration of bone formation and of synthesis of bone matrix has been observed (15).

Hystopathological Findings

Overall, four localization patterns of mastocytic granuloma have been described: peritrabecular, perivascular, lymphofollicular and perisinusoidal (16). Histomorphometric studies demonstrated an increased of the number of mastocytes, both in cortical and trabecular bone (17), an increased number of osteoblasts and osteoclasts (18) and peritrabecular fibrosis. However, the skeletal involvement takes mainly place in the trabecular bone determining a vertebral collapse (19). On the contrary, BMD in sites such as the FN, may also result to be elevated (20). An unusual skeletal involvement, described as a solitary lesion, is represented by mastocytoma (21).

Histomorphometric study

SM represents a rare cause of secondary osteoporosis. A histomorphometric study on 158 biopsies from untreated patients showed a prevalence of 1.25% of osteoporosis, with 2.25% of the patients younger than 45 years of age. The overall male/female ratio was 1:1, whereas in osteoporotic subgroup was 1:2. Osteopenia was detectable in 64% of cases whereas osteosclerosis in 3% (22). The presence of bone fractures in SM subjects was found in 16% of cases. An increase of bone resorption was observed, with an increased number of activated osteoclasts (2).
Histomorphometric studies also demonstrated a reduced mineralization (23), while both an increase of bone resorption and a reduced neoformation may be suggested by the increase of urinary OHPr and reduction of serum OC (24). Most of osteoporotic SM cases occur also in the absence of a cutaneous involvement (25).

Pathogenesis

The pathogenesis of SM-related osteoporosis is thought to be partly due to the ability of mastocytes to infiltrate bone marrow with inhibition on the bone formation. Moreover, mastocytes, releasing heparin, neutrophil and eosinophil chemotactic factors, prostaglandin D2, and several proteases such as arylsulphatase, tryptase, β-hexosaminidase, β-glucuronidase and β-galactosidase that metabolize glycosaminoglycans, may also indirectly activate collagenase by their ability to activate stromelysin-1 (26). Histamine and heparin have a direct effect on the osteoclasts whereas neutrophil and eosinophil chemotactic factors, prostaglandin D2 and leukotrienes would produce a local inflammatory action (27, 28). Moreover, the activation of the osteoclast could occur through a vitamin D deficiency with normal or elevated parathormone (PTH) levels (29).
The existence of a possible mastocyte/osteoclast interaction is also suggested by the mastocytes production of cytokines such as IL-1, IL-3, IL-6 and TGF-β promoting the osteoclasts activation in several *in vivo* models (30). It has been reported that high levels of IL-6 correlate with osteoporosis and bone pain in patients with SM (31).
The effects of histamine have been evaluated in mice with a deficiency of the decarboxylase histamine gene which demonstrated an increase in bone neoformation rate, a reduced number of osteoclasts, evaluated with Tartrate resistant Acid Phosphatase (TRAP), a reduced osteoclastogenesis and an increased calcitriol synthesis together with a deficit of PTH and increased expression of soluble RANK-L, on which a modula-

tion by histamine, interacting with its receptors, could occur (32). The role of the histamine receptors has been demonstrated in animal models. In fact, the use of mepyramine – an H1 receptor antagonist – in mice slows the activation of osteoclasts (33). Moreover, the use of cimetidin – an anti-H2 – slows the bone-resorption in ovariectomized mice (34).
It has been seen that the degranulation of mastocytes with release of histamine is a powerful stimulant of the effects of PTH. Moreover, heparin seems to be responsible for an increase in the effects of PTH on bone resorption (35). It has been established that in the presence of hyperparathyroidism the activated osteoblasts synthesize factors inducing the activation of mastocytes through c-KIT pathway (36).
The Platelet Derived Growth Factor (PDGF), also produced by mastocytes, appears to have effects on bone resorption. In fact, using triazolopyrimidine – a PDGF inhibitor – a reduction of either bone resorption rate or marrow fibrosis has been observed (36).

Past, present and future therapy

According to the above mentioned physiopathological basis, bisphosphonates (BPs) such as pamidronate at a dosage of 60-90 mg monthly or three-monthly patterns (10, 37), neridronate, with a dosage of 25 mg/month (38), or clodronate (29) have been used in the treatment of SM.
In cases non responding to BPs, BMD improvements have been observed with interferon-α2B treatment with a dosage of 3 million U/week (39).
Recent advances in the understanding of the molecular mechanisms leading to mast cells (MCs) proliferation in SM have led to the development of new therapeutical options. A better knowledge on MCs biology has occurred over the past 20 years, and it has been clarified that activating somatic mutations in the c-*Kit* receptor, with a tyrosine kinase (TK) action, underlie the aberrant cell signalling and MCs growth in most of the patients. The TK inhibitor imatinib (Gleevec®) has been recently found to counteract the growth of neoplastic MCs exhibiting wild-type (wt) *KIT* or the rarely occurring *F522C*-mutant variant of KIT (40, 41). In addition, this drug was found to block the growth of neoplastic cells in patients with SM associated to clonal eosinophilia and a FIP1L1/PDGFRA fusion gene (42). However, most of the SM patients have the somatic *D816V* (Asp816→Val) *Kit* mutation and do not respond to imatinib. (43). Novel TK inhibitors that block *Kit D816V* are currently under clinical investigation (44).

Conclusions

Mastocytosis is a neoplastic disease involving mast cells (MC) and their CD34+ progenitors. Symptoms in mastocytosis are caused by biological mediators released from MC and/or the infiltration of neoplastic MC in various organs, the skin and the bone marrow being predominantly involved. The physicians should take into account also this particular and rare disease when they are involved in a differential diagnosis of secondary osteoporosis.

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