Bone 105 (2017) 219–225

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Prevalence and risk factors for fragility fracture in systemic mastocytosis

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ARTICLE INFO

Article history:
Received 26 May 2017
Revised 13 September 2017
Accepted 13 September 2017
Available online 14 September 2017

Keywords:
Systemic mastocytosis
Bone marrow tryptase
Fragility fracture
Osteoporosis
Bone mineral density

ABSTRACT

Objectives: Systemic mastocytosis (SM) is characterized by the accumulation of mast cells in tissues other than the skin. Bone involvement although frequent has not been thoroughly evaluated. Primary objective was to determine risk factors associated with fragility fractures (FF) in SM. Secondary objectives were to evaluate the ability of bone marrow tryptase (BMT) level to identify patients with FF, and to describe bone involvement in SM.
Methods: We analyzed retrospectively all consecutive patients seen in our expert center, with a diagnosis of SM according to the 2001 WHO criteria, and with complete bone assessment. We collected data about lifetime fractures, types of cutaneous manifestations, degranulation symptoms, blood and BMT levels, bone mineral density assessed by densitometry and *KIT* mutation. We performed a univariate analysis investigating the factors associated with FF and then a logistic multivariable regression analysis. We assessed the ability of bone marrow tryptase to identify patients with FF.
Results: Eighty-nine patients with SM were included. Thirty-six patients (40.4%) suffered from osteoporosis and twenty-five (28.1%) experienced lifetime FF. Univariate analysis identified age at diagnosis and disease onset, presence of telangiectasia macularis eruptiva perstans, digestive symptoms, mast cells activation symptoms, elevated BMT, low femoral and lumbar BMD, as associated with FF. Multivariate analysis identified elevated BMT, low femoral T score and older age at diagnosis as independently associated with FF.
Conclusions: Low femoral T-score, BMT level, and older age at diagnosis are markers associated with FF in SM. BMT may represent an important biomarker to predict FF in SM patients.

1. Introduction

Mastocytosis is characterized by a clonal accumulation and/or proliferation of mast cells in various organs [1]. Systemic mastocytosis (SM) is associated with a higher risk of osteoporotic fracture, cytopenia and disabling mast cell activation symptoms [2]. Osteoporosis (OP) occurs in almost one third of patients out of whom 15 to 50% suffer from fragility fractures (FF) [3–5]. Little is known about the risk factors associated with osteoporotic FF in patients with SM. Van der Veer et al. identified: male gender, high crosslaps (CTX) level, low femoral bone mineral density, absence of urticaria pigmentosa (UP) and alcohol consumption as predictors of future FF in patients diagnosed with SM [6].

Bone marrow tryptase (BMT) has recently been shown to be a reliable diagnostic tool for SM [7]. We have previously defined 50 μg/L as the optimal cut-off value for BMT indicating SM.

In the current study, we aimed to identify the risk factors associated with FF in a cohort of patients with SM, to evaluate the ability of the BMT level to identify patients with FF, and to describe bone involvement in SM.

2. Methods

2.1. Aims

The primary objective of this study was to determine risk factors associated with FF in patients with SM.

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https://doi.org/10.1016/j.bone.2017.09.005
8756-3282/

Secondary objectives were to assess reliability of the BMT level to identify FF, and to describe bone involvement in SM.

2.2. Patients

We retrospectively analyzed patients diagnosed with SM, in rheumatology, dermatology, allergology, gastroenterology and internal medicine departments *via* our teaching hospital's expert center and with complete bone assessment, between December 2004 and October 2015. These patients were referred to the tertiary mastocytosis center if they had cutaneous involvement, severe mast cell activation symptoms, severe idiopathic anaphylaxis, severe osteoporosis of unknown cause. All patients fulfilled the 2001 WHO diagnostics criteria for SM [2]. Our cohort consisted of all consecutive adult patients with SM that had a bone mineral densitometry (BMD) assessed at inclusion.

This study was approved by the Institutional Review Board of Necker Enfants Malades Hospital and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.3. Data collection

The following data were recorded by ME, YD and CBL in a specific case report form:

- Demographic characteristics: *i.e.* gender, age at disease onset, age at SM diagnosis.
- SM diagnosis: *i.e.* results of bone marrow biopsy (major and minor criteria) [2], results of bone marrow aspirate, results of mast cells phenotyping regarding CD25 by multiparametric flow cytometry, results of KIT point mutation at codon 816, and level of serum tryptase.
- The presence of general risk factors and etiologies of osteoporosis: *i.e.* smoking (ever/never), excessive alcohol intake when mentioned in the medical record (self-reported consumption >20 g/day for women, >30 g/day for men), body mass index <19 kg/m^2, endocrinopathy, early menopause (<40 years old), and corticotherapy [8].
- Clinical characteristics: *i.e.* cutaneous involvement including telangiectasia macularis eruptiva perstans (TMEP) or UP, the presence of mast cell activation-related symptoms (Mcas) with idiopathic anaphylactic shock, flush, digestive symptoms, presence of B or C findings [2].
- Bone involvement: *i.e.* presence of osteoporosis, osteoprotective treatment, history of fragility fractures, fracture site, type of fracture, T score, Z score and BMD at the lumbar spine (L2-L4) and femoral neck sites, plain radiography of the thoraco-lumbar spine and the flat and long bones (crane, humerus, femoral bone and pelvis).
- Laboratory characteristics: *i.e.* serum and bone marrow tryptase level if available, mutational status of *KIT* in bone marrow and skin, and serum CTX.

2.4. Laboratory assays

- The major criterion of SM was defined by presence of at least two dense aggregates of at least 15 mast cells identified by immunohistochemical study with anti-CD117 antibodies (Dako Cytomation Denmark, Glostrup Denmark) in bone marrow biopsy sections [2].
- The presence of >25% of mast cells with atypical morphology was identified on the histological sections of bone marrow biopsy, and/or on bone marrow smear by immunohistochemistry study with anti-CD117 antibodies [2].
- The abnormal expression of CD25 (BD Pharmingen™, Becton, Dickinson and Company, New Jersey, USA) by mast cells was identified by multiparametric flow cytometry of mast cells, according to the method described by Valent et al. [9].
- The analysis of the *D816V* mutation of KIT was performed by the method described by Lanternier F et al. [10].
- On the same day, venous blood and bone marrow aspirate were sampled into sodium heparin for serum tryptase and into ethylenediaminetetraacetic acid (EDTA) for serum tryptase and BMT measurements, respectively.
- Serum tryptase was determined by a standardized fluoroenzyme immunoassay on a Phadia 250 automated analyzer (ThermoFisher Scientific; Villebon sur Yvette, France).
- Bone marrow aspirate for BMT measurement was obtained from iliac crest aspiration or from sternal puncture. Total serum tryptase and total BMT were determined by a standardized fluoroenzyme immunoassay on a Phadia 250 automated analyzer (ThermoFisher Scientific; Villebon sur Yvette) in accordance with the recommended procedures of the reagent supplier and Good Laboratory Practice (ISO standard 15189). Serum tryptase and marrow tryptase results were determined by P.A.P., who was blinded to the patient's history, including whether the patient had been evaluated for mast cell disorder.
- Serum collagen type 1 cross-linked C-telopeptide (CTX) levels were measured with IDS-iSYS immunoassay system using chemiluminescent detection.

2.5. Definitions

Bone involvement was defined as: densitometric OP or FF or osteosclerosis or bone condensation or bone lysis.

Osteoporotic patients were defined as having a major fragility fracture (hip, vertebra, humerus) identified by anamnesis or by the systematic radiographic assessment, or as having a densitometric osteoporosis, according to the current definitions [11]. Densitometric osteoporosis was defined as a T score ≤ −2.5 standard deviation (SD) regarding femoral neck or rachis (L1-L4) bone mineral density (BMD). Bone assessment consisted in BMD measurement, and plain radiography of spine, pelvis, humerus and femurs.

BMD was measured using dual energy X-ray absorptiometry (DXA) (Lunar DPX-L, GE Healthcare® UK, from 2005 to 2009; Lunar Prodigy, GE Healthcare® UK, from 2009 to 2015). In case of lumbar fracture, we used the range of the unfractured lumbar vertebrae. A past history of FF (spine, femoral, humerus, wrist) was registered by anamnesis. High kinetics trauma fractures, fatigue fractures, and toe and finger fractures were excluded.

Vertebral fracture was assessed for all patients from a plain radiography of the thoraco-lumbar spine in order to identify fractures using Genant's semi-quantitative method and to diagnose any asymptomatic fractures [12]. All X-rays were analyzed independently by 2 expert rheumatologists (ME/YD). Disagreement was solved by a third party (ML, expert rheumatologist). Inter-observer (ME/YD) correlations were: kappa for fracture prevalence = 0.83 (CI95% 0.71–0.94), kappa for fracture grade = 0.71 (CI95% 0.58–0.84).

Generalized increased BMD or osteosclerosis may occur in SM. Osteosclerotic bone was defined as T score > +2.5 SD on DXA and compatible radiography [13,14].

Other bone involvements were defined as a typical condensation or lysis, highlighted on the systematic full skeletal radiographic examination [15]. Miscellaneous bone type was defined as mixed patterns of lysis and focal condensation seen on plain radiography or by “leopard aspect” (Supplemental File 1).

2.6. Statistical analysis

Gaussian-distributed variables were described as means and SD. Non-Gaussian distributed variables were described as median and interquartile range. Dichotomous and ordinal variables were described as numbers and frequencies.