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Hylonome

Clinical Quiz

A 41-years-old man with a vertebral fracture and bone marrow mastocytosis

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Case

A 41-years-old male patient from Greece was referred to our unit for metabolic and dietary consultation. He was overweight (BMI 30.2 kgr/m^2), with a recent history of a vertebral fracture (L1) 50 days ago (Figure 1), and he was instructed to lose weight as part of a conservative approach for his fracture. His past medical history was unremarkable, however the vertebral fracture resulted from a fainting episode during a hot shower following intense exercise at the gym. No neurological or cardiological problems were detected from the initial evaluation of the fainting episode. We were unable to define whether this was a low or a high energy fracture, thus his bone mineral density (BMD) was evaluated by dual X-Ray absorptiometry (DXA) equipment (Lunar, Lunar Corporation, Madison, USA) which uses an Italian male reference population. A BMD below the expected range for age was found in the lumbar spine (L2-L4: 1.101 g/cm^2, Z score:-2.82) but not in his non-dominant femoral neck (1.001 g/cm^2, Z score:-0.79). Laboratory investigation was consequently performed for secondary osteoporosis (Table 1).

Although no clinical manifestations of mastocytosis were either reported or observed, serum tryptase was found elevated, as well as 24h urine N-methyl istamine (Table 1). Bone marrow biopsy revealed multifocal infiltration of abnormal mast cells (>15 mast cells per aggregate) which in addition with the serum tryptase level of >20 ng/mL confirmed the diagnosis of systemic mastocytosis (SM). A skeletal survey revealed no other skeletal involvement. The patient reported

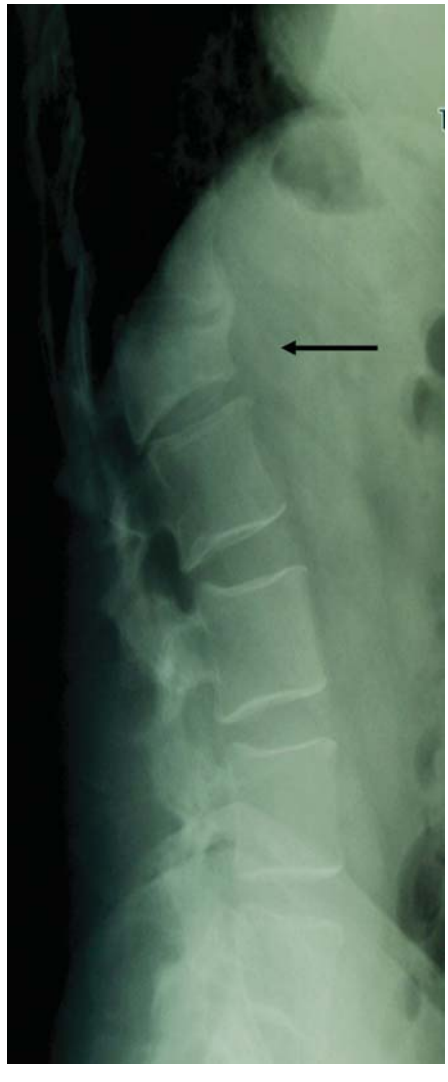

Figure 1. Vertebral fracture (arrow) at L1.

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Parameter		Normal limits
ESR	2	0-15 mm/h
Ca serum	8.5	8.1-10.4 mg/dl
Albumin	4.0	3.0-5.0 g/dl
P serum	3.3	2.5-5.0 mg/dl
ALP	73	30-140 U/L
Bone - ALP	18.6	<20.1 μg/ml
25OHD	24.3	≥30 ng/dl
Mg	2.1	1.5-2.5 mg/dl
PTH	22.0	10-65 pg/ml
Creatinine	1.2	0.7-1.4 mg/dl
Testosterone	3.1	2.8-8.8 ng/ml
TSH	1.9	0.3-4.0 μIU/ml
Ca urine 24h	234	100-300 mg/24h
Cortisol urine 24h	6.2	1.4-7.6 μg/24h
Osteocalcin	13.2	9-37 ng/ml
P1NP	26.38	22-85 ng/ml
NTx (serum)	8.0	5.4-24.2 nM BCE/mM
Tryptase	23.2	<11.4 ng/ml
N-methyl istamine	315	30-200 μg/g creat.

Table1. Laboratory evaluation for secondary causes of osteoporosis.

adequate dietary calcium ingestion, therefore he was treated with weekly alendronate 70 mg and cholecalciferol 5,600 IU (mean daily dose 800 IU). Fourteen months later he had adequate vitamin D levels (45.6 ng/mL), serum tryptase remained stable (>20 ng/mL), while BMD improved significantly both at the lumbar spine (+ 14%) and femoral neck (+ 6,0%).

Commentary

Mastocytosis is a rare heterogeneous disease with a rather broad spectrum of clinical manifestations since it can range from "highly aggressive" with occasionally fatal consequences to "asymptomatic"[1]. The majority of patients suffer from mediator-related symptoms such as flushes, hypotension and tachycardia, and gastrointestinal disorders. Mastocytosis could potentially explain the fainting episode of our patient since hypotension attacks are frequently observed following acute release of mediators from mast cells in response to intense exercise and/or heat exposure.The production of several cytokines and chemical mediators by the mast cell and its proximity to bone remodelling surfaces results in skeletal involvement, as well[2]. Osteoporosis or osteopenia is by far the most frequently observed pathological skeletal signs, although osteolysis and osteosclerosis can also occur, often simultaneously in the same patient. Clinical manifestations from skeletal involvement include generalized bone pain which can be sometimes devastating and is frequently resistant to conventional analgesics.

The WHO classification defines seven disease variants of mastocytosis: i) cutaneous mastocytosis, ii) indolent systemic mastocytosis, iii) systemic mastocytosis with an associated clonal haematological non - mast cell lineage disease, iv) aggressive systemic mastocytosis, v) mast cell leukaemia, vi)mast cell sarcoma, and vii) extracutaneous mastocytoma[3]. It is crucial to differentiate distinctively between cutaneous mastocytosis and the other variants of systemic mastocytosis or mast cell neoplasms. Final diagnosis results in different therapeutic approaches and follow-up. The diagnosis of systemic mastocytosis is defined if at least one major and one minor or at least three minor SM-criteria are fulfilled. Major SM criterion is the multifocal infiltrate of mast cells (MC) in the bone marrow or in other extracutaneous organs (>15 MC per aggregate). Minor SM criteria include, among others, a serum tryptase level >20 ng/mL[1]. In our patient the diagnosis was undoubtedly SM, due to the presence of a major criterion and a serum tryptase above 20 ng/mL, although systemic manifestations were lacking.

Fractures, mostly vertebral, have been reported in approximately 15% of all patients while a low bone mass has been observed in more than one third of patients with SM[2]. Osteoporosis can be the only presentation, especially if the disease is restricted to the bone marrow. In that case the disease is defined as "bone marrow mastocytosis", which is a sub-category of indolent SM with low burden of mastocytes and a good prognosis[1]. Specifically among men with "idiopathic osteoporosis", bone marrow mastocytosis can be found in up to 9% of patients[2]. This was the case in our patient who had only a decreased BMD, which presumably contributed in the vertebral fracture, without any other obvious sign of SM. Bone loss in SM can be also exacerbated by glucocorticoids that are extensively used in the therapeutic approach. Therefore, bone mineral density (BMD) should be assessed in all patients with SM.

Serum tryptase is currently considered as the test of choice in the initial assessment of suspected SM cases[1]. It is a quite sensitive marker of SM since almost all patients exhibit levels above 20 ng/mL. However, its specificity is not that high because it can be increased in renal impairment, acute or chronic myeloid leukaemia, myeloproliferative disorders, as well as following severe allergic reactions. In the latter case, it is recommended to be measured at least two days following the resolution of clinical allergic symptoms[1]. Tryptase levels correlate with the burden of MCs and usually remains stable in indolent SM cases whereas frequently increases during the progression of aggressive SM variants. Tryptase is also recommended as a surrogate marker in the evaluation of the response following cytoreductive treatment[1]. However, there is no physiological way to be affected by bisphosphonates' treatment, and it is expected to remain stable irrespective a positive skeletal response, as it is also observed with the 24-h urine excretion of N-methyl histamine[4]. In accordance with all the above, the diagnosis of SM was initially suspected in our patient from his serum tryptase levels, which remained stable throughout the bisphosphonate treatment.

Treatment for SM is indicated in the presence of a clinically relevant impairment or loss of organ function caused by MC infiltration and includes: interferon-apha plus glucocorticoids;

cladribine (2CdA); polychemotherapy in highly aggressive cases or mastocytic leukaemia; stem cell transplantation; drug-targeted treatment, such as dasatinib, in selective cases[1]. Regarding decreased BMD in SM oral bisphosphonates are considered in osteopenia and are definitely recommended in cases of osteoporosis. In severe cases or oral drug-intolerance, iv administration is also indicated with or without a low-dose of interpheron-alpha[1]. As it was observed in our patient, BMD can be significantly increased following bisphosphonates despite a stable burden of the disease[4]. In resistant local bone pain irradiation can be also applied.

In conclusion, SM can severely affect BMD and bone strength. It should be considered in the diagnostic assessment of "idiopathic" osteoporosis, especially among men. Serum tryptase can be used in the initial diagnostic work-up of suspected cases. However, definite diagnosis requires tissue biopsies, as well. A multi-disciplinary therapeutic approach is frequently needed although bisphosphonates can be the only treatment in bone marrow mastocytosis cases suffering solely from osteoporosis.

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Questions

1. Measurement of serum tryptase is:

A. The most sensisitive and specific marker for the diagnosis of systemic mastocytosis (SM)
B. Major and/or necessary criterion for the diagnosis of SM
C. The recommended initial serum test in the diagnostic approach of SM

Critique

Tryptase is currently the recommended serum test to employ in the initial diagnostic work-up of suspected cases. Almost all patients have serum tryptase >20 ng/ml, which is also a minor criterion for the diagnosis of SM. It is a quite sensitive marker but can be also increased in other conditions such as following severe allergic reactions.
The correct answer is C.

2. The initial therapeutic approach of osteoporosis due to bone marrow mastocytosis includes:

A. Teriparatide
B. Bisphosphonates
C. Interferon alpha

Critique

Oral bisphosphonates are definitely recommended in cases of osteoporosis due to bone marrow mastocytosis. In severe cases of osteoporosis or oral drug-intolerance, iv administration is also indicated with or without a low-dose of interpheron-alpha. Teriparatide is not indicated for the treatment of osteoporosis due to bone marrow mastocytosis.
The correct answer is B.