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Tomographic pattern of bone permeability suggestive of secondary osteoporosis

Introduction
OP is a generalised disease of the skeleton characterised by low bone mass and an alteration in bone micro-architecture, with an increase in its fragility and consequently, a greater tendency to fracture. Primary OP is that in which the reduction in bone mass can be explained by the changes brought about by aging, such as the hormonal changes produced in the menopause; the concept of secondary OP is reserved for that which can be caused or exacerbated by other pathologies or medications. The prevalence of secondary OP is highly variable, depending on age, sex, racial group, etc. In addition, it is not always possible to talk of an isolated cause as the origin of many cases of osteoporosis, rather, a multifactorial etiology is quite frequently found. Thus, while the prevalence of cases of secondary OP in males reaches 64%, in perimenopausal women the prevalence is around 50%, diminishing after the menopause to a not insignificant level of 20 to 30%.

OP is a multifactorial disease to whose genesis contribute numerous genetic and environmental factors; each factor carries a relatively small weight in the development of the disease, with the exception of ageing and the menopause. The causes of secondary OP are multiple, from genetic, endocrinial, gastrointestinal and haematological diseases, to nutritional and pharmacological factors.

Although the diagnosis of OP is established through densitometric criteria, supported on occasions by clinical criteria, there are alterations in other imaging tests –conventional X-ray, computerised tomography (CT) and magnetic resonance (MR)– which should make us suspect this diagnosis. Thus, many cases of OP may be suspected in a casual way through an X-ray examination for another reason, or in subjects with fractures and risk factors for the disease.

The fact which drives the publication of this clinical case in our environment is based on three fundamental aspects: 1) the importance of specific X-ray examinations distinct from bone densitometry in the diagnosis of OP, 2) a review, in practical terms, of the epidemiology of secondary OP and 3) the necessity of maintaining clinical suspicion in selected patients, with negative results in the usual screening tests, which allow us to establish an early diagnosis of potentially curable diseases whose late diagnosis can result in high morbimortality.

Clinical case
A male patient of 46 years of age, allergic to penicillin and roxithromycin, businessman by profession, sedentary for a large part of his working day. Began two months before the start of the study with pain in the lower dorsal region, mechanical in character, radiating towards the abdominal region, which was treated with analgesia and muscle relaxants, with partial improvement. Months before he had suffered an accidental trauma of moderate intensity in the right costal zone, with intense, stabbing pain which reduced on its own in a few weeks.
Physical examination
The patient presented in a generally good state, without any neurological symptoms, good hydration and cutaneo-mucous perfusion, eupneic at rest, with blood pressure of 140/70 mmHg and a cardiac rate of 80 lpm, weight of 60 kg, height of 180 cm, BMI 19 kg/cm². The cervical region was normal. The cardiac tones were rhythmic, without murmurs and the breath sound was conserved. Without alterations in the abdominal examination and in the four limbs. Discrete dorsal kyphosis, with pain when the right lower paravertebral musculature was palpated. The Lassegue manoeuvre was negative. The external genitals and secondary sexual characteristics were normal. He adopted an antalgic posture.

Complementary examinations
The haemogram presented haemoglobin of 11.2 g/dL (normal values 13-18), haematocrit 31.9% (normal values 39-54%), average corpuscular volume 93.5 fL (normal values 80-99), with platelets and white blood cells within normal levels. The velocity of globular sedimentation was normal. Notable in the biochemistry were urate at 7.2 mg/dL (normal values 3.4-7), phosphate 4.6 mg/dL (normal values 2.7-4.5), alanine aminotransferase 45 U/L (normal values 2-41), with the values of renal function, thyroid hormones, parathyroid hormone, folic acid, vitamin B12, ferric parameters, lipid profile, hepatic profile, lactate dehydrogenase, proteins, calcium, C reactive protein, cortisol and testosterone, being normal. The coagulation study were normal. Notable in the biochemical study showed hypogammaglobulinemia with IgG values of 335 mg/dL (normal values 700-1,600), IgA of 119 mg/dL (normal values 70-400), IgM of 5 mg/dL (normal values 40-230). The Mantoux intradermoreaction was negative when taken at 48 and 72 hours. In the simple X-ray of the dorsolumbar spinal column a mild wedging of the vertebral body of D7 was observed. The dorsal MR scan showed a wedging below D7 which fundamentally affected the superior epiphysary platform, without affection of the posterior wall or the adjacent mass of soft tissues (Figure 1). The bone gammagraphy showed a reinforced trace capture in the D7 area, compatible with vertebral crushing. The thoraci-abdominal-pelvic CT scan did not show changes in any solid organs, or adenopathies in any of the lymphatic chains studied. However, there was permissive bone pattern in practically all the bones, with some images of endocystic scalloped bleeding, including some with rupture of the cortex (Figure 2).

In the face of the bone findings and keeping a high level of clinical suspicion, despite the absence of monoclonal hypergammaglobulinemia, an aspiration of the bone medulla was requested which was cytologically compatible with monoclonal gammopathy of type multiple myeloma (MM). The urinary immunofixation detected kappa type Bence Jones protein. With the diagnosis of kappa type Bence-Jones MM, stage IIIB, poly-chemotherapeutic treatment was initiated according to the VAD (vincristine, Adriamycin and
dexamethasone) protocol, together with zoledronic acid, over 4 cycles, with a partial response. The fitting of an orthopaedic corset was required to fix the dorsal lesion, as well as kinesitherapy exercises. Subsequently a self-transplant of peripheral blood progenitor cells as a consolidation treatment, and because he had an HLA-identical brother, an allogenic transplant was carried out, with a very good response, with the patient now being in complete remission after a three year follow up.

Discussion
Multiple myeloma (MM) is a neoplasia of B cells characterised by an uncontrolled accumulation of clonal plasmatic cells in the bone medulla combined with the production of monoclonal immunoglobulin detectable in blood or urine. Clinically it is manifested by signs and symptoms resulting from organic affection, such as anaemia due to medullar deficiency, immune dysfunction with recurrent infections, skeletal lesions with hypercalcemia and renal affection5-10. The bone lesions can take various patterns, with the most common being multiple osteolitic lesions, and much less frequently the development of diffuse osteopenia11, both due to an increase in osteoclast activity.

MM is present principally in subjects over 50 years of age (only 15% in those younger than 50), with a median incidence at 65 years of age, without differences between the sexes, and being more frequent in black people6. In our case, neither the epidemiological data nor the initial analytical values were compatible with the initial diagnosis of MM. The absence of anaemia, hypercalcemia, renal deficiency or hypergamaglobulinaemia, typical in MM, combined with an anodyne clinical picture, can reinforce the direction our diagnosis towards other more probable pathologies. Only the maintenance of a strong clinical suspicion in patients low intensity fractures and tomographic pattern of bone permeability, although other factors may be present for low bone mass or increased risk of fracture, can bring a correct diagnosis.

The bone lesions in MM are due to an asynchronicity between the formation and destruction of bone, and here the increase in the activity of the osteoclasts is not found to be balanced by a comparable level of bone formation activity12,13. The myelomatous cells stimulate the formation and activation of the osteoclasts, due to the interaction which occurs between the receptor for the activation of nuclear factor κB (RANK) on the surface of the osteoclast and the ligand RANKL existing in the stromal cells of the bone medulla. The myelomatous cells increase the expression of RANKL, by a cell-to-cell contact mechanism14,15. The RANK-RANKL signal is normally counteracted by osteoprotegerin, which is reduced by the direct action of the myelomatous cells16. In addition, there is, in advanced stages of bone disease, resistance in the myelomatous cells to some chemotherapies, which could be due in part to the same interaction with the osteoclasts17,18.

The bisphosphonates are an essential component in the treatment of MM, since they reduce skeletal morbidity. In Europe only clodronate, pamidronate and zoledronate are approved for patients with MM and osteolitic lesions. The choi-
ce between them essentially depends on the way they are administered and the patient’s concomitant treatment. Both pamidronate and zoledronate are equally effective and their use is intravenous, with the latter requiring less time for infusion. Zoledronate has shown the capacity to prevent the development of osteolitic lesions and to reduce the mass of bone tumours in patients with MM, as well as reducing the number of bone fractures in patients with OP.

OP has been traditionally considered a women’s disease, but today it is known to have great importance to the male sex. In males OP appears later, due to their higher peak in bone mass in youth, and the lower loss of bone mass, lacking such a marked period of bone loss as the menopause in women, for which reason the complications arising from osteoporosis occur much later than in women. OP, cause of the crushing-fracture of the vertebra, differs in its etiology between the sexes. While in post-menopausal women, 70-75% of cases are due to the menopause itself, in males secondary forms constitute up to 50% of cases. The rest of the male forms of this syndrome are catalogued as idiopathic. The three most important causes of osteoporosis in males are alcoholism, excess of glucocorticoids (both in Cushing's syndrome and in chronic steroid treatment) and hypogonadism, although a long list of secondary causes of OP (Table 1) should also be taken into account. The search for a gastrointestinal malabsorptive pathology must be prioritised, when we do not find the causal process for OP.

In males from 70 years of age, due to the loss of bone mass associated with age, we consider OP to be explained by the aging process, without focussing on the search for secondary causes. However, we found males below 70 with this type of OP and others of a greater age in whom the clinical suspicion results in us focussing on the search for secondary causes or OP.

In conclusion, the causes of OP are multiple, more, even, in males, which includes aging itself. For this reason it is necessary always to maintain a high level of clinical suspicion, in spite of little specific clinical data, to be able to arrive at a correct diagnosis of the underlying disease, thus diminishing the morbimortality of the patient.

Bibliography