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Diagnostic challenges in the phosphorus calcium metabolism in a female patient

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Summary
We present the case of a female patient who had an intervention in a cervical nodule in the context of moderate hypercalcemia, with a histological diagnosis of a possible parathyroid carcinoma, whose later development made it necessary to rethink the diagnosis.

Key words: *moderate hypercalcemia, osteitis fibrosa cystica, primary hyperparathryoidism.*

Introduction
Primary hyperparathyroidism is being diagnosed earlier and earlier due to the routine testing for calcemia. Light hypercalcemia is its most frequent characteristic, and osteoporosis predominantly affecting cortical bone, is the most common finding in the bone. On the other hand, the typical skeletal affectation of this disease, osteitis fibrosa cystica, is nowadays exceptional. For this reason, the presentation of the classic skeletal manifestations of hyperparathyroidism may lead to doubts and diagnostic errors in clinics today.

Clinical case
A woman of 49 years of age, without personal or family history of interest, except an episode of renal lithiasis two years previously, who attended a primary care clinic due to the cardinal symptoms of diabetes of a year's development (polyuria, polydipsia and discrete non-quantified ponderal loss). An analysis was carried out, with the following results: baseline glycemia, 130 mg/dl; calcium, 12 mg/dl (normal values: 8.5-10.5); total alkaline phosphatase, 2,260 U/l (normal values: 98-279); for which reason she was referred to the surgical service for an evaluation of hypercalcemia. Notable in the physical examination was a cervical nodule adhering to deep layers, with growth towards the mediastinum. An X-ray was carried out with technetium sestamibi, which showed capture in the lower right parathyroid gland, which was the reason for deciding to intervene, with the suspicion of parathyroid cancer. A hemithyroidectomy was carried out on the right hand side and the extirpation of the lower right parathyroid, with resulting anatomopathological neoplasms secreting parathormone (PTH) with the phenomenon of vascular microinvasion of low proliferative activity, alongside unchanged thyroid tissue.

After the intervention the patient was referred to the endocrinology service for follow up. At this point the patient complied with the criteria for obesity (weight: 83 kg, height: 1.54 m, BMI: 35 kg/m^2), and presented, in addition, type 2 diabetes

of a year's development since diagnosis, in treatment with diet and exercise. In carrying out an anamneses the patient only reported mechanical pain in the lower limbs and thorax, and tumoration on the right tibia of some months development, which had been examined through conventional X-ray and was waiting for a diagnostic biopsy (Figure 1). The study was completed with X-rays in other locations (Figure 2). After the intervention, various complementary tests were carried out, with the following results: basic biochemistry, normal, except for hyperglycemia of 144 mg/dl; calcemia, 8.8 mg/dl (normal values 8.5-10.5); phosphorus, 4 mg/dl (normal values: 2.5-5); elevated levels of markers for bone remodelling: total alkaline phosphatase, 313 U/l (normal values: 98-279), bone alkaline phosphatase, 62.1 µg/ml (normal values: 7.5-33.7). The thyroid function was compatible with subclinical hypothyroidism, with TSH of 4.4 mUI/ml ().4-4); raised levels of intact PTH (103 pmol/l; normal values 29-85); 24 hour calciuria, normal; glycosylated haemoglobin (HbA1c); 5.5%; and urinary albumin excretion, negative.

Also carried out were: thyroid echography, which showed a solid mass of 22 mm located in the left parathyroid compatible with a recurrent tumour; bone gammagraphy, with intense capture in the distal third of the right tibia and of lower intensity in other locations. Bone densitometry with femoral T-score values of -3.1 and lumbar T-score of -0.8, compatible with cortical osteoporosis.

Given that the benign development of the symptoms are not particularly compatible with the initial diagnosis of parathyroid carcinoma and the presence of the bone lesion, the anatomopathaological study of the intervention was reviewed jointly with the biopsy of the tibial tumour, with the final result of possible osteitis fibrosa cystica associated with parathyroid adenoma. Subsequently, the patient maintained normal levels of calcemia, with slightly raised levels of intact PTH, sufficient metabolic control of her diabetes with diet and exercise and normal thyroid function. There was an intervention in the right tibial tumour with anatomopathological results of areas of fibrosis and trabecular thinning related to osteoporosis. In a later echographic check the size of the parathyroid lesion had reduced, for which reason a conservative approach was maintained. During the follow up the patient remained asymptomatic with improvement in the bone lesions, and analytical checks and cervical examinations were maintained, with no changes over a period of 6 years. In the follow up, a malignant tumour of gynaecological origin was diagnosed, for which treatment with chemotherapy with cisplatin and radiotherapy were initiated. Subsequently, the patient had an episode of peribuccal paresthesia and tetany, with hypocalcemia being confirmed by various analytical test, resulting in the carrying out of a new study of the phosphorus calcium metabolism, with the following results: calcium, 6.2 mg/dl (normal values: 8.6-1.2); phosphorus, 3.3 mg/dl (normal values 2.5-5); magnesium, 0.8 mg/dl (normal values: 1.8-2.6); 25 OH vitamin D, 23.2 ng/ml; hepatic and renal functions unaltered. After assessing different possibilities, a diagnosis was established of functional hyperparathyroidism due to secondary hypomagnesemia resulting from the chemotherapy, and treatment with oral magnesium supplements was initiated, with a good clinical and analytical response.

Discussion

The diagnosis of primary hyperparathyroidism now occurs earlier and earlier due to the carrying out of routine analysis for calcemia, which means that the skeletal affectation typical of this disease, osteitis cystica fibrosa, is becoming ever less frequent. The bone affectation most commonly associated with hyperparathyroidism currently is osteoporosis, with fundamentally cortical affectation[1]. In both entities remineralisation usually happens after treatment for the adenoma[2-3].

The typical analytical profile of primary hyperparathyroidism is raised levels of blood calcium, parathormone, alkaline phosphatase and calciuria, with levels of phosphorus normal or low. An increase in markers for bone remodelling is also observed, of variable duration after surgery[4]. It has been reported that between 11% and 40% of patients having interventions for primary hyperparathyroidism maintain raised levels of PTH during subsequent follow up, despite a normalisation of levels of calcium. Although the pathogeny of this phenomenon has not been well clarified, various theories have been proposed. Thus, the persistence of raised levels of PTH after surgery could be a transitory compensatory response which would favour bone mineralisation[5]. Other authors have described the presence of alterations in renal function as the cause of the raised PTH[6], although later studies do not confirm this finding[7]. The presence of low levels of vitamin D, a frequent finding in different groups in the population should also be considered[8].

Persistent hyperparathyroidism can produce severe skeletal deformities and haemorrhage, which form lytic lesions called "brown tumours" due to the deposit of haemosiderin in their interiors[9]. In the majority of cases, the diagnosis of these lesions occurs in patients previously diagnosed with hyperparathyroidism, although on occasions it may be the first manifestation of the disease. The differential diagnosis of this lesion with other bone lesions, such as osteoclastoma, may raise difficulties, although recent advances in the field of immunohistochemistry facilitates its diagnosis[10].

Parathyroid carcinoma is an infrequent disease, with an estimated frequency of 2.1% of cases of hyperparathyroidism[11]. Among its clinical manifestations are a marked hypercalcemia, above 14 mg/dl in the majority of cases, and levels of PTH 5 to 10 times higher than normal[12]. As with other endocrine tumours, it is difficult to establish the malignant nature of the lesion from histological findings. The typical anatomopathological characteristics include a lobular pattern separated by

Figure 1. Lesion in tibia suggestive of osteoclastoma

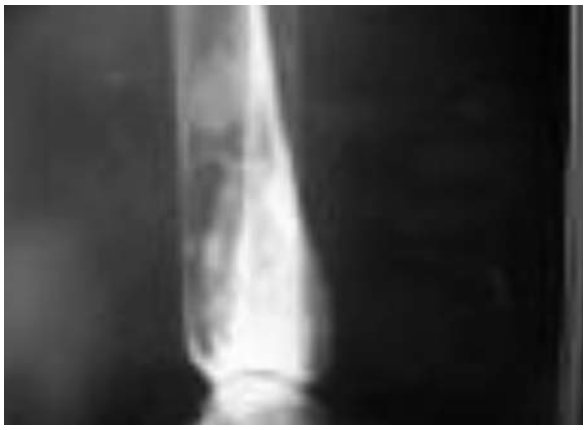
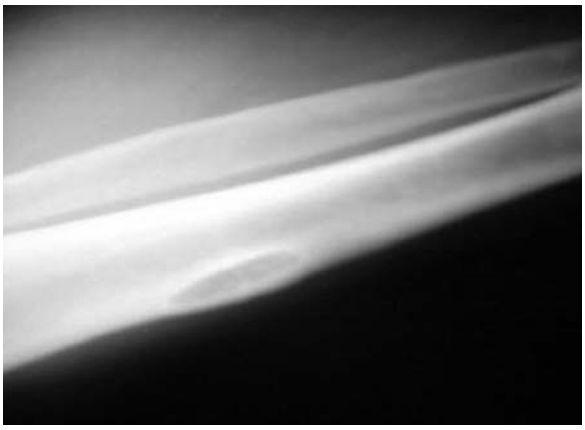


Figure 2. Radiography of forearm which shows cortical lesion



fibrous trabeculae, a high degree of mitosis and invasion of the capsules and blood vessels, although these may also be found in some adenomas. In this case, the moderately raised levels of calcium and intact PTH, their normalisation after surgery, and its later asymptomatic course, made necessary a rethink of the initial anatomopathological diagnosis.

Finally, hypocalcemia is frequent in those patients receiving treatment with cisplatin. In the case of hypomagnesemic hypocalcemia is appears to be the result of a reduction in the secretion of PTH, as well as a higher resistance to its action in the bone and kidney, both caused by hypomagnesemia by means of a complex mechanism which is not totally understood[13]. Although oral supplements appear to be efficacious in the development of hypomagnesemia associated with cisplatin, it does not offer complete protection against the development of this situation.

The singularity of our case is found in the infrequency of the diagnosis of primary hyperparathyroidism with the presence of bone lesions, as well as the development of hypomagnesemic hypocalcemia as a secondary effect of the treatment with cisplatin. In conclusion, we can say that, although its incidence has diminished due to early diagnosis of hyperparathyroidism, osteitis fibrosa cystica should be included in the differential diagnosis of bone lesions. Given that the typical anatomopathological characteristics of parathyroid carcinoma may be found in some cases of adenoma, the initial clinical manifestations and the evolutionary course of the condition may assist in the differential diagnosis. In addition, in patients in treatment with cisplatin analytical checks should probably be carried out to detect the presence of hypomagnesemia and other disorders, such as hypocalcemia

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