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SCIENTIFIC LETTERS

Primary hyperparathyroidism with osteitis fibrosa cystica mimicking a malignant bone tumor☆

Hiperparatiroidismo primario con osteítis fibrosa quística simulando una neoplasia ósea maligna

The most common clinical presentation of primary hyperparathyroidism (PHP) is asymptomatic hypercalcemia, and diagnosis of PHP based on the presence of bone manifestations such as osteitis fibrosa cystica (OFC) is increasingly uncommon. OFC occurs in less than 5% of patients with PHP and suggests a more severe or long-standing disease. OFC is characterized by the occurrence of bone pain associated with the finding of specific radiographic changes such as increased subperiosteal bone resorption in the distal third of the radius and middle phalanges, distal clavicular thinning, ''salt and pepper'' skull, bone cysts, and brown tumors in long bones. Brown tumors result from bone demineralization with osteoclast activation, microhemorrhages, and microfractures, and are so named because of their typical color, due to abundant hemosiderin deposits. Histopathologically, a combination of osteoclastic and osteoblastic activity with cyst formation and many hemosiderin-laden macrophages exists.[1] Differential diagnosis of brown tumors includes giant cell reparative granuloma and giant cell tumor (GCT) of the bone.

The case of a patient with PHP due to a parathyroid adenoma with brown tumors mimicking a metastatic GCT is reported.

A 47-year-old first attended the orthopedic surgery department of a hospital in Castile-La Mancha in May 2008 complaining of pain in the hip and left hand not associated with prior trauma. The patient reported a personal history of dyslipidemia, type 2 diabetes mellitus, arterial hypertension, grade I obesity, and renal colic with calcium oxalate stones. His family history included two daughters who had been diagnosed and undergone surgery for PHP due to adenoma. Plain X-ray of the hip and hand showed a polylobulated cystic image that inflated and thinned cortical bone in the third left metacarpal bone and supra-acetabular and left ilioischiopubic ramus lytic lesions. A CT scan of the pelvis (November 2008) showed large lesions in the iliac ala, ischium, left pubic ramus, and right sacral wing and femoral neck. Based on these findings, in July and September 2009 the patient underwent surgery consisting of curettage and filling with both an autologous graft and bone substitutes of the third left metacarpal bone and the left supra-acetabular lesion. The pathological laboratory reported a GCT. Subsequent controls with CT and MRI of the chest and pelvis revealed the enlargement of polylobulated and expansive lytic lesions in the pelvis (Fig. 1), sacrum, right femoral neck, and L5, with the appearance of a new lesion in the right femoral head and left seventh costal arch (Fig. 2). These changes were attributed to metastatic tumor progression. Because of persistent pain that totally prevented ambulation, the patient was referred to the bone tumor unit of Hospital Universitario La Paz, where a review of pathological samples led to the conclusion that the bone lesions were highly suggestive of giant cell reparative granulomas and histologically indistinguishable from brown tumors. Hyperparathyroidism was therefore ruled out. In November 2010, the patient was referred to the endocrinology department, where additional laboratory tests provided the following results: total calcium 14 mg/dL, corrected calcium 13.2 mg/dL, ionic calcium 1.72 mmol/L, phos-

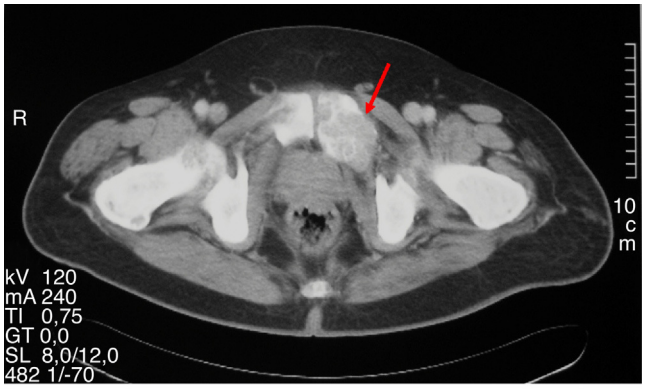

Figure 1 Expansive lytic lesion corresponding to osteitis fibrosa cystica in a pelvic CT scan.

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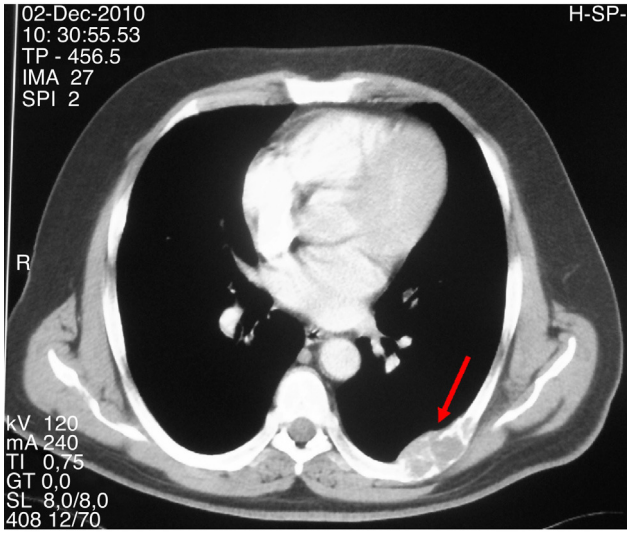

Figure 2 CT scan showing an expansive lytic lesion with lobulated outline and cortical thinning in the seventh left costal arch.

phate 1.9 mg/dL, magnesium 1.86 mg/dL, urinary calcium 968.60 mg/24 h, creatinine 0.55 mg/dL, iPTH 535 pg/mL, vitamin D 13 ng/mL. Total body CT showed a nodule 1.5 cm in diameter in the theoretical location of the right parathyroid gland, and a parathyroid scan with 20 mCi of TC 99-sestamibi revealed findings consistent with right hyperfunctioning parathyroid adenoma. In addition, the presence of an associated pheochromocytoma was ruled out based on both biochemistry and morphology. Right parathyroidectomy was performed, and an intraoperative biopsy was reported as a parathyroid adenoma. The final histopathological study confirmed the presence of a parathyroid adenoma 4.5 g in weight and 2.2 cm × 2 cm × 1.9 cm in size.

After surgery, the patient experienced symptomatic hypocalcemia which required treatment with calcitriol and calcium, which has been continued to date. He continues to be followed up at the endocrinology department, reports significant symptomatic improvement and is able to walk with crutches. A genetic study found no mutations in the MEN-1 gene.

GCT is a highly vascularized tumor which is found in the metaphyses or epiphyses of long bones or in the pelvis, sacrum, or vertebrae.[2] The radiographic and histological appearance of brown tumors typical of OFC may closely mimic a GCT, as occurred in our patient, and differentiation should be made based on clinical signs and laboratory results (iPTH). Some of the authors[3,4] have reported cases of OFC in which secondary metastatic bone disease was initially suspected based on clinical signs and radiographic images. In our patient, however, diagnosis of a metastatic primary bone tumor had been based on histological findings, while the family history, not reported in the above cases, was consistent with PHP.

On the other hand, vitamin D deficiency is often detected in patients with PHP and is[3,5] associated with exacerbation of the biochemical and phenotypical presentation of the disease (higher serum PTH levels, large parathyroid adenomas, and greater risk of fracture), which may have contributed to the florid clinical picture of our patient.

Familial forms of hyperparathyroidism are known to be uncommon (5%), and their most frequent causes include multiple endocrine neoplasia (MEN) type 1 and 2A syndromes, hyperparathyroidism-jaw tumor (HPT-JT) syndrome, and familial isolated hyperparathyroidism (FIHP).[6] In MEN 1, hyperparathyroidism is the earliest and most common presentation (>90%), while in MEN 2A it occurs late and has a low penetrance. Although the genetic study for MEN 1 was negative in our patient, it should be noted that a false negative result may occur in up to 30% of the tested cases as the result of mutation patterns involving different gene regions or mutations in as yet unknown genes affecting menin transcription or action.[7] This, together with the probable asynchronous occurrence of different aspects of MEN-1, makes continuous monitoring necessary. MEN 2A is unlikely in the absence of thyroid neoplastic involvement or pheochromocytoma. Differential diagnosis should also include HPT-JT because of the scale of bone involvement and the large size of the adenoma. The final finding of a parathyroid carcinoma would have supported this diagnosis, because of its frequent occurrence in HPT-JT.[8] However, the absence of mandibular or maxillary fibro-osseous lesions and renal lesions made this unlikely. Finally, although FIHP may represent in some cases a variant of other hyperparathyroid syndromes, the possibility that mutations located in as yet unidentified loci other than those reported in MEN 1 and 2 and in HPT-JT may cause this syndrome cannot be ruled out.

The interest of the reported case lies in the fact that it illustrates the importance of assessing phosphorus and calcium metabolism and parathyroid function in all the patients with bone lesions, of suspecting a potential PHP if suggestive lesions exist, and of searching a probable underlying genetic component through a detailed family and personal history.

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Progressive thyroid lymphocytic infiltration in a patient with chronic hepatitis

Infiltración linfocitaria progresiva tiroidea en paciente con hepatopatía crónica

We report the case of a 53-year-old woman with a personal history of chronic venous insufficiency and recurrent biliary colic who was seen after goiter was detected at during routine medical visit. A physical examination revealed diffuse grade 3 goiter associated with two to four bilateral hard nodules attached to deep planes. There were no adenopathies. No thyroid tenderness or other findings were made during the physical examination. Laboratory test results included: liver enzymes: GOT, 69 IU/L; GPT, 53 UI/L; GGT, 360 IU/L; AP, 2429 IU/L. Thyroid hormones: TSH, 4.16 μU/mL; FT4, 1.07 ng/dL. Anti-thyroid antibodies (anti-thyroglobulin and anti-thyroperoxidase): negative. Acute phase reactants: C-reactive protein, 33.5 mg/L; ESR: 73 mm/h.

Thyroid ultrasound examination: four solid, hypoechoic, non-vascularized nodules 2–5 cm in size were seen, two in each nodule. The predominant nodule, 5 cm in size, was found in the middle portion of the right lobe. Fine needle aspiration: puncture of the dominant nodule was inadequate for cytological study. The patient was therefore referred for endocrine surgery because of nodule size. During surgery, a mass of a woody consistency was found, closely adherent to adjacent tissues, which prevented complete resection. Pathological study of surgical specimen. *Gross examination*: left lobe: brown whitish triangular fragment 1.5 cm in size of elastic consistency, with no normal thyroid tissue upon sectioning.

Right lobe: triangular fragment 1.5 cm in size with similar characteristics to the left fragment. *Immunohistochemistry*: CD-3 and CD-20: positive scattered lymphoid infiltrate.

Kappa and lambda light chains: positive in plasmacellular infiltrate. Cytokeratin pan: negative. Thyroglobulin: positivity for vestiges of thyroid follicles. Microscopic examination: sections showed thyroid tissue in both lobes to be widely replaced by collagenized fibrous tissue, marked thyroid follicle atrophy, and marked infiltration of mononuclear inflammatory cells (Fig. 1). CT of the neck: diffuse decrease of usual density of thyroid parenchyma, with no invasion of adjacent tissues. Based on these findings in supplemental tests, Riedel's thyroiditis was diagnosed.

In parallel to thyroid work-up, and based on recurrent episodes of biliary colic, renal colic and urinary infection, associated with intermittent claudication and chronic venous insufficiency, the internal medicine department performed a CT scan of the abdomen and pelvis that revealed portal thrombosis with abundant esophageal varices and peridiaphragmatic, perisplenic, and pericolonic collaterals; moderate splenomegaly and a small splenic cyst; right renal atrophy, fibrosis of intrarenal excretory system and right ureter entrapment; distal retroperitoneal and periaortic presacral fibrosis and fibrosis around the iliac vessels with complete obstruction of the iliac and collateral veins through prominent gonadal veins (Fig. 2).

As regards liver involvement, biliary cirrhosis (stage A 5–6) was shown, with portal thrombosis that is still present. Anticoagulation was ruled out because of two episodes of upper gastrointestinal bleeding and melena secondary to rupture of esophageal varices that required hospital admission.

Based on these findings, treatment with prednisone (40 mg/24 h in a cyclic scheme) and tamoxifen (20 mg/day) was prescribed. Two years later, thyroid ultrasound examination showed a significant reduction of the size of the thyroid nodules (which became subcentimetric), a marked improve-

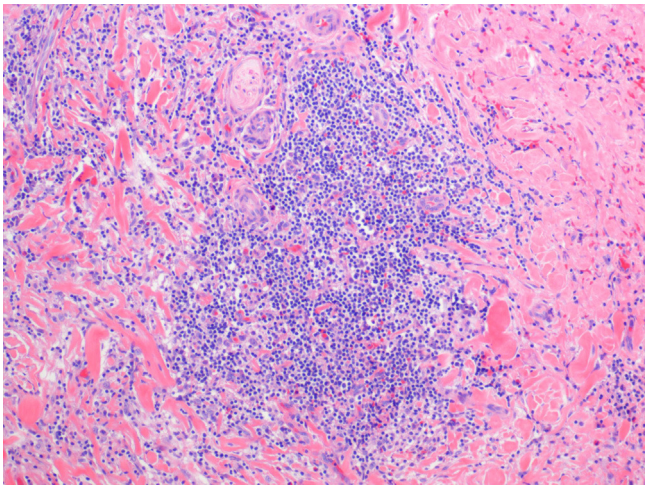

Figure 1 Microscopic view of surgical specimen.

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