

Brief report

Primary hyperparathyroidism with severe bone disease: osteitis fibrosa cystica vs. fibrous dysplasia. Case report and review of the literature

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Abstract

Primary hyperparathyroidism (HPT) is associated with generalized skeletal changes, its full-blown osseous manifestations known as osteitis fibrosa cystica. Fibrous dysplasia (FD), a benign bone disorder, is differentiated from generalized fibrocystic disease caused by hyperparathyroidism. The classic triad of McCune–Albright syndrome includes polyostotic FD, patchy skin pigmentation, and sexual precocity. Other associated endocrinopathies are hyperthyroidism, Cushing's syndrome, acromegaly, and HPT. We describe a patient with severe generalized and focal bone lesions and sexual precocity. HPT was diagnosed and treated with persistence of cystic bone lesions. The similarities between HPT and FD are discussed, focusing on a possible genetically determined mechanism to explain the relationship between them. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Primary hyperparathyroidism (HPT) has long been associated with generalized skeletal changes. The initial lesions show merely a decrease in bone density. In time, they may become very extensive and lead to deformities and fractures. The full-blown osseous manifestations of HPT have been traditionally known as osteitis fibrosa cystica (OFC) or Recklinghausen's disease [1].

Primary HPT is now recognized as a common and often symptomless endocrine disorder with an estimated prevalence of 100 cases per 100 000 normal population [2–4]. The disorder is most common in the fifth and sixth decades and is two or three times more common in women [2,3]. It seems apparent that the availability of accurate and inex-

pensive instruments to measure serum calcium is at least partly responsible for the rapid increase in the diagnosis of HPT [4]. A solitary parathyroid adenoma is the underlying pathology in more than 80% of cases [2,3].

Fibrous dysplasia (FD), a benign bone disorder characterized by extensive proliferation of fibrous tissue, differentiated from generalized fibrocystic bone disease caused by hyperfunction of parathyroid glands by Hunter and Turbull in 1930 [1,5]. In 1937, Albright described the association of FD with various endocrinological and skeletal abnormalities as well as with cutaneous pigmentation [6]. The classic triad of McCune–Albright syndrome includes polyostotic FD, patchy skin pigmentation, and sexual precocity. Other associated endocrinopathies are hyperthyroidism, Cushing's syndrome, acromegaly, hyperprolactinemia, and HPT [6,7]. FD comprises 2.5% of all bone neoplasms and 7% of all benign bone tumors. The incidence of McCune–Albright syndrome is much less than the usual forms of FD, with a ratio of 1 is to 30 or 40 [5].

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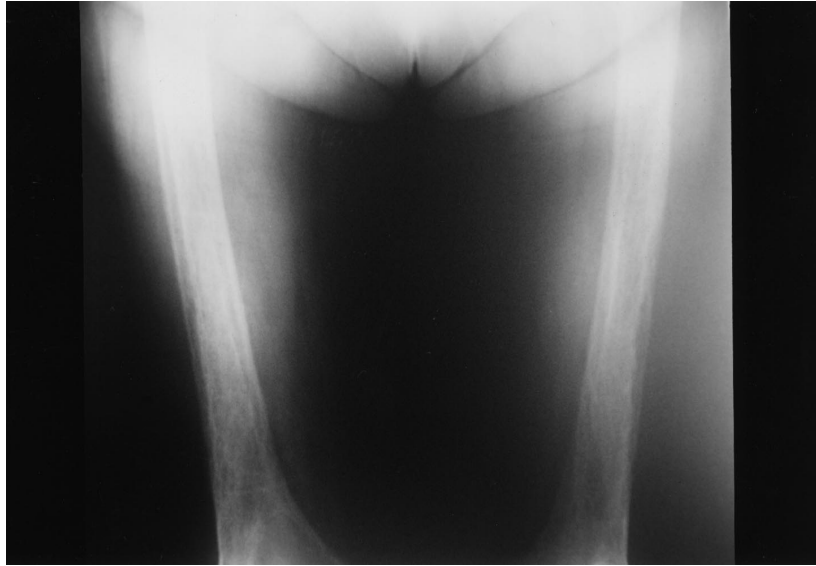


Fig. 1. X-ray of femurs showing diffuse osteoporosis, with cancellous bone hyperdensity and cortical hypodensity.

We describe a patient with severe generalized bone disease, focal osteolytic lesions, and sexual precocity associated with hyperestrogenism, in which HPT was diagnosed.

2. Case report

A 63-year-old Caucasian woman was admitted to the hospital with a 2-month history of intense fatigue, weight loss (4 kg) and bone pain, most prominent in the knees. She had had pulmonary tuberculosis at age 8, and she had

also suffered from a 'bone disease' during childhood. Her gynaecological history included menarche at age 9, one pregnancy with a term delivery, and menopause at age 46. She did not receive hormonal replacement therapy. There was no family history of endocrinopathies or bone disease. Physical examination revealed no abnormalities except pallor.

Laboratory results showed the presence of anemia: red blood cells (RBC) 2 750 000 cells/mm³, hemoglobin (Hb) 7.8 g/dl, hematocrit (Ht) 23.6%, median globular volume (MGV) 85.8 fl; erythrocyte sedimentation rate (ESR) 70

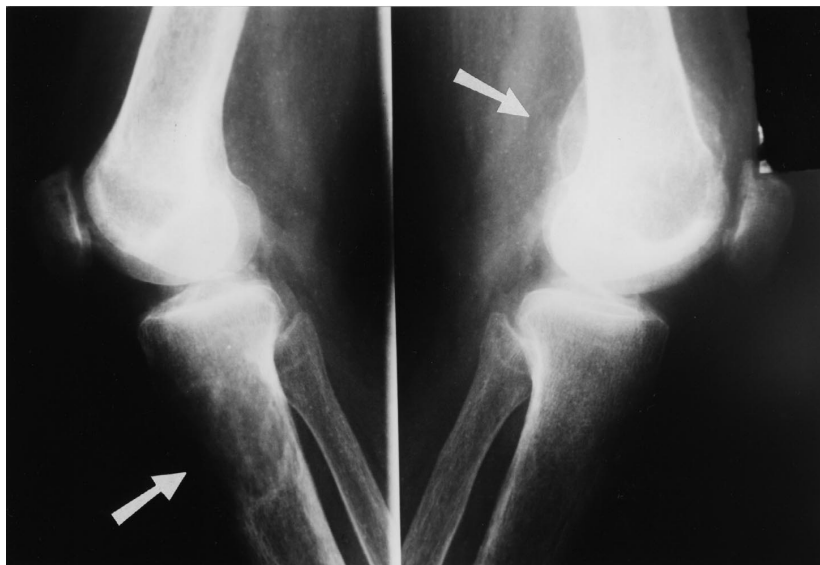


Fig. 2. Osteolytic expansile lesions in distal right femur and proximal left tibia (arrows).

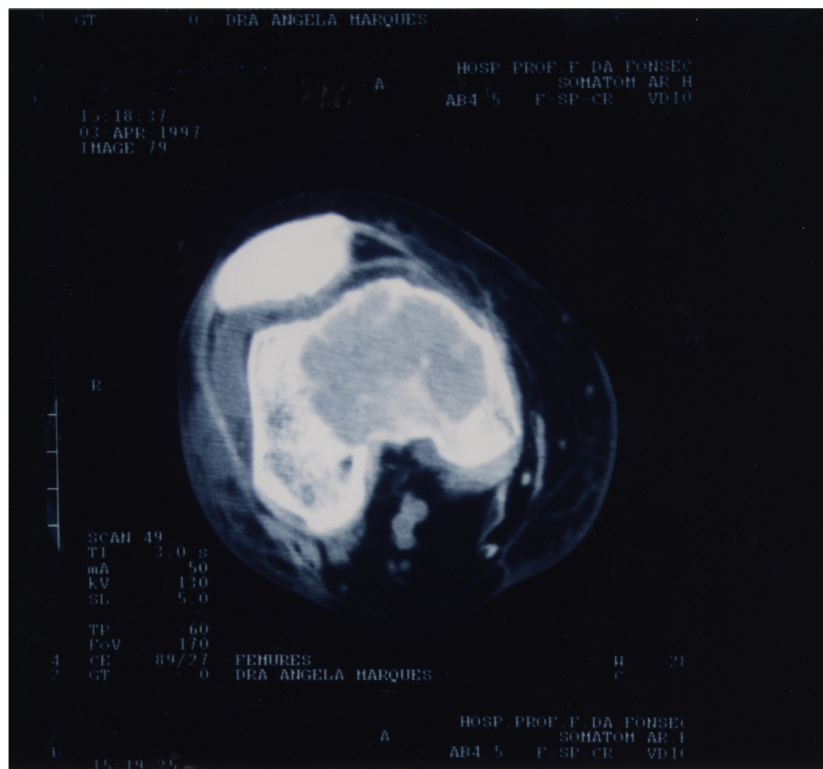


Fig. 3. CT scan of right femur revealing a soft tissue mass.

mm/h; urea 88 mg/dl (14.7 mmol/l), creatinine 1.6 mg/dl (145 mmol/l), uric acid 9 mg/dl (535 μ mol/l), Na_s 145 mmol/l, K_s 4.1 mmol/l, Cl_s 116 mmol/l, Ca_s 15.2 mg/dl (3.8 mmol/l), P_s 2.5 mg/dl (0.8 mmol/l), alkaline phosphatase 757 U/l. Serum and urinary immu-

noelectrophoresis revealed a normal pattern. All other biochemical results were within normal limits, as were measurements of immunoglobulins and tumoral markers. Skeletal radiographs revealed severe diffuse osteoporosis, with cancellous bone hyperdensity and cortical bone hypo-

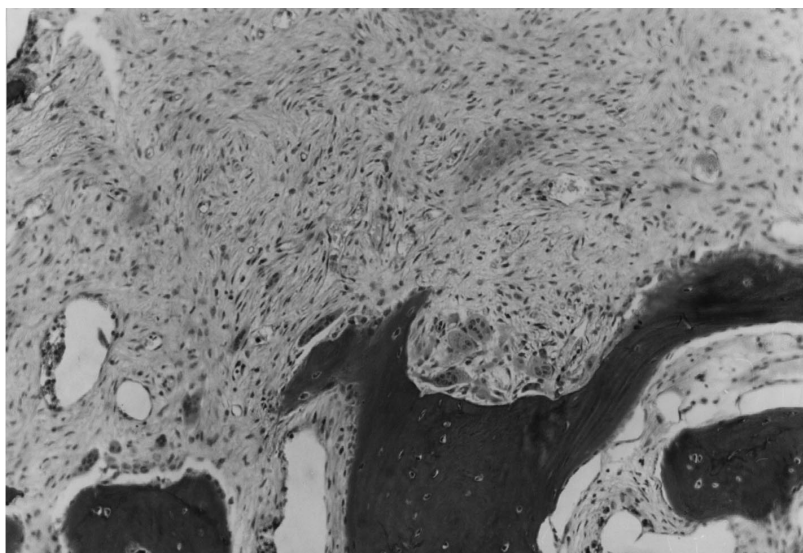


Fig. 4. Photomicrograph of the osteomedullar biopsy showing localized osteoclastic resorption of bone tissue and fibrosis of the marrow (Trichrome Masson stain, 100 \times).

density (Fig. 1), multiple osteolytic expansile lesions, some of which were causing rupture of cortical bone, most prominent in the distal right femur and in the proximal left tibia (Fig. 2). A radionuclide bone scan demonstrated increased uptake in the entire skeleton, most prominent in the extremities. The patient was treated with saline, furosemide, hydrocortisone, indomethacin, and pamidronate (45 mg/24 h, i.v.) to control hypercalcemia. During her stay in the hospital, she suffered pathological fracture of both femoral necks. A computed tomographic (CT) scan revealed a soft-tissue mass within the diaphyseal region of the distal right femur, with disruption and destruction of the cortex, and smaller lesions bilaterally in the proximal femurs (Fig. 3).

Serum intact parathyroid hormone (PTH) was 18 ng/ml ($N < 1.9$); FSH 17.1 mU/ml ($N: 20–138$), LH 2.6 mU/ml ($N: 15–62$), plasmatic 17β -estradiol 40 pg/ml ($N: 10–35$), considering postmenopausal normal values. The levels of prolactin, T_3 , T_4 , TSH, cortisol, and testosterone were normal.

Osteomedullary biopsy of the iliac crest and biopsy of the osteolytic lesion in the proximal left tibia disclosed extensive fibrosis with replacement of bone marrow by connective tissue (Fig. 4). Ultrasonography of thyroid and pelvis were normal. A magnetic resonance imaging (MRI) study revealed a mediastinal, pretracheal mass with a diameter of 3.5 cm. The inferior right parathyroidectomy revealed a chief cell adenoma of the parathyroid gland.

After surgery, there was a period of 2 weeks of hypocalcemia, consistent with a 'hungry bone' syndrome, which was treated. There was normalization of the levels of calcium and PTH under therapy with a bisphosphonate, calcium, and vitamin D. Hemoglobin levels and renal function returned to normal. The progressive remineralization of bones made it possible to implant a bilateral femoral prosthesis. Nevertheless, the radiological follow-up performed 1 year later demonstrated that the cystic femoral and tibial lesions remained unchanged.

3. Discussion

HPT and malignant disorders account for more than 90% of cases of hypercalcemia [2,3]. The initial diagnostic possibility in this patient was primary HPT, which is consistent with the hypercalcemia, the borderline-low serum phosphorus level, and the substantial increase in the chloride–phosphorus ratio, which was 46. Given the presence of anemia and an elevated ESR, another important consideration in the initial differential diagnosis is an occult neoplasm, such as myeloma or a malignant tumour, with bone metastization or with a paraneoplastic hypercalcemia due to production of a PTH-like polypeptide [3]. The finding of diffuse bone changes, in addition to the osteolytic focal lesions, points to a metabolic bone disease. In this case, the measurement of the level of intact PTH,

which is approximately 10 times the upper limit of normal, is consistent with the diagnosis of HPT.

In contemporary practice, bone disease on presentation is seen in only 5% of patients with primary HPT [8]. Thus, OFC, the classic bone disease of HPT, is rarely seen today. Locally destructive lesions, such as bone cysts and 'brown tumors', occur only in more advanced stages of hyperparathyroid bone disease [2,3]. They may present radiologically as expansile, multilocular masses, with alternation of solid and cystic areas [9].

Primary HPT mainly affects cortical bone with sparing of the cancellous bone. It causes demineralization, increased osteoclastic activity with resorption of bone and peritrabecular fibrosis, and marrow fibrosis with the formation of micro- to macrocysts within the enlarged fibrotic marrow spaces [9]. The brown tumors show clusters of hemosiderin-laden macrophages and large, multinucleated giant cells within blood vessels [8]. In OFC, the amount of fibrosis appears related to the severity of the disease [8].

Nowadays, as patients with HPT usually present at an early stage of the disease, the presence of important focal lesions, as demonstrated in our patient, should alert one to the possibility of an unrelated bone disease. In our case, bone examination revealed intense fibrosis, as seen in FD [5,9], instead of the typical histological features of a brown tumor [3]. The extensive replacement of bone marrow by fibrous tissue explains the presence of anemia and its recovery after parathyroidectomy.

In FD with multiple bone lesions, the lower extremities and pelvis are most affected often [5], and it is associated with spontaneous fractures of the femoral neck, as in our case, and deformity, depending on the extent of disease, as well as malignant transformation [8,9]. The radiological appearance of the lesions of the face and skull are predominantly osteosclerotic, whereas those in other areas show more trabeculation, with thinning of the cortex and formation of cyst-like lesions [5]. The cystic form of FD may be confused with the radiological signs of HPT [5,7].

Considering that HPT has been found to be associated with other primary endocrinopathies and the patient's past history of bone disease in childhood and precocious puberty, it was decided to measure the levels of other hormones. A pattern of estrogens and gonadotrophins was found that was not consistent with the postmenopausal state of the patient, with an apparent primary hyperestrogenism, although no ovarian masses were disclosed on ultrasonography. Consequently, we could consider the possibility of microscopic ovarian cysts as the cause of increased levels of estrogens.

Although this patient did not present the classical triad of McCune–Albright syndrome, it is possible that the HPT was not a solitary endocrinopathy but that it was associated with FD and other endocrinological disorders [5]. Except for the McCune–Albright syndrome, concomitance of HPT and FD had been reported in a few patients before, and it has been suggested that this may represent a variant

of McCune–Albright syndrome [7,8]. There is also an apparent histological similarity between OFC, FD, and nonossifying fibroma, and some authors look upon FD as a variant of nonossifying fibroma [8]. Therefore, there may be a basis for viewing the combination of primary HPT and fibro-osseous lesions of bone as yet another example of a clinical endocrine syndrome [8].

Recently, a theory was formulated trying to explain the mechanisms subjacent to these disorders. First, sexual precocity in McCune–Albright syndrome, more accurately termed ‘pseudoprecocious puberty’, is generally accepted not to be mediated via maturation of the hypothalamic–pituitary–ovarian axis, and many of these patients have been found to have autonomously functioning follicular cysts. Second, the other endocrinopathies of this syndrome are likewise thought to be due to autonomously functioning nodular disease [6]. Thus, the most widely accepted hypothesis of the pathophysiology of the disorder has been that multiple, discrete areas of autonomously functioning cells arise in various tissues that harbor embryologically dysfunctional clones of cells. Currently, defective signal transduction for glycoprotein hormones with a G-protein chronically ‘turned on’ is thought to be the central feature of the disorder [6]. Thus, all tumors associated with McCune–Albright syndrome have one thing in common: they arise from cells that are usually under control, in what concerns its secretion and proliferation, of a hormone acting on a receptor coupled with G_s protein, a member of the G-protein family. This may explain why polyostotic FD lesions are sometimes quite similar to the cystic bone lesions observed in HPT, which is due to the hypersecretion of PTH, also a hormone whose receptor is coupled to G_s protein [10].

It may be concluded that the possible relationship between HPT and FD arises from the fact that both diseases may cause similar radiological and histological changes in bones and that HPT has been found to be associated with McCune–Albright syndrome in some patients. Cystic lesions of HPT may continue indefinitely [9], but they

usually become filled with bone and sclerotic tissue, consistent with a healing brown tumor [3]. Follow-up of the changes in bone disease after parathyroidectomy can help one to reach a clear-cut diagnosis [7]. In our patient, the cystic lesions persisted unchanged months after parathyroidectomy, which made us consider the possibility of FD. We admit the bone disease was multifactorial in view of the patient’s primary HPT, the osteoporosis related to her postmenopausal state, and the polyostotic FD [6]. We also feel that it could also be a consequence of a more complex disease involving a mutation of the gene of a G-protein, which is responsible for endocrinological disorders characterized by the autonomous secretion of hormones.

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