Oncogenic osteomalacia in a patient with a fibrocystic nodule of the breast

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Introduction

Oncogenous osteomalacia is a rare paraneoplastic syndrome characterized by bone pain, proximal muscle weakness and fractures, hypophosphataemia along with hyperphosphaturia, and inappropriately low circulating concentrations of 1,25-dihydroxycholecalciferol. This syndrome is associated with the presence of tumours, and resolves after their excision [1–3]. The tumours associated with this syndrome are usually benign, of mesenchymal origin, highly vascular, and composed principally of giant and spindle cells [4]. It is likely that this disorder is more common than suggested by the paucity of reports. Careful clinical examination for odd lumps is essential because the diagnosis is frequently delayed [1]. We report a case of oncogenous osteomalacia in a 51-year-old woman with fibrocystic disease of the breast. She had a nodule in the breast; after removal of the mass, all biochemical abnormalities and clinical manifestations disappeared.

Case

A 51-year-old woman was referred from the Rheumatology Unit in May 1998 for evaluation of persistent hypophosphataemia, i.e. 2.2 mg/dl (normal 2.5–4.9). Her illness began with diffuse bone pain in mid-1994. She experienced progressively increasing skeletal pain in the shoulders, knees, lower legs and back. The diffuse bone pain was accompanied by generalized muscular weakness leading to a severe debilitation, especially difficulty in walking. The electromyogram and nerve conduction studies were normal. The patient was not taking any medications.

There was no family history of hypophosphataemia. Physical examination revealed severe proximal-muscle weakness. A firm, movable mass, measuring 3 cm in diameter was identified in the soft tissue of the left breast. The results of complete blood cell count, biochemical profile, and thyroid function tests were normal except for persistent hypophosphataemia (serum inorganic phosphorus concentrations of 2.1–2.4 mg/dl). Multiple determinations of serum calcium and serum uric acid were within normal limits. Serum concentrations of alkaline phosphatase (114 IU/l), parathyroid hormone (PTH) (43 pg/ml), 1,25-dihydroxycholecalciferol (25 pg/ml), and 25-hydroxycholecalciferol (25 ng/ml) were normal. Serum protein electrophoresis revealed a normal pattern. Twenty-four-hour urinary inorganic phosphorus excretion ranged from 800 to 900 mg. The tubular phosphate reabsorption index of Brodehl [5], i.e. \[(\text{TmP}/\text{GFR} = \text{P}_\text{p} - (\text{U}_\text{p} \times \text{P}_\text{Cr}/\text{U}_\text{Cr}))\] was less than 1.8 mg/dl. No evidence of intestinal malabsorption, renal insufficiency, metabolic acidosis, aminoaciduria, or glycosuria was uncovered.

Suspecting that we were dealing with tumour-induced osteomalacia related to the subcutaneous mass in the left breast, the nodule was excised in July 1998. Histologic examination revealed an adenocortical nodule and fibrocystic disease of breast, with numerous small thin-walled cysts and increasing hyalinised fibrous stroma (Figure 1). Post-operatively, 12 weeks after surgery the patient was asymptomatic, her weakness had improved, and serum phosphate concentration (2.8 mg/dl) as well as tubular phosphate reabsorption (2.2 mg/dl) had increased to normal levels. Twenty-four-hour urinary inorganic phosphorus excretion was 600 mg/day.

Discussion

Tumour-induced (oncogenous) osteomalacia is a rare metabolic bone disease in which phosphate homeostasis is markedly deranged [1,2]. To date, less than 100 cases of oncogenous osteomalacia have been described [4,6–9]. The first such patient was described...
Fig. 1. Microscopic appearance of the fibrocystic nodule of the breast, with small thin-walled cysts and increasing hyalinised fibrous stroma (HE stain, ×50).

by McCance [9] in 1947, but the association between tumour and osteomalacia was first recognized by Prader et al. [10] in 1959. It often presents with diffuse muscle and bone pain, muscle weakness, and recurring fractures. It is characterized by two biochemical features that are the hallmark of this condition: hypophosphataemia and an inappropriately low 1,25-dihydroxycholecalciferol concentration [1,2]. Serum calcium is normal or slightly low and alkaline phosphatase is variably elevated. In our patient, as well as in other cases, the serum alkaline phosphatase concentration was normal [7]. Parathyroid hormone and 25-hydroxycholecalciferol levels are usually normal. The tubular phosphate reabsorption threshold (TmP/GFR) is low, i.e. less than 1.8 mg/dl [3]. In some patients, other abnormalities of proximal renal tubular function have also been encountered, e.g. generalized aminoaciduria and renal glycosuria [12,13].

In oncogenic osteomalacia the syndrome is associated with the presence of a tumour whose successful removal leads to clinical and biochemical cure. The tumours that cause this syndrome are often small and difficult to locate. They are generally of mesenchymal origin and are derived from soft tissue or bone. The most frequently reported tumour types are benign, hemangioma, hemangiopericytoma, fibroma, fibroangioma and osteoblastoma [4,6], with variety of cell types, including spindle cells, osteoid and giant cells [4]. The tumours have been found in the popliteal region, the groin, the suprapatellar area, and the nasopharynx, as well as in relatively inaccessible sites in bone, e.g. in femur, tibia, or sinus [2,4,6]. Head and neck are the second most frequent locations [9]. Oncogenous osteomalacia has also been found in association with malignant tumours [14]. To our knowledge, this is the first reported case of a nodule of fibrocystic disease of breast associated with oncogenous osteomalacia.

The reversal of clinical and biochemical abnormalities following removal of the tumour, indicates it is the source of a humoral factor (phosphatonin) that inhibits Na\(^{+}\)-Pi cotransport in renal proximal tubular cells and reduces 1,25-dihydroxycholecalciferol production [2,7]. This phosphaturic factor may be related to the circulating factor which is responsible for the renal Pi leak in X-linked hypophosphataemia, a genetic disease mimicked in many respects by oncogenous osteomalacia [2]. In light of the fact that PHEX, the gene responsible for X-linked hypophosphataemia, may be involved in the regulation of renal vitamin D metabolism and in the inactivation of a phosphaturic hormone or the activation of a Pi-conserving hormone, it is of interest that PHEX transcripts have been detected in tumours from patients with oncogenic osteomalacia [15]. The loss of PHEX function contributes to the pathophysiology of these disorders [15]. Tenenhouse recently studied Hyp and Gy mice that exhibit the same phenotypic features that are found in patients with X-linked hypophosphataemia. The author identified a specific defect in Na\(^{+}\)-Pi cotransport at the renal brush border membrane, abnormal regulation of 1,25-dihydroxyvitamin D3 synthesis and degradation, and an intrinsic defect in bone mineralization [15].

References


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