Case Report

A rare case of tumor-induced hypophosphatemic osteomalacia associated with tertiary hyperparathyroidism: a case report.

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ABSTRACT

Background

Tumor-induced hypophosphatemic osteomalacia is a syndrome characterized by urinary phosphate wasting related to the presence of a slowly-growing tumor of mesenchymal origin.

The characteristic laboratory findings are normal serum calcium, marked hypophosphatemia, increased serum alkaline phosphatase, markedly reduced renal tubular reabsorption of phosphorus and inappropriately low levels of 1,25-dihydroxy vitamin D (1,25-$(OH)_2D$).

Case presentation

A 65-year-old woman presented with a 17-year clinical history of musculoskeletal pain, muscular weakness in the pelvic girdle, spontaneous fractures and difficulty in walking. Over the ensuing years the patient suffered other multiple spontaneous fractures, surgically treated, and the muscular pains worsened until she became bedridden.

During the years before hospital admission the patient received treatment with clodronate, oral calcium salts and vitamin D therapy.

Laboratory, ultrasonography and scintigraphic findings provided a “convenient” diagnosis of primary hyperparathyroidism, but the low plasma level of phosphorus induced to perform an In^{111}-octreotide scintigraphy. Scintigraphy visualized an area of pathologic increased signal uptake in the left groin, consistent with a mass containing a high density of somatostatin receptors.

After surgery, histologic examination and immunostaining of the resected specimen indicated an hemangiopericytoma.

Neverthless, the persistently low blood phosphorus level, in association with the increased serum calcium and iPTH levels, were attributed to the prolonged phosphate therapy the patient underwent over the years, and the persisting abnormal laboratory indexes indicated the development of a tertiary hyperparathyroidism.

We performed a subtotal parathyroidectomy and intraoperative assay of serum iPTH showed that levels had diminished by more than 80% from preoperative values. Over the ensuing months Ca++, iPTH and serum phosphorus values returned to normal, and the pain symptoms disappeared.

Conclusions

Tumour-induced osteomalacia is a very rare syndrome associated in 5% of cases with tertiary hyperparathyroidism due to long-term therapy with phosphorus and vitamin D.

The initial diagnosis of primary hyperparathyroidism, confirmed by the parathyroid MIBI-scintigraphy, would lead us to an inappropriate surgical treatment. Therefore we want to stress the importance of I^{111}-octreotide scintigraphy in detecting tumours, rich in somatostatin receptors, in presence of an hypophosphatemic syndrome.

BACKGROUND

Tumor-induced hypophosphatemic osteomalacia, to our knowledge a syndrome rarely reported in the medical literature, is characterized by urinary phosphate wasting related to the presence of a slowly-growing bone or soft-tissue tumor of mesenchymal origin that is often difficult to discover. The syndrome affects adults of both sexes; despite peak incidence in the fourth decade the causative tumor often remains unrecognized until the fifth or sixth decades of life.[1,2]

Although hypophosphatemic osteomalacia was first described by McCance in 1947 [3], and later by Prader in 1959 [4], the causative tumors were categorized by Weidner [5] and Santa Cruz only in 1987. The most frequent are giant cell osteoblastomas, hemangiomas, fibromas, hemangiopericytomas, fibroangiomas, osteoblastomas, chondromas, chondroblastomas, fibrous xanthomas but the syndrome arises also from prostate carcinomas, "oat cell" carcinomas, sarcomas, malignant histocytic histiocytomas, neurinomas, multiple myeloma and neurofibromatosis.

The characteristic laboratory findings are normal serum calcium, marked hypophosphatemia, increased serum bone alkaline phosphatase, markedly reduced renal tubular reabsorption of phosphorus and inappropriately low levels of 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$).

The mechanism underlying this rare syndrome is thought to involve humoral factors produced by the causative neoplasm, called "phosphatonins". In a study conducted in 2001, Shimada et al [6] identified "phosphatonin" as a member of the FGF family, namely FGF-23. This growth factor, secreted also by normal tissues, appears to have a central role as a hormone regulator of phosphate metabolism. Owing to overproduction, FGF-23 abundantly expressed by neoplastic tissues appears to induce the hyperphosphaturia syndrome by inhibiting renal tubular reclaimation of phosphorus.

Besides FGF-23, the phosphatonin group comprises other factors including frizzled-related protein 4 (FRP-4), and matrix extracellular phosphoglycoproteins (MEPE), putatively involved in regulating bone mineralization. All three proteins acting synergically or sequentially might reasonably intervene in hypophosphatemia. Both factors are invariably elevated in patients with tumor-induced osteomalacia and after surgical removal of the responsible tumor diminish as the pain symptoms and functional weakness regress [7,8].

We present the case of an adult woman with tumor-induced hypophosphatemic osteomalacia caused by a hemangiopericytoma in the left groin. Prolonged phosphate therapy over the patient's 17-year clinical history led to the development of tertiary hyperparathyroidism thus preventing plasma phosphorus levels from normalizing even after surgical removal of the tumor.

CASE PRESENTATION

A 65-year-old woman presented with a 17-year clinical history of musculoskeletal pain, muscular weakness in the pelvic girdle and difficulty in walking. X-ray films obtained at the age of 52 showed symmetric fractures involving the iliac and ischiopubic branches. A bone-biopsy specimen yielded a diagnosis of "osteomalacia". Therapy was started with calcium, vitamin D and phosphates.

Over the ensuing years the patient suffered other multiple spontaneous fractures surgically treated (right and left femur, right humerus and the proximal third of the first and second metacarpal bones in the right hand) and the muscular pains worsened until she became bedridden. During the years before hospital admission the patient received treatment with clodronate (bisphosphonate), and oral administration of calcium salts and vitamin D.

Standard diagnostic radiographs on admission documented the previous fractures. Radiographs of the cranium and sella turcica and X-ray mammography gave normal findings. A

bone density scan showed severe osteoporosis Total body magnetic resonance imaging (MRI) showed multiple small areas of increased signal on T_2-weighted images and areas of decreased signal on T_1-weighted sequences (previous fractures?; myelomatosis lesions?). Laboratory findings included a negative Bence-Jones test for proteinuria thus excluding a diagnosis of myeloma and confirming that the MRI documented lesions originated from trauma. Laboratory measurements of serum electrolytes, creatinine, glucose, urea nitrogen, white blood cell count and coagulation were normal, as were serum erythrocyte sedimentation rate, electrophoresis, immunoelectrophoresis, immunoglobulin assay, and acid-base equilibrium. Despite a normal total serum calcium concentration the following indexes were abnormal: ionized calcium (Ca++) was high; phosphorus was very low; alkaline phosphatase and bone alkaline phosphatase were high; parathyroid hormone values (PTH) was twice normal; 1,25-$(OH)_2$D was low. Conversely, levels of 25-hydroxyvitamin D (25-(OH)D), the active vitamin D precursor, were normal.

An ultrasound scan of the neck, obtained to investigate suspected primary hyperparathyroidism, disclosed a hypoechogenic area measuring about 0.6 cm in maximum diameter posterior to the left thyroid lobe, initially attributed to a parathyroid gland. Parathyroid scintigraphy showed increased technetium-99 MIBI uptake in correspondence with the left inferior thyroid lobe, consistent with a parathyroid adenoma. These scintigraphic findings along with the suspected primary hyperparathyroidism nevertheless seemed not to justify the patient's grave clinical conditions, especially considering the almost normal findings on ultrasonography, serum PTH values only twice normal and most important, the exceedingly low serum phosphorus associated with low serum vitamin D levels, elevated alkaline phosphatase and a normal total serum calcium concentration.

These findings led our endocrinologists to suspect hypophosphatemic osteomalacia, a suspicion confirmed by a literature review underlining its frequent association with mesenchymal

neoplasms. The patient therefore underwent indium^{111}-octreotide scintigraphy because recent studies have identified somatostatin receptors in mesenchymal neoplasias.[9] Scintigraphy readily and quickly visualized an area of pathologic increased signal uptake at a site corresponding to the left groin, consistent with a mass containing a high density of somatostatin receptors.

Spiral computed tomographic (CT) scanning targeting the scintigraphic findings disclosed an oval expanding lesion (4 cm in diameter) with evident contrast enhancement within the left groin, sited deeply to the femoral muscle insertion and externally to the femoral vessels (Fig. 1). Surgery for removal disclosed within the left groin a roundish, yellowish mass with a variegated appearance and soft consistency; the mass measured 5 x 6 x 3 cm and adhered closely to the surrounding tissues (Fig. 2). Histologic examination of the resected specimen indicated a mesenchymal tumor. Tumor cells stained strongly positive for vimentin and neuron-specific enolase but were negative for cytokeratin, S-100 and synaptophysin immunostaining therefore indicating a diagnosis of hemangiopericytoma.

One week after surgery, without therapy, serum phosphorus values nearly doubled then stabilized and the pain symptoms improved but PTH levels remained high. Assay of fibroblast growth factor type 23 (FGF-23) that preoperatively showed high values progressively became negative.

Over the ensuing months the patient underwent cycles of therapy with calcitriol and phosphorus; even though the symptoms markedly improved, serum phosphorus values never returned to normal ranges but remained low. At the same time, Ca++ and PTH increased.

The persistently low blood phosphorus level, albeit less marked than the preoperative decrease, in association with the increased serum calcium and PTH levels, were attributed to the prolonged phosphate therapy the patient underwent over the years, hence to secondary

hyperparathyroidism associated with chronic parathyroid stimulation. Even though phosphate supplementation was suspended, the persisting abnormal laboratory indexes indicated the development of autonomous parathyroid dysfunction, hence a form of tertiary hyperparathyroidism.

Surgical exploration of the neck showed that both left parathyroid glands and the inferior right parathyroid gland were enlarged and were removed. The upper left parathyroid gland appeared normal in size and was left in situ. Histological frozen sections confirmed diffuse hyperplasia. Intraoperative assay of serum PTH showed that levels had diminished by more than 80% from preoperative values allowing subtotal parathyroidectomy.

Over the ensuing months Ca++ and PTH values returned to normal, serum phosphorus rose to normal value and the pain symptoms and muscle weakness progressively improved until the patient was again able to walk.

CONCLUSIONS

Tertiary hyperparathyroidism associated with hypophosphaturic osteomalacia has rarely been reported in the literature [10,11,12] and complicates no more than 5% of the cases [13,14]. The distinctive feature in this patient was the unexpected finding of a mesenchymal tumor in a patient with suspected primary hyperparathyroidism, a diagnosis that would have led to inappropriate surgical treatment. In our case the correct diagnosis, tumor-induced hypophosphatemic osteomalacia, was suggested by preoperative assay of FGF-23, and confirmed by Indium^{111}-octreotide scintigraphy.

As is typical of patients with hypophosphoremic osteomalacia, our patient had a 17-year history of severe muscle weakness and pain before tumor-induced hypophosphatemic osteomalacia was diagnosed. Even though published reports [15] number more than 100 patients

since McCance first described the disorder, because the syndrome is little known the diagnosis can be delayed even 20 years after the first symptoms manifest [14]. Even though the preceding diagnostic imaging (neck ultrasonography and parathyroid scintigraphy) provided a “convenient” diagnosis of primary hyperparathyroidism, the turning point came when octreotide scintigraphy undertaken to explain the concomitant biochemical humoral changes detected the mesenchymal tumor. Once the primary tumor was removed, plasma FGF-23 almost halved but blood phosphorus values, despite a marked increase, never came within the normal range, indicating that the phosphaturic stimulus persisted. Given the patient’s clinical history and her continued phosphate treatment for many years we therefore attributed this residual phosphaturia to tertiary hyperparathyroidism.

Phosphates act directly by sequestering calcium thus stimulating parathyroid glands. In our case, chronic parathyroid stimulation led to hyperplasia followed by autonomous parathyroid gland hyperfunction thereby worsening renal phosphate wasting. The tertiary hyperparathyroidism prevented the complete normalization of serum phosphorus levels.

The operative confirmation of multiple hyperplasia and the rapid assay for measuring serum PTH during surgery, a technique we consider indispensable in these cases, allowed us to remove the hyperphosphaturic stimulus, without recourse to total parathyroid gland ablation. After surgery blood and urine indexes returned to normal and the patient regained the use of her arms and legs, and resumed normal relationships.

Because mesenchymal tumors of this type tend to recur, often owing to incomplete removal [16], multicentric disease [17] or metastatic disease [14], these patients should undergo long-term surveillance including regular laboratory testing and diagnostic imaging.

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Figure legends

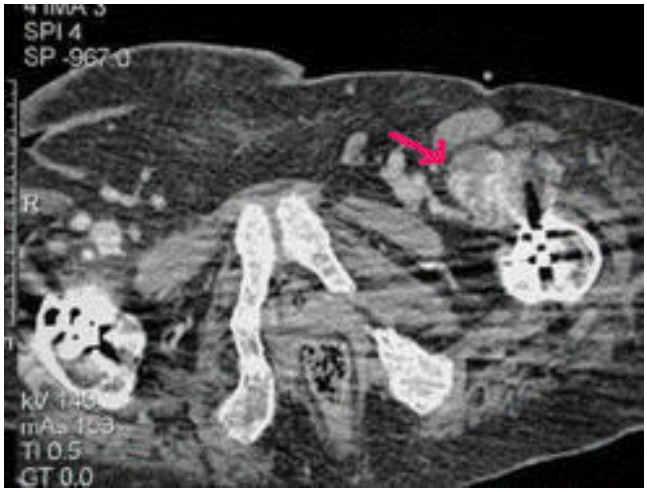

Figure 1. Spiral computed tomographic scan showing an oval expanding lesion (4 cm in diameter) with evident contrast enhancement within the left groin, sited deeply to the femoral muscle insertion and externally to the femoral vessels.

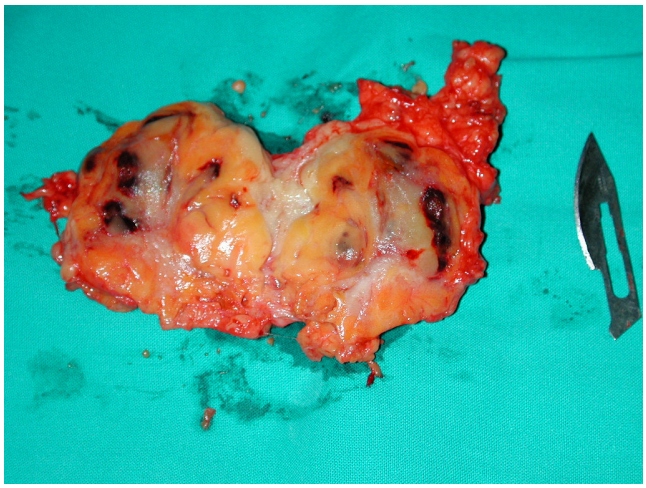

Figure 2. Operative specimen. Histologic examination indicated a mesenchymal tumor. Immunostaining indicated a diagnosis of hemangiopericytoma.