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Following the forgotten phosphorus

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Tumor-induced osteomalacia; hypophosphatemia; FGF-23

PRESENTATION

Migratory pain and fatigue prompted a previously productive 63 year old woman to present with complaints of muscle weakness, generalized fatigue and pain involving her feet, lower back, shoulders and ribs of insidious onset over several months. Initial laboratory and imaging studies undertaken by multiple physicians were nondiagnostic. Technetium 99 bone scan showed increased but non-specific uptake in her ribs, sacroiliac joints and tibia. Subsequent bone scan-directed rib biopsy was non-diagnostic. Concern for a possible underlying infiltrative malignancy prompted referral to our institution for oncologic evaluation. An abnormal positron emission tomography (PET) scan with increased thyroid uptake and subsequent fine needle aspirate were diagnostic for papillary thyroid cancer, prompting sub-total thyroidectomy with postoperative radioactive iodine ablation followed by thyroid hormone suppression therapy. Despite this intervention, her diffuse bone pain persisted and further investigation was pursued.

Imaging for metastatic malignancy was unrevealing, but bone scan again showed multiple areas of abnormal uptake. To investigate a possible bone fragility disorder, dual energy X-ray absorptiometry (DXA) was obtained and demonstrated severely reduced bone mineral density. Magnetic resonance imaging (MRI) of the pelvis unexpectedly revealed bilateral insufficiency subcapital fractures of the femoral neck and remote fracture of the left iliac wing. With a provisional diagnosis of osteoporosis, treatment with bisphosphonates was initiated. However, a trial of intravenous zoledronic acid followed by oral risedronate only resulted in exacerbation of her pain. She was subsequently referred to our endocrinology division for further management of her presumed severe osteoporosis and diffuse pain syndrome.

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ASSESSMENT

On presentation to our clinic, her physical exam was remarkable for multiple sites of bony tenderness on palpation but no findings typical of severe osteoporosis or rickets (kyphosis or lower extremity bowing). Further investigations revealed laboratory abnormalities, including hypophosphatemia (1.5 mg/dL, normal range 2.3–4.3), a slightly low 1, 25-dihydroxyvitamin D (21 pg/mL, normal range of 22–67 ng/mL), elevated parathyroid hormone (152 pg/mL) and elevated alkaline phosphatase (153 U/L, normal range 11–67). Of note, the patient's calcium, renal function and 25-hydroxyvitamin D were all normal. Evaluation was also notable for reduced renal phosphate reabsorption threshold (TmP/GFR = 1.6) with frank phosphaturia. Based on her clinical presentation, with insidious bone pain, reduced bone mineral density with fragility fractures, hypophosphatemia, low or inappropriately normal 1,25-dihydroxyvitamin D and renal phosphate wasting, tumor induced osteomalacia was strongly suspected.

Tumor induced osteomalacia (TIO) or oncogenic hypophosphatemic osteomalacia (OHO) is a paraneoplastic syndrome that results from overproduction of phosphaturic factors or “phosphatonins” by tumor tissue. The most commonly described tumors responsible for this syndrome include a group of histologically polymorphous, mesenchymal, slowly growing lesions that include osteoblastoma-like tumors, ossifying fibrous like tumors, non-ossifying fibrous tumors and phosphaturic mesenchymal tumor of mixed connective tissue type (PMTMCT).¹ The histological evaluation of all of these tumors show multiple components, including vascular elements, giant cells, bone and cartilage matrix, which are typically of a benign nature.²

The pathophysiology of tumor induced osteomalacia is primarily due to renal phosphate wasting, although abnormal vitamin D metabolism also likely contributes indirectly to the osteomalacic syndrome. These abnormalities are attributed to overproduction of phosphatonins, including matrix extracellular phosphoglycoprotein (MEPE), secreted frizzled related protein-4 (sFRP-4), fibroblast growth factor 7 (FGF7) and the most commonly identified and responsible factor, fibroblast growth factor 23 (FGF23).³ FGF23 inhibits phosphate reabsorption by decreasing expression of the sodium phosphate type 2a cotransporter in the renal proximal convoluted tubule.⁴ FGF23 also reduces serum calcitriol levels by directly inhibiting expression of 1-alpha hydroxylase and increasing 24-hydroxylase expression in the renal proximal tubule,^{4,5} which results in reduced intestinal absorption of phosphorus.

As with our patient, most patients present with weakness, fatigue, and bone pain, often times well before the actual diagnosis or onset of atraumatic fractures.^{2,6} Recommended evaluation of patients with symptoms that may represent tumor induced osteomalacia include serum creatinine and calcium, alkaline phosphatase, intact parathyroid hormone, 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D levels and fasting serum phosphorus. The latter is important to note as most comprehensive chemistry panels do not routinely include serum phosphorus. Additionally, a timed two hour serum and urine phosphorus and creatinine after water loading (TmP/GFR) are measured to determine if renal phosphate reabsorption is reduced.⁷ Other disorders with renal tubular defects and phosphate wasting, such as Fanconi syndrome and hereditary hypophosphatemic rickets with hypercalciuria (HHRH), should be excluded by examining urinary calcium, glucose and amino acid levels. Family history can likewise help distinguish tumor induced osteomalacia from inherited disorders of hypophosphatemic rickets, such as X-linked hypophosphatemic rickets (XLH) or autosomal dominant hypophosphatemic rickets (ADHR).

DIAGNOSIS

Given our suspicion for tumor induced osteomalacia, focus turned to localizing the responsible lesion. Identification of the syndrome and responsible tumor is often challenging and can be delayed by years due to the indolent nature, nonspecific clinical symptoms, unusual tumor locations and the general non-inclusion of serum phosphorus in most routine laboratory panels.^{2,6} Commonly described modalities used in localization include octreotide scintigraphy, computed tomography, magnetic resonance imaging, and venous sampling for FGF23.^{2,8,9}

For our patient, a computerized tomography of the sinus, a not uncommon site of tumor occurrence, was unrevealing. Octreotide scan showed left forefoot uptake, thought to be from degenerative changes of her remote bunion surgery (Figure 1). Based on a high clinical suspicion for tumor induced osteomalacia, the patient underwent MRI that revealed a soft tissue mass this area (Figure 2). Biopsy by orthopedic surgery revealed the mass to be a benign histiocytic mesenchymal lesion consistent with a phosphaturic mesenchymal tumor. The patient subsequently underwent partial resection of the left first metatarsal with complete tumor resection and negative surgical margins. Pathologic analysis demonstrated hypocellular, myxoid areas and densely cellular regions (Figure 3), confirming the diagnosis of a phosphaturic mesenchymal tumor.

MANAGEMENT

Once the diagnosis of tumor induced osteomalacia was considered, she was immediately treated with elemental phosphorus and calcitriol with significant improvement of her pain symptoms. Although symptomatic improvement can be seen with correction of the mineral disturbances alone, definitive treatment of this disorder relies on complete resection of the FGF23 producing tumor to restore normal phosphorus and mineral metabolism.¹⁰

Following surgery, the patient was slowly titrated off elemental phosphorus and calcitriol therapy with maintenance of normal laboratory parameters. She experienced gradual and ultimately complete resolution of her pain, as well as improvement in subjective strength and well-being. Follow-up bone densitometry thirteen months after her original study revealed remarkable improvement in bone density compared to pre-operative baseline (Figure 4).

This case demonstrates a rare disorder presenting with a common complaint of pain. The keys to diagnosis were bone pain and fatigue more severe than expected in typical postmenopausal osteoporosis. When suspecting any metabolic bone disorder, a complete history and laboratory evaluation should include serum calcium, phosphorus and 25-hydroxyvitamin D. If abnormal, consideration of secondary causes of osteoporosis or osteomalacia should be considered and subspecialty advice pursued before treatment is initiated, as definitive treatment of the true underlying diagnosis may be quite different.

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Figure 1.
Whole body octreotide scan. Areas of concern are circled.

Figure 2.
T-2 weighted axial view of left forefoot showing soft tissue mass (red arrow) between first and second metatarsals without bone invasion.

Figure 3. Hematoxylin and eosin stain (60X) of tumor showing hypocellular, myxoid area (red arrow), dense cellular area (blue arrow) and mature bone (black arrow).

Figure 4.
Change in lumbar spine and bilateral proximal femur T scores following tumor resection.