Imaging of Oncogenic Osteomalacia

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Key words: oncogenic osteomalacia, tumor-induced osteomalacia, hypophosphatemia, acquired hypophosphatemic rickets, phosphaturic mesenchymal tumors

IMAJ 2007;9:566–567

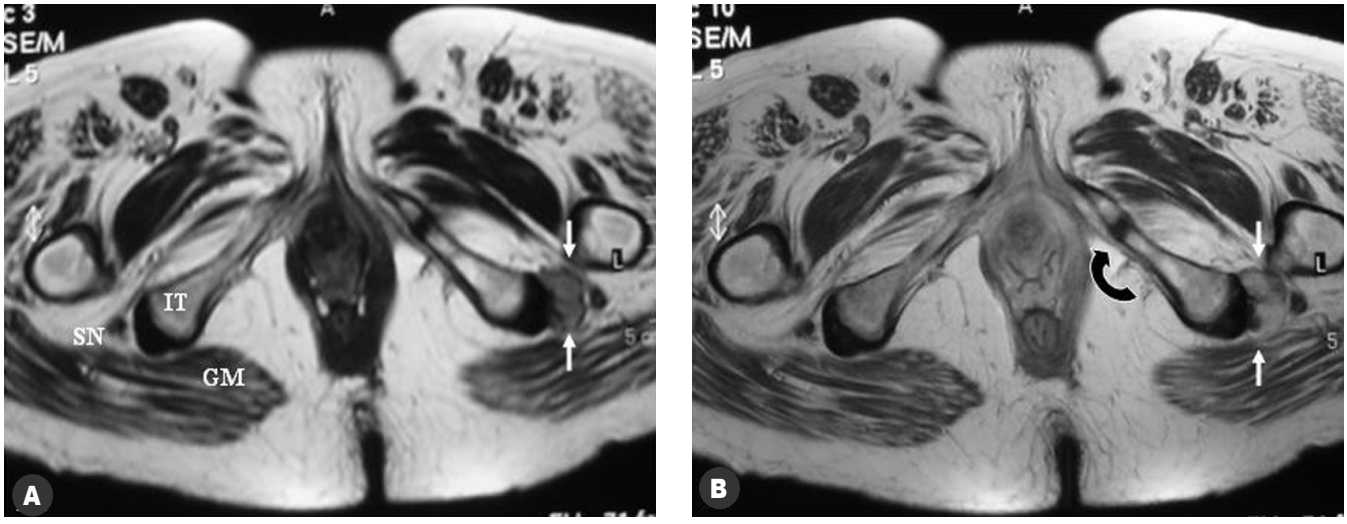
Imaging has a dual role in the detection and localization of mesenchymal tumors that present clinically with hypophosphatemic osteomalacia. Skeletal radiography and scintigraphy are indicated to confirm the diagnosis in patients with symptoms of osteomalacia. In addition, in cases with laboratory findings of hypophosphatemic osteomalacia, a thorough imaging workup is of utmost importance in the search for a causative tumor. Most of the mesenchymal lesions are found in the extremities and the head, and are usually small and slow growing. Magnetic resonance imaging has been recommended in the literature for tumor search [1,2], as well as Indium-labeled octreotide scan and PET-FDG (positron emission tomography-fluorodeoxy-D-glucose) [3].

We describe a rare case of a 50 year old woman who suffered from prolonged severe hypophosphatemia and osteomalacia. Isotope bone scan and computed tomography failed to locate any mass lesion. Only after 4 years, when her clinical condition markedly deteriorated, a small gluteal tumor was found on MRI. Following surgery with partial tumor resection, the patient entered clinical remission with normal phosphorus level. Histology confirmed a phosphaturic mesenchymal tumor.

Patient Description

A 50 year old woman presented with progressive bone and muscle pain. She was previously healthy, with no family history of metabolic bone disease. The initial evaluation revealed mild hypophosphatemia of 2.07 mg/dl (normal range 2.7–5 mg/dl) with normal serum calcium of 8.72 mg/dl (8.5–10.8 mg/dl) and elevated alkaline phosphatase level of 194 U/L (39–128 U/L). Other studies, including complete blood count, erythrocyte sedimentation rate, liver enzymes, renal function, blood glucose and protein electrophoresis were all normal.

Bone scan revealed multifocal non-specific isotope accumulations. CT of the head, chest, abdomen and pelvis revealed diffuse muscular atrophy, osteopenia and osteomalacic bony pseudofractures. Progressively decreasing phosphate levels with abnormal high urinary phosphate excretion of 1594 mg/24 hours (400–1300 mg/24 hr) and very low $1,25(OH)_2$-Vitamin D of 4 pg/ml (16–42 pg/ml) were found. At this point tumor-induced osteomalacia was suspected, but radiographic skeletal survey, bone scan and repeat CT studies failed to identify any tumor. For 4 years the patient was managed with several therapeutic regimens. Initially, oral calcium, vitamin D and oral sodium/potassium phosphate were given, with



A 50 year old woman with oncogenic osteomalacia. **[A]** Axial T1 weighted MRI image shows a small soft tissue mass adherent to the ischium (arrows). GM = gluteal muscles, IT = ischial tuberosity, SN = sciatic nerve. **[B]** The lesion demonstrates marked enhancement after intravenous gadolinium administration (arrows). Note Looser`s zones (Milkman fractures) in the pelvic bones (curved arrow).

symptomatic and laboratory improvement as her phosphate level rose to 2.9 mg/dl and the alkaline phosphatase declined to 158 U/L. Three years later, however, the patient presented with increasing pain and muscle weakness. Despite treatment with high doses of oral phosphate (up to 2.4 g of elemental phosphorus/day) and calcitriol (up to 6 µg/day), her serum phosphate levels dropped to 1.6–1.9 mg/dl. Her clinical condition deteriorated and she was almost bedridden due to severe pain and muscle weakness.

MRI examination revealed a 2 cm soft tissue mass in the left gluteal area, closely attached to the left ischeal bone [Figure A]. The lesion was well defined and showed marked enhancement following gadolinium injection [Figure B]. After meticulous preparation with intravenous phosphate infusion, surgical exploration was performed. Histology confirmed a mesenchymal tumor composed of spindle and stellate cells without atypia, admixed with giant cells and vascular proliferation. One week after surgery the fasting serum phosphorus rose to 2.59 mg/dl, and the treatment with oral phosphate, calcitriol and calcium was gradually reduced. Two years after surgery, the patient is well, with normal muscle strength and no pain. Her phosphate concentration is 3.9 mg/dl and the alkaline phosphatase level is normal.

Comment

Oncogenic osteomalacia is a rare disorder characterized by hypophosphatemia, phosphaturia and osteomalacia mimicking the clinical phenotype of either X-linked or autosomal-dominant hereditary hypophosphatemic rickets. Despite severe disabling clinical presentations, the diagnosis continues to be easily missed. Clunie and colleagues [4] presented the largest series in 2000, where they described four patients who had been followed for up to 23 years. Delay in the correct diagnosis (3–12 years) and prolonged morbidity, despite consultations by several multidiscipline specialists, were common in all the cases. The tumor responsible for the symptoms and signs of oncogenic osteomalacia may be located in almost any part of the body. Most lesions are found in the upper and lower extremities and in the head. Fifty percent of the tumors are located in the skeleton. The lesion is often superficial or subcutaneous, and is easily overlooked. The tumors are of a wide variety of histological types, commonly of mesenchymal origin with prominent fibrous and vascular characteristics. Acquired hypophosphatemic osteomalacia may also be associated with a variety of carcinomas of epidermal and endodermal origin, as well as multiple myeloma, chronic lymphocytic leukemia, fibrous dysplasia and neurofibromatosis [1-3].

Localization of the tumor is important since the diagnosis cannot be confirmed until the tumor is found and removed. The search for tumor includes a thorough physical examination, radiographic survey and bone scintigraphy. CT and MRI of clinically suspicious areas are then indicated. As shown by our case, MRI study of clinically suspicious areas should follow a negative CT examination. Skeletal MRI survey has been recommended to locate the lesion [2]. Seufert et al. [5] demonstrated that these tumors frequently express somatostatin receptor subtype-2 and bind Indium-111 labeled octreotide, a synthetic somatostatin analogue. Administration of isotope-labeled octreotide permits scintigraphic detection of the tumor and octreotide treatment can cause remission of phosphaturia. Surgical removal of the mass alleviates most symptoms. Clinical follow-up is important in these cases and PET-FDG should be performed when abnormal laboratory findings appear.

In summary, imaging has a primary role in making the diagnosis of oncogenic osteomalacia, a tumor that often remains undetected for years because many clinicians are unaware of this rare and unusual paraneoplastic disease. As shown in our case, patients with osteomalcia-rickets not caused by poor nutrition should be thoroughly investigated for tumor-induced disease. Once the occult tumor is found and excised, the patient may enjoy a dramatic return to health with complete reversal of the incapacitating osteomalacia symptoms. A meticulous imaging search for a tiny, inconspicuous mesenchymal tumor should be instituted as a routine in these cases, because when the tumor remains undiagnosed severe clinical deterioration gradually occurs.

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Nothing fixes a thing so intensely in the memory as the wish to forget it

Michel de Montaigne (1533-1592), French essayist