Glomus tumor as a cause of oncogenic osteomalacia

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Summary

Many tumors that occasionally are benign in origin causes hypophosphatemic osteomalacia. Here we present a case of glomus tumor in a 59-year-old man with oncogenic osteomalacia. Diagnosis was made after observation of abnormal increase activity in octreotide scan. The magnetic resonance imaging showed a round lesion in left ankle joint. Surgical excision of tumor was curative and all symptoms and intractable hypophosphatemia improved after few weeks.

KEY WORDS: oncogenic osteomalacia; tumor-induced osteomalacia; hypophosphatemia; acquired hypophosphatemic rickets; glomus tumor.

Introduction

Tumor-induced osteomalacia is a type of hypophosphatemic rickets also known as oncogenic osteomalacia that is an unusual cause of osteomalacia. This is a paraneoplastic syndrome that presents with hypophosphatemia due to renal phosphate wasting and therefore decrease in bone mineralization. The primary tumors usually are small in size and the natural course of disease is usually indolent, hence the detection of tumor site is difficult. However majority of patients cured by surgical resection of primary tumor (1). Usually primary tumors had been detected in hypophosphatemic osteomalacia were benign rather than malignant and the mesenchymal tumors in origin are the main cause of this disease. Generally fatigue, pain, and weakness are the most common presenting symptoms, though normal serum calcium, sever hypophosphatemia, and increased serum alkaline phosphatase are the most common finding in laboratory tests that are important for initial diagnosis (2).

Most of mesenchymal tumors are found in the extremities and head area. The mesenchymal tumors in the head and neck regions are seen in 5-10% of hypophosphatemic osteomalacia (3).

As mentioned before mesenchymal tumor is the most common etiology for tumor induce osteomalacia. Hemangiopericytoma is the most common type though the other more prevalent tumors are fibrous dysplasia, osteosarcoma, chondroblastoma, chondromyxoid fibroma, malignant fibrous histiocytoma, giant cell tumor, haemangioma, paraganglioma, prostate cancer and oat cell carcinoma of the lung, and these tumors occasionally are too small in size that is difficult for detection (4).

Imaging in oncogenic osteomalacia for detecting the primary site of tumor is very important, because the localization of primary tumor is very difficult. Skeletal radiography and scintigraphy are the primary and simple imaging techniques that indicated for diagnosis of these patients (5). Magnetic resonance imaging, indium-labeled octreotide scan and PET-FDG are the additional imaging that has been recommended for patients without obvious tumor (5). Because of limitation in conventional imaging for detection of small tumors, somatostatin-receptor imaging such as octreotide scintigraphy or octreotide SPECT/CT are recommended in patients with hypophosphatemic osteomalacia and normal primary imaging studies (6).

However a large number of tumors remained undetected by octreotide imaging. Consequently studies focused on different SSTR imaging methods such as 68Ga DOTA-TATE PET/CT. It is an effective and promising diagnostic imaging in undetectable small tumors (6).

Various factors including PTH and vitamin D regulate phosphate absorption in the intestine and phosphate reabsorption in kidney. A number of peptides, known as phosphatonins cause hypophosphatemia in patients with oncogenic osteomalacia. These factors are fibroblast growth factor 23, frizzled-related protein 4, fibroblast growth factor 7 and matrix extracellular phosphoglycoprotein (7).

The most important factor is fibroblast growth factor 23, that antibody against it, in difficult case or undetectable primary tumors is an effective therapy for patients with fibroblast-GF23-related hypophosphatemic diseases (8).

Glomus tumors are a hamartoma and also rare, these tumor are 1-5% of all soft tissue tumor of hand and usually are benign, however malignant transformation occasionally may occur. They complain of paroxysmal pain and the tumor may

Table 1 - Details of laboratory tests.

Parameter	Values	Normal values
Fasting calcium	8.5 mg/dL	8.3 - 10.4 mg/dL
Fasting phosphate	1.1 mg/d	3.5 - 5.0 mg/dL
Alkaline phosphatase	873 U/L (GGT 26)	44-147 IU/L
Fasting magnesium	1.97 mg/dl	1.7-2.2 mg/dl
Serum albumin	4.6 mg/dL	3.4-5.4 g/DL
Creatinine	0.9 mg/dL	0.5 - 1.4 mg/dL
Fasting blood glucose	105 mg/dL	70-100 mg/dl
Sodium	144 mg/dL	135 - 145 mg/dL
Potassium	4 mg/dL	3.5 - 5.0 mg/dL
24 hour urine calcium	4.8 mg%, 392 mg/day	100-250 mg/day
24 hour urine phosphate	58 mg%, 406 mg/day	360-1600 mg/day
24 hour urine creatinine	191 mg%, 764 mg/day	500-2000 mg/day
Plasma intact PTH	102 ng/ml	8.0-74.0 ng/ml

be had a local recurrence at the site of resection after 1 to 10 years. Complete excision of this tumor with free margins may be curative (9). This tumor is usually in the extremities and subcutaneous tissue, and usually is benign but other rare sites such as stomach, trachea and lung were reported (10-12).

Case presentation

The patient is a 59-year-old man that diagnosis of oncogenic osteomalacia was made about seven years ago and this case was reported previously in journal of Iranian archive of medicine and was treated for oncogenic osteomalacia with unknown cause. Here we have a new finding in imaging and thus a new pathologic diagnosis for this case. He presents at first with low back pain and gradually progressed to difficulty in walking. Several laboratory investigations revealed normal values except low serum phosphate, low plasma 1,25dihydroxyVitD3 concentration and increased urinary phosphate excretion (Table 1).

The bone mineral densitometry showed osteoporosis. Because of no family history of metabolic disease, diagnosis of tumor induce osteomalacia was made and high dose of phosphate and calcitriol was initiated with partial response. During recent years he has been hospitalized several time for searching of primary tumor when his clinical condition markedly deteriorated in the last time. In new whole body octreotide scan a zone of activity in the left ankle area were seen and magnetic resonance imaging demonstrated an inhomogenous lesion in distal of left leg posterior to tibia (Figure 1). Histopathologic evaluation of the tumor showed vascular spaces lined by normal endothelial cells surrounded by uniform solid proliferation of round cells with perfectly round nuclei and eosinophilic cytoplasm. No necrosis or cytological atypia is seen. Mitoses were very scanty and were 1-2 per 50 high-power fields and all of them were typical ones. According to these findings the tumor diagnosed as glomus tumor, solid variant (Figure 2).

The patient had complete resolution of symptoms few months following complete excision of the tumor.

Discussion

Oncogenic osteomalacia is a type of hypophosphatemic osteomalacia with increase urinary phosphate loss due to phosphatonin effect. It usually secreted from the underlying tumor that may be hidden because of small primary size and indolent course of tumor or confirmed previously. Imaging is a good tool for detection of hidden tumors. Skeletal radiography, Indium labeled octreotide scan, magnetic resonance imaging, PET-FDG are useful for detection of hidden tumors (13). GaTate, is a somatostatin analog, a radiotracer that is used in GaTate PET/CT, it allows whole-body imaging of cell surface expression of somatostatin receptors. The use of GaTate PET/CT together with FDG PET/CT allows identification of tumor (14). Heterogeneity, which provides prognostic information and can be pivotal in guiding biopsy.

Thus in evaluation of hidden tumors magnetic resonance imaging, FDG PET/CT, GaTate PET/CT and octreotide whole body scan with different radiotracer including indium 111 and gallium 68 are useful (15, 16).

The most common site of mesenchymal tumors in oncogenic osteomalacia is the lower extremities, followed by the head and neck area. In the head and neck area the extra-oral sites are more common than the intra-oral sites. The most common location in the extra oral sits is paranasal sinuses followed by the mandible (17).

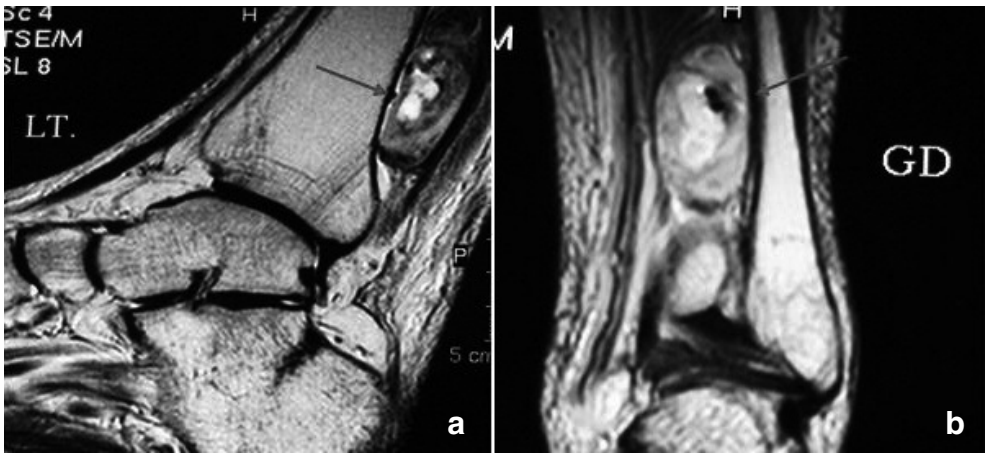

Figure 1 - T2 weighted and post contrast MR images: a lesion demonstrated in distal of left leg posterior to tibia (arrows). It has inhomogenous iso and hypersignal intensity on T2 weighted image and showing diffuse enhancement on post contrast image.

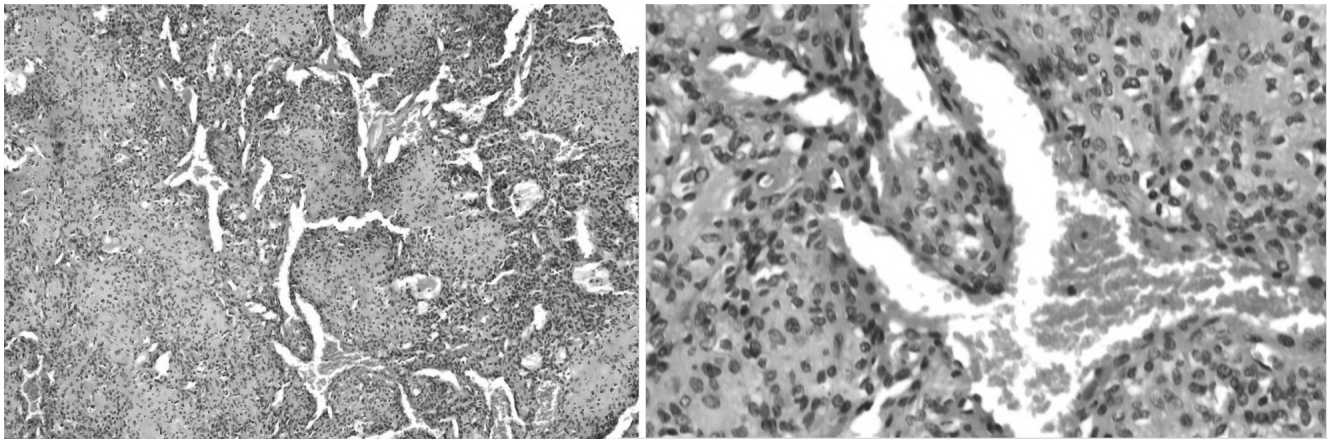

Figure 2 - Histopathologic evaluation of the tumor showed vascular spaces lined by normal endothelial cells surrounded by uniform solid proliferation of round cells with perfectly round nuclei and eosinophilic cytoplasm.

The primary tumor in oncogenic osteomalacia is difficult to detected and diagnosed, because these tumors usually are too small in size and frequently without local signs and symptoms. According to the previously reported cases in literature, difficulty in tumor detection, results in a considerable delay in diagnosis and consequently a delay between the onset of symptoms and surgical resection (18).

Patients with oncogenic osteomalacia present with nonspecific symptoms including fatigue, bone pain, and musculoskeletal weakness that make some difficulty in diagnosis and often lead to a delay in treatment. The median delay in diagnosis was reported about 7.67 years after first presentation of symptoms (19, 20).

Acquired hypophosphatemic osteomalacia usually has diagnostic difficulties, a condition associated with increased renal phosphate clearance and low circulating 1,25dihydroxyvitamin D3. Many patients with this disease are shown to have benign tumors of mesenchymal origin with prominent fibrous and vascular characteristics. Cure is possible after diagnosing and detection of underlying primary tumor with surgical resection. Moreover, developmental evidence supports the role 1α-hydroxylase activity and renal tubular cell phosphate transport in these tumors (21).

The first case of glomus tumor in sinosal area with oncogenic osteomalacia had been reported in Chinese journal of otorhinolaryngology head and neck surgery in 2014 (21, 22).

According to PubMed and Medline search this is the second case of glomus tumor with hypophosphatemic osteomalacia. There are a few report of glomangiopericytoma with hypophosphatemic osteomalacia that is not histologically similar to glomus tumor (23).

Glomus tumor is a neoplasm with mesenchymal origin that usually evolves in the peripheral soft tissue, especially in the distal part of fingers and toes. The glomus tumors usually are benign, and the malignant type is very rare. Diagnosis of malignant glomus tumor is based on the nuclear atypia, necrosis, atypical mitosis and increased mitotic rate (11).

The origin of glomus tumor is from smooth muscle cells and perivascular glomus bodies. Although the usual site of this tumor is the dermis or subcutaneous tissue, it can also occur infrequently in visceral organs such as lung, trachea, stomach, renal pelvis, cecum, and ovary that they are usually benign (11).

This tumor is usually benign and unusual location of this tumor creates some difficulty for detection of primary tumor site. Tumor induces oncogenic osteomalacia usually detected after presentation of complications and unexpected symptoms. The treatment of choice is excision of the tumor by surgery.The sign and symptoms and also abnormal laboratory tests including high alkaline phosphatase and low serum phosphate level will be disappear and recover after complete excision of primary tumor.

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