Tumor-induced hypophosphatemia

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ABSTRACT

Significant hypophosphatemia is commonly due to Vitamin D deficiency. Any sporadic onset of hypophosphatemia in adults warrants workup to identify alternate causes. Hypophosphatemia may also be the only manifestation of an occult malignancy. A high index of clinical suspicion can help diagnose such conditions in early stages. Prompt treatment of the cause can correct this biochemical abnormality. We describe a case report of a woman presenting with severe hypophosphatemia and osteomalacia, leading eventually to the diagnosis of a phosphaturic mesenchymal tumor of the temporo-occipital bone. Surgical resection of tumor led to normalization of the biochemical parameters as well as a complete clinical recovery.

Key words: Hypophosphatemia, malignancy, osteomalacia

Introduction

Tumor-induced osteomalacia/hypophosphatemia (TIO) is a rare acquired disorder. Patients typically present with a history of chronic bone pain, fractures, and proximal motor weakness. The tumors are often benign, small, and difficult to detect. A recent report has suggested that fibroblast growth factor 23 (FGF-23) is the most reliable marker for the detection of these tumors.[1] We report a case of TIO, the tumor being in the posterior cranial fossa. The tumor was successfully resected by a left retromastoid craniotomy approach. Serum phosphorus levels and FGF-23 levels recovered to their normal range immediately after the surgery. The diagnostic evaluation, etiology of hypophosphatemia, and treatment are discussed.

Case Report

A 48-year-old woman consulted an orthopedic surgeon in June 2013 with complaints of pain in both hip joints for 2 months. The pain progressively worsened over 2 months and led to a difficulty in standing up along with severe difficulty in walking. On clinical examination, there was marked proximal muscle weakness in the lower limbs. X-rays revealed severe osteopenia in both hip joints. The blood chemistry showed serum calcium to be 9.0 mg/dl, serum phosphorus - 2.1 mg/dl, serum alkaline phosphatase - 136 IU/ml, intact parathyroid hormone - 61.5 pg/ml, Vitamin D - 19.3 nmol/L, and serum thyroid-stimulating hormone - 10.3 mIU/L. Her renal and liver functions tests were normal. She was initially treated with oral calcitriol, oral calcium supplements (calcium carbonate 500 mg BID) along with parenteral cholecalciferol (6 lac IU) once a month, and thyroxin was added for 6 months. However, there was significant improvement neither in the proximal motor weakness nor the degree of pain. Her rechecked laboratories revealed high Vitamin D levels of 310 nmol/L with a more severe hypophosphatemia (1.5 mg/dl). These results prompted the primary care physician to stop Vitamin D supplements and she was initiated on teriparatide. She did not show significant clinical improvement even with this over the next 6 months. She

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needed support for walking and she stopped injection teriparatide in September 2014.

Her hip and thigh pain worsened progressively and she became bedridden. A magnetic resonance imaging (MRI) done at this point was suggestive of a left femoral neck insufficiency fracture, mild degenerative changes in both hip joints, and stress edema of both acetabulae. Twenty-four-hour urinary phosphorus was 901 mg (normal 500–1000 mg).

A few months later, in January 2015, she developed new symptoms in the form of tinnitus and heaviness of the left ear. An MRI brain and audiometry were done which was normal. Coincidentally, around this time, she was also started on oral phosphate supplements and within a week, she showed marked improvement. Her pain decreased and she was able to walk with support. Blood chemistry showed improvement in serum phosphorus level to 2.2 mg/dl within 2 weeks of starting the supplement.

She was referred to our center for further evaluation of all her problems in March 2015. On evaluating her symptoms, persistent hypophosphatemia with no obvious cause, and persistent new-onset auditory symptoms, there was possibility of TIO. Somatostatin positron emission tomography (PET) scintigraphy was done which revealed a large lytic expansile lesion in left occipital bone including the clivus and occipital condyles with erosion of the mastoid and temporal bone [Figure 1]. Serum FGF-23 was tested, which was found to be very high - 725 RU/ml (normal <180 RU/ml).

Another MRI brain with contrast confirmed a left occipitotemporal bone space occupying lesion (SOL) [Figure 2]. Angioembolization of the tumor was done on March 30, 2015, with polyvinyl alcohol particles, and left retromastoid craniotomy, and excision of the tumor was done on the next day. Her phosphate supplements were stopped perioperatively.

Histopathology of tumor was consistent with the diagnosis of a phosphaturic mesenchymal tumor [Figure 3]. Postsurgery, her serum phosphorus level improved fairly quickly, over 4–5 days. Her hip pain and weakness gradually improved. She started walking without support. We stopped all her treatment. A repeat FGF-23 done on the 10th day postsurgery showed a significant drop to 155 RU/ml. Serum phosphorus also improved to 2.6 mg/dl within 10 days and stayed at the same level even after a month postsurgery without any phosphate supplements.

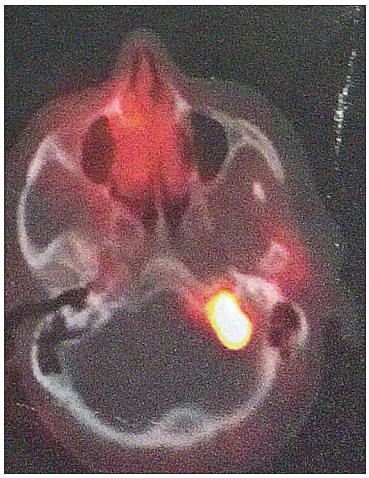

Figure 1: Positron emission tomography scintigraphy revealed large lytic expansile lesion in left occipital bone including the clivus and occipital condyles with erosion of the mastoid and temporal bone

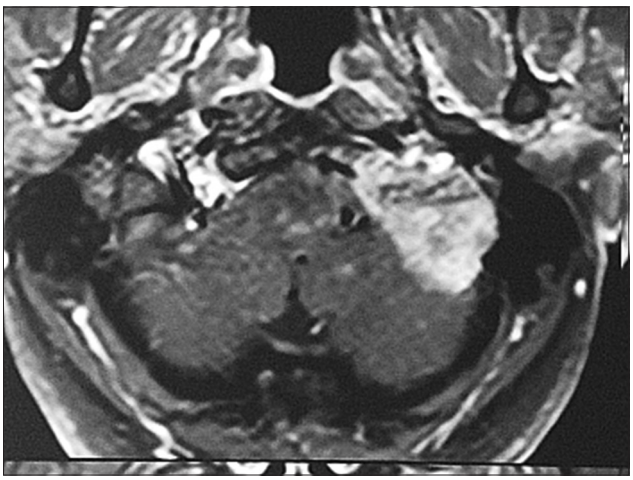

Figure 2: Magnetic resonance imaging brain with contrast confirmed a large left occipitotemporal bone tumor with lytic lesion

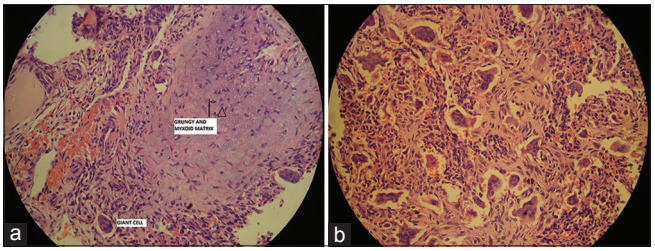

Figure 3: (a) Tumor histopathology shows grungy matrix with osteoclast-like giant cells and mononuclear cell infiltration suggestive of phosphaturic mesenchymal tumor (b) tumor histopathology shows osteoclast-like multinucleated giant cells and mononuclear cells infiltration suggestive of phosphaturic mesenchymal tumor

Discussion

TIO is an uncommon condition. These tumors are usually mesenchymal or mixed connective tissue arising from either soft tissues or bone.[2] They are benign in nature. Even in histologically malignant tumors, local recurrence

or distant metastasis is extremely rare.[2] The most common types of these tumors are hemangiopericytomas.[3] They are located mostly in lower extremities, but arms, face, skull, and neck are other potential sites. Gonzalez-Compta *et al*.[4] reviewed 21 cases of osteomalacia induced by head and neck tumors. The authors reported that 57% of these tumors were located in the sinonasal area and that the mean age at diagnosis was 45 years. Average time from the onset of symptoms and diagnosis is usually more than 2.5 years. Reasons for this delay in diagnosis are the occult nature of the disease, nonspecific symptoms, and the fact that serum phosphate levels are not part of routine chemistry panel.[1] This slow-growing tumor can occur in unusual sites in the body. Pirola *et al*.[5] reported oncogenic osteomalacia of the thoracic spine. However, oncogenic osteomalacia originating from the middle cranial fossa is very rare.

Biochemical analysis often detects abnormalities in serum chemical concentrations. Generally, those patients who have hypophosphatemia have normal calcium levels and a low 1,25-dihydroxyvitamin D concentration. The most reliable marker for the detection of TIO is FGF-23,[6] which is a secreted peptide hormone overexpressed by the tumor in patients with TIO. Fukumoto[7] reported that FGF-23 suppresses phosphate reabsorption by decreasing expression levels of the Type 2a and 2c sodium phosphate cotransporter in the brush border membrane of proximal tubules. At the same time, FGF-23 reduces serum 1,25-dihydroxyvitamin D levels in part by suppressing 1,25-dihydroxyvitamin D production. This process leads to hypophosphatemia. Symptoms resolved once the tumor is totally removed. Therefore, it is necessary to consider the total excision of the tumor as a treatment strategy. To locate these tumors, several imaging modalities have been mentioned in literature, which are used. These include computed tomography (CT), MRI, PET-CT, octreotide and sestamibi scans, and even bone scintigraphy.[8]

Our patient initially underwent whole body MRI which did not reveal any tumor. Later, somatostatin receptor imaging was done which revealed a tumor near the left posterior cranial fossa [Figure 1]. MRI brain with contrast then showed a tumor in left occipital bone including clivus and occipital condyle with temporal bone erosion [Figure 2] which on biopsy revealed phosphaturic mesenchymal tumor [Figure 3].

Conclusions

We treated a case of hypophosphatemia associated with TIO. The tumor was successfully resected by using a left retromasoid craniotomy approach. Phosphate levels recovered to normal immediately after the surgery.

The pattern of abnormalities in serum Ca, P, Vitamin D, alkaline phosphatase, and parathyroid hormone may give a clue to the underlying cause of osteomalacia. Osteomalacia of tumor origin should be suspected in the relevant clinical context.

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Conflicts of interest
There are no conflicts of interest.

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