A case of oncogenic osteomalacia due to occult nasal sinus tumor

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Summary

This paper shows a case of oncogenic osteomalacia in a 35-year-old man who presented with a 2-year history of generalized pain and progressive weakness of lower limbs, eventually became bed bound. At admission he had severe hip pain resulting from atraumatic femoral neck fractures. Laboratory investigations revealed hypophosphatemia, hyperphosphaturia, normocalcemia, elevated alkaline phosphatase, and normal serum levels of parathormone and 25-hydroxyvitamin D. Serum FGF-23 was elevated. Imaging showed osteoporosis and insufficiency fractures of the femoral neck. Whole body functional imaging failed to reveal any areas of increased activity. However, on computed tomography (CT) and magnetic resonance (MR) imaging, a tumor was discovered at left nasal cavity. The patient was treated with phosphate supplements and vitamin D, but his hypophosphatemia persisted. The tumor was surgically removed. Histologically, the tumor was diagnosed as variant of a sinonasal hemangiopericytoma-like tumor. After surgery, his symptoms were relieved and biochemical parameters normalized.

KEY WORDS: oncogenic osteomalacia; hypophosphatemia; fibroblast growth factor 23; nasal tumor; hemangiopericytoma.

Introduction

Oncogenic hypophosphatemic osteomalacia (OHO) is a rare but curable cause of metabolic bone disease. Phosphaturia of oncogenic osteomalacia results from excess fibroblast growth factor 23 (FGF 23) that is secreted from tumor (1). Causative tumors are of mesenchymal origin and are often small and difficult to locate (2). This paraneoplastic syndrome is characterized by hypophosphatemic osteomalacia with hyperphosphaturia, low plasma 1,25-dihydroxyvitamin D, and usually a normal serum calcium, parathormone, and 25-hydroxyvitamin D (3). Patients usually present with a history of bone pain and muscle weakness, which is often disabling. Amongst these tumors that cause osteomalacia, only in a handful of case reports the tumor is located in the nasal fossa and craniofacial sinuses (4-8). However, most of such tumors located in nasal fossa were detected by functional imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET). What is most intriguing in our case was failure to detect any areas of increased activity. Therefore, we stress that careful clinical examination including paranasal sinuses (PNS) may be rewarding in such cases.

Case report

A 35-year-old man presented with a 2-year history of diffuse bone pain affecting the spine, ribs and pelvis. He had proximal muscle weakness and difficulty walking. At presentation, he found difficulty in weight bearing activity and progressive musculoskeletal disability leading to disruption of his activities of daily living. He eventually became bed bound. He had no symptoms referable to his nose or sinuses. He had no history suggestive of malabsorption, or family history of similar symptoms. Physical examination revealed hip tenderness. Initial otorhinolaryngological evaluation was unremarkable. His symptoms were suggestive of malabsorption, or family history of similar symptoms. Physical examination revealed hip tenderness. Initial otorhinolaryngological evaluation was unremarkable. His medications included only intermittent analgesics, which were largely ineffective. Insufficiency fractures of bilateral femoral neck and right ischiopubic ramus were detected on plain radiograph. Non-contrast CT scan of pelvis showed intracortical and trabecular bone resorption (Figure 1A, B). Complete blood cell count, liver function tests, serum total calcium, creatinine, glucose, sodium and potassium, were normal. His initial serum phosphorus concentration was 1.5 mg/dL (normal, 2.5 to 4.5). Serum total alkaline phosphatase was substantially increased at 1756 U/L (normal, 98-251). Both serum intact parathormone (PTH) and 25-hydroxyvitamin D levels were normal. Urine biochemistry confirmed a low tubular reabsorption of phosphate (TRP). Serum FGF23 measured using a C-terminal ELISA was more than 5 times the upper limit of normal. His relevant biochemical abnormalities are summarized in Table 1. DEXA scan of his lumbar spine showed a bone density of 0.592 g per cm² with a Z-score of –4.0, and hip showed 0.458 g per cm² with a Z-score of –3.8. Whole body ⁹⁹mTc sestamibi scintigraphy was negative for any malignant lesion. On computed tomography (CT) and magnetic resonance imaging (MRI), a tumor was discovered in the superior aspect of left nasal cavity with broad area of contact with nasal septum and lateral wall of nasal cavity (Figure 2A, B). Non-obvious orbital extension is noted. He received oral supplements of 1.5 g of phosphate and 0.75 microgram of vitamin D (calcitroil) every day in divided...
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Figure 1 A, B - (A) Frontal pelvic radiograph showing generalized osteopenia, and bilateral impacted subcapital fractures of the femoral neck with coxa vara deformity; (B) Axial non-contrast CT scan of pelvis at the level of hip joint showing bilateral impacted fractures of femoral neck and fracture of left quadrilateral plate of acetabulum.

Figure 2 A, B - (A) Non-contrast axial CT scan revealed a soft tissue density mass lesion (white arrow) in the left nasal cavity with focal areas of hypodensity; (B) Coronal T2W MR image showing an well defined hyperintense mass lesion with cerebriform morphology (white arrow) in the superior aspect of left nasal cavity with broad area of contact with nasal septum and lateral wall of nasal cavity.

Table 1 - Biochemical evaluation in the patient before and after tumor excision (2nd week).

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative</th>
<th>Post-operation</th>
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<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.1</td>
<td>9.8</td>
<td>9-11</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
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<td>2.5</td>
<td>2.5-4.5</td>
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<tr>
<td>Serum alkaline phosphatase (IU/L)</td>
<td>1756</td>
<td>1182</td>
<td>98-251</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>49</td>
<td>25.91</td>
<td>15-65</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)</td>
<td>27.31</td>
<td>32</td>
<td>30-50</td>
</tr>
<tr>
<td>24 hour urine phosphate (mg/24hr)</td>
<td>1752</td>
<td>729</td>
<td>400 -1300 mg</td>
</tr>
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In view of persistent hypophosphatemia despite treatment, we have a concern for oncogenic osteomalacia and a decision was made to remove the possible causative tumour. Otorhinolaryngology department was consulted and this time nasal endoscopy revealed a smooth pinkish mass filling the left nasal cavity. Complete removal of the tumor was performed through lateral rhinotomy. The specimen showed characteristic features of an hemangiopericytoma, which included the presence of branching staghorn like blood vessels lying in a loose textured hyalinised stroma, surrounded by round to spindle shaped cells with scanty cytoplasm and vesicular nuclei. The tumor showed benign cytologic features (Figure 3A, B). Post-surgery, he experienced clinical improvement of his musculoskeletal pains with normalization of the serum phosphorus and phosphate tubular reabsorption. Table 1 summarizes the laboratory findings before and after 2 weeks following the surgical tumor resections.

**Discussion**

This patient had a classic clinical picture of a severe hypophosphatemic osteomalacia due an occult nasal heman-giopericytoma. Oncogenic osteomalacia is an uncommon debilitating metabolic bone disease that occurs in the presence of neoplastic tissue of mesenchymal origin. Phosphaturic mesenchymal tumor is usually located in soft tissue, but intrasosseus as well sinonasal locations have been documented in the past. The mean age at onset of symptoms is 40 years and occurs in both sexes (9). Clinically, it is characterized by slowly progressive musculoskeletal pain, muscle weakness, fatigue, and skeletal abnormalities, including recurring long-bone and vertebral fractures in some cases. Associated biochemical abnormalities are highly characteristic including low maximal renal TRP, hypophosphatemia, phosphaturia, and inappropriately low circulating concentrations of serum 1,25-dihydroxyvitamin D. Phosphaturia in OHO results from tumoral production of phosphaturic factors such as FGF23, which inactivates the sodium-phosphate pump in the proximal tubule of the kidney preventing reabsorption of phosphate (10), and decreases the 1-hydroxylation of 25-hydroxyvitamin D (11). Measurement of serum FGF23 has emerged as an helpful clinical tool. (12) An elevated level in a patient with suggestive features of OHO should mandate a thorough radiological work-up to locate the causative lesion. Tumors associated with this disorder are usually small and are slow growing, and they often are undetected by physical examination and commonly available imaging techniques. Currently, whole body MRI short tau inversion recovery (STIR) is the anatomical imaging modality of choice in the investigation of OHO (13). Suggestive lesions identified using this technique can then be further investigated by focused imaging. CT of the nasal sinuses should be undertaken in patients in whom the MRI STIR is unhelpful or equivocal. F-18 fluorodeoxyglucose positron emission tomography, with computed tomography (FDG-PET/CT), has proven to be most sensitive functional imaging for localizing TIO tumors (14). Whole-body 99mTc sestamibi scintigraphy can also help in locating these lesions and may be a useful and cost-effective initial strategy (15). Emphasis should be placed on making sure these imaging tests cover the entire body, from head to toe, including the hands and feet.

Tumors associated with OHO have included a wide range of histopathological diagnoses, and despite the description and classification scheme proposed by Folpe et al. (16), many clinicians and pathologists continue to be unaware of these tumors as a distinct entity. The prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMTMCT), which is characterized by a distinctive admixture of bland spindled cells with low nuclear and mitotic activity, osteoclast-like giant cells, prominent and variously sized vasculature, smudgy to calcified cartilage-like matrix, and osseous metaplasia. Sinonasal PMT is the rarest variant with its own peculiar histologic features, often differs from the mixed connective tissue type, and more closely resembles...
an hemangiopericytoma-like variant (17). In our case, pathologic examination revealed hemangiopericytoma which is considered main cause of oncogenic osteomalacia. The sinonasal variant of hemangiopericytoma generally has a more benign clinical course (18). To date, immunohistochemistry has not shed light on the cell of origin of these neoplasias, but only served to confirm their mesenchymal origin. However, considering some overlapping histological features between PMTMCs and hemangiopericytomas, it may be useful to assess tumoral FGF-23 expression by immunohistochimical analysis in patients with OHO. PMT is usually located in soft tissue, and sinonasal locations have rarely been reported. The largest published case series of OHO reported that sinus tumours in the account for 5-10% of cases (16). Kenealy et al. (7) found two subjects (22% of the series) having OHO caused by benign tumours of the nasal sinuses. Any site can be affected, with the lower extremities being the most common (40-50% of cases), followed by the head and neck area (15-20%), trunk (15-20%) and upper extremities (around 10%) (13). The treatment of choice for OHO is resection of the tumor with a wide margin to prevent recurrences. In our case, complete removal of the offending tumor results in improvement of symptoms of osteomalacia and biochemical abnormalities. When the tumor cannot be localized or is not surgically resectable, medical therapy with phosphate supplementation and calcitriol or alfalcaldiol is used. When initiating treatment, it is prudent to check weekly labs to guide titration of medications until treatment targets are reached.

To conclude, OHO is an important diagnosis, since localization and resection of the underlying tumor results in cure of the condition. Serum phosphate should be measured in all patients presenting with osteomalacia and/or unexplained musculoskeletal symptoms. Hemangiopericytoma involving nasal sinuses can be associated with osteomalacia as a part of paraneoplastic syndrome. A step-wise approach that involves functional imaging, followed by anatomical imaging is usually successful. Dedicated imaging of the nasal sinuses should be undertaken when patient presents nasal mass with osteomalacia and diagnosis of oncogenic osteomalacia is likely.

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