

CASE REPORT

Oncogenic osteomalacia caused by occult nasal mesenchymal tumor: a monster in the cave

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Abstract

Authors describe 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 bedbound. At admission, he had severe hip pain resulting from bilateral femoral neck fractures. Laboratory investigations revealed hypophosphatemia, hyperphosphaturia, normocalcemia, elevated alkaline phosphatase and normal serum levels of parathormone and 25-hydroxyvitamin D. Serum fibroblast growth factor 23 (FGF23) level was elevated. A radiographic skeletal survey showed osteoporosis and insufficiency fractures of the femoral neck. A whole-body functional imaging failed to reveal any areas of increased activity. However, on computed tomography and magnetic resonance imaging of the head and neck region, a tumor was discovered at left nasal cavity. The tumor was surgically removed. After surgery, his symptoms were relieved and biochemical parameters normalized. We stress that careful clinical examination including nose and paranasal sinuses may be rewarding in cases with hypophosphatemic osteomalacia.

INTRODUCTION

Oncogenic osteomalacia (OOM) is an uncommon but potentially curable cause of metabolic bone disease. Phosphaturia of OOM results from excess fibroblast growth factor 23 (FGF23) and other phosphatonins that is secreted from mesenchymal tumors [1]. Biochemical abnormalities associated with this paraneoplastic syndrome include hypophosphatemia, hyperphosphaturia, inappropriately normal/low serum 1,25-dihydroxyvitamin D and usually a normal serum calcium, parathormone and 25-hydroxy vitamin D. Among these tumors that cause osteomalacia, only in a handful of cases, the tumors are located in the nasal fossa and craniofacial sinuses [2, 3]. However, in majority of the cases, successful localization of the offending neoplasm was accomplished by using 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.

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 in walking. At presentation, he had difficulties in weight bearing activity and progressive musculoskeletal disabilities leading to disruption of his activities of daily living. He had no symptoms referable to his nose or sinuses. He had no known family history of metabolic bone disease. Physical examination revealed hip tenderness bilaterally. Initial otorhinolaryngological evaluation was unremarkable.

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Laboratory evaluation revealed a decreased serum phosphorus level of 1.5 mg/dl (normal, 2.5–4.5), an elevated serum total alkaline phosphatase concentration of 1756 U/l (normal, 98–251) and a low normal serum 1,25-dihydroxyvitamin D value of 16 pg/ml (normal, 19.6–54.3). Both serum intact parathormone and 25-hydroxyvitamin D levels were normal. Urine biochemistry confirmed a low renal tubular resorption of phosphate. Serum FGF23 measured using a carboxy-terminal FGF-23 ELISA was more than five times the upper limit of normal. A radiographic skeletal survey revealed diffuse osteopenia and insufficiency fractures of bilateral femoral neck and right ischiopubic ramus. A non-contrast computed tomography (CT) scan of pelvis showed intracortical and trabecular bone resorption (Fig. 1A and B). DXA scan of his lumbar spine showed a bone density of 0.592 g/cm² with a Z-score of –4.0, and hip showed 0.458 g/cm² with a Z-score of –3.8. The clinical presentation and laboratory findings suggested a diagnosis of OOM. Therefore, an effort was made to localize the tumor. Surprisingly, a whole-body ^{99m}Tc-sestamibi scintigraphy failed to detect any area with increased tracer uptake. However, on CT and magnetic resonance imaging (MRI), a tumor was discovered in the superior aspect of left nasal cavity (Fig. 2A and B).

Meanwhile, we have to start phosphate (1.5 g/day) and calci-triol (0.75 µg/day) supplementations considering his debilitating symptoms. A decision was made to remove the possible causative tumor. The Otorhinolaryngology department was consulted and this time nasal endoscopy revealed a smooth pinkish mass in the region of left choana. Complete removal of the tumor

was performed through lateral rhinotomy and at operation, the mass was found to be highly vascular. On subsequent microscopic examination, the specimen showed characteristic features of a hemangiopericytoma with the presence of branching staghorn-like blood vessels lying in a loose textured hyalinized stroma, surrounded by round- to spindle-shaped cells with scanty cytoplasm and vesicular nuclei (Fig. 3A and B). Post-surgery, he experienced clinical improvement of his musculoskeletal pains with normalization of the serum phosphorus and tubular phosphate reabsorption. Table 1 summarizes the laboratory findings before and after 4 weeks following the surgical tumor resections.

DISCUSSION

This patient had a classic clinical picture of a severe hypophosphatemic osteomalacia due an occult nasal hemangiopericytoma. OOM 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 intraosseous 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. 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.

Phosphaturia in OOM results from tumoral production of phosphaturic factors such as FGF23, which inactivates the sodium-phosphate pump in the proximal tubule of the kidney preventing

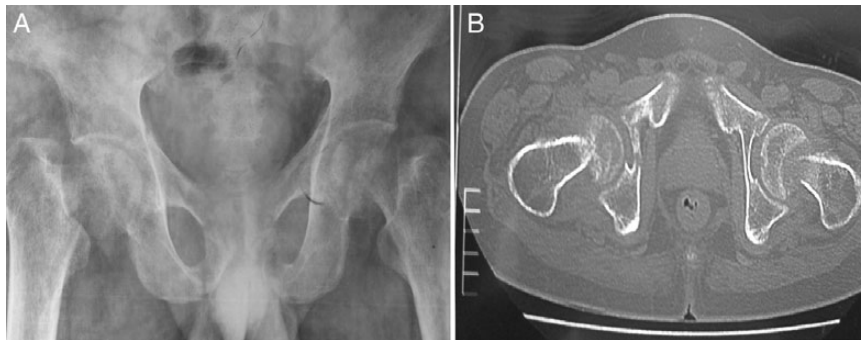


Figure 1: (A) Frontal pelvic radiograph showing generalized osteopenia, and bilateral impacted subcapital fractures of the femoral neck with coxa vara deformity. (B) Axial non-contrast CT scan of pelvis at the level of hip joint showing bilateral impacted fractures of the femoral neck and fracture of the left quadrilateral plate of acetabulum.



Figure 2: (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 T2-weighted MR image showing a well-defined hyperintense mass lesion with cerebriform morphology (white arrow) in the superior aspect of left nasal cavity with a broad area of contact with nasal septum and a lateral wall of nasal cavity.

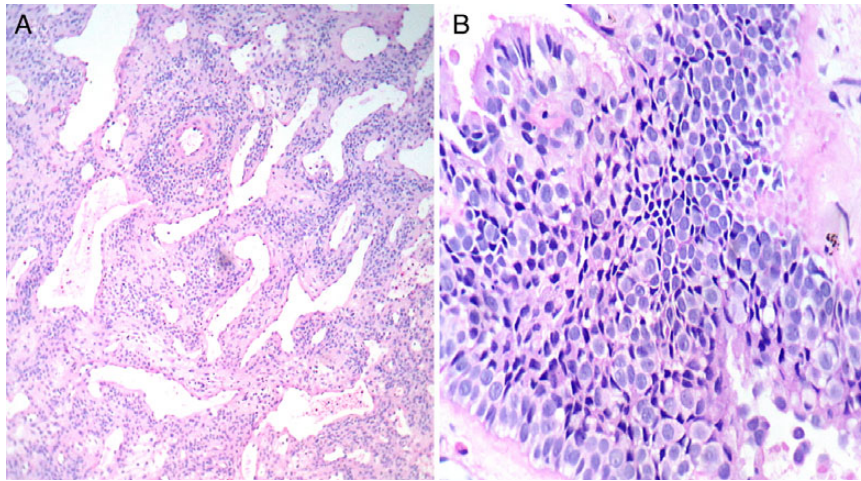


Figure 3: (A) Microscopically, the tumor composed of cells arranged in sheets in a hyalinized stroma and multiple stag horn-shaped blood vessels lined by flat endothelial cells within the mass (hematoxylin and eosin, $\times 100$). (B) Photomicrograph showing round to oval cells with minimal pleomorphism/mitotic activity, nuclei are vesicular with the presence of prominent small nucleoli in a hyalinized stroma; part of respiratory epithelium with pseudostratified ciliated columnar cells also present (hematoxylin and eosin, $\times 400$).

Table 1: Preoperative and postoperative laboratory results

	Preoperative	Postoperative	Normal values
Serum calcium (mg/dl)	9.1	9.8	9–11
Serum phosphate (mg/dl)	1.4	2.5	2.5–4.5
Serum alkaline phosphatase (IU/l)	1756	1182	98–251
Parathyroid hormone (pg/ml)	49	25.91	15–65
25-Hydroxyvitamin D (ng/ml)	27.31	32	30–50
1,25-Dihydroxyvitamin D (pg/ml)	16	60	19.6–54.3
FGF23 (RU/ml)	845.7	–	0–150
TRP	0.49	0.85	0.82–0.95
24 h urine phosphate (mg/24 h)	1752	729	400–1300
24 h urine calcium (mg/24 h)	110	–	50–300

RU, relative units; FGF, fibroblast growth factor; TRP, tubular reabsorption of phosphate.

reabsorption of phosphate [4] and decreases the $1-\alpha$ hydroxylation of 25-hydroxyvitamin D. An elevated level of serum FGF23 in a patient with suggestive features of OOM should mandate a thorough radiological workup to locate the causative lesion [5]. 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 with short tau inversion recovery (STIR) sequence is the anatomical imaging modality of choice in the investigation of OOM [6]. CT of the nasal sinuses should be undertaken in patients in whom the MRI-STIR is unhelpful or equivocal. F-18 FDG-PET, with CT (FDG-PET/CT), has proved to be most sensitive functional imaging for localizing these tumors [7]. Whole-body ^{99m}Tc -sestamibi scintigraphy can also help in locating these lesions and may be a useful and cost-effective initial strategy [8]. However, the sensitivity of this scanning techniques used for this indication has not been thoroughly evaluated. In addition, because of the highly variable underlying pathologic features and locations observed among these lesions, ^{99m}Tc -sestamibi may not consistently localize these tumors. An alternative scanning technique should be considered if initial sestamibi scanning fails. Emphasis should be placed to ensure that imaging tests cover the entire body, from head to toe, including the hands and feet.

Tumors associated with OOM have included a wide range of histopathological diagnoses, and the description and classification scheme was proposed by Folpe *et al.* [9]. The prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant; PMTMT), which is characterized by a distinctive admixture of bland spindled cells with low nuclear and mitotic activity, osteoclast-like giant cells and prominent and variously sized vasculature. Sinonasal PMT is the rarest variant with its own peculiar histologic features, often differs from the mixed connective tissue type and more closely resembles a hemangiopericytoma-like variant [10]. In our case, pathologic examination revealed hemangiopericytoma which is considered the main cause of OOM. Considering some overlapping histological features between PMTMTs and hemangiopericytomas, it may be useful to assess tumoral FGF23 expression by immunohistochemical analysis in patients with OOM.

The largest published case series of OOM reported that sinus tumors account for 5–10% of cases [9]. Kenealy *et al.* [3] found two subjects (22% of the series) having OOM caused by benign tumors 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%) [6]. The treatment of choice for OOM is resection of the tumor with a wide margin to prevent recurrences. In

our case, complete removal of the offending tumor resulted 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 alfacalcidol is used. When initiating treatment, it is prudent to check weekly laboratories to guide titration of medications until treatment targets are reached.

To conclude, OOM is an important diagnosis, since localization and resection of the underlying tumor results in cure of the condition. In adults with hypophosphatemic osteomalacia who lack a family history, the diagnosis of OOM should be considered in the presence of characteristic biochemical abnormalities. Serum phosphate should be measured in all patients presenting with osteomalacia and/or unexplained musculoskeletal symptoms. A step-wise approach that involves functional imaging, followed by anatomical imaging, is usually successful. Diagnostic imaging tests, initially addressed to the head and neck region, where the tumors are more prevalent, may be rewarding.

AUTHORS' CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

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