Oncogenic osteomalacia due to phosphaturic mesenchymal tumor of the craniofacial sinuses

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Summary

Background: **The phosphaturic mesenchymal tumor of the craniofacial sinuses (mixed connective tissue variant) is an extremely rare, distinctive paraneoplastic syndrome that is frequently associated with oncogenic osteomalacia.**
Methods: **In this report is presented a case of 22 years old man indicated four years of progressive generalized pain and weakness, eventually becoming wheel-chair bound. His current presentation was for chest pain resulting from atraumatic rib fractures.**
Results: **Imaging showed osteoporosis and multiple insufficiency fractures. CT and MRI showed an ethmoid mass. He had no symptoms referable to his nose or sinuses.**
Conclusions: **The ethmoid lesion was completely excised, the patient's laboratory parameters returned to normal levels and the patient's symptoms disappeared.**

KEY WORDS: phosphaturic mesenchymal tumor; oncogenic osteomalacia; insufficiency fracture; diagnostic imaging.

Introduction

Phosphaturic mesenchymal tumor (PMT) is an uncommmon tumor that may cause oncogenic osteomalacia (1-6). This is due to an over expression of fibroblast growth factor-23 (FGF-23), a recently described protein capable of inhibiting renal tubular phosphate transport (6). Patients usually complain of a long history of bone pain and muscle weakness, often being so severely affected that they are unable to walk and become wheel-chair bound. We describe herein the radiological imaging and the clinic-pathologic features of a rare case of PMT which involved the craniofacial sinuses of the skull base.

Case report

A 22-year-old man who had been wheel-chair bound for one year and prone to atraumatic fractures for two years, was admitted to the hospital. The patient had no past medical history of note and no abnormality on physical examination. Laboratory investigations revealed hypophosphatemia, hyperphosphaturia, normocalcemia, normocalciuria, elevated alkaline phosphatase, and normal serum levels of parathormone and osteocalcin. Skeletal radiographs revealed homogeneus and fuzzy appearance due to the decline of contrast differences between bone marrow and calcified bone and bone scintigraphy findings were suggestive of osteomalacia. On computed tomography (CT) and magnetic resonance (MR) imaging, a tumor was discovered at the vault of the rhinopharynx,

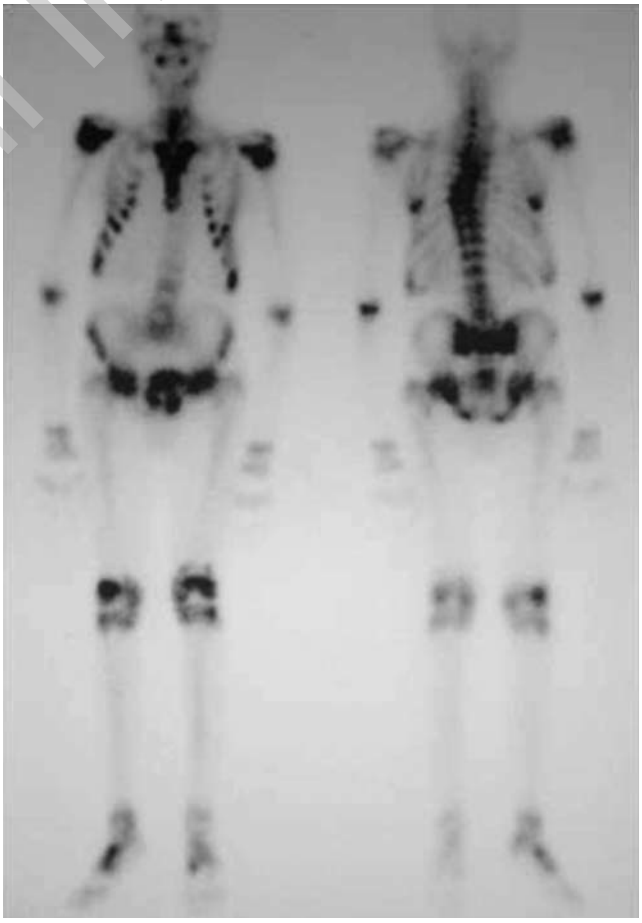

Figure 1 - Whole body bone scintigraphy (anterior and posterior views) shows multiple areas of increased uptake in the thoracic spine, ribs, pelvis and limbs. Note the characteristic H-shaped pattern in the sacrum, typical of insufficiency fractures.

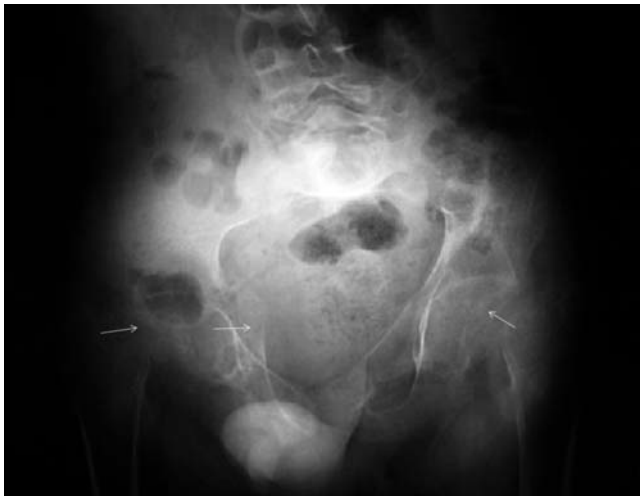

Figure 2 - Frontal pelvic radiograph shows generalized osteopenia, and insufficiency fractures of the femoral neck and pubic rami bilaterally (white arrows) with decline of contrast differences between bone marrow and calcified bone due to the increased density of unmineralized osteoid.

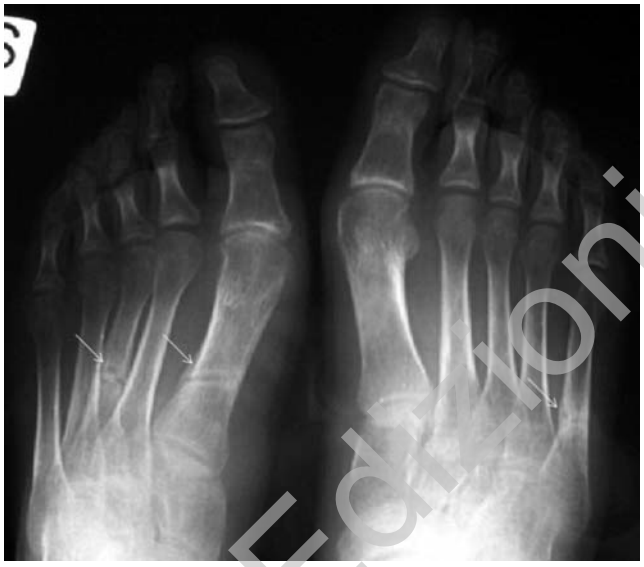

Figure 3 - Frontal radiograph of both feet shows generalized osteopenia and multiple insufficiency fractures (white arrows) with homogenous and fuzzy overall radiographic appearance.

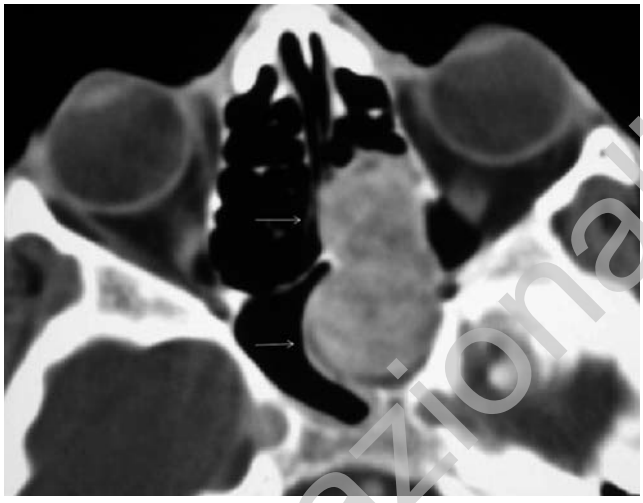

Figure 4 - Contrast-enhanced axial CT image shows a bulging enhancing tumor (white arrows) arising from the left ethmoid sinus.

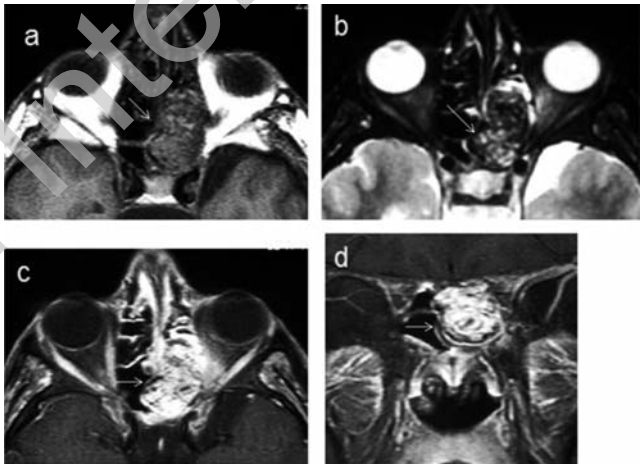

Figure 5 - **a** Axial T1-W, **b** axial T2-W, and contrast-enhanced, **c** axial T1-W and **d** coronal T1-W•MR images show a heterogenous tumor arising from the left sinus (white arrows). It is of mixed hypo-, iso- and hyperintense signals on both T1- and T2-weighted images, and shows marked heterogeneous enhancement.

involving the ethmoid and sphenoid sinuses (Figures 1-5). The tumor was surgically removed. Histologically, the tumor was initially diagnosed as a perivascular myoid tumor and subsequently reclassified as a variant of a sinonasal hemangiopericytoma-like tumor (Figures 6-8). Immunostain for fibroblast growth factor FGF-23 protein was positive (Figure 9). Post-surgery, the patient's metabolic disturbances persisted and further imaging revealed a residual tumor. A second surgical procedure was performed and with complete removal of the tumor, the patient's laboratory parameters returned to normal levels and the symptoms disappeared.

Discussion

We report a rare location of a PMT involving the craniofacial sinuses of the skull base. The typical laboratory findings secondary to phosphate loss are hypophosphatemia and hyperphosphaturia, which finally result in an inadequate mineralization of osteoid in mature bone, a metabolic disorder known as osteomalacia. Oncogenic osteomalacia is dramatically cured by tumor removal but when the tumor is not detected this condition can respond to 1,25 dihydroxyvitamin and phosphate supplementation. Phosphaturic mesenchymal tumor is usually located in soft tissue, but intraosseus as well sinonasal locations are also on record. Histologically, it corresponds to a polymorphous group of neoplastic entities (1-5), the most common of which is the so-called "mixed connective tissue type" (1-6), which is characterized by a distinctive admixture of bland spindled cells, osteoclast-like giant cells, microcysts, prominent and variously sized vasculature, smudgy to calcified cartilage-like matrix, and metaplastic bone. Other histological types of phosphaturic mesenchymal tumors are the osteoblastoma-like tumor, the non-ossifying fibroma-like tumor and the ossifing fibroblastoma-like tumor. Some cases have histological features of malignancy (6).

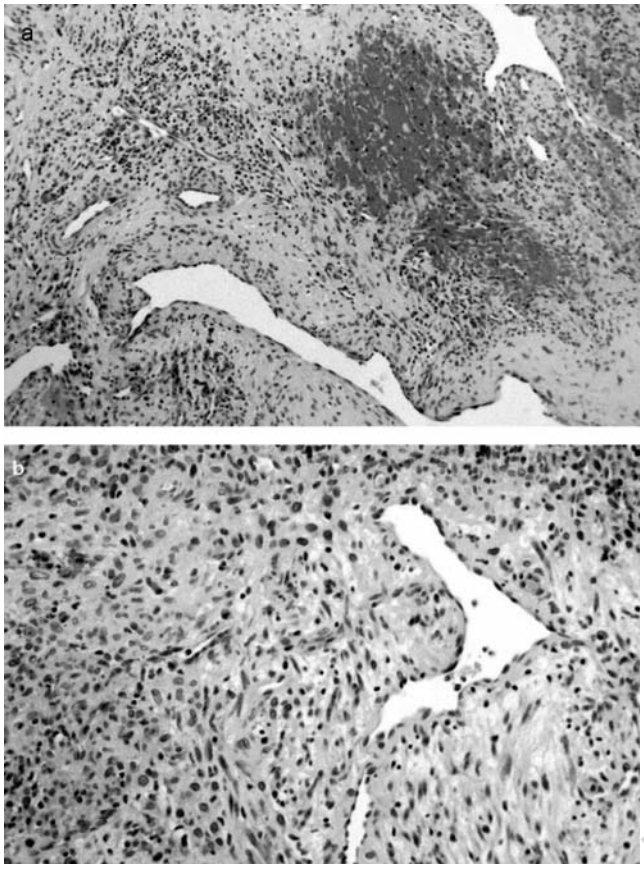

Figure 6 - **a** Characteristic histomorphologic features of a mesenchymal tumor with prominent, partly ramified, vascularization. Oval to spindle tumor cells are embedded in a collagenized to myxoid matrix. An associated mixed inflammatory mononuclear infiltrate is also present, and hemorrhages as well as hemosiderin deposits are visible. **b** Architectural and cytological details of the tumor (Hematoxylin and Esosin. Original magnification, a: x120, b: x240).

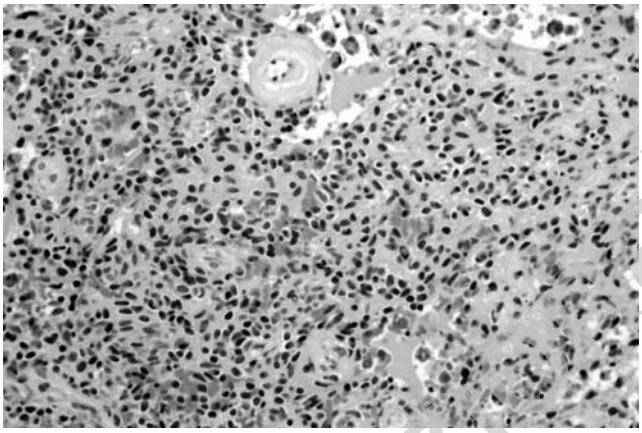

Figure 7 - The tumor showed a variety of cellularity and growth patterns. The neoplastic cells in this illustration show a more oval to round appearances. Top center: a small vessel with perivascular hyalinization is seen (Hematoxylin and Eosin, Original magnification, x 240).

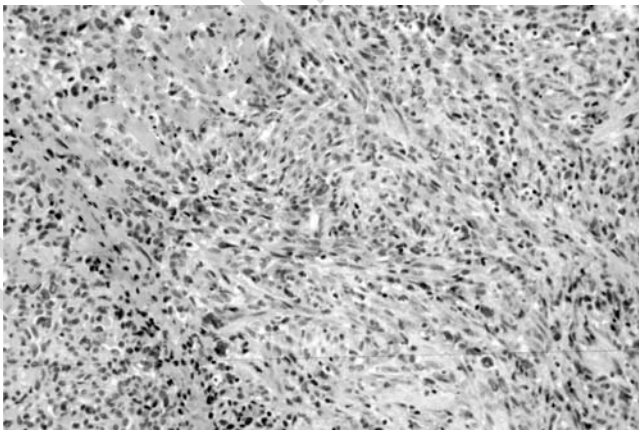

Figure 8 - Fascicular to almost storiform-whorled of the same tumor in a different field (Hematoxylin and Eosin. Original magnification, x 240).

To date, a total of 142 cases are on record in the literature (7), of which only 11 cases were located in the nasal fossa and craniofacial sinuses (Table 1).

Phosphaturic mesenchymal tumor (PMT) is an uncommon, distinctive tumor that is frequently associated with oncogenic osteomalacia, itself a rare paraneoplastic syndrome. 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 sinonasal hemangiopericytoma-like variant (1). PMT is usually a benign tumor, but some cases of malignant transformation have been described (7). Metastatic disease has also been reported (malignant connective tissue variant) (7). Osteogenic osteomalacia – the clinical effect of the tumor – is vitamin D resistant, and is dramatically cured by tumor removal.

PMT is usually located in soft tissue, but intraosseous as well as sinonasal locations have also been reported. In Folpe et al.'s own series of PMT, 18 out of 32 total cases occurred in soft tissue, nine in bone and two in paranasal sinuses, including the present one (2). Patients are usually in their adulthood at the time of diagnosis, but pediatric cases have also been reported (age range: 5 to 63 years). 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%). Unusual locations (e.g. big toe) are not uncommon. Tumor size is variable, ranging from 1 cm to 15 cm, with a median size of 5.6 cm for soft tissue location (3, 4). Somatostatin re-

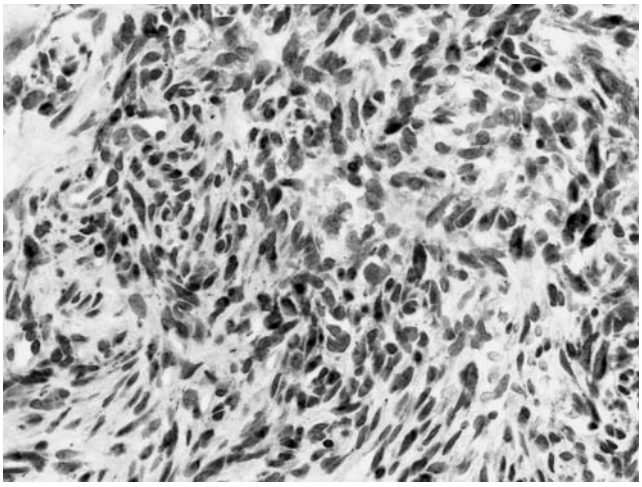

Figure 9 - Immunostain for fibroblast growth factor-23 (FGF-23). Most tumor cells are positive, exhibiting an almost diffuse dark staining of the cytoplasm. (Immunoperoxidase. Diaminobenzidine, nuclear counterstain with Hematoxylin. Original magnification, x 410).

Table 1 - Reported cases of phosphaturic mesenchymal tumors located in the nasal fossa and craniofacial sinuses (8-16).

Reference	Age (yr)/Sex	Site	Histologic Appearance	Outcome	Original Diagnosis	Suggested Revised Diagnosis
Linsey 1982 [8]	54F	Nasopharynx	Uniform small spindled cells, giant cells, many small blood vessels, small bone islands	ANED, normal chemistry	Nasal angiofibroma	PMTMCT
Weidner and Santa Cruz 1987 [9]	35F	Maxillary sinus	Typical PMTMCT	ANED, normal chemistry	PMTMCT	PMTMCT
Papotti 1988 [10]	38F	Nasal cavity	Microcystic, bland spindled cells, granular eosinophilic material, many HPC-like vessels	ANED, normal chemistry	HPC-like/micro-cystic	PMTMCT
Wilkins 1992 [11]	55M	Maxillary sinus	HPC-like neuroendocrine marker negative, rare granules	ANED, normal chemistry	Paraganglioma	Sinonasal HPC-like tumor
Gonzalez Compta 1998 [12]	69F	Ethmoid sinus	Typical PMTMCT	Dead surgical complications	PMTMCT	PMTMCT
Ohashi 1999 [13]	43M	Maxillary sinus	Round cells with dilated vascular spaces	ANED, normal chemistry	Hemangioperi-cytoma-like tumor	Sinonasal hemangio Pericytoma
Clunie 2000 [14]	60F	Ethmoid sinus	Not provided	Died of colon carcinoma; persistent abnormal chemistry	Hemangioperi-cytoma	Insufficient data for analysis
Sandhu 2000 [15]	46M	Ethmoid sinus	HPC-like areas	ANED, normal chemistry	Hemangioperi-cytoma	Hemangioperi-cytoma
John 2001 [16]	54F	Maxillary sinus	Characteristics schwann cells nuclear palisading	ANED, normal chemistry	Hemangioperi-cytoma	Insufficient data for analysis
Folpe 2004 [2]	46M	Ethmoid sinus	Bland spindled cells, thick-walled vasculature	Recurred 1 year after original surgery, reexcised; ANED 12 years, normal chemistry	Hemangioperi-cytoma	Probable variant of sinonasal hemangioperi-cytoma-like tumor
Folpe 2004 [2]	21M	Ethmoid sinus/sphenoid sinuses	Bland spindled cells, thick-walled vasculature	ANED 2 years, normal chemistry	Perivascular myxoid tumor	Probable variant of sinonasal hemangioperi-cytoma-like tumor

ceptor imaging has been recently proved to improve the detection of such tumors, based on the postulate that such tumors express somatostatin receptors (5).

In conclusion, PMT is a rare pathologic entity that is poorly understood by pathologists, clinicians and radiologists. PMT of craniofacial sinuses has peculiar histological features, which often differs from the mixed connective tissue type and which more closely resembles a sinonasal hemangiopericytoma-like tumor variant. Craniofacial PMT should be considered as a rare causative tumor in patients presenting with clinical and radiological features of oncogenic osteomalacia.

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