

Sinonasal Phosphaturic Mesenchymal Tumor: A Rare and Misinterpreted Entity

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Abstract

Keywords

- phosphaturic mesenchymal tumor
- skull base resection
- endoscopic sinus surgery

Objectives Oncogenic osteomalacia is a paraneoplastic syndrome in which the tumor secretes a peptide-like hormone, fibroblast growth factor, resulting in urinary loss of phosphates.

Methods We present the case of a 50-year-old woman with a benign phosphaturic mesenchymal tumor (PMT) involving the ethmoid sinus with obstruction of the ostiomeatal complex causing unilateral nasal airway obstruction.

Results The tumor was initially thought to be an esthesioneuroblastoma based on primary pathology interpretation and on clinical and radiographic appearance. However, a benign PMT was later confirmed by further testing.

Conclusion The tumor was removed entirely by the endoscopic transnasal approach, leading to a full resolution of symptoms.

Introduction

Phosphaturic mesenchymal tumors (PMTs) are very rare tumors frequently associated with oncogenic osteomalacia (OO), a paraneoplastic syndrome that manifests as renal phosphate wasting. The tumor cells produce a peptide hormone-like substance known as fibroblast growth factor 23 (FGF-23), a physiologic regulator of phosphate levels, originally called phosphatonin.¹ It decreases proximal tubule reabsorption of phosphates and inhibits 1- α -hydroxylase enzyme, which reduces levels of 1- α , 25-dihydroxyvitamin D3. Thus overexpression of FGF-23 leads to increased clearance of phosphate in the urine, mobilization of calcium and phosphate from bone, and the reduction of osteoblastic activity causing osteomalacia.²

The patient typically presents with gradual muscular weakness and bone pain or pathologic fractures. The diagnosis is commonly delayed for years due to the nonspecific nature of these symptoms, failure to include serum phosphorus levels in routine blood chemistry testing, and difficulty in identifying the responsible tumor. Additionally, these tumors

are often missed because of their rarity and histologic overlap with other mesenchymal neoplasms.³ Resolution of symptoms, however, does ensue following surgical excision of the neoplasm. We present a case of PMT involving the paranasal sinuses that clinically and radiographically resembled esthesioneuroblastoma (ENB).

Case Report

A 50-year-old woman was referred to the Division of Otolaryngology Head & Neck Surgery at the University of Florida College of Medicine, Jacksonville, with a several month history of progressive right nasal airway obstruction. She was initially evaluated at an outside institution, and office endoscopic examination revealed a polypoid mass involving right nasal cavity. Her symptoms were right nasal airway obstruction along with midfacial pressure and pain. There were no symptoms associated with cranial nerve palsies, epistaxis, or visual deficits. She also complained of generalized weakness and joint pains previously thought to be arthritis.

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Endoscopic examination revealed a large polypoid mass emanating from the right middle meatus. There were no other pertinent endoscopic findings. The remainder of her physical examination was unremarkable. Notably, the patient reported an allergy to laundry and dishwashing detergents. Also, she noted that during her last pregnancy (> 20 years ago) she developed strange calcifications on her teeth that were removed by her dentist. After imaging, a biopsy of the right nasal mass was initially diagnosed as ENB. Computed tomography (CT) scan of the sinuses demonstrated opacification of the right frontal recess, middle meatus, and anterior ethmoid cells with abutment of the cribriform plate of ethmoid bone. Magnetic resonance imaging (MRI) confirmed the findings just described; together with the CT finding and biopsy diagnosis, the mass was highly suspicious for ENB (►Fig. 1A, B).

The pathology specimen was further reviewed by an outside consultation, and special stains and molecular studies

led to a final diagnosis of a benign PMT. This diagnosis was supported by positive tumor expression of FGF-23 detected by reverse transcription polymerase chain reaction and gel electrophoresis on RNA extracted from paraffin-embedded tissue (►Fig. 2A–C). The patient was then referred to our institution for further management. She subsequently had endoscopic transnasal excision of the tumor in its entirety.

Intraoperatively, the tumor did not have any infiltrative components. The base origin of the tumor could not be identified because the mass was hyperemic and resembled the surrounding mucosa (►Fig. 3). Although it was adherent to the normal mucosa, it was amenable to be dissected free of its surrounding normal tissue. The tumor was moderately vascularized and friable upon instrument manipulation. The superior extent of the tumor did not involve the olfactory mucosa and was dissected away from the region of the olfactory mucosa along the roof of the nasal cavity. Because

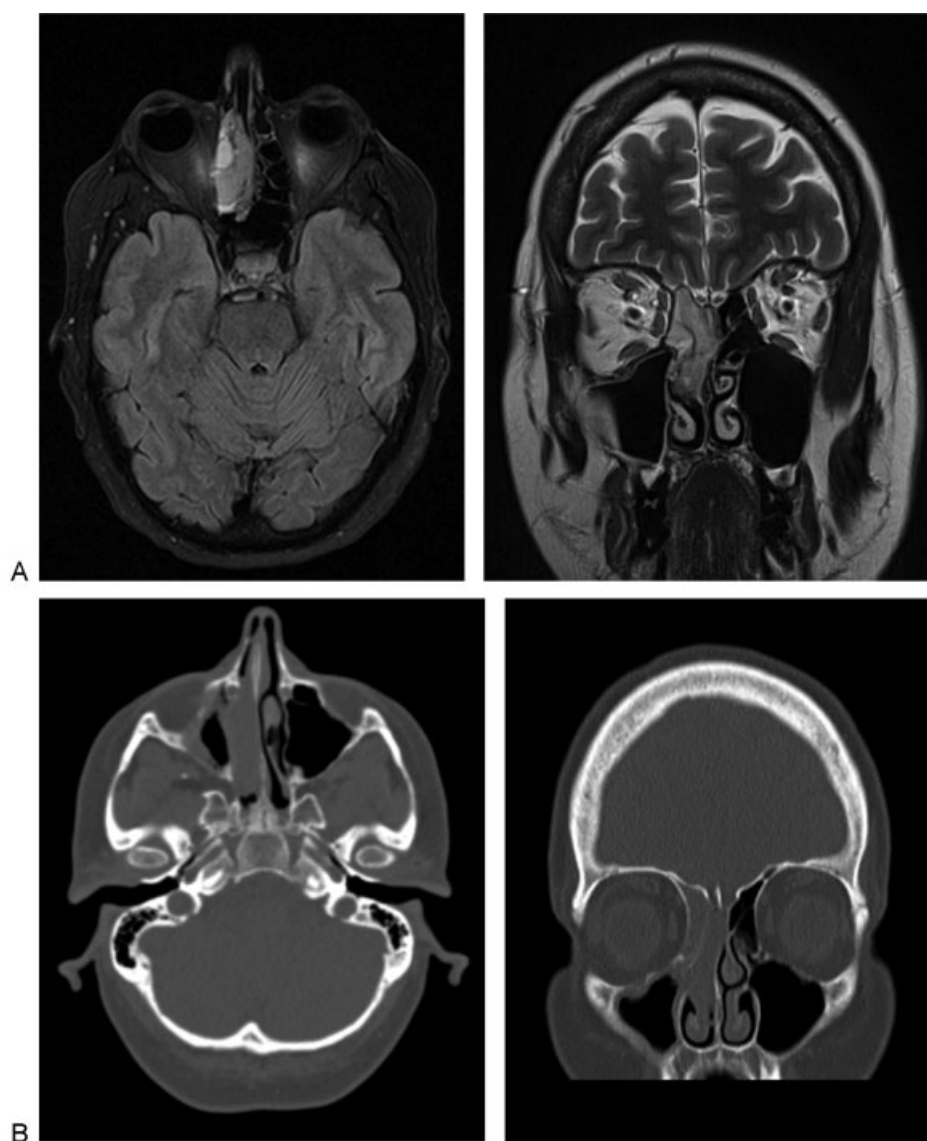


Fig. 1 (A) Axial and coronal magnetic resonance and (B) computed tomography images depicting the level of involvement within the right nasal and paranasal sinus cavities along with associated mass effect upon adjacent bony structures closely resembling an early stage esthesioneuroblastoma.

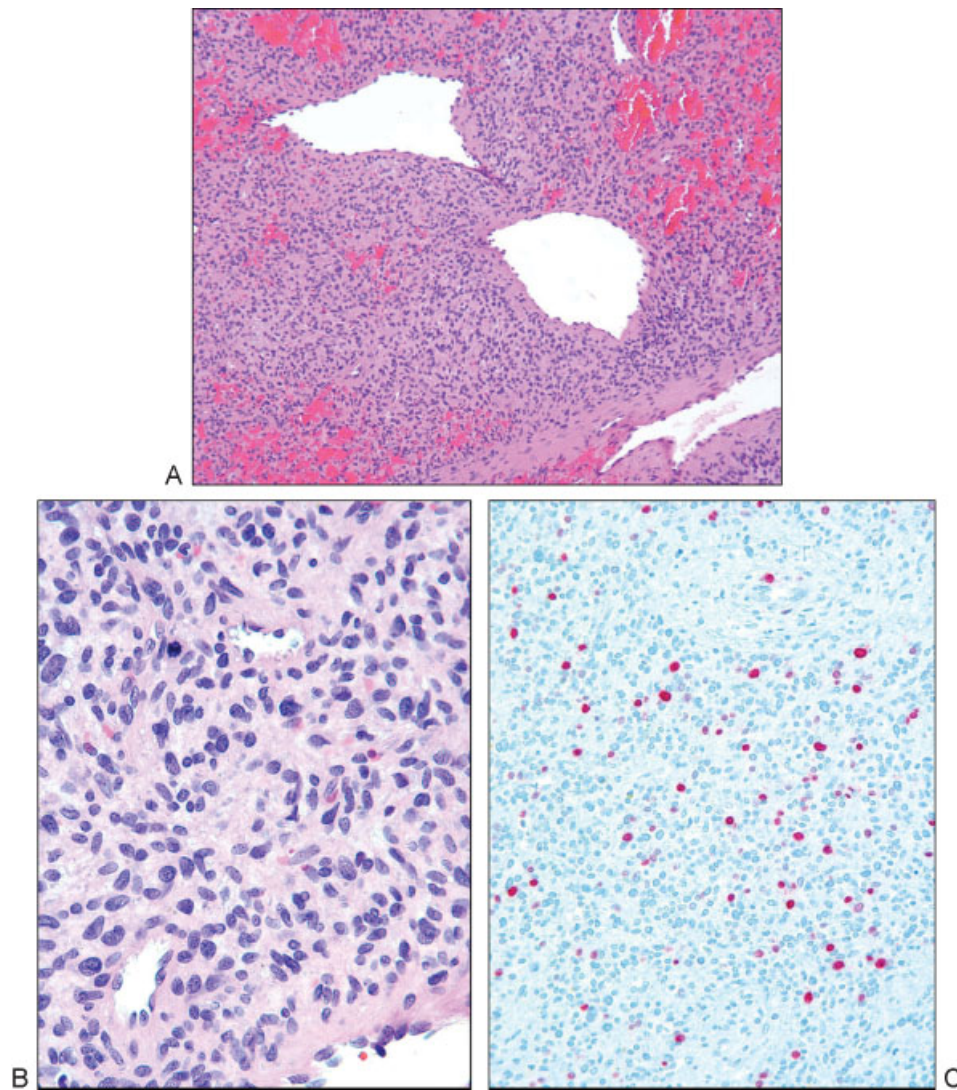


Fig. 2 Tumor histology revealing dense cellularity with hemangiopericytoma-like vessels (A), round to ovoid nuclei with a single mitosis (arrow), mild pleomorphism, granular chromatin, and inconspicuous nucleoli in a fibrillary stroma (B), and proliferation marker Ki-67 labeling ~ 10% of tumor nuclei (C) (H&E stain: A, $\times 10$; B, $\times 40$; and Ki-67 immunoperoxidase stain C, $\times 20$).

of the tumor's resemblance to the surrounding normal tissues, the mucosa was removed from bony structures within the right ostiomeatal unit and surrounding region to ensure complete resection. To preserve the function of the ostiomeatal unit, frontal, maxillary, total ethmoid, and sphenoidotomies were performed on the side of the tumor.

Histologically, the resected tumor was consistent with PMT, displaying moderate to dense cellularity with ill-defined cell borders, ovoid to round nuclei with granular chromatin, inconspicuous nucleoli, and focal nuclear pleomorphism. Thick and thin wall blood vessels were prominent with a hemangiopericytoma-like pattern. The tumor cells were negative for pancytokeratin AE1/AE3, NSE, neurofilament, chromogranin, synaptophysin, S100 protein, desmin, smooth muscle actin, and CD34 immunostains. The tumor lacked the characteristic "grungy" calcification described in PMT.

The patient had normal postoperative convalescence with full resolution of her initial presenting symptoms including

the generalized weakness and joint pains. Unfortunately, her preoperative laboratory work-up only included basic profiles and did not include urine or serum phosphate levels. Serum 25-hydroxyvitamin D levels were low at 15 ng/mL, serum alkaline phosphatase elevated at 224 IU/L (reference range: 44–147 IU/L), and urine phosphate levels slightly elevated at 5.1 mg/dL (reference range: 2.5–4.5 mg/dL) in the immediate postoperative week. Testing for ANA, dsDNA, RNP, SSA, and SSB were all negative. The patient was referred to the rheumatology service for further evaluation and management. Additional diagnostic work-up has included a bone scan, revealing mild osteopenia. She is currently on oral vitamin D supplementation.

Discussion

The first case of OO was described by McCance in 1947, although the relationship between PMT and osteomalacia was not established until 1959 by Prader et al.^{4,5} More than

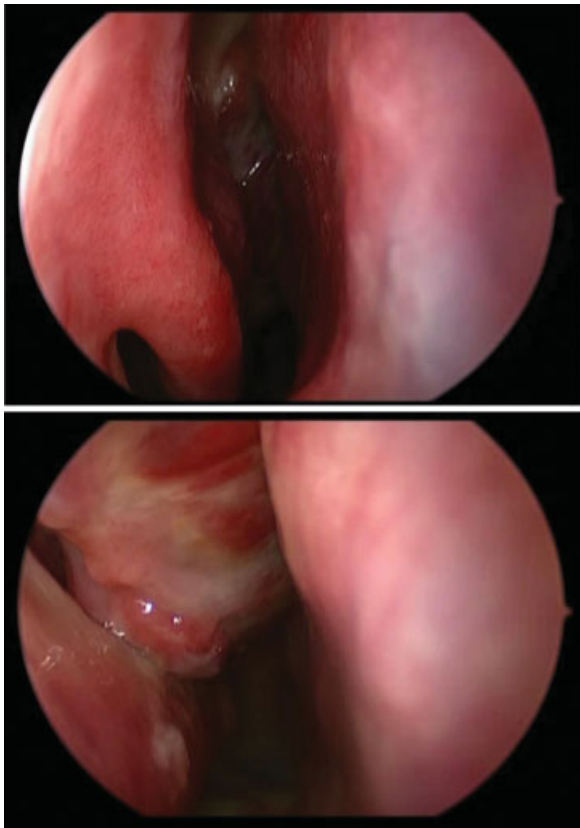


Fig. 3 Endoscopic intraoperative views of the tumor involving the nasal cavity (above) and closely associated with the middle turbinate both along the medial and lateral aspects (below).

100 cases have now been reported, although localization to the paranasal sinuses is extremely rare. Only 17 prior sinonasal cases have been reported in the literature and are outlined in ►Table 1.^{6–37} Tumor-induced osteomalacia is typically caused by a wide range of benign and malignant

mesenchymal tumors such as giant cell tumor, nonossifying fibroma, osteoblastoma, and chondroma.³⁸

Diagnosis of tumor-induced osteomalacia continues to be a challenge because the symptoms are nonspecific. Typical time from the onset of symptoms to a presumptive diagnosis of tumor-induced osteomalacia is often > 2.5 years.³⁹ In this case, the patient did report progressive unilateral nasal obstruction, prompting an otolaryngology consultation and expeditious diagnostic work-up and treatment. The symptoms, along with endoscopic examination findings, initial pathology, and radiologic findings, were highly suggestive of the diagnosis of ENB, which can also be slow-growing tumors with similar nonspecific symptomatology. The gross appearance of the tumor may also be similar among ENBs and PMT, appearing as a polypoid mass on nasal endoscopy.

Imaging with CT and/or MRI cannot differentiate such tumors from others causing nasal obstruction but are useful for identifying the extent of involvement and the presence of locally invasive characteristics that can aid surgical planning and, in case of a malignancy like ENB, for tumor staging. Microscopically, the histologic tumor resemblance in our case to ENB on hematoxylin and eosin(H&E)–stained sections suggested the initial misdiagnosis of ENB.⁴⁰ However, the positive molecular studies for FGF-23 and lack of expression of neuronal markers (such as chromogranin, synaptophysin, neurofilament, and nonspecific esterase) in the tumor established the diagnosis of PMT. Indeed, the spectrum of histologic variation in PMT is wide and reflected by the variety of different initial diagnoses for these tumors such as osteosarcoma, mesenchymal chondrosarcoma, chondroblastoma, atypical enchondroma, spindle cell lipoma, angiolioma, sclerosing hemangioma, hemangiopericytoma with osteoclast-like giant cells, tenosynovial giant cell tumors, and benign mesenchymal tumor among other diagnoses.⁴¹

Tumor-induced osteomalacia should be included in the differential diagnosis in patients with progressive weakness,

Table 1 Reported cases of head and neck phosphaturic mesenchymal tumor

Study	Age, y/Sex	Tumor site	Presence of OO
Sinonasal			
Linsey et al ⁶	54/F	Nasopharynx	Yes
Weidner and Santa Cruz ⁷	35/F	Maxillary sinus	Yes
Papotti et al ⁸	38/F	Maxillary sinus, ethmoid	Yes
Gonzalez-Compta et al ⁹	69/F	Ethmoids, maxillary and frontal	Yes
Kawai et al ¹⁰	53/F	Ethmoids	Yes
Ungari et al ¹¹	24/M	Ethmoids	Yes
Inokuchi et al ¹²	24/F	Maxillary, ethmoids, and frontal	Yes
Koriyama et al ¹³	41/F	Maxillary	Yes
Pedrazzoli et al ¹⁴	37/F	Maxillary	Yes
Shelekhova et al ¹⁵	70/F	Nasal cavity	Yes
	53/M	Frontal sinus	Yes
Peterson et al ¹⁶	33/F	Maxillary sinus	Yes

Table 1 (Continued)

Study	Age, y/Sex	Tumor site	Presence of OO
Parshwanath et al ¹⁷	42/F	Nasal cavity, ethmoids	Yes
Komínek et al ¹⁸	53/M	Frontal sinus, ethmoids	No
Guglielmi et al ¹⁹	22/M	Nasopharynx, ethmoids, sphenoids	Yes
Battoo et al ²⁰	34/F	Nasal cavity, ethmoids, maxillary	Yes
Deep et al ²¹	41/M	Nasopharynx	No
Okamiya et al ²²	35/F	Ethmoid	Yes
Non-sinonasal head and neck PMTs			
Oleksy et al ²³	40/M	Pharynx	Yes
Shenker and Grekin ²⁴	55/M	Neck	Yes
Weidner and Santa Cruz ⁷	27/M	Mandible	Yes
Harvey et al ²⁵	32/D	Thyroid	Yes
Yang et al ²⁶	31/F	Perimandibular soft tissue	Yes
Reyes-Múgica et al ²⁷	9/F	Perimandibular soft tissue	Yes
Dupond et al ²⁸	71/M	Mandibular gingiva	Yes
Woo et al ²⁹	42/F	Mandible	Yes
Kaylie et al ³⁰	46/F	Temporal bone	Yes
Uramoto et al ³¹	48/F	Tongue	Yes
Yun et al ³²	71/F	Floor of mouth	Yes
Savage and Zimmer ³³	73/F	Pterygopalatine fossa	Yes
Mori et al ³⁴	42/M	Maxilla	Yes
Sidell et al ³⁵	24/F	Larynx	No
Syed et al ³⁶	NA	Temporal bone	No
Luo et al ³⁷	NA	Mandible	Yes

Abbreviations: NA, not applicable; OO, oncogenic osteomalacia; PMT, phosphaturic mesenchymal tumor.

bone and muscle pain, and pathologic fractures and alerts physicians to order serum/urine phosphorus panels. The finding of phosphaturia coupled with hypophosphatemia would instigate consideration of the potential causes of phosphate-wasting syndromes including PMT. Furthermore, the correct diagnosis of these tumors is important for several reasons. Severe bone demineralization may lead to pathologic fractures, resulting in permanent disability or rickets if occurring during infancy. Excess FGF-23 can lead to electrolyte imbalance, resulting in complications of several organs such as the heart, kidneys, and brain. In addition, making the correct diagnosis allows for implementation of the proper therapeutic approach. Definitive treatment in this case involved surgical excision with resolution of the patient's symptoms.

Conclusion

PMTs are rare underrecognized neoplasms that are frequently associated with OO through tumor elaboration of a phosphaturic hormone (FGF-23). Although these tumors may have distinct microscopic features, the wide spectrum of histologic variation in PMTs may lead to their misdiagnosis as a different tumor, thereby potentiating radically different treatment and

unnecessary morbidity. A high level of clinical suspicion along with prompt biopsy and laboratory work-up to evaluate phosphate loss is vital for ensuring the correct diagnosis of PMT. This case highlights the close similarity between sinonasal ENB and PMT in both clinical presentation, imaging studies, and histology on H&E stained sections. This is an important consideration because most of these tumors are benign, and complete resection cures intractable OO when present.

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