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Varied presentation of sinonasal phosphaturic mesenchymal tumour: report of a case series with follow-up

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Abstract

Purpose Phosphaturic mesenchymal tumour (PMT) of the paranasal sinuses is a rare tumour that is associated with oncogenous osteomalacia causing predominant musculoskeletal symptoms. We present a series of eight patients diagnosed to have PMT of the paranasal sinuses with varied presentation and highlight the appropriate evaluation required to arrive at the diagnosis.

Methods Retrospective review of eight patients diagnosed to have PMT-causing tumour-induced osteomalacia with follow-up data.

Results Eight patients, 4 males and 4 females, aged 36–67 years (mean = 44 years) presented with vague musculoskeletal symptoms (6 patients) or epistaxis (3 patients). Six patients were found to have hypophosphatemia, phosphaturia and raised FGF-23 levels preoperatively. All eight patients were found to have a tumour in the nose and/ paranasal sinuses with one patient having intracranial extension. All patients were treated with endoscopic excision of these tumours which resulted in resolution of symptoms and normalisation of biochemical abnormalities. In addition, one patient required a craniofacial resection. Histopathological features were consistent with PMT mixed connective tissue variant. Two atypical patients were seen. The longest follow-up was for 5 years and there was no evidence of recurrence during the follow-up period in any patient.

Conclusion Diagnosis of PMT of the paranasal sinuses causing oncogenous osteomalacia requires a high index of suspicion when there are no ENT symptoms. Appropriate biochemical tests and histopathology lead to the correct diagnosis. Total endoscopic surgical excision leads to a good outcome.

Keywords Oncogenic osteomalacia · Paranasal sinus · Hypophosphatemia · Hemangiopericytoma

Introduction

Phosphaturic mesenchymal tumour (PMT) is a term coined for a rare type of mesenchymal tumour which predominantly affects the extremities and appendicular skeleton [1]. Less than 5% of these tumours affect the head and neck region [2]. Some authors report that these sinonasal tumours form a little over 50% of those that involve the head and neck region [3]. These tumours are associated with a paraneoplastic syndrome called oncogenous or tumour-induced osteomalacia which is triggered by the production of fibroblast growth factor 23 (FGF23) by osteocytes within the tumour. These osteocytes inhibit reabsorption of phosphate from the proximal tubules of the kidney, leading to phosphaturia. The tumour affects all ages and shows no predilection for either gender.

Diagnosis of PMT that affect the paranasal sinuses is often delayed, because such tumours are usually asymptomatic at presentation. One report suggests that a mean delay of about 5 years occurs before diagnosis [4]. Patients often present first with bone pains, pathological fractures, and muscle weakness with consequent limitation of mobility. Although this clinical presentation was first described by McCance in 1947 [5], the association of oncogenous osteomalacia with these tumours was unknown at that time. It is well known that several different kinds of tumours in the body can produce similar paraneoplastic syndromes. It was Weidner and Cruz in 1987 who coined the term PMT to

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describe four different morphological types of this tumour which are associated with oncogenous osteomalacia [1].

A review of the literature shows that except for a single recent case series [6], most authors have reported only single cases. A recent review identified 18 published cases of PMT of the sinonasal region in the literature [3]. We report a series of eight cases of sinonasal PMT with oncogenous osteomalacia situated in the sinonasal region to highlight the varied histopathological presentation, evaluation, management, and outcome in these patients.

Materials and methods

This was a retrospective review of all the patients diagnosed with sinonasal PMT-causing oncogenous osteomalacia over the last 10 years in our hospital. Data regarding clinical features, laboratory investigations, imaging features, intraoperative findings, histopathology, and condition at follow-up were extracted from the clinical records of these patients.

Results

Demography

There were a total of eight patients who were diagnosed with PMT during the period of the study. Patient's ages ranged from 39 to 62 years with an equal male: female ratio (Table 1).

Clinical features

The presenting symptoms were body ache, muscle and joint pains in 6 of 8 patients. All patients were symptomatic for more than 2 years with three patients having symptoms for more than 4 years. Two patients (cases 2 and 7) had stress fractures of the neck of femur bilaterally. Two patients in our series (case 5 and case 8) had no musculoskeletal symptoms. They presented with a history of epistaxis of 4 year duration alone. One patient in our series (case 7) had a combination of musculoskeletal symptoms and epistaxis as presenting symptoms.

Investigations

Biochemical parameters

Laboratory analysis of the biochemical parameters in 6 of 8 patients in this series showed hypophosphatemia, phosphaturia, raised alkaline phosphatase and normal parathyroid hormone, calcium, and Vitamin D levels. Two patients (case 5 and case 8) had no biochemical abnormalities such

Table 1 Demography, site of lesion, pre- and post-op biochemical features in affected patients (n = 8)

Case	Age/sex	Symptoms	Duration (years)	PTH (8–74 pg/ml)		Ca (8.3–10.4) g/dL		PO_4 (2.5–4.6) mg/dL		Vitamin D >30 ng/ml		Alk PO4 (40–125 U/L)		Urine Ca < 300 mg/ day		Urine PO4 400–1300 mg/ day		FGF-23 (21.6–91) RU/ml	
				Pre op	Post op	Pre op	Post op	Preop	Post op	Pre op	Post op	Pre op	Post op	Pre op	Post op	Pre op	Post op	Pre op	Post op
1	39/F	Multiple bone pains	2	70.6	–	8.7	9.0	1.3	3.4	9.6	–	426	85	89	–	267	–	260	40
2	36/F	Bilateral stress fractures	2	58	–	8.3	9.1	1.4	3.3	57	–	105	51	49	–	512	–	–	126
3	51/M	Multiple joint pains	3	20	–	8.6	9.1	1.8	3.8	70	–	239	106	125	–	82	429	604	< 5
4	44/M	Multiple joint pains	4	109	–	9.3	9.5	1.5	4.3	47	–	332	233	39	–	368	429	145	94.7
5	39/M	Recurrent epistaxis left nostril	4	–	68.8	–	9.5	–	3.4	–	–	–	–	–	103	–	801	–	–
6	55/M	Multiple joint pains	2	82.1	–	8.7	9.2	1.7	4.0	50.5	33	383	80	38	23	380	206	–	–
7	37/F	Bilateral femur fracture	3	85.3	–	9.2	8.4	1.9	3.1	50.3	–	147	–	116	–	1011	–	695	38
8	62/F	Nose block epistaxis	4	–	–	–	10.2	–	4.4	–	–	–	–	–	78	–	–	–	899

M male, *F* female, *PTH* parathyroid hormone, *Ca* calcium, *Po4* phosphorus, *AlkPo4* alkaline phosphorus, *FGF* fibroblast growth factor

as hypophosphatemia or phosphaturia. Both these unusual cases had all the histological features of PMT and are, hence, included in this series (Table 2).

Rigid nasal endoscopy

A total of 6 of 8 patients underwent preoperative biopsy before surgery in the outpatient area. A positive biopsy was obtained in 5 of 6 patients. All patients underwent excisive surgery under general anaesthesia. The two patients who did not undergo biopsy, as outpatients had no visible tumour on diagnostic endoscopy.

Imaging

Contrast-enhanced CT scan of the paranasal sinuses showed the tumour centered around the ipsilateral middle turbinate in four patients with extension to the adjoining areas such as the cribriform plate, septum, frontal recess, and anterior ethmoids. Two patients had involvement of the posterior ethmoids and one patient had involvement of the sphenoid sinus (Fig. 1). One patient (case 7) had the tumour involving the nasal cavity, ethmoid sinus, erosion of the nasal septum with extension to the opposite side, erosion of the lamina with extraconal involvement of the orbit, and destruction of the cribriform plate and intracranial extension. The intracranial component measured 2 × 1 cm was hyperintense on T2-weighted MRI scan of the paranasal sinus and was predominantly extradural (Fig. 2).

Treatment

All patients underwent complete endoscopic resection of the tumour under general anaesthesia. One patient (case 7) in addition also underwent a craniofacial resection and achieved complete excision of the intracranial and nasal component with repair of the anterior cranial fossa floor defect with fascia lata.

Histopathology

The histopathology specimen was reported as PMT in all eight patients in our series (Table 2). The specific features noted were the presence of spindle cells which were predominately in sheets except in three cases which showed only long spindle cell morphology. All eight patients in the series had a haemangiopericytomatous vascular pattern which consisted of thin spindle cells surrounding the branching blood vessels (Fig. 3). Four patients in our series did not have the characteristic grungy calcification, although they had spindle cells and haemangiopericytomatous pattern. However, in view of the typical clinical features, they were diagnosed to have PMT. One patient (case 7) had in addition to the above features also showed atypical cells with increased mitotic activity in both the nasal and intracranial component of the tumour which was suggestive of a malignant variant of PMT.

Table 2 Histopathological features of the patients in the series ($n = 8$)

Case	Histopathological diagnosis	Spindle cell pattern		Grungy calcification	Giant cells	Hemorrhage	Mitotic activity	Immunohistochemistry
		Epithelioid	Sheets					
1	PMT MCT	Nil	+	Nil	Nil	+	Nil	–
2	PMT MCT	+	+	+	+	Nil	Nil	SMA–Positive
3	PMT MCT	+	+	+	+	+	Nil	–
4	PMT MCT	+	+	Nil	+	+	Nil	(Vimentin; BC12)–Positive EMA–Negative
5	PMT MCT	Nil	+ Storiform intracyto plasmic inclusions	Nil	Nil	Nil	Nil	(Vimentin; TLE-1; CD-34)–Positive (CK; SMA; EMA; S-100) - Negative
6	PMT MCT	Nil	+	Nil	Nil	Nil	Nil	(Vimentin; CD99; SMA; Desmin; CD34)–Positive (S-100;CD68)–Negative
7	Malignant PMT MCT	Nil	+	Nil	+	+	+	–
8	PMT MCT	Nil	+	Nil	Nil	+	Nil	SMA–Positive (CD34; STAT6; EMA; Beta-catenin)–Negative

PMT MCT phosphaturic mesenchymal tumour mixed connective tissue variant, *SMA* smooth muscle actin, *EMA* epithelial membrane antigen

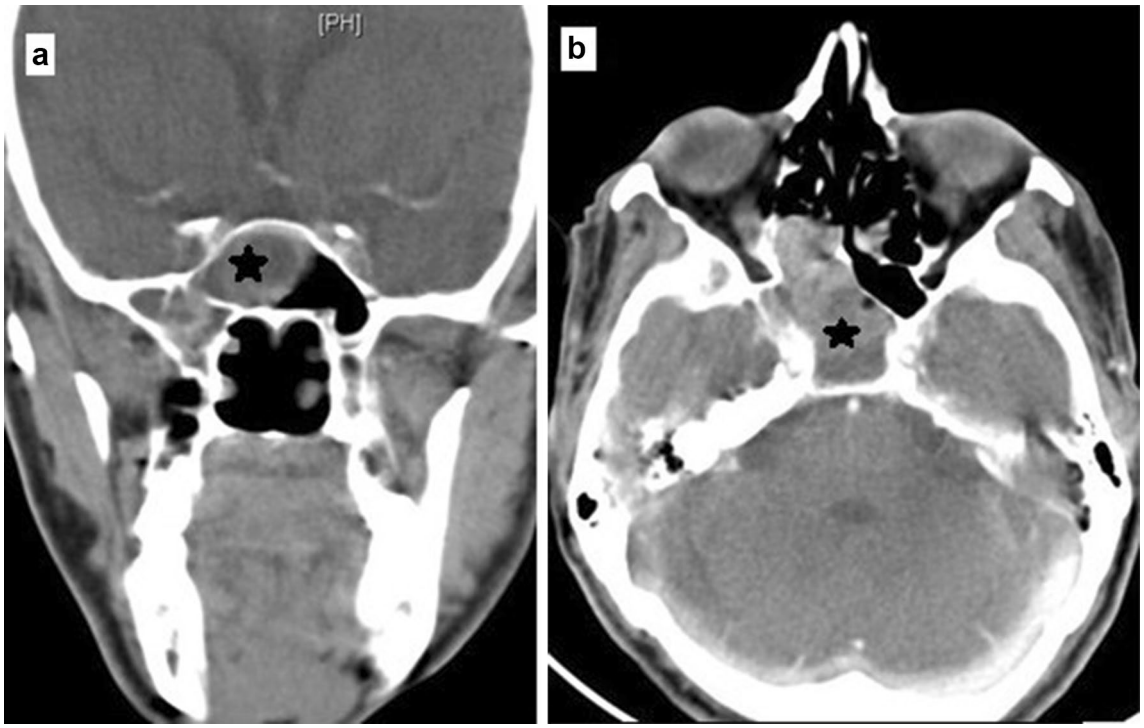

Fig. 1 Preoperative CT scan of the paranasal sinus with contrast **a** coronal; **b** axial cuts showing heterogeneously enhancing mass (black asterix) in the right sphenoid and posterior ethmoid sinus

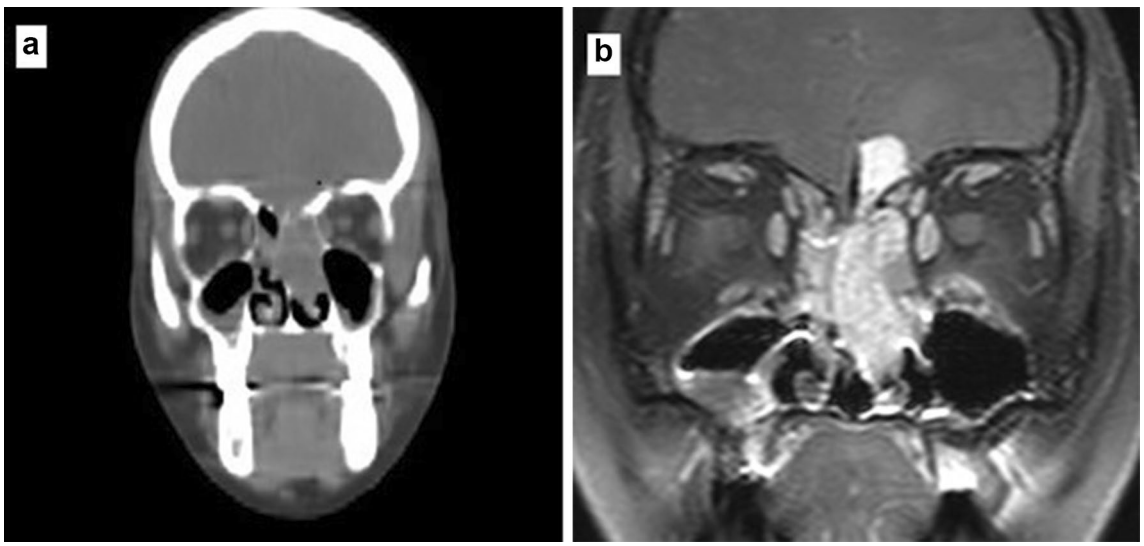

Fig. 2 Preoperative imaging of patient with malignant PMT **a** CT scan of the paranasal sinus with contrast showing the mass lesion involving the left ethmoids with skull base erosion. **b** MRI scan of the paranasal sinus T1 weighted with contrast showing intensely enhancing tumour with intracranial extension

Postoperative period

Postoperatively, patients with musculoskeletal symptoms showed remarkable and rapid recovery of symptoms. Serum phosphate returned to normal within days of tumour excision in all the six patients in whom it was raised. In two patients (cases 5 and 8); as features of osteomalacia were absent clinically, preoperative calcium and phosphate levels were not assessed. Postoperative values were, however, normal.

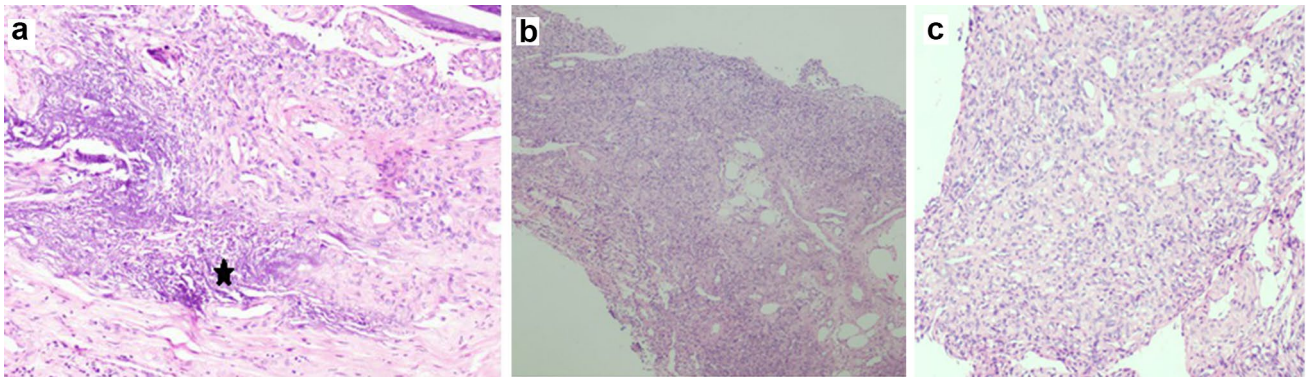

Fig. 3 Photomicrograph of benign PMT showing **a** presence of grungy calcification (asterix); **b** proliferation of vascular channels with dilated irregular appearance set in a spindle celled stroma in low power **c** high power

Unusual presentations

Case no. 5 and Case no 8 in this series were a 39-year-old male and 67-year-old female, respectively, who presented with epistaxis and no musculoskeletal problems. Histopathology of the mass which was excised was diagnostic of PMT. This led us to evaluate for biochemical features of oncogenous osteomalacia (Table 1). However, we found no biochemical features suggestive of osteomalacia in this patient.

Case 7 on this series was a 37-year-old female who had history of bilateral femur stress fractures in the past. She also had symptoms of epistaxis with vague musculoskeletal symptoms. Imaging in this patient showed a large enhancing tumour involving bilateral nasal cavities with intracranial extension, the histopathology of which showed a malignant variant of PMT (Fig. 4). We highlight that these cases to emphasize the unusual variants in presentation and histopathology.

Follow-up

Follow-up ranged from 3 months to 4 years in all eight patients in our series (Table 3). These patients were asymptomatic at follow-up with normal biochemical parameters. Postoperative rigid nasal endoscopy showed no residual tumour. Postoperative imaging showed no evidence of disease (Fig. 5). One patient in our series (case 7) being a malignant variant is undergoing radiation therapy following surgery. Case 8 had a persistent high FGF-23 postoperatively in spite of having a healthy postoperative medial maxillectomy cavity for which she is under further evaluation.

Discussion

PMT encompasses a group of rare paraneoplastic neoplasms which produces symptoms of osteomalacia due to excessive production of FGF-23 that is produced by osteocytes of involved bone. Many affected patients complain of long-standing generalized fatigue and weakness along

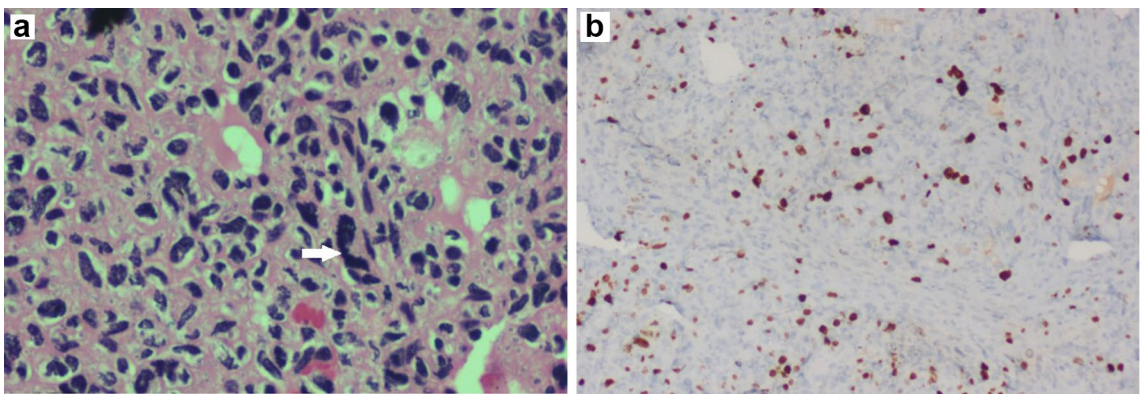

Fig. 4 Photomicrograph of malignant PMT showing **a** atypical mitotic figure with spindle shaped tumour cells set in a collagenous stroma (200×) (white arrow); **b** high MIB-1 index 100×

Table 3 Table showing extent of lesion, surgical treatment, histology, and follow-up

Case	Site	Surgery	Histopathology	Follow op (months)
1	Right nasal cavity, MT	Endoscopic excision	PMT	13
2	Left AE / PE	Endoscopic excision	PMT	58
3	MT, septum	Endoscopic excision	PMT	24
4	MT, frontal recess	Endoscopic excision	PMT	6
5	MT, Cribriform plate, septum	Endoscopic excision	PMT	3
6	PE, sphenoid	Endoscopic excision	PMT	36
7	AE, cribriform plate, septum with intracranial extradural	Craniofacial resection	Malignant PMT	On postoperative radiotherapy
8	Nasal cavity, maxillary sinus, AE, PE, sphenoid	Medial maxillectomy	PMT	3

MT middle turbinate, *PMT* phosphaturic mesenchymal tumour, *PE* posterior ethmoid, *AE* anterior ethmoid

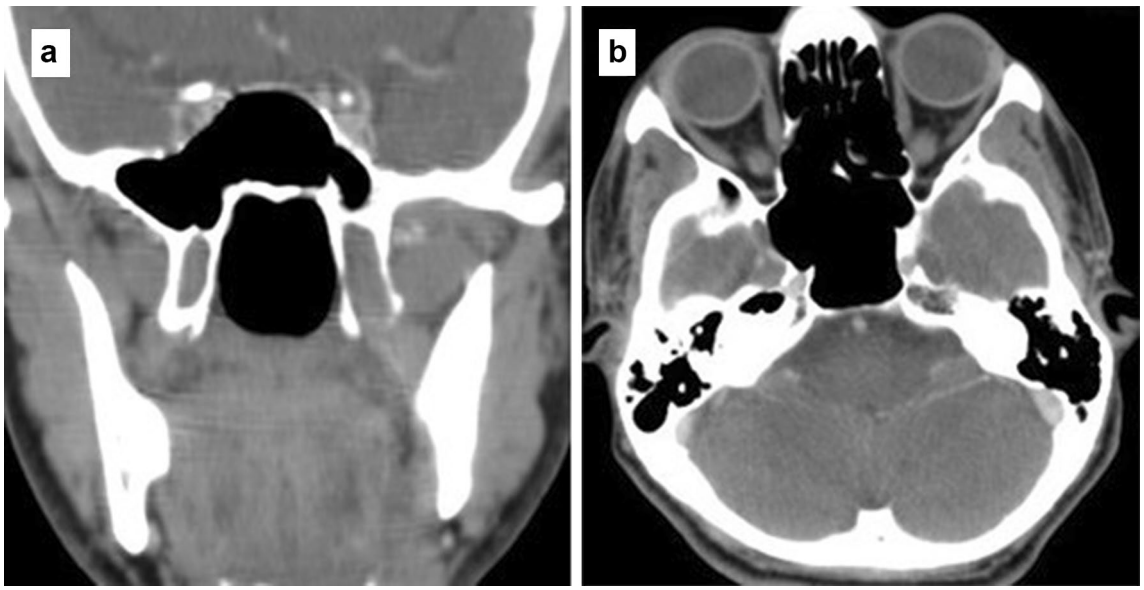

Fig. 5 Postoperative CT scan of the paranasal sinus with contrast **a** coronal; **b** axial cuts showing no evidence of recurrence in the sphenoid and posterior ethmoid sinus

with musculoskeletal pain [7]. In our series too, most of our patients presented with prolonged periods of vague symptoms such as muscle and joint pains before a proper diagnosis could be reached. Once a diagnosis of osteomalacia is made in these patients, biochemical parameters such as serum calcium and phosphate as well as alkaline phosphatase, parathyroid hormone, and Vitamin D levels should be ordered. The lack of inclusion of phosphate levels in routine evaluation of biochemical panels either due to lack of facilities or awareness could lead to further delay in diagnosis of this condition or even misdiagnosis [8].

The pathogenesis of oncogenous osteomalacia in patients with PMT is the production of fibroblast growth factor (FGF-23) by the osteocytes which causes phosphaturia and altered Vitamin D metabolism [9]. The primary transport protein responsible for phosphate reabsorption in the kidney is the Type II sodium–phosphate cotransporter (NPT2a) which is located in the proximal tubule. Downregulation of NPT2a occurs in the presence of raised levels of FGF-23 levels [10] which in turn causes hypophosphatemia and phosphaturia. FGF-23 also causes downregulation of 1α-hydroxylase and upregulation of 24- hydroxylase, which in turn leads to a decrease in 1, 25-dihydroxy vitamin D3. Thus, the typical biochemical alterations seen include hypophosphatemia, phosphaturia, low levels of tubular reabsorption of phosphate, and low renal tubular reabsorption of

phosphate to glomerular filtration rate ratio (TmPO4/GFR) which would confirm renal wasting of phosphate. Associated abnormalities also include normal or low 1–25 hydroxy Vitamin D3 levels and high alkaline phosphatase.

While musculoskeletal symptoms without nasal symptoms are the most common mode of presentation of these patients, some may have only nasal symptoms. This was the case in two patients in our series (case 5 and case 8) who presented with epistaxis alone. Case 5 was found to have an ethmoid sinus tumour by rigid nasal endoscopy and contrast CT of the sinuses. Case 8 had a mass filling the entire left nasal cavity. Both patients underwent total excision of the mass endoscopically. Histopathology confirmed the presence of a PMT. However, this was a non -phosphaturic variant of PMT. Although majority of the patients with PMT present with tumour-induced osteomalacia, a very small proportion of patients have a non-phosphaturic variant of the disease [11]. The reason behind the lack of biochemical abnormalities in this subset of patients could either be the lack of secretion of sufficient quantities of FGF-23 or compensation to prevent any biochemical alterations. Furthermore, the secretory capabilities of the tumour evolve over time and early resection could prevent the commencement of these biochemical alterations [2].

All our patients underwent preoperative evaluation including rigid nasal endoscopy and contrast-enhanced CT scan of the paranasal sinus. These investigations revealed a mass centered around the middle turbinate in six of the eight patients with extension to the adjoining septum, cribriform plate, anterior ethmoids, and frontal recess. Two patients had involvement of the posterior ethmoids and one had extension to the sphenoid sinus. Seven of the eight patients had no evidence of bony erosion with any intracranial or intraorbital extension in spite of the long duration of this disease suggesting the benign nature of the tumour. Case 7 had an extensive tumour with intracranial extension the histopathology of which showed a malignant variant of PMT. A literature review shows only an isolated report of an ethmoidal mass with intracranial extension which required a craniofacial resection followed by radiotherapy [12]. This suggests the very slow growing nature of the tumour and the low propensity to spread to the surrounding structures. These tumours are expansile, enhancing masses with variegated appearance and well-defined margins on CT. On MRI scan, they may show intense enhancement. However, endoscopically and radiologically, they resemble other vascular sinonasal tumours and are not distinctive in appearance.

Weidner et al. subdivided PMT into four categories; mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non-ossifying fibroma-like variant, and ossifying fibroma-like variant. Although the first group were found more commonly in soft-tissue regions, the remaining three types were found in bone [13]. Folpe et al. in his review found that virtually, all the cases which were described initially fell in the category of PMTMCT [2]. Histologically, they present as a spindle celled tumour with short plump spindle cells associated with proliferated thin walled blood vessels with hyalinization of its walls which is a feature of haemangiopericytomatous type of vascular pattern. Because of the similar vascular pattern and presence of spindle cells, many of these tumours are often misdiagnosed as haemangiopericytoma [10]. Sometimes, osteoclastic giant cells, foci of cartilaginous differentiation as well as bone formation may be seen. The presence of amorphous or granular calcification called grungy calcification is diagnostic of this tumour. Stromal hemorrhage is common, but necrosis is not and mitotic figures are rare. All eight patients in our series had spindle cells with a haemangiopericytomatous vascular pattern. Although three patients did not have the typical grungy calcification seen with these tumours, the presence of other histological features such as spindle cells and haemangiopericytomatous pattern with typical clinical features helped us to make the diagnosis.

PMTMCTs are normally benign, but a few malignant variants have been described [14–16]. The presence of benign cellular features and low mitotic activity makes histopathological diagnosis of malignancy very difficult even in the presence of metastatic disease [15]. Case 7 in our series showed features of high mitotic activity with a raised MIB index which was suggestive of a malignant variant (Fig. 4). Other differentials include haemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumours, and osteoblastomas.

Seven patients in our series underwent a complete endoscopic excision of the lesion and one patient underwent a craniofacial resection. Resection with a wide surgical margin is almost always curative, although there are reports of local recurrences [16]. There is a rapid improvement in the clinical symptoms and reversal of biochemical abnormalities within a period of a week to 10 days. This improvement is often diagnostic and the hallmark of this rare condition.

Distant metastasis is seen in less than 5% of the cases and is often associated with malignant change [17]. One patient in our series had histological features of malignant change with no evidence of distant metastasis. Metastasis to the lung is the most common site of distant spread, and therefore, serial imaging surveillance with CT scans is important in those tumours which show malignant changes. Despite the presence of metastasis, reports of survival for 30 years have been reported [18].

Conclusion

Our series highlights the typical clinical features of PMT with oncogenous osteomalacia. We also describe two patients with a non-phosphaturic variant of the disease

which is entirely a histopathological diagnosis as typical clinical and biochemical features of osteomalacia are absent in these patients. One patient in our series had a malignant PMT which is a rare variant of this type of tumour. Detection of these tumours can often be delayed, and therefore, it is important for otolaryngologists to be familiar with this entity. Once detected, surgical resection is completely curative with rapid normalization of biochemical and clinical features.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional review board approval was obtained prior to the commencement of the retrospective study (IRB No:11,448).

Informed consent Informed consent was obtained from all the participants in the study.

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