Phosphaturic Mesenchymal Tumor: 2 New Oral Cases and Review of 53 Cases in the Head and Neck

Hiba Qari¹ · Aya Hamao-Sakamoto² · Clay Fuselier³ · Yi-Shing Lisa Cheng¹ · Harvey Kessler¹ · John Wright¹

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Abstract Phosphaturic mesenchymal tumor (PMT) is a rare neoplasm that secretes fibroblast growth factor-23 (FGF-23) and causes oncogenic osteomalacia. It occurs in adults with equal gender distribution and the most common location is the lower extremities, followed by the head and neck. Besides osteomalacia, the clinical presentation includes bone pain and multiple bone fractures. Microscopic features consist of spindle cells, multinucleated giant cells, and calcifications embedded in a chondromyxoid matrix. Laboratory findings indicate normal calcium and parathyroid levels, hypophosphatemia, and increased levels of FGF-23 that usually revert to normal after surgical removal. Due to its rarity, the purpose of the study was to report 2 new oral cases of PMT and to review the literature in the head and neck. The first case occurred in the gingiva and had been present for 6 years. The second case was a recurrence of a previously diagnosed PMT in the right mandible that metastasized to the lung and soft tissue. The literature review included 53 cases in the head and neck. There was a predilection for extra-oral sites (76 %) compared to intra-oral sites (24 %) with paranasal sinuses considered the most common location (38 %) followed by the mandible (15 %). There were 9 recurrences that included 3 malignant cases indicating a potentially

aggressive tumor. Due to the indeterminate biological behavior of PMT and its rarity, a comprehensive evaluation of medical, laboratory, radiographic, and histological findings are crucial for a definitive diagnosis and treatment.

Keywords Oncogenic osteomalacia · Phosphaturic mesenchymal tumor · Hyperphosphaturia · Hypophosphatemia · Calcium

Introduction

Phosphaturic mesenchymal tumor (PMT) is a rare mesenchymal neoplasm with unpredictable biological behavior that has been associated with oncogenic osteomalacia (OO) [1–3]. It is a paraneoplastic syndrome that is considered to be an acquired type of osteomalacia and is caused by a variety of mesenchymal neoplasms [4, 5]. PMT affects both genders equally and most patients are adults between the ages of 30–40 years but young patients have been documented [6–8]. The most common location for PMT involves the extremities (95 %) followed by head and neck (H&N) sites (5 %) with the sinonasal cavity representing more than half of the cases [9, 10]. There is a roughly equal distribution between hard and soft tissue with perhaps a slight predilection in bone (53 %) [11–13]. Clinical presentation is related to anatomic site affected and may include bone pain, multiple bone fractures, gait disturbance, atrophy of proximal muscles, and osteopenia. Laboratory findings include hypophosphatemia, hyperphosphaturia, elevated levels of alkaline phosphatase, normal to low circulating levels of 1,25 dihydroxyvitamin D (1,25-[OH]₂D₃), normal serum calcium and parathyroid hormone (PTH) [14, 15]. The reason for the phosphate imbalance is due to an overexpression of the ectopic hormone-like substance termed phosphatonin, also known as

✉ Hiba Qari
hqari@bcd.tamhsc.edu

¹ Department of Diagnostic Sciences, Texas A&M University Baylor College of Dentistry, 3302 Gaston Avenue Room # 214, Dallas, TX 75246, USA

² Oral and Maxillofacial Surgery Division, Department of Surgery, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9109, USA

³ Private Practice OMS, Austin, TX, USA

fibroblast growth factor-23 (FGF-23) that is secreted by PMT. High levels of FGF-23 cause phosphate diuresis known as phosphaturia and inhibit renal phosphate reabsorption which results in hypophosphatemia. This will stimulate mobilization of phosphate and calcium from the bone into the blood as a compensatory mechanism causing the bone to become weak and fracture [16, 17]. Microscopically, the tumor is a spindle cell mesenchymal neoplasm with variable cellularity. It contains “grungy” calcification and a chondromyxoid or osteoid like matrix with plump fibroblastic cells. Nuclear chromatin is relatively well dispersed and cell morphology is bland with minimal mitosis. Scattered multinucleated giant cells (MNGCs) and areas of erythrocyte extravasation are also seen [18, 19]. In most cases the tumor is usually slowly growing and its small size makes early detection difficult. It can take up to several years (mean of 5 years) to detect the tumor location [20]. Surgical excision is the treatment of choice [21, 22]. Due to the rarity of the lesion the purpose of the paper is to review the literature in the head and neck and report 2 intra-oral cases of PMT: one in the soft tissue of the mandibular gingiva that had been present for 6 years and another case in bone presenting as a recurrent lesion in the mandible with metastasis to the lungs and soft tissue previously diagnosed with OO.

Materials and Methods

An extensive review of the English language literature from 1972 to 2014 was conducted using Pubmed. We used the keywords PMT, OO, head and neck, intra-oral, mesenchymal neoplasms, bone, soft tissue, paraneoplastic syndrome, and tumor induced osteomalacia. Inclusion criteria included PMTs with documented histologic, clinical, and serological findings in the head and neck which included intra-oral and intracranial lesions as well. Reports of PMT outside the head and neck were excluded. PMT was then divided by location into extra-oral and intra-oral sites.

Results

Case 1

A 60 year old Chinese male was referred for evaluation of a painless slowly growing swelling in his mandibular gingiva for the past 6 years. Medical history was unremarkable for cardiac, pulmonary, GI, renal, hepatic, neurological, and psychological problems. The patient was taking levothyroxine (Synthroid) 25 mcg 8 tablets/week for hypothyroidism. Patient’s history of tobacco and alcohol use was negative. Physical examination

revealed chronic lower back pain. The patient was suffering from osteoporosis in the distal third of the radius, osteopenia affecting the lumbar spine and femoral neck, and a history of atraumatic rib fractures. Multiple myeloma work up was negative. Routine laboratory results revealed high bone turnover with low levels of serum phosphate (PO₄), normal calcium, and parathyroid hormone levels, which were consistent with OO. Intra-oral examination showed a 12 mm dome shaped symmetrical non ulcerated gingival lesion on the lingual gingiva of tooth # 19 (Fig. 1). Panoramic images demonstrated no boney involvement. An Incisional biopsy was performed. Microscopic examination revealed a benign appearing highly cellular spindle cell neoplasm with focal areas of irregularly-shaped small calcifications and scattered MNGCs in a chondromyxoid background. The tumor was cytologically bland and no mitoses were seen (Fig. 2). In situ hybridization (ISH) for FGF-23 showed diffuse strong cytoplasmic expression (Fig. 3). A diagnosis of PMT was made. Two weeks after initial biopsy, complete surgical removal of the tumor was performed and serum phosphate levels gradually returned to normal within a few weeks. Fourteen months follow up was negative for tumor recurrence (Table 1; Fig. 1).

Fig. 1 Clinical presentation of case 1. **a** A smooth surfaced mass in lingual gingiva of tooth #19. **b** No recurrence at the 3 months follow-up after surgical removal

◀**Fig. 2** Histological features of case 1. **a** Cellular spindle cell neoplasm with multinucleated giant cells, prominent vascularity and chondromyxoid background. **b** Spindle cell proliferation with a chondromyxoid background. **c** Spindle cell proliferation with prominent grungy calcification in a chondromyxoid stroma. **d** Spindle cell proliferation without cytological atypia

Fig. 3 Histological features of case 2. **a** Osteoid like production in a background of a spindle cell proliferation. **b** Fascicular spindle cell proliferation

Case 2

A 58 year old Caucasian male patient returned with a swelling in the right mandible after being diagnosed with OO 24 years previously. Radiographically, it was a 1.2 cm destructive osteolytic lesion in right body of mandible between the premolar and first molar with slight displacement of teeth. A biopsy was performed which showed a cellular spindle cell neoplasm with osteoid-like production compatible with the ossifying type of PMT (Fig. 4). The causative tumor went undetected until 5 years later when a lesion was identified in the mid-right mandible. Despite multiple surgeries in the mandible to remove the tumor it eventually metastasized to the lung where it presented as multiple, small, non-obstructive foci of tumor. Seventeen

Table 1 Laboratory values of case 1. Serum calcium, phosphate, and parathyroid hormone levels, before and after surgery

Chemical profile	Normal range	Before surgery			Surgery	After surgery	
		September	December	June	July	August	September
Ca	8.4–10.2 mg/dl	9.7	9.1	9.1	9.0	9.3	9.3
P	2.4–4.5 mg/dl	2.6	2.4	2.3	3.6	3.7	4.0
PTH	15.0–65.0 pg/ml	35.6	57.1	55.9	NA	NA	NA

Ca calcium, P phosphorous, PTH parathyroid hormone, NA not available

Fig. 4 In situ hybridization (ISH) of case 1. **a** Strong diffuse cytoplasmic reactivity of FGF-23 (original magnification $\times 33$). **b** Higher power magnification showing the presence of FGF-23 mRNA in the cytoplasm of the neoplastic cells (original magnification $\times 132$)

years from when the tumor was first detected, it was confirmed that the disease had become widespread with lesions in the soft tissue. The immunohistochemistry (IHC) of proliferation marker, Ki-67, was performed due to the aggressive and metastatic behavior of the tumor even though it was bland in appearance. It highlighted approximately 3 % of the tumor cells. The patient is currently enrolled in an experimental clinical trial whose details are considered proprietary.

Literature Review

Our literature review focused on PMT in the head and neck and a total of 71 articles were collected between 1972 and 2015. Of these, we report 55 cases including our 2 case

reports. We divided the lesions into extra-oral versus intra-oral sites. Forty-four out of 55 cases (80 %) were found in hard tissue while the remaining 11 cases (20 %) occurred in soft tissue. There was a predilection for extra-oral sites which accounted for 42 out of the 55 cases (76 %) compared to 13 intra-oral sites of involvement (24 %). Extra-orally the paranasal sinuses were the most common location in 21 out of 55 cases (38 %). The second most common location was intraorally in the mandible, 8 cases (15 %), which is similar to the findings of Gonzalez-Compta et al. [5]. Females were affected slightly more than male patients (F = 33, M = 21, NA = 1) and the average age was 46 years old. There were 9 recurrences that included 3 malignant cases with metastasis. Our case 2 had a recurrence in the mandible and metastasis to the lungs and soft tissue. Case 9 had multiple recurrences and metastasis to the lungs but site was not mentioned. Case 10 had metastasis to the femur only (Tables 2, 3).

Discussion

The first case of PMT was described in 1947 by McCane [54] but it was not until 1959 that Prader linked the association between tumor and osteomalacia [55]. In 1987 Weidner and Cruz coined the term PMT and suggested dividing the tumor into 4 subtypes, phosphaturic mesenchymal tumor mixed connective tissue type (PMTMCT) which occurs in soft tissue, osteoblastoma like, ossifying fibroma like, and non-ossifying fibroma types which are all found in bone [3, 19]. In 1998 Gonzalez-Compta documented 21 cases of OO associated mesenchymal tumors in the H&N and reported that the most common location was the sinonasal cavity (57 %) followed by the mandible (20 %) [5]. In 2004, Folpe et al. [4] analyzed 32 cases and did a comprehensive review of 106 cases in the literature on OO associated mesenchymal tumors. They concluded that both bone and soft tissue variants were a single entity with a wide histological spectrum. They reported that even though PMT is not the only mesenchymal tumor to cause OO, it is by far the most common one, with 80 % of OO associated mesenchymal tumors being PMT. The remaining 20 % consisted of other mesenchymal tumors such as hemangiopericytoma (HPC), giant cell tumor of bone (GCTB), and osteosarcoma [4, 5].

Table 2 Summary of 42 extra-oral cases of PMT in the literature

Case	Reference (year)	Age	Sex	OO	Location of PMT	Recurrent/metastasis	Follow up (years)
1	Okamiya et al. [23]	35	F	Y	Ethmoid sinus	N	3
2	Deep et al. [9]	41	M	Y	Nasal Cavity	N	2
3	Allevi et al. [24]	NA	F	Y	Maxillary sinus	Y	14
4	Mathis et al. [25]	28	F	Y	Ant fossa	N	2.5
5	Mathis et al. [25]	32	M	Y	Ethmoid/Anterior fossa	Y	2
6	Fatani et al. [26]	67	F	Y	Parotid gland	NA	NA
7	Honda et al. [11]	73	M	NA	Neck	Femur	14
8	Honda et al. [11]	63	F	NA	Nasal cavity	NA	NA
9	Honda et al. [11]	43	M	NA	Maxillary sinus	NA	NA
10	Syed et al. [27]	71	F	N	Temporal bone	Y	1
11	Xian et al. [28]	42	F	Y	Nasal/ethmoid sinuses	NA	NA
12	Xian et al. [28]	43	F	Y	Cavernous sinus	NA	NA
13	Munoz et al. [29]	60	M	Y	Neck	N	1
14	Andreopoulou et al. [30]	NA	NA	Y	Frontal lobe	NA	NA
15	Uno et al. [31]	61	M	Y	Base of skull	NA	NA
16	Uno et al. [31]	53	F	Y	Base of skull	NA	NA
17	Kominek et al. [32]	53	M	N	Nasal cavity	NA	NA
18	Guglielmi et al. [7]	22	M	Y	Ethmoid sinus	NA	NA
19	Sidell et al. [33]	24	F	NA	Larynx	N	<1
20	Pedrazzoli et al. [22]	37	F	Y	Maxillary sinus	N	7
21	Peterson et al. [34]	70	F	Y	Maxillary sinus	N	<1
22	Shelekhova et al. [35]	70	F	Y	Sinonasal cavity	NA	NA
22	Shelekhova et al. [35]	53	M	Y	Sinonasal cavity	NA	NA
24	Parshwanath et al. [36]	42	M	Y	Nasal cavity	NA	NA
25	Winters et al. [37]	55	F	N	Preauricular	NA	NA
26	Viscasillas et al. [18]	64	F	Y	Infratemporal fossa	NA	NA
27	Savage and Zimmer [38]	73	F	Y	Maxillary sinus	NA	NA
28	Gupta et al. [39]	51	M	Y	Sinonasal cavity	NA	NA
29	Honda et al. [11]	24	F	NA	Paranasal sinus	NA	NA
30	Kenealy et al. [40]	79	F	Y	Ethmoid sinus	NA	NA
31	Elston et al. [41]	69	F	Y	Skull	N	<1
32	Kaylie et al. [14]	46	F	Y	Temporal bone	NA	NA
33	Koriyama et al. [42]	41	F	Y	Maxillary sinus	N	<1
34	Inokuchi et al. [43]	24	F	Y	Nasal cavity	N	1
35	Ungari et al. [44]	24	M	Y	Ethmoid sinus	NA	NA
36	Reis-Filho et al. [45]	47	F	Y	Cavernous sinus	N	4
37	Clunie et al. [46]	60	F	Y	Ethmoid sinus	N	4
38	Reyes-Mugica [47]	4	F	Y	Skull	NA	NA
39	Gonzalez-Compta et al. [5]	69	F	Y	Ethmoid sinus	NA	NA
40	David et al. [48]	60	F	Y	Anterior fossa	Y	36
41	Weidner and Santa Cruz [19]	39	F	Y	Maxillary sinus	N	36
42	Olefsky et al. [49]	40	M	Y	Pharynx	NA	NA

PMT phosphaturic mesenchymal tumor, OO oncogenic osteomalacia, F female, M male, Y yes, N no, NA not available, <1 less than 1 year

Another report in 2004 by Shimada et al. [56] focused more on the molecular findings and reported that over-expression of FGF-23 was diagnostic for PMT. In 2013 the

World Health Organization (WHO) classified PMT as an intermediate bone tumor with rarely metastasizing behavior [57]. A recent report by Lee et al. [58] in 2015

Table 3 Summary of 13 intra-oral case reports of PMT in the literature

Case	Reference (year)	Age	Sex	OO	Location of PMT	Recurrent/Metastasis	Follow up (years)
1	Qari et al. (2015), current case	60	M	Y	Gingiva	N	1
2	Qari et al. (2015), current case	58	M	Y	Mandible	Lung + ST	12
3	Luo et al. [8]	13	F	N	Mandible	Y	<1
4	Fatani et al. [26]	58	M	Y	Floor of mouth	Lung	17
5	Honda et al. [12]	20	M	NA	Mandible	NA	NA
6	Monappa et al. [50]	35	M	Y	Mandible	N	1
7	Mori et al. [20]	42	M	Y	Maxilla	N	<1
8	Yun et al. [51]	71	F	Y	Floor of mouth	N	<1
9	Woo et al. [3]	42	F	Y	Mandible	N	<1
10	Uramoto et al. [52]	48	M	Y	Tongue	Y	2
11	Dupond et al. [16]	71	M	Y	Mandible	NA	NA
12	Mugica et al. [47]	9	F	Y	Mandible	N	5
13	Yang et al. [53]	31	F	Y	Mandible	N	<1

PMT phosphaturic mesenchymal tumor, OO oncogenic osteomalacia, F female, M male, ST soft tissue, Y yes, N no, NA not available, <1 less than 1 year

documented that the FN1-FGFR1 fusion gene was identified in 60 % of PMT and proposed the hypothesis that this fusion gene was the pathway of PMT tumorigenesis.

PMT typically occurs in adults but pediatric cases have been reported with no significant gender predilection. In our analysis, extra-oral cases occurred twice as frequently in females, with 28 females and 14 males identified in the published cases. In contradistinction, intraoral cases showed a slight male predominance, with 8 affected males and 5 affected females. We had 3 out of 55 cases (5 %) in pediatric patients verifying how uncommon they are in children. One case was extra-oral occurring in a 4 year old female with a lesion in the skull (Case 38). The other 2 cases were found intra-orally in the mandible. Case 3 was a 13 year old female and case 12 was a 9 year old female. The most common locations are the extremities, followed by head and neck sites, with isolated lesions also found in the chest wall, pharynx, breast, and spinal nerve [50, 59]. In the H&N, the paranasal sinuses were the most favored location for PMT [3]. Gonzalez-Compta mentioned that PMT were most often found in the sinonasal cavity (57 %) followed by the mandible (20 %) [5]. Our data yielded similar results with the two most common sites of involvement being the sinonasal cavity (38 %) and the mandible (15 %). The clinical features of OO are bone pain, muscle tenderness, and multiple bone fractures. Biochemical findings include hypophosphatemia, normal 1,25 dihydroxyvitamin D levels, elevated alkaline phosphatase activity but normal calcium and PTH. Osteomalacia is a metabolic disorder affecting mature bone mineralization in adults. It can be caused by vitamin D deficiency, medication, malabsorption, liver, and kidney disease [3]. OO is a rare clinicopathological type of

acquired osteomalacia secondary to PMT. Classically, the hypophosphatemia caused by PMT is corrected after surgical removal [60]. There is a small percentage of tumors within the histological spectrum of PMT that do not demonstrate phosphate diuresis and have been referred to as PMT non-phosphaturic variant [32, 37, 61, 62]. From our literature review 4 out of 55 cases did not have OO. Three of these 4 cases were extra-oral (cases 10, 17, and 25) and one case was intra-oral (case 3). Although Olefsky [49] recognized a mesenchymal tumor as a cause of OO in 1972 and suggested the name ossifying mesenchymal tumor, it wasn't until 1987 that Weidner proposed the name PMT [17]. This led Folpe to later revise and recognize the histological diversity of PMT as a distinct clinicopathological entity [4]. This could explain the period between 1972 and 1987 when PMT was still an unrecognized entity and the unfamiliar histological features resulted in a variety of diagnoses [4]. Therefore it is important to include PMT in a differential diagnosis of mesenchymal tumors causing OO that includes HPC [63], GCTB [64], and osteosarcoma [65]. HPC shows hyalinized “staghorn” blood vessels that contain round to ovoid cells and which lack the grungy calcifications and the MNGCs that are found in PMT [63]. GCTB expresses numerous MNGCs with agglomeration of around 20–25 nuclei and clear cytoplasm. Even though PMT also contains MNGCs, they are fewer in number and have fewer nuclei [66]. While a similarity between PMT and osteosarcoma is the production of bone, PMT is cytologically bland while osteosarcoma displays cytologic atypia and bone production is variable with many tumors producing some cartilage as well [67]. Folpe also mentioned that PMT comprised only 9 out of over 150,000 mesenchymal tumor consultations seen

at the AFIP over the past 30 years [4]. Our table shows similar data where only 50 cases of PMT in the H&N were documented in the literature during the past 43 years.

Histologically, PMT consists of bland spindle cells with prominent vascularity and numerous multinucleated giant cells embedded in a chondromyxoid matrix with focal areas of calcification. Stromal changes vary from myxoid to chondromyxoid to areas with osteoid. These classic histological features are characteristic of PMT and Folpe suggested that the histological features alone should raise the suspicion of PMT without knowledge of the characteristic clinical and serological parameters. On occasion however, lesions may only have an osteoid like matrix and spindle cell proliferation without MNGCs and calcifications, making it challenging to reach a definitive diagnosis of PMT on histological features alone [61, 68]. A storiform or fascicular pattern with infiltrative growth can also be observed [10]. Although most cases of PMT behave as a benign neoplasm, 10 % recur, and rarely metastasis does occur [26, 52, 69]. Malignant features include nuclear atypia, hypercellularity, and increase in mitotic activity of 5 or more in 10 high power fields [4, 21]. We found 9 recurrences, of which 3 metastasized. It is also interesting to note that in our case 2, while metastatic spread was identified, the tumor showed no cytological features of malignancy and a low proliferative index of approximately 3 %. Therefore, cytological features of PMT cannot always predict behavior. Immunohistochemistry (IHC) of PMT has been reported to be positive for vimentin, indicating a mesenchymal origin, and negative for S-100, CD68, desmin, CD34, and cytokeratin [25, 47].

In addition to the clinical and microscopic findings, molecular testing for serum or tumor FGF-23 is a useful diagnostic tool for PMT. FGF-23 is a protein also known as phosphatonin, a hormone-like protein that inhibits the transportation and reabsorption of phosphate in the proximal renal tubules and it also affects vitamin D metabolism by preventing the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [38, 43].

PMT is a unique neoplasm with diverse but specific histological features that produces FGF-23 and metabolic bone defects. However, other tumors such as fibrous dysplasia, aneurysmal bone cyst, chondromyxoid fibroma, and osteosarcoma can also produce the same effect [70]. The exact mechanism of how FGF-23 affects the phosphate equilibrium is not clear but its function is independent from type IIa sodium phosphate co-transporter (NaPi-2a) that is controlled by PTH which is the key component for renal phosphate reabsorption [56]. Yamashita et al. [71] reported that heparin-like molecules and the MAPK pathway may be the essential vehicle for FGF-23 activity. The best treatment for PMT is wide excision with clear margins which is expected to result in an increase in serum

phosphate levels within a few weeks [39, 44]. In case 1 the patient's phosphate levels returned to normal after surgery and the patient has been free of disease for 14 months. Unfortunately in case 2 the patient had multiple recurrences with eventual metastatic spread. Occasionally it can be difficult to initially detect the tumor due to its small size. Therefore, methods of investigation include MRI, octreotide scintigraphy, and positron emission tomography (PET) [40]. Adjunct therapy, such as radiotherapy and chemotherapy can be considered in areas where it is difficult to remove the tumor by surgery. But the goal for adjunct therapy is typically for tumor shrinkage and not complete resolution.

Conclusion

PMT is a neoplasm of bone or soft tissue that produces paraneoplastic osteomalacia by secreting FGF-23. While it shows some predilection for the head and neck area, and particularly the sinonasal cavity, only 11 cases have been reported in the oral cavity. Due to its rarity and non-specific clinical presentation, a comprehensive evaluation of medical, laboratory, and radiographic findings in combination with microscopic assessment is crucial for a definitive diagnosis. OO should always be considered in a patient with hypophosphatemia, bone pain, and multiple fractures. Surgical excision reverses the metabolic effects and is the treatment of choice. The clinical behavior of PMT cannot always be predicted based on cytological features, therefore, long-term follow-up is warranted.

Compliance with Ethical Standards

Conflict of interest None declared.

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