Phosphaturic Mesenchymal Tumor Involving the Head and Neck: A Report of Five Cases with *FGFR1* Fluorescence In Situ Hybridization Analysis

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Abstract Phosphaturic mesenchymal tumor (PMT) is a rare neoplasm; however, it is the most common cause of tumor-induced osteomalacia (TIO), a paraneoplastic syndrome characterized by renal phosphate wasting and hypophosphatemia. A subset of PMTs harbours an *FGFR1* translocation although this alteration has not been demonstrated in PMT involving a head and neck site. We present a series of five PMTs involving the head and neck and demonstrate the diagnostic utility of fluorescence in situ hybridization (FISH) for detecting *FGFR1* translocations. Patients' age and sex, tumor location, original diagnosis, the duration of symptoms, the presence of TIO, biochemical results, and medical management were reviewed. The median age at presentation was 45 (range, 24–58 years) and TIO was present in three cases. Four tumors involved soft tissue and one involved bone. Four out of the five tumors in our series were initially misdiagnosed. Three tumors were ultimately categorized as malignant PMT (two patients developed metastatic disease). *FGFR1* translocation was present in two out of four cases and remained unknown in one case. In summary, we report on five cases

of PMTs arising in the head and neck and confirm utility of *FGFR1* FISH in the diagnosis of a subset of PMT.

Keywords Phosphaturic mesenchymal tumour · Tumor-induced osteomalacia · *FGFR1* · Fluorescence in situ hybridization · Translocation

Introduction

Phosphaturic mesenchymal tumor (PMT) is a rare neoplasm; however, it is the most common cause of tumor-induced osteomalacia (TIO), a paraneoplastic syndrome characterized by renal phosphate wasting and hypophosphatemia [1, 2]. Patients typically present with pain and weakness and diagnosis is often delayed. Histologically, PMTs are characterized by a proliferation of spindle cells, pronounced pseudovascular spaces, and a calcified matrix. Although the great majority of PMTs are benign, tumors with histologic evidence of malignancy have been described and cases with multifocal or metastatic disease have been reported [1, 3, 4].

PMTs can arise in any bone or soft tissue site albeit mostly in the extremities and appendicular skeleton [1]. Tumors involving the head and neck are extremely rare [3, 5–9]. Half of all PMTs reported in the head and neck have involved the sinonasal tract; other sites include the pharynx, maxilla, mandible, tongue, floor of mouth, and posterior neck. The true incidence of PMT in the head and neck may be higher than reported as tumors in this region are frequently misdiagnosed as a variety of more common entities including glomangiopericytoma, giant cell tumor, or low grade osteosarcoma [10].

Recent evidence indicates that PMTs induce renal phosphate wasting and ultimately osteomalacia through

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production and secretion of phosphatonins, the most common being fibroblast growth factor-23 (FGF23). Phosphatonins prevent reabsorption of phosphate in the renal proximal tubules, which results in hypophosphatemia and ultimately bone loss. The increased expression of FGF23 by neoplastic cells can be demonstrated in formalin-fixed, paraffin-embedded tissue by chromogenic in situ hybridization (CISH) [11]. In a subset of tumors, the overexpression of FGF23 is associated with a fibronectin-1-fibroblast growth factor receptor-1 (FN1-FGFR1) fusion that can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) [12].

In this report, we describe the clinicopathologic features of five patients with PMTs arising in the head and neck and demonstrate the utility of *FGFR1* fluorescence in situ hybridization (FISH) for confirming this diagnosis.

Methods

Case Selection

Five cases of PMT involving the head and neck were retrieved from the institutional files of the authors between 1990 and 2015. Patients' age and sex, tumor location, original diagnosis, the duration of symptoms, the presence of TIO, serum levels of calcium and phosphate, and medical management were reviewed. CISH for FGF23 mRNA

was performed on formalin-fixed, paraffin-embedded tissue in one case according to previously described methods [11]. Two cases have been reported previously without *FGFR1* FISH testing [3, 9].

Fluorescence In Situ Hybridization

FISH was performed using *FGFR1* gene break-apart probe as per manufacturer's recommendations (Cytocell, Cambridge, United Kingdom). The intact gene produces a yellow signal. In contrast, a translocation event results in distinct red and green signals. A blue probe directed at the centromere on chromosome 8 acted as a control. FISH was performed on 6- μ m-thick formalin-fixed and paraffin embedded tissue. At least 60 nuclei were counted for each case.

Results

Clinical Presentation

The clinicopathological variables and translocation status for each case are shown in the Table 1. The median age at presentation was 45 (range, 24–58 years) and three out of five patients were female. Two patients with long-standing (>10 years) TIO were initially treated with supplemental phosphate without effect. In case 2, the patient presented

Table 1 Clinicopathological characteristics of patients with phosphaturic mesenchymal tumor involving head and neck sites

Case	Sex/age	Symptoms/signs	TIO/HPS	Duration of symptoms/follow-up	Head and neck subsite	Original diagnosis	Final diagnosis	<i>FGFR1</i> Translocation	Metastases
1	F/45	Left eye swelling and loss of vision	No	<1 month/no local recurrence or metastatic disease	Left frontal sinus	Cementifying fibroma	Benign PMT	Yes	No
2	M/50	Back pain and multiple pathologic fractures	Yes	2 years/symptom resolution, no metastatic disease	C3 vertebral body	Myxoid neoplasm	Benign PMT	No	No
3	M/58	Pathologic fractures	Yes	>20 years/multiple recurrences, metastasis to lung with wedge resection	Floor of mouth	Benign PMT	Malignant PMT	Failed	Yes
4	F/33	Ricket-like deformities	Yes	>10 years/multi-focal disease with metastasis to the lung	Nasal cavity, lip, and tongue	Benign chondro-mesenchymal tumor	Malignant PMT	Yes	Yes
5	F/24	Airway obstruction	No	<1 week/no local recurrence or metastatic disease	Larynx	Giant cell tumour of soft tissue	Malignant PMT	No	No

PMT phosphaturic mesenchymal tumour, TIO tumor-induced osteomalacia, HPS hypophosphatemic syndrome, M male, f female

with numerous pathologic fractures involving the spine, ribs, sacrum, and calcaneus. In case 4 the patient presented as an adolescent who developed ricket-like skeletal deformities. In both cases, the tumors were not clinically appreciated at the time of presentation and the patients were treated medically for hypophosphatemia and osteoporosis. All tumors were eventually surgically resected. In all cases, except for case 3 [9], a diagnosis other than PMT was rendered after the initial biopsy.

Pre-operative biochemical analysis revealed hypophosphatemic syndrome in three out of five patients. All three patients with TIO were hypophosphatemic at presentation with levels normalizing after resection of the tumor. In case 4, the patient was also noted to have hyperphosphaturia (urine phosphate 1.79 g/24 h), which rapidly corrected (urine phosphate 0.13 g/24 h) after resection.

In case 3, the patient developed metastatic disease involving the lungs 17 years after resection of the primary tumor [9]. In case 4, the patient initially presented with a tumor involving the distal radius and later developed metastatic disease involving the nasal cavity, lip, and

tongue. In case 5, the patient underwent neoadjuvant chemotherapy prior to a total laryngectomy; only the biopsy material was available for this study [3].

Histology

Four tumors involved soft tissue and one involved bone. All cases were infiltrative (Figs. 1a, 2a). Foci of pale gray, flocculent calcifications, a characteristic feature of PMT, were frequently observed (Figs. 1b, 2b). The tumors were composed of spindle or epithelioid cells with well defined cell borders embedded in a chondromyxoid matrix (Fig. 1c) with only occasional multinucleated giant cells. In case 2, micromineralization was seen surrounding individual cells (Fig. 2c).

In cases 3 through 5, the tumors were cellular with infiltrative borders (Fig. 3). The stroma ranged from myxoid to hyalinized with abundant collagen, punctate or flocculent calcifications, and numerous foci of osteoid-like matrix. The tumors were composed of spindle, stellate, or epithelioid cells (Fig. 3c) although one morphological type

Fig. 1 Benign phosphaturic mesenchymal tumor (PMT) with *FGFR1* translocation (case 1). **a** The tumor demonstrates infiltration into the bone (H&E, 40×). **b** Tumor cells and foci of grungy calcification undermine the respiratory-type epithelium (H&E, 200×). **c** Individual

tumor cells are embedded in a chondroid matrix (H&E, 400×). **d** *FGFR1* fluorescence in situ hybridization. Tumor cells with the translocation show distinct red and green split signals in addition to the normal fused yellow signal. H&E indicates hematoxylin and eosin

Fig. 2 Benign phosphaturic mesenchymal tumor (PMT) with intact *FGFR1* (case 2). **a** The tumor is present within bone (H&E, 40 $\times$). **b** As in case 1, large foci of grungy calcification are easily identified (H&E, 200 $\times$). **c** Tumor cells embedded in a chondromyxoid matrix with individual cells surrounded by micromineralization (H&E,

400 $\times$). **d** *FGFR1* fluorescence in situ hybridization. This case was negative for the translocation as the tumor cells demonstrated the two normal fused yellow signals per nucleus. H&E indicates hematoxylin and eosin

tended to predominate in each tumor. All tumors contained numerous osteoclast-like multinucleated giant cells. The blood vessels in these tumors were often thin walled and closely spaced, which imparted “sieve-like” appearance at low power. All three tumors demonstrated areas of increased cellularity, hyperchromatic cells, and significant pleomorphism (Fig. 3c). Case 4 was associated with extensive metastatic disease and the mitotic activity in this tumor was as high as 25 mitotic figures per 10 high power fields (400 $\times$). In contrast, the mitotic activity in case 5 did not exceed 10 mitotic figures per 10 HPF.

FGFR1 Fluorescence In Situ Hybridization

An *FGFR1* translocation was identified in two out of four cases and remained unknown in one case due to unsuccessful hybridization on several attempts. In case 1, a translocation was detected in 80 % of cells (Fig. 1d). In contrast, case 4 demonstrated a complex translocation involving 42 % of the tumor cells (Fig. 3d). As a

comparison, a tumor with a normal signal pattern is shown in Fig. 2d.

CISH performed on tumoral tissue from case 2 demonstrated increased expression of *FGF23* mRNA within neoplastic cells (not shown) [11].

Discussion

PMT is a bone and soft tissue neoplasm that can occur at any age and has no known risk factors. Patients with PMT often present with pain or weakness although the symptoms depend on the site affected and not all patients will develop osteomalacia. Recently, Lee and colleagues used RT-PCR in addition to FISH and Western blot analysis to demonstrate that nine of fifteen PMTs arising in non-head and neck sites harbored a translocation that resulted in a novel *FN1-FGFR1* fusion protein [12]. This fusion protein is believed to cause the upregulation of the FGFR1 receptor. However, FGFR1 may have other translocation partners

Fig. 3 Malignant phosphaturic mesenchymal tumor (PMT) with *FGFR1* translocation (case 4). **a** Undermining the squamous epithelium are lobules of tumor cells with extension deep into the submucosa (H&E, 40 $\times$). **b** Tumor cells including numerous multi-nucleated osteoclast-like giant cells are seen infiltrating skeletal

muscle (H&E, 200 $\times$). **c** Multi-nucleated giant cells and large spindle cells with hyperchromatic nuclei (H&E, 400 $\times$). **d** *FGFR1* fluorescence in situ hybridization. A complex translocation resulted in a solitary green signal in addition to 1–2 normal fused yellow signals. H&E indicates hematoxylin and eosin

that would require multiple sequence specific probes to detect by RT-PCR. In contrast, the break apart FISH assay would detect translocation of *FGFR1* with other partners and can be performed on the formalin fixed paraffin embedded tissue block.

Because PMT is rare, the diagnosis is often not considered by clinicians and pathologists even in patients presenting with osteomalacia. Indeed, most patients ultimately diagnosed with PMT have experienced osteomalacia for years before the tumor is identified [10]. In one of our cases, the young age of the patient and the presence of skeletal deformities at the time of her initial presentation led the clinicians to consider rickets and other diseases related to vitamin D deficiency. In case 2, the older age of the patient and the presence of multiple vertebral and rib lesions raised the clinical possibility of multiple myeloma. It was not, however, until after multiple myeloma was ruled out that an endocrinologist raised the possibility that the largest lesion (in the C3 vertebral body) was a PMT and that the other lesions were in fact pathological fractures.

Not all PMTs result in osteomalacia. Indeed, two patients in our series (case 1 and 5) did not demonstrate evidence of TIO and their serum phosphate levels were normal at presentation. In these instances, the location of the tumor may have resulted in early symptom onset, with the patient presenting before TIO could develop. Despite this, both tumors demonstrated histologic features typical of PMT including multi-nucleated giant cells and flocculent calcifications. On the contrary, some patients who present with TIO are found to have tumors that have histologic features that overlap between PMT and other soft tissue tumors of the head and neck such as glomangiopericytoma [8]. In our opinion, these tumors warrant ancillary molecular investigations such as FISH to confirm the presence of a translocation in *FGFR1* or CISH to detect increased expression of *FGF23*.

PMTs biopsies are often misdiagnosed initially. Only one of the tumors in our series was originally diagnosed as PMT, a pattern consistent with previously published studies [1, 5, 10]. Tumors arising in the head and neck may be

more prone to misdiagnosis as these sites are often biopsied and the small amount of material provided may not demonstrate features that distinguish PMT from similar tumors. For example, in case 2 from our series, the biopsy was very small and in hindsight not representative of the tumor and a preliminary diagnosis of myxoid neoplasm was issued. In these cases, a careful review of the patient's history, laboratory results, and radiological studies for evidence of chronic pain, hypophosphatemia, osteomalacia, or pathological fractures may be particularly informative. The diagnosis is further complicated, however, in patients without a history of osteomalacia. Two patients in our study did not have osteomalacia and the duration of their symptoms was relatively short. In these cases, the patients sought medical treatment for symptoms/signs related to mass effect.

In our series, PMT was initially misdiagnosed as cementifying fibroma, myxoid neoplasm, benign chondromesenchymal tumor, and giant cell tumor of soft tissue. Other soft tissue lesions in the differential diagnosis include solitary fibrous tumor and glomangiopericytoma, both of which share the vascular pattern of PMT but lack the chondromyxoid matrix and 'grungy/flocculent' calcifications. Bone neoplasms that are in the differential diagnosis include giant cell tumor, chondromyxoid fibroma, chondromas, and chordomas. Giant cell tumors are characterized by a proliferation of mononuclear and osteoclast-like giant cells, with both cell types demonstrating similar nuclear features. They may have foci consisting of spindle cells, typically in a storiform pattern, and reactive immature bone, but lack the chondroid matrix of PMT. Chondromas may also possess foci of calcification and in bony sites, giant cells, but lack the predominant spindle cell component of PMT. Chondromyxoid fibroma is usually a well circumscribed, lobulated lesion composed of chondroblasts with abundant eosinophilic cytoplasm embedded in myxoid and poorly formed, hyaline cartilage-type stroma. It tends to be more cellular at the periphery of the nodules and osteoclasts, calcifications, and a spindle cell component, typically within fibrous septa, may be seen. Although there is increased vascularity, the vessels can be distinguished from the hemangiopericytoma-like vessels found in PMT. Finally, chordoma is a rare malignant bone tumor that arises in the midline from the fetal notochord. It is composed of two cell types, oval cells and physaliferous cells arranged in cords and lobules, separated by fibrous septa. The neoplastic cells are embedded in extensive myxoid stroma that lacks the 'grungy' calcification of PMT. Immunohistochemistry is particularly useful in making this diagnosis with chordomas being positive for S-100, cytokeratin, EMA, and brachyury [13].

In case 1, the patient was originally diagnosed with a cementifying fibroma, a rare bone neoplasm that usually

occurs in the mandible; however, it has also been reported in the maxilla and other facial bones [14]. Like PMT, these tumors are composed of bland spindle cells with foci of calcification. However, cementifying fibromas tend to be well circumscribed and contain a variable amount of mineralized material that resembles cementum, features that are not consistent with PMT.

The diagnosis of malignant PMT is even more challenging, as large areas of the tumor may resemble undifferentiated pleomorphic sarcoma. Criteria of malignancy include nuclear atypia, greater than 5 mitoses/10 HPFs, increased cellularity [1]. High grade tumors need to be distinguished from chondrosarcoma and osteosarcoma and the pathologist is encouraged to look for better differentiated areas of the tumor with features more typical of PMT. In these cases, FISH for a *FGFR1* translocation may be particularly useful [12].

In conclusion, a subset of PMT involving head and neck harbor *FGFR1* translocation, an abnormality that can be detected by FISH using a commercially available probe. *FGFR1* FISH appears to be a helpful tool to diagnose PMT, especially in cases with clinical and laboratory findings unknown to the pathologist at the time of tissue biopsy. Further studies on *FGFR1* abnormalities in other soft tissue neoplasms are needed to establish the specificity of this genetic alteration.

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