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Case Report

Phosphaturic mesenchymal tumor of the nasal cavity: Clinicopathologic correlation is essential for diagnosis

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ABSTRACT

Phosphaturic mesenchymal tumor (PMT) is a rare neoplasm in which the tumor cells produce fibroblast growth factor 23 (FGF23), leading to oncogenic osteomalacia and thus a distinct clinical presentation. However, the pathologic findings of PMT are often non-specific and variable, especially in tumors occurring in the head and neck. We present a case of a 66-year-old female who presented with osteomalacia-related symptoms and was found to have a nasal cavity mass. Histopathologic examination was suggestive of PMT but certain characteristic features were lacking, requiring confirmation of the diagnosis by chromogenic in situ hybridization (CISH) assay for FGF23 mRNA. The patient's symptoms and laboratory abnormalities resolved upon resection of the tumor.

1. Introduction

Phosphaturic mesenchymal tumor (PMT) is a very rare neoplasm of bone and soft tissue that is the most common cause of tumor induced osteomalacia (TIO), a paraneoplastic syndrome caused by tumor cell secretion of hormones that impair renal phosphate reuptake [1,2]. Fibroblast growth factor 23 (FGF23) is the most common of these hormones termed “phosphatonins” [2]. In addition to laboratory abnormalities such as hypophosphatemia and hyperphosphaturia, patients with PMT usually present with symptoms and signs related to systemic bone demineralization, such as bone pain, fractures, weakness and gait disturbances [3]. A timely and accurate diagnosis is thus imperative for initiating proper treatment in patients with suspected TIO [2].

The majority of PMTs occur in adults of a wide age range, and there does not seem to be a gender predilection [1,3,4]. PMT most commonly involves the bone or soft tissue of the extremities, while head and neck sites represent only an estimated 5% of cases [3]. Of PMTs occurring in the head and neck, extra-oral sites are more common than intra-oral sites, and the sinonasal region is thought to be the most common site of involvement, followed by the mandible, based on two series [3,5].

The typical microscopic morphology of PMT consists of cytologically bland spindle cells, osteoclast-like multinucleated giant cells, stromal capillary vasculature, and chondromyxoid matrix with areas of “grungy” basophilic calcification [1]. Microcystic change and mature adipose tissue may also be seen [2]. For tumors displaying all of these features, the diagnosis may be achieved without much difficulty, especially in the context of characteristic clinical findings. However, many cases will lack one or more of the above features, leading to a diagnostic challenge [3]. Specifically, sinonasal tumors have been noted to express disparate histologic features including increased cellularity, minimal to no matrix, and prominent hemangiopericytoma-like features [1]. In cases such as these, the detection of FGF23 expression can allow the pathologist to make a definitive diagnosis. Various methods are currently available for detecting FGF23, including immunohistochemistry, reverse transcription polymerase chain reaction (RT-PCR) testing, and a newer method, chromogenic in situ hybridization (CISH) for the detection of FGF23 mRNA in formalin-fixed paraffin-embedded (FFPE) tissue sections [2]. We report a case of a nasal cavity PMT with atypical histologic findings and a diagnosis confirmed by CISH assay.

2. Clinical presentation

A 66-year-old female presented with a one-year history of progressive weakness in the legs and feet, which was later accompanied by upper extremity pain and heaviness. She experienced difficulty standing

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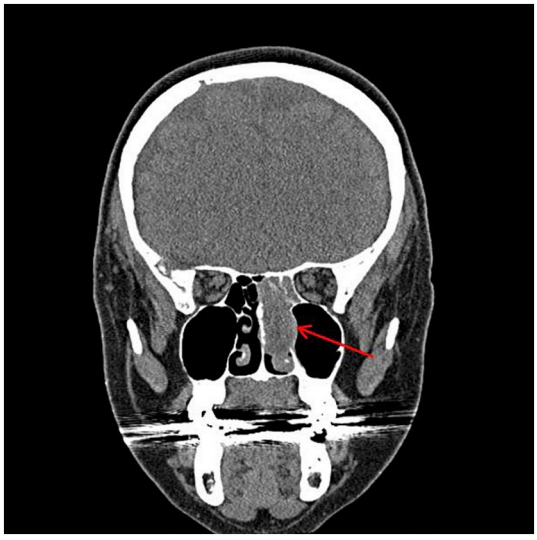

Fig. 1. CT sinuses (coronal view). There is a mass filling the left nasal cavity and abutting the cribriform plate.

up from a seated position, and she also had an abnormal gait and required the assistance of a walker. She later noted symptoms of nasal obstruction, epistaxis, and headache. Additionally, she reported unintentional weight loss of 20 pounds over a 6 month period. Labs were significant for a serum phosphate of 1.5 (reference range 2.4–4.5) mg/dL. PET/CT revealed healing rib fractures and some focal increased FDG uptake in the skull base. CT sinus and MRI skull base revealed a 3.2 cm ovoid mass in the posterior aspect of the left nasal cavity, with abutment of the cribriform plate (Fig. 1). A biopsy of the mass showed a vascular neoplasm of uncertain etiology. The patient was then referred to our institution for further management.

The patient underwent complete endoscopic endonasal resection of the mass with negative margins. Intraoperatively, the mass grossly appeared as an encapsulated vascular mass attached to the septum, middle turbinate, and anterior cranial base. The tumor also extended intradurally into gyrus rectus and olfactory bulbs. Reconstruction was accomplished with synthetic dural replacement and pedicled nasoseptal flap.

3. Pathological findings

Histopathologic examination revealed bland oval to spindled cells arranged in a peculiar configuration, in which the superficial subepithelial space contained a highly cellular band-like zone of tumor cells, and deep to this was a sharply demarcated, hypocellular area containing hyaline to myxoid stroma devoid of calcification. A well-developed vascular network was present throughout the tumor, ranging from small capillaries to larger ectatic, often staghorn vessels. Areas of microcystic change, hemosiderin deposition, and mature adipose tissue were also identified (Fig. 2). There were no multinucleated giant cells present. The tumor possessed histologically benign features, with minimal cytologic atypia, low mitotic activity, and no necrosis. Immunohistochemical stains showed that the lesional cells were positive for FLI-1 and weakly positive for ERG, while they were negative for pancytokeratin, CD31, CD34, D2–40, STAT6, HMB-45, Melan-A, nuclear beta-catenin, smooth muscle actin and HHV-8 (Fig. 3). The Ki-67 proliferation index was 3%. The diagnosis of PMT was confirmed by positive CISH for FGF23 mRNA (Fig. 4).

4. Clinical Follow-up

Following resection of the mass to negative margins, the patient reported resolution of her bone pain and was able to ambulate without a walker by her 3-week postoperative visit. Additionally, the patient's phosphate normalized postoperatively to 4.2 mg/dL within 9 weeks.

5. Discussion

PMT is an extremely rare neoplasm which may be under-recognized by clinicians, surgeons or pathologists, especially when occurring at an uncommon site such as in the head and neck. An additional challenge for the pathologist is that PMTs occurring in the head and neck, specifically in the nose, often lack the distinctive calcified matrix that is characteristic for PMT involving other anatomic sites. The case described here also notably lacked the multinucleated giant cells which are described as a common feature of PMT. These morphologic variations in an already rare entity may elude the pathologist; however close attention to the patient's clinical presentation and laboratory findings is crucial in including PMT in the differential diagnosis among its morphologic mimics. In the current case, the differential included solitary fibrous tumor (SFT), sinonasal glomangiopericytoma, and angiomyolipoma, while in other cases PMT may resemble giant cell tumor, osteosarcoma, or various chondroid lesions.

The unusual and relatively non-specific immunoprofile of PMT adds to the diagnostic difficulty but is valuable in the exclusion of other entities in the differential diagnosis. While a PMT may closely mimic SFT or sinonasal glomangiopericytoma, as it did in the present case due to the striking hemangiopericytoma-like vascular pattern, the immunohistochemical findings (negativity for CD34, STAT6, smooth muscle actin and nuclear beta-catenin) do not support either of these entities. In cases with adipose tissue co-existing with the prominent vascular network, angiomyolipoma should be considered; however, HMB-45 will be positive in angiomyolipoma and negative in PMT. In addition to these pertinent negative stains, PMT has been shown to consistently express ERG, CD56, SATB2 [1], FLI-1 [6] and SSTR2A [7]. The present case showed tumor cell expression of the endothelial markers ERG and FLI-1, while the other common vascular markers CD31, CD34 and D2–40 were negative.

Because the morphology and immunohistochemical findings may be variable, detection of the FGF23 hormone secreted by PMT tumor cells can help rule in or rule out a diagnostic suspicion of PMT. Immunohistochemical testing of FGF23 offers wide availability and preserves the morphology of the tissue, however the commercially available antibody for FGF23 offers suboptimal specificity in diagnosing PMT. Non-neoplastic cells, including osteoclasts and endothelial cells, can show granular cytoplasmic staining with FGF23 immunohistochemistry [4]. SATB2 and SSTR2A stains mentioned above may also show non-specific staining, within osteoblasts and endothelial cells, respectively [1,7]. RT-PCR testing is another option for FGF23 identification and is highly sensitive; however, this method does not permit tissue visualization and can be positive in other bone tumors due to low-level FGF23 mRNA expression in non-neoplastic bone [2]. The CISH assay for FGF23 mRNA developed at Mayo Clinic is highly sensitive (96%) and specific (100%) for the diagnosis of PMT and allows visualization of signals within FFPE tissue, proving to be immensely useful for cases with variant histologic features or in biopsies with limited material [2].

The consistent finding of TIO and FGF23 expression in PMT and the majority of other osteomalacia-associated mesenchymal tumors lends support that these entities represent morphologic variations of a single

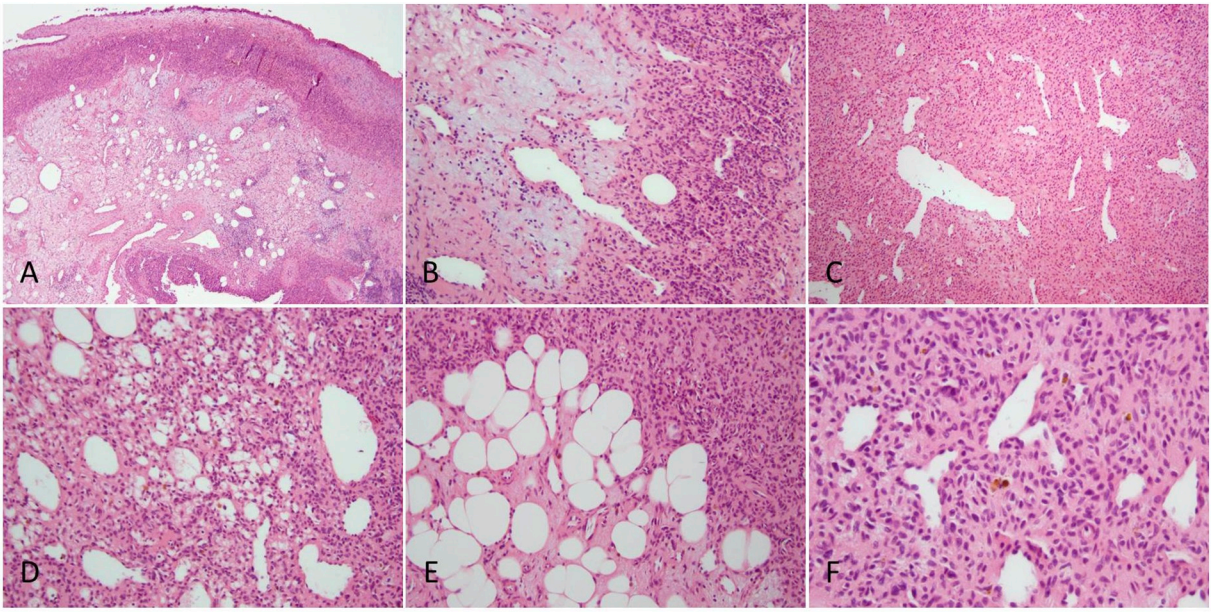

Fig. 2. Histologic findings. Hematoxylin and eosin (H&E)-stained sections show a dense band-like zone of hypercellularity just beneath the surface epithelium (A, x20), transition to a hypocellular area with myxoid stroma (B, x200), prominent hemangiopericytoma-like areas with staghorn vessels (C, x100), microcystic change (D, x200) and mature adipose tissue (E, x200). The lesional cells are oval to spindled with minimal cytologic atypia; hemosiderin deposition is also present (F, x400).

tumor type [4]. Recognition and complete resection is imperative, as the TIO is cured upon removal of the mass. The majority of PMTs behave in a clinically benign fashion, however approximately 10% will recur, and there are rare reports of metastatic tumors. Importantly, cytologic features cannot always predict biologic behavior, as cytologically benign PMTs with metastatic spread have been documented [3].

6. Conclusion

PMT is a rare neoplasm but is the most common cause of TIO; therefore, this diagnosis should be entertained in any patient presenting with osteomalacia and a newly identified mass. The tumor may show histologic heterogeneity leading to a broad differential diagnosis, but confirmatory testing of FGF23 mRNA via CISH is available. While most tumors show benign clinical behavior, recurrence and rarely metastasis have been reported, warranting long-term clinical follow-up.

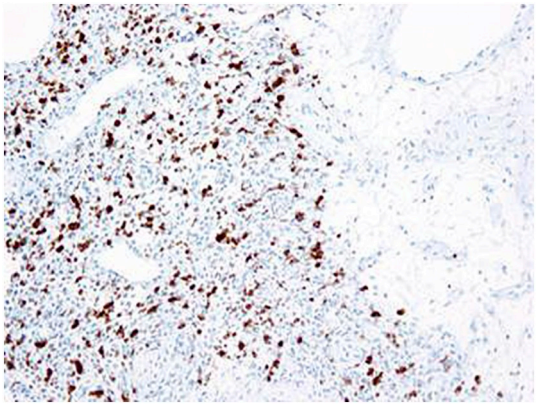

Fig. 4. CISH for FGF23 mRNA. The tumor cells are strongly positive.

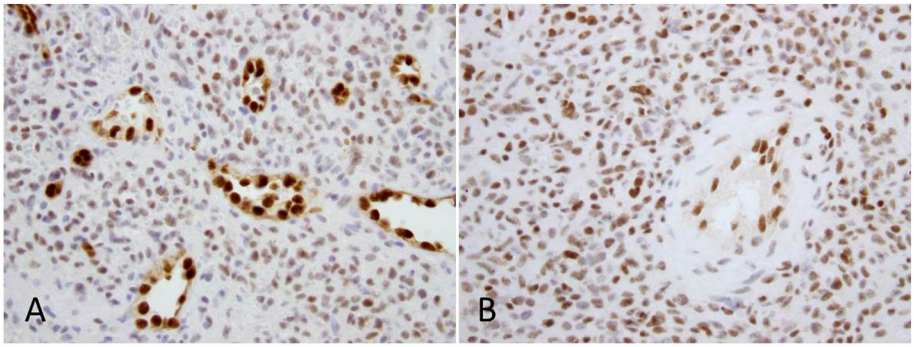

Fig. 3. Immunohistochemical findings. ERG shows strong staining in the endothelial lining of the vessels and weaker staining in the tumor cells (A, x400). FLI-1 shows equally strong staining in the tumor cells and vascular lining cells (B, x400).

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Conflicts of interest

The authors declare no conflict of interest.

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