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Case Report

Intracranial phosphaturic mesenchymal tumor, mixed connective tissue variant presenting without oncogenic osteomalacia

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Abstract

Background: Phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) is a rare tumor typically occurring in soft tissues and bone, causing oncogenic (tumor-induced) osteomalacia (TIO) through secretion of the phosphaturic hormone, fibroblast growth factor-23 (FGF-23). Rare tumors identical to PMTMCT occur without known TIO. Intracranial localization of PMTMCT is extremely rare, with only two cases reported in the literature. We present a very unusual case of a patient with an intracranial PMTMCT that presented with neurologic changes without osteomalacia.

Case Description: A 67-year-old woman presented with progressive incontinence, apathy, and abulia after having undergone a total knee replacement 1 month earlier. Imaging disclosed a large left frontal anterior fossa mass. She underwent uncomplicated surgical resection of this tumor. Surprisingly, histopathology suggested PMTMCT. Reverse transcription polymerase chain reaction (RT-PCR) assay demonstrating FGF-23 expression in the tumor confirmed the diagnosis. Serum FGF-23 levels postoperatively were normal and she had no clinical or laboratory evidence of osteomalacia or phosphaturia.

Conclusion: This report should serve to alert clinicians to the possibility that PMTMCT can be included in the differential diagnosis of intracranial masses even in the absence of tumor-induced osteomalacia.

Key Words: Intracranial, neoplasm, neuropathology, oncogenic osteomalacia

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INTRODUCTION

Phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) is a rare tumor of soft tissue and bone. Although histologically heterogeneous, this tumor is felt to comprise a single entity, and is one of four subtypes of phosphaturic mesenchymal tumors.[4,15] PMTMCT can occur in soft tissue and bone nearly anywhere in the body, but most often arise in the extremities.[5] It has been reported in the head and neck region, particularly in the craniofacial sinuses. Intracranial occurrence of this tumor is extremely rare and only two cases of an intracranial PMTMCT have been described in the literature.[3,11] It is not described in the World Health Organization Classification of Tumors of the Central Nervous System.[7]

PMTMCT is most often discovered when a patient is

found to have osteomalacia. Oncogenic osteomalacia is a rare paraneoplastic syndrome typically associated with mesenchymal tumors that cause biochemical abnormalities including hypophosphatemia and elevated alkaline phosphatase. The link between osteomalacia and mesenchymal tumors was first established by Prader *et al*. in 1959.[10] These tumors produce oncogenic osteomalacia through excessive secretion of fibroblast growth factor-23 (FGF-23), which causes decreased renal tubular phosphate reabsorption.[2,12,16]

We present a unique case of PMTMCT arising intracranially and presenting without oncogenic osteomalacia.

Clinical presentation

A 67-year-old, right-handed woman presented with a 1-month history of progressive abulia, apathy, depression, and urinary and fecal incontinence. She began to notice these symptoms upon being dismissed home from a rehabilitation facility following a total left knee arthroplasty. She presented initially to her primary care provider, who diagnosed depression and prescribed fluoxetine. Several days later, she was brought by family to her local emergency department with a chief complaint of worsening depression. She denied any other symptoms and, specifically, did not have bone pain, muscle pain, or any recent history of fractures. Her past medical history included hypertension, hyperlipidemia, diabetes mellitus type 2, and obesity. She had 17 siblings with a history benign intracranial meningioma in one brother, colon cancer in one brother, bladder cancer in a sister, and Friedreich's ataxia in two sisters and one brother. Neurologic exam on presentation was significant for mild abulia, but the patient was fully oriented, with insight into her personality changes and ability to cooperate with the exam. She had no frontal lobe release signs, and the rest of her neurologic exam was unremarkable.

Imaging and Laboratory Results

A CT scan of the head without contrast revealed a left frontal heterogeneous mass with surrounding edema and some midline shift. A MRI of the brain with and without contrast confirmed a large left frontal mass (7.4 cm × 4.3 cm × 5.1 cm) that was heterogeneously enhancing, partially cystic, and caused adjacent vasogenic edema [Figure 1]. The mass appeared to arise just above the left ethmoid sinus though it was not clear pre-operatively whether this was intra- or extra-axial. There were several areas within the mass that signaled like lipid/fat. Based on these imaging characteristics, the most likely considerations on the differential included glioblastoma multiforme and gliosarcoma. Less likely considerations included an unusual meningioma, esthesioneuroblastoma, and sinonasal undifferentiated carcinoma. A solitary metastasis was felt to be less likely, given the presence of fat within the lesion. Routine laboratory studies on admission were within normal limits, but did not include phosphorus, calcium, or alkaline phosphatase.

Operative and Postoperative Course

The patient underwent bifrontal craniotomy and stereotactic resection of the lesion, with pericranialdural reconstruction. She tolerated the procedure well but her recovery was complicated by the development of deep venous thromboses in her bilateral lower extremities requiring IVC filter placement and warfarin therapy. At the time of dismissal, she was ambulating independently, and her abulia and incontinence were improved. She did very well and had recovered completely neurologically by 4 months post-operatively.

Pathology

Morphologically, the tumor had features of a monomorphous bland mesenchymal tumor composed of spindle cells, with ovale pointed nuclei in a densely fibrous background. No giant cells were present. Cellularity was moderate and mitotic figures were virtually absent. There was no necrosis. Areas of old hemorrhage with fibrosis, mild chronic inflammation, and hemosiderin deposition were noted. The tumor cells showed immunoreactivity exclusively with antibodies to vimentin (Dako Cytomation, monoclonal Mouse Clone V9), a marker typically expressed in mesenchymal cells. Immunostains for S-100 protein (DakoCytomation Polyclonal Rabbit), EMA (DakoCytomation, monoclonal Mouse Clone E29), GFAP (DakoCytomation, polyclonal rabbit), CD34 (Becton Dickinson, monoclonal mouse My10), Factor XIIIa (Novocastra monoclonal mouse E980.1), smooth muscle actin (DakoCytomation, monoclonal Mouse Clone 1A4), CAM 5.2 (Becton Dickinson monoclonal mouse), desmin Novocastra Mouse monoclonal), CD31 (DakoCytomation, monoclonal Mouse Clone JC70A) were negative.[14,15] MIB-1 (DakoCytomation, monoclonal Mouse Clone MIB-1) labeling index was low. Reticulin stain was performed and was largely restricted to perivascular spaces, with only a focally demonstrated reticulin network among tumor cells. Adjacent brain parenchyma showed chronic reactive changes with piloid gliosis and scattered mineralized neurons. The ultrastructural features of the tumor cells were unusual, but also consistent with a mesenchymal neoplasm. The tumor cells had long thin processes with the presence of surface microvilli focally, short stretches of basal lamina, and presence of focal rudimentary cell-to-cell junctions. The FGF-23 gene analysis by rtPCR demonstrated positive amplification within tumor cells.[1] Collectively, these results were consistent with a diagnosis of histologically benign PMTMCT [Figure 2].

Laboratory Evaluation

Serum phosphorus levels were mildly elevated (4.7 mg/dL) on the day following surgery. Serum calcium, phosphorus, alkaline phosphatase, bone alkaline phosphatase, and FGF-23 levels were within normal limits when tested 1 month post-operatively. However, a

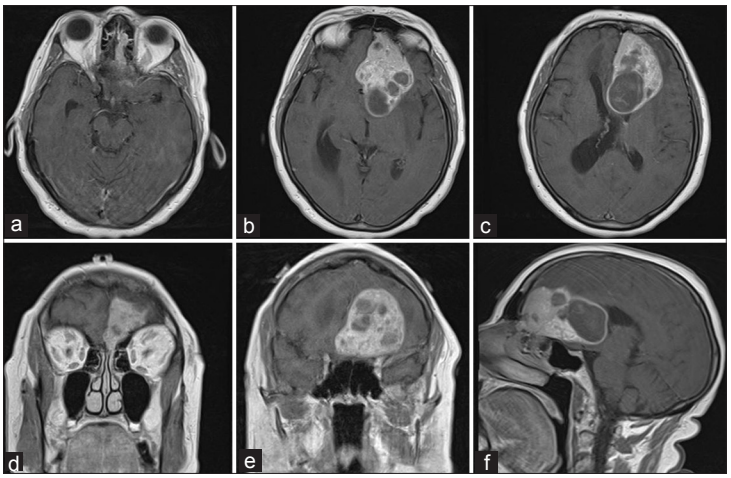

Figure 1: (a-c) Axial (d, e) coronal, and (f) sagittal T1 post-gadolinium MRI demonstrating a heterogeneously-enhancing, partially cystic mass in the left frontal lobe / anterior fossa. The mass extends anteriorly and inferiorly to the cribriform plate at the skull base just above the ethmoid sinus, seen clearly in a, d, and f

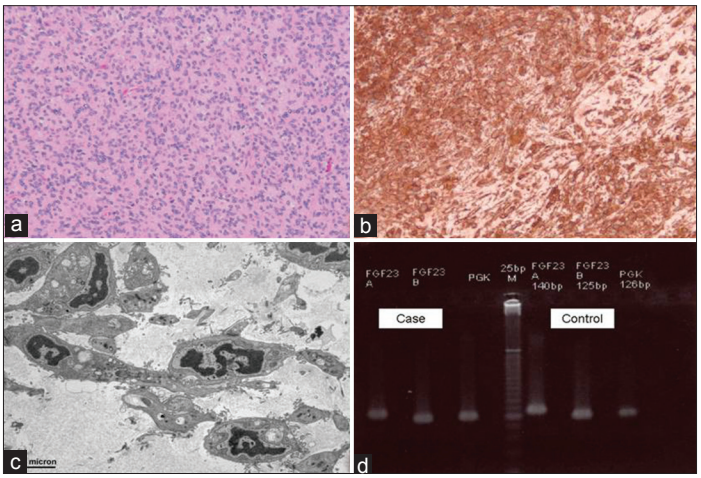

Figure 2: The tumor is composed of bland mesenchymal spindle cells with ovale pointed nuclei (panel a, H and E, ×200), which stains only with antibodies to vimentin (panel b, ×200). At the ultrastructural level (panel c), the cells have elongated, irregular nuclei and relatively abundant cytoplasm continuing in slender processes. Overall, their appearance is consistent with a mesenchymal neoplasm, but they lack features to suggest a precise lineage of differentiation. The FGF-23 gene analysis by rtPCR[1] demonstrated positive amplification within tumor cells (panel d)

25-hydroxyvitamin D3 was moderately low at 11 ng/mL (normal range 25-80 ng/ml in our lab). This was treated with oral supplemental vitamin D.

Outcome

The patient remains well neurologically without any evidence for recurrent or progressive tumor on imaging or tumor-induced osteomalacia 18 months after surgery. Her calcium and phosphorus levels remained normal throughout the follow up. FGF-23 was not rechecked at later follow up, as it was deemed unnecessary given her stable MRIs with no evidence of residual or recurrent tumor.

DISCUSSION

PMTMCT is a rare tumor belonging to a group of mesenchymal tumors that originates within bone or soft tissue, most commonly in the extremities.[5] It typically presents with tumor-induced osteomalacia. Craniofacial localization in or adjacent to the paranasal sinuses has been described in 5% of cases.[5] An intracranial occurrence is extremely rare, with only two other reports of intracranial PMTMCT in the literature.[3,11] Our case represents only the third intracranial PMTMCT reported and the first that was not associated with osteomalacia.

Weidner and Santa Cruz developed a classification of phosphaturic mesenchymal tumors, with four main subtypes: (1) primitive-appearing mixed connective tissue tumors; (2) osteoblastoma-like tumors; (3) non-ossifying fibroma-like tumors; and (4) ossifying fibroma-like tumors.[15] They found that the first group of these tumors, of which our case is also composed, is the most common, comprising 10 of the 17 PMT tumors in their series.[15]

Also, on the differential for mesenchymal intracranial tumors is hemangiopericytoma, which can also present with oncogenic osteomalacia. Our case was pathologically differentiated from hemangiopericytoma based on histopathology and tumor markers. CD34, which is positive in most hemangiopericytomas, was negative in our tumor. Reticulin staining was also scant, with virtually no mitotic figures present, which are both in contrast to hemangiopericytoma.[7]

Classically, PMTMCV is associated with hypophosphatemic osteomalacia due to excessive production of FGF-23 by the tumor with subsequent metabolic derangements.[2,12,16] Oncogenic (tumor-induced)osteomalacia is characterized by hypophosphatemia, normal or slightly low serum calcium, elevated alkaline phosphatase, normal 25-hydroxyvitamin D3, and decreased serum 1,25-dihydroxyvitamin D3 levels. While our patient had a moderately low 25-hydroxyvitamin D3 postoperatively, this is typically normal in osteomalacia, and was likely unrelated. Her other laboratory studies, including calcium, phosphorus, and alkaline phosphatase remained normal.

It has been proposed that there is a spectrum of expression of FGF-23 in PMTMCTs, with those on the lower end producing such small amounts as to be clinically silent.[4,17] In our patient's case, genetic testing did demonstrate amplification of the FGF-23 gene within the tumor.[1] However, her tumor may have produced only small amounts of FGF-23 so as not to cause osteomalacia. Her serum FGF-23 level was not checked prior to surgery, as there was no clinical suspicion for PMTMCT tumor. However, at 1 month post-operatively, a serum FGF-23 level was checked and this was within normal limits at 163 RU/mL.

PMTMCTs typically behave as benign tumors in 90% of cases, with local recurrence being rare, and occurring more frequently with incomplete resection.[15] In the case of the single malignant tumor seen in the series of 10 PMTMCTs evaluated by Weidner and Santa Cruz, they noted that the distinguishing features in this case were increased cytologicatypia and mitotic activity. This patient did well following gross total resection, and was still alive at the time of publication, 6 years out from tumor resection.[15] Our patient will be followed primarily with serial MRI. In patients with tumor-induced osteomalacia, resection of the causative tumor is curative and laboratory values including serum FGF-23 levels can be followed to monitor for tumor recurrence.[5,6,8,9,11,13] While our patient did not have osteomalacia or abnormal laboratory values, her serum FGF-23 level was normal post-operatively and could potentially indicate tumor recurrence if it was elevated in the future. This will be reassessed in follow up if any of her future MRIs demonstrates evidence of recurrence.

In summary, PMTMCT is a rare tumor of the bones and soft tissues that typically presents with oncogenic (tumor-induced) osteomalacia. Our patient demonstrates an unusual case of PMTMCT that did not have an associated osteomalacia, and occurred in an extremely rare location. As a small percentage of PMTMCTs occur in craniofacial locations, it is important to keep this tumor on the differential for intracranial tumors arising in proximity to paranasal sinuses.

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