The phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMT-MCT) is a very rare, histopathologically distinct tumor that is frequently misdiagnosed as other mesenchymal tumors. PMT-MCTs have been identified in a variety of soft tissues and osseous tissues, have a propensity to favor extremities and appendicular skeleton over the trunk or axial skeleton, and are only reported to have intracranial involvement as an extension of the anterior skull base region or cavernous sinuses. PMT-MCTs are almost always associated with tumor-induced osteomalacia (TIO; also known as oncogenic osteomalacia); however, PMT-MCTs without known TIO have been reported to be histologically identical to typical PMT-MCTs. Expression of the FGF23 protein has been seen in 81% of immunohisto logically analyzed samples and in 100% of those analyzed by reverse transcriptase polymerase chain reaction (RT-PCR). The few reported cases of intracranial PMT-MCT in the literature were found close to paranasal sinuses in older patients (typically in the 3rd to 7th decades of life); only one of these tumors was without symptoms of TIO.

**Case Report**

**History and Examination**

An 8-year-old girl woke up with severe headaches. She was unable to walk due to severe imbalance. She was ataxic on physical examination. CT scanning showed a hemorrhagic and partially calcified brain tumor with obstructive hydrocephalus. The CT study also showed a small, bony calvarial defect in the posterior fossa associated with tumor (Fig. 1).

**Operation**

Resection via a right retrosigmoid approach with gross-total resection was performed. Grossly, the tumor was a hemorrhagic, well-encapsulated, partially calcified brain tumor with obstructive hydrocephalus. The CT study also showed a small, bony calvarial defect in the posterior fossa associated with tumor (Fig. 1).
of tumor into dura grossly. The area of bony and dura abnormality was removed. Postoperatively, the patient had an uncomplicated hospital course. The hydrocephalus resolved without shunting, and the patient was discharged home without neurological deficits.

Histological Features

Histopathological analysis was performed and identified a benign solid and cystic neoplasm with cytological and architectural features that were common in aneurysmal bone cysts (ABCs), hemangiopericytoma, and phosphaturic mesenchymal tumor. The tumor showed hyalinized stroma with prominent vascularity and cellular areas with oval- or spindle-shaped cells with oval or elongated nuclei showing no significant cytological atypia or mitotic activity. Scattered multinucleated osteoclast-like giant cells were present. There was mineralization of stroma with foci of “grungy” calcification and osteoid and chondroid features. The cells stained strongly positive for immunohistochemical stains vimentin and CD68 and were negative for epithelial membrane antigen, progesterone receptor, smooth muscle actin, and S100 (Fig. 2).

Molecular studies performed at Mayo Clinic showed that the tumor was positive for FGF23 mRNA expression by RT-PCR, consistent with the majority of PMTs. Fluorescence in situ hybridization (FISH) analysis of this tumor for USP6 fusion gene was negative. Approximately 70% of the ABC contained USP6 fusion genes.

Postoperative Course

Follow-up CT and MRI showed no residual tumor or abnormality. Repeat MRI at 2 years postresection showed no evidence of recurrent lesion. At the 42-month follow-up, the patient had resumed all normal activities, including basketball, with no deficits in vision, balance, strength, or coordination, and she is without headaches. Furthermore, there continues to be thus far no clinical concern for osteomalacia.

Discussion

PMT-MCT is a rare tumor of soft tissue and bone that is most often associated with a distinct paraneoplastic syndrome known as oncogenic osteomalacia or TIO with associated phosphaturia, hypophosphatemia, and osteomalacia. It is estimated that 53% occur in bone, 45% in soft tissue, and 3% in skin. Weidner and Santa Cruz first coined the term “phosphaturic mesenchymal tumor” in 1987 and developed a classification of 4 main subtypes: primitive-appearing mixed connective tissue tumors, osteoblastoma-like, nonossifying fibroma-like, and ossifying fibroma-like. In 2004, Folpe et al. reported on 32 cases and performed a thorough review of all literature. They compared the clinical features and diagnoses, offering revised diagnoses when applicable, and found immunohistochemistry and RT-PCR identification of FGF23 to be a crucial part of the diagnosis (81% and 100%, respectively,
for that cohort). Ninety percent of PMT-MCTs present with hypophosphatemic osteomalacia due to excessive FGF23 expression, but in the absence of osteomalacia, the authors were able to make the diagnosis on the basis of histologically identical features plus FGF23 expression. Our differential diagnosis included chondromyxoid fibroma with ABC. Further quantitative analysis (positive FGF23 on RT-PCR and negative USP6 on FISH) refined our diagnosis and confirmed PMT-MCT.

The great majority of PMT-MCTs are benign and have good prognosis with surgical excision; a wide surgical excision with clean margins is considered definitive treatment. However, rare cases of malignant and metastatic tumors have been reported, and because of potential death, caution should be exercised. Early on it was estimated that 90% of PMT-MCTs were benign; however, a later review of 32 cases found that 9.4% of benign tumors become malignant. This was based on cytology and 1 case of hematogenous metastasis to the lung. The report did not describe mortality. Morimoto et al. presented 2 cases of malignant pelvic PMTs presenting with oncogenic osteomalacia. In the first case, the patient harbored synchronous double cancer associated with thyroid cancer. The patient died after the tumor rapidly metastasized to the lung. The second patient experienced recurrence 2 years after open biopsy and complete resection and also died of metastatic tumor to the lung. Ogose et al. documented local recurrence and malignant transformation from benign PMT over a 17-year follow-up period. Pallavi et al. reported a case of a 46-year-old man with PMT-MCT without evidence of oncogenic osteomalacia or phosphaturia, but the patient was found to have multiple osseous metastases throughout his body on initial workup. The authors noted that in the absence of standard treatment guidelines for metastatic PMTs, these tumors may be treated like metastatic soft-tissue sarcomas. Increased risk of recurrence or progression has been hypothesized to be associated with subtotal excision or lengthy time from onset of symptoms to diagnosis. Tumor recurrence can be monitored with serial imaging using MRI, PET CT, indium-111 pentetreotide or octreotide scintigraphy, and laboratory workup including 24-hour urine phosphorus, serum phosphorus, serum calcium, serum 1-OH and 1,25-OH cholecalciferol, alkaline phosphatase, and serum FGF23, the last of which is regarded as the most direct serological marker for tumor activity. Our patient’s symptoms resolved after excision, and she remained free of tumor recurrence on follow-up MRI.

A discussion of nonphosphaturic variants must be con-

FIG. 2. Microscopic images of the tumor. Phosphaturic mesenchymal tumor with prominent vascularity and cellular areas with bland spindle- to stellate-shaped cells and scattered osteoclast-like giant cells (A and B). The stroma is eosinophilic and hyalinized with characteristic “grungy” calcification (C and D), and focal chondroid and osteoid features (E and F). H & E, original magnification ×40 (A); ×400 (B, C, D, and F); ×200 (E). Figure is available in color online only.
ducted in the context of their phosphaturic counterparts. PMTs are rare and difficult to diagnose; diagnosis is most often made after the onset of symptoms of osteomalacia. Indeed, PMTs were discovered because of their associated paraneoplastic effects. The typical patient will present with symptoms in the 3rd to 7th decades of life, and definitive diagnosis is reached at an average of 7.2 years (range 2–12 years) after onset of symptoms. Upon suspicion, workup for patients presenting with typical TIO symptoms should include first characterizing the laboratory profile (phosphate, calcium, alkaline phosphate, vitamin D, and serum FGF23). Localizing the tumor is the next task and relies on imaging modalities such as radiography, MRI, bone scanning, and octreotide scanning. If possible, surgical excision allows for further histological and immunohistochemical analyses, and serial monitoring with laboratory evaluations and imaging can document a resolution of symptoms as well as alert to the rare chance of recurrence.

While TIO is not specific to PMT, since it is associated with 140 different types of tumors, most TIOs are of a single histopathological entity. Progress has been made in detecting FGF23 and distinguishing TIO from PMTs versus from other etiologies. Imel et al. documented the sensitivity of FGF23 in TIO using 3 different enzyme-linked immunosorbent assay (ELISA) methods. In all 13 patients with confirmed tumors, sensitivity was 100% using the Kainos Intact assay. Of all 22 patients combined (those with suspected TIO and those with confirmed tumors), 19 of 22 (89%) exhibited elevated FGF23 concentrations. In a cross-sectional study, Endo et al. showed clinical utility of FGF23 measurements by demonstrating an ability to differentiate TIO and XLH (X-linked hypophosphatemic rickets) from hypophosphaturic diseases of other etiology (vitamin D deficiency, Fanconi’s syndrome, and Cushing’s syndrome). In patients with other etiologies, FGF23 was undetectable in most patients, regardless of medical treatment. Coupling these findings with low serum phosphate using age-dependent reference ranges, these authors proposed diagnostic criteria to distinguish TIO and XLH from other hypophosphatemic diseases. As noted above, Folpe et al. reported that the role of RT-PCR identification of FGF23 was significant and facilitated the diagnosis of PMT-MCT when combined with histological features in 90% of cases. Bahrami et al. examined RT-PCR analysis for FGF23 and found that 94% of PMTs with TIO and 75% of histologically diagnosed tumors without TIO were positive. They postulated that the absence of TIO in this nonphosphaturic group might be explained by presymptomatic detection, low levels or nonfunctional form of FGF23 expression, unknown compensatory mechanisms, absent prescreatin phosphate levels, or lack of clinical recognition. In this same study, 3 of 23 non-PMT controls were positive, specifically in 2 chondromyxoid fibromas (CMFs) and 1 ABC, all of which were typical histologically and radiographically of their respective tumor type. Another study showed positive FGF23 expression in 29% of CMFs and in 44% of 16 ABCs. Most recently, Carter et al. published on a potentially valuable diagnostic adjuvant of chromogenic in situ hybridization (CISH) assay for FGF23 mRNA in PMT and found a sensitivity of 96% and a specificity of 100%. Their study looked at 25 patients with classic PMTs with clinically documented TIO and compared CISH results with 40 control cases of other types of tumors. Unfortunately, this study did not examine any cases exhibiting morphological features of PMT but without known TIO (“nonphosphaturic variants of PMT”). This subtype can be difficult to quantify without pre- and postoperative laboratory results but can convey adverse effects. Ultimately, nonphosphaturic variants of PMT as well as PMT with TIO are able to be diagnosed by histological morphological findings even without ancillary FGF23 testing. FGF23 mRNA expression by RT-PCR or CISH further supports the diagnosis of PMT.

As our patient was much younger than typical presentation and without the paraneoplastic syndrome, it is thought that her tumor, though positive for FGF23 production, did not have time to develop the characteristic TIO symptoms. The rapid onset of the patient’s other symptoms related to her tumor location led to its fortuitous discovery and allowed for prompt excision; final characterization of the tumor was accomplished later. The histological findings coupled with the confirmation of FGF23 expression in the brain by RT-PCR established our diagnosis with a high probability.

As noted by Bower and colleagues, though extremely rare to present without tumor-induced osteomalacia or phosphaturia, PMT-MCT may present intracranially without such typical associated symptoms. Of the only 8 reported intracranial cases, 7 (88%) occurred in the anterior fossa. Of these 8 tumors, only 6 were ultimately diagnosed as PMT; regarding the 2 remaining tumors, one was ultimately diagnosed as hemangiopericytoma and the other was not resected. Only 3 intracranial hemorrhagic cases have been reported; an elevated index of suspicion for potential recurrence should be noted with cases that initially present as hemorrhagic. As noted in the literature, PMT-MCT is diagnosed much more frequently in adult patients, although it has been found in pediatric patients; the youngest patient diagnosed with an intracranial PMT-MCT was 28 years of age. The mean patient age at diagnosis calculated from these 3 studies was 50.75 years.

Conclusions

PMT-MCTs are benign tumors that can involve the brain. They may occur in the pediatric population. In our case, resection was safe and effective.

References

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Feiz-Erfan, Ellis. Acquisition of data: Ellis. Analysis and interpretation of data: Feiz-Erfan, Ellis, Lal, Nair. Drafting the article: Ellis. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Study supervision: Feiz-Erfan.

Supplemental Information

Previous Presentations

Portions of this work were presented in poster form in 2013 at the Greater Phoenix Academic Excellence Day.

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