Osteomalacia-Inducing Tumors of the Brain: A Case Report, Review and a Hypothesis

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Key words
- Oncogenic osteomalacia
- Osteomalacia-inducing tumors
- Phosphaturic mesenchymal tumors
- Tumor-induced osteomalacia

Abbreviations and Acronyms
FGF23: Fibroblast growth factor 23
HCT: Hemangiopericytoma
OIT: Osteomalacia inducing tumor
PMTMCT: Phosphaturic mesenchymal tumor, mixed connective tissue variant

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Citation: World Neurosurg. (2015) 84, 1:189.e1-189.e5. http://dx.doi.org/10.1016/j.wneu.2015.02.030

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

BACKGROUND: **Osteomalacia-inducing tumors (OIT) are mesenchymal tumors that characteristically secrete fibroblast growth factor 23, resulting in a paraneoplastic syndrome of hypophosphatemic osteomalacia. These tumors are known to occur in soft tissues and bones in various sites. It is very unusual for OITs to occur intracranially, with only 10 reported intracranial cases since their discovery in 1959. The most common intracrainal OITs are phosphaturic mesenchymal tumors and hemangiopericytomas. We report a case of hypophosphatemic osteomalacia caused by a tumor in the right anterior cranial fossa. We also hypothesize, based on our review of the literature, that this entity is underdiagnosed.**

CASE DESCRIPTION: **A 49-year-old woman had a history of a nonhealing ankle fracture that required repeated surgery over 3 years. She subsequently was found to have severe hypophosphatemia and evidence of osteomalacia together with multiple occult fractures. A diagnosis of tumor-induced osteomalacia was suspected. An elevated serum fibroblast growth factor 23 level confirmed the diagnosis. An octreotide scan that was performed to locate the responsible tumor revealed an area of avid uptake in the right frontal lobe. Magnetic resonance imaging showed a large right anterior fossa extra-axial mass. The patient was referred for surgical intervention and was cured clinically after surgical removal of the tumor. Pathologic examination revealed a phosphaturic mesenchymal OIT. Her phosphate levels returned to normal 3 weeks after surgery.**

CONCLUSIONS: **The diagnosis of OIT should be considered in a case of severe hypophosphatemia and metabolic bone disease that is not explained by any other metabolic or hereditary disease. These tumors can occur intracranially and may be confused with a meningioma or a hemangiopericytoma. Taking OIT into consideration in such cases could lead to a shorter time to diagnosis and management, which in our case took 4 years.**

INTRODUCTION

Osteomalacia-inducing tumors (OITs) are mesenchymal tumors that characteristically secrete fibroblast growth factor 23 (FGF23) (3, 4, 8, 16). Elevated levels of FGF23 cause inhibition of renal reabsorption of phosphorus and downregulation of 25-hydroxyvitamin D-1α-hydroxylase, resulting in a paraneoplastic syndrome of hypophosphatemic osteomalacia with progressive weakness, muscle and bone pain, and recurrent fractures (4, 8). Although there are several mesenchymal tumors that can be classified as OITs, >70% of these tumors belong to a single pathologic entity named phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) (4). The other common pathology is hemangiopericytoma (HCT). Although OITs are known to occur in soft tissue and bone in various sites (4), it is very unusual for them to occur intracranially. There have been only 10 reported intracranial cases (1-3, 6, 8, 12, 13, 15, 16) since the discovery of OITs by Prader et al. in 1959 (11).

We report a case of hypophosphatemic osteomalacia caused by a tumor in the right anterior cranial fossa. Our literature review led us to hypothesize that this entity is probably underdiagnosed. In addition to the fact that in almost every case report of intracranial OIT there was a radiologic resemblance to a meningioma preoperatively, 2 studies reported cases of OIT that was not associated with osteomalacia (2, 17), denoting that this pathologic entity may not be associated with clinical symptoms or signs in some rare instances. There also have been pathologic reports of areas resembling OITs inside en plaque meningiomas (9). This means that in many cases of meningiomas, especially cases that are followed conservatively, there is a small chance that OITs are missed.

CASE PRESENTATION

History and Examination

A 49-year-old woman with developmental delay presented with a nonhealing ankle

fracture with multiple complications requiring 5 surgeries over a period of 3 years. During an admission for removal of hardware from her ankle secondary to osteomyelitis, a subtle presentation of hip discomfort led to a computed tomography scan that revealed bilateral femoral stress fractures. Metabolic bone disease was suspected, and an endocrinologist was consulted. Blood tests revealed severe hypophosphatemia (0.24 mmol/L; normal range, 0.87–1.4 mmol/L), normal calcium (2.2 mmol/L), normal parathyroid hormone (3.8 pmol/L; normal range, 1.2–5.8 pmol/L), and normal 25-hydroxyvitamin D (48 nmol/L). The patient did not present with any bone pain; however, a bone scan revealed multiple fractures including anterior ribs, bilateral superior/inferior pubic rami, proximal tibia, and bilateral femurs, compatible with metabolic bone disease and osteomalacia. Further work-up showed extremely high fractional excretion of phosphate in urine (>27,000%). A working diagnosis of tumor-induced osteomalacia was made. An octreotide scan was performed to search for the causative tumor and revealed an area of avid uptake in the right frontal lobe (Figure 1). Magnetic resonance imaging of the brain showed a space-occupying lesion in the right frontal lobe. The constellation of findings led us to suspect this tumor to be an OIT. The patient and her family denied any neurologic symptoms, but stated she had lost almost 15 pounds during the past 6 months. Although she denied focal weakness, she generally did not ambulate on her own since her ankle fracture, but rather used a wheelchair. Neurologic examination revealed no abnormality. Cognitive function could not be properly assessed because of the patient's developmental delay. However, her caregivers did not notice any change from her norm over the course of the last couple of years.

Additional Investigations

1,25-Dihydroxyvitamin D was <10; urinalysis was negative for protein and glucose, with normal urine pH; FGF23 level before surgery was 609 RU/mL (normal range, up to 180 RU/mL). Computed tomography and magnetic resonance imaging of the brain with contrast medium showed a large lobulated extra-axial mass with a broad dural base along the right frontal convexity measuring approximately 4.8 cm × 4.0 cm × 4.7 cm (anteroposterior × transverse × craniocaudal). It contained some cystic components (Figure 2).

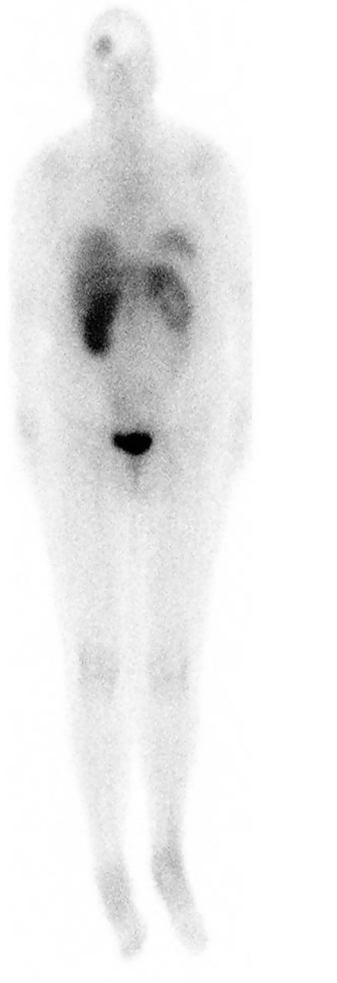

Figure 1. Nucleotide scan showing an area of avid uptake in the right frontal lobe.

Management

The lesion was approached through a right frontotemporal craniotomy. The tumor was partially extradural, yellowish, and slightly vascular (Figure 3).We performed a gross total resection of the lesion and the overlying dura mater with drilling and removal of any abnormal or invaded bone.

Pathologic Examination

Permanent stained sections demonstrated a monotonous proliferation of haphazardly arranged cells with round-to-polygonal, frequently grooved nuclei with modest amounts of eosinophilic cytoplasm. Irregularly shaped microcysts containing myxoid material were abundant throughout the tumor. Osteoclast-like giant cells were present in clusters with a patchy distribution. Focal metaplastic fat, osteoid, and bone were present in the center of the tumor, away from the skull or adjacent soft tissues. The tumor was predominantly well circumscribed, with an irregular interface with the adjacent brain, with occasional foci of glial entrapment.

Immunohistochemistry showed the tumor cells to be strongly positive for vimentin and Bcl-2. Actin smooth muscle showed strong positivity in rare tumor cells. CD34 highlighted blood vessels and confirmed the microcystic nature of most intratumoral spaces. Ki-67 labeled approximately 5% of cells overall. The tumor was negative for epithelial membrane antigen and S100.

Postoperative Course and Follow-Up

The patient was discharged from the hospital 3 days later without any significant postoperative events or complications. Computed tomography scan of the brain with and without contrast medium showed complete resection of the lesion. She was seen in the clinic 3 weeks later, and phosphate levels returned to normal. She is currently not taking any phosphate supplementation. The patient was now able to ambulate on her own via a walking air cast for her ankle. She became much more active and seemed much happier than before. Her metabolic parameters remained normal at 10 months after surgery.

DISCUSSION

The first case of an intracranial OIT was reported in 1996 by David et al. (3). Several intracranial mesenchymal tumors can cause osteomalacia including HCTs (8, 13) and PMTMCT, with the latter accounting for >70% of the cases (4). The present case is the 11th reported case of an intracranial OIT in the English literature since the discovery of this pathologic entity by Prader et al. in 1959 (11). A review of some previous cases is provided in a more recent article by Mathis et al. (8). Our case shares common characteristics with many