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Oncogenic osteomalacia associated with mesenchymal tumor in middle cranial fossa: a case report

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Abstract

Introduction: Tumor-induced osteomalacia is a paraneoplastic syndrome of hypophosphatemia. Osteomalacia causes multiple bone fractures and severe pain.

Case presentation: We present a case of a 57-year-old Japanese man with tumor-induced osteomalacia associated with middle cranial fossa bone tumor. The tumor was successfully resected using a middle fossa epidural approach. Phosphate recovered to a normal range immediately following the surgery.

Conclusions: This report suggests if patients have a clinical and biochemical picture suggestive of tumor-induced osteomalacia, it is crucial to perform a meticulous examination to detect the tumor or tumor responsible lesion. The serum level of fibroblast growth factor 23 is the most reliable marker for evaluating the treatment outcome of tumor-induced osteomalacia.

Key Words: oncogenic osteomalacia, middle cranial fossa, hypophosphatemia
Introduction

Tumor-induced osteomalacia is a rare acquired disorder. It has been reported to occur in patients with hypophosphatemia due to excessive renal phosphate excretion secondary to various types of mesenchymal tumors including hemangiopericytoma, giant cell tumor, fibroma and others. Patients typically present with a history of chronic bone pain, fractures, and proximal motor weakness. Children may exhibit poor growth and lower extremity deformity. The tumors are often benign, small, and difficult to detect. Recent reports have suggested that fibroblast growth factor 23 (FGF-23) is the most reliable marker for this process. (1)

We present a case of tumor-induced osteomalacia associated with middle fossa bone tumor. The tumor was successfully resected via a middle fossa epidural approach. Phosphate recovered to a normal range immediately after the surgery. The diagnostic evaluation, etiology of hypophosphatemia, and treatment are discussed.

Case presentation

A 57-year-old Japanese man was initially referred to our hospital for treatment of multiple bone fractures. In 2007, he had fallen down and fractured his foot. Fortunately, he had recovered with conservative therapy, however the delay of bone fusion in his
case was notable. In 2008, he experienced sudden onset of costal pain with trivial trauma and was diagnosed with multiple costal fractures. The costal pain did not resolve during these 2 years. 2 years after his initial foot fracture, the patient exhibited a serum phosphorus concentration of 1.9 ml/dl (normal range = 2.5-4.5 mg/dl) and a serum calcium concentration of 9.0 mg/dl (normal range = 8.5-10.5 mg/dl). Furthermore, detailed investigation revealed persistent hypophosphatemia and serum 1,25-dihydroxyvitamin-D concentration of 18 ng/dl (normal range = 25-50 ng/ml ). Serum levels of FGF-23 was elevated to 84 pg/ml (normal range = 10-50 pg/ml). Subsequent magnetic resonance (MR) images revealed a tumor in the middle cranial base reaching the temporomandibular joint and 27×18×20 mm in size. This tumor was clearly and homogeneously enhanced on gadolinium MR images (Fig. 1). Bone computed tomography (CT) showed destructive change to bone up to the external cortical layer in the middle cranial base (Fig. 2). We presumed hypophosphatemia and vitamin D deficiency of this patient were related to this tumor.

After 2 months from MR images, we performed the tumor resection via a middle fossa epidural approach. The tumor existed and eroded in the middle fossa cranial base and was easy to remove by curretting. The tumor was adhered to the dura mater in some parts but did not invade the subdural space. Finally, the tumor was totally resected
preserving the temporo-mandibular joint. Histopathological diagnosis was consistent with phosphaturic mesenchymal tumor which showed round or spindled cells embedded within a smudgy blue-gray material (Fig. 3).

The postoperative course was uneventful. His hypophosphatemia and vitamin D deficiency resolved 5 days after the surgery. Serum levels of FGF-23 were decreased to normal (14pg/ml) 7 days after the surgery (Fig. 4). Costal pain in this patient was completely resolved 1 month after the surgery. One year follow-up MR images showed no recurrence of the tumor and his serum phosphate level was normal (Fig. 5).

**Discussion**

Tumor-induced osteomalacia is an uncommon condition. These tumors are usually mesenchymal or mixed connective tissue, arising from either soft tissues or bone.\(^{(2)}\) They are benign in nature. Even in histologically malignant tumors, either local recurrence or distant metastasis is extremely rare. The most common types of these tumors are hemangiopericytomas. Other types include fibromas, chondrosarcomas, neuroblastomas, and prostate carcinomas.\(^{(3,4)}\) The first case was reported by McCance in 1947.\(^{(5)}\) In 1995, Crouzet et al. reviewed 100 cases reported in the medical literature.\(^{(6)}\) Since then, there have been many other case reports about the oncogenic
osteomalacia. Gonzalez-Compta et al. reviewed 21 cases of head and neck tumor-induced osteomalacia.\(^7\) They reported that 57% of these tumors were located in the sinonasal area and the mean age at diagnosis was 45 years old. There has been no finding of gender predominance in the previous reports. Bone pain, muscle weakness, fractures, skeletal deformities and gait disturbance are the most common clinical symptoms. This slow-growing tumor can occur in unusual sites in the body. Pirola et al. reported oncogenic osteomalacia of the thoracic spine.\(^8\) However, oncogenic osteomalacia originating from the middle cranial fossa is very rare.

Biochemical analysis often detects abnormalities in serum chemical concentrations. Generally, those patients who have hypophosphatemia have normal calcium levels and low 1,25-dihydroxyvitamin-D concentration. These imbalances resolve after total surgical exision of the tumor. The serum phosphate level is basically regulated by intestinal phosphate absorption, renal phosphate excretion and dynamic equilibrium between circulatory phosphate and intracellular phosphate or phosphate in calcified bone. Of these, renal phosphate excretion is believed to be the main regulator of the chronic phosphate level. Recently the mechanism of tumor-induced osteomalacia was thought to be secondary to inhibition of ability of the renal tubule to reabsorb phosphorus and to activate calcitriol synthesis. These processes lead to
hypophosphatemia. The most reliable marker for the detection of tumor-induced osteomalacia is FGF-23.\(^{(9)}\) It is a secreted peptide hormone over-expressed by the tumor in patients with tumor-induced osteomalacia. Fukumoto reported that FGF-23 suppresses phosphate reabsorption by decreasing expression levels of the type 2a and 2c sodium phosphate co-transporter in the brush border membrane of proximal tubules.\(^{(10)}\)

At the same time, FGF-23 reduces serum 1,25-dihydroxyvitamin-D levels in part by suppressing 1,25-dihydroxyvitamin-D production. As 1,25-dihydroxyvitamin-D enhances intestinal phosphate absorption, FGF-23 decreases the serum phosphate level partly by reducing intestinal phosphate absorption through suppressing the serum 1,25-dihydroxyvitamin-D level.

Symptoms resolve once the tumor is totally removed. Therefore, it is necessary to consider the total excision of the tumor as a treatment strategy.

**Conclusions**

We treated a case of hypophosphatemia associated with tumor-induced osteomalacia. The tumor was successfully resected using a middle fossa epidural approach. Phosphate recovered to normal levels immediate after the surgery. For patients who have a clinical and biochemical profile suggestive of tumor-induced osteomalacia, it is crucial to
perform an in depth examination to detect the tumor or tumor responsible lesion. FGF-23 is the most reliable marker to evaluate the usefulness of any treatment for tumor-induced osteomalacia.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

IC was involved in the diagnosis and treatment of our patient, and wrote the manuscript. KI and TG and KO were involved in the diagnosis of our patient and helped with revising the manuscript. All authors approved the final manuscript.

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References


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Figure legends
Figure 1
Axial and coronal MR images with contrast showing left epidural mass at middle cranial fossa.

Figure 2
Bone computed tomography images demonstrating a bone eroded lesion at middle cranial fossa.

Figure 3
Photomicrograph of the resected tumor showing small rounded spindled cells with a smudgy matrix (H-E)

Figure 4
Charts displaying pre-and postoperative laboratory date.

OP= operation

Figure 5
MR images with contrast one year after surgery, revealing no enhanced region.