INTERNAL MEDICINE

□ CASE REPORT □

Tumor-induced Osteomalacia Caused by a Parotid Tumor

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Abstract

A 77-year-old man was suspected of having tumor-induced osteomalacia (TIO) because of hypophosphatemia (1.9 mg/dL) and elevated serum fibroblast growth factor 23 (FGF23) level (186.9 pg/mL). We detected a tumor in his left parotid gland, and the FGF23 level in the left external jugular vein indicated that the tumor overproduced FGF23. After the removal of the tumor, the serum FGF23 level rapidly decreased, and the serum phosphate normalized. This is the first case of TIO caused by a tumor in a parotid gland. This case indicates that the responsible tumors for TIO can be quite diverse.

Key words: tumor-induced osteomalacia, fibroblast growth factor 23, phosphaturic mesenchymal tumor mixed connective tissue variant, parotid gland

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Introduction

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by hypophosphatemia with impaired proximal tubular phosphate reabsorption. TIO is caused by overproduction of fibroblast growth factor 23 (FGF23) from the responsible tumors. FGF23 was cloned as a causative humoral factor for TIO (1) and has been shown to work as a regulator of phosphate metabolism. FGF23 is mainly produced by osteocytes and suppresses phosphate reabsorption in the renal proximal tubules and intestinal phosphate absorption by reducing the 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$] level (2). In the clinical setting, it is important to localize the tumors responsible for TIO because this disease can be cured only by complete resection of the causative tumors (3). However, it is sometimes difficult to identify the culprit tumors because of the small size and unpredictable localization of the tumors. Most of the causative tumors are pathologically classified as phosphaturic mesenchymal tumors, mixed connective tissue variant (PMTMCTs) (4). PMTMCTs in the craniofacial region have been rarely reported, except for the nasal sinuses (5). There are no reported cases of TIO caused by parotid gland tumors. In this article, we report a TIO patient with a PMTMCT in the parotid gland.

Case Report

A 77-year-old man had noticed progressive pain in his back and hip joints for the past 8 years. He started using a cane five years prior, as he had trouble walking. While he had visited a hospital and practiced physiotherapy, his symptoms deteriorated. Two years prior, he slipped at home and broke his left hip. X-ray revealed osteopenic bone, and he was referred to our hospital. FGF23-related hypophosphatemic osteomalacia was suspected because of hypophosphatemia (1.9 mg/dL) and elevated serum FGF23 level (186.9 pg/mL: reference range 10.0-50.0 pg/mL) measured by full-length ELISA (Kainos, Tokyo, Japan) (3). Consequently, he was admitted to our hospital for further investigation.

He was 149 cm tall and weighed 47.4 kg. His height had shrunk by 10 cm over the past 8 years. On admission, he suffered from severe pain throughout his whole body and was wheelchair-bound. Besides hypophosphatemia and high FGF23, he also showed a high alkaline phosphatase level (676 IU/L: reference range 115-359 IU/L) and a low ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (Tmp/GFR) (0.9 mg/dL). In addition, serum

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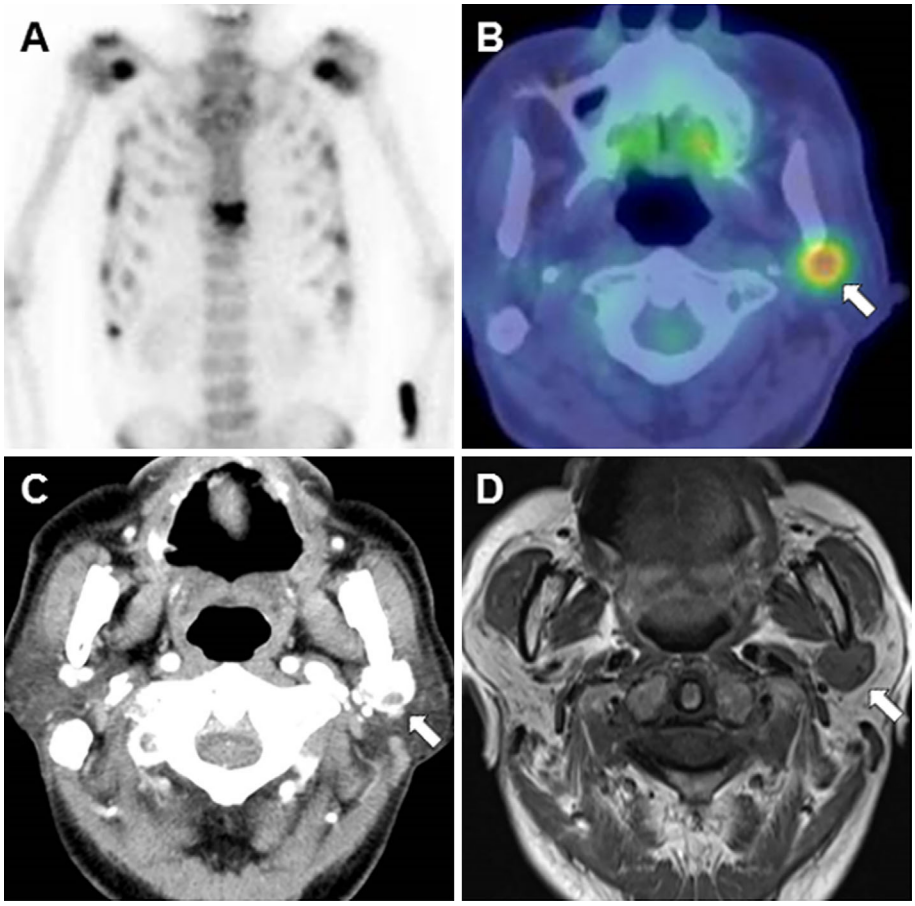

Figure 1. **A) Bone scintigraphy with technecium-99m methylene diphosphonate revealed multiple high-uptake lesions in several sites, including the ribs and shoulders. B) PET/CT indicated the uptake of [^{18}F] fluorodeoxyglucose in the left parotid gland with a maximum standardized uptake value (SUV) of 5.1. Contrast enhanced CT (C) and T1-weighted MRI (D) revealed the presence of the tumor in the left parotid gland.**

urea nitrogen (15.6 mg/dL), creatinine (0.49 mg/dL), calcium (8.6 mg/dL), magnesium (2.1 mg/dL) and intact parathyroid hormone (64 pg/mL) were within the reference range. His whole-body bone mineral density was 87% of the young adult mean (YAM). Bone scintigraphy with technecium-99 m methylene diphosphonate showed multiple uptakes in several lesions, including the ribs and shoulders, indicating the presence of osteomalacia (Fig. 1A).

Because of his age and the absence of affected relatives with rickets or osteomalacia, TIO was suspected as the most likely condition. Positron emission tomography-computed tomography (PET/CT) indicated the uptake of [^{18}F] fluorodeoxyglucose in the left parotid gland region, with a maximum standardized uptake value (SUV) of 5.1 (Fig. 1B). In addition, contrast-enhanced CT and magnetic resonance imaging (MRI) confirmed the presence of a tumor in the left parotid gland region (Fig. 1C, D). The patient complained of tenderness at the left parotid gland region. The possibility of a parotid gland tumor or tumor from the adjacent bones was considered. There were no other tumors revealed by these imaging studies.

Parotid gland tumors are benign in most cases. The histological diagnosis of typical parotid gland tumors includes pleomorphic adenoma and Warthin's tumor. Thus far, no cases with PMTMCT overproducing FGF23 in parotid glands have been reported. We conducted systemic venous sampling in this patient after obtaining his written informed consent, but we could not narrow down the area where the FGF23-producing tumor might exist. Because we collected blood samples through a catheter inserted in the right femoral vein in our systemic venous sampling, it was impossible to collect blood samples from the external jugular veins due to the anatomical angle of these veins. Since the blood from the left parotid tumor seemed to drain into the left external jugular vein, an additional blood sample was collected from the left external jugular vein by venipuncture. The FGF23 level in the left external jugular vein was indisputably higher (1,320 pg/mL) than in other veins. These results collectively identified the left parotid gland tumor as the causative tumor for TIO.

The patient was medicated with inorganic phosphate (1,000 mg/day) and alfacalcidol (2 μg/day) for approximately 1 year with considerable improvement in his symptoms. The left parotid gland tumor was then surgically removed by the otolaryngology department of our hospital. The tumor was considered to be generated from a part of

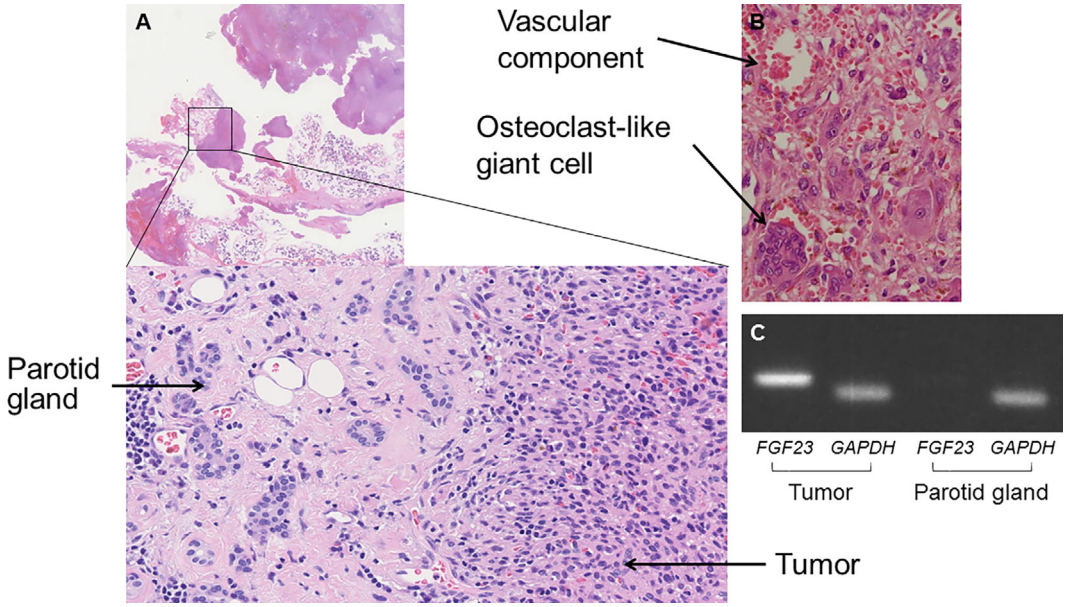

Figure 2. **The findings from the histological and RT-PCR analyses of the tumor. A) The tumor was pathologically diagnosed as a phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT). The tumor and normal parotid gland tissue were continuously adjoined to each other. Small, round, spindle-shaped cells were present in the tumor. B) Distinctive vascular components and some osteoclast-like giant cells were observed. C) Total RNA was extracted using a NucleoSpin RNA (MACHEREY-NAGEL) and analyzed via RT-PCR using primers 5'-GGTGGCCTGATCCACCTGTA and 5'-TGTAATCACCACAAAGCCAGCAT. The expression of *FGF23* was confirmed in the tumoral tissue but not in the adjacent normal parotid gland.**

the left deep lobe of the parotid gland, as the tumor did not adhere to his mandible and was easily separated from it. The tumor was pathologically diagnosed as PMTMCT. A histological examination showed that the tumor and normal parotid gland tissue were continuously adjoined to each other. Small, round, spindle-shaped cells (Fig. 2A) and prevailing distinctive vascular components (Fig. 2B) were present in the tumor, and few mitotic figures were observed. Some osteoclast-like giant cells (Fig. 2B) were also recognized. In addition, a reverse transcriptase-polymerase chain reaction (RT-PCR) analysis revealed the expression of *FGF23* in the parotid gland tumor. The adjacent normal parotid tissue was negative for *FGF23* expression (Fig. 2C).

Just before the operation, the serum phosphate was 3.0 mg/dL, and the FGF23 level had increased to 241.5 pg/mL, probably owing to the treatment with inorganic phosphate and alfacalcidol. After the surgery, the tenderness in the left parotid gland region improved, the FGF23 level dropped sharply to 6.5 pg/mL on postoperative day (POD) 2, and the serum phosphate normalized on POD 4 without replacement of phosphate (Fig. 3). Because of this clinical course, the causative tumor was considered to have been completely resected.

Discussion

We described the first case of TIO due to a parotid PMTMCT. Generally, most cases of TIO are due to PMTMCT, as suggested by Weidner and Santa Cruz in 1987 (4). Most parotid tumors are benign pleomorphic adenomas or Warthin's tumors of epidermal origin. Mesenchymal tumors in the salivary glands are relatively rare and are reported to occur in 1.5% of all registered cases (6). According to the report by Folpe et al., 56% of PMTMCTs occur in soft tissues, 28% in bones, and 6% in craniofacial sinuses (7). TIO-causing soft tissue tumors have been reported to be generated in various sites, including the forearm, hand, deltoid muscle, abdominal wall, back, flank, hip, groin, thigh, leg, and foot. Reported sites of bone tumors responsible for TIO are also widespread. Tumors in sites such as mandible, vertebra, finger, metacarpal bone, iliac crest, sacrum, femurs and tibia have been described previously (7). However, the existence of several different types of mesenchymal tumors such as lipomas and angiomas are known (8, 9). Furthermore, recently, some groups have shown that TIO can be caused by malignant tumors in several different parenchymal organs (10-13). Still, TIO-causing malignant tumors in these parenchymal organs are obviously rare compared to the TIO-causing tumors in bones or soft tissues. The difference in this frequency may be due to differences in the number of mesenchymal cells, a possible precursor of PMTMCTs, in these organs. Nevertheless, these findings clearly indicate that TIO-causing tumors can be quite diverse.

In addition, there is no standardized and secure method of identifying the tumor responsible for TIO. We previously re-

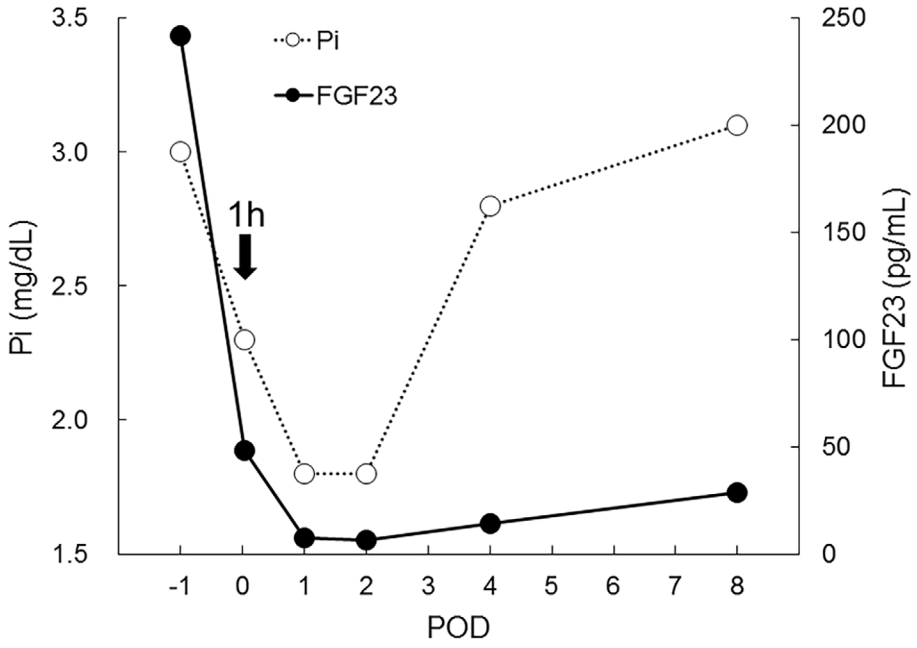

Figure 3. The postoperative course of the patient. The FGF23 level decreased rapidly after resection of the tumor, and the serum phosphate normalized within 4 days without phosphate replacement. POD: postoperative day

ported that systemic venous sampling is useful for locating the TIO-causing tumors in some patients (14, 15). To this end, in the present case, we conducted systemic venous sampling and several kinds of imaging examinations, including PET/CT, contrast-enhanced CT, and MRI. We also measured the FGF23 level in a blood sample obtained from the left external jugular vein by direct puncture. The results clearly demonstrated the presence of a causative tumor in the left-sided head. Thus, measuring the FGF23 level in the veins near the detected tumor may be helpful for determining whether the tumor is overproducing FGF23, even in tumors which have not been previously reported to cause TIO.

In conclusion, we presented the first case of TIO due to a parotid PMTMCT. In addition to the previous reports illustrating that some malignancies can cause TIO, this case further supports the diversity of TIO-causing tumors. We should therefore not rule out the possibility of FGF23 production even in tumors which have not previously been reported to cause TIO.

The authors state that they have no Conflict of Interest (COI).

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