Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4412-19
Intern Med 59: 2523-2527, 2020
http://internmed.jp

【 CASE REPORT 】

Hyperparathyroidism Which Developed after Resection of a Fibroblast Growth Factor 23-producing Tumor

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Abstract:
A 53-year-old woman presented with bone pain and was diagnosed with osteomalacia because of hypophosphatemia, hyperphosphatasemia, bone pain, and radiographic findings. Because her intact-fibroblast growth factor 23 (FGF23) levels were high and contrast-enhanced computed tomography revealed a mass in the anterior ethmoid sinus, FGF23-related osteomalacia was diagnosed. The tumor was resected, but she developed hypercalcemia and elevated blood parathyroid hormone (PTH) levels. Primary hyperparathyroidism (PHPT) was diagnosed, and surgical resection was performed. To our knowledge, this is the first case of a FGF23-producing tumor complicated by PHPT. Because PHPT manifested after resecting the FGF23-producing tumor, FGF23 is thus considered to suppress PTH secretion in humans.

Key words: fibroblast growth factor 23-producing tumor, primary hyperparathyroidism, manifestation

(Intern Med 59: 2523-2527, 2020)
(DOI: 10.2169/internalmedicine.4412-19)

Introduction

Fibroblast growth factor 23 (FGF23)-producing tumors are one of the manifestations of paraneoplastic syndrome. Because these tumors autonomously overproduce FGF23, they cause tumor-induced hypophosphatemic osteomalacia (TIO). The hypophosphatemia caused by FGF23-producing tumors is associated with muscular weakness, bone pain, and osteomalacia. However, it is difficult to detect FGF23-producing tumors because they are small and grow slowly.

In primary hyperparathyroidism (PHPT), parathyroid hormone (PTH) is autonomously and excessively secreted because of neoplastic transformation or hyperplasia of the parathyroid glands. PTH promotes the renal excretion of phosphate (P), as with FGF23, but elevates blood 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] levels in opposition to the action of FGF23. In addition, PTH overproduction causes hypercalcemia and hypophosphatemia.

We herein report a case of concomitant FGF23- and PTH-producing tumors in which hyperparathyroidism manifested only after the resection of the FGF23-producing tumor. We believe this is the first case to demonstrate the coexistence of these tumors.

Case Report

The patient was a 53-year-old woman. In year X-6, she developed bilateral thigh and hip joint pain. In year X-3, hypophosphatemia, indicated by a P level of 1.5 mg/dL, and hyperphosphatasemia, indicated by an alkaline phosphatase (ALP) level of 1,700 U/L, were diagnosed at another hospital. Osteomalacia was diagnosed based on imaging findings, and alfacalcidol (αCal) therapy was initiated. In year X-2, a tumor in the right maxillary sinus was resected. The pathological findings of the excised tumor showed a proliferation of tumor cells with rounded to elliptical nuclei. Vimentin, a marker of mesenchymal tumors, was positive, and S-100 and CD34 were negative, indicating that the excised tumor was a mesenchymal tumor. After tumor resection, her symptoms were relieved. The patient discontinued hospital visits at her own discretion. In year X-1, the bilateral thigh pain relapsed. When she visited our department in year X, her examination revealed 38.9% bone loss (lumber spine) over 4

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Received: December 31, 2019; Accepted: May 18, 2020; Advance Publication by J-STAGE: July 7, 2020
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Table. **Laboratory Data on Admission (X Years).**

Peripheral blood			
White blood cells	4,700 /μL	Urine Phosphate	34.2 mg/dL
Red blood cells	385 $\times 10^4$/μL	Urine Creatinine	74.6 mg/dL
Hemoglobin	12.0 g/dL	Fractional exretion of Calcium	0.78
Platelets	20.9 $\times 10^4$/μL	% tubular reabsorption of phosphate	87.5 %
Blood biochemistry		TmP/GFR	1.84 mg/dL
Total protein	7.8 g/dL	Intact-parathyroid hormone	83 pg/mL
Albumin	4.4 g/dL	25-hydroxyvitamin D	14 ng/mL
Aspartate aminotransferase	23 U/L	Fibroblast growth factor 23	34.2 pg/mL
Alanine aminotransferase	13 U/L	Bone Specific Alkaline Phosphatase	66.0 μg/L
γ-glutamyltranspeptidase	10 U/L	NTx	75.8 mmol/L
Blood urea nitrogen	12 mg/dL		
Creatinine	0.49 mg/dL		
Alkaline Phosphatase	484 U/L		
Bone metabolism related data			
Serum Calcium	9.2 mg/dL		
Serum Phosphate	1.9 mg/dL		
Urine Calcium	10.9 mg/dL		

TmP/GFR: maximal tubular reabsorption of phosphate per GFR, NTx: cross-linked N-telopeptide of type 1 collagen

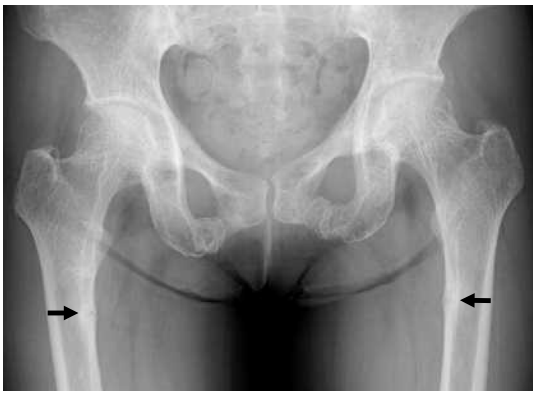

Figure 1. **Pelvic X-ray. Looser's zones were found in both femurs on simple pelvic X-rays.**

years. Calcium (Ca) level was 8.5 mg/dL (8.7-10.3 mg/dL); P level, 1.3 mg/dL (2.5-4.7 mg/dL); ALP level, 529 U/L (115-359 U/L); and intact-PTH level, 67 pg/mL (10-60 pg/mL), indicating hypocalcemia, hypophosphatemia, and hyperphosphatasemia, respectively. She was thus admitted to our department for detailed examination and treatment.

No obvious abnormal physical findings, except for bilateral hip and medial thigh pain, were noted. Biochemical test results revealed P, ALP, and 25(OH)D levels of 1.9 mg/dL, 484 U/L, and 14 ng/mL, respectively, indicating hypophosphatemia and hyperphosphatasemia. The FGF23 level was relatively high at 34.2 pg/mL (Table). In addition, the young adult mean (YAM) bone density (femur) had decreased to 68% on the bone density test. Regarding the imaging findings, whole-body bone radiography showed an overall attenuation of bone shadows, and Looser's zones were observed in both femurs (Fig. 1). Bone scintigraphy showed many areas of an abnormal uptake in both the femurs and ribs.

Major items, hypophosphatemia and hyperbonealpemia, were both noted, and minor items, bone pain, reduced bone density and Looser's zone on simple X-ray, were also observed, thus, osteomalacia was diagnosed.

Because of the high FGF23 level, the presence of a FGF23-producing tumor was suspected. However, no findings indicative of a tumor were noted on contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). In addition, cervical CT and cervical echo revealed parathyroid enlargement or lymphadenopathy, therefore, we performed methoxy isobutyl isonitrile (MIBI) scintigraphy, and no accumulation was observed in the later image. To treat osteomalacia associated with hypophosphatemia and abnormal vitamin D metabolism, αCal therapy was resumed.

After resuming αCal therapy, both the bilateral hip joint pain and medial thigh pain were promptly relieved. After 52 months of treatment, bone scintigraphy showed an improvement in many areas of an abnormal uptake in both the femurs and ribs. However, hypophosphatemia persisted thereafter. In year X+4, the FGF23 level increased to 2,878 pg/mL (Fig. 2). Thus, detailed examination was again performed to determine the presence or absence of a FGF23-producing tumor. Contrast-enhanced CT revealed a new tumor with internal heterogeneity in an area ranging from the superior portion of the nasal cavity to the anterior ethmoid sinus (Fig. 3). FGF23-related osteomalacia was diagnosed, and the tumor was resected. A pathological examination revealed dilated blood vessels, fat components, and grungy calcification, which were features of FGF23-producing tumors (1). Because FGF23 staining showed dot-shaped stains, a FGF23-producing tumor was diagnosed (Fig. 4). After tumor resection, hypophosphatemia resolved, and the FGF23 level decreased from 628 to 7.1 pg/mL (Fig. 2).

After resecting the FGF23-producing tumor, the Ca level

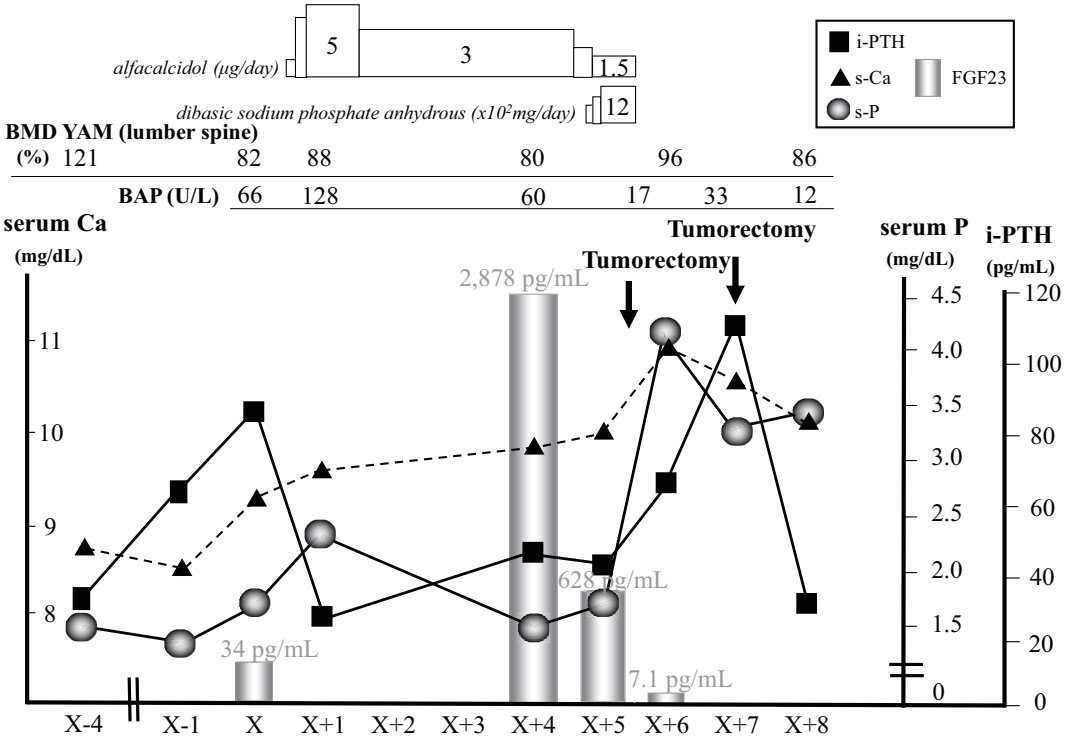

Figure 2. **Clinical course. Hypophosphatemia persisted, and the FGF23 levels increased from 34 to 2,878 pg/mL in the period from X years to X+4 years and decreased to 7.1 pg/mL after the removal of the FGF23-producing tumor. Conversely, after the resection of the FGF23-producing tumor, the intact-PTH and Ca levels increased to 106 pg/mL and 10.7 mg/dL, respectively. BMD YAM: bone mineral density young adult mean, BAP: bone specific alkaline phosphatase, i-PTH: intact-parathyroid hormone, FGF23: fibroblast growth factor 23**

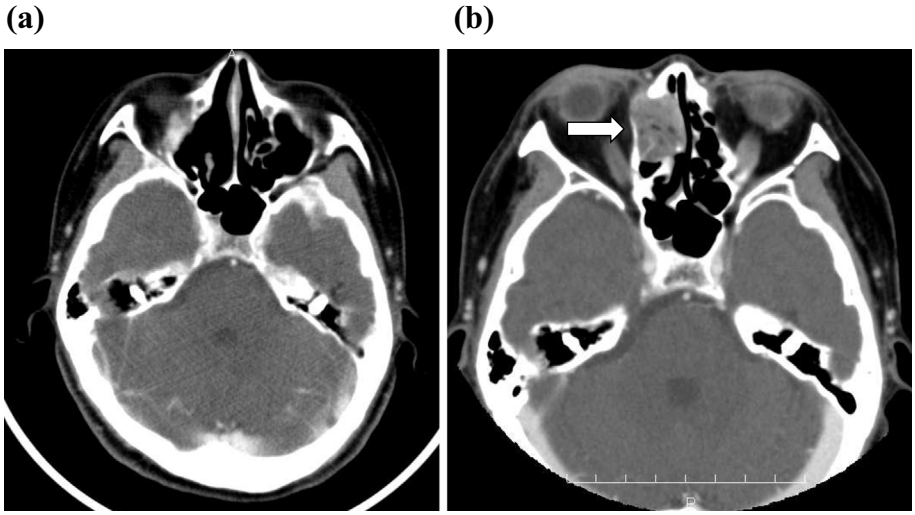

Figure 3. **Computed tomography (CT) images. Longitudinal changes in the CT images are shown. (a) At the initial visit in X, no tumor was observed. (b) When the fibroblast growth factor (FGF) 23 level increased to 2,878 pg/mL, the patient was reexamined. A new tumor with internal heterogeneity was detected in an area ranging from the superior portion of the nasal cavity to the anterior ethmoid sinus.**

was 11.0 mg/dL, indicating the development of hypercalcemia. Subsequently, an elevated blood PTH level was detected with an intact-PTH level of 106 pg/mL (Fig. 2). Thyroid ultrasonography revealed a 9×7×5-mm-sized swelling with poor blood circulation in the posterior-inferior aspect of the left lobe; contrast-enhanced CT also revealed a tumor at the same site. MIBI scintigraphy revealed an abnormal uptake in the lower left parathyroid gland, and thus, PHPT was

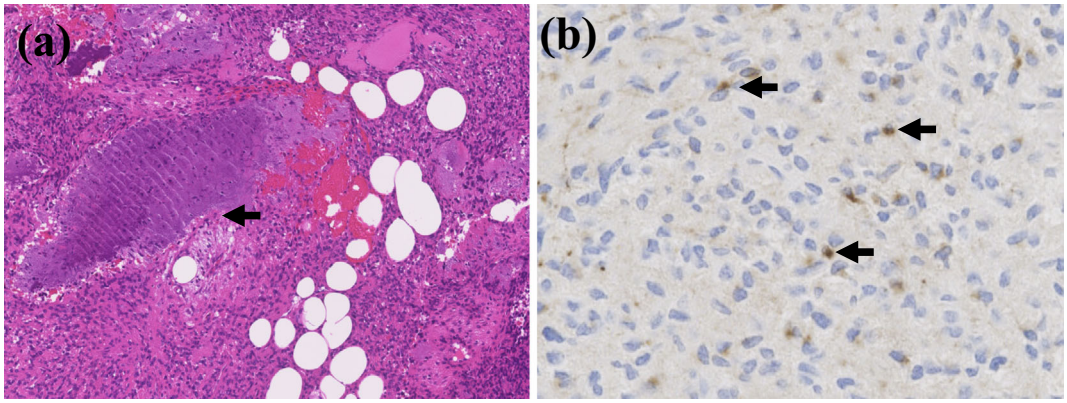

Figure 4. Histopathological examination of the tumor. (a) Hematoxylin and Eosin staining showing a lesion composed of proliferated less atypical spindle cells. Grungy calcification (arrow) and fat components are also observed in the lesion. (b) Fibroblast growth factor (FGF) 23 staining anti-FGF23 antibody (FG322-3) showing dot-shaped positive stains (arrow). Staining was performed by hand dyeing, and the antigen was activated using a pressure cooker and pH 8.0 EDTA. As the antibody, FG322-3, which is commercially available from Adipogen, was diluted 500 times and then used.

diagnosed. The lower left parathyroid gland was resected, and Ca, P, and bone specific alkaline phosphatase (BAP) levels subsequently normalized.

Discussion

To date, there have been no previous reports of the coexistence of a FGF23-producing tumor and PHPT. Because PHPT manifested after the resection of the FGF23-producing tumor, our findings suggest that the FGF23-producing tumor suppressed PTH secretion.

In this case, the diagnosis of PHPT was difficult because the coexistence of the FGF23-producing tumor and PHPT did not lead to hypercalcemia. A study in rats reported that FGF23 inhibits PTH secretion and PTH gene expression (2). Although there have been no reports of the coexistence of a FGF23-producing tumor and hyperparathyroidism, as was observed in our case, the PHPT manifested after the resection of the FGF23-producing tumor, suggesting that FGF23 also inhibits PTH secretion in humans.

In this case, the blood FGF23 level was elevated with tumor growth. Regarding tumor size and hormone levels, there is strong correlation between the weight of a parathyroid adenoma and PTH levels in PHPT (3). In contrast, regarding the FGF23-producing tumor, which was diagnosed based on a FGF23 level of 30 pg/mL or higher (4), there have been no reports on the association between blood FGF23 levels and the size of the FGF23-producing tumor. In our case, the tumor was very small and difficult to detect when the blood FGF23 level was relatively high, whereas when the tumor became enlarged, the blood FGF23 level was markedly higher. This suggests that the size of the FGF23-producing tumor was associated with the blood FGF23 levels. In patients with osteomalacia of unknown cause, the FGF23 levels may increase with tumor growth, as was observed in our patient; thus, a longitudinal assessment of FGF23 levels appears to be important. The tumor resected at X-2 years existed in the same region as the tumor resected at X+5 years, and it was a mesenchymal tumor with the same pathological characteristics as the tumor resected at X-2 years. Considering clinical characteristics, it is highly possible that the tumor resected at X-2 years was also a FGF23-producing tumor. Based on this finding, FGF23-producing tumors may recur after resection, and thus, it is important to measure FGF23 levels regularly after tumor resection. In addition, $1,25(OH)_2D$ was reported to increase the FGF23 levels (5). In this case, the FGF23 levels decreased from 2,878 to 628 pg/mL after a reduction in $1,25(OH)_2D$. Therefore, the effect of active vitamin D preparations is also considered to be a cause of increase in FGF23 levels.

Our patient presented with marked hypophosphatemia until the resection of the FGF23-producing tumor, despite the concomitant use of activated vitamin D and P preparations. FGF23 reduces the blood P levels by inhibiting the renal reabsorption of P by reducing the expression of type IIa and IIc sodium-phosphate cotransporters expressed in the proximal renal tubules (6) and inhibiting the intestinal absorption of P by changing the expression of vitamin D metabolic enzymes to reduce the blood $1,25(OH)_2D$ levels (6). In patients with hypoparathyroidism, the blood P levels are reported to be high, despite the presence of high FGF23 levels (7). This suggests that FGF23 cannot exert a sufficient effect on the P levels without PTH (7). In fact, in patients with TIO whose parathyroid function is suppressed by cinacalcet, the renal reabsorption of P is promoted, which elevates blood P levels. FGF23 is considered to promote renal excretion of P in a manner additive to the action of PTH (8, 9). Our case suggests that hypophosphatemia persisted because the coexistence of the FGF23-producing tumor and PHPT enhanced the effect of FGF23 on the renal excretion of P. PTH is usually suppressed in FGF23-producing tumors, however, in this case, the FGF23-producing tumors and primary hyper-

parathyroidism were complicated. Therefore, the PTH level was relatively high at 43 pg/mL. Hypophosphatemia might have been prolonged because FGF23 enhances the renal excretion of phosphorus. In this case, despite the presence of a FGF23-producing tumor, the %TRP was 87.5% at the time of the initial X year visit. It has been reported that the renal tubular excretion of phosphorus is completely suppressed in hypophosphatemia (10). This case was complicated by a FGF23-producing tumor, it is possible that the %TRP was within the normal range because the patient had severe hypophosphatemia at the time of the initial visit. Actually, the %TRP was within the normal range until the start of diabasic sodium phosphate anhydrous treatment at X+5 years; however, after initiating the treatment, the P levels increased from 1.7 to 2.5 mg/dL and %TRP decreased to 42.8%.

We herein described a case of a coexistent FGF23-producing tumor and PHPT. Because PHPT manifested after the resection of the FGF23-producing tumor, FGF23 also suppressed PTH secretion in humans. In addition, because the FGF23 levels increased with the growth of the FGF23-producing tumor, longitudinal assessments, including those of FGF23 levels, appear to be necessary for patients with osteomalacia of unknown cause.

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

Acknowledgments

The authors gratefully acknowledge the technical assistance of Ms. N. Sakaguchi.

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