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Case Report

Two Cases of Improved Bone Mineral Density Following Treatment of Hypophosphatemic Osteomalacia Due to FGF23 Excess

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Abstract

Excess fibroblast growth factor-23 (FGF23) causes renal phosphorous wasting and impaired activation of vitamin D leading to osteomalacia. Tumor-induced osteomalacia (TIO) is a rare cause of FGF23-mediated hypophosphatemia. We present 2 patients with FGF23-mediated hypophosphatemia who had low bone mineral density (BMD) at diagnosis and remarkable improvements in BMD with treatment. Patient 1 is a 43-year-old man who had years of progressive pain, difficulty ambulating, and multiple fractures. Patient 2 is a 48-year-old nonverbal man with autism and intellectual disability who had months of progressively declining mobility, presumed pain, and multiple fractures. Workup in both cases revealed hypophosphatemia, evidence of renal phosphorous wasting, and elevated FGF23. Patient 1 was diagnosed with TIO when imaging identified a subcutaneous left flank mass and excision resulted in rapid symptom improvement; he experienced a 96% increase in lumbar spine (LS) BMD after surgery. Patient 2 has had multiple scans over several years, but no FGF23-secreting tumor has been identified. He has been maintained on medical treatment with phosphorous and calcitriol with improvement in functioning and 48% increase in LS BMD. Both patients had improvements in BMD with treatment, with more pronounced improvement in the patient with TIO managed surgically.

Key Words: tumor-induced osteomalacia, bone mineral density, FGF23

Introduction

Fibroblast growth factor-23 (FGF23) promotes renal phosphorous wasting and impaired activation of vitamin D resulting in osteomalacia. Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome due to excess FGF23 from phosphaturic mesenchymal tumors (PMTs). Symptoms of FGF23-mediated hypophosphatemia are insidious and nonspecific, including muscle weakness, bone pain, fatigue, and fractures, often resulting in delayed diagnosis (1). Localization and removal of the causative tumor is curative, though in patients whose tumors cannot be localized or removed, medical management typically results in symptomatic improvement (2-5). We present 2 cases of FGF23-mediated hypophosphatemia, 1 with identification and excision of an FGF23-secreting tumor and 1 managed medically since a causative tumor has not been found.

Case Presentation

Case 1

A 43-year-old man presented with 5 years of progressive hip pain, weakness, fatigue, and multiple insufficiency fractures impacting his ambulation. He had previously been on alendronate, then teriparatide, though the etiology of his osteoporosis and fractures remained unclear. He received intra-articular steroid injections and eventually required surgery for a right femur fracture in addition to having a prophylactic left femur fixation. He continued to have pain and weakness. Four years after symptom onset, he was first noted to have hypophosphatemia. Further studies revealed evidence of renal phosphorous wasting given a low tubular maximum for phosphate reabsorption per unit of glomerular filtration rate (TmP/GFR), prompting evaluation for genetic causes of hypophosphatemia (6). An Invitae Hypophosphatemia Panel was negative for pathogenic variants. Subsequently, whole exome sequencing revealed a pathogenic variant of the alpha-galactosidase gene, consistent with Fabry disease. He was prescribed migalastat, resulting in improvement in neuropathic pain, though other symptoms continued. After 5 years of progressive symptoms leading to functional decline and poor quality of life, the patient was evaluated by our endocrinology department.

Case 2

A 48-year-old nonverbal man with autism and intellectual disability presented with months of declining mobility and apparent pain. Dual-energy X-ray absorptiometry (DXA) showed severely low lumbar spine (LS) bone mineral density (BMD) with a T-score of –3.0, and a nuclear medicine bone scan revealed several fractures in different stages of healing. An investigation showed no evidence of abuse, and testing for multiple myeloma was negative. He was admitted to the hospital when he became unable to ambulate unassisted, and imaging revealed a nonoperative fracture of the left hip. Endocrinology was consulted for evaluation of low BMD

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Table 1. Patient lab values prior to diagnosis of FGF23-mediated hypophosphatemia and following treatment

			Patient 1		Patient 2	
Lab value	**Reference range**	**Units**	**Prior to diagnosis**	**After treatment**	**Prior to diagnosis**	**After treatment**
Serum phosphorous	2.7-4.5 0.87-1.45	mg/dL mmol/L	1.3-2.1 mg/dL 0.42-0.68 mmol/L	3.6-5.8 mg/dL 1.2-1.9 mmol/L	1.2-2.3 mg/dL 0.39-0.74 mmol/L	1.8-3.6 mg/dL 0.58-1.16 mmol/L
Urinary phosphorous	400-1300 12.9-42.0	mg/day mmol/day	1759mg/day, 1399 mg/day 56.8 mmol/day, 45.2 mmol/day	824 mg/day, 508 mg/day 26.6 mmol/day, 16.4 mmol/day	507 mg/day, 1222 mg/day, 394 mg/day 16.4 mmol/day, 39.5 mmol/day, 12.7 mmol/day	
TmP/GFR	2.5-4.2 0.8-1.35	mg/dL mmol/L	1.60 mg/dL 0.51 mmol/L		1.43 mg/dL 0.46 mmol/L	
FGF23	< 180	RU/mL	337 RU/mL	38 RU/mL	1070 RU/mL	
25 OH vitamin D	30-60 75-150	ng/mL nmol/L	24-43 ng/mL 60-107 nmol/L	20-32 ng/mL 50-80 nmol/L	22-33 ng/mL 55-82 nmol/L	32-53 ng/mL 80-132 nmol/L
1,25 vitamin D	19.9-79.3 47.8-190.3	pg/mL pmol/L	32 pg/mL 76.8 pmol/L	203 pg/mL, 74 pg/mL 487 pmol/L, 178 pmol/L	7 pg/mL 16.8 pmol/L	
Alkaline phosphatase	40-130	U/L	185-793 U/L	61-530 U/L	196-297 U/L	176-485 U/L
Serum calcium	8.6-10.2 2.2-2.6	mg/dL mmol/L	8.7-9.3 mg/dL 2.2-2.3 mmol/L	8.5-9 mg/dL 2.1-2.3 mmol/L	8.7-10.1 mg/dL 2.2-2.5 mmol/L	9.2-12 mg/dL 2.3-3 mmol/L
Serum creatinine	0.67-1.17 59.2-103.4	mg/dL µmol/L	0.56-0.85 mg/dL 49.5-75.1 µmol/L	0.7-0.9 mg/dL 61.9-79.6 µmol/L	0.52-0.87 mg/dL 46-77 µmol/L	0.57-1.47 mg/dL 50-130 µmol/L
PTH	15-65 1.5-6.8	pg/mL pmol/L	51-211 pg/mL 5.4-22.4 pmol/L	84-360 pg/mL 8.9-38.2 pmol/L	23.3-56.2 pg/mL 2.5-6.0 pmol/L	12.5-50.2 pg/mL 1.3-5.3 pmol/L
LS BMD		g/cm^2	0.601 g/cm^2	1.178 g/cm^2	0.855 g/cm^2	1.264 g/cm^2
LS T-score	≥−1.0[a]	SD	−5.2 SD	−0.3 SD	−3.0 SD	0.5 SD

Abbreviations: FGF23, fibroblast growth factor 23; LS BMD, lumbar spine bone mineral density; PTH, Parathyroid hormone; TmP/GFR, tubular maximum for phosphate reabsorption per unit of glomerular filtration rate.
[a]Criteria based on International Osteoporosis Foundation thresholds (7).

and multiple fractures during his hospitalization, which is when he was first noted to have hypophosphatemia.

Diagnostic Assessment

Case 1

Labs were notable for hypophosphatemia ranging from 1.3 to 2.1 mg/dL (0.42-0.68 mmol/L) (reference range 2.7-4.5 mg/dL [0.87-1.45 mmol/L]) over the previous 9 months with evidence of renal phosphorous wasting given a low TmP/GFR (1.60 mg/dL [0.51 mmol/L]; reference range, 2.5-4.2 mg/dL [0.8-1.35 mmol/L]) (6). Additionally, alkaline phosphatase (ALP) was elevated (438 U/L; reference range, 40-130 U/L), with normal 25-OH vitamin D (32 ng/mL [80 nmol/L]; reference range, 30-60 ng/mL [75-150 nmol/L]), PTH (52 pg/mL [5.5 pmol/L]; reference range, 15-65 pg/mL [1.5-6.8 pmol/L]), calcium (8.8 mg/dL [2.2 mmol/L]; reference range, 8.6 to 10.2 mg/dL [2.2-2.6 mmol/L]), and creatinine (0.56 mg/dL [49.5 µmol/L]; reference range, 0.67-1.17 mg/dL [59.2-103.4 µmol/L]) (Table 1). Repeat DXA 2 years following his previous revealed a 34% decrease in LS BMD despite 1 year of teriparatide. There was high suspicion for TIO given years of progressive symptoms, evidence of hypophosphatemia and renal phosphorous wasting, and negative genetic testing for hypophosphatemia. FGF23 was elevated (337 RU/mL, reference range, < 180 RU/mL), prompting Ga-68 DOTATATE positron emission tomography/computed tomography (PET/CT) imaging, which revealed a 3.5 cm superficial subcutaneous left flank mass, corresponding to a palpable nodule.

Case 2

While hospitalized, the patient had hypophosphatemia ranging from 1.2 to 2.3 mg/dL [0.39-0.74 mmol/L] and evidence of renal phosphorous wasting with low TmP/GFR (1.43 mg/dL [0.46 mmol/L]) (6). Additionally, ALP was elevated (211 U/L), with normal PTH (27.8 pg/mL [2.9 pmol/L]) and calcium (9.6 mg/dL [2.4 mmol/L]), with mildly decreased 25-OH vitamin D (27 ng/mL [67 nmol/L]) and creatinine (0.64 mg/dL [56.6 µmol/L]) (Table 1). After discharge, he continued to have hypophosphatemia refractory to oral replacement. With prior documentation of normal phosphorous and age of presentation, an acquired etiology of hypophosphatemia was suspected. Further evaluation revealed low 1,25-dihydroxyvitamin D (7 pg/mL [16.8 pmol/L]; reference range, 19.9-79.3 pg/mL [47.8-190.3 pmol/L]) and elevated FGF23 (1070 RU/mL), consistent with FGF23-mediated hypophosphatemia (Table 1).

Treatment

Case 1

When the patient was initially seen, he was taking phosphate supplementation (250 mg 4 times daily). Given suspicion for TIO, he was prescribed calcitriol 0.25 mcg twice daily,

which was increased to 0.5 mcg twice daily for persistent hypophosphatemia. Two months after imaging, the mass was surgically removed. Pathology revealed a well-circumscribed tumor with central infarct. The pathology initially reported an infarcted angiolipoma with extensive calcification but upon review of the histopathology of tumors causing TIO was diagnosed as a PMT (8). Phosphorous and calcitriol were discontinued.

Case 2

On discharge, the patient was prescribed vitamin D3 1000 international units (IU) daily, calcium carbonate-vitamin D (600 mg-400 IU) twice daily, and phosphate supplementation (500 mg 4 times daily). Once diagnosed with FGF23-mediated hypophosphatemia, he was prescribed calcitriol 0.5 mcg daily, which was increased to 1 mcg daily for persistent hypophosphatemia.

Outcome and Follow-up

Case 1

Following surgery, the patient had notable improvements in symptoms and functioning and recovered his ability to ambulate. Nine days following his procedure, serum phosphorous was 3.8 mg/dL [1.23 mmol/L], though he developed hyperphosphatemia ranging from 4.6-5.8 mg/dL [1.49-1.87 nmol/L] for 4 months before returning to normal. Five months following surgery, FGF23 normalized (38 RU/mL) (Table 1). A DXA completed 8 months following surgery remarkably showed nearly doubled LS BMD compared to the scan done on the same Lunar Prodigy densitometer (GE Healthcare) a year prior (0.601 g/cm^2 (T-score −5.2) prior to diagnosis of TIO and 1.178 g/cm^2 (T-score −0.3) following surgery). There was no evidence of lumbar compression fracture on concurrent imaging. The patient continues to do well with occasional clinical and laboratory monitoring 2 years following surgery.

Case 2

While undergoing workup for hypophosphatemia, the patient was found to have a right femur fracture that required surgery in addition to a healing stress fracture in the left hip. A month later he had extension of the left hip fracture prompting prophylactic fixation. Shortly afterwards, he was initiated on medical therapy for FGF23-mediated hypophosphatemia, resulting in improvement in mobility. Given no family history of hypophosphatemia and previously documented normal phosphorous levels in adulthood, suspicion was low for genetic causes of hypophosphatemia. Over the course of 7 years, no causative tumor has been found despite extensive imaging, including nuclear medicine octreotide scanning, F-18 fludeoxyglucose PET/CT imaging, whole-body magnetic resonance imaging, and Ga-68 DOTATATE PET/CT imaging.

DXA was repeated 3 years after initiation of medical therapy on the same Lunar Prodigy densitometer (GE Healthcare) as his previous scan and demonstrated improvement in LS BMD (0.855 g/cm^2 [T-score −3.0] prior to diagnosis of FGF23-mediated hypophosphatemia and 1.264 g/cm^2 [T-score 0.5] with medical management). There was no evidence of lumbar compression fracture on concurrent imaging. Since initiation of medical therapy 7 years ago, he has had no further fractures. His phosphorous levels have been low to normal with a range of 1.8 to 3.6 mg/dL [0.58-1.16 mmol/L] (Table 1), and he continues to do well clinically.

Discussion

FGF23-mediated hypophosphatemia causes osteomalacia due to renal phosphate wasting and impaired activation of vitamin D. TIO is a rare cause of hypophosphatemic osteomalacia due to FGF23-secreting PMTs. Patients often have months to years of nonspecific symptoms, including bone pain, weakness, fatigue, and fractures (1). Biochemical hallmarks of FGF23-mediated hypophosphatemia include elevated ALP, evidence of renal phosphorous wasting, and inappropriately normal or low 1,25-dihydroxyvitamin D. When FGF23-mediated hypophosphatemia is suspected, considerations include both heritable and acquired causes. If concern for genetic cause is low and TIO is suspected, localization and excision of the tumor is typically curative, resulting in improvement in patient symptoms, biochemical markers, and osteomalacia. However, these tumors are notoriously difficult to localize. When tumors are unable to be identified or excised, medical management with phosphorous and calcitriol is standard, though more recently, burosumab (an antibody against FGF23) has been used as a treatment (2-5).

Given its rarity, insidious nature, and nonspecific symptoms, FGF23-mediated hypophosphatemia can be challenging to diagnose (3). Our first patient experienced years of symptoms prior to detection of hypophosphatemia and was inappropriately treated with osteoporosis medications and intra-articular steroid injections. Despite evaluation by multiple specialists, he continued to have symptoms for another year before being suspected of having TIO. In a retrospective analysis, Feng et al reported an average time from symptom onset to diagnosis of TIO of 2.9 years with average time from symptom onset to tumor resection of 5.4 years (3). Phosphorus levels are often not part of routine laboratory testing, contributing to delays in diagnosis. The Endocrine Society recommends laboratory evaluation including phosphorous and ALP in men undergoing workup for low BMD (9), and these tests are part of evaluation for secondary osteoporosis in any patient. Patients with evidence of metabolic bone disease who are found to have low phosphorus should undergo testing for renal phosphorus wasting, with subsequent testing based on the results.

Both patients required surgery for fractures and prophylactic hip fixation, emphasizing the negative effects of untreated FGF23-mediated hypophosphatemia. Patients with FGF23-mediated hypophosphatemia have low BMD as a consequence of impaired bone mineralization from renal phosphorous wasting and impaired vitamin D activation. Treatment of hypophosphatemia resulted in improvements in LS BMD in both patients. Our first patient had nearly doubled (96%) LS BMD 8 months following surgical removal, and our second patient had 48% improvement in LS BMD with 3 years of medical therapy. In our review of the literature, few case reports and series have commented on the improvements in BMD with treatment of FGF23-mediated hypophosphatemia. Colangelo et al noted improvements in LS BMD in 7 patients with TIO, with baseline LS BMD of 0.692 g/cm^2 and nearly doubled peak LS BMD of 1.289 g/cm^2 following surgery (10). Rendina et al reported on 5 cases of TIO, 2 treated surgically, and noted increases in LS BMD for all patients, with larger increases in the patients treated surgically with 264%

and 139% improvements in LS BMD, while those managed medically had 37%, 76%, and 52% improvements in LS BMD (11). Though formal comparison of effectiveness of surgical and medical management of TIO is not available, continued search for a causative tumor in patients with suspected TIO is warranted, particularly since resection of the tumor may be curative.

Learning Points

- TIO is a rare cause of osteomalacia due to FGF23-mediated hypophosphatemia.
- Check phosphorous and ALP in patients with bone pain, muscle weakness, and fractures.
- Patients with FGF23-mediated hypophosphatemia typically have elevated ALP, evidence of renal phosphorous wasting, low 1,25-dihydroxyvitamin D, and elevated FGF23.
- Recognizing and treating FGF23-mediated hypophosphatemia can result in substantial improvements in patient functioning, quality of life, and BMD.

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Contributors

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from patient 1. Signed informed consent was obtained directly from patient 2's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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