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Single Case

Tumor-Induced Osteomalacia in a Patient with Crohn's Disease: A Case Report and Approach to Investigating Hypophosphatemia

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Abstract
Introduction: Hypophosphatemia occurs commonly in inflammatory bowel disease (IBD) patients and can cause considerable morbidity. The differential diagnoses in IBD include nutritional causes and hypophosphatemia induced by some formulations of intravenous iron infusions. ***Case Presentation:*** We present the case of a 37-year-old man with active Crohn's disease, presenting with difficulty walking and fractures of the vertebrae and calcaneus. He had long-standing hypophosphatemia. Nutritional causes for hypophosphatemia were considered in the first instance given the presence of chronic diarrhea and vitamin D deficiency; however, there was minimal response to appropriate supplementation with oral phosphorous and vitamin D. Iron infusion-induced hypophosphatemia was then considered, but the nadir phosphate level preceded any iron infusion. Therefore, work-up was undertaken for less common causes. He was ultimately diagnosed with tumor-induced osteomalacia, caused by excess fibroblast growth factor 23 (FGF23) secretion from a phosphaturic mesenchymal tumor about the knee. He had complete resolution of symptoms and biochemical abnormalities following successful resection of the tumor. ***Conclusion:*** This case illustrates the approach to investigation of hypophosphatemia in IBD patients. If the time course and response to phosphate supplementation are not as expected for nutritional or iron infusion-induced hypophosphatemia, less common causes should be considered.

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Introduction

Hypophosphatemia occurs commonly in patients with inflammatory bowel disease (IBD) and can cause an additional insult to bone health. There has been renewed focus on the etiology of hypophosphatemia in this group given reports of iron-infusion-induced hypophosphatemia and the recommendation to monitor phosphate levels in those with risk factors and those receiving multiple high-dose infusions of ferric carboxymaltose (FCM) [1]. The differential diagnoses for hypophosphatemia in IBD include nutritional causes and iron infusion induced. If the time course and response to phosphate supplementation are not as expected for these diagnoses, less common causes should be considered.

Decreased availability of phosphate can cause osteomalacia, a condition characterized by defective bone mineralization resulting in bone "softening." The clinical features include bone pain, muscle weakness, skeletal deformities, and fractures.

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which hypophosphatemia (and subsequent osteomalacia) occurs as a consequence of ectopic fibroblast growth factor 23 (FGF23) secretion, typically from phosphaturic mesenchymal tumors (PMTs) [2]. FGF23 decreases renal tubular phosphate reabsorption, thereby lowering circulating phosphate levels. FGF23 also decreases 1α-hydroxylase activity, which reduces the production of 1,25-dihydroxyvitamin D, limiting the gastrointestinal absorption of calcium and phosphate and exacerbating the hypophosphatemia.

We present the case of a 37-year-old man with TIO on a background of active Crohn's disease, with resolution following successful resection of a PMT. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536136).

Case Report

A 37-year-old man was referred by his gastroenterologist to the endocrinology clinic regarding insufficiency fractures and chronic hypophosphatemia, on a background of ileocolonic Crohn's disease. He reported difficulty walking for 2 years due to weakness and bilateral foot pain. He was mobilizing in a wheelchair. He had lost 6 cm in height and had known fractures of L1 and L2 sustained during a fall 1 year prior. Recent investigations for foot pain included an MRI demonstrating a calcaneal fracture. Hypophosphatemia was present intermittently for 4 years and persisted despite oral phosphate supplementation (elemental phosphorous 1,000 mg daily) for the past 4 months.

He had three bowel resections for Crohn's disease over a 20-year course, further complicated by enterocutaneous fistula. Initial treatment was with azathioprine monotherapy, though adherence had been variable. He had participated in a 2-year etrolizumab (anti-integrin α4β7 and αEβ7) trial but withdrew just prior to presentation due to persistent disease, with a plan to transition to infliximab. His cumulative corticosteroid exposure was minimal. Other history included vitamin D deficiency, iron deficiency anemia, and gastric ulcers. He was a non-smoker.

Current daily medications were azathioprine 100 mg, cholecalciferol 4,000 IU, calcium carbonate 600 mg, elemental phosphorous 1,000 mg, naproxen 500 mg, pantoprazole 40 mg, multivitamin and paracetamol/codeine 1,000/30 mg. Over 2 years, four intravenous iron infusions had been administered (shown in Fig. 1). He had adverse drug reactions to intravenous iron polymaltose and FCM, which caused tachycardia and dizziness.

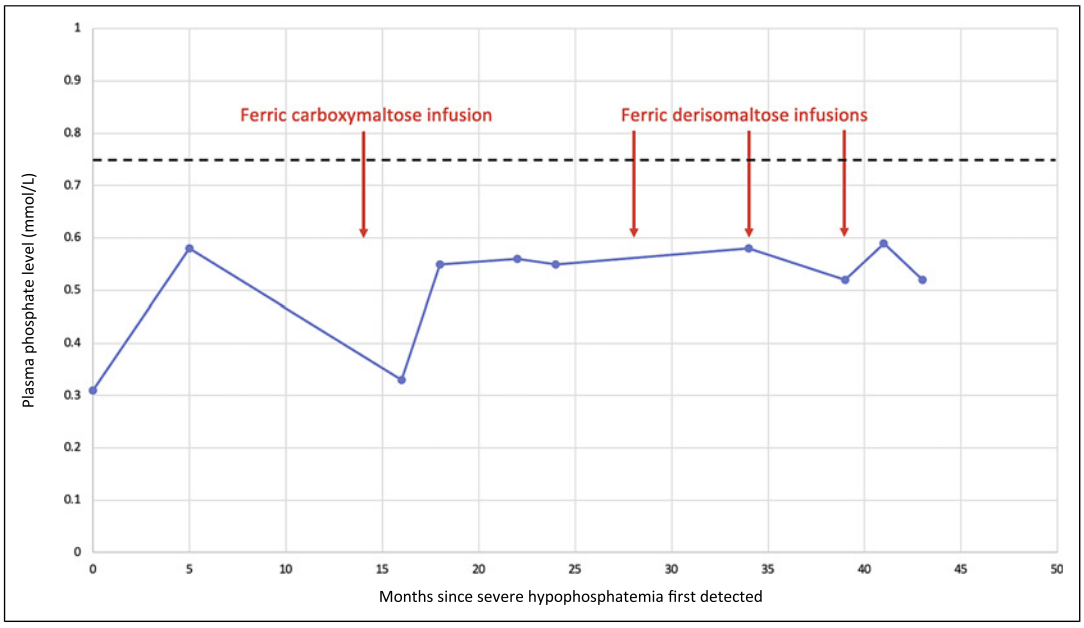

Fig. 1. Plasma phosphate levels over time. Dotted line indicates lower level of normal reference range, 0.75 mmol/L. Red arrows indicate the administration of intravenous iron (at month 14, FCM was administered; subsequent infusions at months 28, 34, and 39 were ferric derisomaltose).

He presented in a wheelchair. His weight was 105 kg and height 191.6 cm, with body mass index 28.5 kg/cm^2. There was lower limb proximal weakness and diffuse tenderness over the feet bilaterally.

Biochemistry at initial endocrinology assessment (Table 1) demonstrated a low plasma phosphate of 0.52 mmol/L (reference range 0.75–1.10). The nadir phosphate level of 0.31 mmol/L, shown in Figure 1, had occurred prior to receiving any iron infusions. Alkaline phosphatase (ALP) was persistently raised in the absence of other liver function abnormalities. CRP was 20 mg/L (<5).

Fasting urine phosphate was 50.1 mmol/L with urine creatinine 25.9 mmol/L. The calculated tubular reabsorption of phosphate (TmP/GFR) was low at 0.42 mmol/L (1–1.30), indicating inappropriate renal wasting of phosphate. Parathyroid hormone (PTH) was normal. There had been a recent normalization of 25-hydroxy-vitamin D level with cholecalciferol replacement. However, 1,25-dihydroxyvitamin D was low at 30 nmol/L (48–190) and plasma FGF23 level was inappropriately elevated at 101 ng/L (23–95).

Dual energy x-ray absorptiometry showed low bone mass, with Z score −3.3 at the lumbar spine and −3.8 at the left femoral neck. Bone scintigraphy, shown in Figure 2a, was consistent with osteomalacia. MRI foot demonstrated a left calcaneal fracture traversing 50% of the depth of the calcaneal tuberosity and a suspected fracture of the medial cuneiform. Taken together, his biochemistry and imaging were consistent with osteomalacia due to FGF23-mediated hypophosphatemia.

A search for the source of FGF23 ensued. DOTATATE PET scan, shown in Figure 2b, identified an avid 10 × 15 mm soft tissue nodule posterior to the right knee. The patient proceeded to an uncomplicated excision of the lesion.

Histopathology shown in Figure 3 demonstrated a highly vascular lesion with spindle cells in short fascicles (Fig. 3a), positive for FGF23 on immunohistochemistry (Fig. 3b). The final histopathological diagnosis was PMT.

Table 1. Biochemical values measured at initial endocrinology assessment, 6 months later (immediately prior to resection of a PMT), 8 months later (2 months following resection of PMT), and 10 months later (4 months following resection of PMT)

	At initial endocrinology assessment	Immediately prior to PMT resection	2 months following PMT resection	4 months following PMT resection	Reference range
Phosphate, mmol/L	**0.52**	**0.62**	1.39	1.36	0.75–1.50
Corrected calcium, mmol/L	2.29	2.24	2.29	2.27	2.10–2.60
Creatinine, μmol/L	**54**	63	65	**59**	60–110
ALP, U/L	**274**	**454**	**351**	**326**	30–110
Bone-specific ALP, μg/L	**78.9**				3.7–20.9
25-hydroxy-vitamin D, nmol/L	77	82	76	55	50–150
1,25-dihydroxyvitamin D, nmol/L	**30**		**340**	**268**	48–190
PTH, pmol/L	6.4		**12**		1.0–7.0
Calculated TmP/GFR, mmol/L	**0.42**	**0.36**	**1.70**		1–1.3
FGF23, ng/L	**101**	**213**	**8.4**	**20**	23–95

Abnormal values are bolded. ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; PMT, phosphaturic mesenchymal tumor; PTH, parathyroid hormone; TmP/GFR, ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate.

Following surgery, FGF23 levels dramatically decreased and plasma phosphate levels completely normalized (Table 1). The bone pain improved over the ensuing months and the patient was able to walk with no aid within 4 months of tumor removal. Two years post-surgery, there was significant improvement in the bone scan appearances, with now largely physiologic activity (Fig. 2c).

Discussion

Hypophosphatemia is commonly missed due to nonspecific symptoms and lack of routine monitoring; however, it can cause considerable morbidity [3]. Symptoms include generalized muscle weakness, fatigue, and osteomalacia with bone pain and fractures. Three primary mechanisms of hypophosphatemia exist: decreased intestinal absorption, redistribution of phosphate from the extracellular to intracellular compartments, and increased renal excretion [3].

The possible etiologies for hypophosphatemia in patients with active IBD can relate to all three of these primary mechanisms. First, decreased intestinal absorption of phosphate can occur in malnourished patients with chronic diarrhea, leading to malabsorption of phosphate and vitamin D. Decreased absorption may also occur due to vomiting or nasogastric suctioning, or with a phosphate-binding agent. Second, intracellular phosphate redistribution can occur in IBD patients with refeeding syndrome or those receiving glucose/insulin therapy. Another cause of redistributive hypophosphatemia is respiratory alkalosis, which may occur

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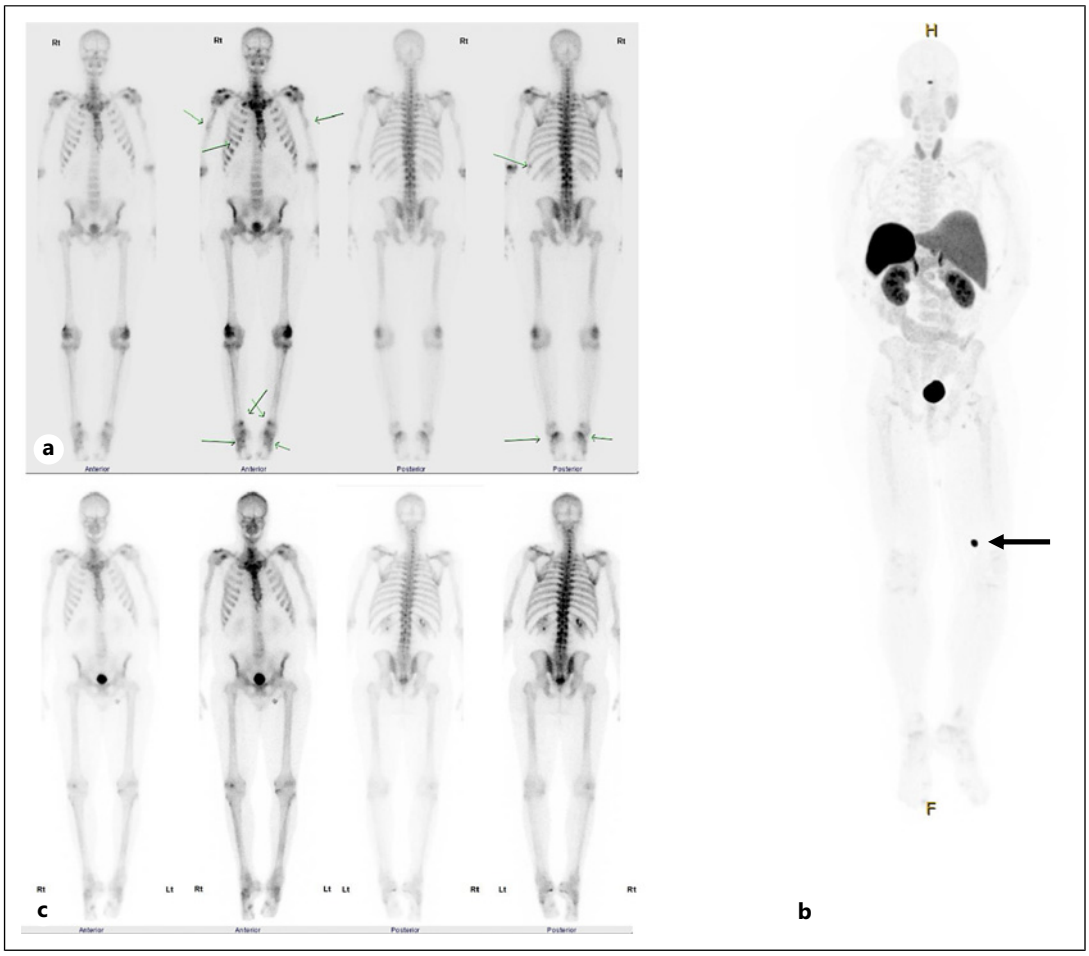

Fig. 2. a Bone scintigraphy at initial work-up shows diffusely increased osteoblastic activity throughout the axial skeleton. There are multiple bilateral insufficiency fractures in the distal tibia and feet (arrows), multiple bilateral nondisplaced rib fractures (arrows), suspected looser zones in the bilateral proximal humeral diaphysis (arrows), and anterior wedge compression fractures of L1 and L2. **b** Maximum intensity projection from PET scan following intravenous injection of 172MBq of Ga68-DOTATATE. There is intense uptake in a small soft tissue nodule posterior to the right knee, measuring 10 × 15 mm (arrow). **c** Bone scintigraphy 2 years post-removal of PMT demonstrates significant improvement in the previously demonstrated metabolic pattern of uptake through the axial and appendicular skeleton, with now largely physiological activity.

in IBD patients with stimulated respiratory drive due to complications such as pain, sepsis, or pulmonary embolism. Third, increased renal excretion of phosphate can occur in IBD patients who have developed secondary hyperparathyroidism from calcium/vitamin D deficiency as this process limits renal tubular phosphate reabsorption. Excess renal excretion of phosphate also occurs with some formulations of intravenous iron infusions, especially FCM, which is now a well-described cause of FGF23-mediated hypophosphatemia. There is a complex relationship between iron status, intravenous iron preparations, and regulation of FGF23 synthesis and degradation [4]. FGF23 can be in the form of active intact FGF23 (iFGF23) and inactive cleaved FGF23 (cFGF23). The balance between glycosylation (which protects FGF23 from proteolytic cleavage) and phosphorylation (which prevents glycosylation and thereby makes FGF23 more prone to cleavage) determines the ratio between iFGF23 and cFGF23 that will be released into circulation [5]. Iron deficiency stimulates transcription and cleavage of

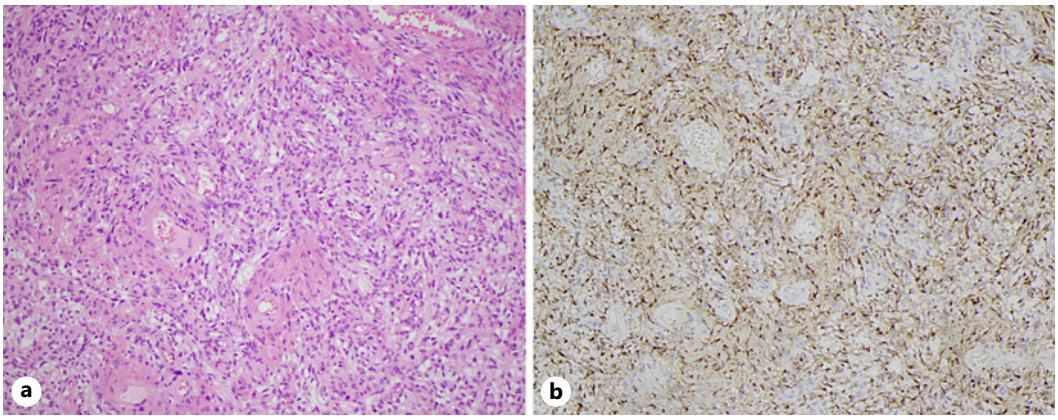

Fig. 3. a Hematoxylin and eosin stain, intermediate power. Tissue from the resected soft tissue lesion demonstrated a highly vascular lesion with spindle cells in short fascicles with zones of cytoplasmic clearing, occasional foamy macrophages, and scattered aggregates of osteoclast-like giant cells. **b** FGF23 immunohistochemistry, intermediate power. FGF23 immunohistochemistry was positive with typical perinuclear dot-like expression.

FGF23 simultaneously [6]. Intravenous FCM leads to an acute increase in iFGF23 levels, while cFGF23 levels are decreased [4]. The exact mechanism by which FCM increases iFGF23 levels is unknown [5]. The iron components and carbohydrate moieties of these agents likely affect different aspects of FGF23 regulation. FCM is associated with a significant increase in iFGF23 levels within 24 h of administration [4]. FCM administration in IBD patients is associated with a 57% incidence of moderate-to-severe hypophosphatemia 2 weeks after infusion, with the time to spontaneous normalization ranging from 1 to 6 months [7]. Finally, IBD patients may develop non-IBD-related causes of hypophosphatemia from any of the three underlying mechanisms outlined above.

An approach to the work-up of hypophosphatemia in IBD patients is shown in Figure 4. History taking is the mainstay of identifying decreased intestinal absorption and cellular redistribution causes of hypophosphatemia. A detailed medication history in IBD patients is essential, specifically looking for inhibitors of phosphate absorption (antacids, phosphate binders, niacin), diuretics, and iron infusions [3]. Among iron infusions, the formulation should be noted, FCM being associated with a significantly higher incidence of hypophosphatemia than iron isomaltoside, iron sucrose, iron dextran, and ferumoxytol [8]. Nadir phosphate levels in FCM-infusion induced hypophosphatemia typically occur approximately 2 weeks after the infusion, then return to baseline by a mean of 12 weeks [9, 10]. Ideally, a review of serial serum phosphate levels should be undertaken in the context of IBD disease activity (especially during episodes of inadequate intake, chronic diarrhea, and refeeding syndrome).

The initial biochemical work-up includes measurement of serum phosphate, calcium, ALP, PTH, 25-hydroxy-vitamin D, and urine phosphate [3]. Urinary loss of phosphate can be quantified by calculating either Tmp/GFR or fractional excretion of phosphate. Low urinary phosphate excretion usually indicates decreased intestinal absorption of phosphate as the cause of hypophosphatemia, as may occur with increased intestinal transit and secretions (chronic diarrhea) or intestinal phosphate binding by calcium, magnesium, or aluminium to form insoluble salts. Less frequently, low urine phosphate is due to intracellular redistribution, as in refeeding syndrome, insulin infusions, or acute respiratory alkalosis.

An inappropriately high urinary phosphate excretion confirms renal phosphate wasting and referral to an appropriate specialist is recommended. This category can be further subdivided into high serum PTH (i.e., PTH-mediated hypophosphatemia, including vitamin D

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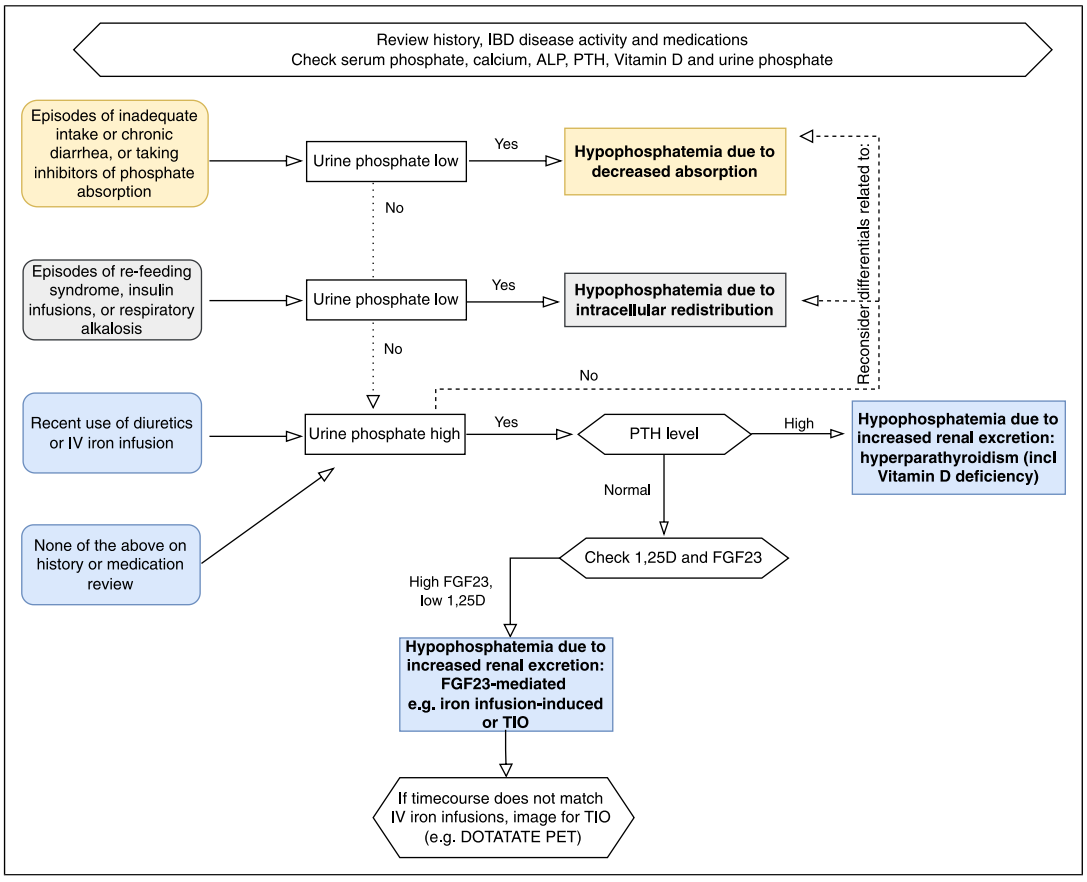

Fig. 4. Diagnostic approach to hypophosphatemia in IBD patients.

deficiency, primary hyperparathyroidism) and normal serum PTH conditions. For those with renal phosphate wasting but normal PTH, further assessment of serum 1,25-dihydroxyvitamin D and, if available, FGF23 will identify those with FGF23-mediated phosphaturia (low 1,25-dihydroxyvitamin D, high FGF23, see Fig. 4). Imaging is relevant if TIO is suspected.

In our patient's case, the lack of responsiveness of hypophosphatemia to supplementation of vitamin D and phosphorous, as well as the time course distinct from iron infusions, warranted consideration of an alternative cause, leading to the diagnosis of TIO due to a PMT. In TIO, the chronic hypophosphatemia induced by ectopic FGF23 secretion leads to suboptimal supply of phosphate to bone and subsequent reduced rate of osteoid mineralization, resulting in osteomalacia [2].

An association between FGF23 levels and inflammatory markers has been established in some groups [11]. FGF23 levels are higher among children with IBD during flares and among psoriasis patients compared to controls [12, 13]. One other case of TIO in IBD has recently been described [14]. However, it is not known if there is any causative link between TIO and IBD.

In conclusion, this case report serves to highlight the mechanisms underpinning hypophosphatemia in IBD patients. Ultimately, a rare cause was identified in our patient; however, regardless of the specific mechanism, hypophosphatemia can result in severe osteomalacia with associated morbidity and addressing the underlying cause can vastly improve quality of life.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

K.H.: writing – original draft and writing – review and editing. A.C.: writing – review and editing. S.L.: conceptualization, writing – review and editing, and supervision.

Data Availability Statement

Data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Snook J, Bhala N, Beales ILP, Cannings D, Kightley C, Logan RP, et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut. 2021;70(11):2030–51.
2 Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, et al. Tumour-induced osteomalacia. Nat Rev Dis Primers. 2017;3(1):17044.
3 Imel EA, Econs MJ. Approach to the hypophosphatemic patient. J Clin Endocrinol Metab. 2012;97(3):696–706.
4 Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. J Bone Miner Res. 2013;28(8):1793–803.
5 Ratsma DMA, Zillikens MC, van der Eerden BCJ. Upstream regulators of fibroblast growth factor 23. Front Endocrinol. 2021;12:588096.
6 David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int. 2016;89(1):135–46.
7 Detlie TE, Lindstrøm JC, Jahnsen ME, Finnes E, Zoller H, Moum B, et al. Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside. Aliment Pharmacol Ther. 2019;50(4):397–406.
8 Bellos I, Frountzas M, Pergialiotis V. Comparative risk of hypophosphatemia following the administration of intravenous iron formulations: a network meta-analysis. Transfus Med Rev. 2020;34(3):188–94.

Case Rep Gastroenterol 2024;18:81–89
DOI: 10.1159/000536136

9 Anand G, Schmid C. Severe hypophosphataemia after intravenous iron administration. BMJ Case Rep. 2017; 2017:bcr2016219160.
10 Schaefer B, Würtinger P, Finkenstedt A, Braithwaite V, Viveiros A, Effenberger M, et al. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. PLoS One. 2016;11(12):e0167146.
11 Munoz Mendoza J, Isakova T, Ricardo AC, Xie H, Navaneethan SD, Anderson AH, et al. Fibroblast growth factor 23 and Inflammation in CKD. Clin J Am Soc Nephrol. 2012;7(7):1155–62.
12 El-Hodhod MA, Hamdy AM, Abbas AA, Moftah SG, Ramadan AA. Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease. BMC Gastroenterol. 2012;12:44.
13 Okan G, Baki AM, Yorulmaz E, Doğru-Abbasoğlu S, Vural P. Fibroblast growth factor 23 and placental growth factor in patients with psoriasis and their relation to disease severity. Ann Clin Lab Sci. 2016;46(2):174–9.
14 Habbsa S, Canakis A, George L, Thomas A, Hu Y, Cross RK, et al. A dancer with fractures: what lies beneath? Dig Dis Sci. 2023;68(1):54–7.