A Case of Hypophosphatemia due to Oncogenic Osteomalacia in a Patient with Natural Killer T-Cell Lymphoma

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Keywords

Hypophosphatemia · Renal phosphate wasting · Oncogenic osteomalacia · Fibroblast growth factor-23 · Natural killer T-cell lymphoma · Tumor-induced osteomalacia

Abstract

Introduction: Oncogenic osteomalacia (Onc-Ost) is a paraneoplastic phenomenon characterized by hypophosphatemia due to elevated fibroblast growth factor-23 (FGF-23). Onc-Ost has been previously reported in patients with germ line mesenchymal tumors and solid organ malignancies. This is the first report of aggressive natural killer (NK) T-cell lymphoma presenting as Onc-Ost. **Case Description:** A 33-year-old Vietnamese female with active hepatitis B and *Mycobacterium avium* complex, on ongoing therapy with tenofovir disoproxil, azithromycin, and ethambutol, presented with persistent fevers and developed refractory hypophosphatemia. Workup confirmed severe renal phosphate wasting. Tenofovir disoproxil was initially suspected; however, presence of isolated phosphaturia without Fanconi syndrome and persistence of hypophosphatemia despite discontinuation of medication led to clinical suspicion of Onc-

Ost. Elevated FGF-23 warranted further workup, leading to a definitive diagnosis of clinically subtle NK T-cell lymphoma. Chemotherapy was initiated; however, patient continued to deteriorate clinically and expired. **Conclusion:** Along with commonly reported germ line mesenchymal tumors and solid malignancies, NK T-cell lymphoma can also present as Onc-Ost. Timely detection of associated tumors and subsequent antitumor therapy would likely reverse hypophosphatemia and improve clinical outcomes.

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Introduction

Oncogenic osteomalacia (Onc-Ost), also known as tumor-induced osteomalacia, is a paraneoplastic syndrome characterized by constellation of elevated fibroblast growth factor-23 (FGF-23), hypophosphatemia, low to normal levels of 1,25-(OH)₂ vitamin D (1,25 dihydroxy vitamin D), and phosphaturia [1]. Abnormal excessive production of FGF-23 by a tumor is recognized as the key element driving the disturbance in phosphate homeostasis. This syndrome is often associated with benign mes-

enchymal tumors and is rarely reported among solid organ malignancies [2–5]. To our knowledge, the association of hypophosphatemia secondary to Onc-Ost in relation to natural killer (NK) T-cell lymphoma has not yet been reported. Herein, we report a case of 33-year-old Vietnamese female who presented with persistent fever, elevated inflammatory markers, and refractory hypophosphatemia secondary to Onc-Ost. Additionally, we discuss diagnostic and treatment strategies for patients with Onc-Ost.

Case Description

A 33-year-old Vietnamese female with active hepatitis B and *Mycobacterium avium complex* (MAC) infection, on ongoing therapy with tenofovir disoproxil, azithromycin, and ethambutol, presented to a regional medical center with recurrent fever, chills, productive cough, and dyspnea of 3-day duration. Upon arrival, the patient was tachycardic and tachypneic with diffuse rales on auscultation. Diagnosis of sepsis due to pneumonia was entertained, and the patient was started on fluids and broad-spectrum antibiotics. She eventually developed respiratory distress with hypoxemia requiring intubation and transfer to our academic medical center for further care. The patient was stabilized after admission to our intensive care unit. The patient developed bilateral pleural effusions that required thoracentesis on day 9 of hospital stay. Elevated ferritin and LDH and abundant lymphoid cells in pleural fluid led to preliminary diagnosis of hemophagocytic lymphohistiocytosis (HLH) that prompted initiation of dexamethasone and etoposide. It was noted that patient's phosphate levels were staying low around 2.3 mg/dL and dropped to as low as 1.3 mg/dL despite intermittent supplementation, prompting nephrology consultation on day 20. Pertinent laboratory results obtained at time of consultation include serum creatinine of 0.5 mg/dL, corrected serum calcium at 8.5 mg/dL, elevated alkaline phosphatase 701 U/L (55–135 U/L), parathyroid hormone (PTH) of 114 pg/mL (9–77 pg/mL), 1,25-(OH)₂ vitamin D 20 pg/mL (20–79 pg/mL), random urinary phosphate of 63 mg/dL, and fractional excretion of urinary phosphate of 43% (Table 1). Tenofovir disoproxil was initially considered as potential cause due to its proximal tubular toxicity and known association with Fanconi syndrome [6]. Additionally, tenofovir disoproxil has been reported to cause hyperparathyroidism by direct inhibition of calcium-sensing receptors, as noted in our case [7]. However, isolated phosphaturia in the absence of glycosuria or aminoaciduria and persistent hypophosphatemia even after cessation of tenofovir prompted consideration for alternate diagnosis. Patient continued receiving aggressive oral and intravenous phosphate supplementation, and serum phosphate levels continued to fluctuate over the course of hospitalization (Fig. 1).

FGF-23 (C-Terminal) 2nd generation ELISA was ordered due to clinical suspicion of Onc-Ost. The FGF-23 levels returned significantly elevated at 1,940 RU/mL (normal: <180 RU/mL), supporting the diagnosis of Onc-Ost. At that point, given the complex clinical scenario of hepatitis B, MAC, HLH and Onc-Ost, a lymphoproliferative disorder was suspected. Bone marrow and lymph

Table 1. Laboratory values at the time of consultation to nephrology

	Patient value	Normal range
Serum		
Sodium, mEq/L	128	136–145
Potassium, mEq/L	3.8	3.4–5.1
Bicarbonate, mEq/L	24	22–29
Chloride, mEq/L	105	96–105
Calcium, mg/dL	5.9	8.6–10.2
Corrected calcium, mg/dL	8.9	8.6–10.2
Albumin, g/dL	1.5	3.8–4.5
Phosphate, mg/dL	1.5	2.5–4.5
Creatinine, mg/dL	0.5	0.5–1.1
Urea nitrogen, mg/dL	15	6–23
Alkaline phosphatase, U/L	701	35–104
PTH, pg/mL	114	15–72
25-Hydroxyvitamin D, pg/mL	8	30–100
1,25-Hydroxyvitamin D, pg/mL	20	19.9–79.2
FGF-23, RU/mL	1,940	<180
Urine		
Phosphate, mg/dL	63	
Creatinine, mg/dL	58	
Fractional excretion of urinary phosphate, %	43	

PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23.

node biopsies were performed, and they revealed occasional EBV+ and CD5+ cells. A definitive diagnosis of NK T-cell lymphoma was established when flow cytometry from repeat thoracentesis performed on hospital day 30 revealed positive staining for CD2, CD7, and CD56 NK T cells. Patient was subsequently initiated on chemotherapy with dexamethasone, cisplatin, gemcitabine, and pegaspargase. She continued to be hypophosphatemic, needing phosphate supplementation. Patient continued to deteriorate clinically and expired on day 34 of hospitalization.

Discussion

Onc-Ost is characterized by persistent hypophosphatemia with clinical manifestations of fatigue, fractures, and other bone abnormalities. We report one of the first cases of Onc-Ost secondary to NK T-cell lymphoma. Our patient's complicated clinical presentation of ongoing infection with HBV, MAC, presumed diagnosis of HLH and possible tenofovir disoproxil-induced phosphate wasting made it particularly challenging to establish the final diagnosis. It was the elevated FGF-23 level, which increased the likelihood of Onc-Ost, prompting further investigations and ultimately leading to the final diagnosis of NK T-cell lymphoma.

Fig. 1. Trajectory of serum phosphate and corrected serum calcium levels and timeline of major events over the course of the hospitalization. NK, natural killer; FGF-23, fibroblast growth factor-23; PO₄, phosphate.

Tenofovir disoproxil in addition to multiple chemotherapeutic agents can cause proximal tubular damage, Fanconi syndrome, and concomitant phosphate wasting [6]. Even though hypophosphatemia secondary to phosphate wasting due to tenofovir disoproxil was initially entertained, lack of glucosuria, bicarbonaturia, lack of improvement of phosphate levels upon discontinuation of the drug, and elevated FGF-23 levels led to an accurate diagnosis. High FGF-23 levels further aided us in narrowing the differential of renal phosphate wasting disorders to Onc-Ost, X-linked hypophosphatemic rickets and autosomal dominant and recessive hypophosphatemic rickets, while the latter are mainly encountered in pediatric population [8].

In the index patient, persistent hypophosphatemia was associated with low active vitamin D and elevated alkaline phosphatase that are likely secondary to increased FGF-23 peptides secreted by NK T-cell lymphoma. It is hypothesized that FGF-23 peptides secreted by tumors bind to fibroblast growth factor receptor 1 isoform IIIc found in proximal tubular epithelial cells and subsequently decrease the reabsorption of phosphate by inhibiting sodi-

um-phosphate cotransporter (NaPi-IIa and IIc) [9]. In addition to directly affecting tubular handling of filtered phosphate, FGF-23 also inhibits 1- α hydroxylase in renal proximal tubule with subsequent decrease in 1,25-(OH)₂ vitamin D levels, further increasing phosphate excretion. Additionally, FGF-23 demonstrates an inhibitory effect on PTH secretion in normocalcemic individuals [10]. However, elevated PTH levels can be seen as encountered in our case and are often driven by elevated FGF-23 and low vitamin D levels [11]. Figure 2 illustrates pathogenesis of hypophosphatemia in Onc-Ost and role of FGF-23.

Onc-Ost is commonly reported among benign mesenchymal tumors such as nasal hemangiopericytoma [12] and femur mesenchymal tumor [13] and is rarely reported among other malignancies including small cell lung carcinoma [2], ovarian cancer [3], and metastatic breast cancer [4]. Elderman et al. [5] reported only case of Onc-Ost secondary to B-cell non-Hodgkin lymphoma, who presented with hypophosphatemia, renal phosphate wasting, and elevated FGF-23 levels. Unlike ours, patient in the report by Elderman et al. [5]

Fig. 2. Role of FGF-23 in the pathogenesis of Onc-Ost. **a** Effect of FGF-23 on inhibiting proximal tubular reabsorption of phosphate. **b** Schematic illustrating global effect of FGF-23 on vitamin D axis and intestinal phosphate handling as well as the pathway to alter direct tubular handling. Onc-Ost, oncogenic osteomalacia; FGF-23, fibroblast growth factor-23.

had a gingival lesion on physical examination and subsequent biopsy confirmed B-cell non-Hodgkin lymphoma. Prompt initiation of chemotherapy led to reversal of FGF-23 and serum phosphate levels within 2 weeks.

History and physical examination may provide vital information on localizing the tumor, but in cases where tumor size is too small, it is suggested to obtain functional imaging like octreotide scan [14], Gallium-68 DOT-ATATE PET/CT, and FDG-PET or anatomical imaging techniques including whole-body magnetic resonance imaging [15] or computed tomography [16]. Table 2 illustrates diagnostic tests to be considered in patient with renal phosphate wasting. Treatment of Onc-Ost is adequate antitumor therapy. When tumors are unresectable or with multiple recurrences, calcitriol and oral phosphate supplementation is recommended [17]. Human monoclonal antibody therapy against FGF-23, burosumab, initially approved for the treatment of X-linked hypophosphatemia [18], is currently being evaluated among patients with Onc-Ost. However, in our patient due to complicated clinical presentation, the diagnosis of NK T-cell lymphoma could not be made early enough and the patient expired within 4 days of chemotherapy initiation.

Table 2. Diagnostic tests to be considered in patient with renal phosphate wasting

Diagnosis and management	
History and physical	
Age/sex	
Family history	
Laboratory abnormalities	
Serum	
Calcium	
Creatinine	
PTH	
Alkaline phosphatase	
Serum FGF-23	
Urine	
Phosphorous	
Creatinine	
Imaging	
Anatomical	
CT/MRI	
Functional	
Gallium-DOTATATE PET/CT	
FDG-PET/CT	
Octreoscan – SPECT/CT	

PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23; PET/CT, positron emission tomography with computed tomography; FDG-PET/CT, F-18 fluorodeoxyglucose positron emission tomography with computed tomography; SPECT/CT, single photon emission and computed tomography.

Conclusion

Onc-Ost should be considered in the workup of refractory hypophosphatemia secondary to renal phosphate wasting, and this could potentially lead to early discovery of clinically subtle malignancies. Obtaining FGF-23 level will likely play a key role in narrowing the differential diagnosis of renal phosphate wasting syndromes. In addition to germ line mesenchymal tumors and solid malignancies, NK T-cell lymphoma can also cause Onc-Ost. Successful antitumor therapy will likely lead to improvement of Onc-Ost.

Statement of Ethics

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images.

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Conflict of Interest Statement

J.C.Q.V. has participated in consulting for Mallinckrodt Pharmaceuticals and Bayer, advisory board for Mallinckrodt Pharmaceuticals, Travere, and speaker bureau for Otsuka Pharmaceuticals.

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Author Contributions

G.Z., T.N., and J.P.C. were involved in describing the case. S.K. helped drafting Introduction and Discussion. J.C.Q.V. helped with formatting and overall supervision.