ACID-BASE AND ELECTROLYTE TEACHING CASE

Elevated Fibroblast Growth Factor 23 in a Patient With Metastatic Prostate Cancer and Hypophosphatemia

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INDEX WORDS: Tumor induced osteomalacia; hypophosphatemia; prostate adenocarcinoma.

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by severe hypophosphatemia, renal phosphate wasting, and osteomalacia.[1] Fibroblast growth factor 23 (FGF-23), a known phosphatonin, is implicated in the pathogenesis of this syndrome. Although increased FGF-23 levels were documented in patients with TIO secondary to various tumors, an association with prostate cancer has not been described to date. We present a case of TIO secondary to metastatic prostate cancer in the setting of an increased FGF-23 level.

CASE REPORT

Clinical History

An 83-year-old man presented with persistent hypophosphatemia detected during workup of generalized weakness. Two years before presentation, high-grade prostate adenocarcinoma was diagnosed. He underwent radical prostatectomy at that time, with a decrease in prostate-specific antigen (PSA) level from 10 to 5 ng/mL. Antiandrogenic therapy was started with goserelin (a synthetic decapeptide analogue of luteinizing hormone–releasing hormone), and PSA subsequently was undetectable for 22 months. At this time, apparent hormone refractoriness developed, manifested by a 10-fold increase in PSA and alkaline phosphatase levels to greater than 1,000 IU/L. Bone scintigraphy showed widely metastatic disease, and 2 years after prostatectomy, chemotherapy was started with docetaxel (75 mg/m^2) every 3 weeks, as well as monthly intravenous zoledronic acid (4 mg). Concurrent with the administration of docetaxel and zoledronic acid, the patient's serum phosphorus level decreased from 3.3 mg/dL (1.07 mmol/L; normal, 2.5 to 4.5 mg/dL [0.81 to 1.45 mmol/L]) to a nadir of 0.8 mg/dL (0.26 mmol/L) over approximately 2 months. Concomitant symptoms included severe fatigue, myalgias, and weakness.

The patient was seen at an outside facility, where intact parathyroid hormone (PTH) level was 270 pg/mL (270 ng/L), 25-hydroxyvitamin D level was normal, and 24-hour urine phosphorus excretion was 1.5 g in the setting of a serum phosphorus level of 1.6 mg/dL (0.52 mmol/L) and normal serum calcium level. A presumptive diagnosis of primary hyperparathyroidism was made, docetaxel and zoledronic acid therapy were withheld, and the patient was treated with up to 8 packets of potassium phosphate (2 g of elemental phosphorus) per day in divided doses. He did not tolerate the supplement well secondary to the development of significant diarrhea. For the next 4 months, serum phosphorus levels ranged from 1.4 mg/dL (0.45 mmol/L) to 1.7 mg/dL (0.55 mmol/L), and fatigue and weakness persisted.

Additional Investigations

On the patient's initial evaluation at our institution 10 months after the start of chemotherapy, serum creatinine level was 0.8 mg/dL (71 μmol/L), serum phosphorus level was 1.4 mg/dL (0.45 mmol/L), and a random urine phosphorus excretion was 44.4 mg/dL (14.34 mmol/L). Fractional excretion of phosphorus was 21%, and renal phosphate threshold (tubular maximum for phosphate corrected for glomerular filtration rate [TmP/GFR]) was low at 1.25 mg/100 mL. Serum calcium and 25-hydroxyvitamin D levels were normal at 8.7 mg/dL (2.17 mmol/L) and 32 ng/mL (2.496 nmol/L), respectively. The 1,25 dihydroxyvitamin D level was low at 20 pg/mL (52 pmol/L), with normal values ranging from 22 to 67 pg/mL (57 to 174 pmol/L). Intact PTH level was 96 pg/mL (96 ng/L; normal, 12 to 75 pg/mL). There was no evidence of glucosuria, amino aciduria, hypouricemia, monoclonal gammopathy, or increased PTH-related peptide. He did not have diarrhea. FGF-23 level was increased at 326 reference units (RU)/mL (normal, 0 to 180 RU/mL). A presumptive diagnosis of TIO was made.

Diagnosis

Given the important role of phosphorus in cell membrane structure, bone mineralization, adenosine triphosphate generation, urinary buffering, and phosphorylation of cellular signaling enzymes, serum phosphorus level is maintained in the 2.5- to 4.5-mg/dL (0.8- to 1.45-mmol/L) range.[1,2] The majority (85%) of the body's 700 g of phosphorus is contained in the bones and teeth, with the remainder found in soft tissues and extracellular fluid.[2] Under the influence of PTH and 1,25 dihydroxyvitamin D, the kidney and small intestine are the main sites of phosphorus reabsorption and excretion. Under normal conditions, approximately 80% of

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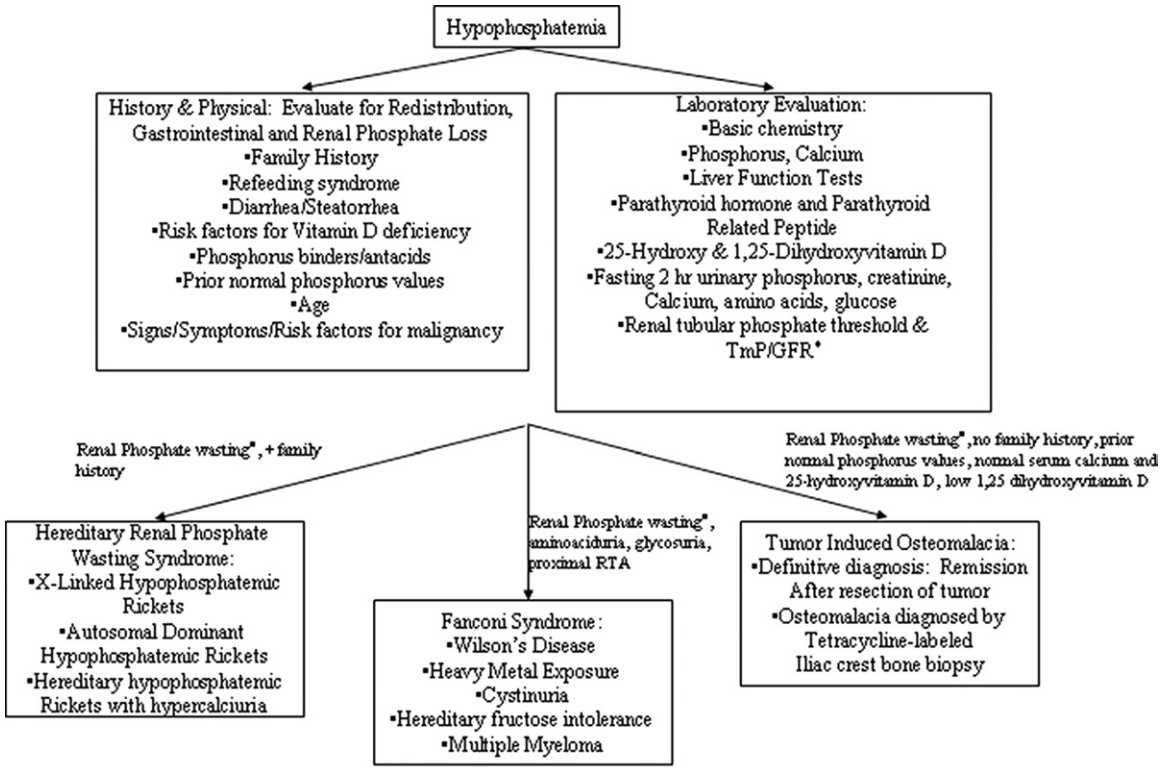

Figure 1. Approach to diagnosing the etiology of hypophosphatemia.

the filtered phosphorus load is reabsorbed in the proximal tubule.[1] However, under conditions of decreased phosphorus intake, fractional excretion of phosphorus can decrease to less than 1%. Hypophosphatemia leads to increased renal 25-hydroxyvitamin D-1α-hydroxylase activity, with a subsequent increase in 1,25 dihydroxyvitamin D levels. Thereafter, calcium and phosphorus reabsorption increases, bone mineral stores are mobilized, and PTH is inhibited.[1]

An approach to hypophosphatemia is shown in Fig 1.[1-3] A renal leak of phosphorous is established by examining urinary excretion of phosphorous. Although intuitively appealing, checking the fractional excretion of phosphorous (ie, percentage of filtered phosphorous excreted) does not take into account the influence of increased filtered load or increase in GFR. Thus, calculating a parameter that accounts for both tubular reabsorption and GFR is preferred, as described in the calculation of the renal phosphate threshold (TmP/GFR) by using a nomogram.[1,3]

Clinical Follow-Up

The patient was treated with 2 μg/d of calcitriol, along with 2 g of elemental phosphorus (as potassium phosphate powder). Chemotherapy with docetaxel was reinstituted, and at clinic follow-up 5 months after initial evaluation at our institution, his symptoms had improved, alkaline phosphatase level had decreased from greater than 1,000 IU/L to 250 IU/L, and PSA level decreased to less than 2 ng/mL. However, he still had a serum phosphorus level of 1.6 mg/dL (0.52 mmol/L), and a repeated FGF-23 level was 2,140 RU/mL. Three months later, at his most recent evaluation, his symptoms had essentially resolved, and laboratory investigation showed the following values: serum phosphorus, 2.2 mg/dL (0.71 mmol/L); alkaline phosphatase, 528 IU/L; PSA, 2.1 ng/mL; 1,25 dihydroxyvitamin D, 42 pg/mL (109 pmol/L; normal, 22 to 67 pg/mL [57 to 174 pmol/L]), and FGF-23, 2,160 RU/mL.

DISCUSSION

TIO is a disorder characterized by renal phosphate wasting, hypophosphatemia, inappropriately low serum 1, 25-dihydroxyvitamin D levels, normal 25-hydroxyvitamin D level, and normal or slightly increased serum PTH values.[1] A definitive diagnosis of TIO requires remission of the syndrome after tumor resection. In cases of metastatic disease in which resection of a