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Case Report

Imatinib and hypophosphatemia: Case report and review of literature

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ABSTRACT

Imatinib mesylate is a potent inhibitor of the BCR-Abl kinases, c-Kit, PDGFR, and fms. Imatinib used for treatment of chronic myeloid leukemia and gastrointestinal stromal tumor. Imatinib has been well tolerated. The most common adverse events reported included edema, nausea, diarrhea, myalgia or musculoskeletal pain, fatigue, dermatitis or rash, headache and abdominal pain. Hypophosphatemia is rare side effect of imatinib treatment. This is the report of a case experiencing severe hypophosphatemia during adjuvant treatment with imatinib for gastrointestinal stromal tumor.

1. Introduction

Imatinib mesylate is a 2-phenylaminopyrimidine derivative that binds to the adenosine triphosphate (ATP)–binding site of a select group of protein tyrosine kinases, thereby precluding ATP-binding and inhibiting kinase activity.[1] Imatinib mesylate is a potent inhibitor of the BCR-Abl kinases, c-Kit, PDGFR, and fms.[2,3] It is currently the "gold standard" treatment for Philadelphia chromosome– positive chronic myeloid leukemia (CML) in chronic phase and for gastrointestinal stromal tumors (GISTs).

Imatinib is generally well tolerated; most side effects are less than grade 2, and the majority of patients can continue treatment without interruption. In general, the side effect profile tends to improve with prolonged therapy.[4] The most common side effects reported in patients receiving imatinib are fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash. Altered phosphate metabolism was first reported in patients receiving imatinib therapy for GIST, CML, and sarcoma by Berman et al.[5] Hypophosphatemia is reported, especially with higher doses.[6]

The reported prevalence of hypophosphatemia varies widely, depending upon the patient population surveyed and the concentration of serum phosphorus used to define hypophosphatemia. Up to 5% of hospitalized patients may have low serum phosphate concentrations (less than 2.5 mg/dl [0.80 mmol/L]), although prevalences of over 30 to 50% have been reported in alcoholic patients and patients with severe sepsis or trauma.[7,8] Serum phosphate or phosphorus normally ranges from 2.5 to 4.5 mg/dl (0.81–1.45 mmol/l) in adults. Hypophosphatemia is defined as mild (2–2.5 mg/dl or 0.65–0.81 mmol/l), moderate (1–2 mg/dl or 0.32–0.65 mmol/l), or severe (<1 mg/dl or 0.32 mmol/l).[9] There are four major mechanisms by which hypophosphatemia can occur (Table 1). Medication, particularly molecular-targeted agents, might induce hypophosphatemia (Table 2). Hypophosphatemia is also associated with cancer and is called oncogenous osteomalacia.

We reported that hypophosphatemia developed in patient with newly diagnosed GIST who had adjuvant imatinib therapy.

2. Case report

A 36-year-old female presented with abdominal pain and diarrhea since 4 months. There was no pathological finding on physical examination. The routine hematological and biochemical examinations were within normal limits. A hypoechoic lesion (5 × 3.3 cm) was detected on the inferior head of pancreas, in abdominal ultrasonography (USG). This lesion was also detected (43 × 31 mm) in fourth part of duodenum on abdominal computerized tomography (CT). Biopsy was performed on the patient with endoultrasonography. Biopsy was reported as GIST. Dog-1,SMA,CD-117 was positive in the pathology report. Small intestine resection

Abbreviations: ATP, Adenosine triphosphate; CML, Chronic myeloid leukemia; PDGFR, Platelet derivated growth factor; GIST, Gastrointestinal stromal tumor; USG, Ultrasonography; CT, Computerized tomography; P, Phosphorus; PTH, Parathyroid hormone; 25-OH-VitD, 25 hydroxy vitamin-D3.

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Table 1
Major causes of hypophosphatemia.

Internal redistribution
Increased insulin secretion, particularly during refeeding
Acute respiratory alkalosis
Hungry bone syndrome
Decreased intestinal absorption
Inadequate intake
Inhibition of phosphate absorption (eg, antacids, phosphate binders, niacin)
Steatorrhea and chronic diarrhea
Vitamin D deficiency or resistance
Increased urinary excretion
Primary and secondary hyperparathyroidism
Vitamin D deficiency or resistance
Hereditary hypophosphatemic rickets
Oncogenic osteomalacia
Fanconi syndrome
Other - acetazolamide, tenofovir, IV iron, chemotherapeutic agents
Removal by renal replacement therapies

Table 2
Etiology of drug-induced hypophosphatemia.

1. Pseudohypophoshatemia
Mannitol
2. Shifts of extracellular phosphate into cells
Acute respiratory alkalosis (salicylate poisoning, mechanical ventilation)
Administration of glucose, fructose, insulin therapy, parenteral nutrition
Catecholamine action: epinephrine, dopamine, salbutamol, xanthine derivatives, hypothermia
Rapid cellular proliferation (erythropoetin, GM-CSF therapy)
3. Decreased intestinal phosphate absorption
Phosphate–binding antacids
4. Increased urinary phosphate excretion
Carbonic anhydrase inhibitors
Diuretics (hydrochlorthiazide, indapamide, furosemide)
Theophylline, bronchodilators, corticosteroids
Drug-induced FS
Volume expansion (drug-induced SIADH, administration of saline)
Bisphosphonates
Estrogens, mestranol
Acyclovir
Imatimib mesylate
5. Hypophosphatemia resulting from more than one mechanism
Drug-induced metabolic acidosis (alcohol, toluene)
Alcohol
Drugs that cause vitamin D deficiency or resistance: phenytoin, phenobarbital
Acetaminophen poisoning
Intravenous iron administration

was performed. Tumor was located in duodenum, diameter was 3.5 cm, mitosis was <5, surgical margin was positive for GIST in microscopic examination. Re-operation was not considered. Patient was considered at high risk for recurrence. Imatinib (400 mg/day) therapy was started. Nausea, fatigue, weakness (grade-2) and muscle cramps was seen 2 months after the start of treatment. Intoleration evolved into drug use. Hypophosphatemia was detected in biochemical test (P: 0.6 mg/dl (grade-4)). In previous tests before starting treatment with imatinib, normal phosphorus levels (3.2 mg/dl) was observed. There is no any etiologic factor that may cause hypophosphatemia for this patient. Imatinib therapy was continued. Phosphorus replacement therapy was performed. Despite the replacement therapy phosphorus level was 0.4 mg/dl (grade 4) measured (Table 3). Parathyroid hormone (PTH) level was detected 125 pg/ml and 25 hydroxy vitamin-D3 (25-OH-VitD) level was detected 24,7 ng/ml. And then calcitriol therapy was added the phosphorus replacement therapy. 1 months later PTH: 50 pg/ml, 25-OH-VitD:38 ng/ml, P: 2.4 mg/dl was measured. The patient's weakness, fatigue, nausea, muscle cramps resolved completely with replacement therapy. PTH: 27 pg/ml, 25-OH-VitD:53 ng/ml, P: 3.2 mg/dl was measured in the last biochemical tests. Calcium levels were always at normal levels. Now the patient continues to imatinib (400 mg/day) without any complaints (see Figs. 1–3).

3. Discussion

Imatinib has been well tolerated in clinical studies with adverse events typically mild to moderate in nature, usually managed without permanent discontinuation of therapy. In general, the side effect profile of imatinib tends to improve with prolonged therapy. In the first report of imatinib efficacy and safety in advanced GIST, treatment with imatinib was well tolerated, although virtually almost every patient (98%) had at least a grade 1 or 2 adverse event that might have been related to therapy. The most common adverse events reported included edema (most frequently periorbital), nausea, diarrhea, myalgia or musculoskeletal pain, fatigue, dermatitis or rash, headache and abdominal pain. Serious adverse events (grade 3 or 4) in that trial occurred in 21% of patients of which the most serious adverse events reported were gastrointestinal or intraabdominal hemorrhages.[10]

Doubling the dosage of imatinib from the standard level (400 mg daily) to a high dose (400 mg twice daily) increases the incidence of severe adverse events.[11] No correlation could be seen between imatinib plasma level and previous grade 3 to 4 toxicity in patients taken a standard dose of 400 mg daily.[12]

Hypophosphatemia was reported as a rare side effect of imatinib during initial trials. Berman et al. described bone-remodeling occurring in 16 patients treated with imatinib in 2006. In this study, hypophosphatemia and a series of associated changes in bone and mineral metabolism occurred in some patients receiving imatinib for either CML or gastrointestinal stromal tumors. They found PTH levels were high in the low-phosphate group. This finding strongly suggests that parathyroid function is in fact abnormal in this group. Imatinib inhibits tyrosine kinases associated with specific diseases, their data suggest that in vivo inhibition of the PDGF receptor may also occur and may have clinical consequences. They adviced routine monitoring of serum phosphate and vitamin D level during imatinib therapy.[5]

Oncogenic osteomalacia is an unusual syndrome that is characterized by multiple biochemical abnormalities, such as hypophosphatemia, hyperphosphaturia, and low levels of plasma 1,25-dihydroxyvitamin D. These abnormalities produce osteomalacia in adults and rickets in children, which clinically manifest as muscle weakness, bone pain, and multiple pathologic fractures. Tumors producing this syndrome secrete a substance that inhibits the renal tubular reabsorption of phosphates, which produces a cascade of biochemical abnormalities.[13] Tumors that cause

Table 3
Hypophosphatemia grades from Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypophosphatemia	<LLN-2.5 mg/dl <LLN-0.8 mmol/L	<2.5–2.0 mg/dl <0.8–0.6 mmol/L	<2.0–1.0 mg/dl <0.6–0.3 mmol/L	<1.0 mg/dl (<0.3 mmol/L) Life-threatening consequences	Death

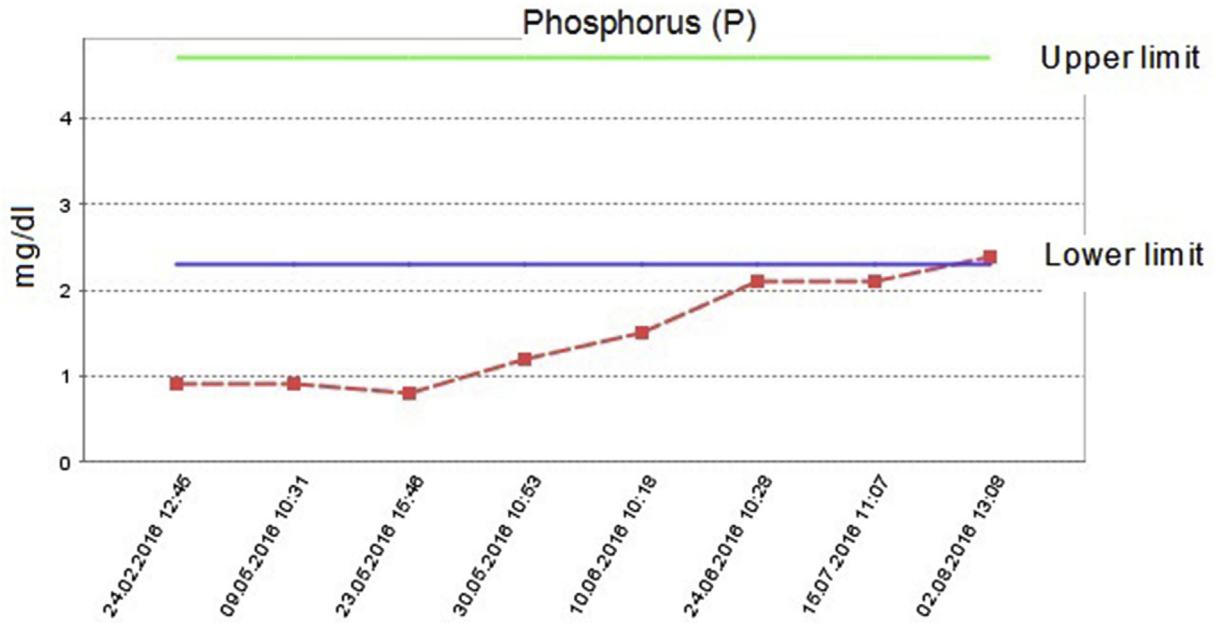

Fig. 1. Phosphorus levels are seen during imatinib treatment. Phosphorus levels reached normal levels with replacement therapy.

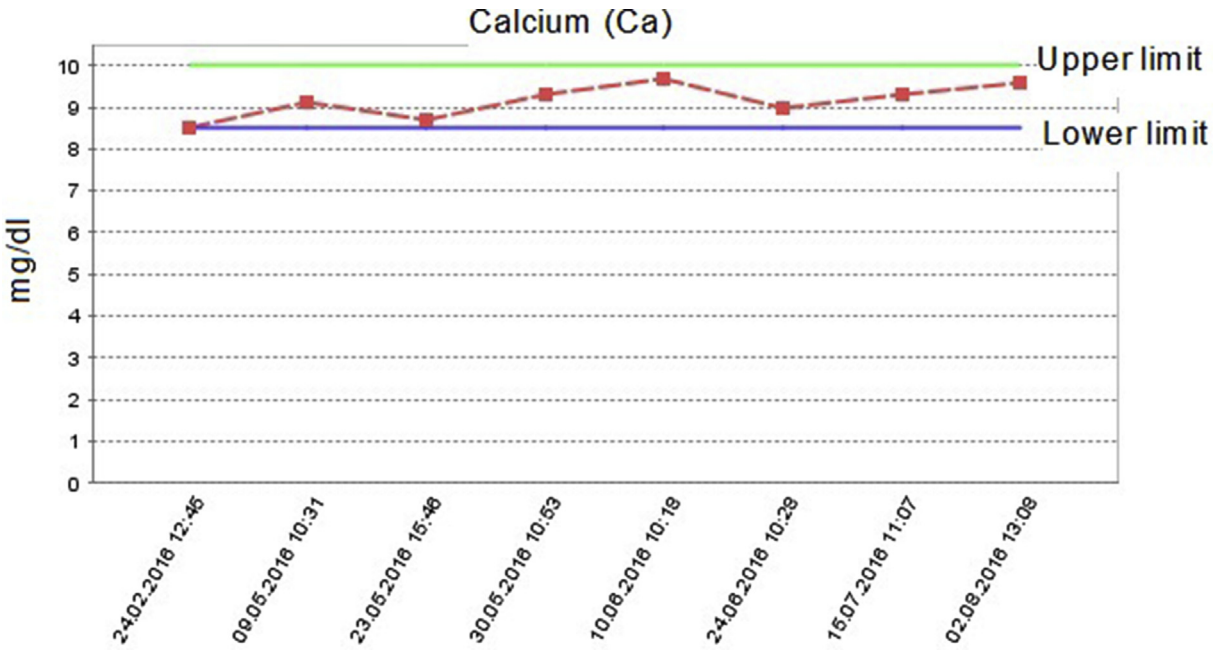

Fig. 2. Calcium levels are seen during imatinib treatment.

Oncogenic osteomacia are often small, slow-growing, vascular, and benign; they are associated with a variety of histologic types and are commonly mesenchymal in origin.[14] Unexplained generalized bone pain or multiple fractures must be tested for calcium and phosphate homeostasis for a complete diagnostic work-up.

The pathogenesis of the hypophosphatemia is not understood. Imatinib inhibits of osteoclasts, by blocking c-fms, c-kit, and PDGFR signaling, and inhibits activation of osteoblast activity through inhibition of PDGFR. Inhibition of bone remodeling may because decreased bone formation and bone resorption. The amount of calcium and phosphorus released from the bone to the extracellular space is decreasing. And then PTH increasing as a compensator. Renal phosphorus excretion is increasing.[5]

In our case, hypophosphatemia developed two months later after starting imatinib treatment. Nausea, fatigue, weakness and muscle cramps have been observed with imatinib therapy. These symptoms were resolved after the treatment of hypophosphatemia. These symptoms are common side effects of imatinib treatment. Hypophosphatemia may develop quickly after imatinib treatment. Berman et al. Reported two patients who have low serum phosphate levels within two weeks after starting imatinib therapy.[5] For his reason, we recommend that routine monitoring of serum

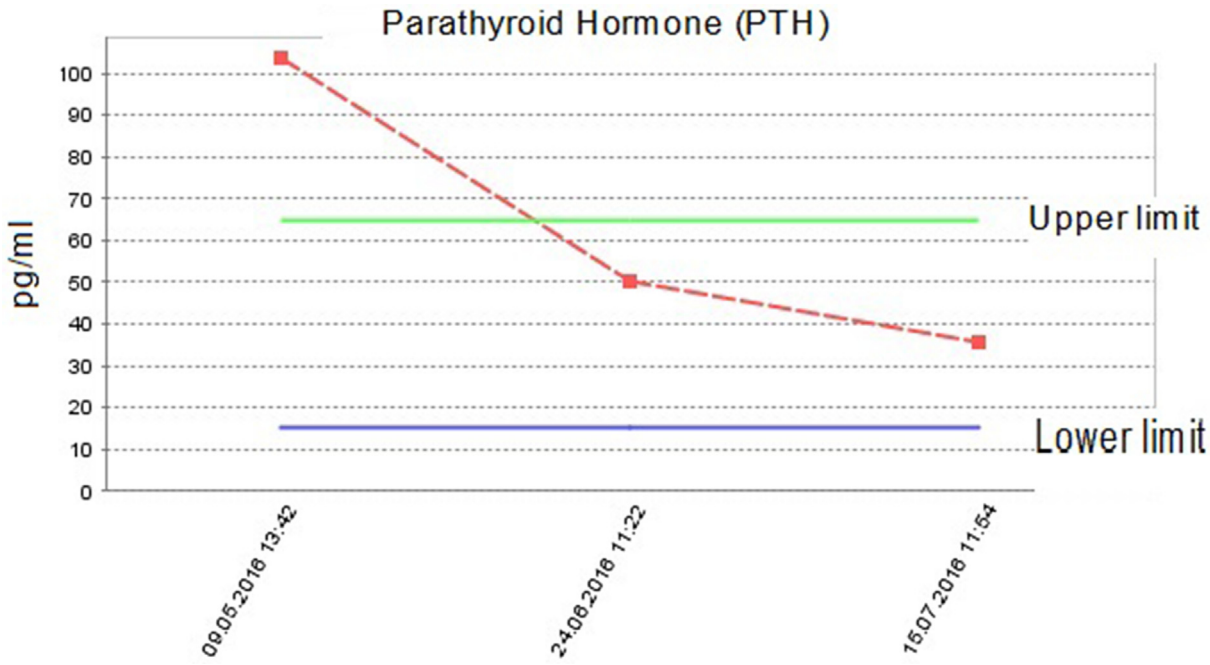

Fig. 3. Parathyroid Hormone levels are seen during imatinib treatment. Parathomone level decreased with calcitriol and phosphorus treatment.

phosphate, PTH and vitamin D level, during imatinib therapy.

Conflicts of interest

All authors have no conflict of interest.

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