A Case of Hypophosphatemia with Increased Urinary Excretion of Phosphorus Associated with Ibrutinib

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Key Words
Hypophosphatemia · Ibrutinib · Phosphate wasting · Tyrosine kinase inhibitors

Abstract
Ibrutinib, an irreversible oral inhibitor of Bruton’s tyrosine kinase, has been used in the treatment of patients with multiple hematologic malignancies. A 59-year-old male with chronic lymphocytic leukemia was treated with 420 mg/day of ibrutinib. No evidence of bruising or diarrhea was noted. The treatment was complicated by a transient increase in creatinine (from a baseline of 1.2 to 1.5 mg/dl) and potassium (reaching a peak of 6.5 mEq/l). Uric acid and calcium levels were normal. The patient developed hypophosphatemia (prior to initiation of therapy the serum phosphorus was 2.9 mg/dl). No metabolic acidosis was noted. Urinalysis showed no glucosuria or proteinuria. Urinary fraction of excretion of phosphate was found to be 345% (normal <5%). Because of these changes, ibrutinib was held, and the patient was given kayexalate. Serum potassium normalized. Serum phosphorus was checked a couple of weeks later and also normalized. A lower dose of ibrutinib (140 mg/day) was restarted. Upon follow-up, the phosphorus level has been between 2.9 and 3.2 mg/dl. No further evidence of hyperkalemia has been noted. Renal function has remained at baseline. To the best of our knowledge, this is the first case report describing the mechanism of hypophosphatemia in a patient treated with ibrutinib.
Introduction

Tyrosine kinase inhibitors (TKIs), a form of targeted therapy, redefined the oncologic treatment of multiple malignancies, ranging from chronic myelogenous leukemia to subtypes of non-small cell lung cancer [1]. The first one of this class was imatinib, which revolutionized the treatment of chronic myelogenous leukemia [2]. Hypophosphatemia, defined as a serum phosphorus level <2.5 mg/dl, is relatively common in hospitalized, critically ill patients, alcoholics and those with decreased intestinal absorption. Only with severe depletion clinical syndrome would develop [3]. Alterations in bone metabolism and hypophosphatemia have been described with TKIs, with most case reports implicating imatinib [4, 5].

Ibrutinib, an irreversible oral inhibitor of Bruton’s tyrosine kinase has been used in the treatment of patients with multiple hematologic malignancies including Mantle cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, Waldenström’s macroglobulinemia and chronic lymphocytic leukemia (CLL). In CLL, it is approved in patients who have received at least one prior therapy and as primary therapy for patients with CLL who have chromosome 17p13.1 deletion [6–8]. Ibrutinib is rapidly metabolized by the hepatic cytochrome P450 3A4 enzyme and to a lesser extent by cytochrome P450 2D6.

We present a case of hypophosphatemia temporally associated with the initiation of ibrutinib in a patient with CLL, with improvement after discontinuation of the drug. We describe the presence of significant urine phosphate wasting as the mechanism of hypophosphatemia.

To the best of our knowledge, this is the first case report describing the mechanism of hypophosphatemia in a patient treated with ibrutinib.

Case Presentation

A 59-year-old male was diagnosed with CLL in 2002 after presenting with left cervical lymphadenopathy. Excisional biopsy revealed small lymphocytic lymphoma that was CD20, CD19, CD5 and CD23 positive. Between 2002 and 2013, he received several treatments with either chlorambucil or rituximab due to symptomatic lymphadenopathy. In 2014, the patient was diagnosed with a Gleason 3 + 4 pathologic T2c N0 M0 S0 adenocarcinoma of the prostate requiring robotic prostatectomy. He was also noted to have calcium oxalate nephrolithiasis.

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Early in 2015, the patient presented with worsening thrombocytopenia. Laboratory testing showed a white blood cell count 18.8 K/μl (normal range 3.6–11), hemoglobin 14.4 g/dl (normal range 13–18), platelet count 71 K/μl (normal range 150–400) and an absolute lymphocyte count of 1.5 K/μl. A bone marrow biopsy showed at least 80% involvement with CLL with decreased myeloid and erythroid precursors; CD38, Zap70 negative with mutated IgHV rearrangement. On examination, the patient had increasing cervical lymphadenopathy. Imaging studies showed diffuse mild to moderate lymphadenopathy in the chest, abdomen and pelvis. After discussing therapeutic options including chemoimmunotherapy, ibrutinib was started at a standard dose of 420 mg/day. The patient had no symptoms of increased bruising or diarrhea. Within 6 weeks of starting treatment, his white blood cell count peaked at 132.4 K/μl, hemoglobin remained stable at 14.2 g/dl and platelet count increased to 122 K/μl.

The treatment was complicated by transient and reversible increases in creatinine (from a baseline of 1.2 to 1.5 mg/dl) and potassium (reaching a peak of 6.5 mEq/l). Concurrently checked uric acid and calcium levels were normal. Incidentally, the patient was noted
to have hypophosphatemia (prior to initiation of therapy, serum phosphorus was 2.9 mg/dl). No metabolic acidosis was noted. Urinalysis showed no glycosuria or proteinuria. Further workup is detailed in table 1. Because of persistent hyperkalemia and hypophosphatemia, ibrutinib was held, and the patient was given kayexalate. The serum potassium normalized. Serum phosphorus was checked a couple of weeks later and also normalized. A lower dose of ibrutinib (140 mg/day) was restarted. Upon follow-up, the phosphorus level was between 2.9 and 3.2 mg/dl. No further evidence of hyperkalemia was noted, and renal function has remained at baseline.

Discussion

Hypophosphatemia has been described with the use of TKIs, affecting 3% of the patients taking imatinib (although the numbers can be as high as 80% in some reports). Furthermore, this appears to be a reversible effect after discontinuation of therapy [9, 10]. Up to 50% of the patients treated with ibrutinib can experience side effects including diarrhea, bleeding, cytopenias, atrial fibrillation, fatigue, nausea, cough, edema and myalgias [11, 12]. Hypophosphatemia has been cited as a side effect with ibrutinib. Nonetheless, the exact mechanism has not been described, although one would expect a similar effect to that achieved with other TKIs, since this is believed to be a class effect.

The most likely cause of hypophosphatemia in patients treated with TKIs is urinary losses. It has been shown that these patients have high parathyroid hormone (PTH) levels and hypocalcemia (which would stimulate the release of PTH). Other possible mechanisms of renal losses include proximal tubular dysfunction (Fanconi syndrome), as several tyrosine kinases are expressed in the kidneys. Some reports have found elevated serum FGF23 concentrations in CLL and plasma cell dyscrasias, which theoretically could have phosphaturic effects [13, 14]. TKIs might also directly stimulate bone formation while restraining resorption, causing hypocalcemia, secondary hyperparathyroidism and hypophosphatemia [15]. Alternative mechanisms of hypophosphatemia in these patients include decreased absorption in the setting of vitamin D deficiency or nausea, vomiting and diarrhea. In the case presented herein, however, serum PTH, calcium and 25-hydroxy-vitamin D levels were within normal limits, suggesting that hyperparathyroidism or vitamin D deficiency were not the cause. The patient had no nausea, vomiting or diarrhea that could point towards gastrointestinal losses either. There was no evidence of metabolic acidosis or glycosuria, making the diagnosis of Fanconi syndrome less likely.

Ideally, a 24-hour urinary excretion of phosphorus should be obtained when there is doubt about the etiology of hypophosphatemia. The patient described here refused to undergo this test, and we had to settle with a random urinary fraction of excretion of phosphorus. The significantly high fraction of excretion of phosphorus suggests renal wasting as the mechanism of hypophosphatemia. Furthermore, the serum phosphorus levels improved to normal values a couple of weeks after discontinuation of ibrutinib, which is similar to what was described with other TKIs.

This case highlights that hypophosphatemia can be seen with ibrutinib, is due to renal wasting and is reversible with discontinuation of the drug for a couple of weeks. The phosphorus level remained normal when using a lower dose of ibrutinib, supporting the belief that hypophosphatemia is a dose-related effect of TKIs [4].

In this patient, neither levels of markers of bone formation (osteocalcin), resorption (urine N-telopeptide) nor FGF-23 were measured, so other contributing factors cannot be
ruled out. The significance of low phosphorus levels in patients taking ibrutinib is unknown. As this medication is administered for prolonged periods of time, it is possible that chronic hypophosphatemia may ultimately lead to phosphorus depletion, skeletal side effects and clinical syndrome. More data is needed to determine whether phosphorus levels should be routinely monitored in patients taking ibrutinib.

**Statement of Ethics**

Informed consent was obtained. IRB approval was not required for the described case. No human or animal experiment was performed.

**Disclosure Statement**

The authors declare that they have no conflicts of interest to disclose.

**References**

Table 1. Laboratory values

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>PTH, pg/ml</td>
<td>32 (15–65)</td>
</tr>
<tr>
<td>Serum calcium, mg/dl</td>
<td>9.3 (8.4–10.2)</td>
</tr>
<tr>
<td>Serum 25-hydroxy-vitamin D, ng/ml</td>
<td>33.1 (30–100)</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio, mg/g</td>
<td>120 (&lt;200)</td>
</tr>
<tr>
<td>Urine phosphorus, mg/dl</td>
<td>18</td>
</tr>
<tr>
<td>Urine creatinine, mg/dl</td>
<td>4.1</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.26 (0.7–1.2)</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>1.6 (2.3–4.7)</td>
</tr>
<tr>
<td>Serum uric acid, mg/dl</td>
<td>4.3 (3.5–7.2)</td>
</tr>
<tr>
<td>Fractional excretion of phosphate, %</td>
<td>345 (&lt;5)</td>
</tr>
</tbody>
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Normal values in parentheses. Fractional excretion of phosphate = \[\frac{UPO_4 \times PCr \times 100}{PPO_4 \times UCr}\].