CASE REPORTS

Partial Fanconi Syndrome Induced by Imatinib Therapy: A Novel Cause of Urinary Phosphate Loss

Helene François, MD, PhD,[1,2] Paul Coppo, MD, PhD,[3] Jean-Philippe Hayman, MD, PhD,[1,2] Bruno Fouqueray, MD, PhD,[1,2] Béatrice Mougenot, MD,[4] and Pierre Ronco, MD, PhD[1,2]

Imatinib mesylate (Gleevec, Glivec; Novartis, Basel, Switzerland) is a specific tyrosine kinase inhibitor that has become the gold-standard treatment for patients with chronic myeloid leukemia. Several tyrosine kinases inhibited by imatinib are expressed in the kidney, and although the drug is usually well tolerated, several cases of acute renal failure were reported. We describe for the first time a case of a patient treated by imatinib for chronic myeloid leukemia who developed partial Fanconi syndrome with mild renal failure, which leads to a discussion of the pathophysiological characteristics of imatinib-induced renal toxicity. Patients on long-term imatinib treatment should be monitored for renal failure, as well as proximal tubule dysfunction, including hypophosphatemia.
Am J Kidney Dis 51:298-301. © *2008 by the National Kidney Foundation, Inc.*

INDEX WORDS: Fanconi syndrome; imatinib; hypophosphatemia; hypouricemia; renal failure.

Imatinib mesylate (Gleevec, Glivec; Novartis, Basel, Switzerland) is an oral anticancer agent that selectively inhibits protein kinases involved in the pathophysiological process of various human cancers, including the Abelson proto-oncogene, c-Kit receptor tyrosine kinase (c-KIT), and platelet-derived growth factor receptor (PDGFR). Imatinib is now the first-line therapy for patients with chronic myeloid leukemia[1] and has proved remarkably efficient in the treatment of patients with gastrointestinal stromal tumors[2] and various myeloproliferative diseases with rearrangements of the PDGFR,[3] including idiopathic hypereosinophilic syndrome.[4] Imatinib mesylate therapy generally is well tolerated, and the most common side effects include gastrointestinal reactions (mainly nausea and diarrhea), edema, cutaneous rashes, myalgias, liver enzyme level increase, and myelosuppression,[5] most of which are dose related. Imatinib is metabolized through the cytochrome enzymes and does not require dose adjustment because plasma clearance of the drug decreases only moderately with renal dysfunction.[6] Isolated cases of acute renal failure secondary to acute tubular necrosis (ATN) were reported.[7,8] Here, we first describe a case of partial Fanconi syndrome induced by imatinib mesylate treatment in a patient with chronic myeloid leukemia and discuss the involvement of imatinib mesylate based on renal expression of several tyrosine kinases specifically inhibited by imatinib mesylate.[9,10]

From the [1]AP-HP, Assistance Publique-Hôpitaux de Paris, Department of Nephrology and Dialysis, Tenon Hospital; [2]Pierre et Marie Curie-Paris 6 University; [3]AP-H, Department of Haematology, Saint Antoine Hospital; and [4]AP-H, Department of Pathology, Tenon Hospital, Paris, France.

Received July 11, 2007. Accepted in revised form October 5, 2007. Originally published online as doi: 10.1053/j.ajkd.2007.10.039 on January 2, 2008.

Address correspondence to Helene François, MD, PhD, Nephrology and Dialysis, Tenon Hospital, 4, rue de la Chine, 75020 Paris, France. E-mail: helene.francois@tnn.aphp.fr

© 2008 by the National Kidney Foundation, Inc.

0272-6386/08/5102-0015$34.00/0
doi:10.1053/j.ajkd.2007.10.039

CASE REPORT

A 50-year-old woman was referred to the Nephrology Department in December 2004 for isolated microscopic hematuria. Blood pressure was 120/80 mm Hg, and physical examination findings were normal. Hemogram showed increased platelet and absolute neutrophil counts ($580 \times 10^3/\mu L$ [580×10^9/L] and $12 \times 10^3/\mu L$ [12×10^9/L], respectively). Serum creatinine level was 0.71 mg/dL (63 μmol/L), with an estimated glomerular filtration rate by means of the Modification of Diet in Renal Disease Study equation of 109 mL/min/1.73 m^2 (1.82 mL/s/1.73 m^2). Urinalysis showed 20 red blood cells/μL, with no casts. Urinary protein-creatinine ratio was 85 mg/mmol, and urinary proteins were composed of 78% albumin. No electrolyte abnormalities were found (Table 1). Renal ultrasound and abdominal computed tomographic scan ruled out the major urological causes of hematuria.

A few weeks later, the patient's white blood cell count reached $20 \times 10^3/\mu L$ (20×10^9/L), with 6% myelemia, which led to the diagnosis of Philadelphia-positive chronic myeloid leukemia with a high level of the bcr-abl transcript. Imatinib mesylate therapy was initiated at 400 mg/d in March 2005. The patient immediately reported myalgias,

Table 1. Outcome of Renal and Proximal Tubule Functions

	January 2005	June 2005	May 2006	Normal Values
Serum creatinine (mg/dL)	0.71	0.96	0.98	0.56-1.02
Estimated glomerular filtration rate (mL/min/1.73 m^2)	109	**77**	**76**	90-120
Serum phosphate (mg/dL)	3.4	2.8	**2.35**	2.5-4
TmPo4/glomerular filtration rate (mg/dL)	—	—	**2.2**	2.5-3.2
Uric acid (mg/dL)	4.65	**3**	**2.35**	4-5.9
Fractional excretion of uric acid (%)	12	—	**25**	6-20
Serum magnesium (mg/dL)	1.82	**1.43**	**1.65**	1.8-2.7
24-h urinary glucose (mg/24 h)	0	0	**90**	0
Urinary β_2-microglobulin (mg/mmol creatinine)	—	0	—	0
24-h urinary amino acids (μmol/mmol creatinine)	—	—	427	252-950
Urinary retinol-binding protein (mg/mmol creatinine)	—	**0.09**	0.08	<0.08
Urinary protein-creatinine ratio (mg/mmol)	**85**	28	15	<30
Urinary albumin-creatinine ratio (mg/mmol)	**46**	**8**	1.8	0-3

Note: Beginning of imatinib treatment in March 2005. Bold type indicates values outside the normal range. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; estimated glomerular filtration rate in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; phosphate in mg/dL to mmol/L, multiply by 0.3229; uric acid in mg/dL to mmol/L, multiply by 59.48; serum magnesium in mg/dL to mmol/L, multiply by 0.4114.

Abbreviations: TmPo4, maximum transport of phosphate.

which were efficiently treated by using dextropropoxyphene and paracetamol (maximum dosage, 2 g/d). Hematologic remission followed by complete cytological and molecular remissions were obtained after 3, 6, and 15 months of imatinib treatment, respectively. However, in June 2005, the patient developed mild renal failure (serum creatinine, 0.96 mg/dL [85 μmol/L]; estimated glomerular filtration rate, 77 mL/min/1.73 m^2 [1.28 mL/s/1.73 m^2]) with no notable changes in urinalysis (Table 1) and normal blood pressure (101/57 mm Hg). The only abnormal biological parameter was low serum uric acid level (3 mg/dL [180 μmol/L]; Table 1). Between June 2005 and May 2006, while the patient remained on treatment with imatinib, 400 mg/d, we found biological evidence of progressive proximal tubular dysfunction (Table 1), including low serum uric acid levels with increased fractional excretion of uric acid (25%; normal range, 6% to 20%), fasting hypophosphatemia with decreased maximal transport of phosphate, and slight normoglycemic glycosuria. Low $TmPO_4$ was not caused by increased parathyroid hormone concentration (55 pg/mL [ng/L]; range, 10 to 65 pg/mL [ng/L]). Bone investigations showed results within the normal range: serum osteocalcin, 6.8 ng/mL; normal, <17.7 ng/mL; serum bone alkaline phosphatase, 11 ng/mL; normal, <22 ng/mL; serum cross-laps, 0.441 ng/mL; normal, <1.016 ng/mL; and 25 and 1-25 hydroxyvitamin D, 15.5 ng/mL (37 nmol/L); normal, 7 to 30 ng/mL (17 to 75 nmol/L) and 27 pg/mL (70 pmol/L); normal, 17 to 67 ng/mL (44 to 175 pmol/L), respectively. The patient also developed hypomagnesemia (magnesium, 1.43 mg/dL [0.59 mmol/L]) of renal origin, with increased urinary magnesium excretion of 5.5 mg/dL (2.25 mmol/L) and fractional excretion of 4.5% (normal, <4%). Serum bicarbonate level was normal, and urinary excretion of amino acids was in the normal range.

Because of decreased renal function and recent occurrence of partial Fanconi syndrome, we decided to perform a kidney biopsy. A small sample containing 4 glomeruli was unremarkable by means of light microscopy. Under electron microscopic examination, proximal tubules showed single-membrane–limited vacuoles at the apical part of some cells (marked with * in Fig 1) without obvious abnormalities in mitochondrial or lysosomal compartments (Fig 1). The only available glomerulus was obsolescent. The progressive appearance and worsening of proximal tubular dysfunction during treatment was highly suggestive of imatinib mesylate toxicity. Because Fanconi syndrome was only partial, with no histological abnormalities, and the underlying hematologic disorder was severe, we decided to maintain treatment with imatinib, 400 mg/d, with phosphate and vitamin D supplementation. Renal function and proximal tubular dysfunction have remained stable after 1 year of follow-up (serum creatinine, 0.97 mg/dL [86 μmol/L]; estimated glomerular filtration rate, 76 mL/min/1.73 m^2 [1.27 mL/s/1.73 m^2]).

DISCUSSION

We report for the first time partial Fanconi syndrome induced by imatinib mesylate treatment and revealed by hypouricemia and hypophosphatemia, both caused by renal wasting. The occurrence of imatinib mesylate–induced hypophosphatemia was recently documented as the possible consequence of abnormal bone turnover caused by PDGFR inhibition leading to secondary hyperparathyroidism.[11] However, in our case, hypophosphatemia was only caused by proximal dysfunction–induced renal wasting because parathyroid hormone level was normal. Berman et al[11] also reported increased phosphate excretion in a subgroup of patients with normal

Download English Version:

https://daneshyari.com/en/article/3851197

Download Persian Version:

https://daneshyari.com/article/3851197

Daneshyari.com