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Case Report

Nephrotic Proteinuria Developed under Dasatinib Treatment in a Patient with Chronic Myeloid Leukemia: A Case Report and Review of the Literature

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Abstract

Dasatinib is a second generation tyrosine kinase inhibitor indicated for the treatment of patients with newly diagnosed chronic phase-chronic myeloid leukemia (CP-CML). The most common non-hematologic side effect, resulting from different clinical trials, is the pleural effusion followed by gastrointestinal disorders, while renal toxicities were seldom reported. We report a case of nephrotic-range proteinuria with hypercholesterolemia probably associated with dasatinib therapy in a young woman suffering from CML. After ruling out all possible causes of nephrotic syndrome, a switch to imatinib was performed according to other similar case reports. After 3 weeks from dasatinib interruption, the patient obtained a complete resolution of all renal parameters: she is still continuing imatinib treatment and is in major molecular response. Despite its rare occurrence, a drug-related toxicity should be considered when an otherwise unexplained renal impairment is observed during dasatinib treatment.

Keywords: Dasatinib; Nephrotic syndrome; Chronic myeloid leukemia

Introduction

Chronic myeloid leukemia (CML) is a malignant disorder of the hematopoietic stem cell characterized by the reciprocal t(9;22) translocation resulting in the fusion gene BCR-ABL, a constitutively active tyrosine kinase (TK) responsible for the development of the disease [1-3].

The central role of BCR-ABL in the pathogenesis of CML has provided the rationale for development of TK inhibitors (TKIs) that specifically abrogate tyrosine kinase activity. Imatinib mesylate (IM) was the first-generation TKI acting through a competitive block of ATP-binding site in the BCR-ABL protein [4]. Since its introduction, IM has proven to be an effective and durable therapy for CML: however, more than 30% of patients need to discontinue IM, mainly due to primary or secondary resistance [5-6].

The discovery and subsequent approval of the second-generation TKIs dasatinib and nilotinib allowed to rescue about 50% of patients resistant to IM. These drugs, initially used in second-line after IM resistance or intolerance, subsequently showed to induce faster and deeper responses compared to IM in newly diagnosed CP-CML patients [7,8] and were approved also for the first-line therapy.

Although very effective, these drugs presented several relatively common side effects including pleural effusion, bleeding, and pulmonary hypertension (dasatinib) or increase in bilirubin, lipase, and glucose levels and cardiovascular/peripheral arterial events (nilotinib) [9,10].

In addition, real-life experience with these drugs led to the evidence of some very uncommon adverse events, such as renal toxicity occurring under dasatinib therapy, which were described only in single case reports [11,12]. Herein, we refer on a case of severe proteinuria related to dasatinib and briefly discuss the few evidences available in the literature concerning this issue.

Case Presentation

A 45-year old woman in April 2014 performed routine blood tests which revealed leukocytosis (WBC 124x10^6/L) and mild thrombocytosis (PLTS 587x10^6/L): concomitantly an abdominal ultrasound documented spleen enlargement (longitudinal diameter 16 cm) and the patient was referred to our hematology department for further investigations.

Peripheral blood smear evidenced a picture of chronic myeloproliferative disease, while bone marrow aspirate showed granulocytic hyperplasia with normal maturation pattern in the absence of blast. Cytogenetic analysis revealed the Philadelphia chromosome in all examined metaphases and molecular analysis was positive for BCR-ABL hybrid gene. Thus, a diagnosis of chronic phase - CML was done.

The patient had no comorbidities and her physical examination was unremarkable except for spleen enlargement (6 cm below costal margin); renal (creatinine 0.8 mg/dl) and hepatic tests were in the normal range. According to the Sokal risk score, the patient was classified as intermediate risk.

After an initial cytoreductive phase with hydroxyurea, dasatinib was started at the standard dose of 100 mg daily. Complete hematologic response (CHR) was achieved after 2 weeks of treatment and at the 3-month evaluation a complete cytogenetic response (CCyR) and a BCR-ABL ratio of 2.67 were detected.

At the 6-month follow up visit, CCyR was confirmed while the BCR-ABL ratio was 0.67. The patient, who was in very good physical conditions without any symptom, performed a routine

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Table 1: Clinical features of case reports with nephrotic syndrome during dasatinib treatment.

Author	Gender	Age (yrs)	Months of dasatinib	Urinary proteins (mg/24h) or UPCR	Creatinine (mg/dl)	BCR-ABL ratio at dasatinib discontinuation	2nd line TKI or treatment	Months to resolution	BCR-ABL ratio at last follow-up
[15]	F	63	3	3853 mg/24h	0.79	Not reported	imatinib	0.5	negative
[16]	F	3	17	UPCR=17 mg/mg	0.3	Not reported	BMT	2	negative
De Luca, *et al.*	F	45	6	3995 mg/24h	0.9	2.67	imatinib	0.5	0.036

TKI: Tyrosine Kinase Inhibitors; UPCR: Urine Protein to Creatinine Ratio; F: Female; M: Male; Yrs: Years; BMT: Bone Marrow Transplantation

general screening with urinanalysis, which showed an unexpected severe proteinuria (300 mg/dl; normal range 0-20 mg/dl) with hypoalbuminemia (3.25 g/dl) in the presence of normal creatinine levels. The patient was apiretic, cardiopulmonary examination was normal, no lower extremities edema was present. Therefore the patient was referred to a nephrologist in order to evaluate the clinical significance of her proteinuria.

Renal laboratory tests confirmed a normal serum creatinine level (0.90 mg/dl), a normal estimated glomerular filtration rate (141.3 ml/min), a severe 24-hour urine protein loss (3995.8 mg/day) with a severe dislypidemia (total cholesterol level 272 mg/dl, triglyceride level 296 mg/dl). Based on these results, a nephrotic syndrome was diagnosed: to exclude all known possible causes, the complete pattern of anti-nuclear antibodies, Ig serum dosage, levels of Complement factors C3, C4 and C1q, serology for Hepatitis B, Hepatitis C, VDRL, HIV 1 e 2 were tested and resulted all normal. Furthermore, the patient had no other comorbidities and did not assume other drugs with the exception of estro-progestinic pill since 8 years.

Before the execution of a kidney biopsy to exclude a primary glomerulonephritis and in the suspicion that Dasatinib could be the cause of the proteinuria, a switch to imatinib was performed also considering that occasional similar cases had been reported in the literature.

After 3 weeks since switch to imatinib, serum total proteins (6.9 g/dl) and albumin levels (4 g/dl) became normal. At the 1-month follow-up, urinanalysis did not reveal proteinuria with urinary protein level of 41.2 mg/dl and 24-hour urine protein level of 411 mg/24h.

At the 3-month follow-up, serum creatinine (0.9 mg/dl), total cholesterol (202 mg/dl), HDL cholesterol (53 mg/dl), triglycerides (144 mg/dl), urinary proteins (42.7 mg/dl) and 24-hour urine proteins (448.35 mg/24h) were in the normal range and are still normal after 13 months from switch to imatinib; the last molecular evaluation (18 months from dasatinib start and 11 months from switch to imatinib, respectively) showed a stable MR3 with BCR-ABL ratio of 0.036.

Discussion

Nephrotic syndrome is a kidney disorder characterized by proteinuria, hypoalbuminemia, peripheral edema and hypercolesterolemia due to damage in the podocytes, with consequent alteration of the glomerular filtration barrier. It may either be a primary glomerular disease or be secondary to a systemic disease. All signs and symptoms result from the increased permeability of the glomerulus, with abnormal loss of proteins from blood into the urine.

Renal failure and nephrotic syndrome have occasionally been reported as side effects during treatment with dasatinib, whose metabolism is almost entirely hepatic [13].

As concerns specifically dasatinib-related proteinuria, its occurrence was reported in 18% of patients treated with dasatinib in a phase I dose-escalation and pharmacokinetic study performed in advanced solid tumors [14].

To the best of our knowledge this is the 3rd case of dasatinib-induced nephrotic syndrome to be described in CML patients, which resolved after switching to another TKI. Wallace, *et al.* [15] reported on a case of nephrotic-range proteinuria related to Dasatinib which resolved after switching to imatinib: the kidney biopsy documented a pattern of thrombotic microangiopaty.

Very recently, Rubner, *et al.* described four cases of pediatric patients with various malignancies who developed nephrotic syndrome during treatment with different TKIs (imatinib, dasatinib, sunitinib and quizartinib). Among them, the case of a 3-year old child suffering from CML who developed proteinuria during treatment with dasatinib was reported: also in this patient the proteinuria resolved within 2 months following dasatinib discontinuation [16]. The main clinical features of these two cases together with those of our patient are reported in the Table 1.

In all instancies, the exact mechanism of kidney injury possibly induced by dasatinib is not completely understood. A hypothetical mechanism could be the inhibition of the Vessel Endothelial Growth Factor (VEGF) expression. VEGF is expressed in the podocytes and is also responsible for podocyte citoskeletal organization [17]. The crucial role of VEGF in the development and maintenance of glomerular endothelium and normal glomerular function was clearly illustrated in a mouse model in which VEGF was deleted from podocytes: after VEGF deletion, all mices developed proteinuria and hypertension with renal biopsy showing features compatible with thrombotic microangiopaty [18]. The physiological regulation of VEGF pathway is controlled by the SRC family kinases [19] which are inhibited, together with many other TK such as c-KIT, PDGFR and EPHA2, by dasatinib [20]. Therefore, by blocking SRC kinases, dasatinib could cause an interruption of the VEGF pathway thus inducing proteinuria [17- 21].

A limitation of present case-report is that a renal biopsy was not performed, so we were not able to confirm the presence of a glomerular damage: however, the temporal relationship between the onset of proteinuria and the start of dasatinib treatment and its resolution after switching to imatinib strongly suggests a relationship between the drug uptake and the renal impairment.

In conclusion, the occurrence of an unexpected proteinuria with a clinical picture of a nephrotic syndrome during dasatinib treatment

although rare, can be observed: it requires drug discontinuation and can be rapidly reversible as observed in the few cases so far reported, without recurrence under second line TKI therapy.

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