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Nilotinib으로 전환 후 호전된 Dasatinib 유발성 단백뇨: 증례 보고

울산대학교 의과대학 서울아산병원 신장내과

전주희 · 이동연 · 안재성 · 백충희 · 김효상

Improvement in Dasatinib-Induced Proteinuria after Switching to Nilotinib: A Case Report

Joohee Jeon, Dongyeon Lee, Jae Sung Ahn, Chung Hee Baek, and Hyosang Kim

Department of Nephrology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, and nilotinib, have been used to treat chronic myelogenous leukemia (CML). The adverse effects of these TKIs vary according to the site of signaling pathway inhibition. Here, we report a case of dasatinib-induced proteinuria. A 56-year-old Korean woman was diagnosed with CML and treated with dasatinib. However, 3 years later, the patient developed hypertension and microalbuminuria. Losartan was ineffective, so a kidney biopsy was performed, which revealed dasatinib-associated glomerular changes. Subsequently, dasatinib was switched to nilotinib. After 1 month, the spot urine protein/creatinine ratio decreased from 2,985.0 mg/g to 237.8 mg/g. This case of heavy proteinuria developed after long-term TKI treatment and improved rapidly after switching to another TKI. The proposed strategy is important because it eliminates the need to discontinue the medication or use immunosuppressive drugs to treat proteinuria. (Korean J Med 2023;98:144-150)

Keywords: Proteinuria; Tyrosine protein kinase inhibitors; Dasatinib; Nilotinib; Leukemia, myelogenous, chronic, BCR-ABL positive

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by the uncontrolled proliferation of mature and maturing granulocytes. This condition develops due to the production of an activated tyrosine kinase (TK) from the fusion of BCR and ABL. The introduction of tyrosine kinase inhibitors (TKIs) into the initial treatment strategy has improved the prognosis of patients with CML. Imatinib, a first-generation TKI, is the first-line agent for the treatment of CML, whereas second-generation TKIs, such as dasatinib and nilotinib, are used in cases with side effects or a poor response to imatinib [1]. The adverse effects of these TKIs vary depending on the site of signaling pathway inhibition. Here, we report a case of dasati-

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Correspondence to Hyosang Kim, M.D., Ph.D.
Department of Nephrology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-1439, Fax: +82-2-2045-4047, E-mail: mateus@amc.seoul.kr

nib-induced proteinuria.

CASE REPORT

A 56-year-old Korean woman with no history of kidney disease was referred to the hematology outpatient clinic due to detection of thrombocytosis during a routine medical checkup. Initial blood examination indicated a white blood cell count of 13.2 × 103/μL, hemoglobin level of 11.0 g/dL, and platelet count of 741 × 103/μL. Based on the results of bone marrow biopsy, the patient was diagnosed with granulocytic-megakaryocytic CML in the chronic phase. Major BCR/ABL rearrangements were also detected. Therefore, dasatinib therapy (100 mg/day) was initiated, and the patient exhibited complete hematological remission within 6 months. However, after 3 years, she presented to a cardiology outpatient clinic with high blood pressure (155/84 mmHg). Microalbuminuria was detected during the medical workup, and she was referred to the nephrology clinic for further evaluation.

During her first visit to the nephrology clinic, she exhibited albumin (1+) levels on routine urinalysis, spot urine albumin/creatinine ratio of 639.4 mg/g, and spot urine protein/creatinine ratio of 823.9 mg/g. Laboratory tests showed a serum creatinine level of 0.88 mg/dL (estimated glomerular filtration rate, 67 mL/min/1.73 m^2 [4-variable modification of diet in renal disease study equation]), blood urea nitrogen level of 18 mg/dL, total cholesterol level of 255 mg/dL, and low-density lipoprotein cholesterol level of 183 mg/dL. Anti-nuclear antibody was positive with a titer of 1:640 and a homogenous pattern. Tests for complement 3 (C3), C4, anti-neutrophil cytoplasmic antibody, anti-double stranded DNA antibody, urine protein electrophoresis, and urine immunoelectrophoresis yielded negative results.

Therefore, losartan (25 mg/day) was initiated to treat hypertension and proteinuria. As the proteinuria worsened despite good medication compliance, the losartan dose was gradually increased to 100 mg/day. After titration with losartan, systolic blood pressure was maintained at < 130 mmHg. Nevertheless, a nephrotic range of proteinuria persisted, and kidney biopsy was performed (Fig. 1).

Light microscopy revealed mildly enlarged glomeruli and leukocyte infiltration. Some glomeruli were globally sclerotic (6/22), and none showed crescent formation. The mesangium was enlarged because of an increase in the matrix with trivial hypercellularity. The glomerular capillary walls were mildly thickened with segmental corrugation and double contouring. The tubules showed mild degenerative changes in epithelial cells, focal dilatation with protei-

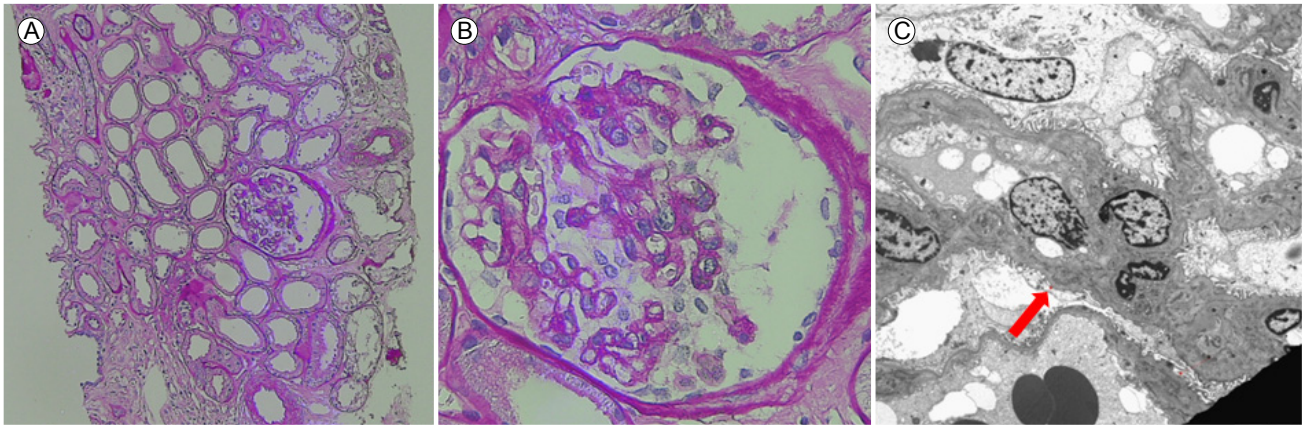

Figure 1. Kidney biopsy results. (A) Low power view of the kidney biopsy specimen with focal global glomerulosclerosis (6/22), no crescent formation, and mild chronic tubulointerstitial changes (periodic acid-Schiff stain; original magnification, ×40). (B) High-power view with diffuse segmental corrugation and double contouring of the glomerular capillary walls (periodic acid-Schiff stain; original magnification, ×400). (C) Electron micrograph. There are some mesangial electron dense deposits and segmental corrugation of the basement membrane. In addition, widening of the lamina rara interna and mesangial interposition are noted (red arrow), along with focal foot process effacement (transmission electron microscope; original magnification, ×3,000).

naceous casts, and mild atrophy. Immunofluorescence microscopy was performed for immunoglobulin (Ig) G, IgM, IgA, C3, C4, C1q, and fibrinogen. Diffuse mesangial staining of the glomeruli was observed for IgM/IgA/C3 (all 2+) and C1q (±) and focal vessel staining was noted for IgM (1+) and IgA/C3/C4 (all 2+). Electron microscopy revealed three glomeruli with mesangial electron-dense deposits and segmental corrugation of the basement membrane. Moreover, widening of the lamina rara interna and mesangial interposition was observed with focal foot process effacement.

The overall morphological findings suggested the possibility of IgA nephropathy and dasatinib-associated glomerular changes. However, the patient's clinical course was more compatible with dasatinib-associated glomerular changes. Therefore, the patient was switched from dasatinib treatment to nilotinib therapy (300 mg twice daily), which has similar efficacy and safety for CML. Losartan administration was continued. After 1 month, the proteinuria had decreased (spot urine protein/creatinine ratio of 2,985.0/237.8 mg/g), but the serum creatinine level remained constant (Fig. 2). Subsequently, complete remission of proteinuria was maintained and there has been no recurrence of CML.

DISCUSSION

Vascular endothelial growth factor (VEGF), epidermal growth factor, and platelet-derived growth factor (PDGF) are key factors in the growth and dissemination of tumors [2]. These factors bind to TK receptors, leading to cell migration and proliferation. Overexpression of these factors is associated with tumor angiogenesis, growth, and metastasis [3]. TKIs play a prominent role the treatment of Philadelphia chromosome-positive lymphoblastic leukemia. The Philadelphia chromosome is a result of reciprocal translocation of the ABL gene on chromosome 9 and the BCR gene on chromosome 22. The BCR-ABL combination produces constitutively active TK, which results in rapid cell expansion and is the major cause of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia. Imatinib mesylate is a first-generation TKI [3]. TKIs primarily inhibit angiogenesis and have been used effectively in the treatment of various types of malignancies, particularly CML. However, TKIs are also associated with side effects, such as bone marrow suppression, diarrhea, nausea, vomiting, rash, and proteinuria.

The pathogenesis of glomerular changes caused by TKIs that lead to proteinuria remains unclear. However, one possible cause

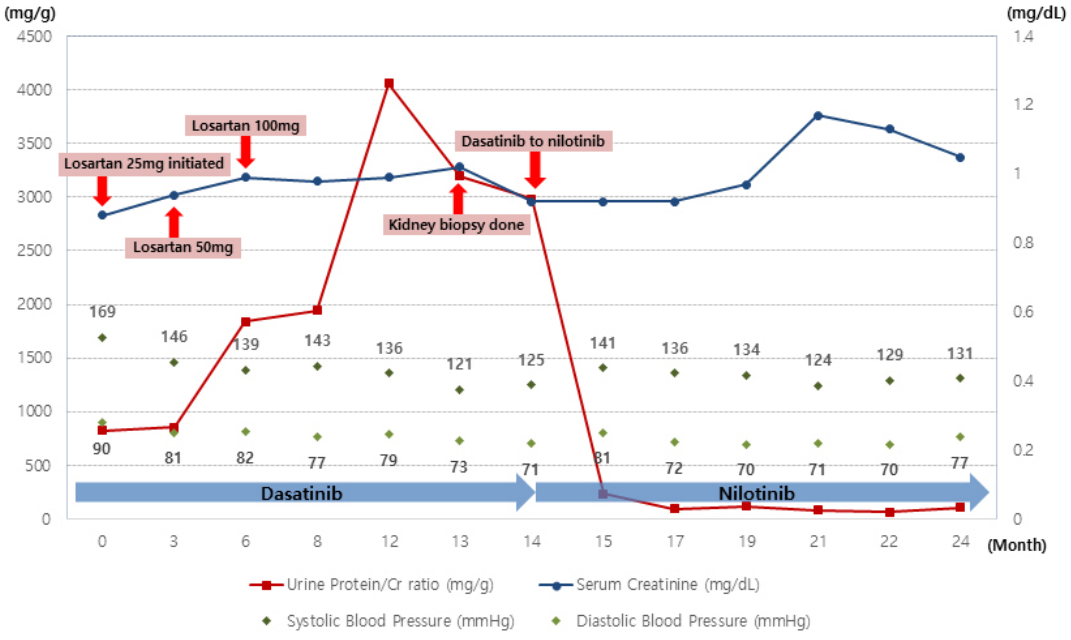

Figure 2. Urine protein/creatinine ratio change. Cr, creatinine.

Table 1. Summary of reported cases of TKI-induced proteinuria showing improvement after switching to another TKI

Case	Age, years	Sex	Cancer	Drug dose	Onset	RAS blocker	Serum Cr, mg/dL	Urine protein	Presentation	Light microscopy	Immunofluorescence	Electron microscopy	Changed TKI	Remission
Maruyama et al. [6]	57	F	Lung Ca	Gefitinib 250 mg/day	6months	?	0.61	8.3 g/day	Edema of the lower extremities	Globally sclerosed (2/34) Slight increase in the mesangial matrix (32/34) Partially mild tubular atrophy and fibrosis	Did not reveal any glomerular deposits of complement or immunoglobulins	Minor glomerular abnormalities with partial foot process effacement	Erlotinib	Yes
Wallace et al. [4]	63	F	CML	Dasatinib 100 mg/day	3months	Lisinopril	0.79	3.8 g/day	Asymptomatic	Mildly increased mesangial matrix. No mesangial or endocapillary hypercellularity The capillary basement membrane exhibited segmental corrugation Up to 5% of interstitial fibrosis	Trace mesangial C1q Cast staining for IgG, IgA, IgM, κ, λ (all 1+)	The focal corrugation of the glomerular basement membranes and a near-global increase in the lamina rara interna Significant thinning of the glomerular basement membrane. Foot processes were only focally effaced	Imatinib	Yes
Holstein et al. [7]	58	F	CML	Dasatinib 140 mg/day	4 days	?	4.41	Urine protein 2+ (urinalysis)	Acute renal failure	X (not performed due to marked pancytopenia)	X (not performed due to marked pancytopenia)	X (not performed due to marked pancytopenia)	Nilotinib	Off dialysis
Our case	56	F	CML	Dasatinib 100 mg/day	3 years	Losartan	0.92	2,985 mg/g (spot urine Prot/Cr)	Asymptomatic	Mildly enlarged glomeruli and leukocytic infiltration. Some glomeruli were globally sclerotic (6/22) Glomerular capillary walls were mildly thickened, with segmental corrugation and double contouring	Diffuse mesangial staining of the glomeruli for IgM, IgA, C3 (all 2+), and C1q (±). Focal vessel staining for IgM (1+), and IgA, C3, and C4 (all 2+).	Three glomeruli with some mesangial electron-dense deposits The segmental corrugation of the basement membrane Widening of the lamina rara interna and mesangial interposition Focal foot process effacement	Nilotinib	Yes

TKI, tyrosine kinase inhibitor; RAS, renin-angiotensin system; Cr, creatinine; F, female; Ca, cancer; CML, chronic myeloid leukemia; C, complement; Ig, immunoglobulin; Prot/Cr, protein-creatinine ratio.

is the inhibition of VEGF by TKIs, which activates VEGF receptor 2 in glomerular capillary endothelial cells [3,4]. Inhibition of VEGF in podocytes results in the loss of endothelial fenestrations in glomerular capillaries, glomerular endothelial cells, and podocytes, leading to the development of proteinuria [5]. *In vivo* experiments showed that VEGF-deficient mice developed hypertension and significant proteinuria, along with features of thrombotic microangiopathy (TMA) on electron microscopy [3]. In human studies, dasatinib was shown to inhibit VEGF-induced phosphorylation of focal adhesion kinase 1 and to induce clinical syndromes with proteinuria, hypertension, and a reduced glomerular filtration rate [4]. Another potential mechanism of renal injury caused by TKIs is the decrease in nitric oxide (NO) production by endothelial cells, which may lead to hypertension and increased proteinuria [3]. The frequent simultaneous occurrence of proteinuria and hypertension as side effects of TKIs suggests that hemodynamic changes, such as elevated pressure in the glomeruli, may be associated with TKI-induced proteinuria. This phenomenon was similar to that observed in exercise-induced proteinuria. Furthermore, the incidence of proteinuria appears to be closely related to the dose of TKIs and development of hypertension [5].

Proteinuria, defined as urinary protein excretion > 300 mg/day, is a common adverse event in patients receiving angiogenesis inhibitors (Table 1). Maruyama et al. [6] reported a 57-year-old woman with advanced lung adenocarcinoma who was treated with the TKI gefitinib and developed nephritic syndrome. In that case, renal biopsy revealed minor glomerular abnormalities, and the patient's symptoms improved after discontinuation of gefitinib; after switching to another TKI, erlotinib, the patient achieved remission of proteinuria. Wallace et al. [4] reported a 63-year-old African American woman without any history of kidney disease who was diagnosed with CML and treated with dasatinib. The patient developed proteinuria after 3 months, and subsequent renal biopsy indicated morphological features consistent with low-grade endothelial injury and chronic TMA. After switching to imatinib, the proteinuria improved rapidly. Holstein et al. [7] reported a 58-year-old woman with CML who was treated with imatinib. After 6 months, RT-PCR of peripheral blood yielded negative results for BCR-ABL. However, 2 years after initiation of imatinib, she was admitted with blast crisis. Therefore, her medication was switched from imatinib to dasatinib, and hydroxyurea treatment was initiated. After 4 days, her creatinine level rose to 122 μmol/L, and urinalysis showed a specific gravity of > 1.030, blood level of 3+, and protein level of 2+. The patient subsequently developed anuric renal failure, and hemodialysis was initiated. Following discharge, the patient was transferred to another facility for management of the blast crisis. Treatment with dasatinib was discontinued, and hydroxyurea was initiated along with nilotinib (400 mg twice daily). Thereafter, hemodialysis was tapered, and urine output improved to 1,100 mL/day [7]. These findings were consistent with the side effects of TKI (proteinuria) observed in this case.

In the abovementioned cases, proteinuria improved after switching to another TKI. The temporal relationship between onset of nephrotic syndrome and TKI therapy, and the resolution of proteinuria with discontinuation of the therapy, strongly suggested an association between TKIs and proteinuria in these patients [3]. To our knowledge, this is the first report of a case in South Korea in which heavy proteinuria developed after long-term TKI treatment (3 years) and improved after switching to another TKI. Although proteinuria appeared to be a delayed renal complication of dasatinib treatment, it improved rapidly after switching from dasatinib to another TKI (nilotinib), followed by complete remission of proteinuria. Complete remission of CML without proteinuria was observed after switching to nilotinib. We will continue to monitor the effects of nilotinib in this case. According to the literature, both imatinib and nilotinib are effective in treating CML and are not associated with proteinuria [4]. Imatinib is a selective TKI that affects the activity of PDGF receptors. Indeed, imatinib exhibits marked renoprotective effects, as reported by Iyoda et al. [8] who found that imatinib suppressed proteinuria and attenuated the development of glomerulosclerosis and tubulointerstitial injury even after short-term use. Furthermore, Iyoda et al. [8] reported that rats treated with nilotinib, a second-generation selective TKI, had less proteinuria, attenuated glomerulosclerosis, reduced tubulointerstitial damage, reduced macrophage infiltration into the tubulointerstitium, and prolonged survival compared to controls [9].

TKIs are associated with a wide range of adverse events, in-

cluding proteinuria. Although most of these events are well tolerated, treatment interruptions, such as dose adjustment or switching to an alternative TKI, are necessary when adverse events are intolerable. After treatment interruption, most adverse events improved, and most patients showed equivocal or improved molecular responses to CML.

Due to the lack of controlled studies on the treatment of nephrotic-range proteinuria and TMA, there are no guidelines for further treatment. If proteinuria is in the non-nephrotic range and the serum creatinine level is stable, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can be initiated. If proteinuria is sufficiently severe to warrant discontinuation of the agent and does not respond to ACE inhibitors or ARBs, the medication can be switched. However, proteinuria commonly persists even after discontinuation of TKIs. Therefore, maintenance of ACE inhibitors or ARBs is often needed [10]. In addition, controlling high blood pressure is important to prevent proteinuria. Based on the results of previous studies, high baseline systolic blood pressure is the only predictive factor for VEGF receptor-TKI-induced hypertension. However, the current clinical guidelines do not specify the use of antihypertensive drugs. In a previous study, no differences were observed with use of calcium channel blockers and angiotensin receptor II blockers as first-line antihypertensive agents [11]. In other studies, ARBs were shown to reduce the pressure on the glomeruli and decrease proteinuria, consequently inhibiting the deterioration of renal function [12-14].

TKIs are thought to cause proteinuria by affecting VEGF and NO levels but, due to the lack of systematic studies on the management of TKI-induced proteinuria, the drug must be discontinued. However, as shown here, in cases of TKI-induced proteinuria, the medication could be switched to another TKI, such as nilotinib or imatinib, which may also help limit the progression of chronic kidney disease. Such a strategy may be clinically important as it obviates the need to discontinue the medication or use immunosuppressive drugs to treat proteinuria. Nevertheless, prospective studies are required to determine the optimal TKIs and antiproteinuric regimens in such cases.

중심 단어: 단백뇨; 티로신 키나제 억제제; 다사티닙; 닐로티닙; 만성 골수성 백혈병, BCR-ABL 양성

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Joohee Jeon, Chung Hee Baek, and Hyosang Kim were involved in the study design and data interpretation. Joohee Jeon, Dongyeon Lee and Jae Sung Ahn were involved in the data analysis. All authors contributed to the final revision of the manuscript.

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REFERENCES

1. Ong R, Lamarche J, Courville C, Peguero A. Dasatinib associated acute renal failure with proteinuria and reversibility after discontinuation. Am J Kidney Dis 2014;63:B85.
2. Izzedine H, Rixe O, Billemont B, Baumelou A, Deray G. Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. Am J Kidney Dis 2007;50:203-218.
3. Ruebner RL, Copelovitch L, Evageliou NF, Denburg MR, Belasco JB, Kaplan BS. Nephrotic syndrome associated with tyrosine kinase inhibitors for pediatric malignancy: case series and review of the literature. Pediatr Nephrol 2014;29:863-869.
4. Wallace E, Lyndon W, Chumley P, Jaimes EA, Fatima H. Dasatinib-induced nephrotic-range proteinuria. Am J Kidney Dis 2013;61:1026-1031.
5. Abbas A, Mirza MM, Ganti AK, Tendulkar K. Renal toxicities of targeted therapies. Target Oncol 2015;10:487-499.
6. Maruyama K, Chinda J, Kuroshima T, et al. Minimal change nephrotic syndrome associated with gefitinib and a successful switch to erlotinib. Intern Med 2015;54:823-826.
7. Holstein SA, Stokes JB, Hohl RJ. Renal failure and recovery associated with second-generation Bcr-Abl kinase inhibitors

in imatinib-resistant chronic myelogenous leukemia. Leuk Res 2009;33:344-347.
8. Iyoda M, Shibata T, Wada Y, et al. Long- and short-term treatment with imatinib attenuates the development of chronic kidney disease in experimental anti-glomerular basement membrane nephritis. Nephrol Dial Transplant 2013;28:576-584.
9. Iyoda M, Shibata T, Hirai Y, Kuno Y, Akizawa T. Nilotinib attenuates renal injury and prolongs survival in chronic kidney disease. J Am Soc Nephrol 2011;22:1486-1496.
10. Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D, Soria JC. VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. Eur J Cancer 2010;46:439-448.
11. Izumi K, Itai S, Takahashi Y, Maolake A, Namiki M. Predictive factor and antihypertensive usage of tyrosine kinase inhibitor-induced hypertension in kidney cancer patients. Oncol Lett 2014;8:305-308.
12. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-2031.
13. Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359: 1004-1010.
14. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. Am J Transplant 2007;7: 2350-2360.