Letter to the Editor

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A Case of Dasatinib-Induced Nephrotic Syndrome in a Child with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

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Tyrosine kinase inhibitors (TKI) were developed as the targeted therapy of cancer and are considered an important treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) or Ph+ acute lymphoblastic leukemia (ALL).[1,2] As the use of TKIs has increased, its side effects have also been reported. A few cases of children who developed nephrotic syndrome following treatment of TKI, have been reported.[3]

A 5-year-old boy was diagnosed with Ph+ ALL with petechiae on both lower legs. He achieved remission through induction chemotherapy including daunorubicin, vincristine, L-asparaginase, and prednisolone and started taking imatinib, the first generation of TKIs (300 mg), after ascertaining BCR-ABL rearrangement. After 2 years, he had developed central nervous system (CNS) relapse of ALL during maintenance chemotherapy. Therefore, reinduction chemotherapy was started on Pediatric Oncology Group 9412 protocol and imatinib was replaced with dasatinib. He achieved remission after chemotherapy and was prepared for hematopoietic stem cell transplantation (HSCT). Twenty-six days after HSCT, he had asymptomatic proteinuria. Urinalysis showed 4+ proteinuria without other symptoms. Urine total protein for 24 hrs was 5636 mg, 234 mg/m^2/hr and spot urine protein-creatinine ratio was 15.24, meeting the diagnostic requirements for nephrotic syndrome. Proteinuria was sustained even after stopping dasatinib for 5 days. Therefore, kidney biopsy was performed for diagnosis. Light microscopically, glomeruli had no cellular proliferation or capillary wall thickening (Fig. 1A). Tubulointerstitium did not show abnormal pathology either. Electron microscopically, most foot processes were fused, but no electron dense deposits were present (Fig. 1B). Immunofluorescent study revealed no positive results for anti IgG, A, M, C3, and C1q. Within 1 week of stopping dasatinib, urinalysis showed no proteinuria and urine total protein for 24 hrs was 395 mg, which was in the nephrotic range of nephrotic syndrome. Since then, post-HSCT course was uneventful until five months after HSCT, when he developed hepatic graft-versus-host-disease and expired.

To the best of our knowledge, this is the first reported pediatric case of dasatinib induced nephrotic syndrome in Korea. Ruebner, et al.[3] described 4 cases with pediatric malignancy with TKI-induced nephrotic syndrome. As in our case, resolution of nephrotic syndrome was achieved in three of the four cases after discontinuation of TKI therapy.

According to the report of the Pone di Legno childhood ALL consortium, the outcome of Ph+ ALL before the imatinib era, was very poor, with a 7-year event-free survival (EFS) rate of 25% and an overall survival rate of 36%.[4] The advent of the first generation of TKIs, imatinib, brought groundbreaking outcome in the treatment of Ph+ ALL. The 3-year EFS was 80% for patients in the Children's Oncology Group AALL0031 trial, which was more than double the EFS rate of historical controls treated without imatinib.[5] Dasatinib is the second generation of TKIs and a multi-kinase inhibitor, which has 325-times stronger activity against BCR-ABL than imatinib. Dasatinib is also known to have much better CNS penetration than imatinib.[6] Nevertheless, asymptomatic proteinuria occurred and urine total protein and spot urine protein-creatinine ratio met the nephrotic range of nephrotic syndrome, suggesting that the cause of nephrotic syndrome was dasatinib medication. Wallace, et al.[7] reported a case of 63-year-old woman with CML

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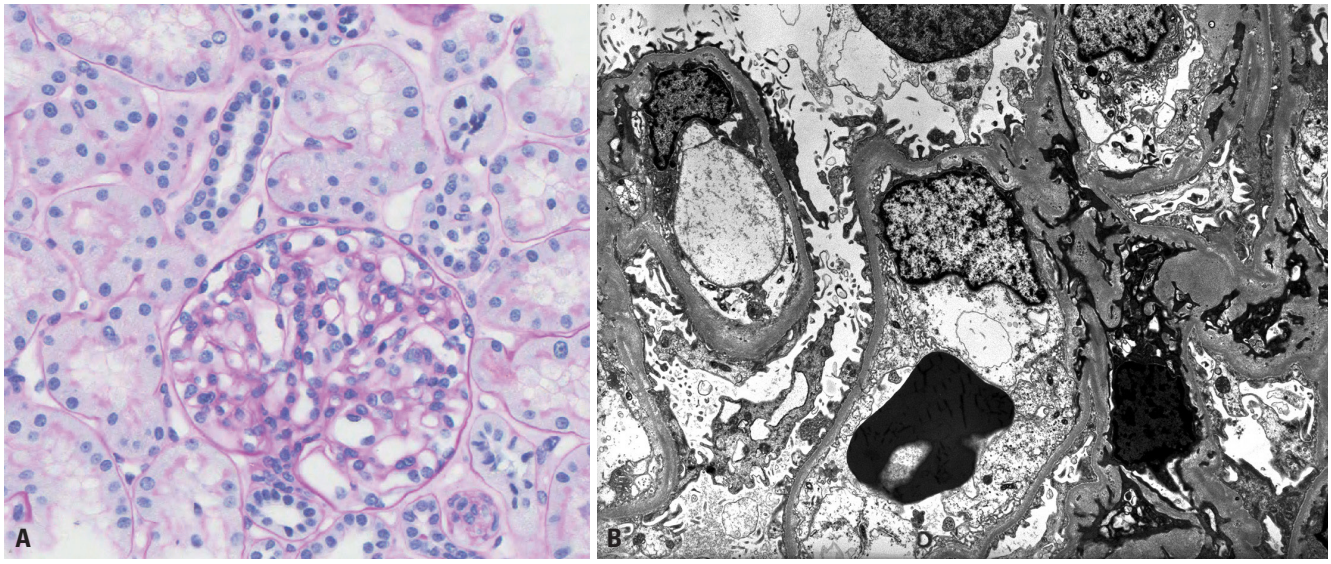

Fig. 1. (A) Glomerulus had no cellular proliferation or capillary wall thickening, and surrounding tubules are also unremarkable on PAS staining (×200). (B) Electron microscopically, most foot processes were fused. Electron dense deposits are not present (×3000).

who was on dasatinib therapy. She also had proteinuria, and symptoms were resolved after discontinuation of dasatinib. One possible mechanism of dasatinib-induced kidney injury was interruption of the vascular endothelial growth factor (VEGF) signaling pathway. In human podocytes of kidney, VEGF is expressed and related to normal glomerular function. Therefore, disruption of this signaling pathway causes kidney injury. Eremina, et al.[8] reported development of massive proteinuria and kidney injury in mice with loss-of-function mutation of VEGF on podocytes of kidney. Dasatinib not only affects the cancer cells, but also inhibits VEGF signaling pathway on podocytes, which damages tubulointerstitial and glomerular compartment of the kidney. In our case, we observed that most foot processes were fused through electron microscopy, which is seen in minimal change disease.

As the numbers of patients taking TKIs, including dasatinib, increase, nephrologists, and oncologists need to recognize adverse effects of TKIs on kidney, especially nephrotic syndrome. In the situation that TKIs medication is needed, the nephrologic workup should be preceded. Further study is needed to understand the pathology of renal injury and long term adverse effect by TKIs.

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REFERENCES

1. Skolnik JM, Adamson PC. Tyrosine kinase inhibitors in pediatric malignancies. Cancer Invest 2007;25:606-12.
2. Hunger SP. Tyrosine kinase inhibitor use in pediatric Philadelphia chromosome-positive acute lymphoblastic anemia. Hematology Am Soc Hematol Educ Program 2011;2011:361-5.
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;29:863-9.
4. Aricò M, Valsecchi MG, Camitta B, Schrappe M, Chessells J, Baruchel A, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998-1006.
5. Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-81.
6. Porkka K, Koskenvesa P, Lundán T, Rimpiläinen J, Mustjoki S, Smykla R, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008;112:1005-12.
7. Wallace E, Lyndon W, Chumley P, Jaimes EA, Fatima H. Dasatinib-induced nephrotic-range proteinuria. Am J Kidney Dis 2013;61:1026-31.
8. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J Clin Invest 2003;111:707-16.