

[CASE REPORT]

Pazopanib-induced Endothelial Injury with Podocyte Changes

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Abstract:

Pazopanib has been reported to induce proteinuria; however, no pathological findings have been reported. We herein report the case of a 31-year-old man with rhabdomyosarcoma treated with pazopanib who developed nephrotic syndrome. A renal biopsy revealed endothelial injury with podocyte changes. Based on the biopsy findings, we diagnosed the patient with nephrotic syndrome caused by pazopanib. Following the discontinuation of pazopanib, the patient's proteinuria gradually decreased without any specific treatment. We should be careful when encountering drug-induced proteinuria in patients taking pazopanib.

Key words: pazopanib, nephrotic syndrome, proteinuria, adverse effect, onco-nephrology, thrombotic microangiopathy

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Introduction

Anti-vascular endothelial growth factor (VEGF) therapy has been reported to induce proteinuria, hypertension and/or renal dysfunction, including bevacizumab, sunitinib and sorafenib. An observational study showed that thrombotic microangiopathy (TMA), minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the most common histological features in patients who receive anti-VEGF therapy (1). Pazopanib, a selective multi-targeted receptor tyrosine kinase inhibitor (TKI) of VEGF receptor, platelet-derived growth factor receptor and c-Kit, has also been reported to induce proteinuria and nephrotic syndrome (NS); however, no pathological examination was performed (2, 3).

We herein report the case of a 31-year-old man with advanced rhabdomyosarcoma treated with pazopanib who developed NS. To our knowledge, this is the first report of histologically documented renal injury caused by pazopanib.

Case Report

A 31-year-old man who had started pazopanib therapy (400 mg/day) for advanced rhabdomyosarcoma 8 months earlier was referred to our hospital due to abnormal urinalysis findings. The laboratory data showed new-onset hypoalbuminemia and proteinuria, strongly suggestive of NS. He was admitted for further examination.

On admission, he had a blood pressure of 104/72 mmHg and a pulse of 66 beats/min with a regular rhythm. Edema of the lower limbs was slightly present. Neurological findings were unremarkable. Chest X-ray and electrocardiography were normal. The laboratory data were as follows: blood urea nitrogen (BUN), 13.3 mg/dL; serum creatinine, 0.87 mg/dL; serum total protein, 5.0 g/dL; serum albumin, 2.8 g/dL; total cholesterol, 235 mg/dL; low-density lipoprotein (LDL) cholesterol, 134 mg/dL; high-density lipoprotein (HDL) cholesterol, 74 mg/dL and triglyceride, 133 mg/dL. His 24-hour urine protein excretion was 6.8 g/day. Anemia, schistocytes and thrombocytopenia were not observed, indicating that there was no evidence of systemic TMA. We

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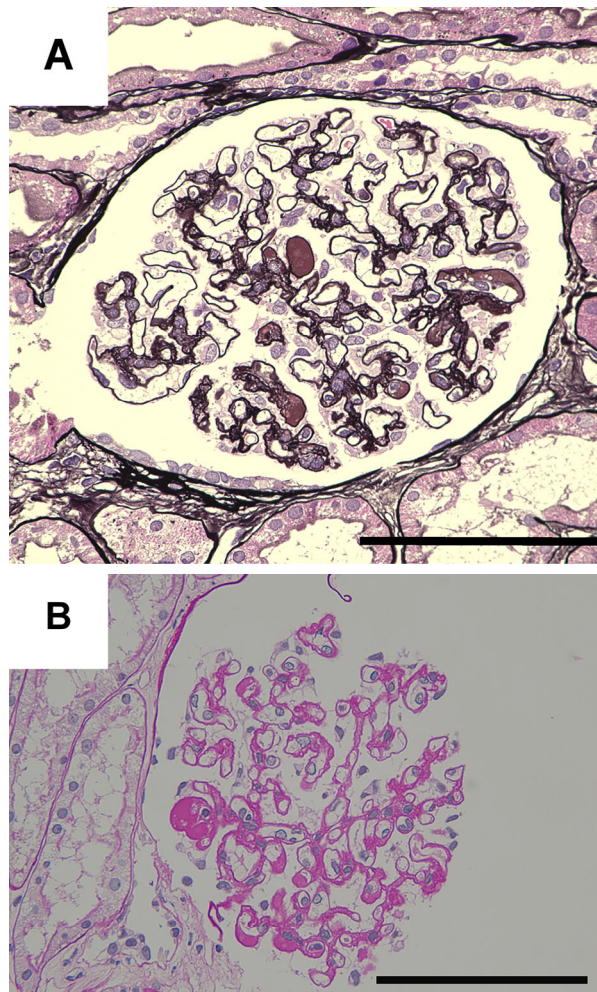


Figure 1. Light microscopy showing narrowing of the glomerular capillary lumina by double contours or hyaline thrombi. (A) Periodic acid-methenamine-silver (PAM) stain (scale bar=100 µm). (B) Periodic acid-Schiff (PAS) stain (scale bar=100 µm).

made a diagnosis of NS. Although pazopanib was strongly suspected as the cause of NS, we performed a renal biopsy to confirm the pathological diagnosis because it was a key drug for the patient. Fourteen glomeruli were sampled for light microscopy, none of which were globally sclerotic. The glomerular basement membrane appeared to show diffuse thickening. The glomerular capillary lumina were narrowed by double contours or hyaline thrombi (Fig. 1). Two glomeruli showed segmental adhesion to the Bowman's capsule. There was no significant tubular atrophy or interstitial fibrosis. Immunofluorescence microscopy revealed weak IgA, IgM, C3, C4, and C1q semi-linear staining along the glomerular basement membrane (Fig. 2). Electron microscopy revealed subendothelial expansion and partial foot process effacement, whereas no electron-dense depositions were detected (Fig. 3). The major renal biopsy finding was endothelial injury without immune depositions, consistent with a diagnosis of TMA. In addition, TMA secondarily led to segmental lesions. Based on these findings, we diagnosed the patient with NS caused by pazopanib. Following the discontinuation of pazopanib, the patient's proteinuria gradually decreased without any specific treatment (Fig. 4). However,

the patient developed systemic metastasis (lung, liver, bone, and lymph node) and died due to respiratory failure a few months later.

Discussion

We herein report a patient with biopsy-proven NS caused by pazopanib. The clinical course of the patient suggested two important clinical issues: Pazopanib induces endothelial injury with podocyte changes similarly to other anti-VEGF drugs, and the drug-induced damage is reversible.

Pazopanib induces endothelial injury with podocyte changes similarly to other anti-VEGF drugs. These drugs are well known to cause proteinuria, but a kidney biopsy is infrequently performed. Pathologically proven renal injury has been reported in patients during anti-VEGF antibody therapy (bevacizumab and aflibercept) and TKI therapy (sunitinib, sorafenib, brivanib, and cediranib) (1, 4, 5). Although a meta-analysis showed that the incidence of all-grade and high-grade proteinuria in patients who received pazopanib was 13.5% and 2.2%, respectively, no pathological examination was performed (6).

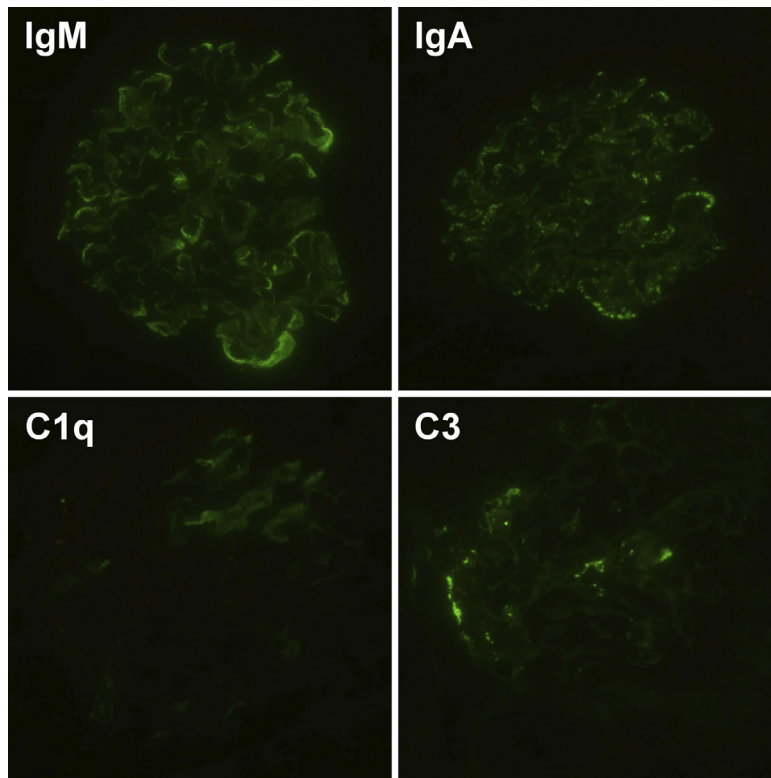


Figure 2. Immunofluorescence microscopy showing weak IgA, IgM, C3, and C1q semi-linear staining along the glomerular basement membrane.

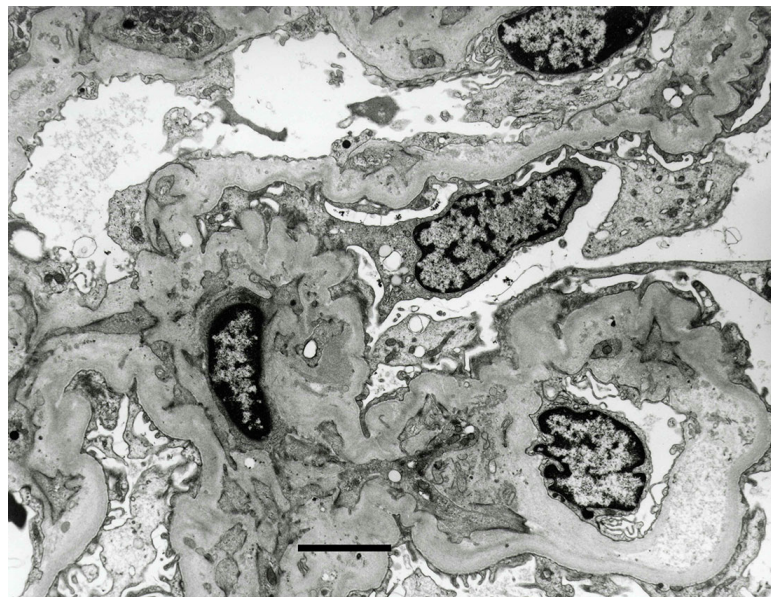


Figure 3. Electron microscopy showing subendothelial expansion and partial foot process effacement (scale bar=2 μ m).

A previous study elegantly demonstrated that renal injury during anti-VEGF therapy comprises two different pathologic subtypes: glomerular diseases, such as endothelial injury like intraglomerular TMA, and podocytopathies, like MCD/FSGS (1). In our case, endothelial injury was prominent, and there were no signs of systemic TMA. In addition, this injury was limited to the kidneys, which is a key feature

of anti-VEGF therapy-induced TMA. While intraglomerular TMA typically occurs in patients during anti-VEGF antibody therapy, we experienced a rare case of TKI-induced endothelial injury and intraglomerular TMA. A previous study demonstrated why VEGF inhibition leads to intraglomerular TMA (7). The authors used a conditional knockout model in which genetic ablation of VEGF produc-

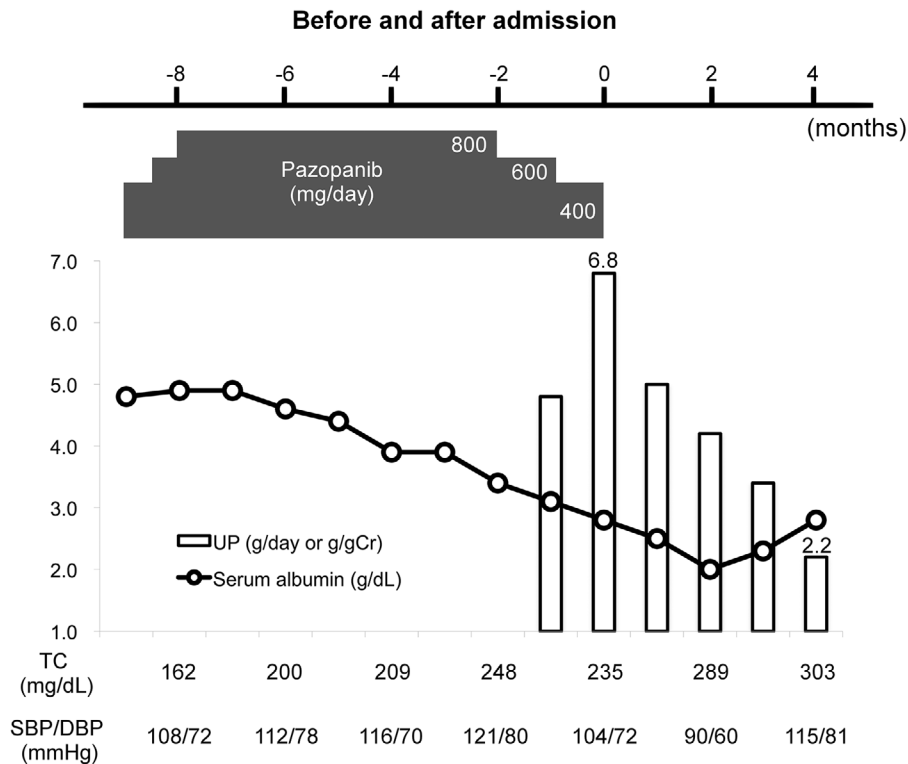


Figure 4. Clinical course. UP: urinary protein, g/gCr: urinary protein/creatinine ratio, TC: total cholesterol, SBP: systolic blood pressure, DBP: diastolic blood pressure

tion in podocytes replicates the damage induced by anti-VEGF drugs. Glomerular endothelial cells possess fenestrations that are maintained by VEGF. The loss of local VEGF production leads to the loss of healthy fenestrations and promotes the development of microvascular injury and TMA. It was also shown that glomerular capillaries have fewer fenestrations with systemic administration of VEGF-inhibiting drugs (8). Therefore, pazopanib, as well as other anti-VEGF drugs, inhibits endothelial VEGF pathways and leads to intraglomerular TMA.

Pazopanib-induced injury is reversible. Indeed, in our case, proteinuria gradually decreased without any specific treatment. At present, there are no effective treatments for renal injury associated with anti-VEGF therapy. Drug discontinuation should be considered; however, we must scrutinize the advantages and disadvantages of drug withdrawal. One case report showed that a hypertensive patient who developed sunitinib-induced proteinuria was treated with irbesartan. Without the discontinuation of sunitinib, the patient's blood pressure remained stable, and proteinuria became undetectable (9). Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are recognized to reduce proteinuria in patients with chronic kidney diseases, but further studies are needed to confirm the same effect in patients with drug-induced proteinuria, especially in those without hypertension, like our case.

In conclusion, we should therefore be careful when encountering drug-induced proteinuria in patients who receive pazopanib. Further studies are required to elucidate how we

should best manage and treat such patients.

Author's disclosure of potential Conflicts of Interest (COI).

Yayoi Ogawa: Employment, GeneticLab.

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