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Case Report

BRAF Signaling Pathway Inhibition, Podocyte Injury, and Nephrotic Syndrome

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Dabrafenib and trametinib, BRAF and MEK inhibitors, respectively, are effective targeted metastatic melanoma therapies, but little is known about their nephrotoxicity. Although tubulointerstitial injury has been the most widely reported renal side effect of targeted melanoma therapy, nephrotic syndrome has not been reported before. We report on a patient with metastatic melanoma who developed nephrotic syndrome during dabrafenib and trametinib treatment. Kidney biopsy showed diffuse loss of podocyte cytoarchitecture, extensive foot-process effacement, and glomerular endothelial injury. Kidney function and glomerular ultrastructural changes recovered fully after drug withdrawal. In vitro, BRAF inhibition decreased PLCε1 expression in podocytes, accompanied by a reduction in nephrin expression and an increase in permeability to albumin. Additionally, these drugs inhibited the podocyte–vascular endothelial growth factor (VEGF) system. In addition to implications for nephrotic syndrome pathophysiology, we suggest that patients given dabrafenib and trametinib be monitored closely for potential glomerular damage.
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INDEX WORDS: Dabrafenib; melanoma; trametinib; podocyte injury; glomerulopathy; nephrotic syndrome; BRAF inhibitor; MEK inhibitor; targeted cancer therapy; BRAF signaling pathway; proteinuria; PLCε1; renal biopsy; nephrotoxicity; case report.

Targeted cancer therapy is the systemic administration of drugs that act on well-defined biological pathways to cause regression or destroy the malignant process, with minimal adverse effects on healthy tissues. Metastatic malignant melanoma treatment is a good example of this.[1] Several studies have confirmed the presence of BRAF mutations in 40% to 70% of patients with melanoma.[2] BRAF is the upstream component of the mitogen-activated protein kinase (MAPK) pathway that regulates cell proliferation and survival.[3] In 80% to 90% of melanoma cases, a gain-of-function mutation consisting of a glutamic acid substitution for valine at amino acid 600 (BRAF V600) is present.[2]

Two drugs, vemurafenib and dabrafenib, have been shown to have robust antitumor activity and efficacy in prospective phase 3 trials in patients with advanced melanoma carrying the BRAF V600 mutation.[4-7] Another drug, trametinib, a highly specific MEK1/2 inhibitor, has been approved for use in patients with metastatic melanoma with the BRAF V600 mutation. Clinical trials have shown that the combination of BRAF and MEK inhibitors yields a higher response rate and longer progression-free and overall survival than the former on its own.[8,9] Both BRAF and MEK inhibitors have cutaneous toxicity,[8,9] but less is known about nephrotoxicity.[10-14] Severe cases of decreases in kidney function following melanoma-targeted therapy have been reported, but these patients had simultaneous risk factors for acute kidney injury, but minimal or no proteinuria.[10]

We report on a patient with radically resected melanoma, treated with dabrafenib and trametinib, who developed proteinuria and nephrotic syndrome.

CASE REPORT

A 65-year-old woman with a history of type 2 diabetes, on metformin therapy (500 mg twice a day), and with no history of hypertension, had melanoma on the right thigh, with regional lymph node metastasis. After melanoma and regional lymph node resection, she was treated with dabrafenib (150 mg twice daily) and trametinib (2 mg once daily). She had received no chemotherapeutic agent beforehand. At baseline, her kidney function was

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within reference ranges (proteinuria with protein excretion < 0.20 g/d; protein-creatinine ratio < 200 mg/g). Eight months later, she developed lower-limb edema and puffy eyes accompanied by pleural effusion and ascites. Cancer restaging excluded local or metastatic recurrence. Urinalysis showed proteinuria (protein excretion, 4.0 g/d; protein-creatinine ratio, 1,644 mg/g). See Item S1 for additional clinical information.

A first kidney biopsy revealed mild diffuse mesangial expansion of glomeruli due to increased matrix, accompanied by focal podocyte swelling and hypertrophy (Fig 1A). Glomeruli did not exhibit segmental sclerosis or Kimmelstiel-Wilson nodules. There was mild patchy interstitial fibrosis and tubular atrophy, intimal sclerosis of medium-sized arteries, and arteriolar hyalinosis. Immunofluorescence microscopy revealed dull linear staining of glomerular and tubular basement membranes for immunoglobulin G (IgG) and focal glomerular parietal staining for IgM (1+), but no detectable staining for other tested antisera (Fig S1A). Transmission electron microscopy showed diffuse glomerular basement membrane thickening (861 ± 48; reference range, 320 ± 50 nm; Fig 1B). Podocytes exhibited severe cytoplasmic swelling, vacuolization, fragmentation, and lysis accompanied by extensive interdigitating foot-process effacement (Fig 1B). Subendothelial regions showed moderate expansion due to the accumulation of electron-lucent material, cell debris, and reactive endothelial cells (Fig 1B). Scanning electron microscopy showed dramatic changes involving podocytes, with loss of cytoarchitecture and barely identifiable interdigitating foot processes (Fig 1C).

Dabrafenib and trametinib treatment were interrupted, furosemide was started, and proteinuria rapidly decreased (protein excretion, 0.15 g/d). Three months after drug withdrawal, a second kidney biopsy confirmed mild diffuse glomerular mesangial expansion, though there was no sign of podocyte swelling or hypertrophy (Fig 1A). None of the glomeruli exhibited segmental sclerosis. Immunofluorescence findings were essentially unchanged (Fig S1B). Transmission electron microscopy confirmed diffuse glomerular basement membrane thickening (851 ± 36 nm), but revealed structural recovery of podocyte bodies and foot processes in most capillary loops, and more preserved endothelium (Fig 1B). Viewed through scanning electron microscopy, podocyte cell bodies were preserved and primary processes showed normal foot-process interdigitating distribution patterns (Fig 1C). At last follow-up, the patient's generalized edema was improved, proteinuria had protein excretion of 0.13 g/d, and computed tomography excluded melanoma recurrence.

To investigate the mechanisms underlying the glomerular structural injury associated with dabrafenib and trametinib, we focused on PLCε1, a slit diaphragm–associated protein that interacts with BRAF. PLCε1 staining was visible in the podocyte cytoplasm of normal glomeruli, while it was weak in the patient's biopsy specimen during drug treatment (Fig 1D). Drug withdrawal was sufficient to restore PLCε1 expression in podocytes (Fig 1D). Immunofluorescence analysis revealed a global reduction of nephrin, a PLCε1 interactor, during drug treatment, which was restored in the patient biopsy specimen after drug withdrawal (Fig 1E).

To further characterize this nephrotoxicity mechanism, we created an in vitro model to study the effect of dabrafenib and trametinib sublethal dose (100 nmol/L) in cultured human podocytes (Fig S2). Dabrafenib, but not trametinib, reduced both BRAF peripheral localization (Figs 2A and S3A) and PLCε1 expression (Figs 2B and S3B), which were restored after drug withdrawal (Fig S3A and B). Double immunostaining revealed that BRAF and PLCε1 colocalized at the cell periphery and that dabrafenib reduced BRAF and PLCε1 colocalization (Fig 2C). To evaluate whether the decline in colocalization was associated with slit diaphragm disruption, we examined nephrin expression and permeability to albumin in podocytes. Dabrafenib downregulated nephrin expression, which was unaffected by trametinib alone (Fig 2D). By evaluating the transepithelial passage of fluorescent albumin (Fig 2E), we detected an increase in albumin permeability across the podocyte monolayer after exposure to dabrafenib, but not trametinib (Fig 2E). We then evaluated vascular endothelial growth factor (VEGF) release in culture medium from podocytes, which was strongly impaired by both drugs and recovered upon drug removal (Fig S4).

DISCUSSION

We describe a patient with melanoma who developed nephrotic syndrome during dabrafenib and trametinib treatment. The most prominent ultrastructural finding was diffuse loss of podocyte cytoarchitecture, extensive foot-process effacement, and endothelial injury. Cancer-induced glomerular disease has been reported previously,[15-19] but our patient had no clinical signs of kidney damage when melanoma was diagnosed, and urinalysis results were normal. She developed nephrotic syndrome only during treatments and notably experienced rapid remission and reversal of glomerular ultrastructural changes after drug withdrawal. This excluded paraneoplastic glomerular disease while supporting the hypothesis of drug-induced glomerular damage.

Also relevant to consider is that diabetic nephropathy can cause nephrotic-range proteinuria in advanced stages of the disease.[20] Podocyte foot-process effacement and endothelial injury are common diabetic nephropathy ultrastructural features.[21] Both kidney biopsies showed mild mesangial expansion, thickened glomerular basement membrane, and mild arteriolar hyalinosis, morphologic hallmarks of early diabetic nephropathy. Notably, the patient had good glycemic control without evidence of diabetic retinopathy. The first kidney biopsy revealed severe podocyte injury and extensive foot-process effacement, which improved dramatically after drug withdrawal despite persisting diabetic changes, indicating that podocyte injury accounted for nephrotic-range proteinuria in a manner independent of diabetes. Thus, we hypothesize that the patient's nephrotic syndrome is most likely a form of podocytopathy superimposed on diabetic nephropathy.

To investigate the drug-induced nephrotoxic mechanism, we focused on PLCε1, identified as a BRAF interactor in podocytes[22] and whose mutations cause a reversible variant of nephrotic syndrome.[23] PLCε1 also interacts with nephrin, another slit diaphragm component that when mutated can lead to nephrotic syndrome.[23-27] Ex vivo studies revealed PLCε1 and nephrin downregulation in the biopsy specimen during drug treatment, leading to slit diaphragm junctional complex dysfunction, which may cause nephrotic syndrome manifestations. The finding that PLCε1 and nephrin restoration accompanied

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