Nephrotic syndrome caused by the angiogenesis inhibitor sorafenib

We report a 50-year-old man, diagnosed with advanced renal cell carcinoma (RCC), who was treated with sunitinib for 7 months until progression. Sorafenib was started as second-line treatment 2 weeks later. Within 10 days after initiation of sorafenib treatment, the patient developed skin rash with erythema, influenza-like symptoms, hypertension, generalized edema and oliguria. Renal failure with a serum creatinine level of 306 µmol/l, proteinuria of 20 g/24 h and hematuria of 150 red blood cells (RBC)/µl was found. Before start of treatment with sorafenib, renal function was normal and similar to before start of sunitinib treatment [estimated glomerular filtration rate (eGFR) using modification of diet in renal disease (MDRD) formula >90 ml/min] with no signs of proteinuria. Treatment with sorafenib was terminated, a kidney biopsy was obtained and the patient was treated with high-dose corticosteroids and angiotensin-converting enzyme inhibitors, in order to lower proteinuria. Serum creatinine levels decreased after initiation of corticosteroids and normalized within 1 month; eGFR using MDRD recovered to 80 ml/min. Clinical symptoms of a nephrotic syndrome dissolved, but proteinuria remained 3.8 g/day, while hematuria almost completely recovered to 10 RBC/µl.

The renal biopsy during treatment with sorafenib showed mild acute thrombotic microangiopathy (TMA), while there were no abnormalities seen in the non-neoplastic areas of the renal biopsy obtained 8 months earlier when advanced RCC was diagnosed (Figure 1A). Light microscopy examination revealed mesangiolyis, dilatation of capillary loops and stasis of erythrocytes (Figure 1B) and ultrastructural subendothelial widening with fluffy proteinaceous material (Figure 1E). A subcortical area in the kidney biopsy contained limited interstitial inflammation (Figure 1C). There were no deposits or glomerular basement membrane abnormalities (Figure 1D) but total foot process effacement in podocytes consistent with minimal change disease (MCD) (Figure 1E). On the basis of these findings, we concluded that sorafenib induced renal failure and a nephrotic syndrome due to a unique combination of acute TMA and MCD. It is unclear whether the switch from sunitinib to sorafenib treatment might have played a role in the cause of the toxicity in this patient.

Sorafenib is an antiangiogenic tyrosine kinase inhibitor which inhibits, among other tyrosine kinases, vascular endothelial growth factor receptors (VEGFRs) [1]. Vascular endothelial growth factor (VEGF) not only is important in pathologic angiogenesis but also plays a role in physiological processes such as the coagulation cascade and blood pressure [2]. In the kidney, VEGF may play an important role in development and maintenance of glomerular endothelium. Glomerular endothelial cells express VEGFRs, and VEGF is produced by podocytes [3].

No proteinuria or renal impairment was observed in early clinical trials with sorafenib. Just lately, sunitinib and sorafenib have been reported to cause proteinuria up to 10.4 g/day [4] and sunitinib and bevacizumab to cause TMA [5, 6]. The etiology of renal TMA is not exactly known, but a disturbance of the homeostasis between vascular cells and the coagulation cascade is expected to be of importance. Angiogenesis inhibitors may interfere in this homeostasis by disturbing the platelet–endothelial homeostasis, causing endothelial cell apoptosis, increased activity of tissue factor, platelet activation and subsequent thrombosis [2].

In conclusion, we report for the first time that sorafenib treatment caused a unique combination of acute TMA and MCD resulting in renal failure and nephrotic syndrome. Further studies are warranted to determine the
underlying mechanisms of toxic effects to angiogenesis inhibitors.

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disclosure

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references


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