Sunitinib induced glomerular thrombotic microangiopathy

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Abstract

Sunitinib contributes to adverse renal events, including proteinuria, hypertension and more importantly thrombotic microangiopathy or TMA. Clinical trials have been conducted regarding the role of bevacizumab and TMA but there is little data to support similar side effects from sunitinib. In this case report, we present a patient with refractory case of pancreatic neuroendocrine tumor started on sunitinib. After continuous use of this drug the patient developed anasarca with acute kidney injury and was found to have TMA on renal biopsy.

Introduction & Background

Sunitinib is a small molecule inhibiting several tyrosine kinase receptors, including vascular endothelial growth factors (VEGF) 1-3 and platelet-derived growth factor receptor-beta (PDGFR-β). It acts as an anti-angiogenesis in cancer treatment, particularly in renal cell carcinoma. [1,2] In experimental animals, it has been proposed that the VEGF has proven to play a role in glomerular endothelium repair in the setting of renal TMA. Use of anti-VEGF can cause thrombosis due to the production of procoagulant phospholipids. These molecules are released with the disruption of the plasma membrane integrity. Additionally, inhibition of the VEGF results in the reduction of nitric oxide levels and prostaglandin I2; further implicating the formation of renal TMA. [3]

Case Description

A 77-year-old female with past medical history of refractory pancreatic neuroendocrine tumor on chemotherapy; Sunitinib 37.5mg daily for approximately four years was admitted to the floor for acute kidney injury, significant proteinuria, and anasarca. Her lab work was significant for creatinine of 3.12mg/dl an increase from 2.12mg/dl in May 2021, BUN 61mg/dl, GFR 14ml/min, and proteinuria of 2.228mg/24 hours. Her retroperitoneal ultrasound showed fullness of the left renal pelvis, mild increased echogenicity of the kidneys suggesting medical renal disease, and mild ascites. She was also noted to be anuric on admission. Medical treatment included holding Sunitinib and initiating diuretic therapy. Dialysis was considered if she did not respond to medical therapy. The profound proteinuria of more than 14 grams of protein excretion a day in the setting of acute renal injury was considered from Sunitinib related focal segmental glomerulosclerosis or membranous nephropathy in the setting of neuroendocrine malignancy. She had a negative work up for vasculitis, autoimmune process, hepatitis A, B and C, and she tested negative for COVID 19 and strep throat. She had negative phospholipase A2 receptor antibodies ruling out primary membranous nephropathy. After ten days of hospitalization her BUN was 66mg/dL, Cr 3.39mg/dL and phosphorous 6.4g/dL. Patient's volume status eventually improved, and her 24-hour urine showed 2.5 L. Diuresis was slowly deescalated and left renal biopsy was performed.

Discussion

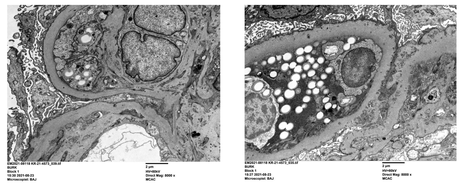
The production of proteinuria and hypertension in the setting of TMA with the use of cancer treatment such as sunitinib is an uncommon but significant finding. The first case of isolated renal finding of TMA on biopsy was reported by Bollee et al., in France in 2009. Since then, several case reports and studies have identified an isolated glomerular renal involvement with sunitinib. [2] However, there remains limited clinical data on sunitinib and TMA. Our patient was started on sunitinib for refractory pancreatic neuroendocrine tumor and developed hypertension with significant proteinuria of > 14 grams per day and was eventually found to have TMA on renal biopsy. We believe this is an important case of TMA with long term use of sunitinib. VEGF, more specifically VEGF-A plays a crucial role in maintaining the integrity of the glomerular filtration barrier, glomerular capillary structure and in the repair, process following injuries of glomerular endothelial cells. It also plays a crucial role as a pro angiogenic factor involved in the development of the kidney. Hence, use of anti VEGF and angiopoietin (Ang)-1 can disrupt glomerular repair and protection resulting in proteinuria and endothelial dysfunction. Additionally, VEGF-A along with endothelium derived nitric oxide (NO) causes vasodilation, maintaining vascular permeability. Use of anti-VEGF affects vascular permeability and leads to inflammation and damage at the glomerulus level. [1,5] Sunitinib associated renal complications calls for further research to fully understand the prothrombotic state and the variation in hypertension, subnephrotic or nephrotic proteinuria. Clinical features of TMA are present in ¾ of cases while renal failure, as in our patient, is also present in ¾ of reported cases. Nephrotic range proteinuria, also present in our case report, is present in about half the cases. Fibrinogen deposition is found in almost all cases reported. Patients on sunitinib should be monitored for declining renal functions such as increase in creatinine, or proteinuria. Clinicians should also suspect complications when there is poorly controlled hypertension in patients treated with sunitinib. They should also be more inclined to perform a renal biopsy in cases like this one. Discontinuation of Sunitinib has shown to reverse renal damage.

Biopsy Results

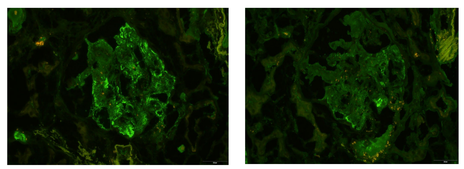
A biopsy specimen from Mayo Clinic confirmed a final diagnosis of subacute to chronic thrombotic microangiopathy (sunitinib-associated/clinical) and moderate arteriosclerosis and arteriolosclerosis.

The predominant findings in the biopsy were those of glomerular microangiopathy characterized by focal mesangiolysis and complex basement membrane remodeling with subendothelial lucency.

Electron Microscopy:



Immunofluorescence:



Conclusions

This case report highlights the risk of developing the uncommon side effect of TMA with the use of sunitinib in cancer patients. It also implicates the importance of renal biopsy in patients on an anti-VEGF agent even when there is mild proteinuria and an absence of renal failure or biological features of TMA. It calls for further research into the selective prothrombotic state in a subset of patients. While sunitinib remains a useful drug in the treatment of cancer; this case presentation offers some insight on a major side effect of an important anti-angiogenesis drug.

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