Nephrotic Proteinuria in Anti-Angiogenic induced TMA

Raad Chowdhury1, MD, Sandra Herrmann, MD1

Mayo Clinic1, Rochester, MN

ABSTRACT

Proteinuria and Thrombotic Microangiopathy (TMA) are well known complications of vascular endothelial growth factor inhibitors (VEGF-i) and Tyrosine Kinase Inhibitors (TKI). However, rarely does the above lead to nephrotic range proteinuria. A clinical dilemma arises when patients are on both VEGFi/TKIs and immune checkpoint inhibitors (ICI), with the latter known to cause acute intestinal nephritis (AIN) with some implications towards podocytopathies. Here we describe two patients on both classes of drugs, presenting with high grade proteinuria and the importance of renal biopsy in selecting the appropriate management.

Case 1: A 66-year-old male with a past medical history of chronic kidney disease (CKD) in the setting of metastatic renal cell carcinoma (RCC) and monoclonal gammopathy of unknown significance (MGUS) s/p left nephrectomy on therapy on pembrolizumab and axitinib for approximately one year, was seen by Onco-Nephrology for evaluation of acute kidney (AKI). The patient’s baseline serum creatinine (SCr) was 1.1-1.3mg/dl, generally tolerating treatment well except for ICI-induced hypothyroidism and TKI related hypertension. Recently, he developed diarrhea which improved after d/c of axitinib one week prior to current visit for a Scr of 4.7 mg/dL. Laboratory workup revealed a urine albumin/creatinine (UACR) of 28mg/g, Serum C-reactive protein (CRP) 10.6 mg/l and retinol binding protein/creatinine (uRBP/Cr) of 638mcg/cr. Current and prior urinalysis (UA) were bland. Patient’s SCr improved to 1.93mg/dl with intravenous fluids and holding losartan. To rule out adverse effects of immuno-therapy, biopsy was obtained which showed predominately acute tubular necrosis (ATN), with poor sampling. A year after this AKI event he was referred again to nephrology due to worsening albuminuria while still being maintained on pembrolizumab and reinitiated on a lower dose of axitinib. During this evaluation, SCr had improved to 1.56mg/dl since the hospitalization, UACR increased to 3.6 mg/g, with a 24-hour collection of 2.6g of proteinuria as well as worsening uRBP/Cr 2155mcg/cr, normal serum albumin, no hematuria, and again serologies were unremarkable. He again underwent a second kidney biopsy with light microscopy showing subacute to chronic microangiopathy and intraglomerular hyaline thrombi, with mild interstitial infiltrate composed of mononuclear cells but no tubulitis. Taking the biopsy findings into consideration, axitinib was discontinued, losartan restarted, and UACR significantly improved to 429 mg/g within 5 months and SCr remained stable at 1.5-1.7mg/dl. Interestingly, His ICI was eventually stopped as he developed pneumonitis and it was felt that his malignancy was stable, he did receive steroids but did not have any positive impact on SCr.

Case 2: A 60-year-old male with CKD III due to solitary left kidney in the setting of RCC on ipilimumab/nivolumab and cabozantinib, last dose four months prior to admission, was seen in consultation by the inpatient renal team for AKI. Patient has a baseline SCr of 1.5-1.8 mg/dl and on admission his SCr was found to be 3.89 mg/dl, uRBP/Cr of 26735, and CRP of 8.2 mg/l. Urine microscopy revealed hematuria and sterile pyuria with a protein/creatinine ratio of 7.02 mg/mg, which has slowly increased over the last two years with concomitant decline in serum albumin, currently 2.9g/dl with
worsening edema. As he was characterizing nephrotic syndrome with a negative glomerular disease workup, renal biopsy was pursued. Light microscopy showed a membranoproliferative pattern with chronic TMA. Electron microscopy showed segmental scarring, no immune complex deposits, and moderate foot process effacement. Chronic TMA was likely as a result of cabozantinib and once discontinued, SCR improved to 1.78 mg/dl, PCR down to 3.28 mg/mg, and serum albumin improved to 3.3 with improvement in edema.

In conclusion, we highlighted two cases where the patient was on both ICI plus VEGF/TKI, presenting with high grade proteinuria. In both cases, the biopsy showed TMA and not AIN, which impacted the management as the VEGF/TKI was stopped. Of note, the ICI in both patients were held going forward either due to disease quiescence or other non-renal adverse events. However, the pathological lesion and the clinical proteinuria both corresponded to a VEGF/TKI related insult, thus highlighting the importance of a renal biopsy.