EVEROLIMUS-INDUCED NEPHROPATHY IN A NON-TRANSPLANT PATIENT

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INTRODUCTION

The mammalian target of rapamycin (mTOR) inhibitors have historically been used as immunosuppressive agents when treating solid-organ transplants. However, these medications have recently been used for their antineoplastic properties, as well. Although proteinuria is a documented adverse reaction to mTOR inhibitors, a vast majority of the literature cites this in renal-transplant patients and is lacking for evidence in their use as antineoplastic agents. Because vascular endothelial growth factor (VEGF) is required for podocyte survival and basement membrane maintenance in the glomerulus (Figure 1), inhibition of the VEGF pathway by mTOR inhibitors likely causes glomerular injury, which allows for significant proteinuria to develop (1-3).

We present a case of a patient who developed nephrotic syndrome as an adverse effect from everolimus, which was being used as an adjunct chemotherapeutic agent.

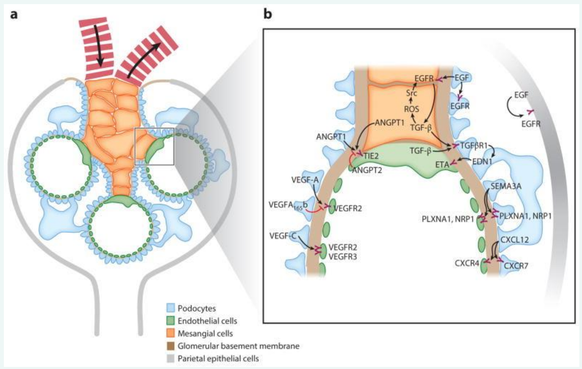

Figure 1. VEGF is integral to glomerular basement membrane maintenance and podocyte function in the glomerulus (3).

SIGNIFICANCE

Current literature does not adequately cite [nephrotic-range] proteinuria as an adverse event of mTOR inhibitors in patients without kidney transplants using the medication for adjunct therapeutic uses (e.g. chemotherapy). The difference between these populations resides largely in the severity of underlying kidney disease present; patients who have required a transplant typically have more severe underlying kidney disease than those who would be using these medications for their antineoplastic properties. This case supports the monitoring of kidney function in these non-transplant patients using mTOR inhibitors to prevent this significant event.

CASE SUMMARY

This patient is a 79-year-old female with a past medical history of carcinoid tumor, hypertension, type 2 diabetes, and hyperlipidemia who was referred to the ED for evaluation of anasarca with severe bilateral lower extremity edema after an outpatient CT scan showed long segment small bowel wall thickening. Regarding the patient's history of carcinoid tumor, she was started on Sandostatin for six months before switching her chemotherapy regimen to Lanreotide 7 months prior to her presentation. She was given everolimus as adjunct therapy to Lanreotide 3 months prior to presentation.

In the emergency department, the patient was hypertensive at 244/108 mmHg. She was given 0.2mg of clonidine which corrected her blood pressure to the 180s/80s mmHg. On physical exam, there was significant pitting edema of the bilateral lower extremities. Pertinent labs on admission were creatinine of 1.8 with normal baseline of 0.9-1.1, albumin of 2.7, with all other labs being within normal limits. Abdominal ultrasound showed no evidence of hepatic or portal vein thrombosis. Urinalysis was notable for 3+ protein and protein/creatinine ratio was 5.71. Transthoracic echocardiogram (TTE) showed evidence of severe concentric hypertrophy and estimated EF >75 %.

Her nephrotic syndrome was confirmed by a urine protein/creatinine ratio of 5.71. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) did not show any evidence of monoclonal protein, ruling out any monoclonal gammopathy (including amyloidosis) as the etiology of her proteinuria. Of note, her hemoglobin A1c was 8.9. She was initially treated with aggressive diuresis, which partially helped her edema. After discontinuation of her everolimus, her symptoms and lab values improved. The lower extremity edema markedly decreased and her creatinine improved to 1.5 from 1.8. There was a rise in her creatinine later in the hospital course, which is thought to be secondary to better blood pressure management, causing a relative pre-renal acute kidney injury.

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DISCUSSION

The use of mTOR inhibitors as chemotherapeutic agents for certain neoplasms is a relatively novel expansion on the utility of these medications. In patients who use mTOR inhibitors for their immunosuppressive properties, proteinuria has been a well-documented adverse event (2, 4-5). However, patients who use these agents for their antineoplastic properties have yet to be studied to the same degree for adverse events.

The primary mechanism for this proposed difference in the incidence of adverse events in the two populations centers around the underlying degree of kidney disease in each group. In patients who use mTOR inhibitors for immunosuppression status-post kidney transplantation, there is likely a significant degree of underlying kidney disease that recurs (6). Whereas patients who use these medications for other purposes may or may not have varying degrees of underlying kidney disease that would predispose them to developing proteinuria as a result of mTOR inhibitors. The mechanism of this medication-induced proteinuria is likely the same in both populations: VEGF pathway inhibition promotes podocyte injury, allowing the glomerular basement membrane's integrity to be compromised and significant proteinuria to occur.

When the patient started taking everolimus, the nephrotoxic effects of this medication compounded with the likely undiagnosed diabetic nephropathy to cause a significant proteinuria. This then manifested as new-onset anasarca on her CT scan and physical exam. Because of this patient's susceptibility to proteinuria from her use of mTOR inhibitors, we postulate that regular monitoring of the patient's kidney function during treatment could have prevented this adverse event from occurring.

CONCLUSION

Proteinuria is a well-documented adverse event of mTOR inhibitors in post-transplant patients. In patients who use these medications for other purposes, who have variable contributions of underlying kidney disease, proteinuria is not well-studied as a side effect of these medications. This case provides evidence that the latter patient population is susceptible to nephrotic-range proteinuria due to mTOR inhibitors, and should have their kidney function monitored during treatment to prevent the development of this syndrome.