

## CLINICAL VIGNETTE

# Nephrotic-Range Proteinuria in a Patient with Glioblastoma Multiforme

Michael Shye, M.D. and Ramya Malchira, M.D.

### Case Presentation

A 63-year old male was referred to nephrology for proteinuria. Two years previous, he had resection of a left frontal lobe glioblastoma multiforme, which recurred after one year. He also had hypertension diagnosed at that time. The patient complained of peri-orbital swelling in the morning and bilateral lower extremity swelling for the past 3 months. He denied foamy urine or dyspnea. He stated that his blood pressure was becoming more difficult to control.

Current medications included bevacizumab 700mg IV q2week for the past 2 years, amlodipine 10mg daily, lisinopril 20mg daily, atorvastatin 10mg po daily, cholecalciferol 1000U daily, fluvoxamine 150mg daily, levetiracetam 1000mg BID, and clonazepam 0.5mg TID.

Vital signs showed: Temp 36.7°C, BP 170/105, HR 60, RR 16. Physical examination was significant for 3+ bilateral lower extremity edema. There was no elevated JVP or peri-orbital edema. Lungs were clear to auscultation bilaterally.

Laboratory results were notable for a serum creatinine 1.0 mg/dL and albumin 3.8 g/dL. Urinalysis did not have blood, RBCs, WBCs, leukocyte esterase, or nitrite and was significant for protein 2-3+. Urine protein/creatinine ratio was 0.1 until 2 months prior when it rose to 0.5, then 1.1 one month ago, and 5.5 at the time of presentation. Twenty-four-hour urine collection showed a creatinine of 833mg and total protein of 3.5g. Lower extremity venous Doppler was negative for deep venous thrombosis.

Due to uncontrolled hypertension, lisinopril was uptitrated to 40mg daily and amlodipine was switched to nifedipine XL 30mg daily. Upon discontinuation of bevacizumab, urine protein/creatinine ratio steadily decreased and returned to normal range over the next 4 months. The blood pressure became easier to control. Nifedipine XL was stopped and lisinopril was continued.

### Discussion

Our patient with glioblastoma multiforme treated with bevacizumab was found to have nephrotic-range proteinuria that improved with discontinuation of the medication.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that selectively binds and inhibits the binding of human vascular endothelial growth factor (VEGF) to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralization of the activity of VEGF results in reduction of

tumor vascularization, leading to reduction of tumor growth. Bevacizumab is particularly effective in highly vascular neoplasms including glioblastoma multiforme in which high levels of VEGF are expressed. The medication was first approved by the Food and Drug Administration for metastatic colorectal cancer in 2004. It also received accelerated FDA approval in 2009 for recurrent adult glioblastoma.<sup>1</sup>

Even though the inhibition of VEGF has a desirable effect on tumor cells, it is important to monitor for proteinuria. Studies have shown that anti-VEGF antibodies can cause rapid glomerular endothelial cell detachment and hypertrophy, associated with a downregulation of nephrin, an important protein in the maintenance of the glomerular slit diaphragm.<sup>2</sup> The proteinuria can range from minimal to nephrotic-range and may result in nephrotic syndrome. Proteinuria is frequently accompanied by hypertension and is usually asymptomatic, detected only through urine testing.

In a cohort of malignant glioma patients, bevacizumab-induced proteinuria occurred in 25% of patients.<sup>3</sup> The likelihood and severity of proteinuria significantly increased with the duration of bevacizumab therapy.<sup>3</sup> In patients who developed proteinuria, the median duration of bevacizumab therapy was 20.4 months.<sup>3</sup> Acute kidney injury was rare (3.8%) and independent of proteinuria.<sup>3</sup> The presence of chronic kidney disease, however, did increase the risk of developing proteinuria with a hazard ratio of 2.9 ( $p = 0.01$ ).<sup>3</sup>

In clinical trials, nephrotic syndrome occurred in <1% of patients, though in some instances with fatal outcomes. Kidney biopsies of six patients with proteinuria showed thrombotic microangiopathy.<sup>4</sup> Collapsing glomerulopathy and cryoglobulinemic and immune complex glomerulonephritis have also been reported

The incidence of high-grade (grade 3 or 4; defined as 3+ on dipstick, >3.5 g of protein/24 hours, or the nephrotic syndrome) proteinuria with bevacizumab was 2.2%.<sup>5</sup> The use of bevacizumab combined with chemotherapy compared with chemotherapy alone significantly increased the risk for high-grade proteinuria (relative risk 4.79) and nephrotic syndrome (relative risk 7.78).<sup>5</sup> Higher dosages of bevacizumab were associated with an increased risk for proteinuria.<sup>5</sup>

Despite the lack of evidence-based guidelines, the United States prescribing information for bevacizumab recommends intermittent monitoring for the development of proteinuria by dipstick urine analysis. Patients with a 2+ or greater dipstick

readings should undergo a 24-hour urine collection. Bevacizumab should be suspended for proteinuria >2 grams/24 hours and resumed when proteinuria is <2g/24 hours. The medication should be permanently discontinued if nephrotic syndrome develops. Discontinuation of bevacizumab leads to a reduction in proteinuria, but persistence can be common. In these cases, angiotensin converting enzyme inhibitor or angiotensin receptor blocker are recommended although there are no controlled studies evaluating for benefit.

### **Conclusion**

Our patient with a history of glioblastoma multiforme developed nephrotic-range proteinuria after receiving bevacizumab for 18 months. This is consistent with the median treatment duration to develop proteinuria described in the literature.<sup>3</sup> The emergence of proteinuria can be significant and can abruptly rise to nephrotic range. Early detection of proteinuria and discontinuation of bevacizumab are important to avoid adverse outcomes including nephrotic syndrome, acute kidney injury, and death.

### **REFERENCES**

1. **Cohen MH, Shen YL, Keegan P, Pazdur R.** FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist*. 2009 Nov;14(11):1131-8. doi: 10.1634/theoncologist.2009-0121. PubMed PMID: 19897538.
2. **Sugimoto H, Hamano Y, Charytan D, Cosgrove D, Kieran M, Sudhakar A, Kalluri R.** Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. *J Biol Chem*. 2003 Apr 11;278(15):12605-8. PubMed PMID: 12538598.
3. **Odia Y, Shih JH, Kreisl TN, Fine HA.** Bevacizumab-related toxicities in the National Cancer Institute malignant glioma trial cohort. *J Neurooncol*. 2014 Nov;120(2):431-40. doi: 10.1007/s11060-014-1571-6. PubMed PMID: 25098701.
4. **Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, Richardson C, Kopp JB, Kabir MG, Backx PH, Gerber HP, Ferrara N, Barisoni L, Alpers CE, Quaggin SE.** VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med*. 2008 Mar 13;358(11):1129-36. doi: 10.1056/NEJMoa0707330. PubMed PMID: 18337603; PubMed Central PMCID: PMC3030578.
5. **Wu S, Kim C, Baer L, Zhu X.** Bevacizumab increases risk for severe proteinuria in cancer patients. *J Am Soc Nephrol*. 2010 Aug;21(8):1381-9. doi:10.1681/ASN.2010020167. Review. PubMed PMID: 20538785; PubMed Central PMCID: PMC2938590.