EJCRIM
European Journal
of Case Reports
in Internal Medicine

WHEN IS A KIDNEY BIOPSY INDICATED DURING THE TREATMENT OF BRAIN CANCER?

Catarina Oliveira-Silva[1], Johanna Viana[1], Claudia Coelho[1], Roberto Silva[2,3], Luís Falcão[1], Joana Rocha[1], Bárbara Ribeiro[1]

[1] Nephrology Department, Unidade Local de Saúde de Braga, Braga, Portugal
[2] Pathology Department, Unidade Local de Saúde de São João, Porto, Portugal
[3] Pathology Department, Unilabs, Portugal

Corresponding author's e-mail: catarina.ors@gmail.com

Received: 30/05/2025
Accepted: 14/07/2025
Published: 19/08/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: : Oliveira-Silva C, Viana J, Coelho C, Silva R, Falcão L, Rocha J, Ribeiro B. When is a kidney biopsy indicated during the treatment of brain cancer? *EJCRIM* 2025;**12**:doi:10.12890/2025_005565

ABSTRACT

Introduction: Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and is widely used in oncology for its anti-angiogenic properties. However, VEGF inhibition may result in significant nephrotoxicity, including thrombotic microangiopathy (TMA). While systemic TMA is well-described, isolated renal-limited TMA remains under recognised.

Case description: We present a 46-year-old woman with WHO grade IV IDH-wildtype EGFR-amplified gliosarcoma. She received second-line treatment with bevacizumab and, after 12 months of therapy, developed progressive hypertension and nephrotic-range proteinuria up to 6.2 g/day, with normal renal function and without anaemia or thrombocytopenia. A kidney biopsy revealed glomerular microangiopathy, and a diagnosis of bevacizumab-associated renal-limited TMA was established. Given the stability of the intracranial disease, the drug was discontinued with complete resolution of proteinuria after seven months.

Conclusion: Anti-VEGF therapy causes renal TMA and may present with nephrotic-range proteinuria associated with a pattern of glomerular microangiopathy. Recognising anti-VEGF-associated nephrotoxicity is essential in the differential diagnosis of proteinuria in cancer patients, and kidney biopsy is fundamental for guiding clinical decisions. Drug cessation led to the complete resolution of proteinuria.

KEYWORDS

Bevacizumab, anti-VEGF, thrombotic microangiopathy, glomerular microangiopathy, gliosarcoma

LEARNING POINTS

- Bevacizumab can cause renal-limited thrombotic microangiopathy and may present with nephrotic-range proteinuria, without renal dysfunction.
- Kidney biopsy is essential to distinguish drug-induced thrombotic microangiopathy from malignancy-associated nephropathies in cancer patients.
- Early recognition and drug discontinuation can lead to complete proteinuria resolution.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION/BACKGROUND

Bevacizumab is a recombinant monoclonal antibody that inhibits the activity of vascular endothelial growth factor (VEGF), targeting neoangiogenesis and the development and progression of malignant cancers. Despite its efficacy, vascular endothelial growth factor (VEGF) inhibition is associated with significant nephrotoxicity[1]. Proteinuria up to the nephrotic range and hypertension are the most common presentations, and glomerular endothelial injury and thrombotic microangiopathy (TMA) represent key histological lesions. In the kidney, VEGF is produced in the podocytes and renal tubular epithelial cells. VEGF signalling is crucial for the survival of endothelial cells, the maintenance of a fenestrated endothelium, and regulation of vascular permeability and local complement activity, such as factor H[1-3]. Hence, VEGF inhibition disrupts the podocyte-endothelial cell signalisation and inhibits alternative pathway complement regulators, leading to endothelial damage and TMA. Bevacizumab-induced TMA is an indication for drug discontinuation, and most cases improve upon its cessation.

In cancer patients, proteinuria, hypertension and kidney failure may arise secondary to the malignancy or anticancer therapies and exhibit different forms of renal injury, such as membranous nephropathy, minimal change disease, immunoglobulin-mediated glomerulonephritis and tubulointerstitial nephritis. In many cases, only a renal biopsy can uncover the underlying mechanism of injury and provide prognostic information essential for guiding treatment decisions. Here, we report a case of bevacizumab-associated TMA presenting as nephrotic proteinuria in a patient with stage IV gliosarcoma.

CASE DESCRIPTION

We describe a 46-year-old woman with a history of World Health Organization stage IV, isocitrate dehydrogenase (IDH)-wildtype gliosarcoma with epidermal growth factor receptor (EGFR) amplification diagnosed at the age of 44. Upon diagnosis, she underwent lesion resection, followed by radiotherapy and chemotherapy with temozolomide according to the Stupp protocol. Nine months after surgery, she developed thrombocytopenia of 111 $\times 10^3$/µl (range 150–400 $\times 10^3$/µl), for which she switched to second-line bevacizumab and lomustine, and later to monotherapy bevacizumab. Twelve months after initiating anti-VEGF therapy, the patient presented with hypertension and progressive proteinuria up to 6.2 g/day and was referred to a Nephrology consultation for further evaluation. She had a serum creatinine of 0.9 mg/dl (range 0.7–1.2 mg/dl), haemoglobin of 15.5 g/dl (range 11.9–15.6 g/dl), platelets of 149 $\times 10^3$/µl (range 150–400 $\times 10^3$/µl), serum albumin of 4.4 g/dl (range 3.4–5.0 g/dl) and an unremarkable urinary sediment. A kidney ultrasound revealed two kidneys of normal size, shape and echotexture, with preserved corticomedullary differentiation and no evidence of obstruction. Additional studies included antinuclear antibodies, anti-double-stranded DNA antibodies, antiphospholipid syndrome antibodies, cryoglobulins, C3 and C4 levels, serum protein electrophoresis with immunofixation, and serologies for hepatitis B, hepatitis C and human immunodeficiency virus, all of which were within normal limits. Based on the presentation of nephrotic-range proteinuria and hypertension, in the absence of renal dysfunction, membranous nephropathy secondary to malignancy or a renal-limited TMA potentially related to malignancy or anti-VEGF therapy were our main diagnostic hypotheses. A kidney biopsy was performed and revealed 29 glomeruli on optic microscopy; 6 were globally sclerotic, 4 had segmental sclerosis and the remaining 19 revealed capillary loops with double contours and mesangiolysis, sometimes with aneurysmatic aspects and occasional thrombi, without crescents or fibrinoid necrosis *(Fig. 1 and 2)*. There was mild interstitial fibrosis and tubular atrophy, no inflammatory interstitial infiltrate, the arterioles were unremarkable, and the arteries showed moderate atherosclerosis. The immunofluorescence study revealed a segmental membrane $IgG^-/IgA^-/IgM^+/C1q^+/C3c^+/lambda^+/$ kappa pattern. Thus, a diagnosis of bevacizumab-associated renal-limited TMA was established.

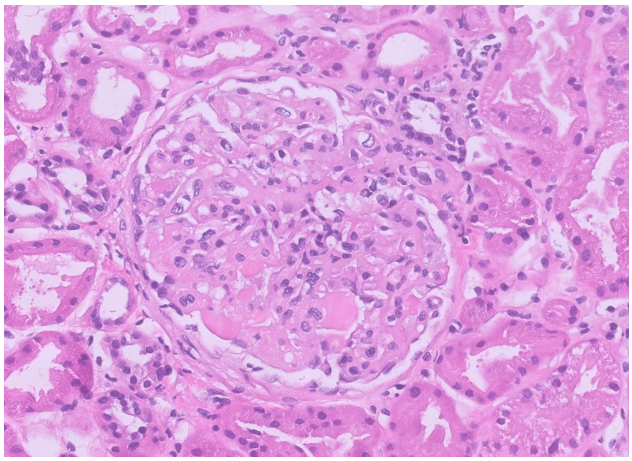


Figure 1. Optic microscopy, haematoxylin and eosin, 200×. Lobulated glomerulus with capillary loops showing double contours and eosinophilic thrombi within the glomerular capillary lumens.

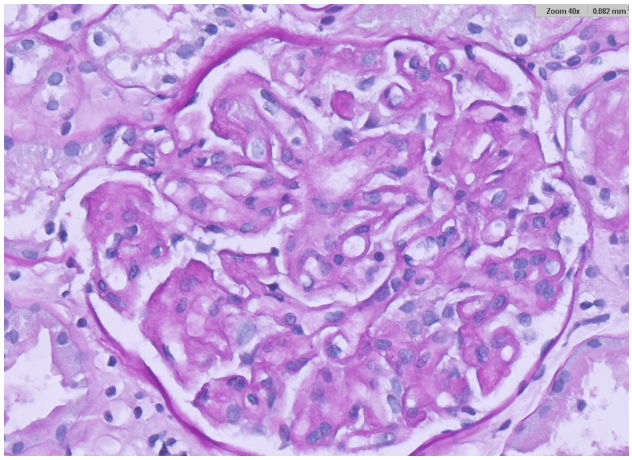


Figure 2. Optic microscopy, periodic acid-Schiff (PAS) stain, 400×. Glomerulus with capillary loops exhibiting double contours, reduced capillary lumen and mesangiolysis.

A cranio-encephalic magnetic resonance (CE-MR) image showed imagological stability and excluded de novo pathologic lesions. After a multidisciplinary discussion, bevacizumab was suspended. The patient started ramipril 10 mg and amlodipine 5 mg once daily. Upon drug cessation and renin-angiotensin system inhibitor introduction, proteinuria improved to 1.3 g/day after two months. A control CE-MR four months after drug suspension revealed tumour progression, so the patient underwent intensity-modulated radiotherapy. She completed ten radiotherapy sessions (a total dose of 35 Gy, 3.5 Gy per day) without adverse events and demonstrated a favourable clinical response. Seven months after the drug was suspended, the patient has a minimal proteinuria of 0.4 g/day and arterial hypertension controlled with ramipril 5 mg once daily.

DISCUSSION

We present a case of bevacizumab-associated renal TMA presenting with hypertension and nephrotic-range proteinuria in a patient with stage IV gliosarcoma. Bevacizumab has been previously established as a cause of TMA, presenting as a systemic disease[2] or limited to the kidney[3,4]. Clinical presentation with nephrotic-range proteinuria or nephrotic syndrome is rare and occurs in approximately 2% of the cases[3]. Person et al.[3] and Izzedine et al.[5] described a pattern of bevacizumab-associated glomerular microangiopathy that correlated with a predominant proteinuric phenotype of renal involvement. Our case shares morphological characteristics with these descriptions and reinforces the hypothesis of a specific intraglomerular morphological pattern of microangiopathy related to VEGF inhibition.

In our patient, the cause of proteinuria and hypertension could be secondary to the gliosarcoma, bevacizumab, lomustine or complement deregulation and present patterns of injury ranging from vascular and glomerular to tubulointerstitial damage. Although renal biopsy is invasive and may carry an increased risk of bleeding or infectious complications in cancer patients, our patient did not have thrombocytopenia or coagulopathy, and the risk was deemed low and outweighed by its diagnostic yield and potential to guide therapeutic decision-making[6]. The resultant TMA pattern presented a temporal and dose-dependent effect[2,3] with bevacizumab, supporting its causative effect.

In most cases, the suggested treatment for drug-induced TMA is drug cessation[5]. The role of therapeutic plasma exchange and complement-targeted therapies in secondary TMA has not been established[7]. However, in this case, the decision to suspend treatment was particularly challenging, given the poor prognosis and low long-term survival[8] associated with stage IV gliosarcoma and the apparent efficacy of bevacizumab in disease stabilisation. On the one hand, drug cessation could lead to gliosarcoma progression. On the other hand, there was a risk of kidney disease progression and systemic TMA that could affect the eligibility for further systemic therapy[5]. Lesion stability and the presence of alternative therapeutic strategies with potential benefit, including EGFR inhibitors or radiotherapy, were factors that favoured drug suspension in our patient. Upon anti-VEGF suspension, hypertension and proteinuria improved and the patient underwent radiotherapy with good tolerance and clinical response. In the absence of nephrotic syndrome and systemic TMA, other approaches described in the literature could include regimens of reduced bevacizumab frequency and renin-angiotensin system inhibitors until proteinuria improvement[9,10]. However, reports of drug continuation or reintroduction resulted in a more severe recurrence of TMA, sometimes with the need for plasma exchange[5].

Despite various clinical cases and case series descriptions of bevacizumab-associated TMA, there are few descriptions in patients with central nervous system tumours to guide decision-making. To the best of our knowledge, this is the first case of bevacizumab-associated renal TMA in a patient with a gliosarcoma.

To conclude, our case underscores the importance of individualised decision-making regarding kidney biopsy in patients with brain cancer. Even in the context of known drug-related nephrotoxicity, histological confirmation guided decisions regarding therapy suspension and will continue to underlie future decisions concerning management. While current recommendations support culprit drug withdrawal in drug-induced TMA, the optimal approach in patients with limited renal involvement and poor oncological prognosis remains elusive, requiring an individualised and multidisciplinary approach.

REFERENCES

1. Estrada CC, Maldonado A, Mallipattu SK. Therapeutic inhibition of VEGF signaling and associated nephrotoxicities. *J Am Soc Nephrol* 2019;**30**:187–200. doi: 10.1681/ASN.2018080853
2. Padilha WSC, Cesar BN, Pacheco ST, De Sousa AA, Ledesma FL, Malheiros DMAC, et al. Bevacizumab-associated thrombotic microangiopathy treated with eculizumab: a case report. *Am J Case Rep* 2023;**24**:e940906. doi: 10.12659/AJCR.940906
3. Person F, Rinschen MM, Brix SR, Wulf S, Noriega MLM, Fehrle W, et al. Bevacizumab-associated glomerular microangiopathy. *Mod Pathol* 2019;**32**:684–700. doi: 10.1038/s41379-018-0186-4
4. Shimamura Y, Maeda T, Takizawa H. Bevacizumab-induced thrombotic microangiopathy and nephrotic syndrome. *Clin Exp Nephrol* 2019;**23**:142–143. doi: 10.1007/s10157-018-1596-9
5. Izzedine H, Escudier B, Lhomme C, Pautier P, Rouvier P, Gueutin V, et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. *Medicine (Baltimore)* 2014;**93**:333–339. doi: 10.1097/MD.0000000000000207. Erratum in: *Medicine (Baltimore)* 2014;**93**:414.
6. Hull KL, Adenwalla SF, Topham P, Graham-Brown MP. Indications and considerations for kidney biopsy: an overview of clinical considerations for the non-specialist. *Clin Med (Lond)* 2022;**22**:34–40. doi: 10.7861/clinmed.2021-0472
7. Kavanagh D, Ardissino G, Brocklebank V, Bouwmeester RN, Bagga A, Ter Heine R, et al. Forum Participants. Outcomes from the International Society of Nephrology Hemolytic Uremic Syndromes International Forum. *Kidney Int* 2024;**106**:1038–1050. doi: 10.1016/j.kint.2024.09.012
8. Kozak KR, Mahadevan A, Moody JS. Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. *Neuro Oncol* 2009;**11**:183–191. doi: 10.1215/15228517-2008-076
9. Bollée G, Patey N, Cazajous G, Robert C, Goujon JM, Fakhouri F, et al. Thrombotic microangiopathy secondary to VEGF pathway inhibition by sunitinib. *Nephrol Dial Transplant* 2009;**24**:682–685. doi: 10.1093/ndt/gfn657
10. Robinson CH, Hart-Matyas M, Morgenstern DA, Noone D, Campisi P. Renal implications of long-term systemic bevacizumab for recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol* 2024;**133**:119–123. doi: 10.1177/00034894231184942