EXCEPTIONAL CASE

Minimal change disease onset observed after bevacizumab administration

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Abstract

This is a report of a patient with minimal change disease (MCD) onset after bevacizumab administration. A 72-year-old man with inoperable Grade 3 astrocytoma was treated with a combination of temozolomide and the vascular endothelial growth factor monoclonal antibody bevacizumab. After two biweekly treatments, he developed nephrotic syndrome. Despite cessation of bevacizumab, his renal function deteriorated and a renal biopsy disclosed MCD. Thereafter, he was started on high-dose oral prednisone and renal function immediately improved. Within weeks, the nephrotic syndrome resolved. Although rare, biologic agents can cause various glomerulopathies that can have important therapeutic implications. MCD should be considered in patients who develop nephrotic syndrome while exposed to antiangiogenic agents.

Key words: angiogenesis, glomerulonephritis, nephrotic syndrome, nephrotoxicity, proteinuria

Introduction

Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) is a humanized monoclonal antibody to the vascular endothelial growth factor (VEGF). It is currently indicated for non-small cell lung cancer, renal cell carcinoma, breast cancer and ovarian cancer [1]. It was recently approved for recurrent high-grade gliomas, particularly glioblastoma multiforme [1–5]. The safety profile is well established and there have been several studies confirming its efficacy as well as tolerability in elderly patients with advanced malignancies [7].

Bevacizumab inhibits angiogenesis by direct binding of VEGF and disruption of VEGF receptor signaling. VEGF receptors are expressed predominantly on vascular endothelial cells. Other sites with increased expression are glomerular podocytes where VEGF receptors cover the glomerular basement membrane [8, 9]. Pathological VEGF signaling has been implicated in proteinuria associated with pre-eclampsia, diabetic nephropathy and treatment with mammalian target of rapamycin (m-TOR) inhibitors such as sirolimus and everolimus [10, 11].

Proteinuria, hypertension and thrombotic microangiopathy (TMA) have been increasingly reported as adverse effects from the administration of bevacizumab and other antiangiogenesis inhibitors [5, 12]. Acute kidney injury (AKI) due to TMA from this class of agents has been well described [13]. This lesion is associated with severe renal failure and is usually treated by withdrawal of the VEGF inhibitor rather than plasmapheresis [14]. The transient nature of proteinuria and self-limiting nature of avastin-induced disease practically means that proteinuria resolves...
only by withholding the offending agent. Biopsies are often only obtained for rare cases of glomerular disease resulting in ongoing proteinuria. New expert opinions are being formed as to how these drugs affect renal molecular biology and physiology. To our knowledge, this is the first reported case of renal failure and de novo MCD associated temporally with systemic bevacizumab use. Previous cases noted above (Pérez-Valdivia et al. [16] and Soto et al. [17]) showed a relapse of MCD after intravitreal bevacizumab administration and Haruhara et al. [18] showed an atypical light microscopic pattern of double contouring without evidence of immune complex deposition. Renal failure, hypertension, and transient proteinuria occur in up to 18% of patients receiving bevacizumab, although sustained proteinuria and renal failure are both rare features of bevacizumab nephrotoxicity [19]. It is important to recognize MCD as an adverse effect of therapy with bevacizumab since this patient did not respond to cessation of therapy alone and required high-dose steroid therapy for restoration of renal functions.

There have been other glomerulopathies associated with treatments of cancer with anti-VEGF and anti-epidermal growth factor (EGF) biologic agents. Bevacizumab has been associated with cryoglobulinemic glomerulonephritis, collapsing glomerulonephritis, membranoproliferative glomerulonephritis (MPGN) and the more commonly reported lesions of TMA [19]. Trastuzumab, which is a related anti-herceptin growth factor receptor monoclonal antibody, has been linked to one case of MCD [19]. Sorafenib, axitinib, gefitinib, imatinib, sunitinib and small molecule tyrosine kinase inhibitors, which target signaling proteins downstream of the VEGF receptor, have been associated with focal segmental glomerulosclerosis (FSGS), ischemic glomerulonephritis, ATN and AIN (see Table 1) [15–30]. Sorafenib has recently been linked with MCD as well [31]. In the case of Haruhara et al. [19] mentioned previously, a complex glomerulopathy was noted that responded to renin–angiotensin systemic blockade with losartan.

There are many reported glomerulopathies that have been reported chronologically and were first compiled by Izzedine et al. [19] in an article published in the American Journal of Kidney Disease [15–30]. A table was compiled to show all the reported cases of glomerulopathies noted in cases of anti-EGF and anti-VEGF therapies and expanded to include the new cases mentioned above [16–18]. The table’s focus is on expanding the new case reports of glomerular disease specific to bevacizumab, while other references to diseases due to anti-EGF therapies and tyrosine kinase inhibitors are adapted from Izzedine et al. [19] (see Table 1).

It is striking that while these angiogenesis inhibitors act on the same pathway, they can cause renal failure by various pathophysiological mechanisms. These adverse events are rare, but compounded together, they form a growing understanding of how these drugs affect renal molecular biology and physiology.

## Case report

A 72-year-old Caucasian man diagnosed with a World Health Organization (WHO) Grade 3 anaplastic astrocytoma presented to Cedars Sinai Medical Center with AKI and 3+ proteinuria on urinalysis 4 weeks after the initiation of bevacizumab. He was initially diagnosed with glioblastoma multiforme in January 2012, after presenting with a generalized tonic–clonic seizure. He received radiotherapy and chemotherapy with dose-dense temozolomide in April 2012, with a good response.

On 7 August 2012, the patient began a combination of temozolomide and bevacizumab, with scheduled bevacizumab every 2 weeks. Prior to initiating therapy he was noted to have type 2 diabetes mellitus without evidence of either diabetic retinopathy or high-grade proteinuria (he had microalbuminuria).

Four weeks later, before his third treatment, he was found to have 3+ proteinuria on urinalysis and a mildly elevated serum creatinine of 88.4 μmol/L [1 mg/dL; baseline 70.72 μmol/L (0.8 mg/dL)]. Bevacizumab was held. The urine protein-to-creatinine ratio was markedly elevated (17.89 g of protein of creatinine). Two weeks later, he returned to his neuro-oncologist with 4+ proteinuria, hypertension, anasarca, severe hypoalbuminemia with serum albumin 231.84 μmol/L (1.4 mg/dL). Repeat urine protein-to-creatinine ratio was 19.51 g/g of creatinine (Figure 1).

He was admitted for further renal evaluation. During that admission he developed progressive nonoliguric AKI with a peak creatinine of 424.32 μmol/L (4.8 mg/dL). Obstructive uropathy, acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) were considered unlikely causes of AKI. Glomerulonephritis, acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) were considered unlikely causes of AKI. Glomerulonephritis, acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) were considered unlikely causes of AKI.

Electron microscopy disclosed complete effacement of podocyte foot processes, lack of electron dense deposits and no evidence of luminal or mural fibrin in the capillaries (Figure 2).

AKI and proteinuria persisted for >2 weeks after the withdrawal of bevacizumab. Deterioration of renal function resulted in worsening volume overload and uremia. Renal replacement therapy was considered. After the biopsy results, 1 mg/kg oral prednisone was started to treat the MCD.

Within 4 days after starting high-dose steroids, the patient’s serum creatinine improved and renal replacement therapy was not needed. Proteinuria improved more gradually and decreased from 19 to 11 g in <1 week. It decreased further to <1 g after 6 weeks of steroid and angiotensin-converting enzyme inhibitor therapy, and subsequently resolved after nearly 2 months of therapy for MCD (Figure 1).

## Discussion

To our knowledge, this is the first reported case of renal failure and de novo MCD associated temporally with systemic bevacizumab use. Previous cases noted above (Pérez-Valdivia et al. [16] and Soto et al. [17]) showed a relapse of MCD after intravitreal bevacizumab administration and Haruhara et al. [18] showed an atypical light microscopic pattern of double contouring without evidence of immune complex deposition. Renal failure, hypertension, and transient proteinuria occur in up to 18% of patients receiving bevacizumab, although sustained proteinuria and renal failure are both rare features of bevacizumab nephrotoxicity [19]. It is important to recognize MCD as an adverse effect of therapy with bevacizumab since this patient did not respond to cessation of therapy alone and required high-dose steroid therapy for restoration of renal functions.

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Fig. 1. Trends of serum creatinine, urinalysis proteinuria/albuminuria and urine protein-to-creatinine ratio. (A) Trend of serum creatinine versus time (serum creatinine in mg/dL). (B) Trend of urinalysis proteinuria versus time (1+ to 4+ proteinuria). (C) Trend of urine protein-to-creatinine ratio (g protein/g creatinine). Arrows: temporal representation of two avastin administrations timed 7 and 21 August 2012.
It is important to record the clinical course we observed in this patient, as this is the first de novo case of MCD linked to systemic bevacizumab. Usually, the proteinuria linked to this agent is transient and may resolve with withdrawal of the agent. The underlying pathologic diagnosis may be important in cases of persistent proteinuria.

Although rare, drug-induced glomerulopathies can be progressive and lead to end-stage renal disease unless diagnosed quickly and appropriately treated. In this patient, proteinuria and renal failure progressed despite stopping the offending agent and only improved after initiation of high-dose steroids. This suggests a role for high-dose steroids in patients with...
MCD associated with bevacizumab use. This diagnosis and associated treatment should be considered in patients with bevacizumab-associated nephrotic syndrome. Other case reports described above mention differing pathological patterns found on biopsy after development of glomerular proteinuria and AKI in conjunction with bevacizumab and other anti-VEGF and anti-EGF therapies [16–19]. In one of these cases, angiotensin receptor blockade resulted in attenuation of proteinuria due to bevacizumab therapy. The lesion in this case was associated with a double contour nonimmune glomerulopathy pattern on renal biopsy. Thus, it is important to distinguish that steroid therapy has only been shown to be efficacious in the literature with MCD pattern glomerular injury after anti-VEGF therapy with systemic or intravitreal bevacizumab [16–18].

Authors’ contribution

E.L. contributed to research on the glomerular disorders previously reported with bevacizumab use. J.W. contributed to the section on the pathophysiology of VEGF blockade. S.B. edited the document and contributed to the discussion section indispensible. A.H.C. is the pathologist who reviewed this case section on the pathophysiology of VEGF blockade. S.B. edited and contributed to the slide captions and the case report segment featuring the tissue pathology interpretation, as well as extensively editing the text.

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The results presented in this article have not been published previously in whole or part, except in abstract form.

Conflict of interest statement

None declared.

Table 1. Cases reports of glomerulopathies and kidney injury due to VEGF and EGF receptor inhibition

| Drug                        | Pathology                                      | Citation                                      |
|-----------------------------|------------------------------------------------|-----------------------------------------------|
| Anti-VEGF monoclonal antibodies (IV, intravitreal) adapted from Izzedine et al. [19] and updated |                                                |                                               |
| Bevacizumab-IV              | MCD                                            | Our case (Hanna et al.) reported 2015         |
| Bevacizumab-IV              | Glomerulopathy with double contouring, nonimmune | Haruhara et al. [18]                          |
| Bevacizumab-intravitreal    | MCD                                            | Soto et al. [17]                              |
| Bevacizumab-intravitreal    | MCD                                            | Perez-Valdivia et al. [16]                    |
| Bevacizumab-IV              | Collapsing glomerulonephritis                  | Johnson et al. [24] (compiled in Izzedine et al.) |
| Bevacizumab-IV              | MPGN                                           | Miller et al. [27] (compiled in Izzedine et al.) |
| Bevacizumab-IV              | Thrombotic microangiopathy                     | Many reviews including Eremina et al. [21]    |
| VEGF-trap/Aflibercept-route | Crescent glomerulonephritis                    | From unpublished data per Izzedine et al.     |
| unknown                     |                                                |                                               |
| Anti-EGF monoclonal antibodies adapted from Izzedine et al. [19] |                                                |                                               |
| Trastuzumab-IV              | MCD                                            | Vidal [29] (compiled in Izzedine et al.)      |
| Trastuzumab-IV              | Focal and segmental glomerulosclerosis         | Vidal [29] (compiled in Izzedine et al.)      |
| Trastuzumab-IV              | Fibrillar glomerulonephritis                   | Vidal [29] (compiled in Izzedine et al.)      |
| Tyrosine kinase inhibitors (PO) downstream from VEGF and EGF signaling pathways adapted from Izzedine et al. [19] |                                                |                                               |
| Axitinib-PO                 | Collapsing glomerulonephritis                  | From unpublished data per Izzedine et al.     |
| Gefitinib-PO                | Minimal change nephropathy                     | Kumasuka et al. [26] (compiled in Izzedine et al.) |
| Gefitinib-PO                | ATN                                            | Wan and Yao [30] (compiled in Izzedine et al.) |
| Imatinib-PO                 | Thrombotic microangiopathy                     | Al Aly et al. [20] (compiled in Izzedine et al.) |
| Imatinib-PO                 | ATN                                            | Pou et al. [28] (compiled in Izzedine et al.) |
| Imatinib-PO                 | ATN                                            | Kitiyakara and Atichartakarn [25] (compiled in Izzedine et al.) |
| Sorafenib-PO                | AIN                                            | From unpublished data per Izzedine et al.     |
| Sunitinib-PO                | Ischemic glomerulonephritis                    | From unpublished data per Izzedine et al.     |

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