Renal Hemosiderosis with Bevacizumab Induced Thrombotic Microangiopathy in a Patient with Hereditary Hemorrhagic Telangiectasia

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Abstract

Bevacizumab has become a frequently used therapeutic option for bleeding complications in hereditary hemorrhagic telangiectasia (HHT). Renal limited thrombotic microangiopathy is a well-documented complication of Bevacizumab therapy. We present an unusual case of Bevacizumab induced thrombotic microangiopathy complicated by glomerular predominant renal hemosiderosis in a patient with HHT-associated bleeding requiring numerous blood and iron transfusions. As most patients with HHT are likely to receive multiple transfusions with many of them also on bevacizumab as maintenance therapy, this case highlights a possible combined toxicity that may complicate the management of these patients.

Keywords
• Bevacizumab
• Hemosiderosis
• Thrombotic microangiopathy
• Hereditary hemorrhagic telangiectasia
• Renal biopsy

BACKGROUND

Hereditary hemorrhagic telangiectasia (HHT) is a disorder of unbalanced angiogenesis resulting in vascular dysplasia and clinical manifestations of mucocutaneous telangiectasias, epistaxis, gastrointestinal bleeding, and iron-deficiency anemia [1]. Vascular endothelial growth factor (VEGF) levels in tissues and blood are elevated in these patients. While more commonly used as an adjunct therapy in certain malignancies, the VEGF inhibitor Bevacizumab is as an effective treatment for intractable bleeding in patients with HHT [2,3]. Unfortunately, it is known to cause a renal limited, but usually reversible thrombotic microangiopathy (TMA) due to a direct effect of its VEGF binding activity [4,5].

Rare cases of Bevacizumab renal toxicity show continued renal functional decline despite discontinuation of therapy [6]. Understanding the etiology behind renal functional decline in these patients is important for determining appropriate interventions and avoiding future episodes.

Here we report a novel case where Bevacizumab induced TMA is complicated by glomerular predominant renal hemosiderosis resulting in progressive renal functional impairment despite Bevacizumab discontinuation.

CASE REPORT

A 73-year-old man with a history of hereditary hemorrhagic telangiectasia (HHT) presents with slowly rising serum creatinine and proteinuria following Bevacizumab therapy. The patient has a 17-year history of HHT that has been complicated by recurrent gastrointestinal (GI) bleeding and high iron and blood transfusion requirements – up to 1 to 3 units weekly – over the past 4 years.

The patient has been receiving intermittent Bevacizumab therapy for 2 years with marked symptomatic improvement in his GI bleeding resulting in reduced transfusion requirements. Approximately 6 months before his renal biopsy, the patient was found to have heavy proteinuria (>3 grams) and mildly elevated serum creatinine (1.9 mg/dL). Bevacizumab therapy was subsequently discontinued. Over the next 3 months, the proteinuria improved (urinary protein to creatinine ratio 1.2); however, his serum creatinine continued to slowly rise (2.3 mg/dL at time of biopsy). A renal biopsy was performed to investigate the cause of the patient's worsening renal function.

By light microscopy (Figure 1) there were 11 non-sclerotic glomeruli sampled. All glomeruli displayed mild to moderate segmental capillary loop double contours and occasional endocapillary hypercellularity. There was no definite mesangiolysis or active thrombosis. Mesangial regions also exhibit hemosiderin deposition, highlighted on iron stain. There were no signs of sclerosis, necrotizing lesions, fuchsinophilic deposits, or crescents. There was mild tubulointerstitial injury and scarring as well as focal mild hemosiderin deposition in tubules and interstitial spaces.

Direct immunofluorescence microscopy revealed no significant glomerular staining with any antibody. Fibrinogen staining did not reveal any vascular thrombi. Ultra structural examination was notable for abundant membrane bound electron-dense coarsely granular material present within the cytoplasm of endothelial cells, mesangial cells, podocytes in all glomeruli and rare interstitial macrophages. Capillary loops exhibited segmental widening of subendothelial spaces with interposition of electron lucent flocculent material and neomembrane formation. Other findings included patchy mild podocyte foot process effacement and mild widening of mesangial regions by matrix. There were no tubuloreticular structures or immune complex type deposits.

The biopsy was interpreted as glomerular predominant renal hemosiderosis likely complicating chronic/resolving Bevacizumab induced thrombotic microangiopathy.

**DISCUSSION**

Renal hemosiderosis is a known complication of intravascular hemolysis, specifically in the setting of mechanical heart valves, sickle cell anemia, and paroxysmal nocturnal hemoglobinuria (PNH) [7-9] as well as hereditary hemochromatosis [10]. Interestingly, to our knowledge, there are no published reports of secondary renal hemosiderosis due to long term blood and iron transfusion. Heme-containing compounds have cytotoxic effects include disruption of the cellular membranes, denaturation of DNA, and activation of cell-damaging enzymes [11]. Most accounts of hemosiderin related renal injury describe accumulation of hemosiderin within proximal tubular epithelium [8] and rarely as intra-tubular casts [7]. Reports of intra-glomerular hemosiderin deposition are rare [10,12]. Furthermore, besides this report, there are no reports to our knowledge demonstrating
mesangial and/or glomerular endothelial cell hemosiderin deposition. In the current case, it is unclear if the presence of an underlying TMA resulted in an increased susceptibility for hemosiderin deposition within the glomerulus. Or, alternatively, if the presence of hemosiderin deposition increased the severity and chronicity of the Bevacizumab associated TMA.

While Bevacizumab associated TMA has been generally characterized as reversible with withdrawal of the drug, several reports have emerged of progressive renal failure even after withdrawal of Bevacizumab [6,13]. Generally, these cases occurred in cancer patients with underlying chronic renal disease or co-administered chemotherapeutic agents. Given the frequency which HHT and cancer patients receive blood products, we speculate that glomerular hemosiderin deposition, a rare sequela, may contribute to renal failure and/or proteinuria in patients with Bevacizumab associated TMA and complicate the management of these patients.

REFERENCES


Cite this article