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Intravitreal Injection of Bevacizumab Induced TMA: A Case Report

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Abstract

The use of vascular endothelial growth factor (VEGF) inhibitors, particularly anti-VEGF agents like Bevacizumab, has become a cornerstone in the treatment of proliferative diabetic retinopathy and diabetic macular edema. While systemic renal side effects of these agents are well-documented, emerging evidence suggests that intravitreal administration may also be associated with significant renal risks. We report the case of a 32-year-old male with a 25-year history of type 1 diabetes who developed thrombotic microangiopathy (TMA) following intravitreal Bevacizumab injections. Diagnostic evaluations ruled out other causes, leading to a diagnosis of drug-induced TMA. Treatment included corticosteroids and plasma exchange, but renal function did not recover, necessitating hemodialysis. This case underscores the critical need for renal monitoring in patients receiving anti-VEGF therapy, particularly those with preexisting renal impairment, to mitigate the risk of serious renal complications.

Keywords

Vascular Endothelial Growth Factor (VEGF), Thrombotic Microangiopathy (TMA), Bevacizumab, Renal Toxicity, Intravitreal Injection

1. Introduction

The discovery of the involvement of vascular endothelial growth factor in the pathophysiology of diabetic retinopathy has led to the increasing use of anti-VEGF agents as first-line treatment for proliferative diabetic retinopathy [1] and diabetic macular edema [2]. The renal side effects of systemically administered anti-VEGF agents have been well-documented for a long time and include hypertension, the onset of proteinuria, and thrombotic microangiopathy [3] [4]. Evi-

dence of renal toxicity from intravitreal anti-VEGF agents is beginning to accumulate, and case reports indicate a risk associated with intraocular injections [5]. We report here the case of a patient who developed thrombotic microangiopathy (TMA) secondary to intravitreal injection of Bevacizumab.

2. Observation

This is a 32-year-old patient with a history of type 1 diabetes for 25 years on rapid-acting insulin. His diabetes is well controlled with glycated hemoglobin levels around 7%. Examination of target organ damage revealed diabetic nephropathy with CKD at stage G3aA2 associated with proliferative diabetic retinopathy. His baseline creatinine was 20 mg/L, corresponding to a creatinine clearance according to CKD EPI of 44 mL/min. The albuminuria/creatinuria ratio ranged between 100 and 250 mg/g. Blood pressure was controlled and ranged between 110 and 135 mmHg systolic and between 65 and 85 mmHg diastolic. His basic treatment included perindopril arginine, rosuvastatin, and esomeprazole. The patient presented with a sudden decrease in visual acuity with blurred vision. Ophthalmological examination revealed rapid worsening of his retinopathy and intravitreal hemorrhage. He received three intravitreal injections of bevacizumab (2.5 mg per month per eye) without significant improvement, leading to the discontinuation of the injections.

Six months later, the patient presented to the emergency department with severe hypertension (210/100 mmHg) and swelling of the lower limbs. He denied taking NSAIDs or nephrotoxic drugs. Physical examination revealed a conscious patient with no fever and edema of the lower limbs reaching mid-calf. The neurological examination was normal. Urinalysis revealed 3 crosses of albumin with no hematuria.

On admission, creatinine was 70 mg/L with no electrolyte disturbances and a proteinuria/creatinuria ratio of 5 g/g. Hemoglobin was 7 g/dl with schistocytes > 5%, decreased haptoglobin, LDH > 5 times normal, and thrombocytopenia at 43,000/mm^3, defining hemolytic anemia. The direct Combs test was negative. ADAMTS13 activity was normal. Immunological tests, including antinuclear antibodies, anti-DNA antibodies, and ANCA, were negative. Viral serology was also negative. Complement fraction measurements and alternative pathway testing revealed no abnormalities. Renal ultrasound was unremarkable. A renal biopsy was indicated but not performed due to persistent thrombocytopenia and the unavailability of transjugular biopsy.

Given this clinical presentation, we ruled out thrombotic thrombocytopenic purpura in the setting of normal ADAMTS13 activity. HIV-associated TMA and atypical hemolytic uremic syndrome (HUS) were also ruled out, given the negativity of the serologies and the absence of abnormalities of the alternative complement pathway. There were no arguments in favor of typical HUS. We finally made a diagnosis of TMA secondary to Bevacizumab.

The patient received three boluses of methylprednisolone. We also performed 10 plasma exchange sessions. Eculizumab was considered for our patient, but he

did not receive it due to a lack of financial resources. The course of the disease was marked by a lack of recovery of renal function, requiring the initiation of renal replacement therapy via a tunneled catheter. To date, the patient is still on hemodialysis with a persistent thrombocytopenia.

3. Discussion

Bevacizumab belongs to the anti-VEGF family. It is a humanized monoclonal antibody that neutralizes vascular endothelial growth factor, inhibiting neoangiogenesis. It is used systemically in the treatment of a variety of cancers. Its intravitreal use is indicated in several retinal vascular disorders.

The renal toxicity of Bevacizumab is responsible for a range of manifestations, including the onset or worsening of proteinuria [3] [6] or arterial hypertension [7]. Among these disorders, TMA is probably the most severe [8] [9].

The main mechanisms of this damage are an alteration in the regulation of nitric oxide production, leading to vasoconstriction with platelet aggregation and microthrombus formation [10]. VEGF is also thought to be responsible for fenestrations in the vascular endothelium [8]. Finally, podocyte-derived VGEF controls the regulation of the alternative complement pathway by stimulating the synthesis of factor H [11].

It has long been thought that the low doses of Bevacizumab used in ophthalmology and the intravitreal route of administration limited systemic passage and the risk of complications. However, Avery *et al.* [12] [13] and other authors [14] [15] have shown through pharmacokinetic studies that systemic absorption is sufficient to cause VEGF inhibition. Several authors have reported similar cases with different results on remission after discontinuation of anti-VEGF treatment (**Table 1**).

Table 1. Cases of TMA induced by intravitreal injection of Bevacizumab.

Authors	Number of cases	Histology
Hanna R. [16]	2 cases	Diabetic nephropathy and chronic TMA
Cheungpasitporn *et al.* [17]	1 case	Graft TMA
Hanna *et al.* [18]	1 case	Scleroderma renal crisis and TMA
Touzani *et al.* [19]	1 case	TMA
Yen *et al.* [20]	1 case	TMA

In our case, despite the absence of histological evidence of TMA, the combination of hematological signs, including mechanical hemolytic anemia and thrombocytopenia, as well as the absence of clear triggering factors and the timing of the onset of symptoms in relation to the injections, led us to make this diagnosis.

Treatment is not yet clearly defined. Discontinuation of the VEGF inhibitor is mandatory and, in some cases, leads to remission of symptoms. However, this measure may be insufficient, and immunosuppressive treatment may be indicated. The use of eculizumab is a promising alternative due to the dysregulation of the alternative complement pathway. Plasma exchange is also used [21], but there is a lack of data on its efficacy in drug-induced TMA. Prevention is based on identifying patients at risk of developing renal complications secondary to anti-VEGF therapy, with close monitoring of blood pressure, proteinuria, and creatinine.

4. Conclusion

VEGF inhibitors have revolutionized the management of retinal damage by improving the functional prognosis of patients with a reassuring safety profile. However, the identification of systemic effects associated with intravitreal injections should lead us to closely monitor markers of renal damage, particularly in patients with proteinuria or chronic kidney disease.

Consent

Consent was obtained from the patient and documented on the condition that no identifiable data be published. This research work does not contain human subject research material, as it is an individual anonymized case report.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

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