Acute renal failure after intravitreal antivascular endothelial growth factor therapy

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Introduction

Macular edema is one of the leading causes of visual impairment in diabetic patients. An intravitreal antivascular endothelial growth factor (anti-VEGF) agent is an effective and crucial treatment. Systemic exposure to these agents after intravitreal administration has been discussed. However, decreasing renal function has scarcely been reported.

Case Report

A 67-year-old male with diabetes, hypertension, and chronic kidney disease (CKD) suffered from persistently blurred vision. His creatinine level in serum was 5.52 mg/dL (glomerular filtration rate 11.1 mL/min/1.73m²), hemoglobin A1c was 6.0%, and blood pressure (BP) was 150/60 mmHg. Proliferative diabetic retinopathy with diabetic macular edema (DME) was diagnosed and his symptoms improved after an intravitreal injection of 1.25 mg bevacizumab. The patient complained about blurred vision again 1 year later and DME in his right eye was noted again. His creatinine level was 8.81 mg/dL and BP was 182/73 mmHg. Intravitreal injection of 0.5 mg ranibizumab was performed after discussing the systemic risk with the patient. The patient had suffered from acute nausea since the first postoperative day and went to the emergency room 4 days later. His BP was 164/72 mmHg but his creatinine level increased to 12.09 mg/dL (Figure 1). Acute on CKD was diagnosed. After emergent hemodialysis and the following regular hemodialysis, his symptoms improved and macular edema subsided for more than 6 months.

Discussion

VEGF is a vital factor which regulates glomerular vascular permeability. Renal toxicity varying from proteinuria or thrombotic microangiopathies to renal insufficiency have been reported in patients receiving systemic anti-VEGF therapy. Although the detailed mechanism causing renal damage has not been clarified yet, disruption of the...
filtration barrier and decrease in the expression of nephrin have been suggested as two possible explanations for renal toxicity after systemic anti-VEGF therapy. In addition, thrombotic microangiography, focal segmental glomerulosclerosis, and tubule-interstitial nephritis have been found in pathology of the affected kidneys.

Although the dosage of intravitreal anti-VEGF therapy is >400 times lower than that of intravenous anti-VEGF therapy, systemic exposure to these agents could be observed in <24 hours after intravitreal administration. It has been estimated that the systemic concentration after intravitreal injection of 1.25 mg bevacizumab, 0.5 mg ranibizumab, and 2 mg aflibercept was 59.8–86.5 ng/mL, 0.2–2.36 ng/mL, and 20 ng/mL, with the half-life as 20 days, 2–6 hours, and 1.5 days, respectively. The concentration of free plasma VEGF could be as low as 10 pg/mL 1 day after a single dose of intravitreal injection.

There are only three patients (1 with macular degeneration and 2 with DME) who have been reported to be suffering from acute renal injury after intravitreal anti-VEGF therapy. Kidney biopsy in the former case showed segmental duplications of glomerular basement membranes with endothelial swelling, tubular atrophy, and noninflammatory interstitial fibrosis, recanalized arteriolar thrombi, and fibrinogen deposits in the hilus of glomerulus. The other two diabetic patients had preexisting Stage 4 CKD and required long-term hemodialysis eventually. In the 2-year results of a randomized trial conducted by the Diabetic Retinopathy Clinical Research network, renal and urinary disorders events were also been reported in 7–28% of patients.

Theoretically, bevacizumab has higher systemic concentration and longer half-life than ranibizumab. However, the patient’s creatinine increased slowly after injection of bevacizumab but significantly after ranibizumab. There are two possible reasons for that. First, it might be caused by a double-hit injury after two intravitreal injections, while there was a 1-year interval between two treatments. Second, the patient had Stage 5 CKD (glomerular filtration rate < 15 mL/min/1.73m²) at the first presentation but even less residual renal function when he received injection of ranibizumab, which might lead to the acute chronic renal failure episode. There was no other notable cause that might coexist in this patient and would interact with the effect of anti-VEGF in those postoperative days.

Although the possible clinical risk factors and dangerous biomarkers for renal damage after anti-VEGF therapy have not been clarified yet, our presenting case implicated that ophthalmologists and internal medicine physicians should pay additional attention and perform a complete framework in performing this therapy for all patients, especially for diabetic patients with preexisting CKD. In addition, this is only a case report, and further collection of cases is needed.

References


