Acute Vision Loss after Intravitreal Injection of Bevacizumab (Avastin) Associated with Ocular Ischemic Syndrome

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Key Words

Bevacizumab • Ocular ischemic syndrome • Diabetic rubeosis

Abstract

Aim: To report a patient with diabetic rubeosis who suffered from acute retinal ischemic change and stroke after intravitreal injection of bevacizumab. **Methods:** A 55-year-old man had diabetes with unilateral rubeosis and macular edema. Three days after receiving intravitreal injection of bevacizumab (1.25 mg in 0.1 ml), he developed acute vision loss and change of consciousness. A complete ocular examination, fluorescein angiography, carotid artery Doppler sonography and brain magnetic resonance imaging were performed. **Results:** Best corrected visual acuity before injection was 6/60 in the left eye. He had underlying left carotid artery stenosis combined with bilateral preproliferative diabetic retinopathy. Three days after intravitreal injection of bevacizumab, acute ocular ischemic syndrome occurred. He also suffered from acute stroke, and brain magnetic resonance angiography showed total left internal carotid artery occlusion. The final visual acuity was no light perception in the left eye and 3/6 in the right eye. **Conclusions:** Patients receiving

intravitreal injections of bevacizumab should be evaluated for potential systemic risk factors such as carotid insufficiency, coagulopathy and poorly controlled diabetes mellitus. Acute ocular ischemic change may be associated with intravitreal injection of bevacizumab in patients with vascular compromised diabetic retinopathy and/or underlying stenosis of the carotid artery.

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Introduction

Treatment of choroidal neovascularization with intravitreal bevacizumab has quickly spread worldwide and has shown short-term safety and efficacy [1]. Several case reports also demonstrate bevacizumab as a treatment option for neovascular glaucoma secondary to central retinal venous occlusion, central retinal artery occlusion or proliferative diabetic retinopathy [2, 3]. Additionally, the use of intravitreal injection of bevacizumab in ocular ischemic syndrome (OIS) showed encouraging results in one report [4]. However, these ocular usages are not formulated, and bevacizumab has only been approved by the Food and Drug Administration for oncology indications

Fig. 1. **a, b** Color fundus photographs showing bilateral cotton wool spots and microaneurysms before any treatment. **c** Color fundus photograph showing diffuse retinal hemorrhage and cherry-red spot on fovea (OS) 3 days after injection of bevacizumab. **d** Color fundus photograph revealing total sheathing of retinal vessels and burned-out retina 2 months later.

[5]. Systemic adverse events possibly related to bevacizumab (intravitreal or systemic use) include cerebrovascular accident, deep venous thrombosis [6, 7], metrorrhagia [8], visual hallucination [9] and retinal pigment epithelium tear [10, 11]. After systemic injection of bevacizumab and irinotecan for recurrent malignant glioma, 4 of 32 cases developed thrombotic events or stroke [12]. We report acute vision loss associated with OIS and acute stroke after an intravitreal injection of 1.25 mg bevacizumab in a patient with neovascular glaucoma.

Case Report

A 55-year-old man reported a 20-year history of diabetes without regular medication treatment. The best corrected visual acuity was 20/50 in the right eye and 20/60 in the left eye after panretinal photocoagulation treatment. Fundus examinations showed severe preproliferative diabetic retinopathy with cotton wool spots and multiple nonperfusion areas in both eyes (fig. 1a, b). He suffered from recurrent hyphema and neovascular glaucoma (OS). After being informed about the off-label use of intravitreal bevacizumab as a treatment option, the patient agreed to receive intravitreal injection of bevacizumab (1.25 mg in 0.05 ml)

Fig. 2. **a** Brain magnetic resonance angiography showing total occlusion of the left internal carotid artery. **b** Angiography showing no blood flow in the lumen of the left internal carotid artery (arrow).

in the left eye for treatment of rubeosis. One day after intravitreal injection of bevacizumab, pain and visual deterioration of the left eye occurred but the patient did not return to hospital. However, after 3 days, he was sent to our emergency department because he became drowsy and had severe headache associated with ocular pain. The ocular examinations demonstrated that visual acuity was no light perception in the left eye, with a dilated, unresponsive pupil and deepened chamber angle but no obvious rubeosis. The patient had high intraocular pressure (IOP; 51 mm Hg) in the left eye. The fundus showed diffuse retinal hemorrhage, cherry-red spot and pale but nonedematous disk (fig. 1c). There were no limitations of extraocular eyeball movement, no periocular redness or swelling of the orbit. However, we could not complete the supranuclear ocular motor system examinations due to the patient's drowsiness. Fluorescein angiography demonstrated delayed choroidal flush and artery perfusion (50 s after fluorescein injection). The sonography of the carotid and ophthalmic arteries showed a total occlusion of the left internal carotid artery and a retrograde flow of the ophthalmic artery, favoring a diagnosis of left-side OIS with stealing phenomenon. However, the patient became progressively more drowsy and weak. Brain magnetic resonance angiography and angiography disclosed a totally occluded left internal carotid artery (fig. 2). The patient was then transferred to the neurological ward for further treatment. Three months later, the left fundus showed total sheathing of the retinal vessels and a burned-out retina (fig. 1d).

Discussion

The wide use of bevacizumab for ocular ischemic conditions, such as severe vascular compromised diabetic retinopathy or systemic vascular insufficiency, may increase the possibility of complications. OIS occurring in patients with diabetes is complicated. Further studies are needed to understand the incidence of thromboembolic events in the intravitreal treatment of such high-risk patients.

The mechanism of acute vision loss associated with bevacizumab intravitreal injection is complicated. Increased IOP after intravitreal injection of bevacizumab was noted, but the IOP spike normalized over 30 min, so that the evidence of retinal damage due to the IOP elevation may not be convincing [13, 14]. To eliminate the risk, we always perform the aqueous paracentesis simultaneously to prevent the increases in IOP during intravitreal injection. The increase in IOP due to intravitreal injection of bevacizumab associated with severe retinal ganglion cell damage or vascular occlusion has never been reported. Vascular endothelial growth factor acts as a vessel dilator by stimulating nitric oxide synthesis and influences the autoregulation in microcircu-

lation [15]. If we block this rescuer, the retina may be damaged further. In primate research, there were ultrastructural alterations in the choriocapillaris after intravitreal bevacizumab injection, increasing the risk of plugs in vessels.

In conclusion, acute ocular ischemic change may be associated with intravitreal injection of bevacizumab in patients with vascular compromised ocular or/and systemic conditions. This case has alerted us to the possibility of acute vision loss and stroke after intravitreal injection of bevacizumab.

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