Neovascularization of angle following trabeculectomy augmented with mitomycin-C

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Abstract:
The purpose of this study was to report a case of neovascularization of angle (NVA) following trabeculectomy with mitomycin-c (MMC) in a patient with primary open-angle glaucoma. This case report describes a 68-year-old woman who developed NVA and hyphema 2 weeks following an uneventful trabeculectomy with MMC. Trabeculectomy may be associated with serious and vision-threatening complications such as hypotony, suprachoroidal hemorrhage, endophthalmitis, and bleb-related complications. However, neovascularization of the anterior segment is not a commonly reported complication. Neovascularization of the anterior segment is a rare postoperative complication that usually occurs following strabismus or retinal detachment surgeries. The underlying ischemic trigger for anterior segment neovascularization is usually a posterior segment pathology or carotid artery insufficiency. These causative factors were excluded in our patient by lack of any abnormal finding in fundus fluorescein angiography and carotid Doppler ultrasonography. The patient received three subconjunctival bevacizumab injections (1.25 mg/0.1 ml) with frequent topical steroids and showed marked regression of the neovessels. The bleb was functional, and intraocular pressure remained at low teen afterward. NVA following trabeculectomy without any posterior segment or carotid pathologies responded well to subconjunctival bevacizumab and topical steroids.

Keywords:
Anterior segment ischemia, mitomycin-c, neovascularization of angle, trabeculectomy

Introduction

Trabeculectomy with antimetabolites is currently the most commonly performed glaucoma filtration procedure worldwide. Cairns introduced trabeculectomy for the first time in 1968, and his reported technique is still being performed today with some improvements, aiming mainly to create long-lasting scleral fistula and enhance bleb survival. The introduction of antimetabolites, including mitomycin-c (MMC) and 5-fluorouracil, in conjunction with filtration surgery has improved its long-term success rate. Although it is the most effective glaucoma surgery in terms of intraocular pressure (IOP) reduction, trabeculectomy still carries some limitations that may be related to the surgery itself or the adjuvant antimetabolites. The well-known reported early postoperative complications of trabeculectomy are hypotony, choroidal effusion, suprachoroidal hemorrhage, shallow anterior chamber, over- or under-filtration, aqueous misdirection, pupillary block, endophthalmitis, loss of central visual acuity (VA), and bleb-related complications.

In 1992, Watson described anterior segment ischemia (ASI) as an unusual complication of trabeculectomy. Intraoperatively, the patient developed severe hypotension without any ocular complications. Postoperatively the patient presented with anterior uveitis, corneal edema, and hypotony and choroidal detachment.

Case Report

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that failed to resolve with drainage. These findings suggested an ischemic pathology, which was confirmed with anterior segment fluorescein angiography and response to high-dose systemic steroids. ASI is a rare but well-documented complication of certain ocular surgeries, mostly after strabismus or retinal detachment surgeries, mainly due to extraocular muscle manipulation and interruption of anterior ciliary arteries. However, a case of ASI was reported after pterygium surgery, which does not impair the anterior ciliary arteries perfusion. The anterior uveal circulation is a highly complex network that interconnects both the anterior and long posterior ciliary arterial systems. The collateral blood flow exists at three levels: the episclera, the ciliary muscle, and the root of the iris. Primate studies have shown that 70%–80% of the blood supply to the anterior segment of the eye is contributed by the anterior ciliary system, in addition to collateral blood supply from the anterior episcleral arterial circle.

The clinical presentation of ASI is diverse, ranging from subtle to severe form. The most common presentations are mild pain and reduced vision. Early signs include a poorly reactive pupil, pupil distortion, episcleral vessel dilatation, conjunctival injection, corneal edema, anterior chamber reaction, rubeosis iridis, and neovascularization of angle (NVA).

We describe a case of NVA following trabeculectomy with MMC treated with subconjunctival bevacizumab injections and topical steroids.

**Case Report**

A 68-year-old African-American primary open-angle glaucoma female patient was referred to Wills Eye Glaucoma Service for uncontrolled IOP of the right eye. She had received selective laser trabecuoplasty 9 years prior in both eyes and phacoemulsification with ab-interno canaloplasty of the right eye 6 months before trabeculectomy.

Preoperatively, she had corrected VA of 20/20 in both eyes. The IOP was 30 mmHg OD and 15 mmHg OS on brimonidine, latanoprost, fixed-combination dorzolamide/timolol OU, and netarsudil OD. The pachymetry was 554 µOD and 544 OS. Anterior segment examination was unremarkable except for posterior chamber intraocular lens OD and minimal nuclear sclerosis OS. Posterior segment examination revealed a cup-to-disc ratio of 0.75 OD and 0.7 OS, without any abnormality in the macula or the retina OU. The angle was open on gonioscopy (D35r in all quadrants OU; Spaeth grading system). Visual field showed superior arcuate scotoma and nasal step OD and superior nasal step OS with a mean deviation of −10.43 OD and −1.03 OS, respectively.

She underwent trabeculectomy augmented by MMC; subconjunctival injection (0.4 mg/ml). In the first 2 postoperative weeks, the patient had a quiet eye, VA of 20/20, a nice bleb, and IOP of 10–12 mmHg. She presented with pain and photophobia on the 3rd postoperative week. Examination revealed VA of 20/40, IOP of 12 mmHg, +1 diffuse conjunctival injection, +1 cells, and flare in the anterior chamber. The provisional diagnosis was rebound inflammation, and topical steroid frequency was increased. In the follow-up, the patient developed a thin layer of hyphema and NVA in the inferior 180° of the angle [Figure 1]. No rubeosis iridis was detected. Retinal evaluation by a retina specialist including fundus fluorescein angiography and optical coherence tomography revealed no signs of posterior segment ischemia [Figure 2]. Carotid Doppler ultrasonography did not show any abnormal findings. Given the lack of any sign of posterior segment ischemia, subconjunctival bevacizumab (1.25 mg/0.1 ml) was administered weekly for 3 weeks. Six months after the surgery, the VA was 20/20 OU, and IOP was 12 mmHg OD without any glaucoma medications and 14 mmHg OS on brimonidine and fixed-combination dorzolamide/timolol. No NVA was detected on gonioscopy, but scattered peripheral anterior synechiae developed in the inferior angle.

**Discussion**

The ocular conditions responsible for neovascularization of the iris or NVA are almost always ischemic in nature. Neovascularization is a multi-step process that involves interactions of angiogenic factors, including vascular endothelium growth factor (VEGF). The most common causes of anterior segment neovascularization are central/branch retinal vein occlusion, proliferative diabetic retinopathy, and carotid artery obstructive diseases. In our case, all were excluded with proper imaging.
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Intravitreal bevacizumab injection was also effective in the treatment of corneal neovascularization. In our case, due to the lack of evidence of posterior segment ischemia, bevacizumab was administered subconjunctivally with frequent topical steroids which resulted in marked regression of the neovessels and suppression of the inflammatory process.

Figure 2: Wide-field color fundus photographs and fundus fluorescein angiography of the right (a) and left (b) eyes show normal vascular filling with no signs of retinal ischemia

ASI usually develops after strabismus surgery when three or more rectus muscles are manipulated, or following retinal detachment surgery using encircling buckle. The mechanism in the former is based on the damage to the anterior ciliary arteries, while the latter has variable mechanisms including compression and occlusion of vortex veins.\(^{14}\)

Although the ASI following strabismus and retinal surgeries could be explained with the changes in the vascular anatomy, there is no definite mechanism regarding uneventful anterior segment surgeries such as trabeculectomy and pterygium surgeries.\(^{11,15}\) Watson postulated that the intraoperative systemic hypotension and ocular hypotony might have caused hypoperfusion of anterior uvea. He also suggested that conjunctival dissection and creation of scleral flap might have damaged the anterior episcleral arterial circle, which is an important collateral link between anterior ciliary arteries.\(^{11}\)

Gunduz et al. reported a case of ASI following uneventful pterygium surgery.\(^{19}\) One week after surgery, the patient presented with pain and a decline of vision. Keratic precipitates were present with 2+ cells in the anterior chamber and ischemic changes in the inferior iris. The anterior segment fluorescein angiography confirmed the diagnosis of ASI, but the underlying mechanism was unknown. The authors postulated that the conjunctival dissection and episcleral catarization might have been the causative factors, the common steps in both trabeculectomy and pterygium surgeries.

In our case, the development of NVA, hyphema, and anterior uveitis is consistent with ischemic stress. The ischemia has possibly been mild given the lack of changes in the iris and cornea and delayed onset compared to those cases reported by Watson and Gunduz et al.\(^{11,15}\)

Although we did not perform the anterior segment angiography, the presentation and great response to subconjunctival bevacizumab and topical steroid are consistent with ASI. The underlying systemic medical conditions of the patient may interfere with blood perfusion and predisposition to ASI,\(^{21,22}\) being former smoker with hypothyroidism, hypercholesterolemia, sleep apnea, asthma, and psoriasis.

One of the MMC active metabolites cross-links with DNA, causing selective interruption of DNA replication and inhibition of mitosis. This makes MMC cytotoxic to both fibroblasts and microvascular endothelial cells, therefore, it does not only reduce the production of fibroblasts, but also affects the microvascular blood supply of the treated area.\(^{23}\) This may promote VEGF production and lead to neovessel formation. Thin-walled, avascular bleb is a common finding with MMC-augmented trabeculectomies.\(^{24}\) There are reports of scleral melting, necrosis, and scleromalacia following trabeculectomy augmented with MMC, possibly due to ischemia.\(^{25-27}\) Studying the filtering bleb in a patient with hypotony who underwent surgical revision showed that the scleral flap and adjacent sclera were avascular and friable. The histopathology of the excised bleb showed acellular avascular subepithelium.\(^{28}\)

The subconjunctival injection of MMC instead of the conventional sponge application results showed that it has comparable safety and success.\(^{29,30}\) The effect of the MMC on vascular endothelial cells and its distribution in wider area after injection might have a role in inducing ischemia. One study evaluating the effects of intravesical MMC in bladder carcinoma in rats showed increased urinary VEGF concentration with upregulated VEGF receptors in both cancerous and normal bladder tissue.\(^{31}\) Such effect has not been studied and reported in the eye with the commonly used concentration, duration, and rinsing after MMC application.\(^{32}\)

Regardless of the underlying pathology, inhibiting the angiogenesis process with anti-VEGF therapy is an effective treatment of angiogenic eye diseases. Bevacizumab is a full-length humanized monoclonal antibody against VEGF type-A which has a central role in ocular neovascular diseases.\(^{33}\) Intravitreal injection of bevacizumab is the standard treatment of neovascular glaucoma complicating posterior segment ischemia.\(^{34}\) Subconjunctival bevacizumab injection was also effective in the treatment of corneal neovascularization.\(^{35}\) In our case, due to the lack of evidence of posterior segment ischemia, bevacizumab was administered subconjunctivally with frequent topical steroids which resulted in marked regression of the neovessels and suppression of the inflammatory process.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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