• Letter to the Editor •

Complications of intrastromal bevacizumab injection in lamellar keratoplasty

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Dear Editor,

We would like to report complications of intrastromal bevacizumab injection for corneal neovascularization (CNV) after lamellar keratoplasty (LK) in two patients. CNV is a significant risk factor for graft rejection. CNV leads to graft failure by disturbing the immune function of the cornea after penetrating keratoplasty (PKP). Studies reported that more than fifty percent of graft failure occurs in this condition[1]. Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that diminished neovascularization by binding to isoforms of vascular endothelial growth factor (VEGF) and inhibiting VEGF receptor interactions. In LK, the risk of graft rejection is very low, however CNV especially interface neovascularization could severely jeopardize graft clarity and subsequently graft success. In this respect, several surveys focused on the role of bevacizumab in the treatment of CNV in patients with a history of LK and publicized hopeful outcomes for the management of CNV[2]. Different forms of bevacizumab (drops, subconjunctival or intrastromal injections) were presented to be effective in diminishing or suppressing vascularization of corneal grafts. It was shown that intrastromal injection provided an acceptable concentration of the drug compared to other forms[2-4].

According to our knowledge, no significant local or general complications have been reported in patients with the intrastromal injection of bevacizumab. To date, studies have not thoroughly evaluated complications of intrastromal injection of bevacizumab. The goal of this paper is to report two complications of intrastromal injection of bevacizumab in the treatment of CNV after LK.

CASE REPORT 1

A 35-year-old man, known case of uncontrolled *Acanthamoeba* keratitis, presented to our department (Figure 1A). The patient was scheduled for LK. After the surgery, the cornea was clear; however, corneal peripheral vascularization (especially in the interface) occurred two months later. Deep intrastromal bevacizumab was injected in a 1.25 mg/0.05 mL concentration in four quadrants. We used a 27-gauge insulin needle to make a pass into the deep corneal stroma, but an unexpected complication occurred. During operation, a localized hemorrhage occurred in the interface, the patient was followed for the possible resorption of the blood. The hemorrhage was not resolved after eight days of follow-up (Figure 1B), so we decided to drain the clot *via* the opening of sutures, the clot was not extracted; finally, we removed the clot by opening all the sutures. Because of the staining of the donor stroma, we decided to exchange the donor with a new graft during a new LK. The graft remained clear until the last follow-up (one year; Figure 1C).

CASE REPORT 2

A 59 year-old-man, known case of corneal scar related to herpetic keratitis underwent LK one year ago. A course of reactivation of necrotizing herpetic keratitis occurred that responded to systemic acyclovir 2 g/d and topical levofloxacin every 2h and topical prednisolone acetate twice a day. However, because of severe vascularization, the patient scheduled for intrastromal bevacizumab injection in a 1.25 mg/ 0.05 mL concentration at the site of CNV. One month later, the patient presented with severe visual loss (Figure 2A). Anterior segment optical coherence tomography (OCT) documented Descemet detachment (Figure 2B). We injected air into the anterior chamber; despite Descemet detachment more than one month, it became attached, and the stroma was clear (Figure 2C, 2D).

DISCUSSION

Graft rejection and interface vascularization can be prevented by the timely diagnosis and treatment of CNV. There are various treatment plans for the management of CNV[4]. Using steroids, nonsteroidal anti-inflammatory agents, argon

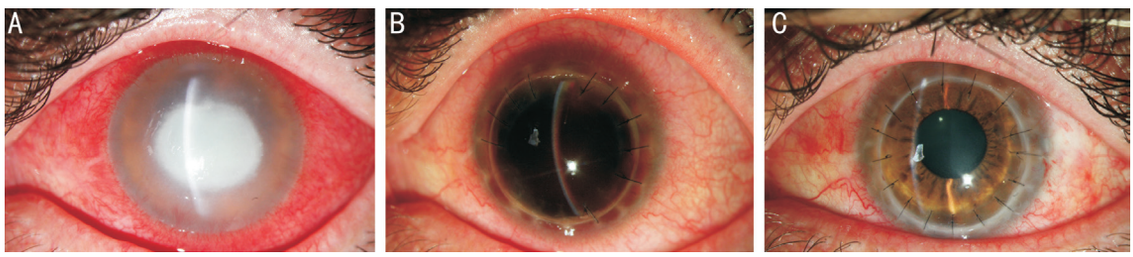

Figure 1 Hemorrhagic Descemet membrane detachment A: The patient underwent LK for uncontrolled *Acanthamoeba* keratitis; B: After intrastromal bevacizumab injection, the hemorrhagic Descemet membrane detachment was not resolved; C: After eight days, the blood was drained, and the donor was exchanged with a new one because of staining.

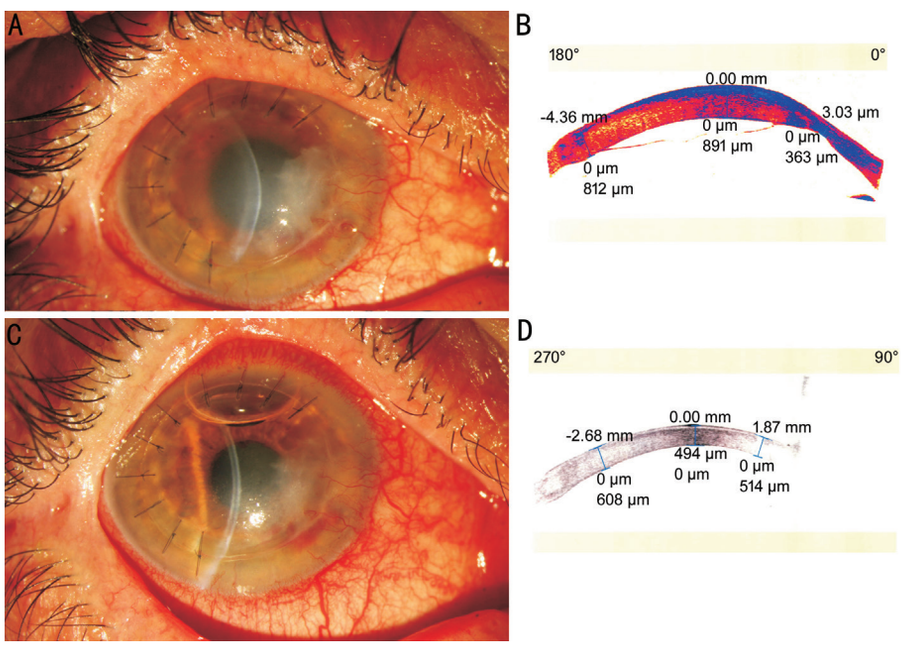

Figure 2 Descemet membrane detachment after intrastromal injection A: This patient with a history of previous LK for herpetic keratitis presented because of one-month visual loss following intrastromal bevacizumab injection; B: Anterior segment OCT documented Descemet detachment; C, D: We injected air bubble into the anterior chamber leading to descemet membrane attachment although it was detached about one month and the cornea became clear.

laser photocoagulation, heparin, photodynamic therapy, cyclosporine, methotrexate, and thalidomide in several human and animal studies have shown anti-angiogenesis effects[3-4]. Steroids have been used commonly for this purpose in the clinical setting. Nevertheless, steroids were not a good choice in some cases because of the side effects of the long term using. Although the mechanism of CNV was not thoroughly understood, it has been showed that CNV caused by an imbalance between angiogenic and antiangiogenic factors. VEGF, mainly VEGF-A, is a sub-family of growth factors that stimulates the angiogenesis and induces new vessels in corneal grafts. Thus, according to this hypothesis, inhibition of VEGF may resolve the neovascularization of corneal grafts and improved graft survival[2]. Recently, anti-VEGF antibodies have been used to diminish CNV. Various levels of regression of new vessels reported in studies, the effects were promising in the management of CNV[4-5]. Mostly, bevacizumab has been used in three methods in the management of CNV, including topical eye drop, subconjunctival and intrastromal injection. The result of studies on the safety of bevacizumab on the cornea was controversial. Huang *et al*[6], in a systematic review and Meta-analysis survey, concluded that studies about anti-VEGF treatment for CNV after keratoplasty were not adequate and further research should be performed on this part. Khalili *et al*[7] reported a case with herpes simplex epithelial keratitis after intravitreal bevacizumab (Avastin) injection. Dong *et al*[8], in an animal study, demonstrated that subconjunctival bevacizumab injection damaged corneal innervations and disrupted epithelial wound healing. However, Merz *et al*[9] showed that bevacizumab had no cytotoxic effects on the corneal endothelium in a short follow up period (4wk). Topical administration of bevacizumab reported being not beneficial in high dose and long duration treatment due to epithelial defects and stromal thinning. Therefore, subconjunctival and intrastromal injections methods considered as an alternative therapy in these patients[4]. Kim *et al*[10], in an animal study,

used stainless steel microneedles to deliver the drug to corneal stroma and showed a hopeful result in controlling CNV. Also, targeted drug delivery with microneedles probably diminishes complications associated with high doses required by other delivery methods.

We reported two cases with Descemet membrane detachment after intrastromal bevacizumab injection in patients with previous LK. The first case developed hemorrhagic Descemet membrane detachment possibly because of an insult to interface vessels. In the other case, the Descemet detachment could be the result of Descemet rupture or direct injection of the drug under Descemet membrane. So far, this injection method was reported to be relatively safe, but to the best of our knowledge, there was no substantial clinical trial study in the safety and efficacy of intrastromal injection method. Belghmaidi *et al*[3], reported that the safety of intrastromal bevacizumab injections should be further examined in a study with large sample size to recognize possible complications. Most of the results were restricted by their small sample size and limited follow-up period[3,6]. Hence, it seems to be necessary to evaluate the safety of intrastromal injection by further studies. On the other hand, studies in this part have not specifically focused on evaluating these complications in LK patients.

Our cases add new evidence to the literature that Descemet membrane detachment and most severely hemorrhagic type may be one of intrastromal injection complications in patients with a history of LK. We should emphasize that these complications were not related to bevacizumab, instead the injection method was involved in these situations. In conclusion, we should be careful about intrastromal injections in patients with a history of LK. It seems that in these patients, the subconjunctival injection may be a safer method for managing CNV.

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