



CASE REPORT

Management of Neovascularization in Recurrent Herpetic Keratitis

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Abstract

Herpetic stromal keratitis activates a cascade of inflammatory processes that stimulate angiogenic factors such as VEGF (Vascular Endothelial Growth Factor) causing the development of blood vessels in the cornea.

In this case report, we describe an unusual case of a 35-year-old man with a known history of herpetic keratitis presenting to the emergency department with pain, haziness and itchiness of the right eye due to extensive neovascularization at the inferotemporal sclera of the corneal stroma extending to the 3 o'clock position. Acyclovir, anti-VEGF (avastin) and argon laser were used in successfully managing the patient. The triple therapy reversed neovascularization and prevented its further extension, leading to a good prognosis for the patient.

Keywords: Argon Laser; Coagulation; Phototherapeutic; Keratitis; Avastin.

Introduction

Herpes Simplex Virus (HSV) is transmitted through various routes and leads to several complications including meningitis, encephalitis, keratitis, uveitis and cutaneous involvement. The incidence of recurrent herpetic keratitis is 31.5 per 100 000 person per year. In the UK, herpes simplex keratitis is the leading cause of corneal blindness and is responsible for 1 in 10 corneal transplants.¹

The immuno-inflammatory process stimulates an angiogenic factor known as Vascular Endothelial Growth Factor or VEGF that increases the number of blood vessels in the eye, causing irritation to the eye and obliterating vision.^{2,3} Many factors could trigger this cascade, such as sunlight, fever, extreme heat or cold, systematic or ocular infection, menstruation and ocular trauma.⁴

In the present case, we report a rare case of recurrent herpetic keratitis complicated by increased vasculature of the corneal stroma with the aim of educating physicians on the diagnosis and management of such an unusual complication of herpetic keratitis.

Case Report

A man, aged 35 years, a known case of keratitis with previous history of multiple episodes of dendritic ulcer in the right eye, presented to the emergency department on February 12, 2019 complaining of pain, haziness, itching sensation with watery discharge in the right eye but no fever or headache. He denied any decrease in vision or double vision.

The patient also denied history of trauma, wearing glasses or contact lenses. The patient had a history of multiple herpetic keratitis attacks of the right eye

in the past, for which he received topical antiviral agents. He had also undergone phototherapeutic keratectomy a year ago and had received oral acyclovir for 1.5 months. Other details of his past medical, family, social history and diet were non-contributory. For further management, the physician referred him to the ophthalmology department of the hospital.

On examination, the visual acuity of his left eye was 6/6 and of his right eye was 6/21. Slit lamp examination of the right eye revealed conjunctiva injection, corneal opacity with overlying superficial punctate keratitis, as well as extensive neovascularization affecting the inferotemporal quadrant. The anterior chamber was deep and quiet, the pupil was rounded, regular and reactive, and the lens was clear and in place. The fundus examination of the left eye was normal. It was observed that sensations were reduced in the right eye compared to the left eye. The intraocular pressure was 10 mmHg in the right eye and 11 mmHg in left eye.

Results of blood investigations showed no sign of infection as all parameters were within the reference range. The history, clinical and laboratory findings provided a working diagnosis of recurrent keratitis complicated by neovascularization.



Figure 1: Slit lamp photo demonstrating emerging new limbal blood vessels of the inferotemporal area of the cornea.

Treatment plan

On presentation, the patient was provided with topical acyclovir 3% ointment (4.5 g) four times daily and a systemic acyclovir 400 mg twice daily for 3 weeks. After one week of starting acyclovir (both systematic and local), the patient was treated with subconjunctival Avastin (bevacizumab) injection under topical anaesthesia, in order to

control the peripheral corneal vascularization, at a dose of 1.25 mg/ml. Six days later, he underwent Argon laser photocoagulation of the remaining limbal blood vessels using a wavelength of 450 nanometer. During this period, the patient was still on acyclovir (topical and systemic) treatment. Marked regression of limbal neovascularization was observed immediately after the treatment and the patient's vision improved as a response to the combination of triple therapy consisting of the anti-VEGF injection. The outcome of therapy was monitored through various follow ups. After 12 months of follow up, the patient's cornea was noted to be no longer vascularized. The visual acuity was 6/6 on both eyes, and the intraocular pressure was 10 mm Hg in the right eye and 11 mm Hg in the left eye. The patient had stopped complaining of itching and redness of the eye and no further referrals to microbiology or internal medicine were required.



Figure 2: Slit lamp demonstrating right eye after using argon laser photocoagulation

Discussion

In most cases, herpetic stromal keratitis is self-limiting and heals without treatment. However, in many cases, the lack of medication and inappropriate treatment worsens the inflammation and prolongs the healing causing deactivation, where the virus undergoes a latency phase, which could stimulate the inflammatory process once again, leading to recurrent keratitis.

According to the guidelines provided by the American Academy of Ophthalmology, permanent vision loss is a primary concern as a complication of recurrent HSV stromal keratitis, due to the continuous scarring and astigmatism. A clinical randomized double masked controlled trial for HSV keratitis demonstrated that providing a prophylactic low dose of antiviral agents such as acyclovir or

valaciclovir was key in decreasing complications, whereas we found no studies suggesting the advantages of famciclovir. This is why we chose acyclovir to be the treatment of choice in the present case.⁵ However, despite the use of the recommended acyclovir dosage, both prophylactic and therapeutic, recurrence was observed, with an atypical complication, as acyclovir alone was not effective against the inflammatory stage of herpetic keratitis.

Corneal avascularity, also known as corneal angiogenic privilege, allows a balance to occur between the proangiogenic and antiangiogenic factors due to its nature. Pathologies such as infections disturb this balance and lead to a disequilibrium between the above factors, causing proliferation and migration of vascular endothelial cells in the stroma of the cornea.

With the patient in the present case, HSV initiated a cascade of immune-inflammatory reactions, activating cytokines and chemokines released by CD4 T cells, causing the expression of VEGF to increase with each recurrence, thus paving the way for blood vessels to develop and grow by upregulating matrix metalloproteinase production by the endothelial cells in the limbal vascular plexus.⁶ This process caused neovascularisation of the cornea at the inferotemporal area. Appearance of new blood vessels can block and diffract light, contributing to a marked diminution of vision. As the immune-inflammatory reactions progress, they allow inflammatory cells to damage the structural integrity of the cornea and eventually lead to lipid deposit and corneal opacification.

Medications such as topical steroids could help in the inflammation and the subsequent neovascularization. However, in the long term, corticosteroids are known to increase glaucoma and cataract formation. Non-steroidal anti-inflammatory drugs and methotrexate do not antagonize the angiogenic factors, causing them to be ineffective in halting corneal neovascularization. Anti-VEGF agents such as bevacizumab have proven to reduce new blood vessel formation, allowing visual acuity to improve.⁷ Bevacizumab is humanized murine monoclonal IgG1 antibody approved by the Food and Drug Administration (FDA) and has been proven to decrease corneal neovascularization and

ergo, improve the corneal clarity. It reduces the diameter of the vascularized area and has further benefits of reducing the inflammatory process.⁸ The only issue with this treatment is that both stable mature vessels as well as deep corneal vessels in chronic neovascularization are less effected by the VEGF blockade, as these vessels are covered by pericytes (previously referred to as Rouget cells), which are mural cells of the microcirculation that wrap around the endothelial cells that line the capillaries and venules throughout the body, preventing bevacizumab to penetrate the mature blood vessels.^{9,10}

To tackle the issue of mature blood vessels, a study by Cherry⁹ in 1978 showed that argon laser with a wavelength of 488 nm was effective in obliterating neovascularization during the reactivation of herpetic keratitis. The laser obliterated efferent vessels (as they are wide and have a relatively slower blood flow) but could not obliterate the afferent vessels since they are thinner, deeper and have a much faster blood flow. Argon laser is now the treatment of choice for the mature blood vessels in neovascularization. However, the laser energy should be minimal, in order to prevent side effects such as iritis, localized iris atrophy, intracranial bleeding and secondary deposition of lipid.¹¹ Due to this limitation, dual therapy with anti-VEGF and phototherapeutic keratectomy using Argon laser, was chosen for the management for our patient over monotherapy, as anti-VEGF would prevent new vessels from forming and the laser would coagulate the vessels that had already formed. To this, we added acyclovir so as to manage the source of this complication and provide protection against inactivation of the virus.¹²

The American Academy of Ophthalmology has also suggested that patients must be followed up for ocular examination regardless of the symptoms, at 1, 3, 6, 9 and 12 months post management, the reason being that if the patient showed repeated reactivation of epithelial disease during his follow up, then corneal collagen cross-linking with riboflavin and ultraviolet-A could be considered.¹³ In addition, a prophylactic dose of ganciclovir gel, in combination with topical ganciclovir has been postulated to be helpful in the treatment of herpetic

stromal keratitis. This new method of treatment is however still under clinical trial.^{14,15}

The aims of management of a case such as this would be to treat the complication both medically and surgically, failure of which would increase the vasculature and scarring, resulting in severe visual deterioration.

Conclusion

Development of new blood vessels in the cornea is an uncommon complication of herpetic keratitis. Successful management of such a condition demands both medical and surgical approaches. It is essential that neovascularization of the cornea be reversed with anti-VEGF and Argon laser be used to stop growth and prevent the production of new vessels. This combination of therapies, along with acyclovir, has proven to be highly effective in the treatment of complicated herpetic keratitis and has been successful in preventing further complications from occurring at the cornea.

Conflicts of interest

The authors of the study have no conflict of interest

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