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Treatment of Corneal Neovascularization from Varicella-Zoster Keratitis

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Abstract

A clear cornea is essential to obtain optimum vision and when corneal neovascularization (CN) occurs it can be devastating to the patient's vision. There are many causes of CN. This article will review a case of Varicella-zoster virus as a cause of CN in a 44-year-old male. The patient was treated with a subconjunctival injection of bevacizumab (Avastin®, Roche, Laval, QC) and prednisolone acetate 1%. Other treatment modalities which have been tried include bevacizumab eye drops, photodynamic therapy with verteporfin and GS-101 antisense oligonucleotide eye drops. There are no current approved treatments for a devastating condition like CN. Diagnosis and prompt treatment of Varicella-zoster is essential in managing patients with this condition.

Introduction

In order to have good vision one needs a good tear film, clear cornea, clear lens, and a healthy macula. Vision can potentially be reduced if any of the structures that refract light onto the retina become damaged. The cornea, which is the most important structure in refracting light onto the retina, needs to be transparent. Making up 90% of the cornea, the stroma's precise arrangement of fibrils in lamellae is why the cornea is transparent.[1] The cornea is also avascular to allow for complete transparency and therefore needs to get its nutrients and oxygen from other sources. The cornea gets its nutrients from three major sources including the tear film, aqueous humor, and pericorneal capillary plexus.[2] Any etiology that compromises adequate nutrient supply to the cornea can cause CN. Other causes of neovascularization include inflammatory conditions, infections, degenerative diseases, and trauma.[3] The new blood vessels can leak inflammatory cells leading to corneal haze.[4] Varicella-zoster virus is just one of a multitude of etiologies that can compromise the integrity of the cornea.

Diagnostic Data

A 44-year-old white male presented to our clinic concerned about decreased vision in his left eye and that the eye looked bloodshot. The patient also noted that his left eye was scratchy and that it was light sensitive. He stated that he was taking loteprednol (Lotemax®, Bausch & Lomb, Vaughan, ON) but had discontinued it four weeks prior and was currently only using artificial tears. He had no known medication allergies. His ocular history was remarkable for cataract in the left eye and a previous episode of herpes zoster virus keratitis of the left eye. His medical history was negative for diabetes, hypertension, and thyroid disease. Entering unaided acuities were 6/6 (20/20) in the right eye, 6/120 (20/400) in the left eye with eccentric viewing and pinhole testing being 6/60-1 (20/200-1) in the left eye. Extraocular muscle testing revealed full motility. Pupil testing was attempted but the left pupil could not be adequately viewed. Intraocular

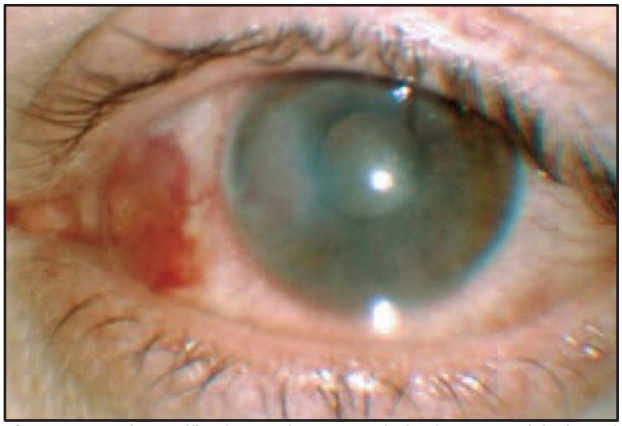

Fig. 1 Corneal opacification and neovascularization at 6 o'clock and 9 o'clock. Subconjunctival hemorrhage is from bevacizumab injection.

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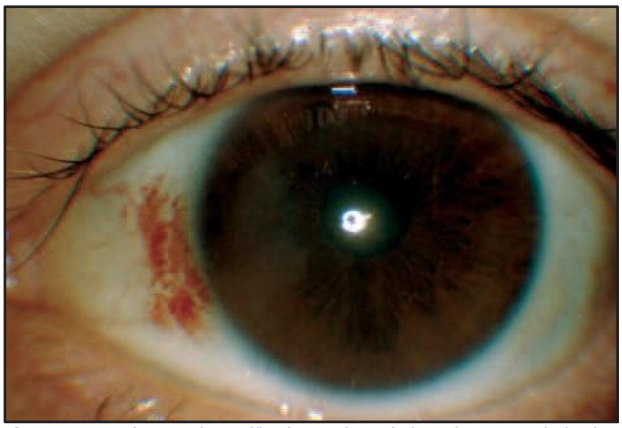

Fig. 2 Improved corneal opacification and resolution of neovascularization 11 days after subconjunctival injection of bevacizumab. Subconjunctival hemorrhage is also resolving.

pressures were 13 mmHg in the right eye and 11 mmHg in the left eye. Slit lamp examination of the anterior structures of the left eye revealed 1-2+ corneal opacification with thickening and dense stromal neovascularization at 6 o'clock and 9 o'clock (Fig. 1). The cornea of the right eye was clear.

Diagnosis

The patient was diagnosed with opacification and neovascularization of the left cornea.

Treatment and Follow-up

Treatment included a subconjunctival injection of 0.625 mg/0.025 mL bevacizumab (Avastin) adjacent to each of the two areas of neovascularization for a total dosing of 1.25 mg/0.05 mL. Prednisolone acetate 1% every hour was also started in the left eye.

On the first follow up visit two days later, vision was still reduced to 6/120 (20/400) in the left eye but subjectively the patient's wife noted the redness had decreased. Intraocular pressure was 16 mmHg in the left eye. Objectively, the corneal haze had decreased and now a few old pigmented keratic precipitates were seen on the endothelium. The neovascularization did not seem to have progressed. The patient was instructed to continue prednisolone acetate 1% every hour while awake until the next follow up in one week.

At this appointment the patient noted seeing a lot better. He felt that things were still a little fuzzy but back to what it was like eight to ten weeks prior to his current recurrence. The patient's wife also noted an overall significant improvement in the appearance of his left eye. Visual acuity was 6/12-1 (20/40-1) in the left eye with pinhole acuity being 6/6 (20/20). The patient noted monocular diplopia and that the second set of letters was overlapping the original letters. Intraocular pressure was 17 mmHg in the left eye. Anterior segment evaluation revealed a significant improvement of the keratitis and a near complete resolution of the neovascularization (Fig. 2). At this point the anterior chamber was visible and showed no cells or flare in the left eye. The patient was instructed to start tapering his prednisolone acetate.

The patient returned about two weeks later and indicated continual improvement in the left eye. Vision was 6/9+1 (20/30+1) and pinhole was 6/6 (20/20) in the left eye. At this appointment, refraction was performed on the left eye and revealed a small refractive error which slightly improved his acuity. Intraocular pressure was 19 mmHg in the left eye. Slit lamp findings showed a persistent anterior corneal stromal haze but reabsorbed neovascularization. The patient was instructed to continue to taper his prednisolone acetate.

Another follow up was scheduled for two weeks. At this exam the patient indicated that the left eye was the same and unchanged. Vision was 6/9 (20/30) and pinhole was 6/6-2 (20/20-2). Intraocular pressure was 13 mmHg in the left eye. Anterior segment evaluation revealed a persistent corneal stromal haze with ghost vessels at 6 o'clock and 9 o'clock (Fig. 3). The patient was instructed to continue to taper his prednisolone acetate.

Discussion

Varicella-zoster virus is often encountered in eye care and with the aging population the number of these cases will probably increase. Varicella-zoster virus is the same virus that causes chickenpox which is a childhood condition seen after initial exposure to the virus.[5] After this initial exposure, the virus will lay dominant in the dorsal root and sensory ganglia where it can be reactivated in adults. The reactivated virus in an adult is referred to as shingles. It is not known why the virus reactivates but it is postulated that decreased immunity and possibly other environmental factors contribute to the reactivation.[6] The virus may also be reactivated when the patient's immune system is compromised either by medications, malnutrition, illness, or aging.[7] It is noted that 99.5% of individuals older than 40 years are at risk for zoster due to being exposed to this virus or having had chickenpox.[8] More than 90% of adults in the United States are serologically positive for the zoster virus, and 10% to 20% of these adults will have reactivation of the virus.[9]

Herpes zoster ophthalmicus (HZO) occurs when the ophthalmic division of the trigeminal nerve becomes involved. HZO typically affects people in their sixth and seventh decade of life and is more severe the older a patient is.[10] About 10% of patients with herpes zoster reactivation will develop eye symptoms.[8] Acute eye signs range from conjunctivitis, episcleritis, scleritis, epithelial keratitis, nummular keratitis, stromal keratitis, disciform

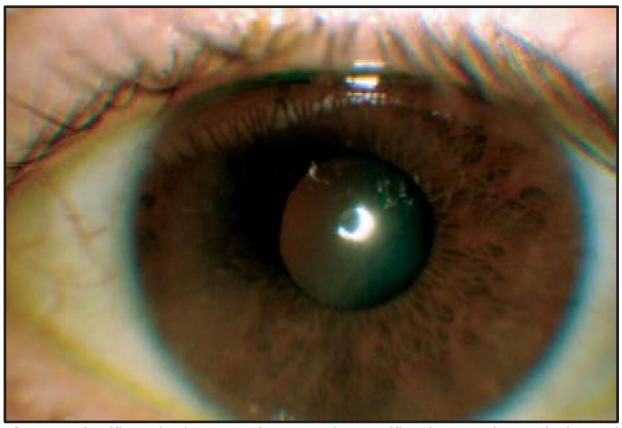

Fig. 3 Significantly improved corneal opacification and resolution of neovascularization after 46 days. Ghost vessels are seen at the 9 o'clock position.

keratitis, anterior uveitis, and other neurologic complications.[10] Chronic eye signs include lid scarring, lipid-filled granulomata, scleritis, mucous plaque keratitis, neurotrophic keratitis, and lipid degeneration.[10] Other less common ocular manifestations include cataract, cranial nerve palsies, retinitis, central retinal vein and artery occlusions, optic neuritis, and choroiditis.[11]

Prompt and aggressive treatment of Varicella-zoster is indicated because of the dire complications that can occur. The first line of therapy are the oral antiviral agents: acyclovir (Zovirax®, GlaxoSmithKline, Mississauga, ON), famciclovir (Famvir®, Novartis, Dorval, QC), and valacyclovir (Valtrex®, GlaxoSmithKline, Mississauga, ON).[11] All three drugs show similar effects in the treatment of HZO. Treatment with these drugs is most helpful if initiated within 48 to 72 hours from the onset of any rash.[11] Other treatments will depend on the various presenting signs of the disease.

The cornea can become involved leading to opacification, decreased sensitivity, and neovascularization.[9] Corneal neovascularization can potentially give rise to other complications such as lipid keratopathy which is the deposition of fat into the corneal tissue.[3] Different treatment options to treat the corneal changes have been investigated. These include topical bevacizumab, subconjunctival bevacizumab injections, photodynamic therapy with verteporfin, and gene signal (GS)-101 antisense oligonucleotide eye drops.

Vascular endothelial growth factor (VEGF) is the main component in corneal angiogenesis. Therefore, blocking neovascularization with anti-VEGF medications such as bevacizumab is a possible treatment option.[12,13] Bevacizumab is a recombinant humanized monoclonal antibody. It was originally designed for cancer therapy to stop new blood vessel growth that could potentially supply nutrients and oxygen to tumors.[4,14] There are no current United States Food and Drug Administration or Health Canada approved treatment options for the anterior part of the eye that utilize anti-VEGF therapy. Topical administration and subconjunctival injection of bevacizumab however have been tried in the treatment of CN.

Kim et al noted that topical bevacizumab can be used as a treatment modality but that it can have delayed side effects.[15] These authors noted in their study that corneal epithelium integrity was lost and that stromal thinning was seen with topical bevacizumab use. Another potential complication seen with blocking VEGF is the disruption of wound healing from ischemia and thus secondary tissue damage.[15]

Subconjunctival injection of bevacizumab for CN has been found to be a good treatment modality for acute neovascularization.[12] Chronic neovascularization therapy with subconjunctival injection of bevacizumab is not as effective since the patient will have to undergo long term therapy with numerous injections. Side effects of subconjunctival bevacizumab include corneal edema and subepithelial infiltrates.[12] Our patient responded adequately after only one subconjunctival injection for his acute episode.

Another treatment option for corneal neovascularization that has been studied is photodynamic therapy with verteporfin. This treatment has been found to be a safe, repeatable, and efficient option for CN.[3] Photodynamic therapy works with the release of oxygen radicals that damage the blood vessel endothelial cells and thus create a blood clot leading to occlusion of the neovascular blood vessel. The side effects of such a treatment include visual disturbances, corneal haze, conjunctival injection, photosensitivity, and back pain.[3]

A potential future therapeutic option is topical treatment with GS-101 antisense oligonucleotide. In the interim results of a randomized phase II trial it was found that twice a day topical application of GS-101 at an intermediate dose was effective at stopping and reducing corneal angiogenesis.[13] GS-101 inhibits the scaffold protein insulin receptor substrate-1 and was specifically designed to work on new blood vessels. It has also been shown to have an anti-inflammatory component that reduces the release of cytokines in vivo. The phase II trial showed GS-101 to have no significant side effects and no safety concerns.[13] The study found that the intermediate dose of 86 micrograms given twice daily was the most effective dose which halted corneal angiogenesis versus a placebo.[13] GS-101 eye drops seem to be a promising treatment option for corneal neovascularization in the future.[13]

Conclusion

Different treatment options for CN include topical bevacizumab, subconjunctival bevacizumab injection, photodynamic therapy with verteporfin, and gene signal (GS)-101 antisense oligonucleotide eye drops. Currently, there are no approved treatments for CN, but as seen in this case report, subconjunctival bevacizumab injection seems to be a good treatment option for acute CN. GS-101 antisense oligonucleotide eye drops also show promising results. More research however needs to be done to identify the best treatment option and the safety of each treatment modality. D

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VOICI

ACUVUE[MD] OASYS MULTIFOCALE

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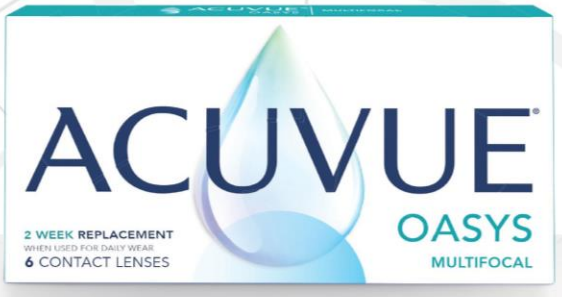

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2. Données internes de JJV, 2014. ACUVUE[MD] MOIST 1-JOUR MULTIFOCALE conçue pour l'œil vieillissant.
3. Données internes de JJV, 2018. Similitudes entre la mucine et la PVP (N-vynil-pyrrolidone).
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