Anti-inflammatory and Healing Properties of Nerve Growth Factor in Immune Corneal Ulcers With Stromal Melting

Immune corneal ulcers are rare ocular surface diseases with multiple etiologies. Immunosuppressive drugs and systemic or topical steroids may occasionally control the inflammatory process, but in the more severe cases, the ulcer may progress to corneal melting and perforation. No suitable therapy is currently available for these patients. In a recent uncontrolled study, topically applied exogenous nerve growth factor (NGF) restored corneal integrity in patients with corneal neurotrophic ulcers. Nerve growth factor might promote corneal healing and is implicated in functional activity of inflammatory cells on the ocular surface.

We evaluated the efficacy of topical murine NGF treatment in 4 patients with severe corneal melting as a consequence of immune-related corneal peripheral ulcers. The patients received 1 drop of NGF solution (10 µg of NGF dissolved in 50 µL of saline solution, 0.9% of sodium chloride) in the conjunctival fornix every 2 hours (from 6 AM to 12 PM), for 2 days, 6 times a day until the ulcer healed. After the ulcer was completely healed, the dose was reduced to 5 µg in 50 µL of solution 4 times daily for 2 weeks. In each case, the corneal ulcer completely healed with NGF treatment. Written informed consent was obtained from the patients, and the study was approved by the local ethics committee.

Report of Cases. Case 1. A 56-year-old man with rheumatoid arthritis and recurrent acute episodes of keratoconjunctivitis and blepharitis, both of which were responsive to topical steroids, developed a peripheral corneal ulcer and scleritis in the left eye (Figure 1, left). Treatment with systemic steroids and methotrexate failed while systemic plus topical steroid therapy induced an improvement in inflammation but a deterioration of the corneal ulcer, which increased in depth, became enlarged, and developed melting and neovascularization. After 5 days of NGF treatment, the ulcer displayed a healing process characterized by epithelial growth through the ulcer’s edges. During the first few days, the patient experienced a local increase in pain and photophobia that progressively disappeared along with the inflammatory reaction. The ulcer healed completely after 21 days of treatment (Figure 1, right).

Case 2. A 63-year-old woman underwent cataract extraction and after 2 months developed necrotizing scleritis with subsequent exposition of choroid. The patient was treated with topical and systemic steroids and immunosuppressive drugs. To avoid the impending risk of eye perforation, we performed a scleral patch to cover the area of dehiscence. The patient had a chronic inflammatory reaction during the postsurgical period despite topical treatment with steroids and systemic immunosuppressive therapy. One month later the patient developed a relapse of the scleromalacia.

Table 1. Characteristics of Patients Enrolled in the Study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Ocular and Systemic History</th>
<th>Ocular Findings</th>
<th>Systemic Treatment</th>
<th>Histopathologic Findings</th>
<th>Positive Blood Examination Results†</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recurrent keratoconjunctivitis</td>
<td>Blepharitis, peripheral corneal ulcer in LE</td>
<td>Prednisone (40 mg/d) Methotrexate (7.5 mg/wk)</td>
<td>Neutrophils and lymphocytes</td>
<td>Rheumatoid factor</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>2</td>
<td>Cataract surgery 2 months before in LE, nonspecific arthritis</td>
<td>Necrotizing scleritis with peripheral corneal ulcer in LE</td>
<td>Prednisone (40 mg/d)</td>
<td></td>
<td></td>
<td>Immune reaction following cataract surgery</td>
</tr>
<tr>
<td>3</td>
<td>Tuberculosis</td>
<td>Scleritis, peripheral corneal ulcers in both eyes</td>
<td>Pyrazinamide (1.25 g/d) Ethambutol (1.25 g/d) Rifampin (600 mg/d)</td>
<td></td>
<td></td>
<td>Necrotizing vasculitis</td>
</tr>
<tr>
<td>4</td>
<td>Recurrent scleritis</td>
<td>Scleritis, peripheral corneal ulcer in RE</td>
<td>Prednisone (40 mg/d) Cyclophosphamide (100 mg/d)</td>
<td>Acetylsalicylic acid (3.5 g/d)</td>
<td>None</td>
<td>Immune ulcer of unknown cause</td>
</tr>
</tbody>
</table>

*LE indicates left eye; RE, right eye; and ellipses, not applicable.
†ANA indicates antinuclear antibody; MPO, myeloperoxidase antibody.
associated with a peripheral corneal ulcer (Figure 2, left). As the eye started to develop stromal melting, topical steroid therapy was replaced by nonpreserved artificial tears; however, the inflammation and ulcer worsened. Topical application of NGF was begun 5 days later. After 7 days, a conjunctival pannus started to cover the ulcer, and a healing process and decrease of inflammation in the area of scleromalacia became apparent. During the first week of NGF treatment, the patient experienced local pain and photophobia. Two months later, the cornea was completely healed with a pannus in the area of the ulcer and the area of dehiscence was markedly reduced. The eye did not show any signs of inflammation (Figure 2, right).

Case 3. A 45-year-old woman affected by lung tuberculosis had been treated with ethambutol, rifampin, and pyrazinamide. She developed erythema, small leg ulcers, and bilateral peripheral corneal ulcers associated with scleritis. Conjunctival and skin biopsy specimens confirmed the diagnosis of systemic and ocular vasculitis. Despite topical and systemic therapy with steroids, the corneal ulcers worsened and stromal melting developed. After 7 days, the right eye (with the more shallow ulcer) was treated with topical 2% cyclosporine 4 times daily, while the left (with a pre–Descemet membrane ulcer) was treated with topical NGF. The patient complained of increased pain and photophobia in both eyes. Two weeks later, the healing process was evident in both eyes, although a marked inflammatory condition was present in the right eye. After 3 weeks of treatment, the right eye had completely healed with a conjunctival pannus in the area of the ulcer, though inflammation persisted. The left eye was completely healed after 4 weeks. A conjunctival pannus developed in the area of the ulcer and the eye did not show any signs of inflammation. During the following 4 months, the patient continued to have persistent ocular inflammation in the right eye with corneal punctate keratopathy not present in the left eye.

At 4 months' follow-up, the patient was found to have a relapse of the corneal ulcer in the right eye that showed a rapid and progressive worsening despite systemic and topical steroid treatment. After 4 days, topical steroid treatment was replaced with 2% cyclosporine therapy, but no improvement was observed after 10 days. Treatment with NGF was begun in the left eye, and the epithelium started to grow through the ulcer's edges after 7 days. The ulcer healed completely in 2 weeks. At 3 months' follow-up, no relapse of the ulcer was observed in the right eye.

Figure 1. Left, A patient affected by rheumatoid arthritis developed a peripheral corneal ulcer associated with stromal melting. Right, The ulcer healed completely after 21 days of nerve growth factor treatment.

Figure 2. Left, A patient developed relapse of scleromalacia associated with peripheral corneal ulcer 1 month after a scleral patch was performed following necrotizing scleritis. Right, The corneal ulcer healed completely after 2 months of nerve growth factor treatment.
Case 4. A 62-year-old man with recurrent scleritis responsive to topical steroids developed a peripheral corneal ulcer associated with scleritis. The patient was treated with systemic steroids and acetylsalicylic acid for nonspecific arthritis. Systemic treatment did not induce an improvement. When topical steroids were added to the treatment, a reduction of the inflammation was observed; however, the corneal ulcer worsened, becoming deeper and wider, and undergoing stromal melting and neovascularization. After 5 days, topical NGF treatment was begun. During the first days of treatment, the patient experienced transient local pain and photophobia. Healing started after 7 days of NGF treatment and the symptoms progressively disappeared. The inflammatory reaction decreased, and the healing process was complete after 24 days of treatment.

Comment. This study shows that topical application of NGF blocks the inflammatory condition and promotes healing within 2 weeks in patients unresponsive to steroid and immunosuppressive drugs, and affected by severe peripheral corneal ulcers with stromal melting caused by multiple immune etiologies. All the corneal ulcers that we have treated with NGF healed within 8 weeks, and no relapse of the disease was observed in any patient during follow-up (3-12 months) (Table 2). The only adverse effect observed during NGF treatment was local pain and photophobia, which preceded the healing process and disappeared soon after the healing was completed.

The inflammatory responses within and outside the nervous system were associated with a transient increase of NGF. Moreover, an increase of immune cells expressing NGF receptors has been reported in ocular inflammatory diseases, such as cicatricial pemphigoid and vernal keratoconjunctivitis. The functional significance of these changes is not known. However, it is possible that NGF is involved in treating ocular inflammation, reducing cell damage, and promoting corneal healing. The hypothesis of the anti-inflammatory role of NGF has already been reported. It has been shown that NGF exerts an anti-inflammatory action on experimentally induced inflammation, i.e., is 10 times more active than dexamethasone, and 1000 times more active than nonsteroid anti-inflammatory drugs in animals. In addition, a direct action of NGF treatment in promoting healing is consistent with previous in vitro findings, showing that NGF induces proliferation and differentiation of corneal epithelial cells. In addition, clinical observations suggest that NGF treatment restored the corneal integrity and improved the sensitivity of 12 patients with neurotrophic ulcers. The beneficial effect of the interruption of topical steroid administration observed in case 1, and the frequent administration of preservative-free lubricants, might also contribute to corneal healing. A prolonged washout and the presence of concomitant treatments should be carefully assessed in a masked controlled study. However, the experimental data and the good clinical response of all the patients treated with NGF encourage further investigation of the mechanisms of NGF action on corneal diseases and the potential use of NGF in other corneal diseases.

Our data represent the first evidence that topical application of NGF might promote corneal healing and inflammatory recovery in ocular immune diseases unresponsive to existing therapies.

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Table 2. Effects of Nerve Growth Factor Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Associated Systemic Treatment</th>
<th>Onset of Healing, d</th>
<th>Complete Healing, d</th>
<th>Pain and Photophobia, d</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prednisone (40 mg/d) Methotrexate (7.5 mg/ wk)</td>
<td>5</td>
<td>21</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone (40 mg/d) Cyclophosphamide (100 mg/d)</td>
<td>7</td>
<td>60</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Pyrazinamide (1.25 g/d) Ethambutol (1.25 g/d) Rifampin (600 mg/d) Prednisone (40 mg/d)</td>
<td>14</td>
<td>28</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Prednisone (40 mg/d) Cyclophosphamide (100 mg/d) Acetylsalicylic acid (3.5 g/d)</td>
<td>7</td>
<td>24</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>
Retinal and Subhyaloid Hemorrhage as a Complication of Laser Iridectomy for Primary Angle-closure Glaucoma

Retinal hemorrhage following glaucoma surgery is a rare complication reported as decompression retinopathy\(^1\) and central retinal vein occlusion\(^2\) following trabeculectomy for open-angle glaucoma. To our knowledge, we report the first retinal hemorrhage occurring as a complication of argon laser iridectomy for primary angle-closure glaucoma. Two patients had retinal hemorrhage and 2 others had a hemorrhage mainly in the subhyaloid space.

Report of Cases. Case 1. A 68-year-old Japanese woman with a dark iris was diagnosed with acute angle-closure glaucoma in her left eye. The initial visual acuity was hand movements\(^1\). The intraocular pressure (IOP) was 70 mm Hg OS despite medical treatment. She suffered from mild anemia, angina pectoris, and mild hypertension, all controlled with medication. Funduscopic examination revealed a pale, edematous optic disc. After an intravenous drip infusion of a hyperosmotic agent and administration of 1% pilocarpine hydrochloride eye drops, laser iridectomy was performed using an argon laser (wavelength, 514 nm, Coherent 930 Argon/Dye; Coherent Co, Auburn, Calif) and an Abraham iridectomy lens. Stretch burns were placed in a circle using a 200-µm spot size, 150 mW of power, and a 0.2-second duration. Punch burns were applied using a 50-µm spot size, 600 to 1000 mW of power, and a 0.05-second duration. A total of 407 burns were placed. The IOP was 24 mm Hg OS immediately following the procedure.

On day 1, the iridectomy closed and the IOP increased to 62 mm Hg. Laser iridectomy was performed again resulting in a total of 147 punch burns. The patient noticed blurred vision the next day, and funduscopic examination revealed a hemorrhage in the subhyaloid space on and around the optic disc and along the superotemporal vascular arcade (Figure 1, A). A small amount of retinal hemorrhage was also observed. Retinal veins were moderately tortuous. Fluorescein angiography revealed no prolonged retinal circulation time or occlusion of retinal vessels (Figure 1, B). The indocyanine green videoangiography showed pulsation of the central retinal vein and staining of the retinal artery and vein on the optic disc (Figure 1, C). Following phacoemulsification of the lens with intraocular lens implantation and goniosynechialysis, the IOP was controlled at 14 mm Hg OS without medication. Bimicroscopic examination and ultrasound echography revealed a posterior vitreous detachment (PVD). Six months later, the subhyaloid hemorrhage had disappeared and the patient’s visual acuity was 20/30 OS.

Case 2. A 53-year-old Japanese woman was diagnosed with acute angle-closure glaucoma in both eyes. Her general health was good. Initial visual acuity was hand movements OD and 20/25 OS. The IOP was 76 mm Hg OD and greater than 76 mm Hg OS. Funduscopic examination revealed no remarkable change. Laser iridectomy was performed on both eyes using an argon laser, with additional enlargement by Q-switched Nd:YAG laser (Microruptor III; LASAG, Thun, Switzerland) using a single pulse of 0.5 mJ and total energy of 3.9 mJ to the right eye and 6.9 mJ to the left eye, respectively. Immediately following the procedure, the IOP decreased to 14 mm Hg OD and 53 mm Hg OS.

The next day, the IOP was 14 mm Hg OD and 34 mm Hg OS, and funduscopic examination revealed subhyaloid hemorrhage, retinal hemorrhage, tortuous and dilated retinal veins, and an edematous optic disc in the left eye. There was no abnormal change in the right fundus. Fluorescein angiography revealed no retinal vein occlusion. Ultrasound echography showed a PVD. On day 3, the subhyaloid hemorrhage proceeded to a hemorrhage in the vitreous gel. Following argon laser gonioplasty, the IOP was con-

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**Figure 1.** Patient 1, left eye. A. Twenty-two days after argon laser iridectomy the subhyaloid hemorrhage is present. B. Fluorescein angiography 1 day after the second laser iridectomy revealed no central retinal vein occlusion (23 seconds after dye injection). C. The indocyanine green angiography 1 day after the second laser iridectomy showed staining of the retinal artery and vein on the optic disc (14 seconds after dye injection).
trolled at 18 mm Hg OD and 19 mm Hg OS. Two months later, the vitreous hemorrhage had resolved and visual acuity had improved to 20/15 OD and 20/20 OS.

Case 3. A 78-year-old Japanese woman was diagnosed with acute angle-closure glaucoma in the left eye. She had mild hypertension controlled with medication. Visual acuity was 20/40 OS and the IOP was 70 mm Hg despite receiving medication. There was no fundus abnormality and ultrasound echography revealed no PVD. Laser iridectomy was performed using an argon laser.

On day 1, the IOP was 19 mm Hg; a 4-blot hemorrhage was noted in the retina and another on the optic disc. Fluorescein angiography revealed no abnormalities. Ultrasound echography showed a PVD. Three months later, the retinal hemorrhage had resolved. Visual acuity was 20/20 OS and the IOP was controlled (<20 mm Hg) without medication.

Case 4. A 66-year-old Japanese woman was diagnosed with acute angle-closure glaucoma in the left eye. She had mild hypertension controlled with medication. Visual acuity was 20/50 OS and the IOP was 76 mm Hg despite receiving medication. There was no fundus abnormality and ultrasound echography revealed no PVD. Laser iridectomy was performed using an argon laser, and immediately after the procedure the IOP was 42 mm Hg OS.

On day 1, the IOP was 11 mm Hg OS; a 2-blot hemorrhage was noted in the retina, 1 of which had a white center (Figure 2). No optic disc edema or tortuosity of the retinal vessels was noted. Visual acuity improved to 20/20 OS and the IOP was controlled (<20 mm Hg) without medication.

Comment. Retinal hemorrhage is a rare complication of glaucoma surgery. Fechtner et al reported retinal hemorrhage as a complication of trabeculectomy for open-angle glaucoma, referring to it as “decompensation retinopathy.” They suggested that acute lowering of the IOP probably reduced resistance to blood flow and that the increased blood flow likely had overwhelmed the mechanical stability of the capillaries, resulting in multiple focal endothelial leaks. Defects in the autoregulatory mechanism in patients with glaucoma also have been suggested as contributory to the development of hemorrhage. Although decompensation retinopathy usually occurs in young and generally healthy patients, our 3 patients were elderly and hypertensive.

In patients 1 and 2, acute lowering of the IOP might have induced tortuosity of retinal veins, optic disc edema, and retinal hemorrhage. However, in these 2 patients, the hemorrhages in the subhyaloid space were marked. Retinal hemorrhage resembling central retinal vein occlusion has been reported as a complication of trabeculectomy. However, in our patients there was no disturbance in the retinal circulation angiographically and the hemorrhagic pattern was different from that in central retinal vein occlusion. The hemorrhage in the subhyaloid space could occur in severe decompensation, but another hypothesis might be suggested as the cause of subhyaloid hemorrhage in our patients. In an acute phase of angle-closure glaucoma, the volume of aqueous humor in the posterior chamber increased markedly caused by pupillary block, and vitreous gel was pushed toward the posterior pole (Figure 3, A). In our 2 patients, the preoperative IOP in the affected eyes was extremely high, resulting in a correspondingly significant displacement of vitreous gel. However, following laser iridectomy, aqueous flowed slowly from the posterior chamber to the anterior chamber through the iridectomy. Additionally, outflow through the trabecular meshwork and the administration of a hyperosmotic agent and carbonic anhydrase inhibitor further decrease aqueous volume, and hyperosmotic agents remove fluid from the vitreous and may accelerate contraction of the vitreous. The forward displacement and contraction of the vitreous gel would induce a rapid PVD, disrupting small vessels in the retinal surface or optic disc (Figure 3, B). Posterior vitreous detachment, in fact, was observed in these 2 patients after laser iridectomy, although ultrasound examination was not performed before the procedure. Posterior vitreous detachment was also observed after laser iridectomy in patient 3. However, there are still some problems to be solved in this hypothesis; eg, does the normal anterior hyaloid face offer significant resistance to aqueous passage in pupillary block? Retinal hemorrhage has been reported following the administration of hyperosmotic agents. Therefore, the exact mechanism resulting in subhyaloid hemorrhage remains unclear.
Since, as our cases demonstrate, retinal and subhyaloid hemorrhage can occur after laser iridectomy for acute angle-closure glaucoma, especially in patients with extremely high preoperative IOP, surgeons should be aware of this possible complication.

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Peripheral Corneal Infiltrates Following Oral Diclofenac Administration

Diclofenac sodium is a nonsteroidal anti-inflammatory drug that has been used systemically and topically for the control of many forms of inflammation. Diclofenac and other topical nonsteroidal anti-inflammatory drugs have been used topically for the control of discomfort and pain following photorefractive keratectomy.1,2 The drug has been shown to decrease corneal sensitivity following topical use.3 Peripherial corneal infiltrates have been observed following topical application of diclofenac and soft contact bandage lenses following photorefractive keratectomy.1,4

To my knowledge, peripheral corneal infiltrates following the use of oral diclofenac have not been previously reported. Here I report a case of peripheral corneal infiltrates following oral use of diclofenac.

Report of a Case. A 37-year-old male physician had a history of pain, redness, irritation, and photophobia in the left eye of 2 days’ duration. His medical history revealed a history of backache, for which he received diclofenac sodium, 50 mg orally twice daily for a period of 1 week. The patient denied a history of systemic illness and had no previous episodes of blepharitis or conjunctivitis. He also denied using contact lenses for the past year.

On examination, the patient was found to have a visual acuity of 20/20 OD and 20/20 OS with correction. Biomicroscopy of the right eye revealed normal conjunctiva and peripheral 360° corneal micropannus. Biomicroscopy of the left eye revealed normal eyelids with no eyelid disease and no blepharitis. There was mild conjunctival hyperemia. A 360° corneal micropannus was noted, and 2 peripheral corneal infiltrates measuring 1.0 mm in diameter each were noted at the 2-o’clock and 6-o’clock positions. The corneal epithelium was intact and no staining with fluorescein was noted. The infiltrates were subepithelial with a 1.0 mm lucid interval between the corneal infiltrates and the limbus. Cultures of the eyelids and corneal infiltrates on blood agar, chocolate agar, and thioglycolate medium were negative for organisms. Giemsa-stained corneal scraping revealed polymorphonuclear cells. The patient was treated with topical 0.1% fluorometholone eyedrops 3 times daily. Backache, for which he received diclofenac, the patient resumed diclofenac administration and after 3 days developed 2 peripheral corneal infiltrates in the left eye. This time, the patient was asked to discontinue the use of diclofenac and no topical treatment was given. The infiltrates subsided within 7 days after the discontinuation of the use of oral diclofenac.

Comment. Peripheral corneal infiltrates have been reported with the topical use of diclofenac. Sher et al1 noted peripheral corneal infiltrates in 3 patients following administration of topical diclofenac. The peripheral corneal infiltrates of my patient occurred at 3 different occasions following 3 different courses of diclofenac. The appearance of these peripheral corneal infiltrates is probably secondary to the use of oral diclofenac. The mechanism may be similar to that seen with topical diclofenac. The presence of preexisting contact lens–induced peripheral corneal vascularization may have predisposed to peripheral corneal infiltrations. Although the exact mechanism is not well understood, it could be due to inhibition of cyclooxygenase 1 and 2 with a subsequent shunt to the lipoxygenase pathway leading to the synthesis of leukotrienes such as LTB4—a chemotactic factor that may attract polymorphonuclear cells to the corneal periphery.

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3. Szeryni K, Sorken K, Garbus JJ, Lee M, McDonnell PJ. Decrease in normal human corneal sen-
Conjunctival Cryptococcosis in the Acquired Immunodeficiency Syndrome

Intraocular infection with Cryptococcus neoformans in people with the acquired immunodeficiency syndrome (AIDS) is very uncommon compared with meningeal and optic nerve involvement. When it does occur it is mostly in the posterior segment.1,2 For lesions in the anterior segment, a MEDLINE search revealed only 1 case of iris involvement3 and 2 of small conjunctival granulomas.4,5 We describe a patient with a larger conjunctival lesion mimicking a carcinoma.

Report of a Case. A 28-year-old Ugandan man had a 6 × 10-mm lesion of the temporal interpalpebral conjunctiva of the right eye, encroaching 1 mm onto the cornea (Figure 1). There was marked surrounding hyperemia. In site and appearance it resembled a conjunctival carcinoma except that the surface was less rough and opaque than usual. Visual acuity in the eye was 6/18+2 and the fundus was normal. The left eye was normal with an acuity of 6/6. Aside from having oral candidiasis, he was well and had not lost weight. The lesion was excised with a lamellar sclerokeratectomy as it was firmly fixed to the underlying coats. Alcohol was applied to the corneal edge after resection. The defect was closed with a pedicle graft from the upper bulbar conjunctiva. It healed well and postoperative acuity was 6/9. After pretest counseling, results from human immunodeficiency virus (HIV) testing with 3 different tests were positive (1 agglutination test and 2 enzyme immunoassay tests). He received posttest counseling and was referred to the nearby AIDS Support Organization for management of his general condition. Findings from a cryptococcal antigen test done retrospectively on stored serum were 1+.

One month later he developed a wasting syndrome with recurrent fever, diarrhea, and stomatitis. He did not complain of headache, and meningitis was not suspected. His condition deteriorated rapidly and he died 2 months postoperatively.

Histopathologic Findings. Histopathologic findings (Figure 2) showed that beneath the conjunctival epithelium there were numerous giant cells arranged in a loose granulomatous pattern. The pseudocystic spaces containing the fungus were evident. A Grocott stain (Figure 3) showed abundant C. neoformans yeasts, some within mucoid pseudocystic spaces.

Figure 1. A 6 × 10-mm lesion of the temporal interpalpebral conjunctiva encroaching onto the cornea, found to be a cryptococcal infection.

Figure 2. Histopathologic finding showing giant cells and pseudocystic spaces containing fungi beneath a normal epithelium (hematoxylin-eosin, original magnification ×1000).

Figure 3. Abundant cryptococci are shown, some with mucoid pseudocystic spaces seen (Grocott, original magnification ×1000).
Comment. The preoperative diagnosis was squamous cell carcinoma since so many of these are now being seen in Uganda (more than 150 a year were seen by our team alone). Histologic study showed this preoperative diagnosis to be incorrect. In retrospect, the smoother surface and total fixation to the sclera were unusual for a moderately sized carcinoma. Excision appeared curative for the amount of time he survived thereafter. T-lymphocyte subsets were not measured, but the course of the disease makes it very likely he was severely immunosuppressed. The possibility of meningeval or pulmonary cryptococcosis was not considered during his terminal illness, but it might have been obscured by the other features. It is therefore uncertain whether the eye lesion was isolated or associated with cryptococcal infection elsewhere. It is known that cutaneous lesions can appear before dissemination. In one of the previously reported conjunctival cases, systemic disease in the form of multifocal choroiditis was present. In another case disease was isolated and preceded seroconversion to HIV. These cases (one from Brazil and the other from Germany) had inconspicuous nodules (largest, $5 \times 5$ mm) of uncertain nature until biopsy was performed. This raises the possibility that such lesions are being overlooked in ill patients and yet would provide a useful pointer to the diagnosis of cryptococcosis. In Uganda this is unlikely to be true because this case is the only cryptococcal infection found in our current study of more than 400 conjunctival biopsy specimens, most of which (65%) were from people who are HIV positive.

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Report of a Case. A 47-year-old woman visited our clinic with a gradual decrease and dimming of central vision that she had first noticed about 20 years previously. When she was 12 years old, her physician prescribed chloroquine (300 mg/d), which she took for 2 years to treat renal failure of unknown cause. Her best-corrected visual acuity at the initial visit was a $10.5$-diopter (D) sphere OD, and $20/200$ OU with a $11.0$-D sphere OS. Fundus examination revealed a large macular hole (MH) in each eye with a vertical diameter of $3580 \mu m$ OD and $2910 \mu m$ OS (Figure 1). Scanning-laser ophthalmoscope microperimetry images revealed that both eyes’ fixation point was located at the upper edges of the MHs (Figure 2). Optical coherence tomography showed that the edges of the MHs were swollen (Figure 3). The patient rejected undergoing fluorescein angiography. To prevent further visual reduction, a pars plana vitrectomy with 12% perfluoropropane gas tamponade was performed.

Bilateral Giant Macular Hole

We describe a 47-year-old woman with an extremely large macular hole in each eye, with vertical diameters of $3580 \mu m$ OD and $2910 \mu m$ OS. Her best-corrected visual acuity was $20/200$ OU. A flattening of the macular hole’s edge was observed in the right eye after a pars plana vitrectomy; however, the visual acuity remained unchanged. The cause of the macular holes was uncertain but the presence of high myopia and/or her history of taking chloroquine were suspected.

Figure 1. Fundus photograph of the right (A) and left (B) eyes on the initial visit showing large macular holes with vertical diameters of $3580 \mu m$ OD and $2910 \mu m$ OS.
formed on the right eye. A flattening of the MH edge was observed (Figure 4); however, the postoperative visual acuity remained unchanged.

Comment. Banker et al\(^1\) reported that the size of idiopathic MHs range from 177 µm to 917 µm (in a study of 164 eyes). Extremely large MHs, as in our relatively young patient, are quite unusual. Although the cause of the MHs in our patient is uncertain, the presence of high myopia or a patient’s taking a cumulative dose of greater than 200 g of chloroquine, which is sufficient for causing retinopathy,\(^2,3\) may be associated with MH formation. Visual prognosis may not be favorable for vitrectomy for extremely large, chronic MHs.

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Figure 2. Scanning laser ophthalmoscope microperimetry images of right (A) and left (B) eye on the first visit. Fixation points of both eyes are located on the upper edges of the holes.

Figure 3. Vertical sections of optical coherence tomography images through the center of the right (A) and left (B) macular holes showing swollen edges of both sides.

Figure 4. Postoperative fundus photograph of the right eye (A) and vertical sections of optical coherence tomography images through the center of the macular hole in the right eye (B) showing flattening of the edges.
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Bilateral Lymphomatous Optic Neuropathy Diagnosed on Optic Nerve Biopsy

Involvement of the central nervous system (CNS) in non-Hodgkin lymphoma (NHL) most commonly occurs as secondary spread from systemic disease rather than as a primary CNS malignant neoplasm and generally carries a poor prognosis.1 Optic nerve involvement is rare and the diagnosis is often elusive since the results of repeated lumbar punctures and neuro-imaging are frequently normal.2 We report a case in which a definitive diagnosis of lymphomatous optic neuropathy was made following optic nerve biopsy.

Report of a Case. Following a flu-like illness, a 74-year-old woman was found to have mild lymphocytosis and marginal thrombocytopenia. She experienced intermittent monocular visual obscurations and 12 months later noticed inferotemporal visual field loss in the left eye that was confirmed on Amsler chart testing. Her visual acuity was 20/15 OU and she was found to have bilateral optic disc swelling (Figure 1), but no cells in the vitreous. An infiltrative optic neuropathy was suspected and a magnetic resonance imaging scan performed with contrast medium showed enlarged optic nerves that did not enhance. A bone marrow biopsy revealed a low-grade lymphoproliferative disorder and a chest radiograph showed no abnormality. Analysis of peripheral blood with lymphocyte markers was positive for B-cell markers CD19, CD20, and CD68 and for k light chains and IgM. Two lumbar punctures were performed showing raised cerebrospinal fluid protein levels of 0.62 and 0.55 g/L. No cells were present in the samples from the first procedure. However, the second lumbar puncture samples yielded cerebrospinal fluid containing 4 mature lymphocytes. However, no evidence was noted of malignant neoplasms or atypia.

Four months later visual acuity had deteriorated to 20/30 OD and 20/80 OS with a left relative afferent pupillary defect. Advanced bilateral visual field constriction was noted with almost total loss of visual field in the left eye (Figure 2). A diagnostic left optic nerve biopsy was, therefore, performed using the optic nerve sheath fenestration method with a biopsy performed of the underlying optic nerve substance. Gross examination of the optic nerve sheath was not diagnostic, but material from the optic nerve substance showed infiltration by a low-grade B-cell NHL (Figure 3).

Immediately postoperatively visual acuity had deteriorated to light perception OS but improved to 20/60
over the next 5 months following low-dose radiotherapy to the optic nerves (total dose 30 Gy to the optic nerves in 15 fractions over 3 weeks). Goldmann visual fields 3 months after biopsy and 1 month after radiotherapy showed that progressive deterioration had been arrested (Figure 2).

Eleven months after optic nerve biopsy, the optic discs had become atrophic (Figure 1) with a visual acuity of 20/40 OD and 20/80 OS. The patient has required local radiotherapy for a right lower eyelid lymphomatous mass, but no systemic therapy has been administered as the patient has remained otherwise well.

Comment. Central nervous system NHL most commonly involves the leptomeninges, nerve roots, cerebral parenchyma, and dura with optic nerve infiltration in just 5% of the patients. There are reports of isolated optic neuropathy occurring with other lymphoproliferative disorders, but we are aware of only 3 reported cases of CNS NHL seen with an isolated infiltrative optic neuropathy.2-4 The patient described by Kansu et al2 was seen with an isolated infiltrative optic neuropathy with no other systemic or CNS involvement2; whereas, in the case reported by Strominger et al,3 the optic neuropathy was preceded by a 2-year history of leukopenia. According to Walsh and Shewmake,4 their patient developed third, fourth, and sixth cranial nerve palsies 3 weeks after the visual loss. In all 3 cases initial cerebrospinal fluid examination did not show lymphomatous cells and the diagnosis of NHL was made, respectively, on results from a craniotomy and optic nerve excisional biopsy,2 temporal artery biopsy,3 and biopsy of an abdominal lymph node following a jejunal perforation.4 It is perhaps surprising that findings from a biopsy of the optic nerve sheath in this case were not diagnostic given the predilection of NHL for dural spread over optic nerve involvement.2 To our knowledge, our case is the first such reported in which localized biopsy performed on the optic nerve substance was used to confirm the diagnosis of NHL; in the case reported by Kansu et al2 it appears that the optic nerve was sacrificed to allow histological examination.

Optic nerve biopsy carries a risk of permanent visual loss and may yield false-negative results since the size of the biopsy specimen is limited by the necessity of preserving vision. However, the case reported herein illustrates that diagnostic optic nerve biopsy can be invaluable in cases in which diagnosis of CNS lymphoma is impossible by any other means, eg, such as biopsy of lymph nodes, bone marrow, or masses. Despite temporary visual deterioration after the biopsy—presumably caused by neuropraxis—there was later improvement of optic nerve function to at least the prebiopsy level. Although there was a degree of subsequent visual decline owing to optic atrophy, this initial visual recovery...
suggests that optic nerve biopsy may be considered for diagnosis in enigmatic cases even when some visual function remains.

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Figure 3. Optic nerve biopsy specimen with crush artefact (A) (hematoxylin-eosin, original magnification \( \times 40 \)) shows lymphomatous infiltration, but monomorphic cellular morphology is definitively seen in the peripheral optic nerve biopsy (B) (hematoxylin-eosin, original magnification \( \times 400 \)). C, View of the lower eyelid subcutaneous mass (hematoxylin-eosin, original magnification \( \times 12.5 \)). D, View shows a similar monomorphous cellular appearance (hematoxylin-eosin, original magnification \( \times 400 \)).