

Bromfenac-induced neurotrophic keratitis in a corneal graft

Nimmy Raj , Arnav Panigrahi , Mahboob Alam, Noopur Gupta 

Cornea, Cataract and Refractive Surgery Services, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, Delhi, India

Correspondence to

Dr Noopur Gupta;
noopurgupta@hotmail.com

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SUMMARY

A man in his 30s, with a history of two operated penetrating keratoplasty (PK), primarily for viral keratitis, presented with pain, redness and diminution of vision in his left eye of 4 days duration. Postoperatively, he was prescribed oral antivirals, topical steroid eyedrops, lubricants and antiglaucoma medications. Eight months after transplantation, an epithelial defect with heaped up margins was noted on anterior segment evaluation on a routine follow-up visit. On checking his medications, it was found that the patient was unknowingly using bromfenac drops in place of brimonidine tartrate for the past month. A diagnosis of neurotrophic keratitis was made in the setting of PK performed for viral keratitis, incited by use of topical bromfenac. The patient was prescribed preservative-free lubricants with immediate discontinuation of bromfenac drops. Topical steroid drops were withheld till the epithelial defect healed. Complete healing of the defect was noted after 4 weeks of therapy.

BACKGROUND

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in ophthalmic practice, especially following cataract surgery to control inflammation and prevent occurrence of cystoid macular oedema. However, they can act as a double-edged sword with deleterious effects in patients with compromised ocular surface due to previous surgeries, presence of viral keratitis, chronic use of preserved topical drops or presence of systemic disease like rheumatoid arthritis. Accidental use of NSAIDs for a short duration may incite unwanted consequences in such patients. This may occur due to easy availability and over-the-counter use of these drugs, complicated by illegible medical prescriptions. Illustrating this problem, we report a case of neurotrophic keratitis (NK) due to over-the-counter use of topical bromfenac, dispensed by mistake, in place of a similar sounding antiglaucoma medication (brimonidine).

CASE PRESENTATION

A male patient in his fourth decade presented to our outpatient department with complaints of redness, pain and watering associated with diminution of vision in his left eye (LE) for the past 4 days. There was no history of any trauma to the eye. His previous history was significant with penetrating keratoplasty (PK) performed twice in the LE, nearly 4 years back for healed viral keratitis and around 8 months from the current visit for post-PK graft infection. He was also a diagnosed case of secondary (post-PK) glaucoma in the same

eye. After the second surgery, his pinhole acuity was noted to be 0.6 logMAR units and the patient was prescribed topical antibiotic, topical steroid, lubricant eyedrops and antiglaucoma medication postoperatively. He continued oral acyclovir 400 mg two times per day as antiviral prophylaxis regimen. The patient was lost to follow-up after the initial postoperative visits due to the nationwide lockdown implemented in the country in view of the COVID-19 pandemic.

On examination, visual acuity in the LE was 1.3 LogMAR units with raised intraocular pressure on digital palpation. An epithelial defect of 4×3.5 mm was noted in the central cornea with anterior stromal involvement of approximately 10%–20% depth ([figure 1A,B](#)) of the cornea. The distinct punched-out margins of the epithelial defect along with heaped-up unhealthy epithelium at the edges pointed to a clinical diagnosis of NK. The underlying stroma was clear and there were no infiltrates surrounding the defect. Central graft clarity was mildly affected with few descemet's membrane folds. Rest of the corneal graft was clear with well-apposed graft-host junction. Corneal sensations, as assessed qualitatively by a cotton-tipped applicator, were diminished in the LE. Cochet-Bonnet aesthesiometer was not available for use due to the ongoing COVID-19 pandemic. Anterior chamber was quiet, without any signs of inflammation. Presence of posterior subcapsular cataract was noted. Fundus details were hazily visible on the initial visit.

On checking the patient's compliance to topical medications, it was found that he was using topical bromfenac solution in place of brimonidine tartrate advised for post-PK glaucoma. It was wrongly dispensed by the pharmacist and the patient had been using this for the past month, unaware of the confusion thus created. The patient was counselled about the wrong medication he was using and was asked to ensure usage of correct medications in the future. A decrease in size of epithelial defect was noted after stopping bromfenac eyedrops and initiation of therapy for NK ([figure 1C](#)).

INVESTIGATIONS

Serial anterior segment optical coherence tomography imaging helped in documenting the clinical course of neurotrophic keratitis in our patient. It confirmed the presence of the persistent epithelial defect (PED) with denuded epithelium ([figure 2A](#)) and heaped up margins. Reduction in size of the defect was noted at follow-up visits ([figure 2B,C](#)) followed by complete healing of the defect with residual corneal opacity ([figure 2D](#)).



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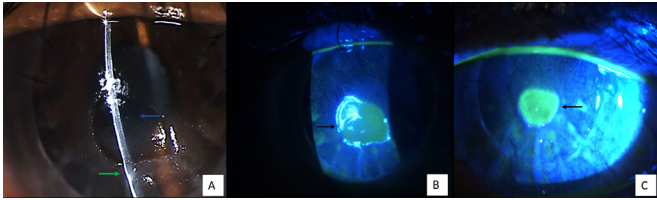


Figure 1 Slit lamp photographs of the patient with neurotrophic keratitis in the donor corneal graft showing (A) central 4×3.5 mm punched-out epithelial defect in the central cornea (blue arrow) with epithelial heaping at the margins of the defect (green arrow). Cobalt blue filter with fluorescein stain (B) enhances the epithelial defect (black arrow) and demonstrates the sharp borders. The epithelial defect (black arrow) decreased in size (C) after a week of therapy and removal of the inciting drug, bromfenac eyedrops, delineated clearly with fluorescein staining visualised under cobalt blue filter.

Microbiological investigations were performed aided by gentle corneal scrapings from the edge of the corneal epithelial defect. Gram stain, Giemsa stain, KOH (potassium hydroxide) mount, bacterial culture on blood agar, fungal culture on Sabouraud dextrose agar and thioglycollate broth were performed. Microbiological analysis did not reveal growth of any microorganism on culture.

DIFFERENTIAL DIAGNOSIS

Viral keratitis.

Neurotrophic keratopathy (no-Bromfenac-related).

TREATMENT

The inciting agents for development of neurotrophic keratitis in our patient, bromfenac eyedrops, were immediately stopped. Topical steroid drops were withdrawn temporarily to enhance wound healing. The patient was managed with topical lubricants (preservative-free carboxymethylcellulose 1% every 2 hours), prophylactic topical antibiotic (chloramphenicol 0.5% three times a day), oral vitamin C (500 mg two times a day) and night time taping of lids after instilling lubricating ointment (carbomer and vitamin A palmitate gel). Antiglaucoma medication (combination of brimonidine tartarate and timolol maleate along with

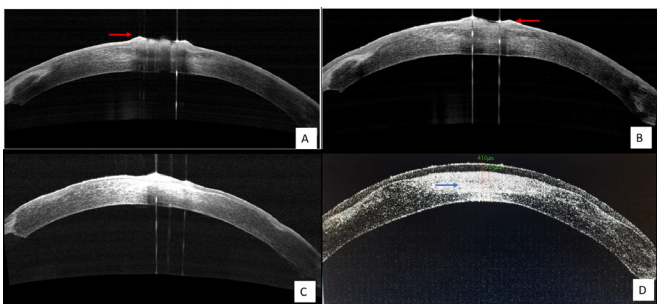


Figure 2 Serial anterior segment optical coherence tomography (ASOCT) images of the left eye taken at 1 week interval showing course of healing of the persistent epithelial defect. Note the denudation of corneal epithelium centrally (A) with heaped up margins (red arrow) at the time of presentation. Reduction in size of defect (B) was noted at follow-up visits followed by complete healing of the defect (C) along with irregular epithelial surface and underlying stromal inflammation. At the completion of 4 weeks, a residual macular corneal opacity (D) involving the anterior stromal layers (blue arrow) and relative sparing of the posterior stromal layers was noted.

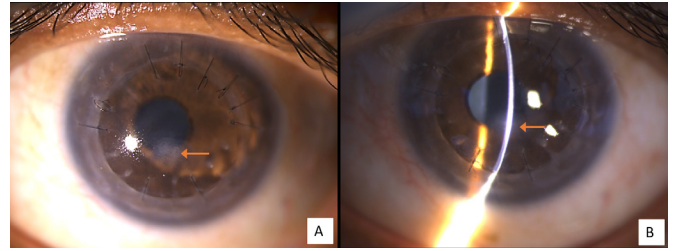


Figure 3 Slit lamp photographs of the patient showing (A) healed epithelial defect with residual macular corneal opacity (orange arrow). Optical section (B) confirms the same, showing the presence of a corneal opacity (orange arrow), surrounding clear cornea and well apposed graft-host junction.

oral glycerol six teaspoons) two times a day was started to control the intraocular pressure.

OUTCOME AND FOLLOW-UP

Reduction in the size of the epithelial defect was noted with treatment and the epithelial defect eventually healed completely by the end of 4 weeks. It resulted in anterior stromal scarring leading to formation of a macular corneal opacity (figure 3A,B). At the last follow-up visit, he achieved a visual acuity of 0.50 LogMAR units with a refractive correction of -3D sphere and -3D cylinder at 130° in the LE. The suboptimal BCVA in the LE was attributed to early development of cataract.

DISCUSSION

Topical NSAIDs have proved their efficacy in many conditions like controlling postoperative pain and inflammation, preventing development of cystoid macular oedema following cataract surgery, maintaining intraoperative mydriasis and also off-label use for ocular inflammatory conditions like allergic conjunctivitis, pingueculitis and episcleritis.¹⁻³ Being an effective alternative to topical steroids, absence of side effects like cataract and glaucoma makes its use quite prevalent in ophthalmic practice. Topical NSAIDs and steroids have shown similar efficacy in controlling inflammation after cataract surgery, hence making the former a safer, but not inferior, alternative.⁴

As with almost all available medications, they are not devoid of adverse reactions, which range from mild symptoms like redness, transient burning and stinging sensation to more serious ones like superficial punctate keratitis, epithelial defects, corneal melts, ulcerations and perforations.⁵ Mechanisms for such inadvertent side effects associated with topical NSAIDs are not clearly elucidated; speculated hypothesis includes activation of matrix metalloproteinases, impairment of wound healing and neurotrophic effect, resulting from analgesic action of these drugs, the latter being unlikely in the absence of ocular surface disease.^{6,7}

Bromfenac is a phenylacetic acid derivative that has been approved by the Food and Drug Administration as 0.09% ophthalmic solution for two times per day instillation in the treatment of pain and inflammation after cataract surgery.⁶ Bromfenac is considered comparatively safer than other NSAID drops with regards to ocular surface complications. Reports of corneal melt associated with bromfenac are rare, with less than four cases reported in the literature.⁸ However, this complication is frequently associated with use of alternative NSAIDs like diclofenac and ketorolac.^{5,9,10} Although the use of NSAIDs is implicated in corneal melts in many case reports, development of neurotrophic keratitis following use of these agents has not reported as yet. Risk factors like

concurrent use of topical steroids, undiagnosed dry eye disease,¹¹ previous history of ocular surgery like pterygium surgery using bare sclera technique, preservatives present in topical medications, immunological disorders like rheumatoid arthritis¹² or Sjogren's syndrome¹³ and systemic diseases like diabetes mellitus can all contribute to the multifactorial pathogenesis of PED in these cases.

Neurotrophic keratitis is characterised by epithelial breakdown that progresses from punctate keratitis and focal epithelial loss in early stages (stage 1) to persistent non-healing epithelial defects (stage 2), stromal ulceration and melting in late stages (stage 3).¹⁴ The very fact that the anterior stroma was affected indicated an advanced stage of neurotrophic keratitis in our patient, which warranted immediate intervention with cessation of the inciting bromfenac eyedrops.¹⁵ The possible factors that led to the development of NK in our patient can be attributed to trigeminal damage secondary to iatrogenic injury, chronic use of preserved eyedrops for glaucoma with the concurrent use of topical steroids and bromfenac solution adding to the mishap. Reduced corneal sensation, secondary to healed viral keratitis and multiple corneal transplantation, added a neurotrophic component to the epithelial defect. The cascade of inflammatory events accompanying the PED and the healing response which followed eventually led to a central macular corneal opacity.

The very first step in management of neurotrophic keratitis involves cessation of all topical medications, and starting the patient on preservative-free lubricants.¹⁵ The rationale behind the former is to avoid potential toxicity to the epithelium by the active compound and/or preservatives used in various eye drops. If drug-induced, as in our case, cessation of the inciting agent brings the destructive pathogenic processes to a halt, allowing repair of the damaged regions by normal healing response of the eye. Topical medications, like antibiotics and antiglaucoma medications in our patient, should be used in preservative-free formulations, if deemed absolutely necessary. These medications were started in our patient considering the high risk of infection, owing to advanced stage of disease and stromal involvement. Topical steroids should not be used in an attempt to control the inflammatory damage, as it impairs stromal healing and increases the risk of corneal melt and perforation. Surgical modalities like tarsorrhaphy, use of conjunctival flap, tissue adhesive or amniotic membrane transplantation have been described to improve tissue healing and prevent perforation.¹⁶ These methods were not considered in our patient, owing to the satisfactory response seen with conservative management, including topical lubrication, antibiotics and night time eye patching.

This unfortunate complication could easily have been avoided by proper communication between the three parties involved: the patient, the practitioner and the pharmacist. The very fact that doctors are stereotyped and take the brunt of jokes for their illegible handwriting is nothing to be laughed at or felt proud of; it may sometimes lead to improper medication and dosage,¹⁷ and occasionally fatality.¹⁸ The pharmacists are not less to blame, with lack of appropriate qualification and unethical practices not uncommon in India.¹⁹ Patients need to be aware of these fallacies prevalent in medical practice, as it is them who use these medications, reap their benefits and suffer their deleterious effects. Doctors need to educate the patients regarding the medications and their use; this will go a long way in preventing such avoidable mishaps, alleviating some load off the healthcare system.

Patient's perspective

I was quite scared when I was told that I had developed a problem in my recently operated corneal graft due to use of wrong eye drops. I had already been operated two times, and the thought of losing vision and undergoing another surgery haunted me. Thankfully, the problem resolved with timely intervention from my doctor with resolution of my symptoms and gaining back my vision. Henceforth, I will ensure proper use of medications, and buy them only after confirming with my doctor.

Learning points

- ▶ Topical non-steroidal anti-inflammatory drugs and steroids should not be used together, as they impair epithelial healing and significantly weaken the ocular defence mechanism, especially in patients with compromised ocular surface.
- ▶ It is important to note that persistent epithelial defects are common in patients undergoing penetrating keratoplasty for healed herpetic keratitis due to reduced tear function and neurotrophic deficiencies.
- ▶ The case scenario described is ordinary and common; however, early recognition and prompt treatment of iatrogenic neurotrophic keratitis is important to minimise the risk for subsequent ulceration and visual loss.
- ▶ Over-the-counter medications must be used judiciously, as they may have deleterious side effects, which are usually overlooked due to their ease of availability.
- ▶ Legibility of the prescription must be ensured by the doctor, with instructions regarding the correct use of medications being clearly imparted to the patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs

Nimmy Raj <http://orcid.org/0000-0002-3921-3615>

Arnav Panigrahi <http://orcid.org/0000-0002-0036-3624>

Noopur Gupta <http://orcid.org/0000-0001-8022-6656>

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