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CASE REPORT

A Case of Corneal Melting Associated with Topical Diclofenac After Phacovitrectomy for Macular Pucker in a Patient with Rheumatoid Arthritis

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Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used perioperatively and postoperatively in ocular inflammation and pain management. However, NSAIDs may cause ocular adverse effects. Postsurgical complications, including corneal stromal inflammation with or without epithelial ulceration and stromal melts, have been reported after anterior segment surgery, such as cataract surgery, penetrating keratoplasty, and photorefractive keratectomy. However, these drugs are also frequently used in vitreoretinal surgery for several indications, including the prevention and treatment of postoperative cystoid macular edema.
Case Presentation: A 61-year-old man with rheumatoid arthritis, with no prior history of ocular surface disease, underwent uneventful combined phacovitrectomy in the right eye for macular pucker and cataract. Postoperatively, diclofenac 0.1% was added to the topical therapy. Within two weeks, the patient reported blurred vision and discomfort. Slit-lamp examination showed diffuse corneal edema with Descemet's membrane striae and a large epithelial defect with stromal ulceration in the inferior paracentral cornea. Best-corrected visual acuity (BCVA) dropped to counting fingers. Corneal topography revealed a wide thinning area. Diclofenac was immediately discontinued, and treatment with preservative-free dexamethasone 0.15%, ofloxacin 0.3%, and artificial tears was initiated. During follow-up, progressive improvement was observed with reduction of corneal opacity and thinning, along with recovery of BCVA. At the final visit, anterior segment OCT confirmed complete re-epithelization, a hyperreflective anterior stromal band, and mild residual thinning. BCVA improved to 20/20 with refractive correction (−3.50 sphere −3.25 cylinder axis 10).
Conclusion: Corneal melting has usually been described after anterior segment surgeries. Our case highlights the need for caution in the postoperative use of topical NSAIDs, particularly diclofenac, also in vitreoretinal surgery. Patients with autoimmune diseases, such as rheumatoid arthritis, may be at higher risk of adverse corneal effects, and careful consideration should be given when prescribing NSAIDs in this context.

Plain Language Summary: This case report highlights a rare but serious postoperative complication in ophthalmic surgery. We describe the development of corneal melting in a 61-year-old man with rheumatoid arthritis, two weeks after an uncomplicated combined phacovitrectomy performed to treat epiretinal membrane, a condition causing wrinkling of the central retina, and cataract. Topical diclofenac 0.1%, a nonsteroidal anti-inflammatory drug (NSAID), was added postoperatively to prevent inflammation and cystoid macular edema.

Shortly after starting the diclofenac, the patient experienced significant vision loss and corneal pain. Examination revealed a large epithelial defect and stromal ulceration in the inferior paracentral cornea, consistent with corneal melting. The diclofenac was immediately stopped, and intensive treatment with preservative-free corticosteroids, antibiotics, artificial tears, and a therapeutic contact lens was initiated. Over time, the cornea re-epithelialized, opacity reduced, and visual acuity fully recovered to 20/20.

Although NSAID-related corneal toxicity has been well documented after anterior segment procedures, this case highlights that the same risk may extend to posterior segment surgeries, especially in patients with systemic autoimmune conditions such as rheumatoid arthritis.

This report emphasizes the need for caution when prescribing topical NSAIDs after vitreoretinal surgery. Identifying patients with risk factors—such as ocular surface disease or autoimmune conditions—may help prevent severe complications. Prompt drug discontinuation and early management were critical to achieving a favorable visual outcome in this case.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently utilized during both the perioperative and postoperative phases to manage ocular inflammation and pain.[1] Topical NSAIDs find extensive use in addressing post-operative inflammation following cataract extraction and various refractive surgical procedures.[2] Additionally, they are commonly employed for the prevention and treatment of postoperative cystoid macular edema (CME). Recent findings from the ESCRS Prevention of Macular Edema study have demonstrated that the combination of a topical corticosteroid and an NSAID is more effective than using either agent alone to reduce the risk of CME after cataract surgery in nondiabetic patients.[3]

Nonetheless, NSAIDs come with potential side effects that can adversely affect the eye. Complications documented in the literature include punctate keratitis, subepithelial infiltrates, stromal infiltrates, immune rings, and persistent epithelial defects.[4–7] More severe complications encompass keratitis, ulceration, and corneal melting. These effects have predominantly been documented following surgical interventions involving the anterior segment, including cataract surgery, penetrating keratoplasty, and photorefractive keratectomy, with the highest incidence associated with the administration of topical ketorolac sodium and diclofenac sodium.[8,9] Although the true incidence of NSAID-associated corneal melt after anterior segment surgery is unknown, it is likely very low, with only sporadic cases described in surveys and case series.

Risk factors for adverse corneal events encompass systemic inflammatory diseases, concurrent use of topical steroids, and the presence of epithelial keratopathy.[1,9,10]

We present a case of corneal melting following an uncomplicated combined phacovitrectomy surgery, specifically a cataract surgery with pars plana vitrectomy (PPV) for epiretinal membrane, in a patient with rheumatoid arthritis treated with topical NSAIDs. Our case highlights the need for caution in the postoperative use of topical NSAIDs also in vitreoretinal surgery.

Case Presentation

A 61-year-old man was referred to our hospital in December 2020 with a history of blurred vision and metamorphopsia in his right eye (RE) due to macular pucker. He had been suffering from hypertension for 15 years and from rheumatoid arthritis, for which he had been on methotrexate therapy (Reumaflex® 12.5 mg once weekly) for the past three years.

He had been visually impaired in his left eye (LE) since 1976 due to head trauma from a car crash that caused retinal detachment and optical nerve damage. He did not report any other pathologies or risk factors. At presentation, best corrected visual acuity (BCVA) in the RE was 20/32 with a refractive correction (−2.00 sphere −0.75 cylinder axis 45°) and 20/63 in the LE.

In January 2021, an uneventful combined surgery (phacoemulsification and PPV) was performed in the RE at our department. Postoperative medication included tobramycin 0.3% combined with dexamethasone 0.1% eyedrops at one drop four times daily for one week, then tapered by one drop every seven days, alongside levofloxacin 5 mg/mL eyedrops at one drop four times daily for seven days.

Upon examination on the first and seventh days after the operation, the cornea was clear, the conjunctiva was quiet, and the anterior chamber was deep without cells or flare. BCVA was 20/25. The patient was instructed to continue tapering the tobramycin 0.3% and dexamethasone 0.1% eyedrops. Moreover, diclofenac 0.1% was added at one drop, three times daily. A follow-up visit was scheduled.

However, the patient returned after two weeks, complaining of blurred vision and discomfort in the RE. A slit lamp examination revealed diffuse corneal edema with Descemet's membrane striae and a large epithelial defect (4.5 mm X 3.0 mm) with stromal ulceration located in the inferior paracentral cornea. Tissue loss was observed in the area corresponding to the epithelial defect. BCVA acuity had dropped to counting fingers, and the conjunctiva was mildly hyperemic. The rest of the ocular examination was unremarkable.

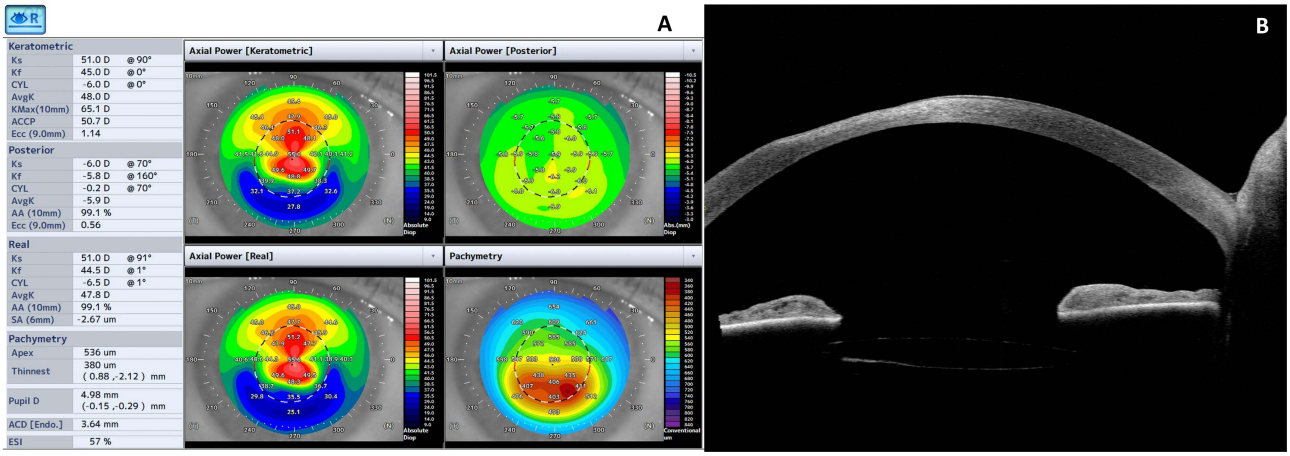

Figure 1 Topography and anterior segment tomography of the right eye. **(A)** Corneal topography showing keratometric values of 51.0 D and 45.0 D and corneal thinning, with the thinnest point being 380 µm. **(B)** Anterior segment tomography showing hyperreflective anterior stroma with corneal thinning.

A wide corneal thinning area was detected with a central corneal thickness of 536 µm, and 380 µm its thinnest. The keratometric values were 51.0 D and 45.0 D (Figure 1A). Tomographic examination showed a hyperreflective anterior stroma with corneal thinning corresponding to the area of the lesion (Figure 1B).

A diagnosis of diclofenac-associated corneal melting was hypothesized. Alternative diagnoses and confounding factors were carefully considered. No clinical signs of infectious keratitis, scleritis, or concurrent eyelid disease were present, supporting the attribution of the corneal melt to postoperative diclofenac therapy. The diclofenac was then immediately suspended, and topical preservative-free dexamethasone 0.15% was prescribed three times daily, alongside preservative-free ofloxacin drops 0.3% three times daily and artificial tears. A therapeutic contact lens was applied to promote epithelization.

After seven days, the corneal epithelial defect had reduced, and the corneal edema had nearly disappeared. The contact lens was replaced, and the topical drops were maintained. BCVA was 20/200.

After one month, the keratometric values were 49.8 D and 43.8 D (Figure 2A). The tomography (Figure 2B) confirmed that the epithelial defect had entered a healing phase, but the hyperreflectivity of anterior stroma was still present. Slit lamp microscopy revealed stromal opacity corresponding to the site of the corneal thinning. Monthly visits were then scheduled.

During the ensuing visits, the corneal opacity decreased progressively but did not regress completely. Corneal thinning and keratometric values gradually improved alongside BCVA.

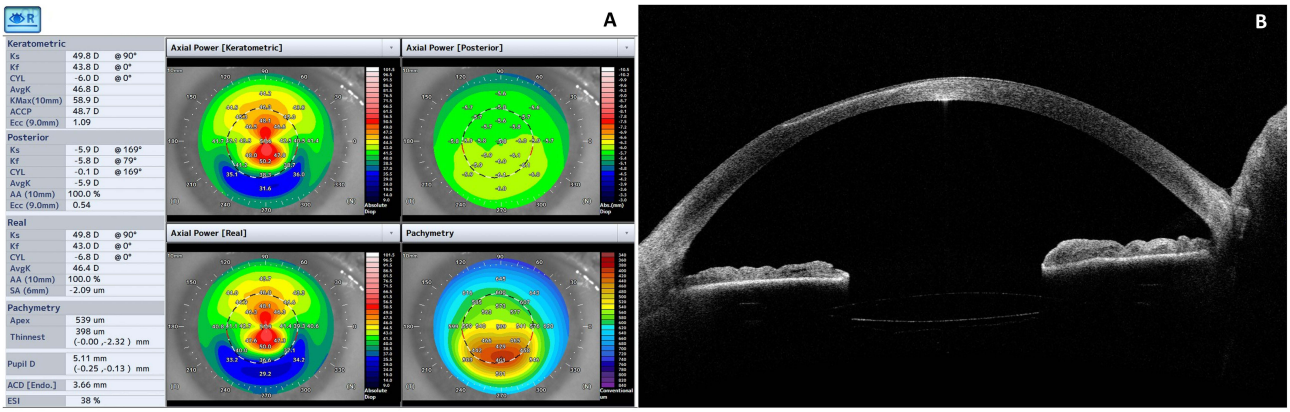

Figure 2 Topography and anterior segment tomography one month after diclofenac discontinuation. **(A)** Corneal topography showing keratometric values of 49.8 D and 43.8 D and corneal thinning with the thinnest point being 380 µm. **(B)** Anterior segment tomography showing the persistence of anterior stroma hyperreflectivity.

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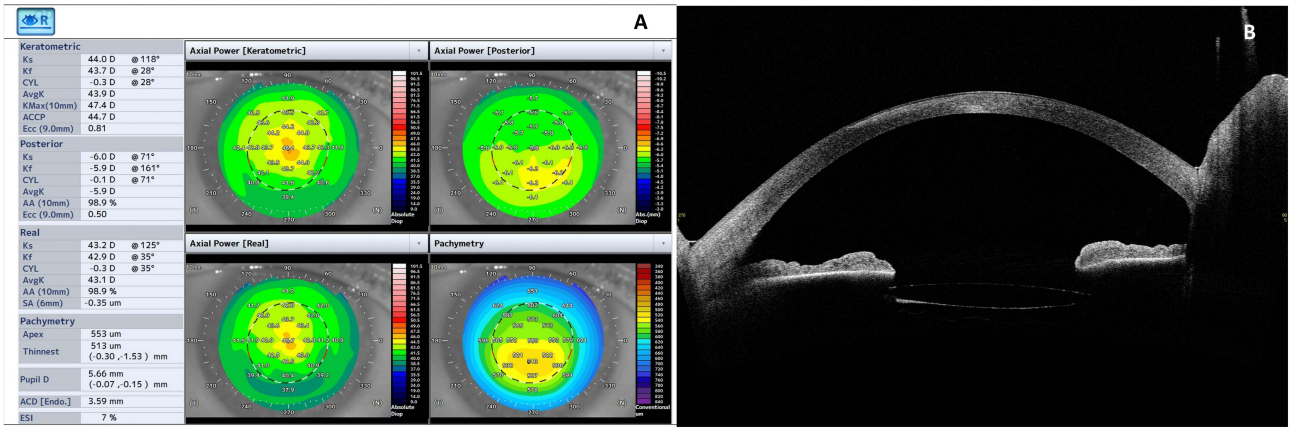

Figure 3 Imaging of right eye at the end of follow-up. **(A)** Topography. **(B)** Anterior segment tomography.

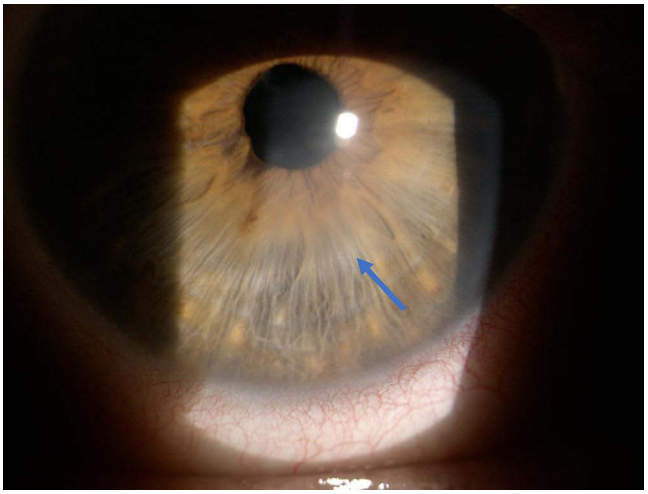

Figure 4 Slit lamp photograph at the end of follow-up showing an inferior paracentral leukoma (arrow) with stromal thinning.

At the end of follow-up, 21 months after surgery in October 2022, the keratometric values were 44 D and 43.7 D (Figure 3A). Anterior segment tomography showed complete re-epithelization, a hyperreflective zone in the anterior stroma and minimal corneal thinning (Figure 3B). BCVA was 20/20 with refractive correction −3.50 sphere −3.25 cylinder axis 10°. During slit lamp examination, the cornea exhibited an inferior paracentral leukoma with stromal thinning (Figure 4).

Discussion

Ophthalmic NSAID formulations, including diclofenac, ketorolac, and nepafenac, have been associated with corneal stromal inflammation, sometimes accompanied by epithelial ulceration, and stromal melts. This adverse effect of topical NSAIDs has predominantly been documented after anterior segment procedures such as cataract surgery, penetrating keratoplasty,[9] and photorefractive keratectomy.[10] With regard to incidence, recent systematic reviews[11,12] have confirmed that NSAID-associated corneal melting after anterior-segment surgery is such an exceptionally rare event that no reliable pooled estimates are available. The absence of quantitative epidemiological data itself reflects the extreme rarity of this complication. To date, corneal melting has rarely been described after vitreoretinal procedures, with only a single case previously reported in the literature.[13]

Regulatory authorities have issued warnings on severe adverse corneal events with topical ophthalmic NSAIDs. The FDA label for diclofenac warns of epithelial breakdown, thinning, ulceration, and perforation, while EMA product

information for bromfenac and nepafenac provides equivalent class warnings. These cautions emphasize the need for vigilance when prescribing diclofenac in susceptible eyes.

Corneal melting and perforation have been observed in association with NSAID use, particularly when there is preexisting epithelial disruption.[9] The proposed mechanisms underlying this phenomenon include compromised wound healing, neurotoxic effects stemming from the analgesic properties of these medications, and the activation of matrix metalloproteinases.[14–17]

The primary pharmacological action of NSAIDs is the inhibition of cyclooxygenase, which subsequently prevents the conversion of arachidonic acid into prostaglandins. This inhibition leads to a reduction in the production of inflammatory mediators. Arachidonic acid can also undergo metabolism through a separate pathway mediated by lipoxygenase, resulting in the generation of leukotrienes, lipoxins, and hydroperoxyeicosatetraenoic acids (HPETE). Additionally, a third pathway dependent on P450 enzymes has been described.[9] The selective inhibition of cyclooxygenase by NSAIDs may potentially redirect unused arachidonic acid towards the lipoxygenase metabolic pathway.[18,19] This diversion can lead to the accumulation of HPETE and leukotrienes, which act as potent chemoattractants for neutrophils and also function as vasoconstrictors and enhancers of vascular permeability. Within the cornea, these agents may augment the ability of neutrophils to infiltrate the tissue. The accumulation of these agents has been suggested as a potential contributing factor in the development of noninfectious stromal infiltrates following the administration of NSAIDs in patients who have undergone refractive surgery.[20,21] Furthermore, during the inflammatory response, neutrophils release granules containing collagenase and other hydrolytic enzymes. Once released in the cornea, the accumulation of collagenase may potentiate corneal melting.

Diclofenac stands out among NSAIDs because, in addition to its inhibition of cyclooxygenase, it also indirectly influences the lipoxygenase pathway.[22] Laboratory data suggests that diclofenac may inhibit the proliferation of keratocytes in vitro, which could potentially lead to reduced wound healing and an elevated risk of corneal ulceration.

Another mechanism contributing to corneal injury associated with NSAID use is their impact on matrix metalloproteinases (MMPs), which can be elevated in corneas experiencing ulceration and melting. There is compelling evidence suggesting that MMPs play a role in stromal degradation, as well as in various processes that take place during corneal ulceration and the subsequent repair, including re-epithelialization and tissue remodeling.[23,24] Reviglio et al demonstrated the involvement of MMPs in NSAID-induced ulceration in rat corneas. Their study revealed that eyes treated with diclofenac exhibited elevated expression of MMP-1 and increased levels of MMP-8.[25] Furthermore, O'Brien et al demonstrated MMP-8 staining in corneal epithelial cells in cases of ulcerative keratolysis linked to diclofenac usage.[15] These studies underscore the crucial role played by proteases in corneal degradation and emphasize that NSAIDs may lead to their overexpression. Furthermore, several prior studies[26,27] have linked NSAIDs to a reduction in corneal epithelial cell migration and delayed wound healing. Consequently, when underlying surface abnormalities are present, the ability of the corneal epithelium to self-repair is likely compromised, potentially making it more susceptible to a more severe reaction, such as corneal melting, even with a minor insult.

Additionally, certain conditions may make patients more susceptible to corneal damage resulting from NSAID use. These conditions can include autoimmune diseases, rosacea, dry eye, and alterations in the ocular surface.[9,28–30] Considering that individuals with dry eye resulting from connective tissue diseases or Type 1 diabetes mellitus often have reduced corneal sensitivity,[28,31] the potential for topical NSAIDs to further decrease corneal sensitivity reinforces their contraindication in the presence of these disorders.

Regulatory agencies have highlighted the potential for serious corneal adverse events associated with topical NSAIDs. For example, the FDA label for diclofenac ophthalmic solution (Voltaren Ophthalmic) includes warnings regarding keratitis, ulceration, and corneal melting, particularly in patients with compromised epithelial integrity.[32] In high-risk patients, alternative postoperative regimens have been proposed. Nepafenac has demonstrated favorable safety profiles in the prevention of postoperative cystoid macular edema,[33,34] while loteprednol monotherapy represents another option with a lower risk of steroid-related complications.[35] A summary of current post-phacovitrectomy anti-inflammatory options and their reported keratopathy risks is presented in Table 1, to provide a practical overview for clinicians.

Table 1 Post-Phacovitrectomy Anti-Inflammatory Options and Reported Keratopathy Risks

Drug/Class	Typical Use	Reported Keratopathy Risk	References
Diclofenac 0.1%	NSAID, CME prophylaxis, inflammation control	Rare but serious: corneal melts and ulceration	Flach 2001;[35] FDA 2012[32]
Ketorolac 0.5%	NSAID, CME prophylaxis	Sporadic reports of corneal ulceration and toxicity	Lin 2000;[8] Guidera 2001[9]
Nepafenac 0.1–0.3%	NSAID, CME prophylaxis (favorable safety)	Very rare; no corneal melts reported in clinical trials	Sarfraz 2017;[32] Giarmoukakis 2020[34]
Prednisolone acetate	Corticosteroid, strong anti-inflammatory	No direct corneal melt risk; risk of steroid-induced IOP rise	Standard clinical use
Loteprednol	Corticosteroid, lower IOP elevation risk	Minimal keratopathy risk; favorable safety profile	Flach 2001;[35]

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; CME, cystoid macular edema; IOP, intraocular pressure.

In our case, the patient had been diagnosed with rheumatoid arthritis for three years, which may have contributed to the corneal melting. Consistent with prior literature, our case confirms that in specific patients already predisposed to corneal or scleral damage (such as those with rheumatoid arthritis, other autoimmune systemic diseases, ocular surface diseases, dry eyes, or neurotrophic keratopathy), topical NSAIDs may act as "trigger" for corneal melting through the mechanisms elucidated above. Hence, this class of medications, and especially diclofenac, should be employed cautiously in patients with these predisposing conditions, as well as in those with epithelial defects or any epithelial irregularities during the immediate postoperative period.

In vitreoretinal surgery, NSAIDs are frequently used for several indications, including the prevention and treatment of postoperative CME, a possible complication after PPV. Our case highlights vitreo-retinal surgeons should exercise caution in the use of NSAIDs after combined phacovitrectomy procedures, since corneal damage may occur, as most frequently described after anterior segment surgical procedures.

In contrast with other reports, in our case good visual recovery was reached. This may have been due to the prompt patient presentation, immediate NSAID discontinuation, and early treatment to facilitate corneal repair. However, this report is limited by its single-case nature, which precludes generalization of the findings. Other limitations are the absence of baseline ocular surface assessments (eg, Schirmer test, tear break-up time, corneal sensitivity) to document pre-existing dryness or neurotrophic changes and the lack of detailed tear or corneal matrix metalloproteinase assays to corroborate the proposed biochemical mechanism.

In conclusion, caution is recommended when using NSAIDs in the immediate postoperative period, both after anterior segment procedures and combined phacovitrectomies. There seems to be a vulnerable period when a disruption in the corneal epithelium exists, increasing the susceptibility to ulceration, melting, or even perforation. In individuals at risk due to factors like autoimmune diseases, the use of these drugs, particularly diclofenac, should be avoided.

In conclusion, caution is recommended when prescribing topical NSAIDs in the immediate postoperative period after anterior-segment procedures and combined phacovitrectomies. There appears to be a vulnerable period when epithelial disruption increases susceptibility to ulceration, melting, or perforation. Accordingly, preoperative ocular-surface assessment may be advisable. In high-risk individuals (eg, autoimmune disease or ocular-surface disease), preferential use of topical corticosteroids or NSAIDs with lower reported keratopathy rates should be considered, and diclofenac should be avoided.

Data Sharing Statement

All data supporting the findings of this study are included within the manuscript. No additional datasets were generated or analyzed.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was not required according to institutional and national guidelines, as this is a retrospective case report. Written informed consent was obtained from the patient for the publication of this case and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no financial or non-financial competing interests related to this work.

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