INDOMETHACIN-INDUCED CORNEAL MELTING AFTER CATARACT PHACOEMULSIFICATION

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Abstract. Cataract remains the leading cause of reversible blindness worldwide. Inflammatory postoperative complications remain a significant challenge associated with cataract phacoemulsification. These include corneal melting, also known as aseptic keratomalacia, a sight-threatening inflammatory condition that precedes corneal perforation. Case description: a 70-year-old patient underwent cataract phacoemulsification and subsequently developed indomethacin induced corneal erosion. Despite 2 months of conservative treatment, the erosion progressed to a corneal ulcer. To prevent corneal perforation, a prophylactic conjunctival flap was performed. Dry eye disease and Sjogren's syndrome were diagnosed postoperatively. Follow-up was 5 years. Conclusions: the presented case demonstrates for the first time the role of indomethacin as a trigger of corneal melting after cataract phacoemulsification. Corneal melting, potentially leading to corneal perforation, may occur after successful surgery not only in patients with diagnosed dry eye disease and systemic collagenosis but also in asymptomatic patients. Torpid progression, resistance to conventional therapy and a high risk of corneal perforation require a specialist to select appropriate therapeutic and surgical treatment methods as soon as possible. Treatment begins with withdrawal of NSAIDs, local and systemic steroid therapy, intensive corneal lubrication and objective monitoring using anterior segment optical coherence tomography.

Keywords: cataract, corneal ulcer, inflammation, keratomalacia, dry eye disease.

List of Abbreviations

DED – Dry eye disease
IFN – Interferons
IL – Interleukin
MMP – matrix metalloproteinase
NSAIDs – Non-steroidal anti-inflammatory drugs

Introduction

Cataract remains the leading cause of reversible blindness worldwide, with more than 30 million cataract extraction procedures performed annually (Svetozarskiy *et al.*, 2020). Corneal melting, also known as aseptic keratolisis or keratomalacia, is a rare sight-threatening inflammatory complication of cataract phacoemulsification that precedes corneal perforation and is characterised by progressive corneal tissue destruction (Ashena *et al.*, 2022). It is mainly associated with the topical use of non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, nepafenac, bromfenac, ketorolac (Ashena *et al.*, 2022; Rigas *et al.*, 2020) and comorbidities such as severe dry eye disease (DED) (Harada *et al.*, 2018) and rheumatic diseases (García De Oteyza *et al.*, 2017; Rodriguez-Garcia *et al.*, 2021). Keratomalacia has also been described after cataract phacoemulsification in association with radiotherapy (Dervenis *et al.*, 2021) and preservative-containing eye drops (Cabourne *et al.*, 2020). Some authors recognise diabetes mellitus as a risk factor (Ashena *et al.*, 2022).

The development of such a rare disease can lead to difficulties in the interpretation of a clinical situation, late medical decisions and the development of undesirable consequences. The aim of the present study was to report a case of indomethacin-induced corneal melting after cataract phacoemulsification for the first time.

Case Description

A 70-year-old woman complained of decreased vision in her right eye. Visual acuity was 0.8 in the right eye and 0.7 in the left eye. Ophthalmic examination revealed incipient cat-

aract in both eyes without obvious signs of DED. Comorbidities included arterial hypertension, coronary artery disease, bronchial asthma and chronic hepatitis B.

Before cataract surgery, the patient instilled indomethacin 0.1% and combined tobramycin/dexamethasone drops for 3 days. Uncomplicated phacoemulsification of the cataract in the right eye was performed through a 2.8 mm incision in the transparent part of the cornea using the quick chop technique on a Laureate machine (Alcon, USA) with implantation of a hydrophobic IOL (SN60AT, Alcon, USA). The patient received post-op instillations of 0.5% moxifloxacin, 0.1% indomethacin and 5% dexapanthenol and 0.18% hyaluronic acid drops. Steroidal anti-inflammatory drugs were discontinued due to corneal micro-erosion detected at the first post-operative visit (day 1).

At the visit on day 3, there was an erosion of 2 mm in diameter in the central corneal area, and the visual acuity had decreased to 0.2. Close examination revealed signs of severe DED and meibomian gland dysfunction in both eyes. There was a marked reduction in tear production, characterised by a Schirmer I test of 0–1 mm, a Norn test of 3 s and a tear osmolarity of 333 m/Osm/L. Topical cyclosporine A 0.05% was also prescribed, but the patient soon refused to take it.

Two weeks after surgery, the diameter of the erosion increased to 5 mm. Persistent corneal erosion was treated with a soft bandage contact lens, hourly application of hyaluronic acid eye drops, 0.5% moxifloxacin, 0.1% indomethacin and 5% dexapanthenol. During treatment, corneal oedema increased and visual acuity decreased to 0.05. At postoperative week 6, 0.1% indomethacin was discontinued. Moderate positive changes were observed thereafter, including a slight decrease in erosion size (Fig. 1A).

Control blood tests showed no pathological changes, rheumatoid factor and anti-nuclear antibodies were absent. Conjunctival smear cultures for flora and fungi showed no pathogens, conjunctival scrapings showed signs of an inflammatory reaction (small amounts of lymphocytes, up to 3 mast cells per field of view, up to 5 eosinophils per field of view).

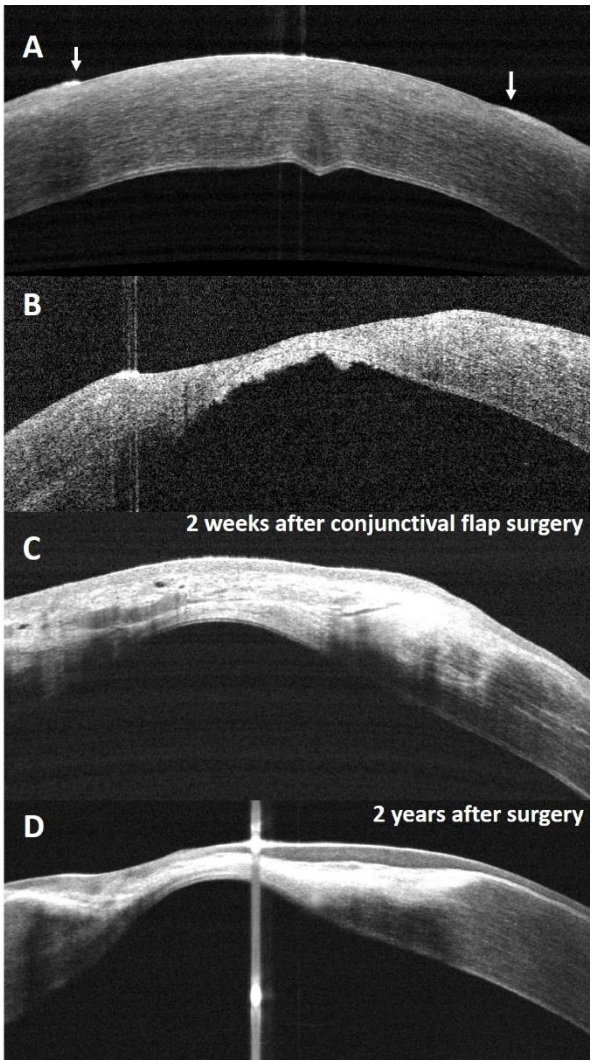

Fig. 1. Monitoring of corneal melting by optical coherence tomography. A – Erosion of the corneal epithelium with a diameter of 4 mm, the borders of the erosion are marked with arrows. B – Corneal ulcer with thinning up to 140 μm, signs of inflammatory exudate on the endothelium. C – The defect was filled with an autoconjunctival flap. D – Reduction of total corneal thickness to 200 microns with stable epithelialisation

After 8 weeks of disease, the patient was lost to follow-up and resumed 0.1% indomethacin for mild ocular pain. A corneal ulcer was found when the patient returned to the hospital. Swabs taken from the base of the ulcer showed no evidence of flora or fungi. The corneal ulcer was treated for 5 weeks with intensive corneal lubrication, topical antibiotics, cyclosporine A and autohaemotherapy; NSAIDs were excluded. The patient refused blepharorrhaphy. Despite

continuous treatment, the central corneal thickness decreased steadily and reached 140 μm (Fig. 1B). Due to the high risk of perforation, the corneal defect was treated with an autologous conjunctival flap, as the patient refused to undergo surgery with heterologous material in the form of amniotic membrane.

Regular lid hygiene and hyaluronic acid drops did not improve tear production. The patient was referred to a rheumatologist where she was diagnosed with primary Sjögren's syndrome involving the lacrimal, salivary and genital glands, activity 0–1. A course of hydroxychloroquine 400 mg daily and prednisolone 5 mg daily did not result in any significant changes. Tear production according to the Schirmer I test did not exceed 1 mm during the entire 5-year follow-up.

As a result, the patient developed a persistent decrease in visual function (visual acuity - 0.02) due to central corneal opacity. Due to the doubtful prognosis and the patient's refusal, penetrating keratoplasty was not performed on the affected eye.

Discussion

As far as we know from the available scientific literature, the case presented demonstrates for the first time the role of indomethacin in inducing corneal melting following cataract phacoemulsification. Late diagnosis of DED not detected during preoperative examination, surgical trauma, prolonged treatment with topical NSAIDs and absence of steroidal anti-inflammatory drugs in postoperative management should be considered as preventable factors for the development and progression of corneal complications in this patient. Undiagnosed prior to surgery Sjögren's syndrome with severe DED were predisposing factors. Inadequate attention to the problem of tear deficiency and incomplete preoperative evaluation are associated with the risk of postoperative complications (Harada *et al.*, 2018; Ting & Ghosh, 2019), which is clearly demonstrated by the described observation. If severe DED had been detected in the presented patient prior to surgery, it would be advisable to postpone the procedure and make efforts to improve the tear production parameters as part of a comprehensive treatment (cyclosporine A, lubricants, eyelid hygiene) and to determine the aetiological factors (consultation with a rheumatologist).

It is known that cataract phacoemulsification can lead to progression of DED in previously asymptomatic patients by increasing inflammatory cytokines in the tears (Li & Fang, 2021). When DED is detected in patients preparing for anterior segment surgery, it is important to identify associated systemic diseases. In the case of the patient presented here, it is clear that a routine preoperative examination, including a common list of serological tests, will miss many rheumatic diseases, including Sjogren syndrome.

Patients with Sjögren's syndrome develop a complex of morphological and functional changes in the lacrimal organs, including lymphocytic infiltration of the lacrimal gland and conjunctival acini by B cells along with CD4+ and CD8+ T cells, leading to increased antibody production and damage to the tissue microenvironment. Environmental factors, including viral infection and surgical trauma, can activate the production of pro-inflammatory cytokines such as IL-1β, IL-17 and IFN-γ in patients with Sjögren's syndrome (Ogawa *et al.*, 2018). IL-1β and IFN-γ are known to play an important role in the development of squamous metaplasia of the conjunctival and corneal epithelium with loss of the epithelial glycocalyx in response to chronic inflammation. The described cascade of cellular reactions induced by surgical trauma may have contributed to the development of corneal melting in the presented case.

Corneal melting was previously considered a manifestation of autoimmune aggression in rheumatic patients, however, there is now evidence that aseptic keratolysis can be present in apparently healthy patients with no evidence of rheumatic disease or DED (Jesus *et al.*, 2020). In addition to surgical trauma, topical NSAIDs may act as triggers initiating the corneal melting process (Rigas *et al.*, 2020)

Several possible mechanisms of keratolysis associated with the action of NSAIDs have been described (Tu & Hou, 2019). Selective

blocking of the cyclooxygenase pathway reduces prostaglandin synthesis, increasing the formation of leukotrienes from arachidonic acid, which are chemoattractants and stimulators of neutrophil degranulation. Neutrophil and macrophage granules contain matrix metalloproteinases (MMPs), in particular MMP-8 and MMP-9, leading to corneal epithelium disintegration and stromal extracellular matrix degradation. In this regard, the use of drugs inhibiting MMP expression such as cyclosporine A, glucocorticosteroids, tetracycline antibiotics, ascorbic acid and acetylcysteine is pathogenetically justified. In addition, all currently used ophthalmic drugs from the NSAID group decrease corneal sensitivity, which triggers the mechanism of neurotrophic epitheliopathy, preventing epithelial regeneration. At the stage of ulcerous defect, NSAIDs inhibit keratocyte proliferation.

Corneal melting after phacoemulsification is characterised by a high risk of corneal perforation even with timely intensive treatment (Ashena *et al.*, 2022; Cabourne *et al.*, 2020; Dervenis *et al.*, 2021; García De Oteyza *et al.*, 2017; Harada *et al.*, 2018; Jesus *et al.*, 2020; Murtagh *et al.*, 2018; Rodriguez-Garcia *et al.*, 2021; Ting & Ghosh, 2019). In most cases, an unfavourable outcome with corneal perforation was associated with the patient's late arrival at the clinic. Long term (up to several months) topical and systemic use of glucocorticosteroids, lubricants, and bandage contact lenses could help to avoid perforation (Cabourne *et al.*, 2020; Harada *et al.*, 2018; Jesus *et al.*, 2020; Tu & Hou, 2019). Preventive surgery with amniotic membrane or conjunctival flap is required in progressive cases (Tu & Hou, 2019). The functional outcome of amniotic membrane is superior to that of conjunctival flap, but amniotic membrane is not always available in routine clinical practice. Tectonic and penetrating keratoplasty performed for corneal perforation were characterised by a high risk of complications, in particular 2 cases of corneal melting recurrence after penetrating keratoplasty were described (Ashena *et al.*, 2022; García De Oteyza *et al.*, 2017).

Conclusions

This clinical observation highlights the need for further research into the prognosis, diagnosis and management of inflammatory complications of cataract phacoemulsification. Corneal melting, potentially leading to corneal perforation, may develop after successful surgery not only in patients with diagnosed DED and systemic collagenosis, but also in asymptomatic patients. If aseptic corneal melting is suspected, several measures should be taken. These include discontinuation of NSAIDs, evaluation of tear production and diagnosis of systemic collagenosis, topical and systemic corticosteroid therapy, intensive corneal lubrication and objective monitoring using anterior segment optical coherence tomography. In the case of uncontrolled progression of corneal melting, it is advisable to cover the corneal defect with an amniotic membrane or conjunctival flap due to the high risk of corneal perforation.

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