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Case Report

Management of Calcareous Corneal Degeneration from Medication Washout to Corneal Transplantation. Case Series and Review of the Literature

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Abstract

Calcareous corneal degeneration is a rare disease characterized by calcium phosphate deposition into the deep corneal layers. Corneal calcification has a multifactorial origin and is associated with various systemic and ocular conditions. Several treatment options showed promising results in the management of this disorder. Herein, two cases of calcareous degeneration occurring postoperatively in patients undergoing surgery for retinal detachment (case #1) and glaucoma (case #2) were reported. Despite normal serum calcium and phosphate levels, the patients developed corneal calcification after using topical steroid-phosphate drops. Treatment involved discontinuation of topical therapy and substitution with unpreserved phosphate-free lubricants. While case #1 resolved with conservative measures, which allowed a satisfactory visual recovery, case #2 required superficial keratectomy due to refractory calcification. Therefore, a correct diagnosis, careful lesion analysis, and tailored management are advisable in corneal calcification, with conservative measures being effective in most cases. At the same time, surgical intervention is necessary in refractory or advanced diseases.

Keywords
Calcareous corneal degeneration; calcium deposition; corneal calcification; corneal transplantation; steroid-phosphate preparations

1. Introduction

Corneal calcification is defined as the deposition of calcium phosphate in different layers of the cornea. This condition can occur in two morphological forms: band keratopathy and calcareous degeneration. The former is a band-shaped, horizontal, corneal opacity, which presents calcium deposition in the Bowman's layer and superficial stroma, mainly in the interpalpebral zone. Conversely, the latter presents as a more diffuse calcium deposition involving the deeper part of the cornea [1-4]. These disorders occur as primary diseases or in association with systemic conditions (hypercalcemia, hyperphosphatemia, renal failure, acquired immunodeficiency syndrome) or ocular pathologies (severe dry eye, uveitis, intraocular silicone oil, intracameral viscoelastic substances, graft-versus-host disease [GVHD], phthisis bulbous and postoperative complications) [1, 3, 5-9].

Moreover, calcareous degeneration has been reported secondary to the use of several topical compounds such as tear substitutes, corticosteroids, β-blockers, retinoic acid, preservatives, fluoroquinolones, and phosphate-containing drops, especially in the presence of persistent epithelial defect of the cornea [1, 2, 10-17]. Although the typical slit lamp appearance of the corneal features makes easy clinical diagnosis, histopathologic examination remains the gold standard for definitive diagnosis, being able to offer a detailed microscopic analysis of the tissue. Despite the exact pathogenesis of the more profound form of calcium deposition not being fully understood, conservative and surgical treatment options have been proposed for its management [1-4, 18-23].

Herein, we describe the management strategies employed for two cases of corneal calcareous degeneration that developed during the postoperative course for rhegmatogenous retinal detachment (RRD) and uncontrolled primary open-angle glaucoma (POAG).

2. Case Series

2.1 Case #1

A 77-year-old pseudophakic female underwent elsewhere uncomplicated pars plana vitrectomy (PPV) with SF6 gas tamponade for RRD in her right eye. Postoperatively, the patient was prescribed Tobramycin 0.3% and Dexamethasone-phosphate 0.15% eye drops 4 times daily. Two weeks after surgery, the patient complained of the sudden onset of a white spot in the operated eye with a progressive decrease in visual acuity. Postoperative therapy was stopped, and Tobramycin 0.3% and Ofloxacin 0.3% eye drops were prescribed every two hours. Given the lack of response to the clinical picture, the patient was referred to our tertiary center for a second opinion consult.

Upon presentation to our institution, slit lamp examination showed a significant epithelial defect of the cornea (approximately 9 mm width × 8 mm height) with an underlying area of corneal opacification (Figure 1A, 1B). Corneal sensitivity was abolished entirely. Best corrected visual acuity (BCVA) was limited to hand motion. Intraocular pressure (IOP) was 15 mmHg, and B-scan ocular ultrasound showed a completely attached retina. The anterior segment-optical coherence

tomography (AS-OCT) showed an irregular anterior surface of the cornea with a hyperreflective signal involving both Bowman's layer and corneal stroma (Figure 1C)

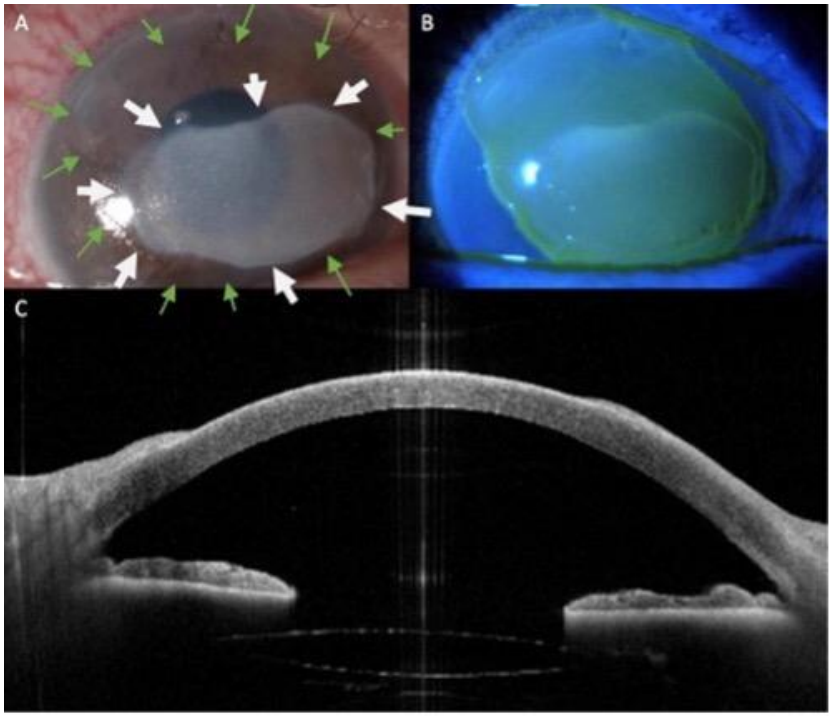

Figure 1 A, B. Slit lamp pictures of the affected eye at the time of patient presentation showing an extensive calcium deposition (white arrows) underneath an epithelial corneal defect (green arrows), better highlighted by fluorescein positive staining with the cobalt blue filter. C. AS-OCT of the affected eye reveals an irregular anterior surface of the cornea corresponding to the epithelial defect and a hyperreflective signal involving Bowman's layer and corneal stroma.

Although the patient's general history was unremarkable, serum phosphate and calcium levels were tested to exclude metastatic calcification. Still, they were found within normal ranges (3.7 mg/dL and 9.5 mg/dL, respectively). Therefore, a clinical diagnosis of corneal calcification was reached, the ongoing therapy was discontinued, and an unpreserved phosphate-free hyaluronic acid-based tear substitute was prescribed 3 times daily. Three weeks after the initiation of washout, a marked reduction of both the size of the epithelial defect of the cornea (approximately 3 mm in width × 3 mm in height) and the intensity of the corneal calcification was observed (Figure 2A, 2B). In parallel, Snellen BCVA improved to 0.1. Therefore, The patient was prescribed to continue the same treatment regimen and attend regular follow-up visits.

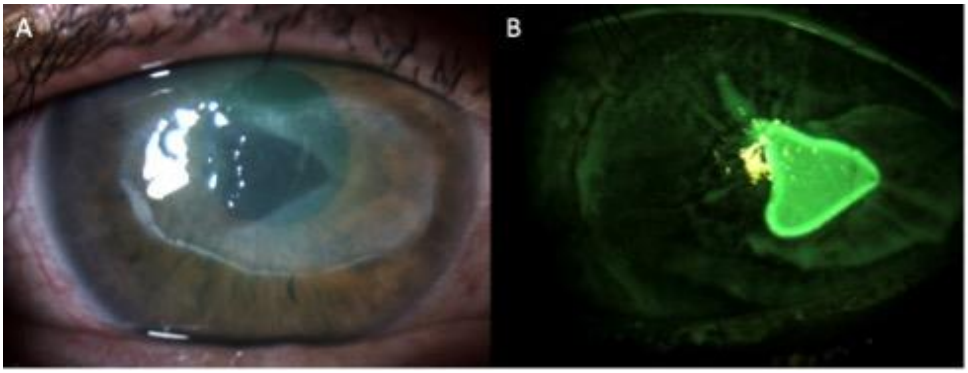

Figure 2 A, B. Three weeks after the patient's presentation slit lamp photograph showed a reduction in the size of the corneal epithelial defect (3 mm × 3 mm) with a decrease in the calcium deposition.

At the 2-month follow-up visit, the epithelial defect of the cornea was completely healed, but a mild central calcific deposit was still present (Figure 3A, 3B). Corneal imaging with AS-OCT showed a more regular profile of the anterior cornea with a reduced hyperreflective signal (Figure 3C). Snellen's BCVA improved to 0.4.

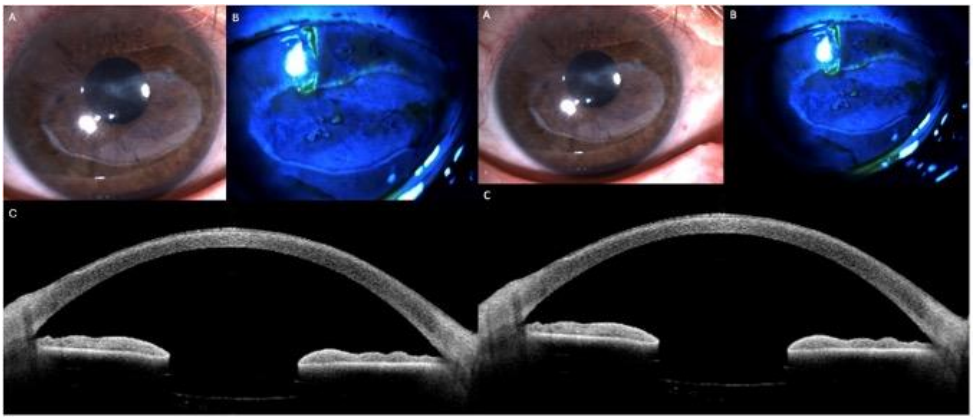

Figure 3 A, B. Slit lamp pictures showing the complete closure of the corneal epithelial defect and the marked improvement of corneal transparency. C. AS-OCT of the affected eye confirms the epithelial defect's closure with the persistence of a mild hyperreflective signal involving corneal layers.

At the last follow-up visit 5 months after the patient’s initial presentation, corneal epithelium resulted in integrum, and the entire cornea's transparency further improved (Figure 4A, 4B, 4C). Snellen's BCVA increased to 0.5.

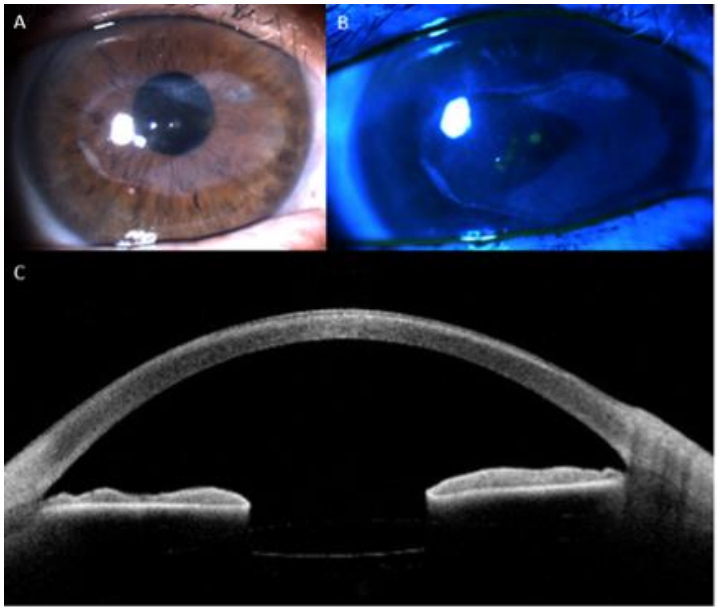

Figure 4 A, B. Slit lamp pictures showing an integral corneal epithelium with a further improved cornea transparency. C. AS-OCT showed an intact corneal epithelium with a slight hyperreflective signal affecting corneal layers.

2.2 Case #2

A 76-year-old pseudophakic female underwent an uncomplicated Preserflo MicroShunt (Santen, Osaka, Japan) implant in her right eye for not medically controlled POAG (preoperative IOP of 27 mmHg and Snellen BCVA of 0.1). Postoperatively, the patient was treated with Tobramycin 0.3% and Dexamethasone-phosphate 0.15% ophthalmic drops 4 times daily. Three weeks after surgery, the patient reported a sudden appearance of a white lesion in the operated eye, accompanied by a gradual decline of visual acuity. The patient was referred to our center for a second opinion.

Upon presentation at our institution, the slit lamp showed a large whitish deposit of the cornea of (approximately 10 mm width × 6 mm height) with a peripheral corneal neovascularization (Figure 5A). Corneal sensitivity was abolished entirely, while BCVA was reduced to light perception. The IOP was 20 mmHg.

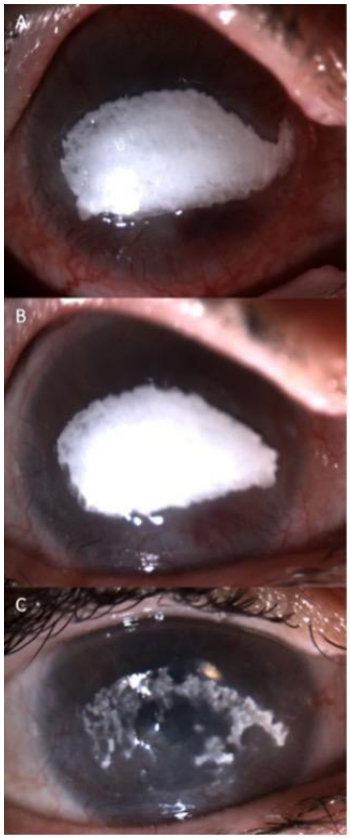

Figure 5 A Slit lamp image of the affected eye showing an extensive calcium deposition accompanied by peripheral corneal neovascularization at baseline. B Changes of calcific deposit after drug washout with a mild reduction of the material in the nasal sector of the cornea. C Corneal appearance after superficial keratectomy showing few residual calcific deposits not involving the visual axis.

The patient's past medical history was unremarkable, and serum phosphate and calcium levels were normal (3.3 mg/dL and 10.1 mg/dL, respectively). The diagnosis of corneal calcareous degeneration was reached, the ongoing therapy was interrupted, and the patient was instructed to use an unpreserved, phosphate-free hyaluronic acid-based tear substitute 3 times a day. Three weeks after the drugs' washout, only a mild reduction of the calcareous deposition was observed in the nasal part of the cornea (Figure 5B). Snellen BCVA was unchanged.

Seven weeks after the patient's initial presentation, the corneal picture remained unchanged, and a superficial keratectomy was performed to remove calcific material. One month after the surgical procedure, residual corneal calcification was present and did not affect the visual axis (Figure 5C). Snellen BCVA improved to counting fingers. Considering the advanced stage of POAG and the poor visual potential, the patient refused to undergo keratoplasty.

3. Discussion

In the present case series, different approaches for treating two patients who developed calcareous corneal degeneration after various types of ocular surgery are documented. Although this corneal disorder is rarer than band keratopathy, it can grow faster and more aggressively, especially in a persistent epithelial defect of the cornea [24]. The origin of the deposit can be

metastatic or dystrophic. Metastatic calcification typically arises in the context of abnormal systemic levels of calcium or phosphate [18]. However, in the two cases reported herein, patients' calcium phosphorus serum levels were within normal range, and there were no elements for the suspicion of metastatic calcification.

Conversely, the calcium deposition resulted from a process of dystrophic calcification triggered by local factors. Indeed, changes in the balance of calcium and phosphate in tears can lead to precipitation [11]. This delicate equilibrium can be disturbed by various factors, such as pH alterations, evaporation, inflammation, and eye drops [14].

Previous reports evaluated the relationship between corneal calcification and the use of steroid-phosphate preparations [1, 10, 11]. In our cases, dexamethasone-phosphate eye drops associated with the inflammatory response occurring in the postoperative course may have played an essential role in the development of calcareous degeneration. Furthermore, an impaired epithelium in the presence of high levels of phosphate ions provided a favorable environment for the rapid deposition of calcium salts. In case #1, the subsequent intensive use of topical antibiotics further exacerbated the condition, promoting increased penetration of calcium through the corneal layers.

It is paramount to differentiate calcareous degeneration from band keratopathy to choose the correct treatment. In this regard, even if we did not confirm the chemical composition of the opacity, the typical slit lamp appearance, along with the AS-OCT findings, is a valuable tool for studying the precise extension of calcium deposition [23] showing a hyperreflective signal located into the deeper layers of the cornea, confirmed the suspicion of calcareous degeneration.

Excellent results in treating calcific band keratopathy have been documented after superficial keratectomy, with or without ethylenediaminetetraacetic acid (EDTA) chelation [19, 25]. Instead, although a preferred therapy has not yet been established for calcareous degeneration, several medical and surgical treatments have been reported, such as discontinuation of the topical therapy, unpreserved phosphate-free lubricating eye drops, autologous serum, bandage contact lens, superficial keratectomy, amniotic membrane transplantation, up to lamellar and penetrating keratoplasty [1-4, 10, 11, 18, 19, 21-23, 26].

The normal ion equilibrium in tears of patients with calcareous degeneration is impaired. Therefore, preventing the topical insult offered by various agents has been demonstrated to restore the ocular surface's physiological environment [2, 10]. Autologous serum and bandage contact lens wearing were employed as supportive measures without showing positive results in advanced diseases [2, 3]. Superficial keratectomy could be considered in cases where the opacity involved mainly the superficial stromal layers [18, 20]. Thanks to the anti-inflammatory effects, amniotic membrane transplantation has been proved effective in managing eyes with calcium deposition [3, 22]. Corneal transplantation, either lamellar or full-thickness, represents the last option for deep calcareous deposition in eyes with severely impaired vision. However, a poor prognosis has been documented in these cases due to the high risk of recurrence of calcification, particularly in eyes with severe inflammation [1, 3, 11, 18, 21, 23].

In case #1, the patient was managed with a complete washout of topical drugs, maintaining only unpreserved phosphate-free lubricants to dilute inflammatory products at the ocular surface. This conservative approach allowed the full closure of the epithelial defect of the cornea as well as a marked improvement of cornea transparency with a recovery of satisfying visual acuity.

In case #2, despite similar management based on the withdrawal of topical drugs, the calcific deposition did not regress, and a surgical approach was required for mechanically removing the residual calcareous material.

Therefore, while conservative measures may suffice in some cases, surgical interventions may be necessary in advanced or refractory cases.

In conclusion, corneal calcareous degeneration is a rare, multifactorial, potentially severe corneal disorder that can occur after intensive treatment with dexamethasone-phosphate drops in the presence of predisposing conditions. A prompt diagnosis is advisable for excluding infectious conditions and making the proper treatment decision tailored for each patient. Despite different therapeutic approaches that have shown efficacy in managing this disease, conservative measures involving discontinuing the ongoing topical therapy represent the first-line treatment and can provide satisfying outcomes. However, surgical procedures represent a viable alternative when the calcific material does not regress after washout.

Author Contributions

F.L. and B.P. analyzed the literature and wrote the original draft. G.G. conceived the article and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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