Corneal Stromal Calcification
After Topical Steroid-Phosphate Therapy

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Secondary corneal calcification involving the full thickness of the stroma is a rare potential complication of severe dry eye conditions, recurrent corneal ulcerations, chronic ocular inflammation, or multiple surgical procedures. We describe on a patient with unusual, hitherto unreported calcareous degeneration of the corneal stroma after topical steroid-phosphate therapy for chronic keratoconjunctivitis after Stevens-Johnson syndrome. The patient’s serum levels of calcium and phosphorus were normal. Histopathologic and electron microscopic examination of the corneal button revealed mainly intracellularly located crystalline calcium deposits throughout all layers of the corneal stroma but sparing the Bowman layer. Energy-dispersive x-ray analysis confirmed the presence of calcium phosphate. The calcium deposits were closely associated with intracellular and pericellular accumulations of glycosaminoglycans. Our findings indicate that corneal stromal calcification may develop after topical steroid-phosphate medication, and suggest a possible role of alterations in the glycosaminoglycan metabolism of stromal keratocytes in the calcification process.

Corneal calcification may occur as a primary condition or a secondary response to diseases causing hypercalcemia or hyperphosphatemia, to chronic ocular inflammation, severe dry eye conditions and chronic corneal ulcerations, repeated ocular trauma, ocular surgery, and various drugs. In most cases, deposition of calcium salts occurs in the Bowman layer, the basement membrane of the corneal epithelium, and the most superficial anterior corneal stroma in the form of calcific band keratopathy. In contrast, calcareous corneal degeneration involving the posterior layers of the corneal stroma is rare.

Previous reports have described the development of band-shaped keratopathy in association with the use of topical steroid-phosphate preparations. We report an unusual case of calcareous degeneration with intracellular calcium deposition in all layers of the corneal stroma after topical dexamethasone-phosphate medication for chronic keratoconjunctivitis after Stevens-Johnson syndrome.

A 39-year-old white woman was treated for acute Stevens-Johnson syndrome in 1986. The triggering factor was not identified. She developed chronic keratoconjunctivitis that was treated with topical antibiotics, hydrocortisone, and 0.1% dexamethasone-phosphate drops for several years with breaks lasting for several months. Occasionally, to decrease discomfort, she applied anaesthetic drops (proparacaine hydrochloride). She was also taking a calcium supplement orally 1 to 2 times a year for periods not exceeding 2 weeks.

The patient’s visual acuity gradually decreased with bilateral recurrent corneal erosions and dense whitish opacities in the central and paracentral parts involving the full thickness of the corneal stroma. She also developed tear defi-
ciency and peripheral corneal neovascularization. After visual acuity had decreased to counting fingers OU, she was admitted to the University Eye Hospital in Lublin, Poland, for corneal transplantation in the left eye.

On admission, the patient's visual acuity was counting fingers at 0.5 m OU, and both corneas showed dense vascularized scars that appeared more granular and crystalline towards the periphery (Figure 1). The Schirmer test was 2 mm in both eyes and increased after cautery of the lacrimal puncta to 7 mm. Routine laboratory values, including serum calcium and serum phosphate levels, were normal.

After topical steroid therapy was discontinued in 1996, the patient's right eye temporarily improved with topical lubricant therapy, the density of the opacification cleared up, and visual acuity improved to 20/100 OU, but later deteriorated again to counting fingers at 1 m OU.

In June 1996, the patient underwent a 7.2 mm-penetrating keratoplasty in the left eye. The corneal button measuring 7 × 7 mm in diameter was processed for light microscopy, transmission electron microscopy, and scanning electron microscopy combined with energy-dispersive x-ray analysis. The graft remained clear for 8 days and thereafter stromal haze and nonhealing epithelial erosions developed. Lateral tarsorrhaphy was performed but did not prevent corneal perforation, and rekeratoplasty was performed in July. Keratoplasty, including 2 lamellar and 2 mini-keratoplasties, was repeated 5 times. Currently, the graft is opaque and moderately vascularized, but no evident calcification can be seen.

By light microscopy (Figure 2), the nonkeratinized corneal epithelium appeared irregularly thickened but intact and showed slight basal edema and focal bullous detachment from the Bowman layer. The Bowman layer was mostly continuous and normal in appearance, but focally absent and replaced by subepithelial fibrous connective tissue. The Descemet membrane and corneal endothelium appeared normal.

Extensive deposition of a granular basophilic material and peripheral corneal vascularization were seen variably in all layers of the corneal stroma (Figure 2, A). Extensive granular calcification extending from the Bowman layer to the deeper stromal lamellae was confirmed as seen by von Kossa stain; the corneal epithelium, Bowman layer, and Descemet membrane were not involved (Figure 2, B). The granular calcium deposits frequently had a beaded appearance and were associated with degenerative keratocytes (Figure 2, C). No signs of inflammation were observed.

Staining for glycosaminoglycans (Mowry colloidal iron and Alcian blue stains) disclosed focal accumulation of glycosaminoglycans in areas of calcification (Figure 2, D). Other histochemical stains, such as Gram, Giemsa, Masson trichrome, and Congo red, did not show any evidence of infection or stromal dystrophy.

Transmission electron microscopy (Figure 3) showed the granular deposits to consist of crystalline aggregates of fine, needle-shaped, radially oriented crystals forming a concentric ring architecture. The deposits were mainly localized intracellularly within the cytoplasm of degenerative necrotic keratocytes, often with pyknotic nuclei, and were usually associated with accumulations of a finely granular material with electron-lucid areas (Figure 3, A through C). Smaller spherules appeared to coalesce to form larger intracellular conglomerates with a concentrically stratified center and a periphery composed of denser spicules. Part of the keratocytes involved appeared activated with dilated cisterns of rough endoplasmic reticulum (Figure 3, B).

Some crystalline deposits were additionally found extracellularly in the corneal stroma in association with a finely granular vascular material accumulating in the periphery of keratocytes (Figure 3, D and E).

Scanning electron microscopy in conjunction with energy-dispersive x-ray analysis of corneal sections showed a pattern of granular deposits corresponding to the light micrographs (Figure 4, A) and confirmed the presence of calcium phosphate (Figure 4, B).

**COMMENT**

Previous reports have described the development of band keratopathy, the most classic form of corneal calcification, after the use of various drugs including topical steroid-phosphate preparations, either
alone or in combination with β-blockers. Extracellular calcium salt precipitation within the Bowman layer, the epithelial basement membrane, and the most anterior stromal lamellae seems to be initiated by minor local events such as an increase in the local concentration of calcium or phosphorus, an elevation of pH, or concentration by evaporation and desiccation. The rapid onset of calcific-band keratopathy associated with prednisolone-phosphate or dexamethasone-phosphate medications has been attributed to high phosphate concentrations in tear and interstitial fluid in the presence of persistent corneal epithelial defects. The corneal changes were largely reversible after discontinuing the medication or switching treatment from prednisolone phosphate to prednisolone acetate drops.

To our knowledge, this is the first report of another rare potential complication of steroid-phosphate drops; ie, the non-banded calcification of the corneal stroma with involvement of both the superficial and deep stromal layers by clinical and histological evidence. The usual site of corneal calcification, the Bowman layer, was notably free of calcium deposits.

This less-common type of corneal calcification, calcareous degeneration of the cornea, which involves all layers of the corneal stroma but often spares the Bowman layer, may be metastatic or dystrophic. Metastatic calcification occurs in the presence of abnormal systemic calcium or phosphate metabolism, eg, in hypercalcemia or hyperphosphatemia. Because the patient’s serum concentrations of calcium and phosphorus were within normal limits and the general examination showed no evidence of metastatic calcification, calcium deposition in this case was apparently caused by a mechanism of dystrophic calcification in association with necrotic keratocytes secondary to local factors.

Secondary stromal calcification is mainly seen in eyes with atrophy or neoplasms or after extensive trauma, and has also been described in patients with keratoconjunctivitis sicca and persistent epithelial defects or recurrent corneal ulcers, with chronic herpetic keratitis, with acquired immunodeficiency syndrome, and after multiple surgical procedures. The calcification in these cases often occurs relatively rapidly and the calcium salts are typically deposited extracellularly, but examination of the pathologic tissues often has been limited to light microscopy.

Our case had several unusual aspects. The pattern of stromal calcification developed gradually and the calcium precipitated mainly in the cytoplasm of degenerative stromal keratocytes. Both intracellular and pericellular calcium deposits occurred in direct association with increased accumulations of proteoglycans, obviously synthesized by the keratocytes. A relationship between the accumulation of proteoglycans and the deposition of calcium has also been observed in previous studies. However, the lesions described in our case vary, both by ultrastructure and location, from those of a previously re-
ported case of metastatic corneal calcification, which resulted mainly in intranuclear calcium precipitation within epithelial cells, keratocytes, and endothelial cells.9

These observations indicate that metabolically altered stromal keratocytes may be participating in the formation of calcium-phosphate binding materials, such as glycosaminoglycans, resulting in calcium salt precipitation in the presence of locally increased phosphate and calcium levels.

We assume that the topical use of dexamethasone phosphate drops predisposed the patient’s eyes to the development of calcification by increasing the interstitial concentration of phosphate. The supplemental calcium intake may have also been a contributing factor facilitating calcium deposition. In view of the rarity of the problem, additional complicating factors may include the prolonged presence of epithelial defects, the use of multiple topical medications with preservatives, and a history of Stevens-Johnson syndrome with immuno-

Figure 3. Transmission electron microscopy of the left cornea. A, Calcium aggregate (star) within the cytoplasm of a stromal keratocyte. N indicates nucleus (bar = 2 µm). B, Intracellular calcium deposits (asterisk) and prominent rough endoplasmic reticulum (rer) in a degenerative stromal keratocyte (bar = 2 µm). C, Small intracellular calcium spheres (arrows) in association with a finely granular and vacuolar material (gm) and dilated cisterns of rough endoplasmic reticulum (r) (bar = 0.5 µm). D, Larger calcium spheres (star) in association with a finely granular material (gm) with electron lucid areas in the corneal stroma (bar = 1 µm). E, Extracellular calcium deposits coalescing into larger aggregates (star) in the corneal stroma (bar = 2 µm).

Figure 4. Scanning electron microscopy of the left cornea. A, The calcified areas appear bright in the back-scattered electron imaging mode. B, Energy-dispersive x-ray microanalysis of calcified deposits using an ultrathin window system reveals the presence of calcium (Ca) and phosphorus (P) in addition to carbon (C) and oxygen (O).
logically mediated chronic keratoconjunctivitis and dry eyes. In such a sensitized condition, the addition of phosphate-containing medications may have pushed the equilibrium toward the gradual intracellular and pericellular precipitation of calcium phosphate.

Therefore, in concordance with previous reports, we recommend that predisposed patients who are using phosphated eye drops be followed up carefully for this potential complication of corneal stromal calcification. If possible, nonphosphated corticosteroid eye drops should be used.

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