Confocal Microscopy of Stellate Stromal Deposits in Two Cornea Grafts Treated with Moxifloxacin and Prednisolone Acetate

Angela Y. Chang, BA,[1] James D. Auran, MD,[1] Asma Asghar,[2] James Flatow, BA,[2] George J. Florakis, MD[2]

ABSTRACT

Purpose: To describe unusual anterior stromal stellate deposits, imaged by confocal microscopy, appearing in corneal graft stroma shortly after penetrating keratoplasty (PK) with postoperative topical moxifloxacin and prednisolone acetate treatment.

Methods: We report two cases and a review of the literature. Corneas were evaluated using the Heidelberg Retinal Tomograph II confocal laser scanning ophthalmoscope with the Rostock Corneal Module.

Results: Two corneal grafts, treated with topical moxifloxacin and prednisolone acetate, developed birefringent stellate deposits at all stromal levels. On confocal microscopy, they appear as blunt- and sharp-ended spikes radiating from a central nexus (rosette form) up to 50 microns in diameter. Morphologically, they resemble fluoroquinolone and (more so) calcium phosphate (blunt-ended needle, rosette form) crystals and do not resemble lipid (spikes with sharp ends), cholesterol (rhomboid, rectangular, notched, polychromatic), or prednisolone (birefringent, irregular, branched, and pleomorphic) crystals in solution. However, these deposits do not resemble the typical anterior stromal, epithelial, or surface punctate or plaque deposition of calcium or fluoroquinolones.

Conclusions: This is the first report of stellate intrastromal deposits following PK and topical moxifloxacin and prednisolone acetate, with the deposits morphologically similar to those reported in a single case in a PK graft following gatifloxacin and prednisolone acetate treatment. The cause and composition of these deposits remain unknown, but the etiologic role of fluoroquinolones, prednisolone acetate, and calcium must be considered.

Key words: corneal deposits, confocal, crystals, fluoroquinolone deposits, moxifloxacin

Topical fluoroquinolones, specifically ciprofloxacin, norfloxacin, ofloxacin, sparfloxacin, tosufloxacin, and moxifloxacin, have been associated with precipitation and deposition on the corneal surface.[1] Fluoroquinolones are soluble in acidic conditions and have low solubility in neutral or alkaline environments.[1,2] Disturbances in physiologic conditions from surgery or ocular pathology as well as factors such as older age, decreased tear secretion, and poor tear mixing can create an alkaline ocular surface and lead to fluoroquinolone precipitation.[1] At normal aqueous tear pH (7.4) and at the pH in the bottle (6.8), moxifloxacin remains neutrally charged, a state that enhances permeability into the cornea but also decreases solubility and increases the likelihood of drug precipitation.[3]

Here, we present two cases of stellate polychromatic intrastromal deposits in the cornea following PK and topical moxifloxacin and prednisolone acetate administration, imaged by confocal microscopy. To our knowledge, this is the first description of moxifloxacin-associated crystalline stromal corneal deposition described in the literature. All collection and evaluation of patient health information was Health Insurance Portability and Accountability Act-compliant, this study received IRB approval, and this report adheres to the Declaration of Helsinki.

CASE REPORTS

Case 1

A 65-year-old man with history of herpes simplex virus keratitis and advanced glaucoma in the left eye presented with worsening corneal edema and count fingers visual acuity. Past ocular history was significant for three glaucoma procedures with mitomycin C ten years earlier, and one with 5 fluorouracil 26 years previously. Full thickness penetrating keratoplasty (PK) was performed. Post operatively, the patient received moxifloxacin QID for one month,

Author Affiliations:
[1] Columbia University Medical Center
[2] Barnard College

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prednisolone acetate drops QID, and oral valacyclovir 1000 mg BID. Postoperatively, the patient had a 50% epithelial defect. Two months postoperatively, small intrastromal crystal-like polychromatic deposits were observed in the cornea at all stromal depths (Figure 1A, 1B). The crystals were exclusively on the donor button and not the host. In vivo examination of the cornea with the Heidelberg Retinal Tomograph (HRT II) confocal laser scanning ophthalmoscope with the Rostock Corneal Module, a wide field scanning slit confocal microscope with a 0.7 NA objective lens showed stellate intrastromal deposits at all stromal depths (Figure 2A). At the time the crystals first appeared, there was no epithelial defect present. The crystals remained stable for seven months, after which they had diminished in the lower half of the cornea. Two years after surgery, the remaining crystals were still present.

Case 2

An 81-year-old woman with a past ocular history of limbal stem cell deficiency presented with a perforated corneal ulcer in the left eye. Ocular surgical history included Descemet's stripping automated endothelial keratoplasty (2014), PK (2008), and a glaucoma procedure (1993). Repeat PK was performed in the left eye. Postoperatively, the eye was treated with topical moxifloxacin QID, prednisolone acetate QID, and brimonidine-timolol BID. One month postoperatively, polychromatic stellate crystals were observed at all stromal depths (Figure 1C, 1D) and imaged by confocal microscopy as was done in the first case (Figure 2B). The patient had a 90% corneal epithelial defect that gradually lessened at each follow-up visit. At the time

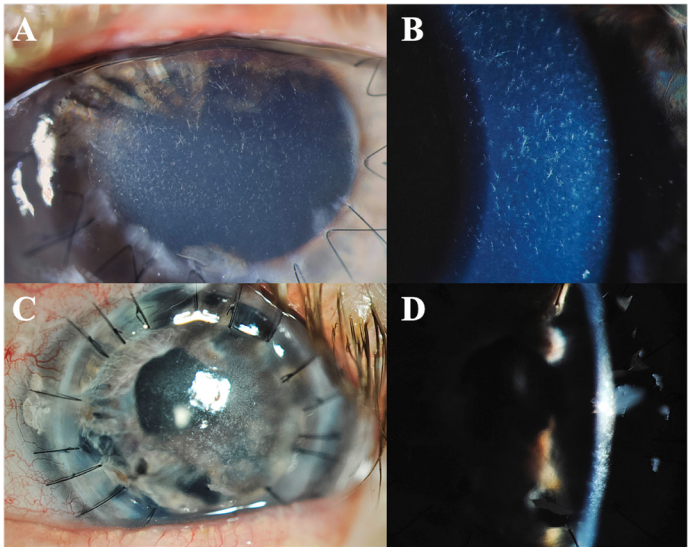

***Figure 1**: Slit lamp photography of the cornea with diffuse stellate intrastromal crystalline deposits on donor graft following PK and crystalline structure of deposits in Case 1 (A, B) and in Case 2 (C, D).*

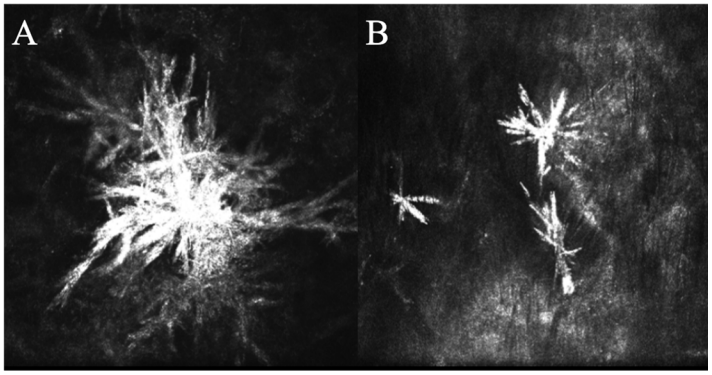

***Figure 2**: Confocal imaging showing stellate crystalline structure of corneal deposits in Case 1 (A) and Case 2 (B)*

the crystals appeared, the patient at a 1 x 2 mm corneal epithelial defect in the graft. Moxifloxacin was discontinued and prednisolone continued at that time. These deposits remained present and stable in the cornea seven months after they first appeared.

The Eye Back for Sight Restoration reported that the corneas of the contralateral eyes of both donors were successfully transplanted without formation of corneal deposits.

DISCUSSION

Crystals are objects of homogenous solid material of geometrically regular form consisting of atoms or molecules with a highly organized microscopic lattice structure. Crystal formation as well as crystal shape depend on concentration, pH, and temperature, among other factors. The cornea, being avascular and subject to dehydration and to high tissue levels of topically administered medication, is an advantageous place for crystal formation. The anatomical arrangement of collagen lamellae in the cornea encourages two-dimensional intralamellar growth of crystals in planes roughly parallel to the corneal surface.

Deposition of fluoroquinolones following topical administration on the corneal surface, in the corneal epithelium, and in the anterior stroma has been reported, typically as a plaque, or less frequently as small amorphous punctate deposits that resolve within two months after cessation of drug treatment.[4] Corneal epithelial defect, edema, and impaired epithelialization are risk factors for corneal deposits.[5] These factors may have contributed to the formation of these deposits in our cases.

Fluoroquinolone crystals in the urine and kidneys are described as refringent or birefringent, with myriad shapes, including sharply pointed needles, sheaves, stars, and fans, although the authors could locate no images of crystals with the distinct rosette formation observed in the present

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case. Ciprofloxacin birefringent crystals with blunt ends, although not in a rosette formation, have been noted ex vivo[6] and in corneal epithelial plaque deposition.[7] There is a prior case report of stellate crystal formation in the corneal stroma in a patient receiving gatifloxacin and prednisolone acetate drops in the donor tissue following PK.[8] Confocal microscopic imaging of the crystals in that case are remarkably similar to the confocal images of the presently described patient – a rosette pattern (spikes emanating from a central nidus).

Another possible cause of these deposits is calcium phosphate precipitation from postoperative use of steroid drops. Calcium and phosphate have relatively low water solubility and the concentration in the aqueous tears is near the concentration in which precipitation can occur.[9] Calcium phosphate may form crystals of a variety of morphologies, including blunt ended needles and rosettes. Calcium phosphate deposits are typically surface or epithelial, forming anterior stromal plaques, although small epithelial punctate deposits have been observed, representing early stages of plaque formation.[10] Calcium phosphate deposits are typically permanent, often due to ongoing pathologic processes, although occasionally transient calcium phosphate deposits have been reported.[10]

For both of the present cases, that the contralateral donor cornea button did not develop similar deposits once transplanted argues against a metabolic defect in the donor cornea. It is also unlikely that both patients had unique underlying predisposition to crystal development. The deposits observed do not resemble stromal deposits of prednisolone (birefringent, irregular, branched, pleiomorphic), tamoxifen (punctate), lipid (birefringent, sharp-ended, spikes), 5 fluorouracil (amorphous or cuboidal), cholesterol (rhomboid, notched, polychromatic), nor that of stromal infectious crystalline keratopathy (multimillimeter length, non-birefringent, tree-branch pattern).

The postoperative timing of crystal development suggests a temporal connection with moxifloxacin and/or prednisolone acetate administration in combination with a deranged anterior segment environment. Based on timing and crystal morphology, it is possible that the deposits in the present case are related to the combination of prednisolone acetate and fluoroquinolone drops after PK, although why only two cases of this have been reported (making this an exceedingly rare phenomenon) remains a mystery. To our knowledge, this is the first report of moxifloxacin and/or prednisolone acetate-associated corneal stromal deposition following PK. The authors suggest that cornea transplant surgeons screen for stellate stromal deposits in host buttons after prolonged use of topical fluoroquinolones and prednisolone following corneal transplantation to gain a better understanding of the frequency, severity, and etiology of these deposits.

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