A Case of Corneal Crystals

Anne Eliott,* a 75-year-old African American retired nurse, visited us for her annual eye exam. She had a history of dry eye syndrome, cataract, and mild hypertensive retinopathy. She thought that her vision was slightly worse compared to last year, particularly in her right eye, and wondered if her cataracts could be the cause since she noticed more glare when driving at night.

Mrs. Eliott's medical history included well-controlled type 2 diabetes mellitus and hypertension. In addition, she was recently diagnosed with several other systemic disorders: seropositive rheumatoid arthritis, for which she was taking rituximab and leflunomide; anemia, thought to represent anemia of chronic disease from her rheumatoid arthritis; and osteoporosis. Her review of systems was positive only for pain in her hands, ankles, and back and numbness in her right hand.

What We Saw

When we examined Mrs. Eliott, her best-corrected visual acuity was 20/30 in her right eye and 20/25 in her left. In both eyes, pupillary examination was normal, visual fields were full on confrontation testing, ocular motility was normal, and intraocular pressure was 17 mm Hg. External examination was normal, but slit-lamp biomicroscopy revealed inferior punctate epithelial erosions and 1 to 2+ nuclear sclerotic cataracts in both eyes. Her dilated fundus examination was normal except for arterial attenuation and scattered peripheral drusen.

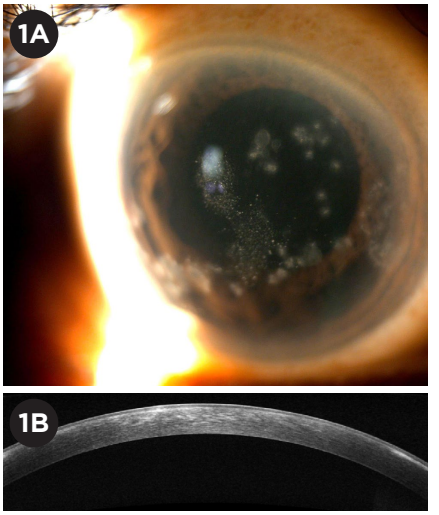
Unusual findings. In both corneas we observed central polychromatic, needlelike crystals in the anterior and mid stroma, with surrounding subepithelial nummular opacities (Fig. 1A). On optical coherence tomography (OCT), the opacities and crystals were hyperreflective (Fig. 1B).

We reviewed her chart and found that a note from a year prior mentioned a small area of crystalline changes in the right cornea at the 3-o'clock position. Her note from two years earlier was unremarkable.

Differential Diagnosis

Given Mrs. Eliott's age and the documentation of a normal ocular exam two years earlier, we put paraproteinemic keratopathy at the top of our differential. This condition is protean in its presentation and often initially misdiagnosed as lattice, granular, Schnyder, pre-Descemet, or gelatinous drop-like corneal dystrophy. It can also mimic cystinosis and lecithin-cholesterol acyltransferase deficiency and can even masquerade as interstitial keratitis, limbal stem cell deficiency, or Salzmann nodular degeneration.[1-3]

We reviewed her chart for lipid serologies, which were normal, arguing against Schnyder corneal dystrophy.



WHAT WE SAW. *(1A) Slit-lamp biomicroscopy and (1B) OCT revealed some unusual corneal findings.*

Additionally, Mrs. Eliott had no history of topical quinolone use or exposure to *Dieffenbachia* plants, both of which can cause crystalline keratopathies; nor did she have a history of penetrating keratoplasty, which would have raised suspicion for infectious crystalline keratopathy.

What the Tests Revealed

We ordered serum and urine protein electrophoresis, which revealed a monoclonal spike (M-spike), and immunofixation confirmed the presence of monoclonal IgG κ light chains. In conjunction with her primary care provider, we referred Mrs. Eliott to an oncologist, who performed a bone marrow biopsy, which revealed 7% plasma cells, and flow cytometry confirmed excess κ light chain reactivity

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without high-risk cytogenetics.

Positron emission tomography/computed tomography (PET/CT) was performed, showing fluorodeoxyglucose (FDG)-avid lytic lesions of the manubrium and L1 vertebral body (see Fig. 2 online at aao.org/eyenet). With normal renal function and serum albumin but elevated lactate dehydrogenase, she met diagnostic criteria for Durie-Salmon stage IIIA and Revised International Staging System stage II multiple myeloma. She underwent cytoreductive external beam radiation therapy for her lytic lesions before starting chemotherapy with lenalidomide and dexamethasone.

Discussion

The association between crystalline keratopathy and paraproteinemia was first described by Meesmann in 1934.[4] Immunoglobulin deposition in the cornea can occur in monoclonal gammopathy of unknown significance (MGUS), Waldenström macroglobulinemia, and multiple myeloma; less commonly, it may be associated with leukemia, lymphoma, cryoglobulinemia, and even intravenous immunoglobulin therapy. Among patients with known paraproteinemia, crystalline keratopathy is rare, occurring in only 1% of patients with MGUS.[5] Because prompt institution of chemotherapy or autologous stem cell transplant can improve survival for many patients with multiple myeloma, it is important for ophthalmologists to consider this diagnosis in elderly patients with new corneal opacification or crystalline deposits.

Pathophysiology. The pathogenesis of paraproteinemic keratopathy remains incompletely understood. It is seen most frequently in patients with κ light chain monoclonal gammopathies. Peripheral deposits are thought to diffuse from the limbal vasculature. Central deposits, on the other hand, are probably transported via the tear film and crystallize as the immunoglobulins encounter lower temperatures in the anterior stoma. Deeper deposits are speculated to diffuse from the anterior chamber and may be more likely to arise in the setting of endothelial pump dysfunction.[3]

Presentation and patterns. Because the clinical presentation is highly variable, paraproteinemic keratopathy poses a diagnostic challenge. Bilateral crystalline deposits in any layer of the cornea with surrounding patch-like opacities is the classic presentation.

However, Lisch et al. described paraproteinemic keratopathy as "chameleon-like" and proposed the following nomenclature to describe five possible morphologic patterns of corneal involvement: crystalline-like, lattice-like, peripheral granular-like, peripheral band-like, and peripheral patch-like.[1]

Diagnosis. Diagnostic testing should begin with a complete blood count with differential, serum and urine protein electrophoresis with immunofixation, and serology for cryoglobulinemia. If serology or urine studies demonstrate an M-spike, the patient should be referred promptly to an oncologist for a bone marrow biopsy and skeletal survey.

Many cases are also diagnosed by corneal biopsy, and electron microscopy is particularly useful. The ultrastructural appearance of the crystalline deposits can be as diverse as the clinical presentations. If biopsy reveals hollow, tubular crystalline deposits measuring 32 to 50 nm in diameter, the condition is termed immunotactoid keratopathy, owing to the similarity of the corneal deposits to the immunoglobulin deposits that are seen in immunotactoid glomerulopathy.[3]

Treatment. Paraproteinemic keratopathy is usually visually asymptomatic. For patients with visual symptoms, topical corticosteroids may be tried, but the results are often disappointing. Corneal transplantation can be performed for severe cases, but the crystalline deposits can recur in the graft.

Recently, several cases were described that improved with systemic chemotherapy, but data are limited on the efficacy of systemic chemotherapy for the keratopathy.[2] Of note, patients who carry a diagnosis of paraproteinemic keratopathy secondary to MGUS should follow up at least annually with an oncologist, as up to 20% of these patients will convert to multiple myeloma over the course of their lifetime.[1]

Our Patient's Course

We started Mrs. Eliott on topical 1% prednisolone acetate, twice daily in both eyes. After one month, she had no improvement in her crystalline keratopathy, and we discontinued the medication. She continued to complain of glare; so we performed cataract surgery, and the glare improved significantly. Further, after four cycles of chemotherapy, her paraproteinemic keratopathy resolved, although she achieved only a partial response systemically. At her most recent follow-up, she refracted to 20/20 in both eyes and was happy with her vision.

Conclusions

Paraproteinemia should be considered in the differential for any new corneal opacification in an adult. The diseases associated with paraproteinemic keratopathy can be life threatening, and timely diagnosis can facilitate early intervention and may improve survival. Mrs. Eliott's corneal findings demonstrate the classic appearance of this rare condition, though the clinical presentation is highly variable. This case demonstrates that, in some patients, the keratopathy resolves with systemic chemotherapy, and observation may be reasonable prior to recommending more invasive procedures such as corneal transplant.

*Patient name is fictitious.

1 Lisch W et al. *Cornea.* 2012;31(1):55-58.
2 Milman T et al. *Ophthalmology.* 2015; 122(9):1748-1756.
3 Garibaldi DC et al. *Surv Ophthalmol.* 2005; 50(1):61-80.
4 Meesman A. *Ber Dtsch Ophthalmol Ges.* 1934; 50:311-315.
5 Bourne WM et al. *Am J Ophthalmol.* 1989; 107(2):192-193.

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EXTRA **MORE ONLINE.** For PET/CT imaging (Fig. 2), see this article at aao.org/eyenet.