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Paraproteinemic Keratopathy

The Expanding Diversity of Clinical and Pathologic Manifestations

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Purpose: To describe 7 patients with paraproteinemic keratopathy and to highlight the clinical and pathologic diversity of this rare entity and the importance of timely, systemic evaluation.

Design: Retrospective, multicenter collaborative case series.

Participants: Seven patients with paraproteinemic keratopathy.

Methods: Clinical and pathologic records were reviewed to identify patients with well-documented corneal immunoglobulin deposits. Detailed ophthalmologic and medical histories were assembled. In 6 patients, corneal tissue was evaluated histochemically and immunohistochemically; in selected cases, corneal tissue was evaluated by in situ hybridization and ultrastructurally.

Main Outcome Measures: Visual acuity and anterior segment examination at presentation and follow-up; local therapy; systemic diagnosis and management; and histopathologic, immunohistochemical, in situ hybridization, and ultrastructural findings.

Results: Seven patients were identified with corneal immunoglobulin deposition. In addition to previously reported crystalline, nummular, patch-like, and lattice-like corneal opacities, prominent corneal vascularization was present in 2 patients mimicking interstitial keratitis and limbal stem cell deficiency. All patients had evidence of paraproteinemia in a setting of monoclonal gammopathy of undetermined significance, smoldering plasma cell myeloma, or Waldenström macroglobulinemia. Corneal findings were the first manifestation of systemic disease in 4 patients, and the diagnosis was not suspected in 3 of these patients. Pathologic evaluation of biopsied corneal and conjunctival tissues demonstrated immunoglobulin deposits. Previously unreported ultrastructural patterns in the cornea were noted: large scroll-like immunotactoid deposits, immune complex-like deposits, and randomly arranged fibrils morphologically intermediate between amyloid and immunotactoid deposits. Surgical intervention to improve vision was performed in 4 patients, with recurrence of deposits in 3 patients. Three patients underwent systemic therapy with diminution of the deposits and improvement in vision in 1 patient.

Conclusions: The clinical and pathologic expressions of corneal immunoglobulin deposits are protean and present a diagnostic challenge. Early recognition of this rare entity is important to address the potentially serious associated systemic disease. *Ophthalmology 2015;122:1748-1756 © 2015 by the American Academy of Ophthalmology.*

Corneal deposits in association with paraproteinemia have been described since the early 1900s.[1] They were subsequently identified as immunoglobulin by Klintworth et al[2] using immunofluorescent and immunohistochemical methods. The diagnosis of immunoglobulin deposition in the cornea or conjunctiva essentially implies the presence of paraproteinemia, typically in a setting of monoclonal gammopathy of undetermined significance (MGUS) or plasma cell myeloma. Much less frequent causes of corneal immunoglobulin deposits include lymphoma, cryoglobulinemia, and autoimmune disorders.[1]

The clinical manifestations of corneal immunoglobulin deposits have been described as "chameleon-like" by Lisch et al.[3] The classic appearance is that of bilateral gray-white, yellow, gray-brown, or polychromatic iridescent dot-like crystals in any layer of the cornea often combined with diffuse or patch-like deposits. The clinical presentation can mimic cystinosis, arcus lipoides, lecithin-cholesterol acyltransferase deficiency, or Salzmann's nodular degeneration, as well as Schnyder, lattice, granular, gelatinous drop-like, and pre-Descemet corneal dystrophies.[1,3]

The pathologic features of corneal immunoglobulin deposition are similarly manifold. Immunoglobulin can be observed in any layer of the cornea as intracellular or extracellular, nonbirefringent, eosinophilic deposits that are acid fuchsinophilic with Masson's trichrome stain and demonstrate positive results with periodic acid–Schiff (PAS), but negative results with Congo red. Immunohistochemical and immunofluorescent techniques demonstrate reactivity of the deposits for immunoglobulin light or heavy chains, or both.[1,2] In the 1990s, Henderson et al[4] and

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Table 1. Clinical and Pathologic Manifestations of 7 Patients with Immunoglobulin Corneal Deposition

Patient No.	Age (yrs)	Gender	Clinical Appearance	Presumed Clinical Diagnosis	Immunoprotein	Systemic Diagnosis	Tissue	Method of Study	Site of Deposits	Pathologic Features of Deposits	Clinical Course
1	60	F	Bilateral deep stromal linear, branching, lattice-like opacities	Lattice corneal dystrophy	IgG λ	MGUS, corneal findings (presenting sign of disease)	Corneal disc	Cornea: HC, IHC; systemic: *TGFBI*, SPEP, UPEP, BM biopsy	All layers of stroma	HC: predominantly extracellular, fusiform, eosinophilic, Masson's trichrome positive, Congo red negative; IHC: IgG λ positive	Follow-up: 3 yrs; PVA: 20/40−20/60 both eyes; PKP right eye with recurrence; CTX with progressive deposits right eye and stable deposits left eye; FVA right eye, 20/20; VA left eye, 20/60
2	67	F	Bilateral central anterior stromal fine, needle-like, crystalline opacities	Schnyder corneal dystrophy	IgG	MGUS, corneal findings (presenting sign of disease)	N/A	Systemic: *UBIAD1*, SPEP, UPEP, BM biopsy	Central anterior stroma	N/P	Follow-up: 1 yr; PVA: 20/30 right eye, 20/25 left eye; observed without therapy
3	87	M	Bilateral epithelial and subepithelial crystalline opacities	Immunoglobulin corneal deposition	κ	WM; known systemic disease	Corneal biopsy	Cornea: HC, IHC	Epithelium, anterior stroma	HC: intracellular, angulated (geometric), eosinophilic, Masson's trichrome positive; IHC: κ positive	N/A
4	74	M	Bilateral gray nummular and focally linear stromal opacities with "beaten-metal" appearance	Atypical lattice dystrophy; interstitial keratitis, staphylococcal hypersensitivity	IgG λ	MGUS; corneal findings (presenting sign of disease)	Corneal disc	Cornea: HC, IHC, TEM; systemic: UPEP, SPEP, BM biopsy	Subepithelial; all layers of stroma	HC: extracellular, fusiform, eosinophilic, Masson's trichrome positive, Congo red negative; IHC and ISH: IgG λ positive; TEM: mostly extracellular, paracrystalline, regularly arranged 7-nm filaments with 10-nm periodicity	Follow-up: 4 yrs; PVA: 20/200 right eye, 20/100 left eye; CXT: Velcade, prednisone, melphalan before PKP; PKP right eye after CXT with recurrence; FVA: 20/100 both eyes
5	76	F	Bilateral stromal haze with peripheral deep stromal vascularization	Interstitial keratitis	IgG κ	MGUS; known systemic disease; information not known at the time of initial eye examination	Corneal discs	Cornea: HC, IHC, ISH; systemic: SPEP, UPEP, BM biopsy	Subepithelial; all layers of stroma	HC: predominantly extracellular, diffuse, eosinophilic, Masson's trichrome positive, Congo red negative; IHC and ISH: IgG positive; TEM: extracellular paracrystalline deposits and tubular, scroll-like deposits 100−300 nm in diameter	Follow-up: 2 yrs; PVA: CF right eye, 20/200 left eye; PKP both eyes, no recurrence; Oncologic restaging confirmed MGUS, observation without systemic therapy; FVA: 20/40 both eyes

(*Continued*)

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