

Histopathology of Explanted Collar Button Keratoprostheses: A Clinicopathologic Correlation

E.J. Dudenhofer, M. Nouri, I.K. Gipson, K.H. Baratz, A.S. Tisdale, T.P. Dryja, J.C. Abad, and C.H. Dohlman

Purpose. To compare the histopathology of three PMMA collar button type keratoprosthesis (KPro)/corneal specimens, explanted due to various complications, with that from one KPro/corneal specimen taken postmortem from an otherwise “healthy” enucleated eye. **Methods.** Patient 1 (chemical injury) had no problems for 3 years after KPro placement; the entire eye was obtained postmortem. Patient 2 (repeated graft failures, nonautoimmune disease) developed an “unlaserable” retroprosthesis membrane 4 months after KPro placement. A new KPro was placed. Patient 3 [ocular cicatricial pemphigoid (OCP)] developed tissue melt at the KPro–cornea interface 7 months after KPro placement, and the KPro was replaced. Patient 4 (OCP) developed progressive corneal melt around the KPro 3.5 years after placement resulting in replacement. All KPro/cornea specimens were processed and sectioned for histology with the KPro in place. **Results.** All patients exhibited growth of corneal or conjunctival derived epithelium under the KPro front plate. In patients 1 and 2, no epithelial downgrowth was noted and the keratocyte density appeared normal with few inflammatory cells present. Dense fibrous tissue was present behind the KPro in patient 2. Patients 3 and 4 showed massive inflammatory cell infiltration and tissue necrosis with “melt” adjacent to the stem resulting in epithelial downgrowth. **Conclusions.** Corneal inflammation and degradation after KPro placement correlate well with the preoperative diagnostic category. Patients with immune-related corneal surface disease can exhibit marked inflammatory responses leading to necrosis, stromal melting, and the formation of an epithelial fistula. In contrast, patients without autoimmune corneal disease demonstrate a remarkably noninflamed cornea with intact keratocytes and without epithelial ingrowth, commensurate with their clinical appearance.

Key Words: keratoprosthesis, cornea, corneal pathology, ocular pemphigoid, graft failure

In cases of bilateral corneal blindness in which traditional penetrating keratoplasty has either failed repeatedly or has no chance of survival, as in patients with progressive cicatrizing ocular surface disease and some chemical burns, a keratoprosthesis (KPro)

may offer the only means of visual rehabilitation. Several keratoprosthesis designs are in use for this purpose. The two most common styles include those composed of a central cylinder with an implantable skirt composed of various materials and those utilizing a collar button configuration that sandwiches the corneal tissue around a central stem between front and back plates (Fig. 1). The polymethylmethacrylate (PMMA) Dohlman-Doane keratoprosthesis is of the latter collar button type and has been implanted into over 190 eyes since 1990. Two variants of the device have been developed to serve, on one hand, patients with good ocular surface hydration (type I) and, on the other hand, those with very dry eyes (type II) (Fig. 2). A description of this keratoprosthesis and the surgical technique for its placement has been reported elsewhere.^{1,2}

In the course of treatment with a KPro, several complications can arise which threaten long-term prognosis. These include the formation of a retroprosthesis membrane, corneal necrosis and melting, epithelial ingrowth, glaucoma, retinal detachment, and endophthalmitis. In some instances, treatment of these complications involves removal and replacement of the KPro and its supporting corneal graft.³

The histopathology of tissue removed during reoperations or from eyes obtained postmortem while bearing an uncomplicated Dohlman-Doane KPro has not previously been described in the literature. In this paper, we describe and compare the histologic features of three KPro–cornea complexes explanted due to various complications with that from one KPro/corneal specimen taken postmortem from a relatively uncomplicated eye.

CASE REPORTS

Case 1

Patient 1, a 79-year-old man, suffered a bilateral chemical burn several decades prior to type I KPro placement. After several failed grafting attempts, the corneas were severely vascularized and opacified. He underwent uneventful type I KPro placement with concurrent extracapsular cataract extraction (ECCE) without vitreous violation, as well as Ahmed valve placement. Immediately postoperatively, hypotony due to a wound leak around the KPro stem was noted. This was repaired successfully by suturing a small, thin wedge of fresh donor lamellar cornea trimmed to fit under the KPro front plate. The KPro remained in place for 3 years before his death. He achieved 20/20 visual acuity with no evidence of corneal melt, KPro extrusion, intraocular inflammation, or glaucoma noted during that period. The eye was donated postmortem.

The dimensions of the type I KPro were front plate diameter of 7.0 mm and back plate diameter of 8.5 mm (eight holes).

Submitted October 8, 2002. Revision received March 12, 2003. Accepted March 12, 2003.

From the Department of Ophthalmology (E.J.D., M.N., I.K.G., A.S.T., T.P.D., J.C.A., C.H.D.), Harvard Medical School, Massachusetts Eye and Ear Infirmary, Schepens Eye Research Institute, Boston, Massachusetts, U.S.A.; Mayo Clinic (K.H.B.), Rochester, Minnesota, U.S.A.

Support provided by Joint Clinical Research Center of the MEEI and SERI.

Address correspondence and reprint requests to Claes H. Dohlman, MD, PhD, Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, 243 Charles Street, Boston, MA 02114.

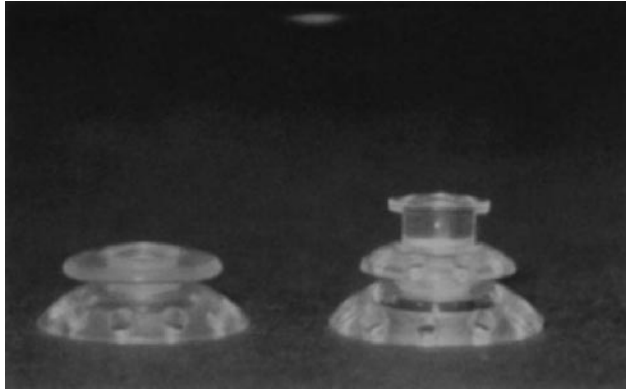


FIGURE 1. Type I (left) and II (right) collar button style keratoprostheses.

Case 2

Patient 2, a 62-year-old man with Meretoja syndrome type lattice corneal dystrophy, developed dense central corneal scarring OD after three separate episodes of *Pseudomonas aeruginosa* keratitis. Two penetrating keratoplasties were rejected within months of placement. The second procedure involved ECCE, anterior vitrectomy, and anterior chamber intraocular lens (ACIOL) placement. He subsequently underwent type I KPro placement with a best corrected visual acuity (BCVA) of 20/60. Four months later, a dense retroprosthesis membrane developed, which reformed quickly after YAG laser capsulotomy and became too thick and vascular for further laser treatments. Progressive thinning of the supporting graft, without ulceration or leak, was also noted and was believed to threaten the stability of the KPro. The KPro and its supporting graft were replaced by a new type I KPro in a fresh donor graft 8 months after the initial KPro surgery.

The dimensions of the type I KPro were front plate diameter of 5.5 mm (no holes) and back plate diameter of 7.0 mm (no holes).

Case 3

Patient 3 was a 70-year-old man who had developed bilateral dense corneal scarring and neovascularization due to advanced ocular cicatricial pemphigoid (OCP) with vision reduced to light perception. A type I KPro in a fresh corneal graft was implanted with vision improvement to 20/15 within 2 months. By 7 months postoperatively, corneal necrosis with tissue melt developed near the optical stem of the KPro. The size of the melting area progressively increased and resulted in aqueous leakage 18 months later, requiring two surgeries in which wedges of corneal lamellae were sutured around the stem, beneath the KPro front plate. A new corneal melt was noted 6 months later. The area of melting increased in size over 8 months resulting in aqueous leakage. Despite three surgeries in the next 4 months using wedges of donor corneal tissue as well as dehydrated strings of corneal tissue to plug the area of leak, persistent corneolysis and leakage required the removal of the KPro and its graft. A type II KPro was then successfully implanted. In spite of the periodic complications, the two devices in this patient have resulted in 20/20 vision for a cumulative 5.5 years.

The dimensions of the type I KPro were front plate diameter 7.0 mm (no holes) and back plate diameter 8.5 mm (eight holes). Also, a 9.0-mm diameter silicone membrane (0.125 mm thick) was applied behind the skin, anterior to the front plate.

Case 4

Patient 4, a 76-year-old woman, maintained only light perception vision due to end-stage OCP OD. A type II KPro in a frozen stored corneal graft was implanted. Within 4 months, vision improved to 20/30. Retroprosthesis membrane formation 5 months postoperatively required five YAG laser capsulotomies during the following year. The final membrane was resistant to laser treatment and required a modified pars plana vitrectomy to clear the visual axis. One month later, melt with threatening leak was repaired with dehydrated strings of donor sclera. Globe integrity was maintained for 3 months when further progressive melting led to aqueous leakage. The KPro–cornea complex was removed and replaced with a new type II KPro in a frozen stored corneal graft.

The dimensions of the type II KPro were front plate diameter of 7.0 mm (six holes) and back plate diameter of 8.5 mm (no holes).

MATERIAL AND METHODS

Immediately after surgical removal, the cornea–KPro complexes were placed in half-strength Karnovsky's fixative. All specimens were dehydrated in ethanol, soaked in acetone for 1 to 2 months to soften the PMMA of the KPro, and then embedded in methacrylate. Sections of the entire KPro–cornea complex were stained with hematoxylin and eosin and evaluated using a Zeiss Photoscope 3 microscope with affixed Spot RT Color camera (Diagnostic Instruments, Inc.).

RESULTS

Analysis of the tissue response to the Dohlman-Doane PMMA KPro has been impeded by difficulties obtaining sections through the hard plastic with surrounding tissue. We found that soaking the KPro in acetone softened the device sufficiently to allow sectioning after embedding in methacrylate. Even after softening, sectioning was difficult. Spreading and flattening of the sections onto microscope slides without wrinkles and folds in the sections were not possible. Thus, the micrographs in Figures 3 to 6 show artifactual folds and wrinkles, especially at low magnification. Retraction of the tissue from the front and back plates is also an artifact due to shrinkage of tissue after long periods of dehydration.

Case 1

The epithelium was noted to have migrated beneath the KPro front plate and extended to the KPro stem (Fig. 3). The epithelium

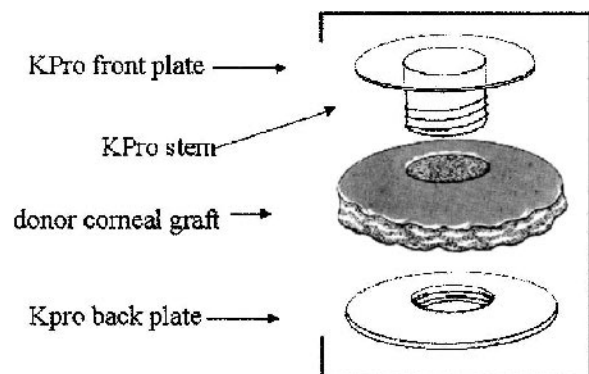


FIGURE 2. Assembly of a collar button KPro. The donor tissue is placed over the stem and sandwiched between front and back plates that screw together.

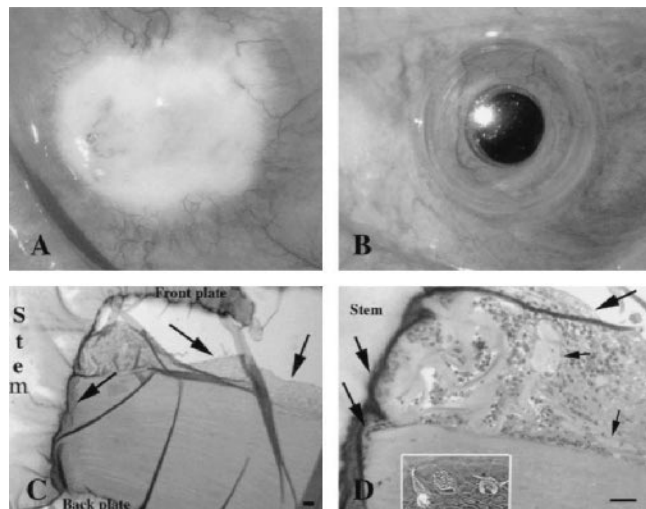


FIGURE 3. Patient 1. Status post-chemical burn. Appearance of eye before (A) and 2 years postoperatively, just before death (B). Progressively higher magnification views of the KPro–cornea junction: low power (C) and higher power (D) views of the sectioned KPro–cornea complex. C: The epithelium (*large arrows*) extends beneath the front plate and enters a superficial cleft between stem and tissue but halts without further downgrowth. The tissue above the stroma contains a superficial conjunctiva-derived epithelium (*large arrows*) overlying inflammatory cells, which surround coiling strands of extracellular matrix material. Blood vessels (*small arrows*) are present in the matrix. Inset demonstrates goblet cells that are present in the epithelium under the front plate. Folds present in the tissue and KPro are artifacts produced by sectioning through hard KPro PMMA and tissue interface. Bar = 50 μ m.

then entered a superficial cleft between stem and corneal graft stroma, but it extended posteriorly only to the point at which there was tight KPro–cornea apposition. Goblet cells were present in larger numbers outside the front plate, but several were noted under the front plate as well. No epithelial downgrowth into the anterior chamber could be found. It appears that the corneal graft stroma holding the KPro had become somewhat reduced in thickness. The void up to the front plate was filled with loose vascu-

larized connective tissue containing inflammatory cells. This material may be the remaining thin wedge of fresh donor lamellar cornea that had been placed under the KPro in response to a wound leak (see Case Report). Minimal inflammation was noted in the stroma, and the keratocyte density appeared normal.

Case 2

The cornea was scarred with dense opacification adjacent to the stem without evidence of tissue melting (Fig. 4). Corneal epithelium extended beneath the small front plate and stopped at the KPro–cornea interface (Fig. 4B). No area of epithelial downgrowth could be found. Inflammatory cells were present in the stroma in small numbers, and there was intralamellar acellular proteinaceous debris (Fig. 4D). The keratocyte density appeared normal. A dense avascular retroprosthesis membrane consisting of keratocytes in a noninflamed fibrous stroma was present across the visual axis (Fig. 4C).

Case 3

A zone of fibrinous necrotic tissue involving all cornea layers separated the KPro stem from the supporting tissue in one quadrant (Fig. 5). The epithelium exhibited downgrowth that extended to the back plate area (Fig. 5B,C). Severe stromal scarring was present with few keratocytes. Also present were many acute and chronic inflammatory cells as well as superficial and deep vascularization in varying degrees throughout the donor graft.

Case 4

A zone of tissue necrosis filled with both acute and chronic inflammatory cells separated the KPro stem from the supporting corneal tissue in the area of stromal melting (Fig. 6). The epithelium exhibited downgrowth in this region that extended into the anterior chamber and onto a dense and vascularized retroprosthesis membrane that crossed the visual axis. The membrane may have developed in response to inflammation but its origin could not be ascertained because it extended across the entire back plate. Many foreign body giant cells were present at the edge of the necrotic tissue. The adjacent viable tissue was vascularized and had nu-

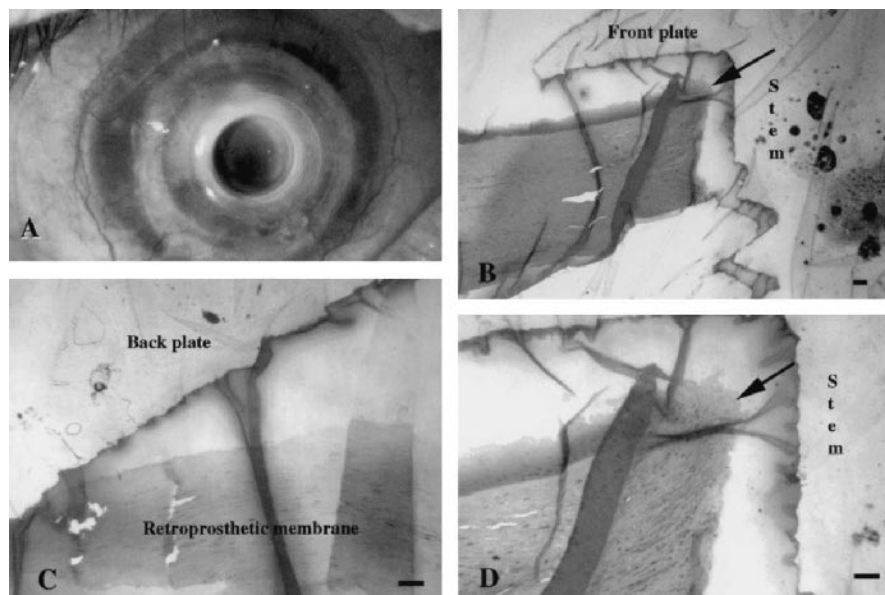


FIGURE 4. Patient 2: Meretoja syndrome. A: Eye before KPro replacement. There is no evidence of tissue melting (B), but a dense retroprosthetic membrane is present across the visual axis (C). B,D: Progressively higher magnification views of the KPro–cornea junction. The corneal epithelium extends beneath the front plate and stops at the stem–cornea interface (*large arrow* in B and D). A few chronic inflammatory cells and some intralamellar acellular proteinaceous debris are present in the stroma. There are normal numbers of keratocytes. C: A dense retroprosthetic membrane consisting of fibroblasts in noninflamed stroma without vascularization is present behind the back plate. Separation of the back plate at the level of the screw threads seen in B is an artifact of processing. Bar = 50 μ m.

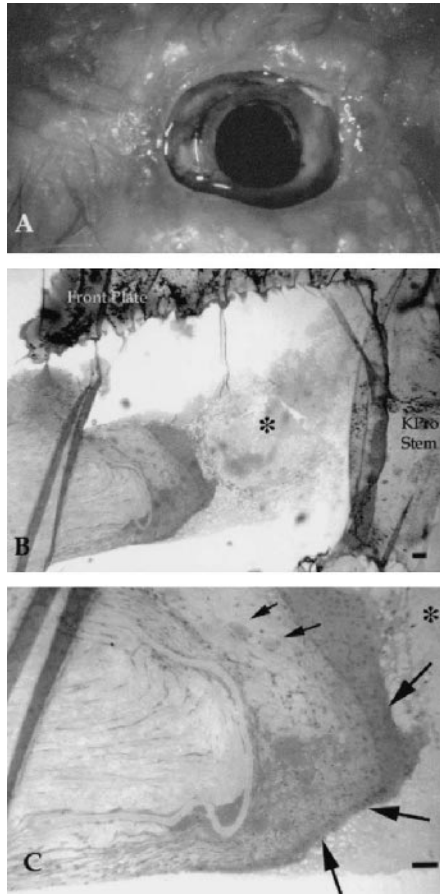


FIGURE 5. Patient 3: Ocular cicatricial pemphigoid. **A:** Eye before KPro replacement. Extensive tissue necrosis and melting have occurred behind the front plate. **B,C:** Progressively higher magnification views of the KPro–cornea junction. A zone of tissue necrosis (*) involving all corneal layers separates the KPro stem from the supporting tissue. The epithelium exhibits downgrowth (*large arrows*). Severe stromal scarring is present, with few keratocytes, many acute and chronic inflammatory cells, and vascularization (*small arrows*). Bar = 50 μ m.

merous chronic inflammatory cells. There was no retained stromal architecture. More peripheral tissue showed a similar pattern of stromal keratocytes and collagen replaced with chronically inflamed vascular tissue.

DISCUSSION

Placement of a collar button style keratoprosthesis can significantly improve visual function in patients with corneal blindness due to conditions with minimal to no realistic expectations for successful standard penetrating keratoplasty. The prognosis for long-term success with KPro, however, has been linked to the patient’s preoperative diagnostic category.³ These categories, in turn, are based on the presence or absence of high degrees of past ocular inflammation. Those patients with corneal blindness due to noncicatrizing ocular disease carry a significantly better prognosis than those suffering from cicatrizing processes. Vision-threatening complications including tissue necrosis and melting, often with aqueous leakage and epithelial downgrowth, occurred far more frequently within the latter group of patients. The histopathologic findings of this study are consistent with these assertions.

The histopathology of patients 1 and 2, who had nonautoimmune corneal disease and who had experienced multiple graft failures previously, was characterized by mild inflammation in the corneal tissues limited to the region surrounding the KPro–cornea junction. Clinically, mild tissue necrosis was present in patient 2 that may correlate with the areas of acellular proteinaceous debris noted in the sections; however, keratocyte density and stromal architecture remained normal in appearance, as it did in patient 1. Tissue vascularization was mild in both cases. These findings suggest much better biostability of the Kpro–cornea complex, with less tissue destruction in such patients, and correlate well with the clinical course that we have come to expect from patients in this category with this type of KPro.

The tissues of patients 3 and 4, however (both with histories of end-stage cicatrizing autoimmune keratoconjunctivitis without continued systemic immunosuppressive therapy), were character-

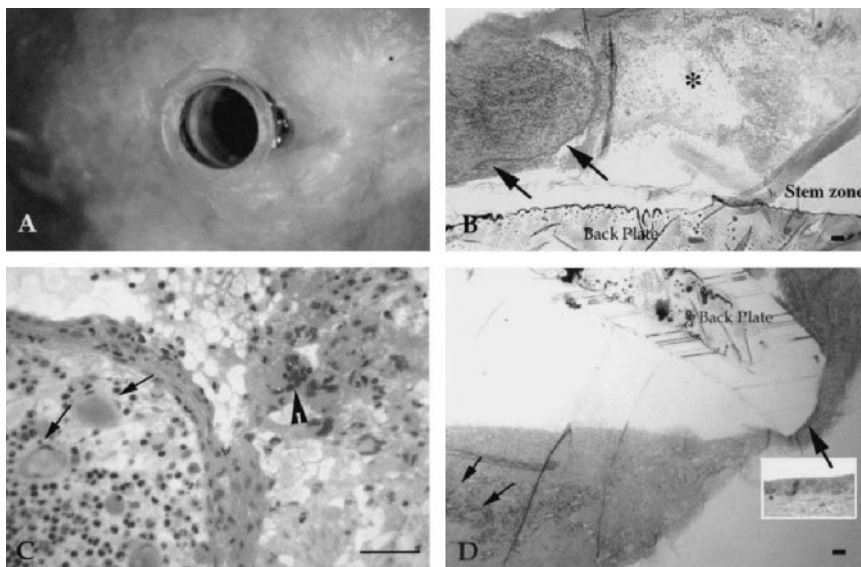


FIGURE 6. Patient 4: Ocular cicatricial pemphigoid. **A:** Eye before KPro replacement. A tarsorrhaphy is present with a protruding optical stem of the type II KPro. An area of leak is present on the side of the stem. **B:** A zone of tissue necrosis (*) filled with both acute and chronic inflammatory cells separates the stem from the supporting corneal tissue. The epithelium exhibits downgrowth (*large arrows*). **C:** Many foreign body giant cells (*arrowhead*) are present at the interface of necrosis. The area of tissue is composed mostly of chronically inflamed vascularized tissue (*small arrows*). **D:** A dense retroprosthetic membrane with blood vessels (*small arrows*) is present behind the back plate. **Inset:** *Arrow* shows the site of the micrograph demonstrating the presence of epithelial downgrowth onto the retroprosthetic membrane. Bar = 50 μ m.

ized by marked acute and chronic inflammatory reactions both in the area of the KPro–cornea junction and in the periphery of the originally healthy corneal graft, where the normal corneal stromal architecture was replaced by varying degrees of neovascularization and dense infiltration by chronic inflammatory cells. This was most pronounced in patient 4, in whom the majority of the donor cornea was replaced by chronically inflamed vascular tissue. In both patients, these changes were associated clinically with stromal necrosis, melting, aqueous leakage, and subsequent epithelial fistula formation. Both fresh donor corneal tissue (patient 3) and frozen stored corneal tissue (patient 4), used to support the KPro and secure it to the host, appear to be susceptible to this process.

These types of inflammatory tissue changes have also been described histopathologically within the osteodental lamina of osteo-odontokeratoprosthesis (OOKPs) in patients with immune-mediated cicatrizing diseases (linear IgA dermatosis and OCP). Stoiber et al.⁴ reported a chronic inflammatory reaction in two such patients that led to necrosis, aqueous leakage, and epithelial downgrowth in the first patient and a massive lymphocyte infiltration with dense vascularization in the second.

These findings suggest that the immunologic process leading to ocular surface failure and corneal blindness remains active in these cases of end-stage disease and support the more guarded clinical prognosis reported for this population with cicatrizing autoimmune disease and a history of intense ocular inflammation. Topical prednisolone acetate, medroxyprogesterone, and tetracyclines have been used in the past to act as anti-inflammatory and anticollagenolytic agents in this patient population, with varying degrees of success.⁵ However, given the degree of change noted by histopathology in these patients, the issue of continued systemic chemotherapy with immunosuppressive agents deserves to be explored in the future.

In addition to providing support to clinical prognostic hypotheses based on disease category and inflammation history, these histopathologic findings shed light on the question of epithelial ingrowth around a collar button KPro. All types of keratoprostheses are susceptible to epithelial ingrowth extending to the interface of human and artificial tissues.^{6–9} In this series, all four cases demonstrated migration of cornea- or conjunctiva-derived epithelium beneath the KPro front plate that was prevented from migrating into the eye by the tight KPro–cornea junction, except in the two cases in which full-thickness tissue necrosis and melt were present. This is consistent with previously published descriptions of complications and histopathology of other types of keratoprostheses (including those with intralamellar skirts and OOKPs).^{4,6–9} In these reports, epithelial downgrowth was always associated with localized tissue necrosis and melting with loosening of the KPro or aqueous leakage. In most reported cases, the epithelium did not extend to the corneal periphery or chamber angle,^{6,8} as in our patient 3. However, occasional cases did experience more extensive spread,^{7,9} as we saw in patient 4.

The presence of epithelial downgrowth in our last two cases, despite attempts to fortify areas of necrosis and melting via the insertion of donor cornea lamellae or dried strips of donor sclera, suggests that repair procedures may have little effect on this process. Early KPro replacement with a new supporting graft may therefore be warranted in instances of necrosis with deep stromal melting prior to development of an aqueous leak.

The techniques of keratoprosthesis application and methods for managing complications are evolving gradually. New therapies

have been introduced and clinically appear to improve the prognosis for useful vision with a collar button KPro in all categories of patients. Thus, laser treatments¹⁰ and modified vitrectomy techniques¹¹ have reduced retro-KPro membrane–related obstruction of the visual axis. The introduction of topical vancomycin prophylaxis, as suggested by Nouri et al.,¹² has eliminated infectious endophthalmitis for the nearly 3-year period since its institution in the treatment regimen (unpublished data). The use of glaucoma shunts, sometimes with extension tubing that allows drainage into the ethmoid or maxillary sinuses, has reduced glaucoma.^{13,14} The application of soft hydrophilic lenses in type I KPro patients seems to reduce peri-KPro surface drying,¹⁵ and the addition of holes in the KPro back plate to allow enhanced nutrition to the corneal stroma adjacent to the KPro stem appears to be reducing the incidence of tissue necrosis and melting in minimally inflamed, non-cicatrized eyes (see case 4, in which the back plate had no holes). Control of ocular inflammation in patients with autoimmune disease, however, has only partly been achieved with frequent topical and subtenon applications of anti-inflammatory corticosteroids.

Further histopathologic study, especially including an analysis of inflammatory mediators, may provide a more definitive understanding of the interaction taking place at the KPro–cornea interface in all disease states, as will a more definitive understanding of the immunology of this region and of the effectiveness of our interventions to modulate it.

REFERENCES

- Doane MG, Dohlman CH, Bearse G. Fabrication of a keratoprosthesis. *Cornea*. 1996;15:179–184.
- Dohlman CH, Waller SG, Netland PA. Keratoprosthesis surgery. In: Lindquist TD, Lindstrom RL, eds. Chicago: Mosby-Year Book, 1997:1–31.
- Yaghouti F, Nouri M, Abad JC, et al. Keratoprosthesis: preoperative prognostic categories. *Cornea*. 2001;20:19–23.
- Stoiber J, Csaky D, Schedle A, et al. Histopathologic findings in explanted osteo-odontokeratoprosthesis. *Cornea*. 2002;21:400–404.
- Dohlman CH, Doane MG. Some factors influencing outcome after keratoprosthesis surgery. *Cornea*. 1994;13:214–218.
- Polack F. Corneal optical prosthesis. *Br J Ophthalmol*. 1971;55:838–843.
- Ferry AP, Gordon BL. Epithelialization of the anterior chamber: a complication of prosthokeratoplasty. *Arch Ophthalmol*. 1974;91:281–284.
- Girard LJ, Moore CD. Prosthesclerokeratoplasty—implantation of a keratoprosthesis using full-thickness onlay sclera and sliding conjunctival flap. *Trans Am Acad Ophthalmol Otolaryngol*. 1969;73:936–957.
- Hayano S. Histological study on a human cornea with a keratoprosthesis. *Acta Soc Ophthalmol Jpn*. 1996;70:8–10.
- Bath PE, McCord RC, Cox KC. Nd:YAG laser discission of retroprosthetic membrane: a preliminary report. *Cornea*. 1983;2:225–228.
- Ray S, Khan BF, Dohlman CH, et al. Management of vitreoretinal complications in eyes with permanent keratoprosthesis. *Arch Ophthalmol*. 2002;120:559–566.
- Nouri M, Terada H, Alfonso E, et al. Endophthalmitis after keratoprosthesis: incidence, bacterial etiologies, and risk factors. *Am J Ophthalmol*. 2001;119:484–489.
- Netland PA, Terada H, Dohlman CH. Glaucoma associated with keratoprosthesis. *Ophthalmology*. 1998;105:751–757.
- Dohlman CH, Grosskreutz C, Dudenhoefer EJ, et al. Can a glaucoma shunt tube be safely extended to the lacrimal sac or the ethmoid sinus in keratoprosthesis patients? Preliminary findings. *Dig J Ophthalmol*. 2001;7:3.
- Dohlman CH, Dudenhoefer EJ, Khan BF, et al. Protection of the ocular surface after keratoprosthesis surgery: the role of soft contact lenses. *CLAO J*. 2002;28:72–74.