# Keratoconus Following Bilateral Corneal Transplants: An Unusual Case Report and Literature Review

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## ABSTRACT

**Purpose**: To report a rare case of clinical keratoconus (KC) in bilateral penetrating grafts confirmed by electron microscopy at the time of repeat penetrating keratoplasty (PK).

**Methods**: A case review of a female patient with bilateral severe vernal keratoconjunctivitis (VKC) who underwent bilateral corneal transplants in 1983 at age 12 for indolent vernal ulcers that progressed to descemetoceles and perforated. She subsequently underwent repeat PK's in both eyes (right eye (OD):2010; left eye (OS):1987) and twenty-seven years later, had developed KC in both transplants. The patient underwent topography and anterior segment ocular coherence tomography (OCT), and the corneal button from her repeat PK OD was sent for electron microscopic (EM) evaluation. A comprehensive literature review was performed evaluating the occurrence of KC in both lamellar and penetrating corneal transplants.

**Results**: EM and histopathologic findings from the corneal button from the repeat PK OD revealed central loss of bowman's layer, peripheral thinning of the corneal stroma, thickening of the epithelium at the site of stromal thinning, and several fragments of descemet's membrane embedded in the posterior corneal stroma, all consistent with KC. Topography and anterior segment OCT of both repeat PK's and her own corneal tissue revealed similar changes consistent with KC.

**Conclusions**: Late development of KC in corneal transplants occurs with increasing frequency over time and is more prominent in older corneal donors. Although the exact cause(s) of KC seen in this patient's own cornea and bilateral grafts is unknown, the risk appears to be associated with her possible genomic predisposition and her history of severe atopy and VKC. Younger atopic patients undergoing PK should therefore be cautioned that late development of KC may occur.

**Keywords**: atopy, cornea, penetrating keratoplasty, vernal keratoconjunctivitis, keratoconus

Keratoconus (KC) is a progressive, non-inflammatory, bilateral degeneration characterized by a localized conical protrusion and thinning of the central and inferior paracentral corneal stroma. Current management options for KC include spectacles, contact lenses, usually rigid gas permeable lenses, and penetrating (or lamellar) keratoplasty (PK) is the treatment of choice for contact-lens intolerant eyes with excellent visual results and uniformly low complication rates.[1] PK in theory is a curative surgical treatment that involves removing the central diseased corneal tissue, thereby providing visual rehabilitation. An alternative surgical procedure is deep anterior lamellar keratoplasty (DALK), which is a surgically more challenging technique than PK, but with the advantages of preservation of host endothelium, no graft rejection, more rapid wound healing, and a shorter topical corticosteroid regimen.[2] Corneal crosslinking, a newer but now established treatment for KC, utilizes riboflavin sensitization with ultraviolet A radiation to induce stromal crosslinks that alter the corneal biomechanics, thereby increasing corneal stiffness and arresting the progression of stromal thinning.[3]

The onset of recurrent KC after successful PK manifests clinically with optical signs including increasing astigmatism, failure of optical correction with spectacles or rigid lenses, and distorted images.[4] Multiple theories exist as to the cause of KC in donor grafts, but a single etiology remains unestablished. Initial predisposing factors for developing KC include genetic, constitutional or environmental factors, mechanical eye rubbing, or other metabolic imbalances, which may continue to subsist in the host after PK; however, although progressive structural and topographic changes may occur very slowly, often over many

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years, clinically identifiable stromal ectasia in a PK itself is rarely observed.[4]

The association of vernal keratoconjunctivitis (VKC) with KC is well known; however, there are few reports of PK for KC associated with VKC. We review a compilation of theories from the literature for the etiology of recurrent KC, as well as report an unusual case in a patient with a history of VKC and atopy that underwent bilateral PK's for corneal perforations and later developed KC in the corneal grafts after 28 years.

## METHODS

After obtaining University of Texas Southwestern Institutional Review Board approval, a comprehensive chart review of both electronic and paper records was performed, including records dating back to age 10. The patient was evaluated, signed appropriate medical release for inclusion in the study, and underwent photography and imaging to evaluate the current state of her disease. In addition, a comprehensive literature review was performed evaluating KC in corneal transplants.

## CASE REPORT

We report a rare case of a patient with a long history of bilateral persistent VKC and severe atopic disease for many years. She underwent extensive allergy testing at age 11, that identified atopic allergic rhinitis from a combination of inhalants, including dust, feathers, mold, dog and cat dander, tree pollen in spring, grass in summer, and ragweed in fall. She had a long history of red watery itchy eyes, positive family history of atopy, and allergic conjunctivitis and dermatographism. At a very young age, her vision decreased due to marked corneal vascularization and leukoma formation. At age 12, she developed an indolent central vernal ulcer in the right eye that progressed to a descemetocele which perforated despite therapy, and was treated with a right PK in March of 1983. Shortly after, she developed a persistent similar central vernal ulcer in the left eye that developed into a leaking descemetocele and a left PK was performed in May of 1983. Subsequently, she developed a recurrent left chronic corneal epithelial defect inferiorly with neovascularization and scarring and underwent a second PK in the left eye in August of 1987. Both transplanted eyes remained clear postoperatively. Of note, neither cornea manifested keratoconus pre-perforation.

Although she was a difficult candidate for rigid contact lens wear, she was successfully fitted for many years with varying contact lenses, including rigid gas permeable and piggyback lenses, which provided functional vision. She had severe myopia in both eyes, with progressive steeping of her corneas, and in 1990, 7 years post-transplants, she had a refraction of -18.00 -4.00 x 070 in the right eye and -16.50 -2.25 x 096 in the left eye. Keratometry readings were 52 x 46 in the right eye, and 52 x 49 in the left eye. Over the next twenty years, she slowly developed progressive high astigmatism that was treated with photorefractive keratectomy (PRK) in the right eye in February 2008. She later developed graft rejection and a cataract in the right eye while on long-term treatment with topical corticosteroids. She also developed progressive posterior subcapsular cataracts and secondary glaucoma in both eyes, and had bilateral Baerveldt tube shunts placed in 2007. She developed central and inferior peripheral thinning, scarring, and KC in the right graft and underwent a repeat PK in the right eye in April 2010 with lensectomy. Secondary IOL placement was delayed and performed in the right eye in early 2011. Most recently, she had diode laser treatment in the right eye in February of 2015 for uncontrolled intraocular pressure while on additional maximum medical glaucoma therapy. Her corneal button from her repeat PK OD was sent for histopathologic evaluation and electron microscopy (EM). Histopathology revealed central loss of bowman's layer, peripheral thinning of the corneal stroma, thickening of the epithelium at the site of stromal thinning, and in the area of thinning several fragments of descemet's membrane were embedded in the posterior corneal stroma.

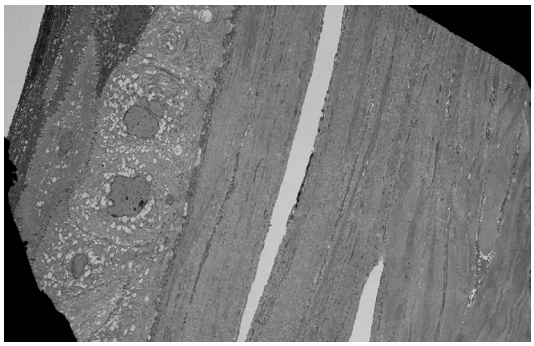

***Figure 1A**: EM (x 700) of repeat PK OD showing abnormal thickened basement membrane with no bowman's layer, equivalent to breaks in bowman's layer in KC*

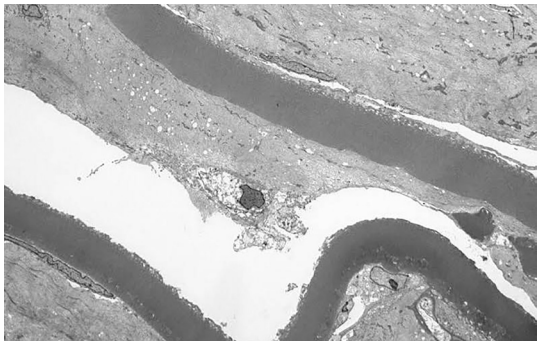

***Figure 1B**: EM (x 700) of repeat PK OD showing breaks in descemet's membrane with retro-corneal fibrosis*

Despite her long struggle of gradual visual deterioration with development of keratoconus in bilateral corneal grafts, she was able to maintain a very high level of function and even received a law degree and practiced as a lawyer for many years. Current medications include latanoprost (Xalatan) QHS, brimonidine/timolol (Combigan) BID, and loteprednol (Lotemax) BID in both eyes, as well as frequent use of artificial tears. She is now 44 years old, remains contact lens intolerant with very limited vision (her most recent vision was 20/400 OD and CF at 3 Feet OS), is visually disabled secondary to her disease, and has developed severe peripheral thinning in the left eye. (**Figures 2A-C**)

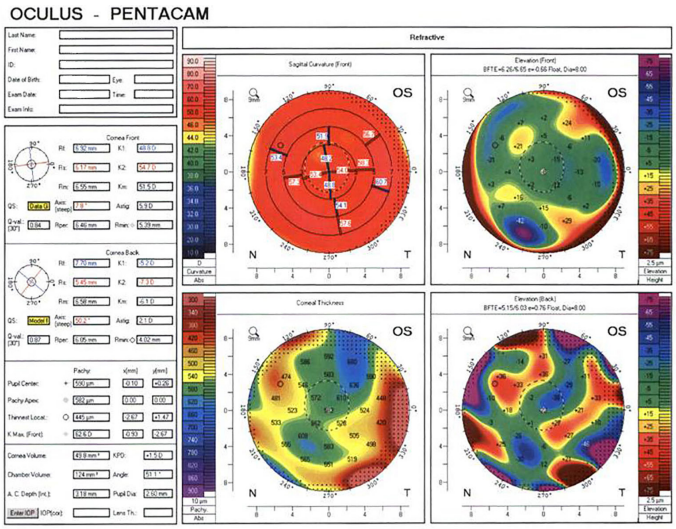


***Figure 2A**: Pentacam of left eye demonstrating diffuse steepening and irregular astigmatism*

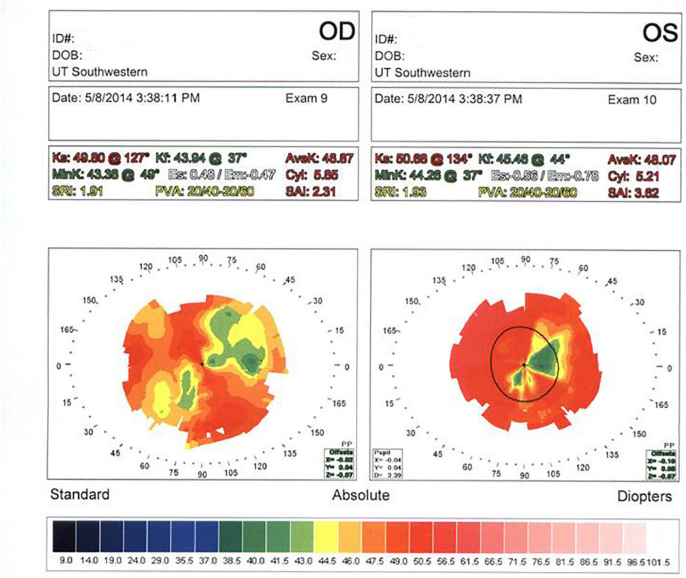


***Figure 2B**: Corneal tomography demonstrating diffuse corneal thinning OS*

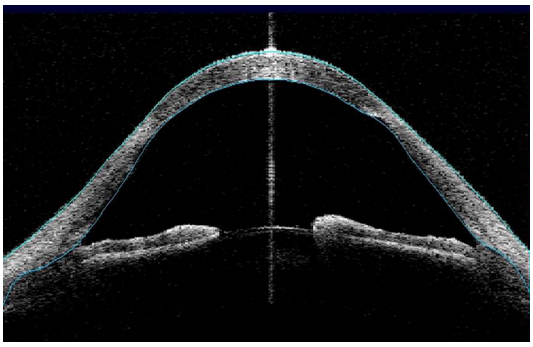

***Figure 2C**: Visante OCT of left eye demonstrating keratoglobus*

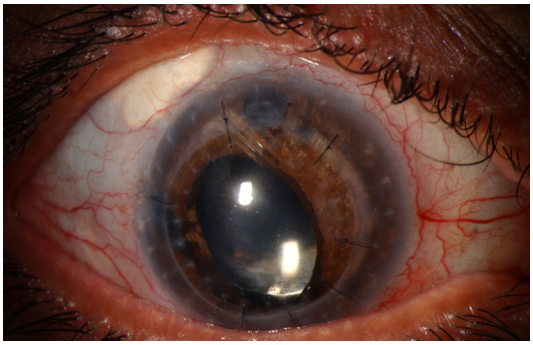

***Figure 3A**: Clinical photo OD demonstrating a clear graft*

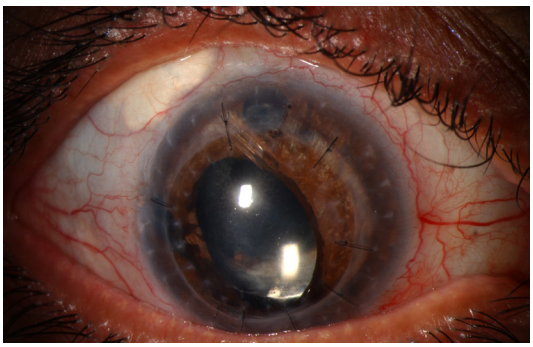

***Figure 3B**: Clinical photo OS showing an edematous graft*

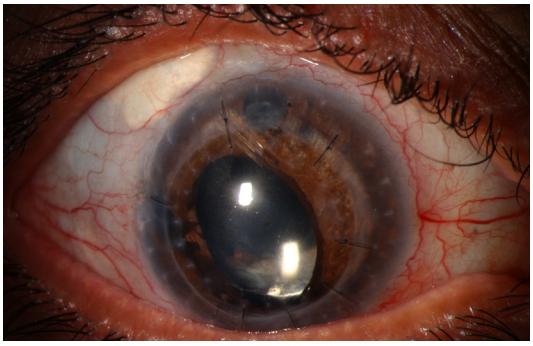

***Figure 3C**: Clinical Photo OS demonstrating Munson's sign*

The right PK is clear and the left PK is edematous with an increasing posterior subcapsular cataract. (**Figures 3A-C)**

## DISCUSSION

Multiple theories exist as to the etiology of the development or recurrence of KC in donor grafts. One theory suggests it is mainly a process caused by recurrence or progression of host disease. For example, small size grafts, eccentric placement of the graft, failure to remove the peripheral portion of the cone during trephination, could all possibly give rise to a recurrence of KC owing to incomplete excision of ectatic tissue. Epithelium eventually covers the donor stromal tissue with ectasia of the graft mediated through degradative enzymes originating from defective host epithelium. Alternatively, abnormal host keratocytes may cause a slow but progressive replacement of donor keratocytes associated with abnormal collagen metabolism and stromal thinning in the donor tissue.[5] Recurrence of KC in a corneal transplant may also be secondary to differences in graft or recipient bed diameters, trephining and suturing techniques, post-operative suture management, asymmetric wound healing, and post-operative trauma including eye rubbing.[5] Yeniad et al reported a case of a 23 year old after bilateral PK with recurrent KC 3 years after PK with severe ocular itching, hyperemia, and a history of vigorous eye rubbing from allergic conjunctivitis. This suggests that recurrent KC can occur because of persistent itch-provoked eye rubbing and that all patients who have had a PK should be treated vigorously for uncontrolled ocular allergies.[6] Patel et al evaluated recurrent ectasia in corneal grafts after the first PK for KC and found that thinning was diagnosed on average two decades after PK, was often bilateral, and occasionally recurred after re-grafting. Taken together, these findings suggest combined genetic host cellular and biochemical factors may be responsible for the recurrent KC clinical phenotype.

Another theory includes the possibility of incipient KC undetected in the donor graft. This is supported by a unilateral occurrence in a patient who underwent bilateral corneal transplants.[5] In 2001, Krivoy et al attempted to determine if KC is caused by recurrence of host disease or transferred by donor graft. These authors reported the development of post-keratoplasty KC in a non-KC patient, who had undergone PK for pseudophakic bullous keratopathy and later developed classic KC in the donor tissue, supporting the possibility of transfer of disease from the donor to recipient.[8]

In 1980, Abelson et al. first reported in the literature EM confirmation of late recurrence of KC in a graft.[9] As in our case, histologic documentation of recurrent KC revealed breaks in the epithelial basement membrane (BM), irregularities in bowman's layer filled with elastic connective tissue, stromal thinning, and abnormal keratocytes, all findings consistent with KC.[5] Bourges et al studied 12 cornea buttons in patients undergoing repeat PK's 10-28 years after initial PK for KC, with indications for re-grafting including endothelial deficiency in 7 cases, irreversible immune graft rejection in two cases, and corneal ectasia in three cases.[4] As expected, EM revealed fracture of bowman's layer with thickening of the basal lamina, fissure of bowman's layer, plication of the stroma, and granular and stromal deposits consistent with keratoconus.[4] KC changes appeared more prominent in older corneal buttons, and the authors postulated that a slow recurrence within the donor graft occurs during the entire life of the graft, with a cellular invasion from the recipient and renewal of resident cells.[4] Similarly, late recurrences of keratoconus have been reported by Pramanik et al from 7 to 40 years after keratoplasty, with a mean latency of 17 years, and all cases were supported by histopathologic findings.[10] EM from the corneal button of our patient showed typical KC characteristics.

Visual prognosis following PK for KC has been uniformly reported as excellent. Niziol et al attempted to predict the 20-year probability of graft survival, which was reported at 88%.[11] They found that KC recurrence occurred in 6 of 219 grafts, ranging 9 to 27 years after surgery with a mean of 10 years, with a 20-year probability of 10%.[11] Pramanik and colleagues reported 7.1% recurrence at 20 years and 11.7% at 25 years, with a mean time to recurrence of 17.9 years. Post-keratoplasty astigmatism of 6-8 diopters occurred in 20-30% of patients.[10]

KC has also been reported to occur in corneal grafts after DALK. Feizi et al reported 2 cases of patients with recurrence of KC at 49 and 52 months after DALK out of 126 cases reported over 4 years, with a recurrence rate of 1.6%.[2] Earlier recurrence after only a few years could be attributed to differences in surgical technique including retained abnormal keratocytes in the graft that invade healthy tissue and cause earlier recurrence. Also, removal of descemet's membrane could weaken the donor tissue causing earlier manifestation of recurrent ectasia in the graft and recurrence of KC.

In a series of 85 patients with both KC and VKC who underwent PK, Mahmood et al reported 68.8% of eyes achieved 20/40 or better with a mean follow up of 47.7 months.[1] Garg et al reported a case of KC in a patient with VKC who developed a shield ulcer in the graft after PK. They recommended that a transplant should not be performed during active or medically uncontrolled phase of

VKC, and that deferring surgery until allergic disease becomes inactive is warranted to avoid this rare documented complication in patients with KC and VKC.[12]

Our patient with a history of atopy and VKC developed KC in bilateral grafts after PK OU. Wagoner et al evaluated PK outcomes in VKC versus PK without VKC in a retrospective review of 464 eyes that underwent PK, 80 (17.2%) eyes with VKC and 384 (82.8%) without VKC.[13] They found that the five-year graft survival was 97.3% with VKC and 95.5% in eyes without VKC. Additionally, postoperative complications and visual outcome were comparable after PK for KC in eyes with or without VKC.[13] These results were further confirmed and extended by Thomas et al in 2011, who evaluated the role of atopy in corneal graft survival and found no statistically significant difference in probability of graft survival in patients with and without a history of atopy.[14] Taken together, data from both of these studies highlight the rare occurrence of developing bilateral KC after bilateral PK's as seen in our patient.

The acceleration of corneal ectasia after excimer laser PRK is well known.[15-16] In our case, PRK was performed only in the right eye in central donor tissue; however both grafts developed identical KC.

In conclusion, multiple, and as yet unproven, theories exist at to the development or recurrence of KC in donor grafts. The uniqueness of this case is the development of KC seen in both this patient's own cornea and bilateral grafts. Although her risk(s) of recurrence of KC is unclear, it appears to be associated with her possible genomic predisposition and her history both severe atopy and VKC. This is in contrast to prior case reports of KC development in the donor graft only in which the recipient had no genetic predisposition to developing KC.

Late recurrence of KC can be observed with increasing frequency over time and appears more prominent in older corneal donors. Given the increasingly younger age at which patients undergo PK, the possibility of recurrence of KC is important to incorporate into the pre-operative counseling of patients. In general, possible preventative approaches should be taken early before a patient develops post-surgical atopic-associated or recurrent KC. Avoiding eye rubbing, controlling atopic disease, the use of rigid gas permeable or scleral lenses to maintain functional visual acuity, stabilization treatment with corneal crosslinking, and other post-keratoplasty surgical methods including crescentric wedge excision to remove recurrent disease in the host early on, are all potentially useful strategies to manage recurrent KC.

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