10.5005/jp-journals-10025-1053
REVIEW ARTICLE

Recurrent Keratoconus

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ABSTRACT

Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning and protrusion. Keratoconus recurrence after corneal transplantation although rare is present and has been confirmed histologically. Host, donor, genetic, mechanical and environmental factors have been proposed as predisposing factors to initiate keratoconus recurrence. The time-to-recurrence post-deep anterior lamellar keratoplasty seems to occur earlier than after penetrating keratoplasty. Wound dehiscence and high astigmatism post-transplant are plausible differential diagnosis for this entity. The treatment options are similar to primary keratoconus. Since, the era of collagen corneal cross-linking, early diagnosis is desirable as it could halt the progression of recurrent keratoconus.

Keywords: Recurrent keratoconus, Deep anterior lamellar keratoplasty, Penetrating keratoplasty.

How to cite this article: Barbara R, Barbara A. Recurrent Keratoconus. Int J Kerat Ect Cor Dis 2013;2(2):65-68.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Keratoconus (KC) is a progressive noninflammatory degenerative disease of the cornea.[1] The pathogenesis of the disease in not clear, however, abnormal synthesis of glycoaminoglycans and collagen and increased degradation of extracellular matrix have been proposed as potential causative mechanisms.[2-5] Predisposing factors to the development of KC are genetic, metabolic, mechanical (eye rubbing) and environmental.[6]

KC recurrence in the donor cornea has been described[7-12] and confirmed histopathologically.[7,11] It has been reported to usually occur two decades after penetrating keratoplasty (PK) which is the period needed for a primary KC to develop.[13]

KC can recur after PK and deep anterior lamellar keratoplasty (DALK).[10] It has been reported as early as 2 months and up to 40 years after corneal grafting.[14,15] While recurrence post-PK occurs after two decades,[7-9] in DALK it appears to occur much earlier. The recurrence rate in one study after PK was 5.4% (6 eyes of 112 eyes) with the mean time to recurrence of 17.9 years, Kaplan Meier analysis showed a recurrence rate of 11.7% at 25 years.[16] Another study demonstrated a recurrence rate of 1.6% (2 eyes of 126 eyes) at 61 months post-DALK.[17]

Clinical Findings of KC Recurrence

- Increased astigmatism
- Subepithelial and anterior stromal scarring
- Corneal thinning
- Increased endothelial reflex
- Vogt's striae
- Munson sign
- Visibility of the nerve fibers in the cornea.

Histopathologic findings of KC Recurrence

- Focal thickening and irregularity of the epithelium or epithelial edema
- Discontinuity of the basal lamina and breaks in the Bowman's layer especially in the mid-peripheral region
- Absence of Bowman's layer
- Dense microgranular deposits in the perikeratocytes space
- Thinning of the graft stroma
- Normal smooth interface
- Although, it can exhibit healthy descemet membrane (DM) and endothelium, lipid deposits and thickening of the DM of up to 25 microns has also been described.

Proposed Mechanism for KC Recurrence after PK

- Failure to completely excise the cone and progression of KC in the host tissue with possible involvement of the donor cornea.[9] This might manifest as progressive thinning in the host and secondary astigmatism
- The use of donor cornea with undiagnosed KC[10]
- Liberation of degenerative enzymes by abnormal host residual epithelium around the graft[10,18,19]
- Infiltration of graft by abnormal host keratocytes leading to abnormal collagen production.[18-20]

Proposed Mechanism for KC Recurrence after DALK

- Residual keratocytes in the stromal bed may invade donor tissue and induce KC[10]
- Weakened donor tissue as DM is removed prior to grafting resulting in earlier manifestations of ectasia.[10]

TREATMENT

Treatment options of recurrent KC are similar to those of primary KC[14,21] and include an initial spectacle and contact lens wear. As in primary KC, collagen corneal cross-linking has been found to be successful in arresting the disease progression in three eyes of three patients developing recurrent KC two decades after PK.[13]

Laser-assisted *in situ* keratomileusis (LASIK) and photorefractive keratotomy (PRK) are known used methods for the correction of ametropia post-PK which manifests mainly as astigmatism.[22-24] High astigmatism may also be a sign of recurrent KC. It is not clear whether LASIK plays a role in accelerating KC recurrence. As one would want to improve the refractive outcome and yet not contribute to the progression of the recurrence, intrastromal corneal ring segments could be a valid option in a graft with recurrent keratoconus. Coskunseven et al reported implantation of intrastromal ring segments in a patient with recurrence KC, 15 years after PK. Ten months postoperatively the patient's vision improved from counting fingers to 20/100.[25] No long term follow-up is present in the literature.

Repeat PK can treat the disease but recurrence of ectasia after a repeat PK has been documented.[26] Nowadays, there is a trend toward DALK. Likewise, a repeat DALK could potentially be performed. keratocytes migration to the donor cornea is postulated to be the cause of recurrence, in DALK less tissue is exchanged than in PK, that would suggest an increased incidence of recurrent KC post-DALK surgery than PK.[13]

DISCUSSION

KC recurrence is a complication of corneal grafting which should be kept in mind even in eyes undergoing corneal transplantation for corneal pathologies other than KC. Recurrence rate and time to recurrence vary among studies with DALK presenting an earlier disease recurrence.[17] Topographic changes in recurrent KC are similar to those of high astigmatism, even many years after PK, and hence early diagnosis of recurrent KC could be potentially missed.[21]

Graft host junction may never exhibit full wound healing[27] and a stress test confirms weak graft host interface[28] which means that healing occurs at the level of the corneal epithelium and endothelium. Reports of late onset wound dehiscence may be confused with recurrent KC. Nevertheless, recurrent KC does exist and is confirmed by histology.

Debate exists to whether the donor or host tissues are responsible for disease recurrence. Genetic, mechanical and environmental factors seem to play a role similar to primary KC. Unal et al reported recurrence of KC as early as 1½ years post-PK in two eyes, one keratoconic and the other post-corneal leucoma, both corneal grafts were from the same donor. They claim that recurrence of KC in the eye with no pre-existing keratoconus confirms this theory as not a true recurrence, but a transmission of the disease from the donor cornea.[29] Krivoy et al reports a similar case.[30] Recurrences occurring shortly after surgery are thought to stem from the grafted donor corneas which likely to have had KC prior to transplantation.[29,30] While recurrence of the disease is low, the aforementioned still raises up the question whether KC screening in all corneal donors is plausible. To date there are no clinically useful methods to exclude KC in a donor cornea several hours after death due to the development of intraocular hypotony. [31]

De Toledo et al, has reported an initial stabilization of keratometric astigmatism 7 years after suture removal in PK for KC and progression from 10 years onward, concluding that the disease is host based. That would give the assumption that a small sized graft would increase the risk of recurrence. However, no correlation was found in previous studies. In their study they noted a peripheral crescent thinning at the graft host junction and an absence of Bowman layer on histopathology.[20] Bourges et al reported on 12 failed PK grafts 10 to 28 years after transplantation for KC (3 ectasia, 7 endothelial deficiency and 2 graft rejection). All eyes in the study had undergone topographic mapping showing astigmatism ranging between 2.5 to 12 D which had progressed over the years after a period of stability. Seven eyes had asymmetric bowing, two round patterns and three irregular patterns. All examined cornea buttons exhibited pathological features of the KC recurrence. This included; localized epithelial edema and duplication or discontinuity of the basal lamina, breaks in Bowman's layer mainly at the periphery, dense microgranular deposits in the perikeratocytes space, lipid deposits and thickening of the DM of up to 25 microns. No central stromal thining was noted probably due to secondary stromal edema in these failed grafts. Since the prevalence of KC in the population is low, it is unlikely that all 12 button were keratoconic to start with, the authors concluded a progressive slow development of KC in PK grafts even when no clinical manifestations of the disease are present. Slow cellular migration from the host cornea with cellular renewal are the mechanisms resulting in KC recurrence.[1]

KC associated systemic diseases may continue expressing the disease in the transplanted donor cornea.[15] A recurrence has been reported to occur after PK in a patient with Leber congenital amaurosis (LCA), the donor cornea was examined prior to transplantation at the eye bank excluding KC, moreover, it exhibited normal slit-lamp appearance and corneal thickness, the authors assume genetic factors to be 'aggressive' in LCA leading to manifestation of the disease in the transplanted healthy donot cornea.[31]

Bearing in mind that the KC is multifactorial[35,36] some have attributed recurrence of the disease to atopy and eye rubbing which are known risk factors for KC.[15,32-34] The use of steroids in the early postoperative period might suppress

the allergic symptoms which would recur once tapered down and ceased.

It had been suggested that corneal grafting itself may initiate structural changes within the cornea that lead to ectasia. Moreover, a decentered graft that bisect the host cone may have tendency for ectasia.[21]

While genetic and biochemical factors can be transmitted to the healthy donor graft, environmental factors leading to KC remain unchanged after transplantation. Together, we believe these factors can increase the risk of KC recurrence in a corneal graft whether it is DALK or PK, although the process may take years to progress and develop. Early recognition and diagnosis are essential to aim to halt its' progression and improve the refractive outcomes by the means of collagen cross-linking with/without intacs and LASIK/PRK. Finally, corneal transplant surgery whether repeated PK, re-DALK or DALK on a PK are plausible options when other methods to restore useful vision have fail.

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