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Post-keratoplasty atopic sclerokeratitis in keratoconus patients

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Purpose: To report the incidence and risk factors of post-keratoplasty atopic sclerokeratitis (PKAS) in keratoconus patients undergoing keratoplasty.

Design: Retrospective, noncomparative, interventional case series.

Participants: Two hundred and forty seven eyes with keratoconus.

Methods: We reviewed the medical records of all keratoplasty cases of keratoconus between May 2000 and December 2005 at Tokyo Dental College Ichikawa General Hospital. The incidence and clinical details of cases consistent with PKAS were recorded.

Main Outcome Measures: Cases with acute sclerokeratitis during the early postoperative period were retrospectively evaluated.

Results: A total of 247 keratoconus eyes were followed at our clinic following keratoplasty. Thirty-five eyes of 29 patients (14.2%) had a history of atopic dermatitis, of which 6 eyes of 5 patients (2.4 %) developed PKAS. Mean age of PKAS patients was 29 (23-39) years old. The mean period between keratoplasty and onset of PKAS was 26 (11-41) days. Loosening of running sutures and wound leakage was observed in 3 eyes, persistent epithelial defects (PED) in 3 eyes, graft melting in 2 eyes of which 1 eye perforated. Preoperative atopic blepharitis and corneal neovascularization were identified as risk factors for PKAS.

Conclusions: PKAS is a potentially severe complication in atopic patients undergoing keratoplasty. Systemic immunosuppression should be considered in patients with active blepharitis and corneal neovascularization.

Post-keratoplasty atopic sclerokeratitis (PKAS) is a severe form of sclerokeratitis observed after keratoplasty in atopic patients^{1,2}. PKAS is reported to develop within 1 to 4 weeks following keratoplasty, with clinical signs of early loosening of sutures, persistent epithelial defects and severe sclerokeratitis. Although typical signs of endothelial rejection have been associated with PKAS, these findings are secondary to a more acute inflammatory episode of the ocular surface. The etiology of PKAS is still unknown since acute graft rejection occurring within a few weeks is uncommon following keratoplasty. Immunological rejection of the central cornea is considered a delayed-type hyper-reaction that usually occurs at least several weeks to months following surgery³⁻⁶.

Early diagnosis and prompt treatment of PKAS is necessary since prolonged inflammation can lead to irreversible opacification of the donor due to scarring or secondary bullous keratopathy¹. Early intervention is especially important since systemic immunosuppression was found to be effective in most cases reported previously^{2,7}. However, clinical reports of PKAS are still scarce, and there is little information concerning potential risk factors that may be associated with PKAS. Herein, we report the incidence and details of patients with clinical symptoms consistent with PKAS in a group of 247 keratoconus cases receiving keratoplasty in our institution. We investigated possible risk factors of PKAS, and discussed prophylactic measures that may be used to prevent PKAS in high-risk cases.

Patients and Methods

We performed a retrospective observational case series to investigate the incidence of post-keratoplasty atopic sclerokeratitis (PKAS) in keratoconus patients treated at Tokyo Dental College Ichikawa General Hospital between May 2000 and December 2005. Clinical records were retrieved from a computerized keratoplasty database, and a detailed review of medical charts was done for patients with a history of atopic dermatitis.

PKAS was diagnosed by strong inflammation occurring shortly after surgery that lead to wound dehiscence, failure of epithelialization and early rejection. The following information was collected for each patient: age, sex, systemic complications, timing of developing PKAS, slit examination and prognosis (final visual acuity and graft clarity). Treatment following PKAS was also recorded including the use of topical and systemic corticosteroids, systemic cyclosporin and secondary surgery.

Results

Thirty-five eyes of 29 patients out of a total of 247 keratoconus eyes (14.2%) were associated with atopic dermatitis, of which 6 eyes of 5 patients (17.1%) developed PKAS following keratoplasty. Demography and symptoms of all cases are shown in Table 1. The mean age of PKAS patients was 29 (23-39) years old, and the mean period between keratoplasty and onset of PKAS was 26 (11-41) days. Initial clinical finding consisted of early loosening of sutures, epithelial defects and graft melting (Table 2). All cases required removal or replacement of sutures and immunosuppression to control symptoms. Three eyes developed secondary endothelial rejection and two eyes developed progressive melting of the graft, which eventually perforated in 1 eye. The

perforated eye was regrafted under systemic immunosuppression and has been followed to date without further complications.

Preoperative findings in PKAS cases were compared with non-PKAS atopic patients (Table 3). Eyes that developed PKAS had a significantly higher incidence of atopic blepharitis and preoperative corneal neovascularization. There was no significant difference in the incidence of atopic keratoconjunctivitis, positive microbial conjunctival cultures or the use of steroid eye drops prior to surgery.

Case Reports

Case 1. A 27-year-old male keratoconus patient with corneal neovascularization (1 quadrant) due to a bacterial corneal ulcer underwent penetrating keratoplasty (PKP) without complications. Thirty-six days after PKP, ocular pain and loosening of the single running suture was observed simultaneously with acute deterioration of atopic blepharitis. Sutures were removed 1 week after the symptoms occurred (Fig 1A, 1B). Endothelial rejection with a typical Khodadoust line and stromal edema developed 5 days after suture removal (Fig 1C). Systemic betamethasone (1mg for 2 months followed by 0.5mg for 3 months) and systemic cyclosporine (375mg for 4 months, 200mg for 2 months, and 100mg for 2 months) were immediately administered. Topical betamethasone drops were also applied. Corneal graft finally cleared at 11 months after PKP (Fig 1D). His spectacle corrected visual acuity was 20/20 on last examination.

Case 2. A 26-year-old male keratoconus patient received PKP following perforation of an ulcer due to severe atopic keratoconjunctivitis. He had corneal neovascularization in all 4 quadrants preoperatively. Following an uncomplicated early postoperative stage, an

epithelial defect appeared 28 days after PKP. The donor graft eventually perforated after 10 weeks, at which point a therapeutic lamellar keratoplasty was performed. However, the donor graft melted again and perforated after only 2 weeks despite the use of systemic corticosteroids (Fig 1E, 1F). An emergency PKP procedure was performed, this time with both systemic steroids and systemic cyclosporine (375mg) for 11 weeks. Histopathology of the resected cornea revealed infiltration of neutrophils and eosinophils in the stroma (Fig 1G). No recurrence of PKAS was observed, and the corneal graft remained clear upon final examination 28 months following the last PKP (Fig 1H).

Case 3. A 30-year-old male keratoconus patient was prescribed with 0.1% fluoromethorone eye drops for the treatment of atopic keratoconjunctivitis prior to receiving PKP. Early postoperative course was good despite 4 quadrants of neovascularization. However, an epithelial defect appeared 41 days after PKP with symptoms of epiphora (Fig 2A). The epithelial defect was successfully treated with amniotic membrane patching and systemic betamethasone (Fig 2B). The graft remains relatively clear upon last examination.

Case 4 and 5. A 39-year-old man suffered loosening of sutures and progressive corneal melting 21 days after PKP in his right eye (Case 4) for keratoconus. The single running suture was removed and replaced with several interrupted sutures. He underwent PKP in his left eye (Case 5) 5 months after PKP of his right eye. Epithelialization was not achieved for up to 20 days after surgery, at which time the running suture started to become loose (Fig 2C). Suture removal and an amniotic membrane patch were done on

the following day, and systemic steroids were administered. Epithelialization was complete 1 week after AM patching, however, recurrence of PKAS was observed 2 months later (Fig 2D). On final presentation, the graft in his right eye was clear, however his left cornea was opaque due to scarring of the stroma.

Case 6. A 23-year-old woman received PKP for keratoconus in her right. She felt tearing 11 days after PKP and slit lamp examination revealed loosening of the running suture and wound leakage. Although the wound leakage was treated with a bandage soft contact lens, she required removal of sutures due to progressive suture loosening. She received PKP in her left eye 27 months after surgery of her right eye. Due to signs of PKAS observed during her previous surgery, PKP was done with interrupted sutures and systemic betamethasone was used to prevent PKAS. No complications were observed in her left eye following surgery.

Discussion

The average onset of PKAS in our series was 26 ± 10 days after surgery, which is similar to previously reported cases^{1,2}. Clinical findings include early loosening of sutures in 3 eyes, persistent epithelial defect in 2 eyes, including 1 case that developed a severe sterile ulcer that eventually required additional keratoplasty following perforation. Initial symptoms were epiphora (2 eyes), pain (2 eyes) and photophobia (2 eyes) which are all signs associated with the condition.

One differential diagnosis of PKAS is immunological rejection of the donor graft. Three cases in our series presented with signs of immunological endothelial rejection several days after the onset of PKAS. One other case in the literature suffered

immunological rejection following PKAS¹. The appearance of an acute epithelial defect 2 to 3 weeks following PKP does not rule out the possibility of a rejection response against donor epithelium. Therefore, PKAS may be a type of acute epithelial rejection observed in atopic patients, which may or may not induce immunological response against the endothelium. A previous report suggested that atopic patients are at a high risk of immunological rejection due to alterations in systemic T cell-mediated responses to allogenic antigens⁸. Both type I and type IV allergic responses are accelerated in atopic patients⁹⁻¹¹, suggesting that a clear differentiation between PKAS and epithelial rejection may be difficult.

Infection is another differential diagnosis of PKAS since staphylococcal infection is a complication observed following buckle surgery for retinal detachment in atopic patients¹². However, extensive immunosuppression with corticosteroids and cyclosporin was effective in PKAS cases, which makes bacterial infection an unlikely cause. Histopathology of Patient 2 showed infiltration of both neutrophils and eosinophils with no signs of bacterial infection. Since atopic patients have a high prevalence of latent staphylococcal infection¹³⁻¹⁵, bacterial antigens may play an indirect role in the etiology of PKAS.

We compared the 6 PKAS eyes with the remaining 29 non-PKAS atopic eyes after keratoplasty to examine possible risk factors for the condition. We found that both atopic blepharitis and pre-operative neovascularization were conditions related with PKAS with statistical significance. Other factors that were observed with PKAS include atopic keratoconjunctivitis (AKC), positive preoperative swab cultures and the use of steroids prior to surgery. These results suggest that patients with active atopic disease of the ocular surface and lids are at a risk of developing PKAS following keratoplasty.

Serum IgE levels, another sign of active disease^{16, 17}, was also reported to be high in PKAS patients prior to surgery^{1, 2}. Among the 6 PKAS cases in our series, 1 case had bronchial asthma, and 2 cases had diabetes mellitus (DM) suggesting that patients with systemic disease in addition to atopic dermatitis may be at a risk of PKAS. Similar findings were observed in previous reports where 6 out of 8 cases had asthma^{1, 2}.

The management of PKAS includes early intervention by removing any loose sutures, and resuturing in early cases with poor donor-graft adhesion. All 6 cases in our study required early surgical intervention including suture removal in 4 eyes, resuturing in 2 eyes, and keratoplasty for 1 case that perforated following melting of the donor cornea. Systemic immunosuppression is standard protocol for PKAS, and cyclosporin should also be considered when corticosteroids alone are not sufficient to control inflammation. Two eyes in our series, and 3 cases in the literature² were successfully treated with the addition of cyclosporin, suggesting that eosinophils or mediators unresponsive to corticosteroids such as IL-5 may play key roles in the etiology of PKAS.

Systemic corticosteroids may be effective in preventing PKAS during the early stages following surgery. Cyclosporin was also reported to be effective in the prevention of PKAS in high risk cases when applied both topically⁷ and systemically¹⁸. We found that systemic immunosuppression effectively prevented PKAS in 2 cases in our study. Both cases suffered PKAS during previous keratoplasties of the same (Case 2) or opposite eye (Case5), for which immunosuppressives were not prescribed. Case 2 required both corticosteroids and cyclosporin, while Case 5 was managed with systemic corticosteroids alone.

PKAS is a potentially devastating complication following keratoplasty in

atopic patients. Since active atopic disease seems to be a risk factor for PKAS, treating atopic blepharitis and keratoconjunctivitis is advised prior to PKP. If surgery is to be performed, prophylactic corticosteroids should be used systemically, and keratoplasty using interrupted sutures alone should be considered since early suture loosening is a common finding. If PKAS is observed, as in 17.1 % of atopic dermatitis patients in our series, prompt diagnosis and aggressive intervention with suture management and systemic immunosuppression should be done to prevent irreversible damage to the donor cornea.

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Figure Legends

Figure 1: Post-keratoplasty atopic keratitis (PKAS) in Case 1 and Cases 2. Loosening of sutures 36 days following penetrating keratoplasty (PKP) in Case 1 (A, B), followed by secondary endothelial rejection 5 days after suture removal (C). Both conditions were controlled with systemic corticosteroids and cyclosporin, and cornea remains clear at 11 months (D). Severe corneal melt in Case 2 that perforated 2 weeks after therapeutic lamellar keratoplasty (E, F). Histopathology of the cornea shows infiltration of neutrophils and eosinophils (G). Clear donor graft 28 months after final PKP using systemic corticosteroids and cyclosporin (H).

Figure 2: Post-keratoplasty atopic keratitis (PKAS) in Case 3 and Case 5. Sclerokeratitis and an epithelial defect appeared 41 days following an uneventful penetrating keratoplasty (PKP) in Case 3 (A). Inflammation was controlled with systemic steroids and an amniotic membrane patch (B). Loosening of sutures following a persistent epithelial defect 20 days after PKP in Case 5 (C). Although the defect was treated with systemic corticosteroids and an amniotic membrane patch, PKAS recurred 2 months later (D).

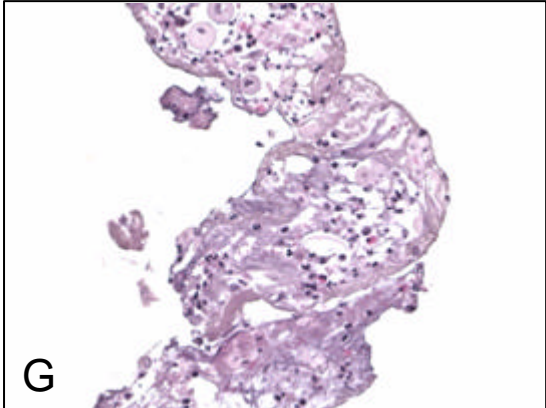
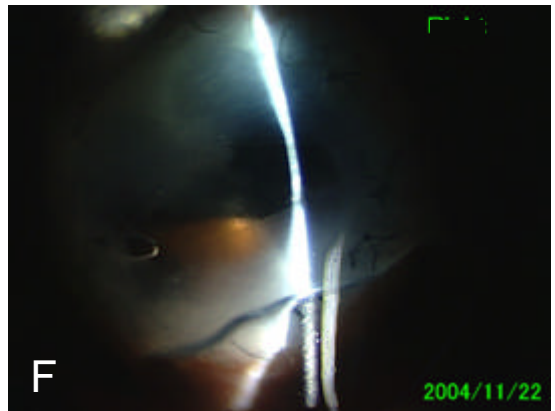
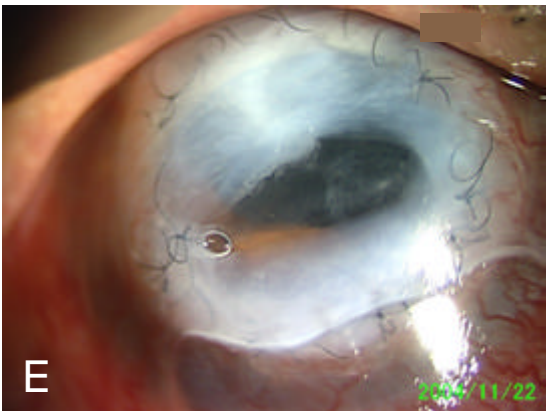
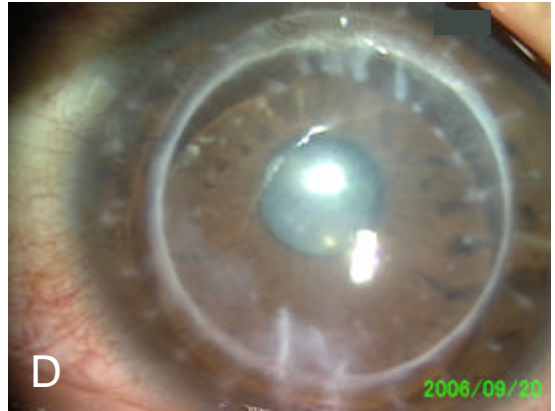
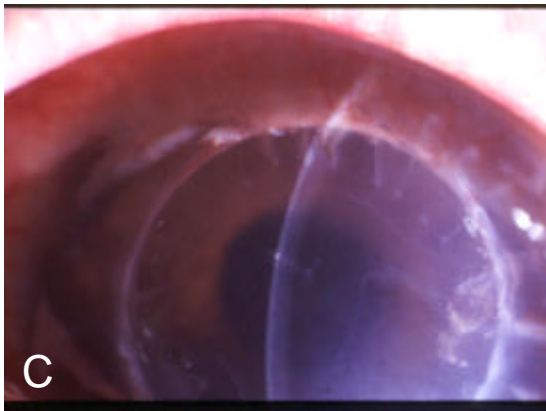
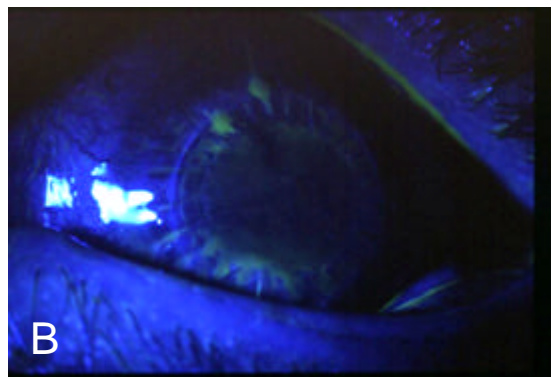


Figure 1

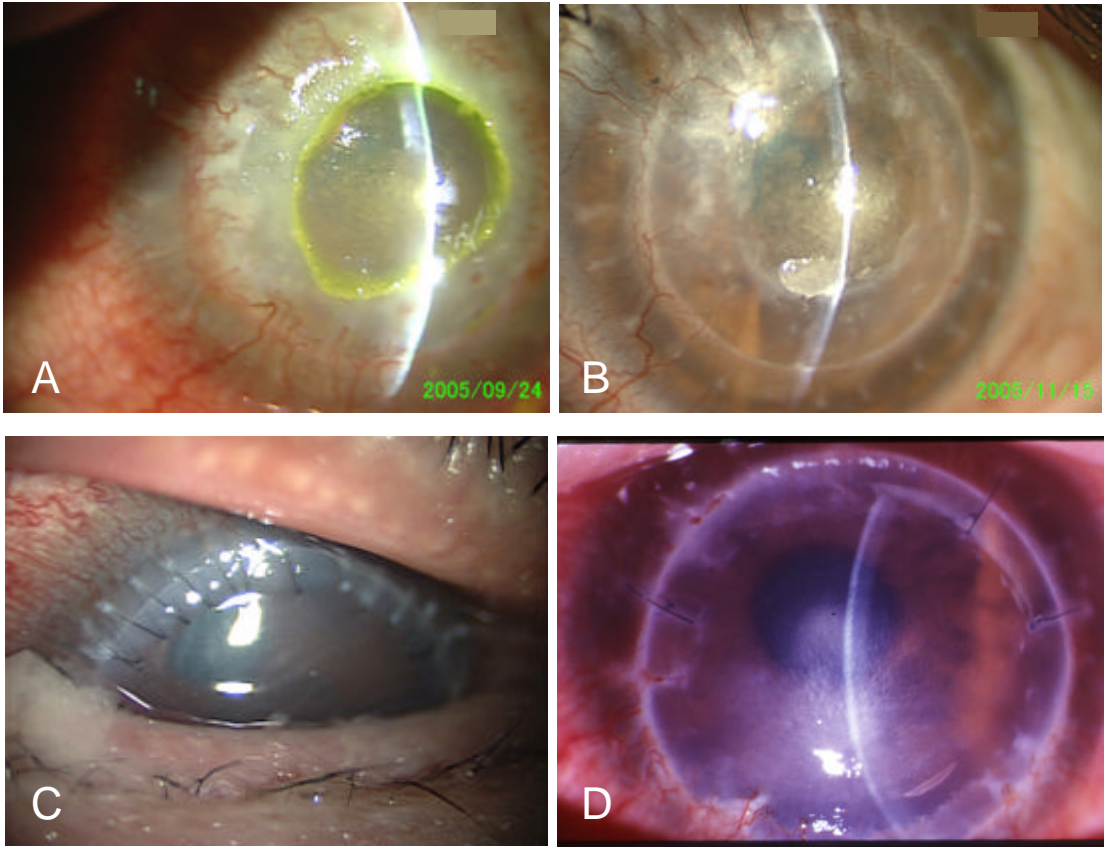


Figure 2

Table 1: Demography of PKAS Cases

Case	Sex	Age	Blepharitis	Conj. Culture	Corneal NV	Pre-op Steroids	Onset (days)	Symptoms
1	M	27	-	-	1 quadrant	-	36	pain
2	M	26	-	-	4 quadrants	-	28	epiphora
3	M	30	+	-	4 quadrants	0.1FM	41	pain
4	M	39	+	+	-	-	21	photophobia
5	M	39	+	-	-	-	20	photophobia
6	F	23	+	+	4 quadrants	0.1FM	11	epiphora

PKAS = post-keratoplasty atopic sclerokeratitis, M = male, F = female, FM = fluorometholone

Table 2: Clinical Presentation, Treatment and Prognosis

Case	Clinical Findings	Therapy	Systemic Therapy	Prognosis
1	loosening rejection	suture removal	steroid,cyclosporin	clear
2	loosening, leak, PED, melting, perforation	regraft	steroid,cyclosporin	clear
3	PED rejection	AM patch	steroid	clear
4	loosening, melting	suture removal+resuture	none	clear
5	PED, loosening, leak rejection	Suture removal+resuture+AM cover	steroid	BK
6	loosening, leak	suture removal	none	clear

PED = persistent epithelial defect, AM = amniotic membrane, BK = bullous keratopathy

Table 3: Comparison of PKAS vs. Non-PKAS Atopic Cases

	PKAS (6 eyes)	Non-PKAS (29 eyes)
Age	29 ± 6	25 ± 9
Pre-op VA	0.06	0.04
AKC	6 (100%)	20 (69%)
Atopic Blepharitis	4 (67%)*	6 (21%)*
Positive Cultures	2 (33%)	2 (7%)
Pre-op Corneal NV	4 (67%)*	1 (3%)*
Pre-op Steroid Drops	2 (33%)	4 (14%)
Systemic Complications	2 DM, 1 asthma	6 asthma

PKAS = post-keratoplasty atopic sclerokeratitis, VA = visual acuity, AKC = atopic keratoconjunctivitis, NV = neovascularization, DM = diabetes mellitus.

* (p<0.05) chi-squared test