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Endothelial Graft Failure after Contralateral Autologous Corneal Transplantation

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Abstract

Purpose—To report on outcomes after contralateral autologous penetrating keratoplasty (APK).

Design: Case series.

Patient population: 5 patients who received a contralateral APK and a simultaneous allogeneic PKP in the donor eye at the Bascom Palmer Eye Institute and the Miami Veterans Affairs Hospital.

Results—The median patient age at the time of surgery in our 5 patients was 67 years (range, 58–88 years); 4 patients were male and 1 female, 1 patient was white and 4 black. The surgery was uneventful in all cases and no operative or immediate post-operative complications occurred in either eye. Follow-up time ranged from 18–54 months (mean, 35 months; median, 34 months). During this time, 4 of the autologous grafts failed due to endothelial attenuation. Identified risk factors for failure in the autologous eyes included the presence of a glaucoma tube (5/5), previous graft failure (4/5) and anterior synechiae in (2/5).

Conclusion—This study is the first to describe graft failure due to slow endothelial attenuation after APK. This study underscores the importance of non-immunologic factors in endothelial cell loss after corneal transplant surgery and highlights the need for further research to understand and modulate endothelial loss.

Keywords

Autologous corneal transplantation; endothelial graft failure

INTRODUCTION

The first successful allogeneic penetrating keratoplasty (PKP) was performed in Czechoslovakia by Eduard Zirm in 1906.¹ This feat was quickly followed by the first contralateral autologous transplantation by lamellar technique in 1908.² It was not until 1958 that a fuller demonstration of the procedure was presented by Joaquin Barraquer and Ariza, who reported three cases in which penetrating autokeratoplasty was successful.^{3, 4}

Contralateral autologous PKP (APK) is a good option in patients who have lost corneal function due to loss of clarity in a potentially seeing eye, and have a clear cornea in an eye

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Conflicts of Interest

No author has a conflict of interest to report.

with poor or no vision due to non-corneal disease.^{5–8} Since the transplanted tissue is isogenic, there is no risk of immunological graft rejection. Accordingly, the surgery is especially beneficial in patients at high risk for graft rejection (e.g. multiple graft failure). Autologous grafts have been reported to remain clear and free of vascularization, even when transplanted into densely vascularized host beds.^{4, 5, 7, 9–13} Furthermore, this surgery is of benefit when poor compliance with postoperative topical medications is likely or where ophthalmic services are limited.¹² However, given the necessary pre-operative criteria of a clear contralateral cornea with poor visual potential, opportunities do not frequently present themselves for its use.^{9, 14}

Since 1908, there have been sporadic publications covering approximately 47 patients who underwent contralateral autologous PKP with generally good results. The overall mean time frame for follow up was 23 months (range 0.1 – 216 months) from 39 patients recorded (Table 1).^{2, 4–22} Of those patients, 7 complications have been described including 1 patient with an immediate post operative complication (poor suture healing after surgery)¹⁵, and 6 patients with later complications from uveitis⁸, retrocorneal membrane growth, posterior epithelial downgrowth, infection after retinal surgery¹⁵, superficial punctate keratopathy²¹, and corneal scarring due to dry eye syndrome.¹¹ We herein report the first cases of late endothelial failure after autologous PKP surgery to make clinicians aware of this potential complication and highlight the need to better understand factors associated with ongoing endothelial cell loss after successful surgery.

MATERIALS AND METHODS

As all cases were performed and reviewed by the study authors (2 by AG, 3 by ECA), the project was deemed to meet criteria for a case series by the University of Miami and the Miami Veterans Affairs Medical Center institutional review boards (IRB). Therefore, no IRB submission was required prior to reviewing the cases. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

Retrospective case series of patients who underwent APK at the Miami Veterans Affairs Administration (VA) Hospital and Bascom Palmer Eye Institute. During the period between 1990 to 2011, 5 APK procedures were performed. Information collected from patient charts included pre-operative history, operative information, and post-operative course.

Surgical technique

The surgical technique involved removing the donor cornea (in the blind eye) by full thickness trephination using a Hessburg-Barron instrument after the anterior chamber aqueous humor was replaced by a viscoelastic. The cornea was then placed in eye bank corneal donor preservation (Optisol) media. An allograft was sutured into place using 16 interrupted 10-0 nylon sutures. In cases 2, 3, and 4 the eye with the corneal disease which was trephinated using a Hessburg-Barron instrument and the recipient donor autograft was then sutured with 16 interrupted 10-0 nylon sutures. In cases 1 and 5, a temporary keratoprosthesis was placed followed by pars plana vitrectomy and glaucoma tube repositioning (case 1) or placement (case 5) into the vitreous, and then the donor was sutured into place using 16 interrupted 10-0 nylon sutures. In all patients, prednisolone acetate 1% was started 4 days prior to surgery in both eyes and continued at this dose after surgery.

RESULTS

Five patients underwent contralateral APK surgery over an 12 year period. Median age at the time of surgery was 67 years (range 58–88); 4 patients were male (Table 2).

All patients had complicated ophthalmic histories in the recipient AKP eye including previous graft failure in 4 patients, glaucoma in 5 patients, the presence of a glaucoma drainage device (GDD) in 4 patients, pseudophakia in 5 patients, and anterior synechiae in 2 patients. All donor eyes had a history of glaucoma, but no GDD, and all had normal anterior chamber organization. Pre-operative endothelial cell density information was available in 2 patients for the donor eye and was 2545 cell/mm² in case 3 and 995 cell/mm² in case 4.

All patients underwent APK surgery from the donor eye to the recipient eye, simultaneously receiving an allogeneic penetrating keratoplasty (PKP) in the donor eye. There were no operative or post-operative complications. All APK grafts were initially clear with improvement of best corrected visual acuity in 4 of 5 patients; visual acuity in one patient did not improve due to glaucoma.

During a median follow-up of 34 months, 4 of the 5 APK grafts failed without any evidence of inflammation or an immune reaction (Table 2). Below are case descriptions of the 5 patients.

Case 1

A 62-year-old black male presented for decreased vision in the left eye. Past ocular history was significant for absolute glaucoma in the right eye. His left eye had a history of GDD placement, cataract extraction with posterior chamber intraocular lens implantation (PCIOL) and synechialysis. At the time of presentation, the patient's visual acuity was no light perception (NLP) in the right eye and hand movements (HM) in the left eye. Slit-lamp examination of the right eye revealed a clear cornea with pachymetry of 521µm. Findings in the left eye included a thickened cornea with pachymetry of 810 µm, 360° high peripheral anterior synechiae, shallow anterior chamber depth, and a GDD tube in near proximity to the cornea.

The patient underwent APK surgery from the right eye to the left eye, simultaneously receiving an allogeneic penetrating keratoplasty (PKP) in the right eye (Table 2). Three months after surgery, best visual acuity improved to 20/40 vision and both corneal transplants were clear. Sixteen months after surgery, visual acuity measured 20/200 in the left eye and slit-lamp examination disclosed slight microcystic edema, haze, and thickening of the graft with a pachymetry of 717 µm. No signs of immunological rejection were noted. Despite increased prednisolone use, the corneal appearance remained unchanged with pachymetry readings of 468 µm on the right eye and 695 µm on the left eye.

Case 2

An 82-year-old black female presented for vision loss in the right eye. Her past ocular history was significant for glaucoma and cataract surgery in both eyes. The patient's right eye also had a history of PKP combined with GDD placement. At presentation, the patient's visual acuity was HM in the right eye and light perception (LP) in the left eye. Slit-lamp examination of the right eye was notable for a thickened corneal graft with pachymetry of 1004 µm, a well-positioned GDD, and a well-centered anterior chamber IOL. Examination of the left eye revealed a clear cornea with pachymetry of 457 µm.

The patient underwent APK from the left to the right eye, simultaneously receiving an allogeneic PKP in the left eye (Table 2). One week after surgery, visual acuity was 8/200 E

and the corneal was noted to be clear, however a fibrin membrane was noted anterior to the lens and the AC was found to be shallow. Five months after surgery, visual acuity improved to 20/100 in the right eye with normal IOP; however, mild cornea edema was observed. Seven months after surgery, the patient presented with decreased vision in the right eye and visual acuity of 20/200. Slit-lamp examination disclosed worsening corneal edema with no signs of immunological rejection. The patient underwent a second allogeneic PKP with extraction of a pupillary membrane 1 year after APK.

Case 3

A 67-year-old black male presented for corneal transplant failure in his left eye. His ocular history was significant for absolute glaucoma in the right eye. His left eye had multiple procedures including 2 trabeculectomies, 2 GDDs, cataract extraction, and 2 PKPs. At presentation, the patient's visual acuity was NLP in the right eye and 4/200E in the left eye. Slit-lamp examination of the right eye revealed a clear cornea with pachymetry of 544 μm and endothelial cell count of 2545 cell/ mm^2 . Left eye revealed a GDD away from the graft, and corneal edema with pachymetry of 612 μm and an endothelial cell count of 921 cell/ mm^2 .

The patient underwent APK from the right eye to the left eye, and simultaneously received an allogeneic PKP in the right eye (Table 2). One month after surgery, best visual acuity improved to 5/200E with normal IOP and clear grafts in both eyes. Thirty months after surgery, visual acuity decreased to HM in the left eye and slit-lamp examination showed new corneal edema with no signs of corneal rejection. A third allogeneic PKP was performed with tube repositioning almost 3 years after the APK.

Case 4

An 88-year-old white male presented for corneal graft failure in the right eye. His past ocular history was significant for glaucoma, hypertensive retinopathy, and Fuchs endothelial dystrophy in both eyes. Loss of left eye vision occurred due to a central vein occlusion. The patient's right eye underwent several procedures including cataract surgery, 2 trabeculectomies, 3 PKPs, and BGI placement. At presentation, the patient's visual acuity was LP in the right eye and NLP in the left eye. Right eye examination revealed a thickened, opaque graft with 4+ Descemet's folds. Left eye examination revealed a clear cornea with a cornea thickness of 469 μm and endothelial cell count of 1005 cell/ mm^2 .

The patient underwent APK from the left eye to the right eye, and simultaneously received an allogeneic PKP in the left eye (Table 2). Two months after surgery, visual acuity improved to 4/200 E and both corneas were clear. Six months after surgery, patient had a decrease in visual acuity to light perception and slit-lamp examination revealed a right eye with a pupillary membrane and an opacified graft. Ultrasonography revealed a right eye retinal detachment. One year and 8 months after APK, a fifth penetrating keratoplasty and retinal detachment repair were attempted but were unsuccessful.

Case 5

A 58-year-old black man presented for corneal transplant failure in the right eye. Past ocular history was significant for endophthalmitis and end stage glaucoma in the left. The patient's right eye had a history of uveitis and glaucoma. The patient had multiple procedures in the right eye including a BGI, cataract extraction, PKP with removal of fibrinous membrane and later, BGI removal. At presentation, the patient's visual acuity was LP in the right eye and NLP in the left eye. Slit-lamp examination of the right eye revealed a hazy, opacified thickened cornea, 360° iridocorneal touch, and 360° corneal neovascularization extending onto the graft peripherally. The left eye revealed a clear cornea.

The patient underwent APK from the left eye to the right eye, and simultaneously received an allogeneic PKP in the left eye (Table 2). Almost 2 years following APK, the patient had stable visual acuity of LP and both corneal grafts remained clear. Complete cupping of the right optic nerve explained the lack of visual improvement after surgery.

DISCUSSION

Autologous penetrating keratoplasty (APK) surgery is a potentially advantageous technique as it eliminates the risk of immunologic rejection of foreign tissue. However, our cases illustrate that this technique does not eliminate the risk of failure due to other causes. Our case series is the first to report on late endothelial failure after contralateral APK. These cases help answer the question of whether graft failure in the absence of clinical signs of rejection represents sub-clinical rejection or endothelial attenuation due to other causes. Our cases lend support to the idea that other factors, besides immune response to foreign antigen, maybe responsible for graft failure in this situation. Understanding these factors is critical for the attainment of optimal results after surgery.

Data from the Corneal Donor Study (CDS) demonstrated that ongoing endothelial cell loss is a problem plaguing the field of corneal transplantation.²³ In grafts considered at low risk for immunologic rejection, the central cell density continued to decrease year after year with a median decrease of 70% at 5 years after corneal transplantation.²³ While the specific processes behind this cell loss are not fully understood, several risk factors have been identified that increase the overall risk of graft failure including the presence of glaucoma^{24, 25}, glaucoma drainage devices^{26–35}, anterior synechiae²⁴, previous graft failure^{24, 31}, and small graft size.^{24, 25}

In comparing our 5 APK patients to those in the literature, our patients were at overall higher risk for graft failure when considering the above criteria. We hypothesize that factors such as GDD and the presence of anterior synechiae contributed to the ultimate graft failure in our APK patients. All our recipient eyes had glaucoma compared to 12/47 of historical controls. Furthermore, all recipient eyes in our series had a GDD (4 prior to surgery, 1 placed at the time of APK surgery) compared to 1/47 in historical APK cases. Other factors which likely elevated the risk of failure in our patients included the presence of anterior synechiae (2/5 cases) and previous PKP (4/5 cases) as compared to 5/47 and 5/47 in the reported AKP cases, respectively.

The exact mechanism for why these risk factors increase the risk of graft failure is not fully elucidated and are likely multifactorial. With regards to glaucoma, one potential mechanism could be an increase in oxidative stress.^{36–38} A case control study comparing aqueous humor antioxidant enzymes in patients with glaucoma (n=24) and cataract patients without glaucoma (n=24) showed significant increases in superoxide dismutase and glutathione peroxidase activity in patients with glaucoma compared to patients without glaucoma.³⁶ With regards to GDD, possibilities include mechanical trauma during placement, ongoing trauma due to eye movements, rubbing, and blinking, and changes in the anterior chamber milieu.^{28, 39} A study comparing proteins in patients with (n=11) and without GDD (n=11) found significant increases in pro-inflammatory proteins in GDD eyes.³⁹

Given the issue of endothelial loss after surgery, our current approach to maximize endothelial health is to start prednisolone in the donor eye prior to surgery (typically 4 days prior to surgery) as some studies have demonstrated a positive effect of corticosteroids on endothelial cells through increased Na, K-ATPase activity.⁴⁰ Other studies, however, failed to observe an effect of corticosteroids on corneal endothelial regeneration.^{41, 42} Other considerations include using a large graft in order to transplant the maximum number of

endothelial cells and moving glaucoma tubes from the anterior chamber to the vitreous. Despite such measures, 4 of our grafts failed highlighting the need for better endothelial protective agents. One such potential class of compounds are Rho-associated kinase (ROCK) inhibitors. ROCK is a protein involved in regulating the cytoskeleton, cell migration, apoptosis, and proliferation.⁴³ In a rabbit model, the use of a topical ROCK inhibitor after cryogenic injury improved corneal transparency, wound healing, and corneal thickness compared to a control group.⁴⁴

As with all studies, this work has limitations which need to be considered when interpreting the study results, including a small sample size, the use of various topical mediations (e.g. carbonic anhydrase inhibitors), non-uniform surgical techniques and variable post-surgical management. Furthermore, information on pre-operative endothelial cell density and pachymetry was not available in all patients. Another limitation is that all donor eyes had some ocular pathology (e.g. glaucoma), which may have affected overall endothelial health. Despite these limitations, our cases illustrate that while APK surgery has many advantages, this technique does not eliminate the risk of overall graft failure. This finding emphasizes that research on non-immunological factors that lead to endothelial attenuation after surgery is greatly needed. A better understanding of such factors will allow us to develop more specific endothelial protective therapies that can improve the prognosis after autologous and allogeneic corneal transplantation alike.

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Table 1

Published cases of contralateral autologous penetrating keratoplasty

Author Year	Age range (yrs)	Corneal vessels [†]	Glaucoma [†]	GDD [†]	Previous graft failure [†]	Anterior Synchia [†]	Adjuvant procedure	Autograft range (mm)	FU range (mos)	APK status (n)
Rycroft 1957 ¹³	50	Yes	No	No	No	No	None	6	30	Clear (1)
Barraquer 1958 ⁴	60–90	1/4	No	No	No	1/4	Cataract extraction (2)	5–11	6–48	Clear (4)
Maumenee 1959 ¹⁰	14–72	1/5	4/5	No	1/5	1/5	Iris manipulation (3) Remove downgrowth (1)	10–13.5	6–17	Clear (5)
Gundersen 1965 ¹⁷	78	No	No	No	No	Yes	None	9	0.4	Clear (1)
Ring 1966 ¹⁴	72, 76	No	1/2	No	No	No	None	7,7.5	1, 1.2	Clear (2)
Romanes 1966 ⁷	76	Yes	No	No	No	No	None	5	15	Clear (1)
Boruchoff 1967 ¹⁵	52–78	1/8	3/8	No	1/8	1/8	None	7–8.5	0.75–8	Failed (4); poor suturing, downgrowth, infection, retrocorneal membrane Clear (4)
Louw 1969 ⁹	48–58	1/3	No	No	1/3	No	None	7–8	0.01–14	Clear (3)
Matsuda 1988 ¹⁹	64	No	No	No	No	No	None	6.5	72	Clear (1)
Lustbader 1988 ¹⁸	64	No	Yes	No	No	No	Anterior vitrectomy	14	216	Clear (1)
Shriwas 1993 ⁸	75, 77	No	No	No	No	No	Anterior vitrectomy (2)	7.5	3–5	Failed: uveitis (1) Clear (1)
Hodkin 1994 ⁵	41	Yes	No	No	Yes	No	None	8.0	3	Clear (1)
Price 1995 ²¹	64–76	No	No	No	1/3	No	Anterior vitrectomy (1)	7.5	66–84	Failed: SPK (1) Clear (1)
Oplinger 1998 ¹¹	50–82	1/4	1/4	No	No	No	Lens removal (3) Anterior vitrectomy (1)	8–8.5	*	Failed; dry eye (1) Clear (3)
Pearson 2000 ¹²	40–70	1/4	2/4	1/4	1/4	No	None	7–11	3–36	Clear (4)
Rao 2000 ⁶	52–60	No	No	No	No	1/3	Cataract extraction (1)	6.5–8	6–26	Clear (3)
Browning 2001 ¹⁶	78	No	No	No	No	No	Cataract extraction	7.5	10	Clear (1)
Mehta 2009 ²⁰	67	No	No	No	No	No	None	8 × 7.75	24	Clear (1)
Tannen 2011 ²²	0.8	No	No	No	No	No	None	7 × 6.5	36	Clear (1)

^{*} long-term;
[†] factors found in recipient eye;

n=number of patients; APK= autologous penetrating keratoplasty; Yrs=years; GDD=glaucoma drainage device; FU=follow up; mos=months; SPK= Superficial punctate keratopathy

Table 2
Risk factors for failure and outcomes in 5 patients who underwent contralateral autologous penetrating keratoplasty

Case	Age	Gender	Reason for initial PKP	Risk factors for failure prior to PKP*	Size (mm) APK recipient/donor	Preop ED/pachymetry APK donor	Concomitant surgery	Meds at time of APK	APK status	FU (mos)
1	62	M	PBK/GDD chafing	GDD x1, Anterior synechiae	7.5/7.75	521µm	Temp Kpro, PPV, GDD repositioning	Atropine	Edema at 16 mos	23
2	82	F	PBK	GDD x 1, PKP x 1	8.0/8.25	457 µm	None	-	Edema at 5 mos → allogeneic PKP	46
3	67	M	PBK	GDD x 2, PKP x 2	7.75/8.0	2545/mm ² /544 µm	None	Brimonidine Dorzolamide /Timolol	Edema at 30 mos → allogeneic PKP	34
4	88	M	PBK	GDD x2, PKP x 4, retrocorneal membrane	8.0/8.25	995/mm ² /469 µm	Retrocorneal membrane & IOL removal	Dorzolamide /Timolol	Edema at 9 mos → allogeneic PKP	54
5	58	M	PBK/Uveitis	Corneal vessels, glaucoma, PKP x 1, anterior synechiae, uveitis	7.75/8.0	-	Temp Kpro, PPV, IOL removal, GDD placement	Brimonidine Dorzolamide/Timolol Travatan	Clear	18

* risk factors found in recipient eye;

APK =autologous penetrating keratoplasty; Mos=months; Temp Kpro=temporary keratoprosthesis; PPV=pars plana vitrectomy; ED= endothelial density; IOL=intraocular lens; GDD=Glaucoma drainage device; PKP=penetrating keratoplasty; M=male; F=female; PKB= pseudophakic bullous keratopathy; NA=not available; M=male, F=female