Long-term Outcomes of Penetrating Keratoplasty in Chronic and Delayed Mustard Gas Keratitis

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Purpose: To report the long-term outcomes of penetrating keratoplasty (PKP) in war victims with chronic and delayed mustard gas keratitis.

Methods: This noncomparative interventional case series includes patients with advanced chronic or delayed mustard gas keratitis who had undergone PKP from 1989 to 2006. Best-corrected visual acuity (BCVA), graft clarity, episodes of graft rejection, duration of steroid use, and complications were evaluated. Histopathologic features of excised corneal buttons were also evaluated.

Results: Overall, 22 eyes of 19 patients underwent PKP. Mean age at the time of surgery was 41 ± 4.6 years (range, 36–54 years), and mean follow-up duration was 40.9 ± 48 months (range, 4–204 months). The graft remained clear in 17 (77.3%) eyes and failed in 5 (22.7%) eyes. Overall, 13 (59.1%) eyes experienced episodes of endothelial rejection, and 5 (22.7%) eyes had subepithelial immune rejection, 4 of which had simultaneous endothelial rejection. Fifteen (68.2%) eyes received topical steroids for >6 months. Fourteen (63.6%) eyes developed cataracts, leading to cataract extraction in 7 eyes. One eye developed steroid-induced glaucoma after multiple episodes of endothelial graft rejections. Mean preoperative BCVA was 1.92 ± 0.63 logMAR, which improved to 1.04 ± 0.65 logMAR (20/200) overall and 0.8 ± 0.3 logMAR (20/120) in eyes with clear grafts ($P < 0.001$). Main histopathologic features of excised corneal buttons included corneal thinning and ulceration, loss of keratocytes, acute and chronic inflammation, stromal vascularization, and degenerative sequelae of long-standing inflammation.

Conclusions: PKP in chronic or delayed-onset mustard gas keratitis should be considered as a high-risk graft; however, with appropriate management, graft clarity and visual outcomes may be favorable.

Key Words: mustard gas, keratitis, penetrating keratoplasty

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Mustard gas–related injuries have been well known since World War I.[1–3] Various degrees of ocular involvement are seen in 75%–90% of individuals exposed to mustard gas.[4–7] Ocular manifestations can be divided into immediate and late categories. After exposure, immediate ocular lesions present within a spectrum of severity. More severe injury may follow 3 courses: complete resolution, persistent smoldering inflammation (chronic form), or reappearance of lesions after improvement after a latent period (delayed form). These late complications occur in ~0.5% of those severely exposed.[6] In contrast to immediate damage, chronic and delayed mustard gas lesions usually cause progressive and permanent reduction in visual acuity and even blindness. Delayed manifestations have been reported up to 40 years after exposure,[3] but we have encountered cases as early as 1 year after injury.[2]

The purpose of this study is to report the long-term outcomes of penetrating keratoplasty (PKP) in war victims who had suffered chronic or delayed-onset mustard gas keratitis (MGK). To the best of our knowledge, this is the first case series with long-term follow-up on the outcomes of PKP in advanced MGK.

MATERIALS AND METHODS

From 1989 to 2006, a subset of patients with chronic or delayed-onset MGK underwent PKP necessitated by corneal haziness, vascularization, or severe thinning. All these subjects were war victims who suffered from multisystem (eye, respiratory, and integumentary) involvement after mustard gas exposure during the Iraq–Iran war. Eleven eyes (50%) had peripheral superficial and deep corneal vascularization in >2 quadrants of the cornea before surgery (8 eyes with 360 degrees and 3 eyes with 180 degrees of vascularization). Six eyes of 6 patients had previously undergone living related stem cell transplantation in 1 or 2 quadrants. All operations were performed by 1 surgeon (M.A.J.).

Standard PKP was performed by using the Barron–Hessburg suction trephine. Donor size varied from 7 to 8 mm depending on the corneal diameter and the extent of corneal involvement. Donor–recipient disparity was 0.5 mm, and

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16 interrupted 10-0 nylon sutures were used in all cases. Five eyes of 5 patients simultaneously received stem cell transplantation from a first-degree living related donor. A 90- to 110-degree arc of tissue was harvested from the superior limbus of the donor eye starting with lamellar dissection in the cornea 1 mm anterior to the limbus, extending 2 mm posterior to the limbus, leaving behind the tenon capsule as much as possible. This arc of tissue was transplanted to the bared ischemic sector of the recipient eye, which was at the interpalpebral or inferior limbal area, and was fixed with 10-0 nylon sutures. The operation was performed under general anesthesia in most patients; peribulbar anesthesia was applied in cases with severe respiratory compromise.

Postoperative medications included topical steroids (betamethasone 0.1%) and antibiotics (chloramphenicol 0.5%) 4 times a day. Antibiotics were usually discontinued after complete epithelialization, and the steroid was gradually tapered after 1 month. In cases of extensive corneal vascularization, oral corticosteroids (prednisolone, 1 mg/kg/d) were started and discontinued after 1–2 weeks. Eleven cases with previous or simultaneous limbal stem cell transplantation received immunosuppression with oral cyclosporine 3–5 mg/kg/d starting 1 week before surgery, which was continued at maintenance dosage (2–3 mg/kg/d) for 2–3 months.

Variables included patient age; follow-up duration; number of immune rejection reactions including epithelial, stromal, and endothelial; duration of steroid intake; graft clarity; complications; additional ocular procedures; and final best-corrected visual acuity (BCVA).

RESULTS

Twenty-two eyes of 19 patients (all men) with advanced chronic or delayed MGK underwent PKP. The mean age at the time of surgery was 41 ± 4.6 years (range, 36–54 years). The mean duration from mustard gas exposure to keratoplasty was 209.9 ± 43.7 months (range, 38–248 months). Mean follow-up was 40.9 ± 48 months (range, 4–204 months). The graft was clear in 17 (77.3%) eyes and failed in 5 (22.7%) eyes at final follow-up. A Kaplan–Meier graft survival diagram is depicted in Figure 1. The cumulative probability for a clear corneal graft was 94% at 1 year and 68% at 5 years after PKP. Causes of graft failure included multiple rejection episodes and ocular surface abnormalities. Figure 2 shows a clear graft in 1 of our cases.

Episodes of endothelial rejection were observed in 13 (59.1%) eyes that occurred once in 9 eyes, twice in 3 eyes, and 3 times in 1 eye. Subepithelial rejection was seen in 5 (22.7%) eyes, which occurred once in 3 eyes and twice in 2 eyes. Four eyes had simultaneous subepithelial and endothelial graft rejections.

Mean preoperative BCVA (logMAR) was 1.92 ± 0.63 (20/1600), which increased to 1.04 ± 0.65 (20/200) overall and 0.8 ± 0.32 (20/120) in patients with clear grafts ($P < 0.001$). The causes of limited visual acuity despite a clear graft were cataracts, in addition to corneal epithelial irregularity and an unstable ocular surface.

Six eyes had received living related stem cell transplantation before PKP, and 5 eyes underwent this procedure simultaneously. Episodes of endothelial rejection occurred in 3 eyes in the former group, but all grafts remained clear. In comparison, episodes of endothelial rejection occurred in 4 eyes of the latter group, leading to graft failure in 3 eyes.

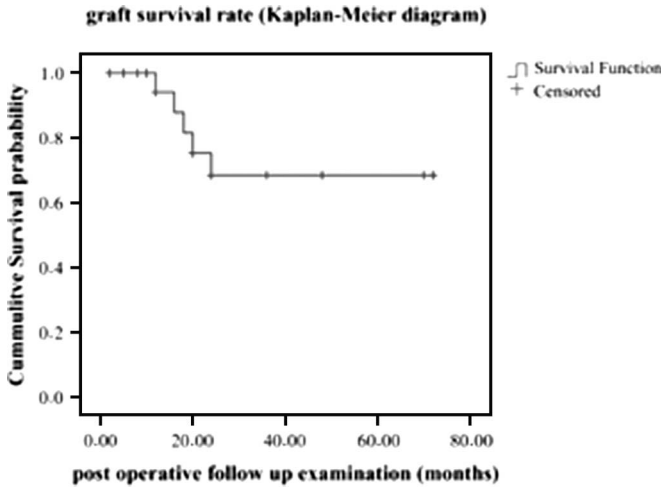

FIGURE 1. Kaplan–Meier diagram showing cumulative graft survival probability.

Topical steroids were administered for <6 months in 7 (31.8%) eyes and >6 months in 15 (68.2%) eyes. Only 1 eye was a steroid responder and developed high intraocular pressure (IOP), which was controlled with 1 topical medication. Fourteen (63.6%) eyes developed cataracts after surgery; necessitating phacoemulsification and intraocular lens implantation in 7 (31.8%) eyes. Mean preoperative BCVA in these eyes was 1.80 ± 0.79 logMAR (20/1300), which improved to 1.00 ± 0.77 logMAR (20/200) postoperatively ($P < 0.017$). Punctal occlusion was performed in 17 (77.3%) eyes.

Report of a Case

A 44-year-old man with history of mustard gas exposure in 1985 who suffered from ocular, respiratory, and skin involvement underwent simultaneous PKP and stem cell

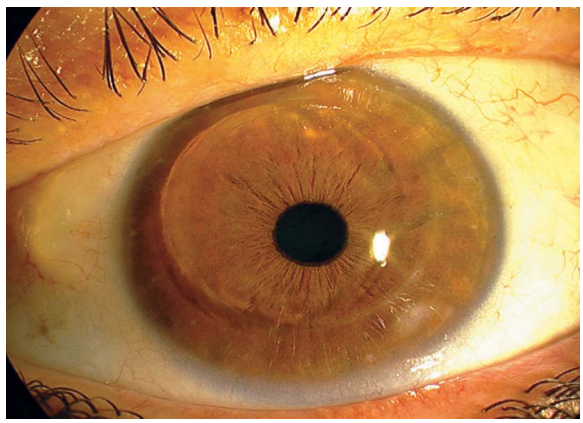

FIGURE 2. Clear corneal graft in a patient without peripheral vascularization.

transplantation in the right eye in February 2001. Preoperative visual acuity was hand motions, which increased to 20/80 at 1 year after surgery. The limbal stem cell transplantation gradually failed, and corneal vascularization progressed over the cornea. There were multiple attacks of endothelial graft rejection caused by peripheral anterior synechiae. The graft eventually failed, and visual acuity decreased to counting fingers at 20 cm (Fig. 3). The left eye also had visual acuity of hand motions. PKP was performed in the left eye in July 2002 with multiple peripheral iridectomies. However, this graft also had multiple attacks of endothelial immune rejection. Because of long-term use of steroids, a cataract developed and IOP increased, which was controlled with timolol eye drops 0.5% twice a day. The patient underwent phacoemulsification and intraocular lens implantation. Visual acuity increased to 20/80 at 1 year after PKP. IOP was 10 mm Hg with the above medication, but visual acuity gradually decreased to 20/200 because of corneal epithelial irregularity. However, the graft remained clear (Fig. 4).

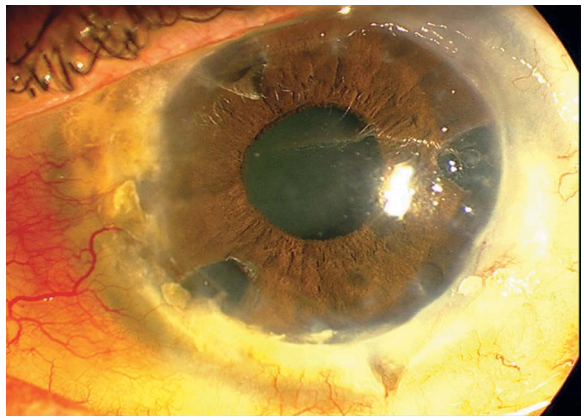

FIGURE 4. Clear corneal graft in the left eye of the same patient (Fig. 3) with multiple peripheral iridectomies.

Histopathology of Corneal Buttons

The histopathologic features of corneal buttons in our case series varied from focal corneal thinning and ulceration (Fig. 5A), together with loss of keratocytes (Fig. 5B) and endothelial cell loss, to foci of mild to moderate acute and chronic inflammatory cell infiltrates, stromal vascularization, band keratopathy (Fig. 5C), lipid keratopathy, amyloid deposition, scar formation, and retrocorneal fibrosis. In all specimens, the corneal epithelium was markedly attenuated with no evidence of goblet cells on periodic acid–Schiff (PAS) staining.

DISCUSSION

Various degrees of ocular involvement are seen in 75%–90% of individuals exposed to mustard gas.[5–7] More severe exposure may lead to chronic persistent or delayed-onset inflammation, which is more destructive and severe.[3] The combination of impaired corneal sensation, damaged limbal vasculature, neovascularization, and recurrent epithelial erosions produce corneal irregularity and thinning, which may extend to deep layers of the cornea, producing descemetoceles and occasionally leading to perforation.[8–12]

Corneal epithelial cells are extremely susceptible to mustard gas injury because of rapid turnover, high metabolic rate, and prolonged interaction with the agent, which concentrate in the lipid layer of the tear film. Mustard gas also targets endothelial cells, inducing apoptosis at lower concentrations and both apoptosis and necrosis at higher concentrations.[6] Mustard gas damages viable tissues only, the mechanism of which is not clear. Theories accounting for this include liberation of intracellular hydrochloric acid, formation of new compounds acting as alkylating agents, neuronal action through an axonal reflex, and finally formation of oxidative derivatives.[7,13–17]

In this study, all patients were war victims with chronic or delayed-onset MGK leading to dry eye,[5] blepharitis and meibomianitis, limbal stem cell deficiency, progressive corneal vascularization, infiltration of inflammatory cells, lipid

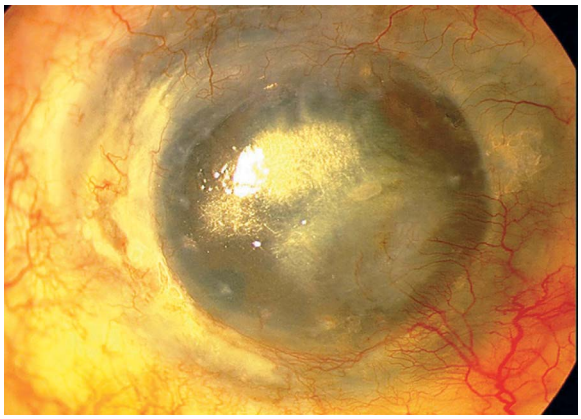

FIGURE 3. Failed vascularized corneal graft with severe lipid and amyloid deposition in the right eye of the reported patient.

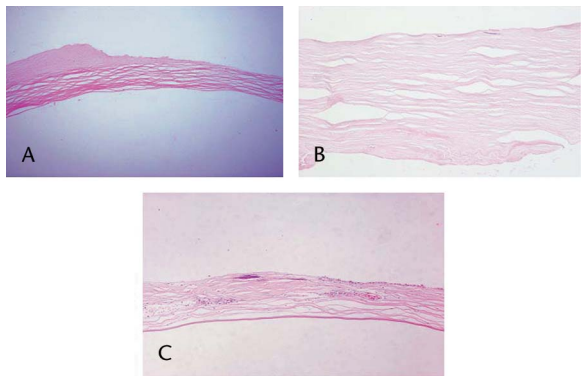

FIGURE 5. A, Marked corneal thinning and ulceration (hemotoxylin–eosin [H&E] stain; magnification, ×25). B, Severe loss of keratocytes (H&E stain; magnification, ×100) in severe MGK. C, Note the stromal vascularization and band keratopathy in a case with severe MGK (H&E stain; magnification, ×25).

deposition, band keratopathy, and eventually corneal haziness and progressive thinning necessitating corneal transplantation. To the best of our knowledge, previous reports on PKP in advanced MGK are limited,[18] and this is the first report with a significant number of patients and considerable follow-up. With a mean follow-up of >3 years, graft clarity was 77.3% and BCVA was significantly improved. Episodes of endothelial rejection were seen in 59.1% of cases and subepithelial rejection occurred in 22.7% of cases.

In a study reporting outcomes of PKP with a 14-month follow-up in 97 eyes with chemical injuries, the success rate was 22%,[19] which is significantly less than this study (77%). Another study described the early results of PKP after limbal stem cell transplantation. The ocular surface remained stable in most cases, and visual acuity improved in the early postoperative period in all patients. Both the numbers of cases and the follow-up period were limited in this study.[20] Agarwal et al[21] reported the results of simultaneous PKP and limbal stem cell transplantation in severe ocular injury resulting from chuna packets (calcium hydroxide glue) who gained visual acuity of 1/60 after 2 years, which is significantly less than our series: 20/200 overall and 20/120 in eyes with clear grafts. The major vision-limiting factors after PKP in our cases were irregularities in the corneal epithelial layers caused by partial limbal stem cell deficiency, tear film instability, and cataracts. One confounding factor affecting visual outcomes in our series is visual improvement after cataract surgery, which was performed in 7 eyes.

Graft survival after PKP is influenced by several factors, including the indication for corneal transplantation. MGK can theoretically be considered a type of chemical injury with guarded prognosis because of the presence of risk factors for graft rejection and failure such as corneal stromal vascularization, chronic inflammation, and decreased sensation.[22–25] However, our experience showed fairly good outcomes, which may be caused by a lack of structural defects in the ocular adnexa, symblepharon formation, or corneal exposure. In addition, the limbal stem cell deficiency is usually partial, and dry eye is not as severe as in patients with other forms of chemical injury. Punctal occlusion and tarsorrhaphy (which had been performed in most of our patients) can also help stabilize the ocular surface. The other noteworthy issue was the absence of other conditions that limit graft survival (such as peripheral anterior synechiae and glaucoma) in most of our cases.

The rate of immune rejection episodes approaches 70% in high-risk grafts even with maximal local and systemic immune suppression.[26] The rate of endothelial rejection was 59% in our series. Although endothelial immune rejections were relatively common in our patients, most of them did not lead to graft failure. These fairly good outcomes may be caused by regular postoperative examinations, immediate diagnosis, and proper treatment of rejection reactions. Various immunosuppressive agents are used for prophylaxis and treatment of rejection in high-risk corneal grafts, including topical and systemic cyclosporine, tacrolimus (FK506), and systemic mycophenolate mofetil.[27] However, our patients received systemic cyclosporine only in cases of concomitant or previous limbal stem cell transplantation (11 eyes).

We observed more frequent graft rejection episodes in eyes undergoing simultaneous stem cell transplantation than in sequential cases: 4 of 5 eyes versus 3 of 6 eyes, which also led to more failed grafts in the former group (3 of 5 eyes vs. 0). Whether concomitant stem cell transplantation is an independent risk factor for graft failure in PKP or if these eyes are already more predisposed to rejection and failure remains an unresolved issue.

In conclusion, PKP in MGK should be considered high risk. However, graft survival and visual outcomes may be fairly favorable with regular follow-up examinations, adjunctive measures such as punctal occlusion and tarsorrhaphy, and use of immunosuppressive agents.

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