Lamellar Keratoplasty for the Treatment of Fungal Keratitis

Lixin Xie, M.D., Weiyun Shi, M.D., Zhaosheng Liu, M.D., and Shaowei Li, M.D.

Purpose. To determine the therapeutic value of lamellar keratoplasty (LKP) in the treatment of fungal keratitis not curable by antifungal chemotherapy. Methods. Fifty-five patients, in whom a diagnosis of fungal keratitis was confirmed by microscopic analysis of corneal scrapings or confocal microscopy, and who were not cured by topical and oral antifungal medication, were given LKP. After LKP, topical antifungal treatment was continued for 2 weeks with gradual tapering of the drugs. The excised recipient lamella was used for microbial culture and histopathologic examination. Results. Therapeutically beneficial results were achieved in 51 cases (92.7%) of the 55 LKPs that were performed. In these 51 cases, there was no recurrence of infection, and the resulting visual acuity ranged from 20/63 to 20/20. Patient follow-up ranged from 6 to 18 months. In four cases (7.3%), there was a recurrence of the fungal infection within 2 weeks of LKP. In these four patients, the infection was cured by performing a penetrating keratoplasty (PKP). Forty-six of the recipient lamellae were culture positive for fungal infection was cured by performing a penetrating keratoplasty within 2 weeks of LKP. In these four patients, the infection was cured by performing a penetrating keratoplasty (PKP). Forty-six of the recipient lamellae were culture positive for fungi. Thirty-three of these cultures were identified as Fusarium, six as Aspergillus, three as Candida, one as Penicillium species, and in the other three cases, unidentified septate hyphae were noted. In the four cases of recurrent infection, microbiologic culture revealed three cases with Fusarium species and one case with Aspergillus species. Histopathologic analysis of periodic acid-Schiff (PAS)-stained tissue sections of donor lamellae revealed fungal filaments in all samples. Immune reactions to the lamellar grafts were not observed and the donor lamellae remained clear for the duration of follow-up. Conclusion. Lamellar keratoplasty can be effective for treating fungal keratitis that is not cured by antifungal therapeutics. In addition, LKP can provide useful vision with few complications. Furthermore, corneal tissue used in LKP may be obtained more easily than healthy tissue used in PKP. Key Words: Lamellar keratoplasty—Fungal keratitis—Antifungal therapy—Penetrating keratoplasty.

The incidence of fungal keratitis has increased significantly in the last decade in some areas of China. The clinical diagnosis of fungal keratitis has been hampered by the availability of rapid diagnostic methods. With the advent of the confocal microscope, the visualization of the anterior segment, especially the cornea, has enabled ophthalmologists to visualize fungal morphology in vivo. Unfortunately, the confocal microscope is not widely available for the diagnosis of microbial keratitis in China. Often, fungal infection is identified only from histopathologic specimens obtained after penetrating keratoplasty (PKP). Several studies have shown that early diagnosis and immediate use of antifungal chemotherapy were crucial to the control of fungal keratitis. In some patients, PKP was found to be the only way to preserve the patient’s eye and restore useful vision in the infected eye. This is especially true when antifungal therapy fails to cure the infection. In some studies, lamellar keratoplasty (LKP) was thought to be a contraindication to the treatment of fungal keratitis. There are complications subsequent to PKP, including allograft rejection, especially when the donor graft is greater than 8.5 mm in diameter. In addition, refractive errors and other visual problems may occur in these patients. Recently, the advent of new ophthalmic surgical procedures and the availability of instruments used to perform corneal surgery, including LKP, have significantly enhanced our ability to achieve good visual rehabilitation. Consequently, we decided to investigate the value of LKP as a treatment of fungal keratitis in patients not cured by antifungal chemotherapy. In this study, the clinical features, laboratory tests, treatment, and outcome of LKP for fungal keratitis were analyzed. The details of the cases in which LKP failed also are discussed.

MATERIALS AND METHODS

Patients

From January 1998 to August 1999, 358 cases of fungal keratitis were referred to our hospital. The diagnosis of fungal keratitis in these patients was based on clinical examination with slit lamp microscopy, examination of corneal scrapings after a wet mount potassium hydroxide procedure, and confocal microscopic examination of the corneal lesion.

The 55 patients in this study were those whose disease was not arrested or cured after 7 or more days of topical and systemic antifungal therapy, but in whom the infection had not penetrated into the anterior chamber. The age of these 55 patients ranged from 31 to 59 years, with a mean age of 38.7 years. Twenty-seven of the patients were men and 28 were women. Twenty-four of the patients reported a recent history of eye trauma or the sensation of foreign matter on their corneas. In three cases, the patients had a history of herpetic keratitis and had used steroid drops for a period of 6 months. Two of the patients were contact lens wearers. Thirty-one of the patients did not report an event that might have led to...
the development of fungal keratitis. The approximate time between
the day of infection and diagnosis was between 13 days and 3
months, with a mean of 26.5 days.

The main clinical feature of fungal keratitis in these cases was
a corneal ulcer involving the central cornea. The visual acuity in 47
of the 55 patients was less than 20/200. In eight cases, the fungal
ulcer was located in the peripheral cornea and the visual acuity was
between 20/200 and 20/100. Measurement of the diameter of the
fungal lesion revealed that in 6 cases the diameter was greater than
9 mm, in 10 cases the diameter was 8 to 9 mm, and in 39 cases the
diameter of the lesion was 6 to 8 mm. The depth of the fungal
lesion was determined by slit lamp microscopy and Z-scan with
the confocal microscope. Eighty percent of the patients had lesions
involving one half to three fourths of the depth of the cornea. In
nine patients, a line of hypopyon was seen, and in four patients,
endothelial plaques were seen.

Antifungal Chemotherapeutic Treatment

In all 55 cases, the patients were hospitalized and received 1% fluconazole combined with either 0.25% amphotericin B or 5% natamycin drops every hour, alternating on the half-hour. All pa-
tients also received oral fluconazole according to the recom-
mended dosage. The fungal lesions in all patients were scraped and
curred to eliminate superficial necrotic tissue. Antifungal oint-
ments of 1% fluconazole and 1% amphotericin B were applied to
the cornea at night. The patients with hypopyon were treated with
intravenous injection of fluconazole at a dose of 100 mg twice
daily and atropine drops once or twice daily. Antifungal treatment
was carried out for 7 days to 1 month, with an average time of 11
days. If the infection was not arrested or cured, the patients were
recommended for LKP.

Surgical Procedure

The surgical procedure in all patients was begun using a Hess-
burg-Barron trephine with a diameter 0.5 mm larger than the area
of fungal corneal infection. The depth of the trephine incision,
350–400 µm, usually was deeper than that of the actual penetration
of the fungal ulcer. After removing the infected cornea, the sur-
geon adjusted the microscope (Zeiss, Germany) to high magnifi-
cation. The recipient LKP bed was washed with 0.2% fluconazole.
The fungal lesion revealed that in 6 cases the diameter was greater than
9 mm, in 10 cases the diameter was 8 to 9 mm, and in 39 cases the
diameter of the lesion was 6 to 8 mm. The depth of the fungal
lesion was determined by slit lamp microscopy and Z-scan with
the confocal microscope. Eighty percent of the patients had lesions
involving one half to three fourths of the depth of the cornea. In
nine patients, a line of hypopyon was seen, and in four patients,
endothelial plaques were seen.

Antifungal Chemotherapeutic Treatment

In all 55 cases, the patients were hospitalized and received 1% fluconazole combined with either 0.25% amphotericin B or 5% natamycin drops every hour, alternating on the half-hour. All pa-
tients also received oral fluconazole according to the recom-
mended dosage. The fungal lesions in all patients were scraped and
curred to eliminate superficial necrotic tissue. Antifungal oint-
ments of 1% fluconazole and 1% amphotericin B were applied to
the cornea at night. The patients with hypopyon were treated with
intravenous injection of fluconazole at a dose of 100 mg twice
daily and atropine drops once or twice daily. Antifungal treatment
was carried out for 7 days to 1 month, with an average time of 11
days. If the infection was not arrested or cured, the patients were
recommended for LKP.

Surgical Procedure

The surgical procedure in all patients was begun using a Hess-
burg-Barron trephine with a diameter 0.5 mm larger than the area
of fungal corneal infection. The depth of the trephine incision,
350–400 µm, usually was deeper than that of the actual penetration
of the fungal ulcer. After removing the infected cornea, the sur-
geon adjusted the microscope (Zeiss, Germany) to high magnifi-
cation. The recipient LKP bed was washed with 0.2% fluconazole.

Histopathology

The lamellar dissections from all patients were cut into two
equal parts, one of which was used for fungal culture, and the other
for histopathologic examination.

RESULTS

By performing a complete lamellar dissection, it was possible to
remove the infected corneal tissue in 22 of the patients with 1
surgical procedure. In 28 of the patients, it was necessary to per-
form 2 lamellar dissections to accomplish complete removal of the
infected tissue, and in 5 cases, 4 dissections were required. Perfor-
 ration of the cornea was not observed in any of the 55 patients.

Edema of the donor lamellar graft was noted for 3 to 5 days after
surgery, but the donor tissue remained transparent. The epithelium
covered the donor tissue for 7 to 12 days after surgery. The
hypopyon in the nine patients disappeared within 1 week after
surgery and the endothelial plaques seen in four patients disap-
peared within 2 weeks after surgery. No surgical complications
were observed in these 55 cases. The procedure was successful in
51 of the patients (92.7%) in terms of curing of the fungal keratitis.
Best-corrected visual acuity ranged between 20/63 and 20/20.

One example of successful treatment of fungal keratitis by LKP
is shown in Figs. 1 and 2. A 22-year-old man weeks after getting
foreign matter in his eye was referred to our clinic. The patient
reported blurred vision and tearing in the right eye. He had been
treated with topical antibiotics and corticosteroids without effect.
Corrected visual acuity was 20/200. The patient was diagnosed as
having fungal keratitis by confocal microscopic examination and
microscopic examination of a potassium hydroxide–stained cor-
neal scraping. The patient was hospitalized and treated with topical
and systemic antifungal agents, which did not resolve the infec-
tion. A slit lamp photograph shows the extensive involvement of
the patient’s cornea in this infection (Fig. 1). Six months after
LKP, the patient’s cornea was clear with no recurrence of the infec-
tion (Fig. 2).

Patients were followed for 8 to 18 months. There were four
cases (7.3%) of recurrent fungal infection within 2 weeks after
surgery. The recurrent fungal infections were controlled by per-
forming PKP.

Forty-six of the surgical specimens obtained from the 55 pa-
patients were culture positive for fungal filaments, including 33

FIG. 1. Slit-lamp photograph of a case of fungal keratitis that had not
resolved with aggressive antifungal chemotherapy for 2 weeks.
Fusarium, Aspergillus, Candida, and Penicillium species. In three other instances, septate hyphae that were not identified as to genus were seen. Microbiologic cultures in the patients in whom recurrent infection occurred identified either Fusarium species (3) or Aspergillus species (1).

Histopathologic examination of the surgical specimens after PAS staining revealed fungal hyphae in all specimens. Thirty-eight of the specimens showed numerous fungal hyphae in the superficial corneal stroma, and in the remaining specimens, fungal hyphae were present in the deep stroma. There was a tendency for the hyphae of the Aspergillus to grow perpendicular to the orientation of the corneal stromal layers (Fig. 3). On the other hand, the fungal hyphae of Fusarium tended to be arranged in a horizontal pattern (Fig. 4).

Immune rejection was not observed in any of the LKP patients and the grafts remained clear during follow-up.

DISCUSSION

The first, and preferred, treatment option for fungal keratitis is the use of antifungal therapy, including oral fluconazole combined with topical natamycin, amphotericin B, or fluconazole. This approach has been reported to be effective in controlling fungal infection at its early stage. In some cases, antifungal therapy has to be prolonged, and in 25–35% of patients whose infection was not halted or in whom the infection progressed after chemotherapy, surgery is required. Some ophthalmologists believe that LKP is not a viable treatment alternative, and prefer to use a conjunctival...
flap as a way of treating small fungal ulcers or even large ulcers.4,7 Sanders7 used conjunctival flaps to treat nine cases of fungal keratitis that did not respond to antifungal chemotherapy. Favorable results were obtained in five cases, although one of them required a repeat conjunctival flap. The other four cases were failures, with abscess formation and perforation through the flap. Ultimately, a clinical cure was obtained after a PKP.5

Most ophthalmologists have noted that fungal hyphae in the stroma grow in a direction perpendicular to the corneal stromal collagen, and penetration of the hyphae to the corneal endothelium results in perforation. In such instances, LKP is not adequate completely to remove the infected tissue, and PKP may be the only way to control the fungal infection. However, in some previous studies, numerous surgical complications were reported after PKP for fungal keratitis. Sanders4 and Forster and Rebell8 reported a number of cases of fungal keratitis treated by PKP in which the resulting vision was very poor. Anterior and posterior synechiae, cataract formation, and glaucoma also were noted in these operated eyes. An additional problem encountered when large penetrating corneal graft procedures are performed to eliminate fungal keratitis is immunologic rejection. Thus, when a donor graft larger than 8.5 mm is placed, immune graft reactions are likely to occur, leading to graft failure. Thus, PKP as a means of treating fungal keratitis has limitations, and the first line of therapy is, as always, medical and chemotherapeutic treatment of fungal infection, with surgical treatment as a last resort. Anderson et al.5 reported the failure of LKP in the treatment of fungal keratitis, and concluded that this approach is not appropriate for the treatment of this infectious process.

One of the interesting aspects of fungal growth in the corneal stroma that we have observed is that different fungal species appear to grow in different patterns.8 In many cases, the fungal hyphae are arranged in a parallel growth array, or may be perpendicular to the arrangement of corneal collagen lamellae. The relationship between the genus of the fungus and its growth pattern is still under investigation. We have noted that Fusarium is the most commonly isolated fungus in our patient population. Corneal infection by this fungus is associated with ocular trauma, and the infection occurs more commonly in patients living in temperate geographic locations. Histopathologic examination reveals that 85% of Fusarium fungal hyphae are present in the superficial corneal stroma, and in 15% of these cases, the hyphae were growing perpendicular to the corneal collagen lamellae. On the other hand, all of the instances of Aspergillus and Candida infection showed a growth pattern that was on a horizontal plane with the corneal stroma lamellae.

Low et al.10 and Wagoner et al.11 showed, in many cases of fungal keratitis, that the infected tissue can be thoroughly removed by LKP. These studies provided the impetus for carrying out the current study of the efficacy of LKP for treating fungal keratitis. Identification of the fungal species before surgery may provide the ophthalmic surgeon with valuable information regarding the surgical dissection procedure to use when performing LKP.

Previous studies have reported that 25–35% of cases of fungal keratitis require performance of a surgical procedure at the acute stage.2 Based on our experience, at least 32% of cases of fungal keratitis require a surgical procedure, such as LKP or PKP. Our experience in patients with fungal keratitis supports the previous observation that such patients require therapeutic keratoplasty more frequently than patients who have bacterial or viral keratitis.12

It is the ophthalmic surgeon who judges which patients have a deep corneal infection that is unresponsive to antifungal therapy. In general, we believe that performing surgery earlier rather than later decreases surgical complications and ensures the return of good vision. In this study, we noted that in 51 of 55 cases (92.7%), infection was controlled by LKP and that surgical complications were rare. Even with the availability of effective antifungal agents, such as natamycin, antifungal therapy may be only 70–80% effective in Fusarium infection.13,14 Topical amphotericin B is used for the treatment of corneal Candida infection, but there are serious side effects with prolonged treatment, and when the infection has penetrated deeply into the cornea, such treatment seldom is efficacious. Kaufman and Wood15 reported on 15 patients, 4 of whom had corneal ulcers that became worse after treatment with amphotericin B. In our experience, with accurate diagnosis and optimized treatment, approximately 30% of the patients failed to respond to antifungal chemotherapy and required surgical intervention. We concluded that LKP was the best approach in patients whose infection failed to respond to topical and systemic antifungal therapy after 7 days of intensive treatment. Prolonged antifungal chemotherapy may not be of value in achieving a good therapeutic response. On the other hand, we recommend that antifungal therapy be performed at least 1 week before LKP so that the eye is less inflamed. Balanced against this is the danger of delaying surgical intervention and subsequent surgical complications and resulting poor vision.15,16

We conclude that it is critically important that the LKP dissection completely remove infected tissue. The surgeon must carefully evaluate the infected cornea and determine the depth of penetration of the fungal infection before performing LKP. Nevertheless, on occasion it may be necessary to perform a PKP when it is found that the infection extends through the entire cornea.

In our study, the patients had blurred vision for 1 week after LKP. This was thought to be caused by donor tissue edema that resolved in the following weeks. Visual acuity improved and, in this study, 49 of the 55 patients achieved a visual acuity of between 20/63 and 20/20 3 months after surgery. Previous studies have shown that visual acuity results with LKP and PKP are similar in long-term follow-ups.8,15,16

In summary, our approach is to treat fungal keratitis aggressively with systemic and topical drugs, and then to explore the surgical options within a week after treatment. We believe that therapeutic LKP is one of the most effective approaches for the treatment of fungal keratitis that is not controlled by antifungal medication. Few surgical complications occur, and the corneal tissue needed to perform such procedures may be obtained more easily than tissue needed for PKP.

REFERENCES