·Clinical Research·

Surgical management of fungal endophthalmitis resulting from fungal keratitis

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Abstract

• AIM: To report the fungal organisms, clinical features, surgical treatment strategies, and outcomes of patients with culture-proven exogenous fungal endophthalmitis (EFE) secondary to keratitis, and evaluate the role of surgery in the treatment.

• METHODS: The clinical records of 27 patients (27 eyes) with culture-proven EFE resulting from fungal keratitis treated at Shandong Eye Institute from January 2007 to January 2015 were retrospectively reviewed. Information about fungal culture results, clinical features, surgical procedures, and final visual acuity was obtained.

• RESULTS: There were 39 positive culture results from samples of cornea, hypopyon, vitreous and lens capsule, accounting for 56%, 26%, 15% and 2.5%, respectively. Fusarium was identified in 44% (12/27) of the eyes, followed by Aspergillus in 22% (6/27). Posterior segment infection was involved in 78% (21/27) of the patients. The corneal infection was larger than 3 mm×3 mm in 89% (24/27) of the patients, and 22% (6/27) of them had the entire cornea, and even the sclera involved. Three eyes had silicone oil tamponade, and two eyes had retinal detachment. Twenty-two eyes (81.5%) underwent penetrating keratoplasty (PKP), and over half of them (54.5%) were operated within 3d from the onset of antifungal therapy. Fourteen eyes (52%) underwent intracameral antifungal drug injection, and three of them required repeated injections. Fifteen eyes (55.6%) underwent pars plana vitrectomy (PPV). The rate of the eyes undergoing PPV as the initial surgical procedure was 60% (9/15), lower than 77% in PKP. Intravitreal injection was given in 59% of the eyes (16/27), and 75% of them required repeated injections. The final visual acuity was 20/100 or better in 37% of the eyes, and better than counting fingers in 55.6% of the eyes. Five eyes (18.5%) were eviscerated. In the two eyes with concurrent retinal detachment, one achieved retinal reattachment, and the other was eviscerated. In the three eyes with silicone oil tamponade, two eyes received silicone oil removal, and the other one was eviscerated.

• CONCLUSION: Fusarium and Aspergillus are the dominant pathogens in EFE resulting from keratitis. Aggressive antifungal surgeries including multiple intravitreal injections, PKP and core vitrectomy (especially in the initial surgery) are helpful procedures to improve prognosis of severe EFE secondary to keratitis.

• KEYWORDS: exogenous fungal endophthalmitis; fungal keratitis; penetrating keratoplasty; vitrectomy; antifungal therapy; retinal detachment surgery
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INTRODUCTION

Exogenous fungal endophthalmitis (EFE) has been regarded as a devastating disease with poor prognosis[1]. Fungal endophthalmitis resulting from contiguous spread of fungal keratitis is regarded as one of the classical clinical categories of EFE [2]. There has been a few studies about this category of fungal endophthalmitis, and the majority of cases obtained favorable results [2-3]. However, surgeons are still puzzled, especially when confronted with severe cases presenting a large corneal ulcer and simultaneous posterior segment involvement. Although antifungal agents of voriconazole has been widely applied as a new generation of triazole and shown excellent antifungal activity in ocular infections [4], we believe that surgical treatment also plays an irreplaceable role in infection control, especially in severe cases of EFE resulting from keratitis. The microbiology, clinical features, surgical strategies, and outcomes in a series of cases of EFE secondary to keratitis were presented and evaluated in our study.

SUBJECTS AND METHODS

In this retrospective study, all procedures involving human participants were in accordance with the Declaration of Helsinki. Written informed consent was obtained from the subjects. Medical records of patients with culture-proven EFE resulting from keratitis treated at our institution from January 2007 to January 2015 were reviewed.

Fungal specimens were obtained from corneal scraping specimens, corneal buttons, lens capsule, hypopyon or vitreous of patients under suspicion of endophthalmitis. Fungal culture and identification were performed as described previously[5]. Patients with a positive culture result of any of the specimens and the clinical characteristics of EFE from keratitis were included. For patients that only suffered from fungal keratitis and hypopyon, positive culture result of the hypopyon was required for exclusion of aseptic hypopyon from keratitis.

Topical antifungal agents were administered in all cases and systemic drugs were given if necessary after the diagnosis. Indications of different surgical procedures are described as follows. It was urgent to carry out penetrating keratoplasty (PKP) if the keratitis was with corneal ulcer, perforation, melting or large endothelial plaque, otherwise, corneal infection could be treated by administration of antifungal agents systemically and topically under close monitoring. But the period was generally not more than half a month. Anterior chamber washout and antifungal drug injection were always performed combined with PKP.

Prompt vitrectomy was carried out when there was evidence of severe posterior segment infection. But the opaque cornea and adhesion of pupil always made the fundus invisible, which made it not easy to find evidences. Three methods were mainly applied for the judgement of posterior segment infection. 1) Ultrasound B mode evaluation was employed (except for an eye with silicone oil tamponade). The status of vitreous, retina, and choroid was obtained from the images. The dynamic changes of vitreous opacity were always good indications of infection changes. 2) Abscess in the posterior chamber and anterior vitreous might be detected during PKP. 3) The red reflex of the fundus after PKP implementation could always be visible, and invisibility of red reflex frequently meant severe posterior infection. Intravitreal antifungal medication was given at the end of vitrectomy or after vitreous aspiration for fungal detection.

Lensectomy was performed when the lens was ruptured, opaque or adhered with plenty of exudate. When it was impossible to eliminate vitreous abscess completely through vitrectomy, repeated intravitreal injections and even a second vitrectomy were required. Interval between two intravitreal injections was about 3d. Sometimes repeated intracameral washout and antifungal drug injections were also needed for elimination of massive hypopyon. If the infection aggravated for poor response to drug and surgery, evisceration of the eye was performed for unendurable pain.

RESULTS

Demographics, Culture Results, and Clinical Features Twenty-seven eyes from 27 patients were included in this study. Nineteen patients (70%) were men. The mean age was 48.3y. The duration between the onset of symptoms and visiting to our hospital varied from 4d to 6mo. Agricultural trauma was the most common (48%) cause of EFE resulting from keratitis, followed by unknown cause (26%), metal trauma (19%), and corneal graft ulcer (7%) (Table 1).

There were 39 positive culture results for the twenty-seven eyes. They were from samples of corneas, hypopyon, vitreous, and lens capsules, accounting for 56%, 26%, 15%, and 2.5%, respectively. Causative fungal pathogens included Fusarium (12 eyes, 44%), Aspergillus (6 eyes, 22%), Alternaria (2 eyes, 7%), Phialophora (1 eye, 4%), Scedosporum Apiospermum (1 eye, 4%), Rhinocladiella (1 eye, 4%), Mucor (1 eye, 4%), Candida (1 eye, 4%), and unidentified species (2 eyes, 7%).

Twenty-one of 27 patients (78%) had fungal endophthalmitis with posterior segment involvement. Three eyes had silicone oil tamponade, and 2 eyes had retinal detachment. The corneal infection was larger than 3 mm×3 mm in 89% of the patients, and 6 of them had the entire cornea and even sclera involved. The initial visual acuity ranged from no light perception to counting fingers.

Antifungal Surgical Interventions Twenty-two eyes (81.5%) underwent PKP. Among the other five eyes receiving no PKP, four eyes were eviscerated, and one eye with dot infiltration in the cornea was cured by medical treatment. PKP was performed as the initial surgical procedure in 77% (17/22) of them. The mean interval between onset of antifungal therapy and PKP was 4.5d in these operated eyes, and within 3d in 54.5% of them. As a further procedure for hypopyon elimination, 14 eyes (52%) underwent intracameral antifungal injection, of which only 3 (21%) required repeated injections (Table 2).

Fifteen eyes (55.6%) underwent pars plana vitrectomy (PPV), and the proportion of eyes underwent PPV as the initial surgical procedure reduced to 60% (9/15) in comparison with 77% of PKP. The mean interval between onset of antifungal therapy to PPV performance was 3.9d; 53% of the eyes had PPV within 3d; 40% of the eyes had PPV within 1d. Intravitreal injection was given in 59% of the eyes. Six eyes with the posterior segment involvement did not undergo intravitreal injections, including 4 eviscerated eyes, 1 silicone oil tamponade eye with posterior segment infection already controlled, and 1 eye with mild anterior vitreous abscess. Compared to intracameral injection, the percentage of eyes which required repeated intravitreal

Table 1 Demographics, culture results, clinical features and initial visual acuity in patients with exogenous fungal endophthalmitis secondary to keratitis

Case No.	Gender/age (a)	Interval between onset of disease to therapy	Cause of disease	Organism	Sources of specimen	Clinical features	Size of corneal infection (mm^2)	Initial visual acuity
1	F/31	40d	Unknown	Fusarium	Cornea	FK, hypopyon, PC empyema	6×5	HM
2	F/35	1mo	Agriculture trauma	Fusarium	Cornea	FK, PC empyema , vitreous abscess	7×7	HM
3	F/32	24d	Unknown	Fusarium	Cornea, hypopyon	FK, hypopyon	5×3	CF
4	F/45	13d	Unknown	Fusarium	Cornea, hypopyon	FK, hypopyon	6×6	HM
5	F/44	1.5mo	Metal trauma	Fusarium	Cornea	FK , vitreous abscess, silicone oil tamponade, retinitis	8×8	LP
6	F/47	1mo	Agriculture trauma	Fusarium	Hypopyon, vitreous	FK, hypopyon, vitreous abscess	3 dots	LP
7	F/64	1mo	Agriculture trauma	Fusarium	Cornea, hypopyon	FK, hypopyon, vitreous abscess	6×5	HM
8	M/41	10d	Unknown	Fusarium	Cornea	FK, hypopyon, vitreous abscess	Entire cornea	HM
9	M/58	15d	Unknown	Fusarium	Cornea, lens capsule	FK, hypopyon, PC empyema	4×4	HM
10	M/72	12d	Unknown	Fusarium	Cornea, hypopyon	FK, hypopyon, vitreous abscess	Entire cornea	LP
11	M/46	9d	Agriculture trauma	Fusarium	Cornea, hypopyon	FK, hypopyon	Entire cornea	HM
12	M/41	20d	Agriculture trauma	Fusarium	Cornea	FK, hypopyon, vitreous abscess	6×5	HM
13	F/39	1mo	Agriculture trauma	Aspergillus	Cornea, hypopyon	FK, hypopyon	5×5	CF
14	M/60	12d	Metal trauma	Aspergillus	Vitreous	FK, hypopyon, vitreous abscess, retinitis	8×8	HM
15	M/64	21d	Metal trauma	Aspergillus	Vitreous	FK, hypopyon, RD	Entire cornea	LP
16	M/44	7d	Metal trauma	Aspergillus	Cornea, vitreous	FK , vitreous abscess, retinitis	4×3	CF
17	M/25	3mo	Metal trauma	Aspergillus	Cornea	FK, endothelial plaque, hypopyon, vitreous abscess, silicone oil tamponade, retinal erosion, RD	5×4	LP
18	M/48	22d	Agriculture trauma	Aspergillus	Cornea, hypopyon	FK, hypopyon	7×7	HM
19	M/74	2mo	Agriculture trauma	Alternaria	Cornea, hypopyon	FK, hypopyon	3×2	CF
20	M/40	4d	Corneal graft ulcer	Alternaria	Cornea, vitreous	FK, vitreous abscess, orbital cellylitis	Entire cornea	NLP
21	M/49	6mo	Agriculture trauma	Phialophora	Vitreous	FK, hypopyon, vitreous abscess	7×5	HM
22	M/59	50d	Agriculture trauma	Scedosporum Apiospermum	Hypopyon	FK, hypopyon, vitreous abscess, silicone oil tamponade, retinal erosion	Entire cornea	LP
23	M/60	2mo	Agriculture trauma	Rhinocladiella	Cornea	FK, anterior and posterior chamber infiltrate	7×6	CF
24	M/35	1mo	Unknown	Mucor	Cornea	FK, hypopyon, vitreous abscess	7×6	HM
25	M/62	15d	Corneal graft ulcer	Candida	Cornea	FK, vitreous abscess	8×8	HM
26	M/51	1mo	Agriculture trauma	Unidentified	Cornea	FK, hypopyon, vitreous abscess	6×5	HM
27	M/48	2mo	Agriculture trauma	Unidentified	Cornea	FK, hypopyon, vitreous abscess	3×3	CF

FK: Fungal keratitis; PC: Posterior chamber; RD: Retinal detachment; HM: Hand moving; CF: Counting fingers; LP: Light perception; NLP: No light perception.

injections rose up to 75%, and the mean number was 4.4 times for each injected eye.

Eleven eyes (41%) required cataract extractions. Five eyes (18.5%) were eviscerated finally for aggravation of the disease.

For the antifungal medication application in the intraocular injection, each intracamerally injected eye received one kind of drug, voriconazole (5 eyes) or fluconazole (9 eyes). Fourteen intravitreally injected eyes received one kind of drug, including voriconazole for 13 eyes and amphotericin B for 1 eye. Two intravitreally injected eyes received two kinds of drugs of which one was with voriconazole and fluconazole, and the other was with amphotericin B and fluconazole.

Visual and Anatomical Outcomes The 100% preserved eyes were followed up for at least 3mo. The final visual acuity was 20/100 or better in 37% eyes, and more than half eyes (55.6%) achieved visual acuity of better than counting fingers.

Out of 22 eyes underwent PKP, the corneal graft was transparent in 10 eyes and opaque in 11 eyes at the final follow-up (one PKP eye was eviscerated at end of therapy). Total 16 patients received grafts preserved in the corneal storage medium, and 5 of the grafts were opaque finally, including one underwent a second transplantation. The other 6 patients received grafts preserved in glycerin, and although one of them underwent another transplantation of a graft

Table 2 Surgical procedures and final visual acuity in patients with exogenous fungal endophthalmitis secondary to keratitis

Case No.	Interval between onset of therapy to PKP implementation (d)	Interval between onset of therapy to PPV implementation (d)	No. of different surgical procedures						Final visual acuity and following up period
			PKP	ICI	PPV	IVI	CE	EV	
1	2	-	1	1	0	3	1	0	CF, 21mo
2	3	3	1	0	1	5	1	0	CF, 41mo
3	3	-	1	1	0	0	0	0	20/32, 5mo
4	5	-	1	1	0	0	0	0	20/63, 3mo
5	7	7	1	0	1	0	0	0	HM, 40mo
6	-	0	0	0	3	9	1	0	20/100, 29mo
7	5	7	1	1	2	5	1	0	20/63, 8mo
8	1	5	1	1	1	2	1	0	20/125, 33mo
9	2	-	1	3	0	0	1	0	20/50, 17mo
10	1	-	1	1	0	0	0	1	NLP
11	5	-	1	1	0	0	0	0	20/200, 3mo
12	4	7	1	1	2	10	1	0	2/40, 4mo
13	1	-	1	1	0	0	0	0	20/200, 12mo
14	1	1	1	0	2	3	0	0	NLP, 67mo
15	-	-	0	1	0	1	0	1	NLP
16	16	3	1	0	1	3	1	0	20/63, 13mo
17	1	1	1	0	1	6	0	0	20/100, 3mo
18	2	-	1	1	0	0	0	0	20/63, 41mo
19	16	-	1	2	0	0	0	0	20/32, 14mo
20	-	-	0	0	0	0	0	1	NLP
21	-	1	0	0	1	1	0	1	NLP
22	-	-	0	0	0	0	0	1	NLP
23	7	7	1	0	1	2	0	0	CF, 10mo
24	1	10	1	3	1	7	1	0	20/50, 20mo
25	1	1	1	0	1	1	0	0	HM, 33mo
26	5	5	1	0	1	0	1	0	CF, 4mo
27	11	0	1	0	4	12	1	0	20/200, 3mo

ICI: Intracameral injection; IVI: Intravitreal injection; CE: Cataract extraction; EV: Evisceration; CF; Counting fingers; HM: Hand moving; NLP: No light perception.

preserved in the corneal storage medium, the graft became opaque at the final follow-up.

One of the eyes with concurrent retinal detachment achieved retinal reattachment and the other was eviscerated for progress of the disease. Two of the silicone oil tamponade eyes received silicone oil removal and the remaining one was also eviscerated finally.

DISCUSSION

Fungal keratitis is not rare in China [6], and advanced fungal keratitis many lead to fungal endophthalmitis. The current study was a comprehensive report on cases of EFE resulting from corneal fungal infection with a larger number of cases than ever [2-3], and with microbiology, clinical features, surgical strategies, and final visual acuity in detail. Moreover, most cases were seriously diseased with a large fungal focus on cornea and/or posterior segment of eye involvement.

Xie *et al* [5] reported that Fusarium was the most frequently isolated pathogen in fungal keratitis. In this study, Fusarium was also confirmed to be the dominant pathogen of EFE resulting from keratitis. Aspergillus, as another main pathogen of fungal endophthalmitis[2,7], ranked second among all pathogens. In the culture positive samples, cornea accounted for over half. Though it is not reality for surgeons to submit all keratitis corneas, hypopyon, or vitreous abscess samples for culture, this result could partly indicate that corneal scraping specimens or corneal buttons might be the most likely samples to obtain positive culture results in EFE resulting from fungal keratitis. The possible reason might be that cornea was the tissue where the infection initially spread from. This emphasized the importance of obtaining corneal scraping samples, especially prior to the antifungal treatment.

It was reported that in China, 35.1% of eyes with fungal keratitis required surgery of PKP [6]. In our series of fungal endophthalmitis, the PKP ratio rose up to 81.5% . We encountered two types of corneal opacity during the therapy. One type was a large area of opacity resulting from corneal ulcer, melting or endothelial plaque, which always required prompt surgery. The other type was a small scope of infiltration after injury with chestnut thorns (cases 6, 19, 27, Table 1). In these cases, surgery was not that urgent, and finally, drug treatment was feasible in case 6 (Table 2), but

PKP was performed in the other two cases (although case 19 experienced a temporary improvement; Table 2). Surgical intervention has been recommended to be performed after 1wk of medication therapy in fungal keratitis [6,8]. However, when combined with fungal endophthalmitis, PKP was always performed earlier. The mean time was 4.5d between onset of antifungal therapy to PKP implementation in our study and over half of the PKP eyes were within 3d. PKP was able to clear original infection focus and provide access to evaluation and treatment of intraocular infection. In addition, lamellar keratoplasty was not applicable in fungal endophthalmitis from keratitis due to the full-thickness infiltration and high risk of recurrence[9].

Vitrectomy was an effective and efficient procedure for abscess drainage. Shen *et al* [10] reported a 75.9% percentage for vitrectomy application in endogenous fungal endophthalmitis, and the vitrectomy rate in our exogenous fungal endophthalmitis study was only 55.6%. The lower vitrectomy rate might be relative to the specific infection expanding way in our cases. On one hand, 22% patients were only anterior segment of the eye involved; on the other hand, the opaque cornea damaged the visual access to the posterior segment and sometimes made surgeons difficult to decide whether the vitrectomy was required. But we are still in support of a prompt vitrecomy once we confronted with a large amount of vitreous abscess or treatment failure after intravitreal injection. However, in eyes with EFE from fungal keratitis, it was hard to perform the initial vitrectomy completely due to the unclear media [11], and core vitrectomy was performed in such cases. Aggressive vitrectomy increased the risks of retinal damage. The media would get clearer gradually accompanied by effective infection control, which made a second vitrectomy possible if necessary.

Prognosis of fungal endophthalmitis with concurrent retinal detachment is usually poor with severe visual impairment and sometimes phthisis bulbi[12-13]. We successfully conserved a fungal endophthalmitis eye with concurrent retinal detachment (case 17, Tables 1, 2) and achieved favorable final visual acuity. In our experience, it was crucial to determine the time point for retinal reattachment procedure performance. If the eye was still infected, the substitute of vitreous body applied for retinal reattachment would be obstruction of further antifungal surgery, and it was also hard to achieve complete posterior vitreous detachment. If too late, severe proliferative vitreoretinopathy may occur and obstruct retinal expansion. We recommend prompt retinal reattachment surgery after confirmation of infection control. Moreover, we do not recommend silicone oil tamponade in an uncontrolled endophthalmitis eye. Some previous studies supported that silicone oil tamponade was antimicrobial and helpful for better anatomical and functional results in endophthalmitis [14-15]. However, it was recently found that silicone oil might play a weaker role in antifungal therapy than antibacterial therapy [16]. It also might be a problem in the subsequent intravitreal injection because nontoxic concentrations of intravitreal drugs created toxicity in a silicone oil-filled eye[17].

PKP and vitrectomy were always performed with simultaneous intraocular injections. Intraocular injections provided higher drug concentrations than systemic medication or topical eye drops did, and were frequently employed procedures in the treatment of endophthalmitis, especially the intravitreal injection [18-19]. They were also commonly used as the initial antifungal surgery if PKP and PPV were not urgent, and for the administration of residual intraocular abscess elimination. Repeated injections were necessary, especially after vitrectomy, because of rapid clearance of drugs [4]. In the current study, as high as 75% eyes required repeated intravitreal injections, and the mean injection number was 4.4 times for each eye. The interval between two injections was generally around 3d.

Narang *et al* [20] regarded corneal infection as an independent risk factor for final visual outcomes of fungal endophthalmitis. In our research, we noted that most conserved eyes required PKP and after that, the status of corneal transparency, graft location, and corneal astigmatism might impact on the final visual results. EFE is a disease with both anterior and posterior segments of the eye involved. Collaboration of surgeons specializing in anterior and posterior segments and appropriate administration of surgical strategies, such as aggressive multiple intravitreal injections to keep the concentration of antifungal drugs, prompt PKP after judgment of treatment failure with drugs, prompt core initial vitrectomy to remove fungi efficiently but avoid retinal damage, will be greatly beneficial in salvaging eyes with severe EFE.

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