



## Original article

# A lack of ongoing diabetes is an important factor in preserving eyes from late or suboptimally treated endogenous endophthalmitis secondary to *Klebsiella pneumoniae* liver abscess



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## ABSTRACT

**Purpose:** The purpose of this study is to identify the possible factors for preserving the eyes after late or suboptimally treated endogenous endophthalmitis secondary to *Klebsiella pneumoniae* (KP) liver abscess.

**Methods:** A retrospective chart review was conducted for patients admitted with KP liver abscess from January 1991 to June 2012.

**Results:** Six hundred and ninety-three patients with KP liver abscess were recorded, in which endophthalmitis was identified in 53 cases (65 eyes, 8.29%). Diabetes was significantly associated with the development of endophthalmitis ( $p = 0.014$ ). Eleven eyes received their last ocular treatment  $\geq 10$  days and final vision  $\geq$  counting fingers, and were defined as benign type KP endophthalmitis. The absence of diabetes was the only consistent candidate factor for benign type KP endophthalmitis.

**Conclusion:** A lack of ongoing diabetes is an important factor in preserving eyes with late or suboptimally treated endogenous endophthalmitis second to KP liver abscess.

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## 1. Introduction

Endogenous bacterial endophthalmitis (EBE) is a potentially blinding form of intraocular endophthalmitis resulting from the hematogenous spread of bacteria from a focus of infection into the eye. *Klebsiella pneumoniae* (KP) has been recognized as a major cause of EBE in Asian populations.<sup>1–8</sup> It is also an emerging infectious disease in the United States and the rest of the world.<sup>9,10</sup> The visual outcome of KP EBE is generally poor, ranging from finger counting to evisceration or enucleation of the eyes.<sup>8,11,12</sup> However, some eyes have been preserved even after a period of late or suboptimal treatment in our general practice. The purpose of this study was to identify the possible factors important for preserving eyes after late or suboptimal treatment for endogenous KP endophthalmitis.

Conflicts of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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## 2. Methods

A retrospective chart review was conducted for patients admitted to our hospital with a diagnosis of KP liver abscess from January 1991 to December 2012. This is an extension of our previous study, which was published in 2011.<sup>12</sup> Ninety-one cases were added. The Institutional Review Board and Ethics Committee (Kaohsiung Veterans General Hospital) approved this study, which adhered to the tenets of the Declaration of Helsinki. Because of the retrospective nature of this study, patient consent was not required. A case was defined as the presence of one or more liver abscesses, detected by sonography or computed tomography (CT) scan, and culture-confirmed KP isolated from an abscess or blood. The possibility of diabetes was checked in all patients. Ophthalmologic consultations were performed upon request of the physician (during hospitalization) or the patient (during a clinic visit prior to the diagnosis of KP liver abscess). Although not all of the patients had ophthalmologic consultation during admission, all the charts were reviewed to include any related findings.

The thorough ophthalmologic examination included visual acuity, slit-lamp biomicroscopy, intraocular pressure, indirect

ophthalmoscopy, and ultrasonography, as needed. KP-related endogenous endophthalmitis was suspected in patients with KP liver abscess if there was significant inflammation in the eye and no other exogenous or endogenous origin was found. Intravenous as well as intravitreal antibiotics were given upon suspicion of endogenous endophthalmitis. Data variables recorded included demographics, history of medical diseases, systemic conditions, laboratory examination, initial and final visual acuity, slit-lamp biomicroscopy, intraocular pressure, fundus examination, endophthalmitis course, and treatment.

The statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean  $\pm$  standard deviation. Fisher's exact test and Pearson's Chi-square test were used to compare the proportions in the  $2 \times 2$  groups and contingency tables, respectively. Means of normally distributed variables were compared with the Student *t* test. Odds ratio were also calculated. The *p* value or 95<sup>th</sup> percentile confidence interval was shown, as appropriate. Variables not showing a normal distribution were compared using the nonparametric Mann-Whitney *U* test. For statistical analysis, decimal fractions of visual acuity were converted to a logarithmic scale (the logarithm of the minimal angle of resolution). According to the results of Holladay,<sup>13</sup> blindness was defined as 0.00125/2.9 (decimal/logarithm of minimal angle of resolution), light perception at 0.0025/2.6, hand motion at 0.005/2.3, and counting fingers at 0.014/1.85.

### 3. Results

Data were collected on 693 patients with KP liver abscess, including 444 males and 249 females with an average age of  $60.84 \pm 14.40$  years. None of the patients were human immunodeficiency virus (HIV) reactive or received immunosuppressive drug for organ transplantation or autoimmune disease. Endophthalmitis was identified in 53 cases (65 eyes, 8.29%): bilaterally in 12 patients (22.64%), in the right eye of 19 patients, and in the left eye in 22 patients. The mean interval between the diagnosis of liver abscess and endophthalmitis was  $5.89 \pm 12.73$  days (0–66 days, excluding 9 cases with ocular symptoms prior to the diagnosis of liver abscess). Diabetes is the most common underlying disease (397/693, 57.29%). After adjusting for all related factors, diabetes remained significantly correlated with the development of endophthalmitis ( $p = 0.024$ ; Table 1). In conscious patients, the

**Table 1**

Characteristics and major predisposing disorders of patients with *Klebsiella pneumoniae* liver abscess and *K. pneumoniae* endophthalmitis.

Variables	<i>K. pneumoniae</i> liver abscess			
	Total ( <i>N</i> = 693)	No Endophthalmitis ( <i>N</i> = 640)	Endophthalmitis ( <i>N</i> = 53)	<i>p</i>
Age (y)	$60.84 \pm 14.40$	$60.98 \pm 14.55$	$59.06 \pm 12.51$	0.291 <sup>a</sup>
Sex (male/female)	444/249	410/230	34/19	1.000 <sup>b</sup>
Underlying disease				
Diabetes mellitus	397	358	39	0.014*
Hypertension	262	238	24	0.302 <sup>b</sup>
Hepatocholangic disease	177	168	9	0.145 <sup>b</sup>
Carotid artery disease	35	32	3	0.744 <sup>c</sup>
Conscious disturbance	131	121	10	> 0.99 <sup>b</sup>

\* $p < 0.05$  was considered to be significant.

<sup>a</sup> Student *t* test.

<sup>b</sup>  $\chi^2$  test.

<sup>c</sup> Fisher's exact test.

most common chief complaints were blurred vision and ocular pain. In patients with an initial disturbance of consciousness, red eye was the main reason for ophthalmic consultation. For the cases collected after the year 2000, ophthalmologists were consulted after the diagnosis of KP liver abscess was made or highly suspected. Ocular symptoms developed prior to the diagnosis of liver abscess in nine cases.

Initial visual acuity ranged from no light perception to 6/6. Initial vision was less than counting fingers in 38 eyes, counting fingers or better in 19 eyes, and missing in eight eyes (6 patients). Antibiotics were given systemically in all patients except two, who had received systemic antibiotics for KP liver abscess previously at another hospital. Intravitreal injection of antibiotics was performed in 63 eyes, including amikacin 400  $\mu$ g/0.1 mL, gentamicin 0.05 mg/0.1 mL, ceftazidime 2.25 mg/0.1 mL, and vancomycin 1 mg/0.1 mL, every other day (only vancomycin and ceftazidime have been used in the most recent 10 years). Pars plana vitrectomy was performed in 21 eyes (18 patients). The indications for vitrectomy included retinal detachment ( $n = 4$ ), vitreous opacity ( $n = 10$ ), and uncontrolled ocular inflammation ( $n = 7$ ). Enucleation or evisceration was performed to relieve pain or infection in 14 eyes. The mean interval between endophthalmitis and vitrectomy was  $8.09 \pm 15.70$  days (0–74 days). Final vision was no light perception in 32 eyes; light perception or hand motion only in 12 eyes; better than counting fingers but <6/60 in seven eyes; and 6/60 or better in 12 eyes (missing data in 2 eyes).

Surprisingly, the interval between ocular symptoms and first ocular treatment was  $12.95 \pm 21.89$  days for those with final vision  $\geq$  counting fingers, but  $5.34 \pm 8.08$  days for those with final vision < counting fingers. Moreover, the visual outcomes did not differ significantly between the cases collected prior to the year 2000 and those collected after the year 2000, although the time interval between ocular symptom and first intravitreal injection was considerably shorter after the year 2000 ( $13.89 \pm 23.69$  days vs.  $4.87 \pm 4.81$  days). We speculated that there might be a group of patients whose vision could be preserved even if the treatment was delayed or inadequate. We defined this group as benign type KP endophthalmitis. For statistical comparisons, we defined those who had their last ocular treatment (intravitreal injection or vitrectomy)  $\geq 10$  days and final vision  $\geq$  counting fingers. Of the 19 eyes with final vision  $\geq$  counting fingers, 11 eyes fit these criteria. All were unilaterally involved. Five of the 11 cases in the benign group had diabetes, and six of the eight others had diabetes. The mean interval between the onset and the last treatment was  $31.4 \pm 19.39$  (12–64) days for the benign group and  $6.83 \pm 1.33$  (5–8) days for the other eight eyes. A lack of ongoing diabetes was the only consistent candidate factor for benign type KP endophthalmitis prior to or after adjustment ( $p = 0.017$ , adjusted  $p = 0.04$ ). We even tried to analyze the influence of HbA1C, but the results were not conclusive due to many missing data in this item. There was a trend toward males having the benign form of endophthalmitis, but this was not statistically significant (Table 2).

#### 3.1. Case presentations

Case 8 involved a 49-year-old woman with a history of poorly controlled noninsulin-dependent diabetes that had been ongoing for 5 years. She suffered from chills and fever for 5 days prior to visiting our hospital. Blood and urine cultures isolated KP in another hospital, where she received intravenous antibiotics. The patient's vision became blurred and she was transferred to our emergency room. Liver abscess and septic emboli over both lungs were diagnosed upon CT scan. At the initial ophthalmological examination, her vision was light perception only in both eyes, which showed lid swelling, conjunctiva chemosis, exudate in the anterior

**Table 2**  
Analysis of possible factors to be a benign candidate of *Klebsiella pneumoniae* endophthalmitis.

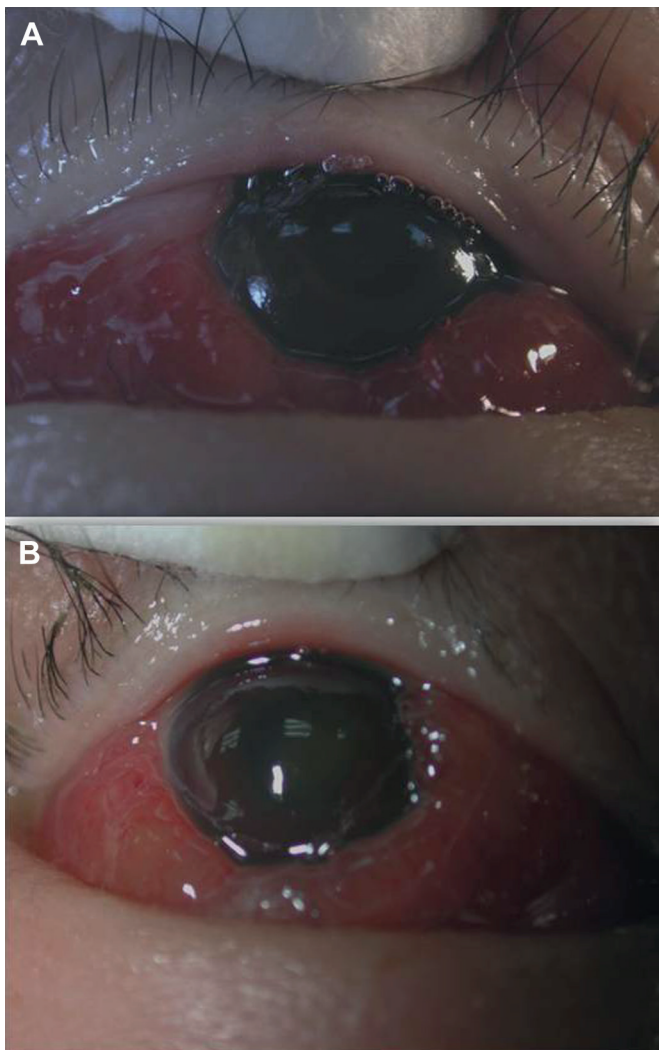
Factors	Nonbenign (N = 54)	Benign (N = 11)	p	Adjusted p
Age	59.02 ± 13.07	59.36 ± 11.00	0.93	0.94
Sex (male)	32 (59.3)	10 (90.9)	0.07	0.11
Diabetes mellitus	44 (81.5)	5 (45.5)	0.017*	0.046*
Initial vision ≥ counting fingers	14 (29.8)	5 (50)	0.22	0.37
Liver abscess → endophthalmitis (day)	6.00 ± 12.77	5.91 ± 7.71	0.98	0.26
Physical symptom → IV ABx (day)	6.00 ± 7.35	20.82 ± 27.14	0.63	0.45

Data are presented as n (%) or mean ± SD.

\*p < 0.05 was considered to be significant.

IV ABx = intravenous antibiotics.

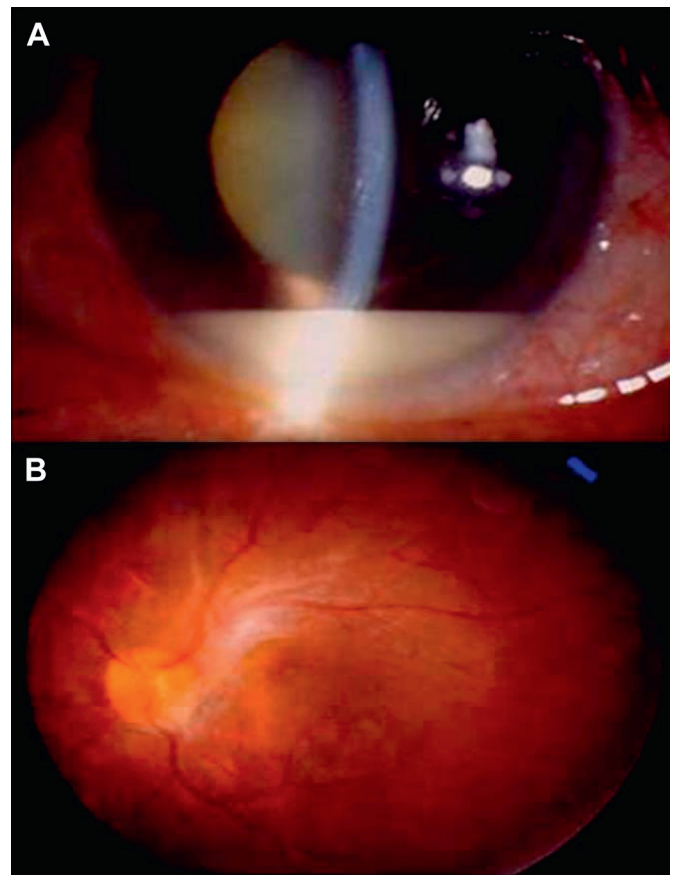
chamber, and dense vitreous opacities (Fig. 1). Intravitreal injection of vancomycin (0.1 mL/1 mg), ceftazidime (0.1 mL/2.25 mg), and dexamethasone (0.1 mL/400 µg) was given three times, but in vain. The inflammation progressed and a pars plana vitrectomy was attempted in order to débride the abscess in the right eye. Total necrosis was found intraoperatively. Both eyes ultimately progressed to bulbar atrophy.



**Fig. 1.** Case 8. (A) Right eye. (B) Left eye. Both eyes showed lid swelling, conjunctiva chemosis, exudate in anterior chamber and dense vitreous opacities.

Case 10, a 63-year-old man with a history of upper gastrointestinal bleeding and KP liver abscess, came to our clinic for progressive blurred vision in his left eye for 2 months. Ophthalmological examination showed unremarkable findings in the right eye. The left eye had hand motion vision, hypopyon in the anterior chamber, and dense vitreous opacity. The patient received intravenous antibiotics and intravitreal amikacin, vancomycin, and decadron. Because of the persistent vitreous opacity, we performed vitrectomy and lensectomy in his left eye 1 week later and a second vitrectomy to relieve the macular pucker with secondary intraocular lens implantation. The inflammation resolved and the eye remained silent with final vision of 4/60 (Fig. 2). The patient's diabetes survey was negative.

Case 53 involved a 48-year-old man who suffered from fever and chills followed by blurred vision in his right eye. Uveitis was initially diagnosed and was treated with systemic and topical steroids by a local physician, but the patient's symptoms worsened and he visited another hospital, where KP endophthalmitis secondary to pyogenic liver abscess was diagnosed. Based on the diagnosis, he received an intravitreal injection of antibiotics twice and vitrectomy twice combined with cataract surgery. Because of persistent blurred vision and impending atrophy of the eye, the patient was referred to our hospital for further management. Ophthalmological examination showed hand motion vision, with 3(+) cells in the anterior chamber and total vitreous opacity. A B-scan suggested retinal detachment, which proved to be closed funnel proliferative vitreoretinopathy (PVR) intraoperatively. Intravenous rocephin and topical ceftazidime were administered, followed by pars plana vitrectomy, relaxing retinotomy, silicone oil



**Fig. 2.** Case 10. (A) Prior to the operation, the left eye presented with hand motion vision, hypopyon in anterior chamber, and dense vitreous opacity; (B) after the operation, the inflammation resolved and the eye remained silent with final vision of 4/60.

tamponade, and endophotocoagulation. The inflammation cleared and the retina remained attached with vision of counting fingers (Fig. 3). The patient had negative result for diabetic survey.

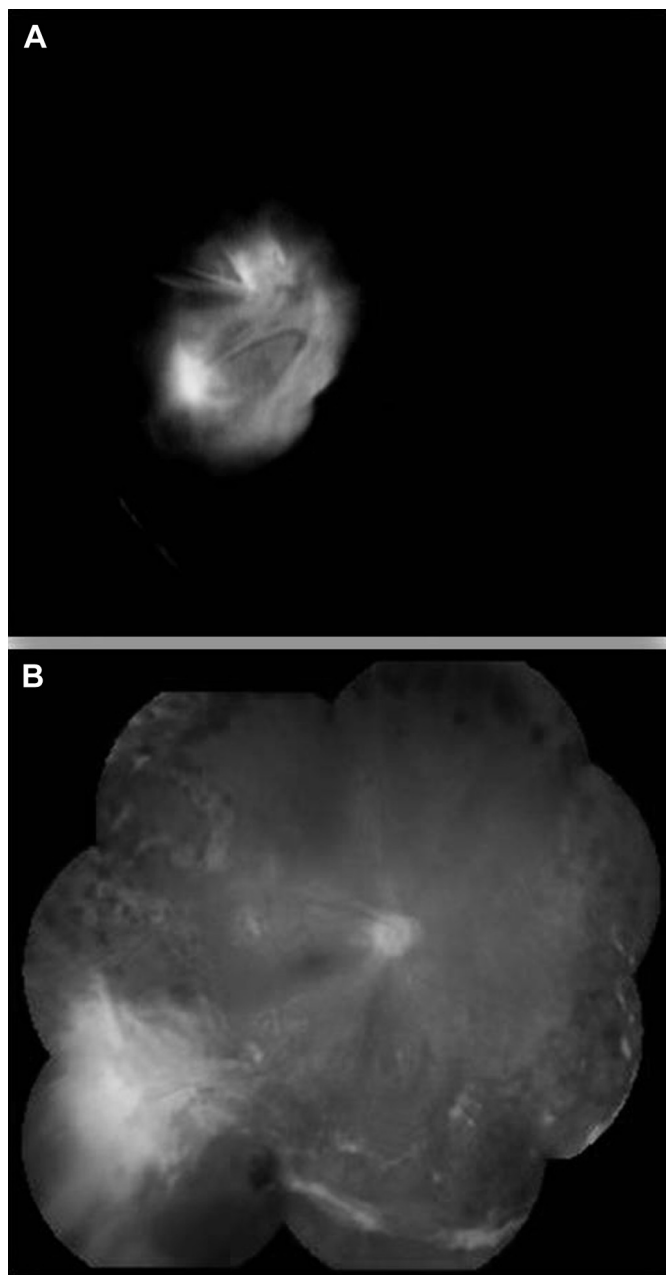
#### 4. Discussion

KP endophthalmitis is a devastating metastatic infection associated with KP liver abscess, a leading cause of pyogenic liver abscess (PLA) in Taiwan.<sup>14,15</sup> According to a nationwide, population-based database, endophthalmitis was found in 0.84% of patients with PLA, and 0.07% in an unaffected comparison group. The study showed that KP was the major causative organism among 75.5% of PLA cases, but only 33.4% of the comparison group.<sup>16</sup> At a tertiary medical center in southern Taiwan, physicians at our hospital have

long treated KP liver abscess and its related complication, endophthalmitis. In this retrospective study spanning 2 decades, endophthalmitis was identified in 53 patients (7.65%) within a series of 693 KP liver abscess cases. Diabetes was the most common underlying systemic disease and was significantly associated with the development of endophthalmitis, consistent with other reports in the literature.<sup>5–8,11,12</sup> A lack of ongoing diabetes was the only consistent factor identified as a candidate for preserving the eyes from late or suboptimally treated KP endogenous endophthalmitis.

With the continued cooperation and education between internists and ophthalmologists, the time interval between ocular symptoms and the first intravitreal injection of antibiotics was reduced about threefold ( $13.89 \pm 23.69$  days for the cases collected prior to the year 2000 versus  $4.87 \pm 4.81$  days for the cases collected after the year 2000). In general, the internists consulted ophthalmologists after the diagnosis or high suspicion for KP PLA, and abdominal sonography was on the standard checklist for patients with EBE. Unfortunately, the visual outcomes were not improved in the cases collected after the year 2000 compared to those before the year 2000, although the physicians were much more alert in the diagnosis and were more aggressive in the treatment of KP endogenous endophthalmitis. Some eyes simply progressed to an untreated status in spite of early and aggressive treatment. On the contrary, vision in some eyes was preserved even after a period of late or suboptimal treatment. Regarding the three aforementioned cases, the eyes of the latter two cases were preserved even when the treatment was somehow delayed or suboptimal initially. When making a comparison to the first case, the major factor could have been diabetes. Our results revealed the possibility that diabetes is a key factor in determining whether an eye can be preserved from late or suboptimally treated KP endophthalmitis. According to several reports, patients with diabetes are particularly susceptible because they are predisposed to metastatic infection.<sup>2,8,11,12,17,18</sup> Diabetes is known to interfere with the chemotaxis of polymorphonuclear leukocytes and to impair phagocytosis of capsular serotype K1 or K2 KP in patients with type 2 diabetes and poor glycemic control.<sup>19,20</sup> An animal study also showed that the diabetic ocular environment facilitates the development of KP EBE, possibly via increases in the permeability of the blood-retinal barrier.<sup>21</sup> Diabetes might compromise the ocular architecture and thus enhance the ability of organisms to invade the eye during systemic infection. In fact, the eyes of patients with diabetes might already be invaded by KP pathogens prior to the presentation of ocular symptoms.

As suggested by various reports, capsular serotype K1 or K2 KP may play an important role in determining the risk of patients for endophthalmitis, and also accounts for the high prevalence of KP EBE in Asia.<sup>1,15,22–24</sup> Diabetes status might also have an important role in determining the outcome of KP EBE. In a recent report by Kashani and Elliott,<sup>10</sup> two cases received aggressive treatment, but had completely different outcomes. Diabetes might have been the underlying reason for the second case having a poor visual result. The current results showed that ocular structures might be better able to withstand the invasion of KP pathogen in patients without diabetes compared to those with diabetes. According to both an animal study and clinical observation, the eye might be overrun by the KP pathogen long before the presence of ocular symptoms or even systemic symptoms of liver abscess.<sup>18,21</sup> It has been reported that KP can colonize the gastrointestinal tract of humans, and the colonization may precede invasion of the intestinal mucosa and portal venous flow or ascending biliary infection, which is typically followed by the development of liver abscess.<sup>25,26</sup> Chung et al<sup>27</sup> confirmed the fecal carriage of a serotype K 1 KP ST 23 strain closely related to liver abscess isolates in Koreans living in Korea. We might be able to identify patients at risk by stool specimen or



**Fig. 3.** Case 53. (A) Closed funnel proliferative vitreoretinopathy seen intraoperatively. (B) The inflammation cleared and retina remained attached with vision of counting fingers after the operation.

rectal swab and give prophylactic treatment against the KP pathogen in high-risk patients.<sup>28</sup> The identification and characterization of the antigen as a vaccine candidate against KP would be the future goal to spare patients from this devastating EBE.<sup>29</sup> Even though the visual outcomes of KP EBE are generally poor, especially in patients with diabetes, most reports showed that better initial vision was associated with better outcomes. Other reports also showed immediate, early treatment with pars plana vitrectomy and/or intravitreal antibiotics was also reported to help preserve useful vision.<sup>30–32</sup> Compared to these reports, the timing of vitrectomy in our series was relatively late as many patients were systemically critical and not able to withstand the risk of anesthesia. Ophthalmologists should consider endogenous KP endophthalmitis as an emergency condition, especially in patients with diabetes. Management should be done using a well-organized team approach, including ophthalmologists, internists, and anesthesiologists.

In conclusion, the visual outcome of KP endophthalmitis is generally poor. However, some eyes can be saved even in under-treatment or delayed treatment circumstances. A lack of ongoing diabetes is an important factor in preserving the eyes from late or suboptimally treated endogenous endophthalmitis secondary to KP liver abscess.

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