

[CASE REPORT]

Endogenous Endophthalmitis Associated with Pyogenic Liver Abscess Caused by *Klebsiella pneumoniae*

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Abstract:

We report 2 cases of endogenous endophthalmitis associated with pyogenic liver abscess caused by *Klebsiella pneumoniae*. Case 1 involved a 70-year-old woman and case 2 involved a 50-year-old man who were admitted to our hospital with diagnoses of liver abscess and endogenous endophthalmitis, respectively. The liver abscess resolved with antibiotics and percutaneous transhepatic drainage in case 1 and with antibiotics alone in case 2. Even though both cases underwent ophthalmic surgery, they were discharged from our hospital without the recovery of their eyesight. An earlier diagnosis and treatment are needed to improve the prognosis of endophthalmitis.

Key words: liver abscess, endophthalmitis, *Klebsiella pneumoniae*

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Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative pathogen that is a common cause of severe infections, such as pneumonia and urinary tract infections, as well as liver abscess, endophthalmitis, and meningitis (1). The incidence of pyogenic liver abscess (PLA) caused by *K. pneumoniae* has increased in Southeast Asia and is an emerging infectious disease worldwide (2-5). In particular, PLA caused by serotype K1 *K. pneumoniae* has increased in incidence and can affect healthy adults without underlying diseases (6). Kang et al. reported that age >65 years and diabetes mellitus (DM) were risk factors for the development of PLA (7). The prognosis of PLA has improved with the advent of cross-sectional imaging with computed tomography (CT) or ultrasound sonography (US) and the use of effective antibiotics. In fact, the mortality rate of PLA was >50% before 1980 and decreased to 6.3% by 2011 (8).

The most organs most commonly affected by extrahepatic syndrome caused by *K. pneumoniae* are (in descending order) the lungs, eyes, and central nervous system (9). Endogenous endophthalmitis (EE) is an infection inside the eye involving the vitreous and/or aqueous humor. EE, especially

when associated with PLA caused by *K. pneumoniae*, can lead to poor outcome in terms of visual acuity (VA) (10, 11). Jackson et al. reported that among the whole population of patients with EE, 44% had VA of light perception (LP) and 25% patients required ophthalmectomy (12). On the other hand, Yang reported that among patients with EE secondary to PLA caused by *K. pneumoniae*, 48% had VA of LP or below and 41% underwent ophthalmectomy (10).

We herein report 2 cases of EE associated with PLA caused by *K. pneumoniae* in which the VA did not improve after treatment. We discuss their clinical characteristics and compare the cases with past reports.

Case Reports

Case 1

A 70-year-old woman with a high fever consulted a hospital and was treated with clarithromycin. However, her symptoms did not resolve and she developed blurring of vision and was therefore referred to our hospital on day 18. She had no family history of liver disease. She had no underlying diseases, including DM, and was not an alcohol

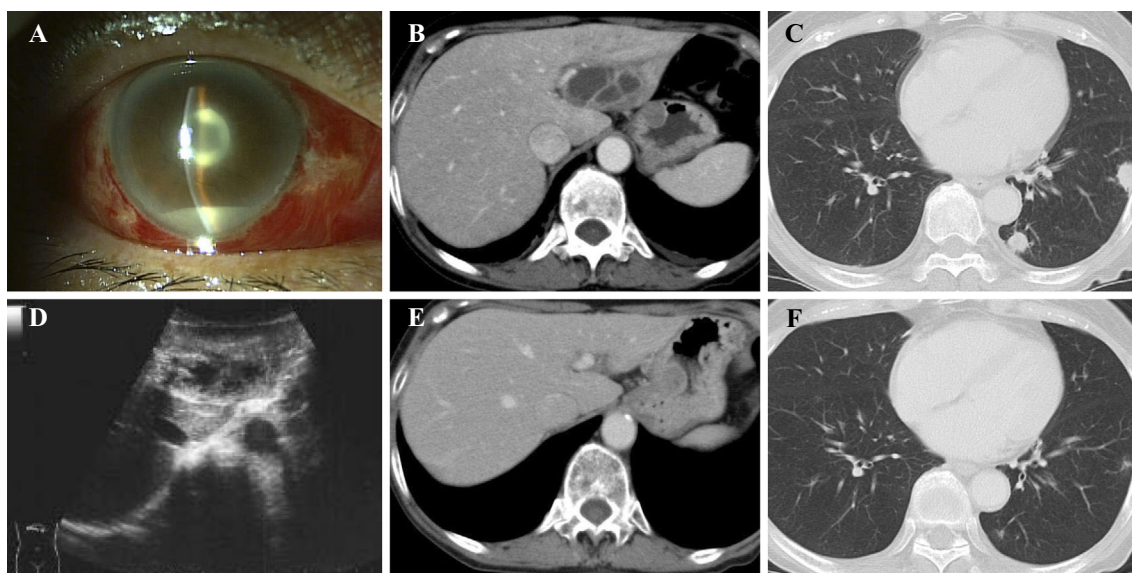


Figure 1. The right eye findings in case 1. A: Grossly, the right eye is slightly erythematous with slight swelling of the eyelid. B: Abdominal CT shows a 50-mm multilocular mass on segment 2 of the liver. C: Chest CT shows multiple lung nodules. D: US shows an isoechoic mass with a hypoechoic multilocular mass on segment 2 of the liver. E, F: A month after discharge, CT shows improvement of the liver abscess and lung nodules. CT: computed tomography, US: ultrasound

drinker or a smoker.

On admission, the patient was alert and her body temperature was 38.0°C. Her right eye exhibited slight erythema and eyelid swelling (Fig. 1A). Her VA was strongly impaired, and only her light sense was maintained. The results of heart, respiratory, and abdominal examinations were normal. No abnormalities were identified on the chest, abdomen, or skin. A laboratory analysis revealed a severe inflammatory status, with a white blood cell count of 13,200/ μ L and a C-reactive protein (CRP) level of 7.91 mg/dL (Table 1). Chest and abdominal CT showed a multilocular mass measuring 50 mm on segment 2 of the liver and multiple lung nodules (Fig. 1B and C). Abdominal US showed an isoechoic mass with a hypoechoic multilocular mass (Fig. 1D). There were no remarkable findings on esophagogastroduodenoscopy (EGD), colonoscopy, or echocardiography. The patient was diagnosed with PLA, multiple septic lung emboli, and EE.

She underwent emergent phacoemulsification and aspiration (PEA) and vitrectomy (VIT) of the right eye after admission. Blood and vitreous cultures grew *K. pneumoniae*. After the operation, she was treated with antibiotics (sulbactam sodium/cefoperazone sodium) and percutaneous needle aspiration (PNA) of the abscess revealed white fluid, a culture of which grew *K. pneumoniae* (Fig. 2A). Thereafter, she recovered from her high fever and the laboratory findings showed the improvement of her severe inflammatory status (Fig. 2).

On day 30, the patient underwent ophthalmectomy of the right eye, because corneal melting was observed at the operative site (Fig. 2B). On day 31, she was noted to have severe periodontitis, for which she received odontectomy and

treatment with levofloxacin. She discharged from our hospital on day 44, and CT performed a month after discharge showed the improvement of the liver abscess and lung emboli (Fig. 1E and F).

Case 2

A 50-year-old man with a high fever (40°C) and pharyngeal pain consulted a hospital. A laboratory analysis revealed a severe inflammatory status (CRP: 26 mg/dL), and the patient was treated with cefteram pivoxil. Although the symptoms improved steadily, he developed worsening blurring of vision on day 4 and was referred to our hospital on day 6. He had no family history of liver disease. He had DM and chronic thyroiditis. He was not an alcohol drinker or smoker.

On admission, the patient was alert and his body temperature was 36.4°C. The results of heart, respiratory, and abdominal examinations were normal. No abnormalities were identified on the chest, abdomen, or skin. His right eye exhibited slight erythema and eyelid swelling (Fig. 3A). His VA was strongly impaired, and only light sense was maintained. Contrast CT showed a multilocular mass measuring 40 mm on segment 8 of the liver (Fig. 3B). The laboratory findings revealed a severe inflammatory status, with a white blood cell count of 10,600/ μ L and a CRP level of 13.65 mg/dL (Table 2). Abdominal US showed a hypoechoic mass (Fig. 3C). There were no remarkable findings on EGD. The patient was diagnosed with PLA and EE and was treated with clindamycin and cefazolin. We hypothesized that the patient recovered from pharyngitis with cefteram pivoxil, but that the remaining pathogen locally formed lesion in the liver and the vitreous.

Table 1. Laboratory Findings on Admission in Case 1.

Hematologic test		BUN	14 mg/dL
White blood cells	13,200 / μ L	Creatinine	0.56 mg/dL
Neutrophil	85 %	Sodium	135 mmol/L
Lymphocyte	8 %	Potassium	4.7 mmol/L
Monocyte	6 %	Chloride	100 mmol/L
Eosinophil	0 %		
Basophil	1 %	CRP	7.91 mg/dL
Red blood cells	359 \times 10 ⁴ / μ L	PCT	0.29 ng/dL
Hemoglobin	11.4 g/dL		
Platelet count	33.2 \times 10 ⁴ / μ L	Glucose	108 mg/dL
		Hemoglobin A1c	6.2 %
Coagulation			
PT	78.8 %	Alpha fetoprotein	3.8 ng/mL
		PIVKA-II	69 mAU/mL
Chemistry		Carcinoembryonic antigen	2.0 ng/mL
AST	26 U/L	Carbohydrate antigen 19-9	12.6 U/mL
ALT	47 U/L		
LD	168 U/L	HBs-Ag	(-)
ALP	638 U/L	HCV-Ab	(-)
γ -GTP	152 U/L	Anti-amoebic antibody	<100 times
Total bilirubin	0.6 mg/dL		
Total protein	7.3 g/dL	Laboratory culture	
Albumin	3.0 g/dL	Blood	<i>Klebsiella pneumoniae</i>
		Vitreous	<i>Klebsiella pneumoniae</i>

PT: prothrombin time activity, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: γ -glutamyl transpeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, PCT: Procalcitonin, PIVKA-II: protein induced by Vitamin K absence or antagonists-II

On day 7, the patient underwent PEA, VIT, and the insertion of an intraocular lens (IOL) on the right eye. A vitreous culture grew *K. pneumoniae* and the antibiotic was changed from cefazolin to cefepime on day 9. Considering the risk for pneumothorax and the size of the liver abscess cavity, PNA was not performed. Thereafter, a laboratory analysis revealed the improvement of the severe inflammatory status (Fig. 4). On day 23, the patient underwent VIT, an encircling procedure, and the insertion of an IOL because of the retention of gas in the vitreous fluid and was discharged from our hospital on day 38. His VA remained LP.

Discussion

PLA, especially when caused by *K. pneumoniae* has a severe prognosis. Chen et al. reported that male sex, respiratory distress, low blood pressure, jaundice, EE, and multiple organ failure were risk factors for mortality (13). Another study showed that age, sex, abscess size, underlying disease, and laboratory findings did not differ between patients with PLA due to *K. pneumoniae* and those with PLA caused by other pathogens (14). On the other hand, a single abscess, unilobar involvement, solid appearance, association with thrombophlebitis, and hematogenous septic complications were more frequently observed in patients with PLA caused by *K. pneumoniae* than among those with PLA caused by other pathogens (14). Our cases, especially case 1, showed

characteristics of previously reported cases.

The reported incidence of endophthalmitis is 3-7.8% (15, 16), while that of EE secondary to PLA caused by *K. pneumoniae* is 14-20% (17, 18). Jackson et al. reported that the primary diseases associated with EE include liver abscess (19%), pulmonary infection (8%), and infectious endocarditis (8%), and that the most common pathogen was *K. pneumoniae* (27%) (19). *K. pneumoniae* liver abscess, bacteremia, and underlying DM have been reported as risk factors for EE secondary to liver abscess (20). Case 1 in our study had a *K. pneumoniae*-related liver abscess and bacteremia, while case 2 had a *K. pneumoniae*-related liver abscess and DM. Thus, both patients had two of these risk factors.

The management of endophthalmitis includes systemic therapy for the underlying infection and intravitreal antibiotic injection (21). Todokoro et al. recommended intravitreal injection of vancomycin and ceftazidime in combination as the standard treatment regimen for EE to target Gram-positive and Gram-negative bacteria (22). On the other hand, VIT is associated with a better visual prognosis and a lower rate of evisceration. In fact, Jackson et al. reported that VIT increased the rate of VA preservation 3 times and reduced the rate of evisceration to one third (12). In addition, VIT is useful for the detection of the causative pathogen, with a high rate of positivity (62.5%) that is equivalent to the positive rate of blood cultures (57.1%) (21, 22). In our cases,

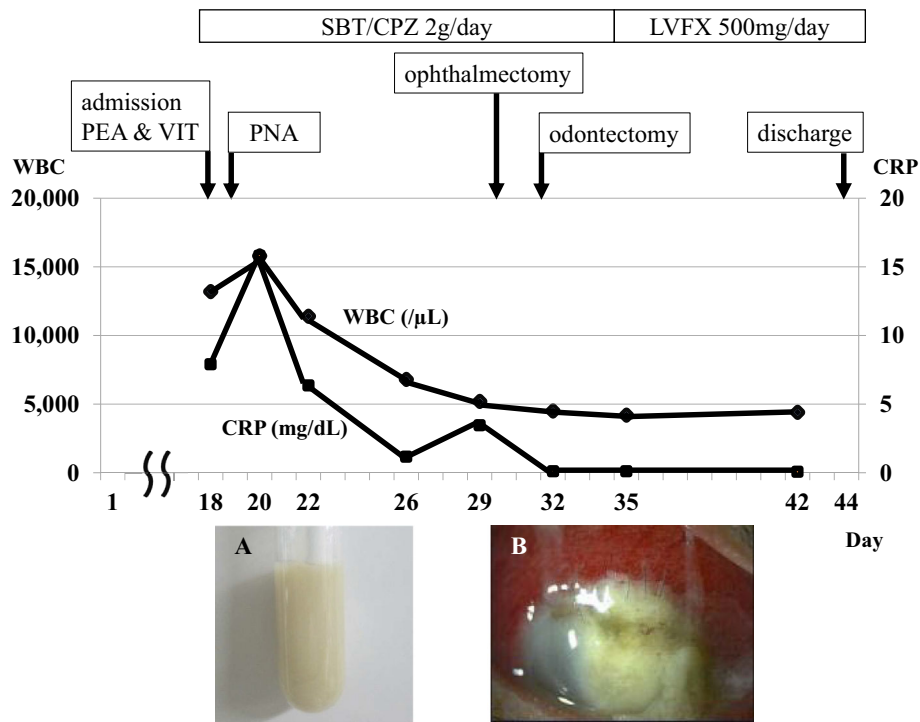


Figure 2. The clinical course in case 1. After admission to our hospital, the patient underwent PEA, VIT, antibiotic therapy, and PNA. Thereafter, the high fever resolved, and the laboratory findings of severe inflammation improved. The patient then underwent ophthalmectomy of the right eye and odontectomy, and was discharged on day 44. A: White abscess contents were drained during PNA and grew *Klebsiella pneumoniae* on culture. B: Corneal melting on the right eye was observed on day 30. PEA: phacoemulsification and aspiration, VIT: vitrectomy, PNA: percutaneous needle aspiration, SBT/CPZ: sulbactam sodium/cefoperazone sodium, LVFX: levofloxacin, WBC: white blood cell, CRP: C-reactive protein



Figure 3. The right eye findings in case 2. A: Grossly, the right eye was slightly erythematous with slight swelling of the eyelid. B: Abdominal CT showed a 40-mm multilocular mass on segment 8 of the liver. C: Abdominal US showed a hypochoic mass on segment 8 of the liver. CT: computed tomography, US: ultrasound

the vitreous cultures of both patients revealed *K. pneumoniae* growth. Of note, case 2 did not undergo PNA because of the risk of pneumothorax, the size of the liver abscess cavity, and the absence of pathogens on blood culture.

Several case reports (5, 23-32) and reviews (10, 11, 33-35) have described the clinical characteristics of EE secondary to PLA caused by *K. pneumoniae*. We showed the clinical characteristics in our patients and the previous reports (Table 3, 4). In all patients, *K. pneumoniae* was isolated from liver abscess, blood, or vitreous culture.

Nine of 21 (43%) patients, including case 2 in our study, had DM. This result differed from the reviews of EE secondary to PLA. On the other hand, all but three of the individuals in the middle-high age group developed EE caused by *K. pneumoniae* liver abscess; this result was similarly to the reviews. Although the size and location of the abscesses differed, 15 of 21 (71%) patients had a severe visual outcome. In the previous reviews, patients had severe visual prognoses; the final VA was less than CF in more than half of the patients. In half of them, the duration of ocular symp-

Table 2. Laboratory Findings on Admission in Case 2.

Hematologic test		BUN	9 mg/dL
White blood cells	10,600 / μ L	Creatinine	0.54 mg/dL
Neutrophil	77 %	Sodium	137 mmol/L
Lymphocyte	17 %	Potassium	3.8 mmol/L
Monocyte	5 %	Chloride	104 mmol/L
Eosinophil	1 %		
Basophil	0 %	Thyroid stimulating hormone	41.8 μ IU/mL
Red blood cells	404 \times 10 ⁴ / μ L	Free T4	0.86 ng/dL
Hemoglobin	12.7 g/dL	Free T3	1.27 pg/mL
Platelet count	24.1 \times 10 ⁴ / μ L		
Coagulation		CRP	13.65 mg/dL
PT	90.0 %	Glucose	158 mg/dL
		Hemoglobin A1c	8.0 %
Chemistry		Alpha fetoprotein	1.9 ng/mL
AST	18 U/L	PIVKA-II	91 mAU/mL
ALT	42 U/L	Carcinoembryonic antigen	2.7 ng/mL
LD	166 U/L	Carbohydrate antigen 19-9	3.4 U/mL
ALP	464 U/L		
γ -GTP	169 U/L	HBs-Ag	(-)
Total bilirubin	0.8 mg/dL	HCV-Ab	(-)
Total protein	6.0 g/dL	Anti-amoebic antibody	<100 times
Albumin	2.5 g/dL		
		Laboratory culture	
		Vitreous	<i>Klebsiella pneumoniae</i>

PT: prothrombin time activity, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: γ - glutamyl transpeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, PCT: Procalcitonin, PIVKA-II: protein induced by Vitamin K absence or antagonists-II

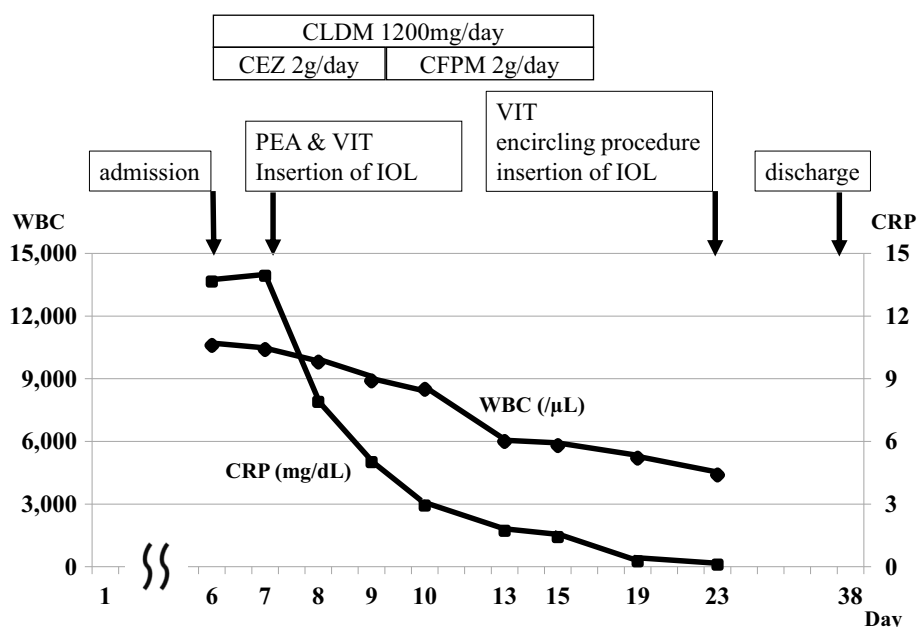


Figure 4. The clinical course of case 2. Upon admission, the patient was treated with antibiotics. On day 7, the patient underwent PEA, VIT, and IOL insertion. Postoperatively, the high fever resolved, and the laboratory findings of severe inflammation improved, without percutaneous needle aspiration. On day 23, the patient underwent VIT, an encircling procedure, and IOL insertion and was discharged from our hospital on day 38. PEA: phacoemulsification and aspiration, VIT: vitrectomy, IOL: intraocular lens, CLDM: clindamycin, CEZ: cefazolin, CFPM: cefepime, WBC: white blood cell, CRP: C-reactive protein

Table 3. Case Reports of Endogenous Endophthalmitis (EE) Associated with Pyogenic Liver Abscess (PLA) Caused by *Klebsiella Pneumoniae*.

Reference	Age	Gender	Underlying illness	Liver abscess			Culture			Interval between initial symptom and diagnosis of EE, days	Duration of antibiotics before the onset of EE, days	Ocular symptomatic days before diagnosis of EE	Interval between diagnosis of EE and PLA, days	Initial symptom	Eye	Initial visual activity (OS/OD)	Final visual outcome (OS/OD)
				Size (mm)	Location	Abscess	Blood	Vitreous									
(23)	64	F	DM	unknown	right lobe	(+)	(+)	(+)	4	0	0	unknown	drowsiness, headache, ophthalmalgia	OU	unknown	LP/LP	
(24)	91	F	(-)	50	S5	(+)	(+)	(+)	8	2	1	3	fever, anorexia	OU	NLP	enucleation	
(5)	33	M	DM	70	S4	(+)	(+)	(+)	11	11	0	4	fever, abdominal pain	OD	0.8/0.5	Unknown (lost to follow up)	
(25)	43	M	DM	50	right lobe	(+)	(+)	(+)	60	unknown	7	0	fever, abdominal pain	OS	NLP	NLP	
(26)	70	F	HTN, DM, BA, ischemic heart disease	unknown	unknown	(+)	(+)	(+)	3	0	1	0	abdominal pain	OU	LP/LP	LP/NLP	
(26)	79	M	HTN	50	S6	(+)	(+)	(+)	2	0	2	0	visual loss, ocular pain, fever, anorexia	OS	HM	LP	
(27)	36	M	(-)	63x54	S8	(+)	(-)	(-)	14	0	3	0	shivering	OD	LP	LP	
(28)	63	M	(-)	30x20	S6	(+)	(+)	(+)	4	0	1	0	fever	OU	LP/LP	NLP/NLP	
(29)	61	F	DM, HTN, DCMP	70	post	(+)	(-)	(-)	unknown	8	4	8	fever, disorientation	OS	CF2m	CF2cm	
(70)	70	F	DM, HTN	35	S4	(+)	(-)	(-)	unknown	7	1	7	fever, abdominal pain	OD	HM	HM	
(77)	77	F	HTN, CBD stone	40, 25	left lobe, S7	(+)	(+/-)	(-)	unknown	1	1	1	abdominal pain	OD	CF1m	0.4	
(82)	82	M	DM, pneumonia	50	left lateral	(-)	(+)	(-)	unknown	30	14	30	fever, general ache	OD	CF1m	CF3m	
(85)	85	M	(-)	80x50	left lobe	(-)	(+)	(-)	unknown	12	10	12	fever, disorientation	OS	0.5	CF50cm	
(64)	64	M	septic arthritis	120	dome	(+)	(+)	(+)	unknown	0	1	3	visual disturbance	OD	0.4	NLP	
(58)	58	M	DM	50	left lateral	(+)	(-)	(+)	unknown	0	3	0	visual disturbance, ocular pain	OS	HM	HM	
(72)	72	M	(-)	25	S6	(+)	(+)	(+)	unknown	0	7	1	eyelid swelling, ocular pain	OD	HM	enucleation	
(30)	79	F	(-)	ophthalmoneuritis, ventriculitis	S7	(+)	(-)	(+)	26	26	14	15	fever	OD	LP	enucleation (death)	
(31)	51	M	HL	57, 51	S7	(+)	(+)	(+)	3	0	1	0	visual loss, ocular pain	OU	HM/0.5	0.25/0.5	
(32)	78	M	Af, HTN, HL	122	left lobe	(+)	(+)	(+)	8	1	0	1	abdominal pain	OD	unknown (more than LP)	NLP	
Case 1	74	F	(-)	lung septic emboli	S2	(+)	(+)	(+)	17	15	0	0	fever	OD	LP	enucleation	
Case 2	57	M	DM, chronic thyroiditis	35x30	S8	(-)	(-)	(+)	6	5	2	1	fever	OD	LP	LP	

DM: diabetes mellitus, HTN: hypertension, BA: bronchitic asthma, DCMP: diastolic cardiomyopathy, CBD: common bile duct, Af: atrial fibrillation, S: segment of liver, OD: right eye, OS: left eye, OU: both eyes, NLP: no light perception, LP: light perception, HM: hand movements vision, CF: counting fingers vision

Table 4. Reviews of Endogenous Endophthalmitis (EE) Associated with Pyogenic Liver Abscess (PLA) Caused by *Klebsiella pneumoniae*.

Observation period	Reference	The number of patients (eyes)	Age, mean (range)	Gender (male/female)	Diabetes mellitus (%)	Ocular symptoms days before diagnosis of EE, mean (range)	Interval between diagnosis of EE and PLA, mean days (range)	Initial visual activity, eyes			Final visual outcome, eyes			The number of deaths
								≥CF	<CF (HM-LP/NLP)	unknown	≥CF	<CF (HM-LP/NLP)	Enucleation	
1992-2002	(11)	36 (47)	51.4 (34-84)	27/9	unknown	5.4 (1-30)	unknown	19	28 (17/10)	0	13	32 (2/30)	1	2
1994-2001	(10)	22 (27)	54.5 (33-78)	17/5	15 (68%)	4 (1-15)	unknown	4	23 (13/10)	0	3	24 (0/24)	11	0
1991-2012	(33)	53 (65)	59.1±12.5	34/19	39 (74%)	9.3	5.9±12.7 (0-66)	19	38	8	19	44 (12/32)	14	0
2004-2013	(34)	12 (16)	64.3±14.0	7/5	6 (50%)	unknown	unknown	15	1	0	2	14 (3/11)	0	0
2006-2015	(35)	19 (24)	67.9±10.2 (54-84)	12/7	11 (58%)	6.0±7.89	unknown	15	9	0	9	15 (0/15)	9	4

CF: counting fingers vision, HM: hand movements vision, LP: light perception, NLP: no light perception

toms before the diagnosis of EE was more than 2 days. Furthermore, in all but three of the reviews, this duration was also more than 2 days. Chou et al. reported that a more than 2-day delay in the initiation of treatment for EE resulted in a severe visual outcome (36); thus, the early diagnosis of EE is important. In our cases, although duration of ocular symptoms before the diagnosis of EE was not shorter than 2 days, the VA was LP or below in both patients. As both patients were treated with the preoral antibiotics before the onset of EE, we considered that these treatments were incomplete to cure the liver abscess and a cure might have been possible if they had been treated with strong antibiotics earlier. Notably, some patients were reported to have a rapid deterioration of VA; this sudden aggravation of VA should be taken into consideration when managing patients.

In a previous report, poor initial VA was reported to be related with a poor visual outcome (37). Chen et al. reported good visual outcome after treatment of EE caused by *K. pneumoniae* in patients with VA of counting fingers or better before the initiation of treatment (11). In fact, in our cases and those in previous reports, there were no patients who achieved a good visual outcome when the VA before treatment was LP or worse (Table 3). Thus, in patients with liver abscess, an early diagnosis and treatment, including strong antibiotic therapy and PNA, are important.

At present, there are no preventive measures against PLA. Furthermore, PLA is difficult to diagnose based on clinical abdominal findings, which include localized peritonitis and right upper quadrant tenderness. Previous reports showed that these signs were found in 15-55% of cases (38-40). In a previous report, 47 patients with PLA had markedly elevated CRP levels (mean, 27.2 mg/dL) (8). Cho et al. reported that a high CRP level was a risk factor for septic shock in patients with PLA (41). Furthermore, in a Japanese retrospective multicenter study on 25 patients with EE (32 eyes), Todorokoro et al. reported that an elevated body temperature (64%), high serum CRP (96%), and leukocytosis (52%) were frequently observed (22). In patients with high fever and markedly high CRP, the possibility of liver abscess should be entertained, and strong multidisciplinary therapy should be administered immediately to prevent PLA complications, including EE.

The authors state that they have no Conflict of Interest (COI).

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