



Case Report

Acute-on-chronic Liver Failure in a Patient with *Candida Endophthalmitis*: A Case Report

Ying Cao¹ , Ying Fan¹ , Yanbin Wang¹ , Xiyao Liu² and Wen Xie^{1*}

¹Center of Liver Diseases, Capital Medical University Affiliated to Beijing Ditan Hospital, Beijing, China; ²Department of Ophthalmology, Capital Medical University Affiliated to Beijing Ditan Hospital, Beijing, China

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Abstract

Acute-on-chronic liver failure (ACLF) is a risk factor for fungal infection. Endogenous fungal endophthalmitis is a serious, sight-threatening disease. Common causes include immunocompromised state and intravenous drug use, permitting opportunistic pathogens to reach the eye through the blood stream. We report a case of *Candida endophthalmitis* in a 47 year-old woman who was admitted to our hospital with ACLF and poorly controlled diabetes. In addition, she was treated with glucocorticoids due to severe jaundice. After treatment for ACLF, the patient experienced fever with blurred vision in the left eye and was diagnosed with candidemia, endogenous *Candida endophthalmitis* in the left eye, and chorioretinitis in the right eye. Systemic and topical antifungal treatment was administered based on the positive *Candida albicans* test in intraocular fluid using second-generation sequencing. The patient underwent vitrectomy in the left eye and *C. albicans* was confirmed in vitreous cultures. Follow-up visit, at 6 weeks after the operation, showed only light perception in the left eye and stable visual acuity in the right eye. Physicians should be aware of endogenous fungal endophthalmitis in patients with ACLF, especially those with *Candida* infection, a history of glucocorticoid use, and diabetes. A dilated retinal examination should be performed by an ophthalmologist if ACLF patients develop fever and fungal infection.

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Introduction

Acute-on-chronic liver failure (ACLF) is associated with a

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Abbreviations: ACLF, acute-on-chronic liver failure; BCVA, best-corrected visual acuity; IFI, invasive fungal infections; EFE, endogenous fungal endophthalmitis; IDSA, Infectious Diseases Society of America; MELD, model for end-stage liver disease; T-SPOT, T cell enzyme-linked immuno-spot.

*Correspondence to: Wen Xie, Center of Liver Diseases, Capital Medical University Affiliated to Beijing Ditan Hospital, No. 8, Jingshun East Street, Chaoyang District, Beijing 100015, China. ORCID: <https://orcid.org/0000-0002-7314-8175>. Tel: +86-10-84322816, Fax: +86-10-84322818, E-mail: xiewen6218@163.com

poor outcome. Invasive fungal infections (IFIs) are common in patients with ACLF due to defects in the host immune system, complications, widespread antibiotic use, and invasive procedures.¹ IFI indicates patients with a high mortality risk in the long term.² Many studies have reported that the common sites of fungal infection in ACLF are the respiratory tract, kidneys, skin/soft tissue, esophagus, oropharynx, and peritoneum.^{3–5} There are few reports of endogenous fungal endophthalmitis (EFE) in patients with liver failure.^{6,7}

In this case report, a 47-year-old woman with diabetes developed endogenous *Candida endophthalmitis* in the clinical course of ACLF. We suggest that endogenous *C. endophthalmitis* should be considered in patients with ACLF who have fever and *Candida* infection. In addition, it is important to perform ophthalmologic examinations and implement appropriate approaches to eliminate fungal infection.

Case report

A 47-year-old woman was hospitalized with acute onset of marked jaundice at a local hospital in April 2019. The most disturbing symptoms were asthenia, anorexia, and dark urine. The patient received supportive liver protection and glucocorticoid therapy for jaundice at a local hospital, while liver function became progressively worse. The patient was diagnosed with ACLF and transferred to our hospital on May 24, 2019. Her past medical history suggested that she had been a carrier of hepatitis B surface antigen for the past 10 years, in addition to having poorly controlled sugar levels. A physical examination, conducted after admission to our hospital, revealed the following findings: body temperature, 36.3 °C; blood pressure, 114/67 mmHg; heart rate, 87 beats/m; and respiratory rate, 17 breaths/m. There were small ecchymoses in the skin, serious yellow sclera and skin, suspicious abdominal shifting dullness, and lower limb edema. Heart and lung examinations were without remarkable findings. The abdomen was not distended. The liver and spleen were not palpable. There was no presence of ascites. Clinical examination revealed normal mental status and vital signs.

The laboratory data were as follows: increased white blood cell count ($11.30 \times 10^9/L$), neutrophile granulocyte (89.60%), red blood cells ($3.29 \times 10^{12}/L$), hemoglobin (104.0 g/L), platelets ($143.0 \times 10^9/L$); prothrombin time activity 58%; international normalized ratio 1.50; severe liver function damage (alanine aminotransferase 252.5 U/L, aspartate transaminase 182.0 U/L, total bilirubin 477.2 $\mu\text{mol}/L$, direct bilirubin 384.4 $\mu\text{mol}/L$, gamma-gluta-

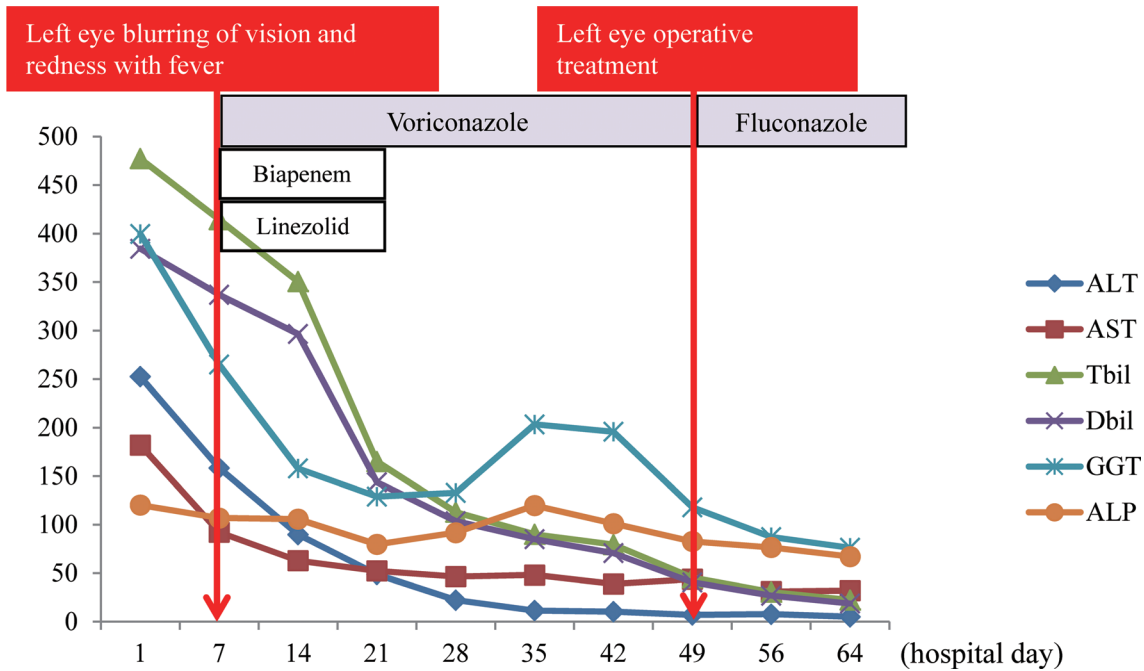


Fig. 1. Clinical course and changes of biochemistry parameters after the patient was admitted to our hospital. The levels of hyperbilirubinemia slowly trended downward, from over 470 μmol/L to 30 μmol/L. ALP, alkaline phosphatase (U/L); ALT, alanine aminotransferase (U/L); AST, aspartate transaminase (U/L); Dbil, direct bilirubin (μmol/L); GGT: gamma-glutamyltransferase (U/L); Tbil, total bilirubin (μmol/L).

myl transpeptidase 399.6 U/L, alkaline phosphatase 120.2 U/L, and albumin 39.0 g/L; elevated HbA1c level (7.2%). The hepatitis B virus DNA viral load was 292 IU/mL. Tests for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody were positive. Magnetic resonance cholangiopancreatography revealed small stones in the gallbladder, without intrahepatic or extrahepatic bile duct dilatation; computed tomography enhancement scanning revealed a low enhancement area around the portal vein and little intraperitoneal free fluid but no vascular abnormalities. On the basis of clinical manifestations, she was diagnosed with ACLF, having an ACLF model for end-stage liver disease (commonly referred to as MELD) score of 24, chronic hepatitis B, and type II diabetes mellitus. She was administered entecavir (0.5 mg/day) antiviral therapy, oral methylprednisolone (gradually decreased by reduction of 5 mg/week and then ceased), which protected the liver, reduced enzyme activity, and eliminated jaundice, and insulin subcutaneous injection to control blood glucose. Her liver function improved. The changes in biochemistry parameters are shown in Figure 1.

However, the patient developed a high fever, blurred vision, and redness in the left eye at 7 days after hospitalization. Ophthalmologic examinations were performed immediately. The best-corrected visual acuity (commonly referred to as BCVA) was 8/20 in the left eye and 8/20 in the right eye. The intraocular pressure was 12 mmHg in both eyes. Slit lamp examination revealed ciliary hyperemia, hypopyon, and Tyn (2+) in the left eye, but no significant abnormality in the right eye. Funduscopy examination revealed severe vitreous opacity, invisible fundus in the left eye, and the presence of a well-demarcated yellowish-white round exudate below the macula in the right eye (Fig. 2A, B). Optical coherence tomography revealed a small, highly reflective clump in the sub-retina of the right eye, and a highly reflective clump above the retina of the left eye in the first examination (Fig. 3A, B). Laboratory tests showed decreased lymphocyte count ($0.74 \times 10^9/L$) and CD4-positive

T lymphocyte count (124 cells/μL). The results of the blood levels of white blood cell count ($12.98 \times 10^9/L$), C-reactive protein (39 mg/dL), procalcitonin (0.60 ng/mL) and 1, and 3-β-D glucan (240 pg/mL) were increased on the same day. Interferon-γ release assays were performed using T cell enzyme-linked immuno-spot (commonly known as T-SPOT) tuberculosis assay, and the results were positive (the number of spot-forming cells was $100/2.5E+5$ peripheral blood mononuclear cells).

The microbial DNA amplification of the aqueous humor using second-generation sequencing technology showed positive results for fungal 26s ribosomal RNA, strongly suggestive of *Candida albicans* infection. The urine culture showed *C. albicans* infection. Blood cultures were positive for *Staphylococcus aureus* infection. Chest computed tomography images showed nodules in the upper and lower lobes of the right lung, considered to be newly infectious nodules. Thus, we suspected candidemia, endogenous *C. endophthalmitis* in the left eye, chorioretinitis in the right eye, and sepsis. The patient was immediately started on systemic intravenous administration of antibiotics (biapenem 300 mg twice daily and linezolid 600 mg/day) and antifungal agent (voriconazole, loading dose 400 mg twice daily for 2 doses, followed by 200 mg twice daily), plus binocular intravitreal injection of amphotericin B deoxycholate for 6 weeks. Intravitreal injections were administered based on the response to treatment. The patient received a dose of 10 μg in 0.1 mL of intravitreal amphotericin-B, every 3 days in the left eye and one injection in the right eye for the first week, and every week thereafter in both eyes for the next 5 weeks. Oral methylprednisolone was discontinued. The patient became afebrile 48 h after starting the systemic antifungal therapy. The results of white blood cell count, C-reactive protein, and procalcitonin were normal, and blood and urine cultures were negative after 2 weeks of antibiotic therapy, and antibiotics were stopped.

After 6 weeks of systemic antibiotics and intravitreal injections, the anterior chamber reaction improved in both

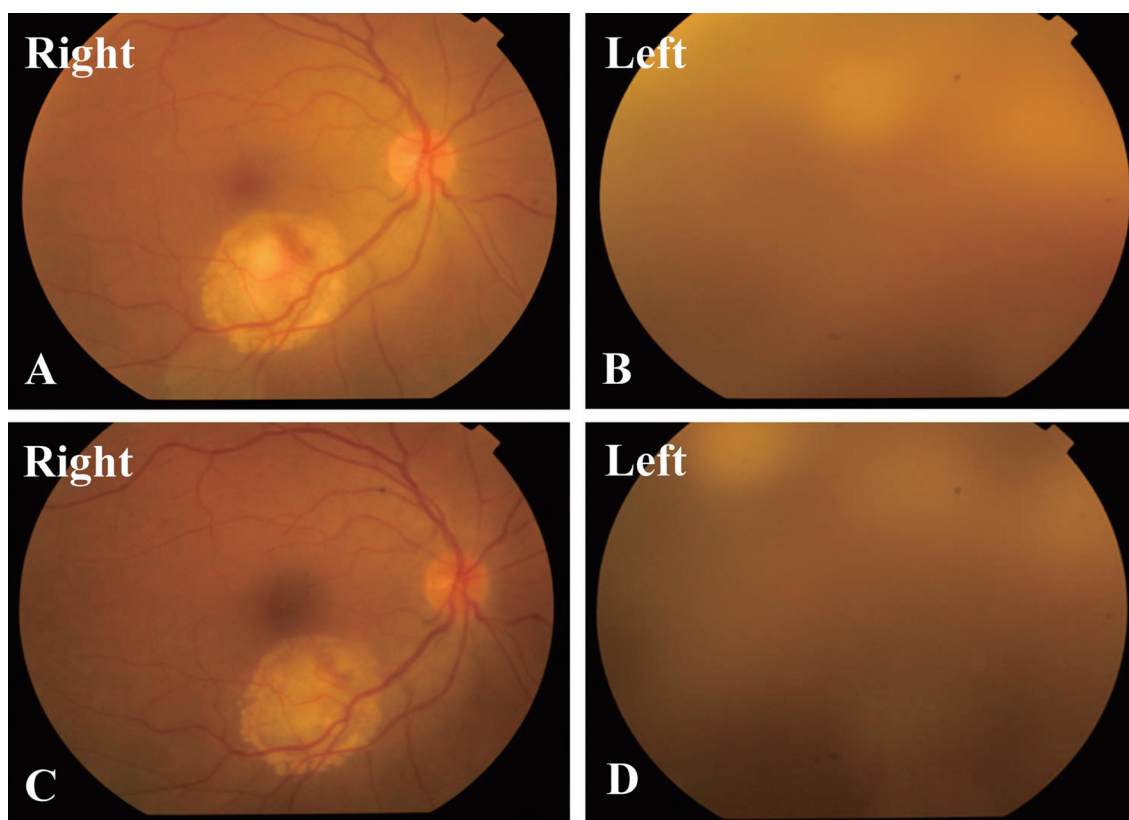


Fig. 2. Funduscopy images. (A–B) First funduscopy examination. (A) A yellowish-white round lesion was seen in the right eye. (B) Vitreous opacity was observed in the left eye. (C–D) After 6 weeks antifungal treatment. (C) The lesion in the right eye became thin and localized at this site. (D) Vitreous opacity still existed as before in the left eye.

eyes. The routine blood count and liver function test results were almost normal. The broad-range real-time PCR and cultures of the vitreous fluid, blood, and urine cultures were all negative. However, the blood level of 1, 3- β D glucan was still positive (171 pg/mL). Before the vitrectomy, slit lamp examination revealed ciliary hyperemia, corneal edema, and Tyn (2+) in the left eye. The fundus of the left eye remained invisible. The lesion in the right eye became thinner and localized, but the lesion in the left eye showed no improvement (Fig. 2C, D and Fig. 3C, D). The BCVA of the left eye was reduced to light perception only. Before the vitrectomy, slit lamp examination revealed ciliary hyperemia, corneal edema, and Tyn (2+) in her left eye. The fundus was invisible in her left eye as Binocular B-scan was performed in the first examination and before the vitrectomy. The images were shown in Figure S1.

We performed a complete lensectomy, pars plana vitrectomy, and silicone oil tamponade. During vitrectomy, the dense yellowish-white opacity in the vitreous adhered closely to the retina, the proliferating membrane shrank and the retina completely detached. There was no hole in the retina. The patient received intravitreal amphotericin B injections (10 μ g/0.1 mL). After vitrectomy, the vitreous cavity was filled with silicone oil and the retina was reattached.

A culture of the vitreous tissue revealed *C. albicans* growth. Based on the bacterial culture test results, fluconazole (loading dose 800 mg, then 400 daily) was administered with intravenous fluids for 2 weeks, and a 200 mg oral fluconazole was administered daily for 2 weeks (Table 1). Finally, 1 month after surgery, the lesions in the right eye disappeared by funduscopy examination; the BCVA was still 16/20 in the right eye and light perception only in the left eye.

Discussion

In the present study, we report a female patient with a history of ACLF and diabetes who developed sudden decrease in both eyes' vision due to endophthalmitis caused by *C. albicans*. ACLF patients usually have immune disorders, hypoalbuminemia, ascites, dysregulation of intestinal flora, impaired gastrointestinal barrier function, susceptibility to flora migration, and reduced body defense. On the other hand, such patients also often have prolonged antibiotic therapy, various kinds of complications, or severe endocrine and metabolic disorders (such as diabetes), systemic corticosteroid use, the use of central venous catheters, and receipt of liver replacement therapy. Therefore, ACLF patients with IFI are not uncommon.⁸

In the Asian Pacific Association for the Study of Liver ACLF consensus of 2019, it is recommended that hospitalized patients with ACLF are closely monitored for the presence of infections in order to enable early diagnosis and treatment. Prophylactic administration of antifungal agents in ACLF patients with high-risk factors can be performed using echinocandins.^{9,10} In the former reports, the most common site of IFI infection in liver failure patients is the lung, followed by the intestinal tract, urinary tract, abdominal cavity, bloodstream, and others; intra-ocular infections are rare. Toshikuni *et al.*⁶ reported the case of a 69 year-old man who developed fungemia due to *C. albicans* and bilateral endogenous endophthalmitis associated with liver failure due to decompensated liver cirrhosis during hospitalization. Kaburaki *et al.*⁷ reported a case of *C. albicans* endophthalmitis with subretinal abscess formation in a patient who under-

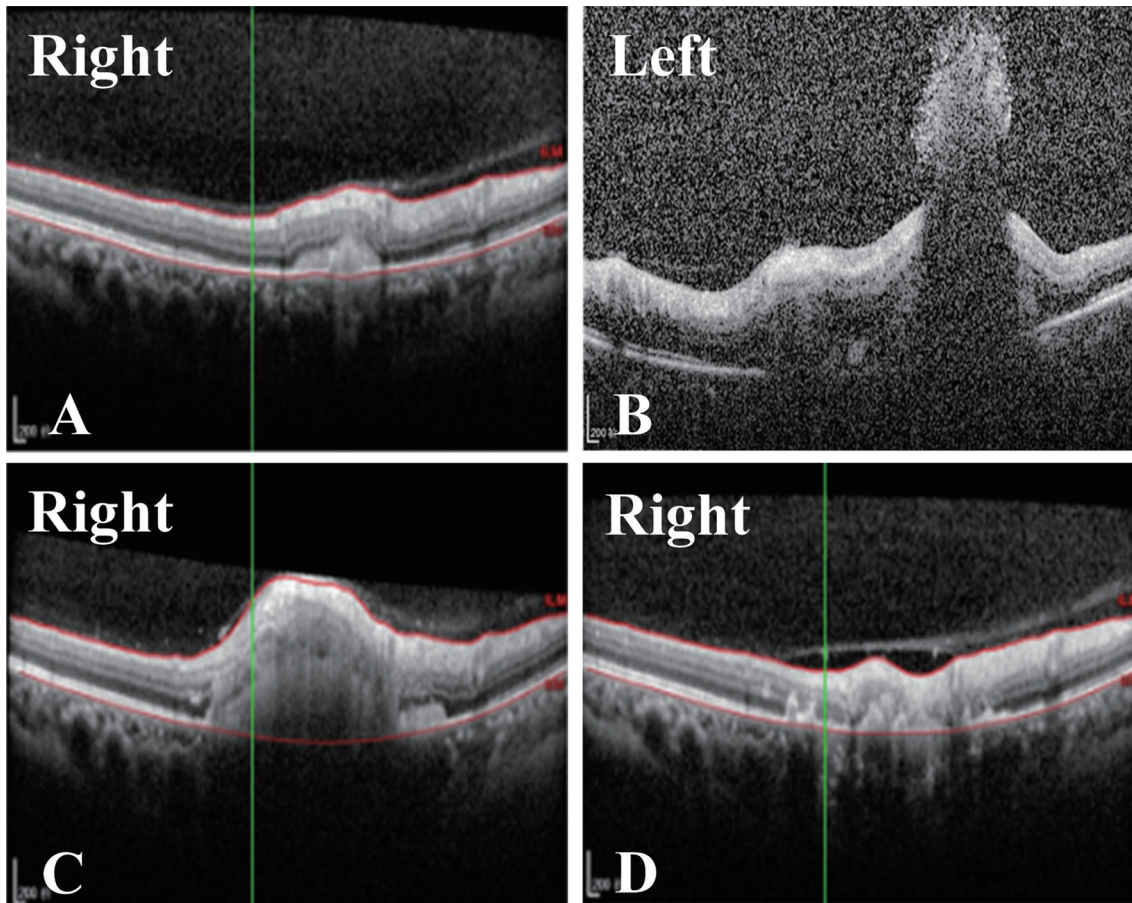


Fig. 3. Eye optical coherence tomography images. (A–B) First optical coherence tomography examination. (A) Small high-reflection was observed in the sub-retina. (B) Clumps of high reflection were found in front of the retina. (C) After 2 weeks anti-infective therapy. The sub-retina high-reflection was significantly thicker than before. (D) After 6 weeks antifungal therapy. The lesion was significantly thinner.

went liver transplantation for cirrhosis caused by hepatitis C. To our knowledge, there have been no reports of ACLF with endogenous *C. endophthalmitis*. EFE is a rare but sight-threatening condition that requires immediate diagnosis and appropriate treatment. EFE is derived from systemic fungal infections outside the eye, which are usually caused by candidemia. *Candida* is the most common EFE organism.¹¹ Once candida enters the bloodstream, it can access the eyes via the short posterior ciliary artery. Infection typically progresses vertically, via chorioretinal infiltration, and the vitreous is a primary site of localization. It has been suggested that higher glucose concentrations support the growth of *Candida* in the vitreous.¹² Our patient had a history of diabetes and poor blood glucose control, therefore at higher risk for

development of endogenous *C. endophthalmitis*. One unilateral case of *C. endophthalmitis* after liver transplantation has been reported.⁷ The incidence of *C. endophthalmitis* is rare in patients with candidemia, ranging from 0% to 1.6%.¹³ In contrast, Ueda *et al.*¹⁴ reported that the overall incidence of endogenous *C. endophthalmitis* was 21.2%.

The most common symptom of endophthalmitis is decreased vision. Eye pain or discomfort and a red eye are also common. Systemic symptoms, such as fever, are often present in cases of endogenous endophthalmitis. Diagnosis of EFE is based on eye findings rather than vitreous cultures in most cases of documented candidemia. Risk factors for EFE, such as central venous catheters, total parenteral nutrition, broad-spectrum antibiotics, recent abdominal surgery, neutropenia, glucocorticoid therapy and intravenous drug use, have been identified.¹¹ In this case, the patient had high-risk factors of diabetes and a history of glucocorticoid therapy. Unfortunately, there is a lack of understanding for factors that could predict EFE. Therefore, early diagnosis, timely identification of pathogens, and appropriate treatment are particularly important.

All patients with candidemia are recommended to undergo funduscopic examination at the time of diagnosis and should be closely monitored within 2 weeks of candidemia onset, as ocular involvement sometimes appears later.^{15,16} Our patient received systemic antifungal treatment for at least 6 weeks, intravitreal amphotericin B injections, and had left eye vitrectomy. Both procedures were deemed ef-

Table 1. Bacterial culture test results for *C. albicans*

	Cut-off	MIC, mg/L	
5-Fluorouracil		<=4	
Fluconazole	≥8≤2	4	SDD
Voriconazole	≥1≤0.125	0.5	I
Amphotericin B		<=0.5	
Itraconazole	≥1≤0.25	0.25	S

I, intermediate; MIC, minimum inhibitory concentration; S, sensitive; SDD, susceptible dose-dependent.

fective in controlling endophthalmitis. Voriconazole is an oral antifungal agent valued for its broad spectrum of activity, favorable side-effect profile, and relatively good ocular penetration. In the Infectious Diseases Society of America (commonly known as IDSA) guidelines, fluconazole or voriconazole are strongly recommended as the first-line systemic medication for *C. endophthalmitis* due to their broad spectrum of activity and superior ocular penetration. The IDSA 2016 guidelines suggest that systemic treatment be administered for at least 4–6 weeks, as determined by repeated ophthalmological examinations to verify the resolution.¹⁶ The IDSA 2016 guidelines strongly recommend that *Candida* chorioretinitis without vitritis be treated with a systemic antifungal agent for at least 4–6 weeks, while the treatment for *Candida* chorioretinitis with vitritis requires systemic therapy plus intravitreal antifungal injections; the final duration of treatment should be based on the resolution of the lesions, as determined by repeated ophthalmological examinations. The guidelines also strongly suggest that vitrectomy should be considered in patients with significant vitritis. The literature demonstrates that vitrectomy plays an important role in the diagnosis of EFE, enhancing the treatment of infection and the management of vision-threatening post-infectious sequelae.^{17,18} While the role and timing of vitrectomy for EFE is still unclear, randomized controlled trials are needed to measure its effect.

Conclusions

In conclusion, patients with liver failure, especially those with high risk factors such as long-term hospitalization, corticosteroid uptake, and diabetes, should be wary of the occurrence of EFE. It is recommended that patients with candidemia have routine funduscopic examinations. Appropriate systemic and topical antifungal treatment combined with surgical intervention can lead to a beneficial clinical outcome.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (WX, YC), acquisition of data (YC,

YF, XL), analysis and interpretation of data (YC, YF, XL, YW, WX), drafting of the manuscript (YC), critical revision of the manuscript for important intellectual content (YC, YF, XL, YW).

Data sharing statement

All data are available upon request.

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