

***Candida albicans* Endophthalmitis after Extracorporeal Shock Wave Lithotripsy in a Patient with Liver Cirrhosis**

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Abstract

A 69-year-old man was referred to our hospital because of hepatic failure after extracorporeal shock wave lithotripsy. The diagnosis of urinary tract infection and fungemia due to *Candida albicans* associated with decompensated liver cirrhosis and renal failure was made. Bilateral endogenous endophthalmitis developed during hospitalization. Candidemia, endophthalmitis and hepatorenal failure improved with intensive therapy. After discharge, endophthalmitis of the left eye relapsed and vitrectomy was performed. Clinicians should be aware that fungemia complicated by endophthalmitis can be caused by extracorporeal shock wave lithotripsy. There might be a risk of such complications among patients with liver cirrhosis in an immunocompromised state.

Key words: *Candida albicans*, fungemia, endophthalmitis, extracorporeal shock wave lithotripsy, liver cirrhosis

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Introduction

Candidemia has become a frequent complication of many medical treatments (1). Risk factors for candidemia are the use of intravenous access devices, complex surgical procedures, and treatment with antibiotics. Candidemia can be a life-threatening infection especially in patients in an immunocompromised state. Furthermore, *Candida* endophthalmitis is one of the sight-threatening ocular infections. Extracorporeal shock wave lithotripsy (ESWL) has been widely performed for the treatment of urinary stones. Serious complications of ESWL including urosepsis have been reported (2). We describe a rare case of *Candida albicans* (*C. albican*) endophthalmitis associated with hepatorenal failure after ESWL in a patient with liver cirrhosis.

Case Report

A 69-year-old man had been treated for chronic cystitis at another hospital since March 2005. In June 2005, he complained of left lumbar pain. A left ureteral stone was diag-

nosed and completely disintegrated by ESWL. A double-J stent was then placed in the left ureter, and a bladder catheter was inserted. From 1 week before ESWL, prophylactic antibiotics, cefpiramide sodium and imipenem/cilastatin sodium, had been administered. One day later the patient felt generalized fatigue, and 3 days later liver function deteriorated. He had chronic hepatitis C virus infection; however, he had not been followed up. He had no history of alcohol abuse. He was referred to the Department of Internal Medicine at our hospital 5 days after ESWL.

On admission, the patient had a temperature of 38.5°C and jaundice. There was no disturbance of consciousness, tachycardia, or hypotension. Laboratory data showed an inflammatory response and hepatorenal dysfunction: white blood cell count, $208 \times 10^2/\mu\text{l}$ (normal, 31×10^2 - 92×10^2); C-reactive protein, 3.0 mg/dl (normal, <0.5); aspartate aminotransferase, 108 IU/l (normal, 8-35); alanine aminotransferase, 64 IU/l (normal, 5-43); lactate dehydrogenase, 305 IU/l (normal, 106-211); alkaline phosphatase, 845 IU/l (normal, 104-338); γ -glutamyl transpeptidase, 171 IU/l (normal, 5-50); total bilirubin, 6.5 mg/dl (normal, 0.3-1.1); albumin, 2.5 g/dl (normal, 3.8-5.1); prothrombin time, 76%

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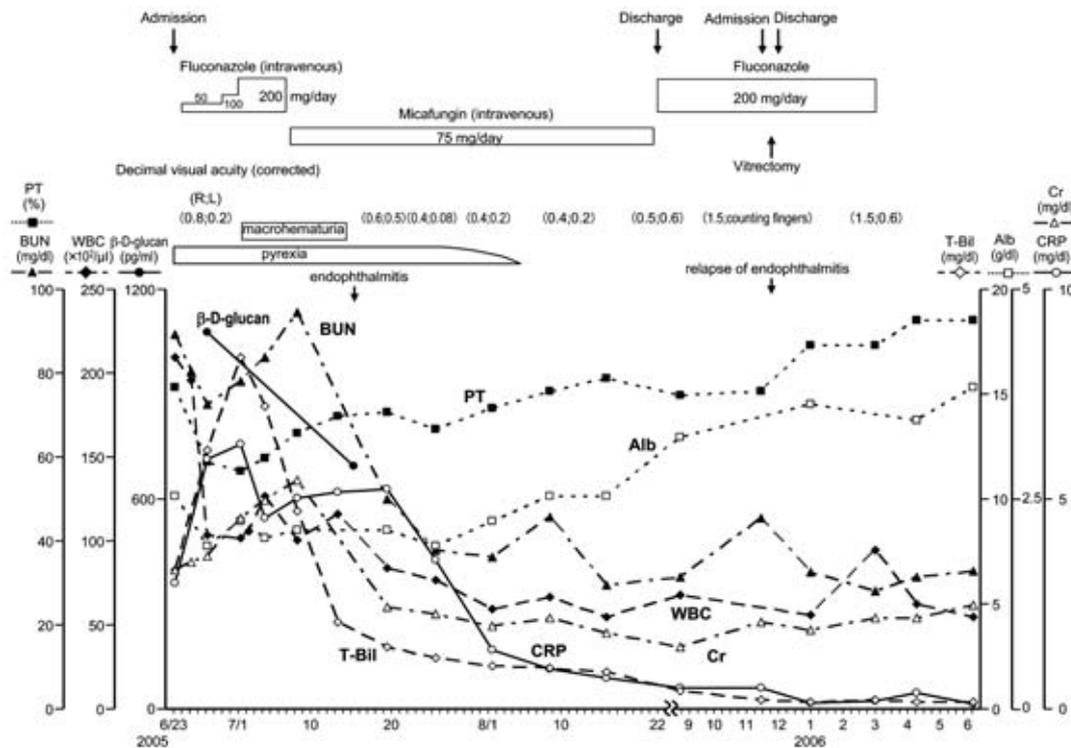


Figure 1. The clinical course of the patient. Abbreviations: PT, prothrombin time; BUN, blood urea nitrogen; WBC, white blood cell count; R, right; L, left; T-Bil, total bilirubin; Alb, albumin; Cr, creatinine; CRP, C-reactive protein.

(normal, 70-130); blood urea nitrogen, 88.6 mg/dl (normal, 8-20); and creatinine, 3.3 mg/dl (normal, 0.4-1.2)(Child-Pugh grade C). Diabetes mellitus was not observed. Ultrasonography showed a cirrhotic liver with ascites. Hepatocellular carcinoma was not detected. Gallstones were detected, but there was no finding of cholecystitis. Microscopic examination of the urine demonstrated many white blood cells, red blood cells, and ovoid yeast forms. *C. albicans* was isolated from the urine (qualitative, +3). The level of serum β -D-glucan was increased at 1070 pg/ml (normal, <20). The *Candida* antigen titer by latex agglutination test was 1:4. The results of blood cultures performed on day 2 turned out to be positive for *C. albicans* (qualitative, +1) on day 5. Stool cultures were negative. The patient had not been receiving parenteral nutrition through a central venous catheter. A prosthetic device was not used. On the basis of these findings, urinary tract infection and fungemia due to *C. albicans* associated with decompensated hepatitis C virus-related liver cirrhosis and renal failure was diagnosed.

Fig. 1 shows the clinical course of the patient. Antifungal therapy with fluconazole, 50 mg intravenously daily, was started on day 2, and the dosage was gradually increased to 200 mg daily. On day 5, ophthalmoscopic examination was performed because of decreased visual acuity of several months' duration. Bilateral cataracts were detected, but endophthalmitis was not observed. Decimal visual acuity was 0.3 (corrected, 0.8) in the right eye and 0.04 (corrected, 0.2)

in the left eye. The double-J stent was removed on day 12. Fluconazole did not seem to be sufficiently effective because of the continuous high fever and little improvement in the inflammatory response. Furthermore, renal function deteriorated. Therefore, antifungal therapy was changed to micalfungin, 75 mg daily, on day 16, which was continued to the day of discharge. The results of blood cultures performed on day 22 turned out to be negative for *C. albicans* on day 25. On day 23, the patient complained of bilateral blurred vision. Visual acuity in the left eye was counting fingers. Ophthalmoscopic examination showed the findings of several small, yellowish-white, circumscribed chorioretinal lesions and fluffy, round vitreous opacities (Fig. 2A and 2B). Based on the fact that the endophthalmitis showing characteristic findings occurred following candidemia, *C. albicans* endophthalmitis was diagnosed. Imaging studies showed that there were no findings indicating disseminated candidiasis in the liver, spleen, or kidney. Fluconazole was used in eye-drops in addition to systemic administration of micalfungin. The *Candida* antigen titer and the level of serum β -D-glucan decreased, and the lesions of both eyes showed improvement. Blood transfusions were performed on days 15 to 17 because of severe anemia, red blood cell count of $252 \times 10^4/\mu\text{l}$ (normal, $425\text{-}580 \times 10^4$) and hemoglobin of 6.4 g/dl (normal, 12.6-17.9), due to hemorrhage from the bladder. After repeated irrigation of the bladder and electrocoagulation of the bleeding lesions of the bladder mucosa on day 20,

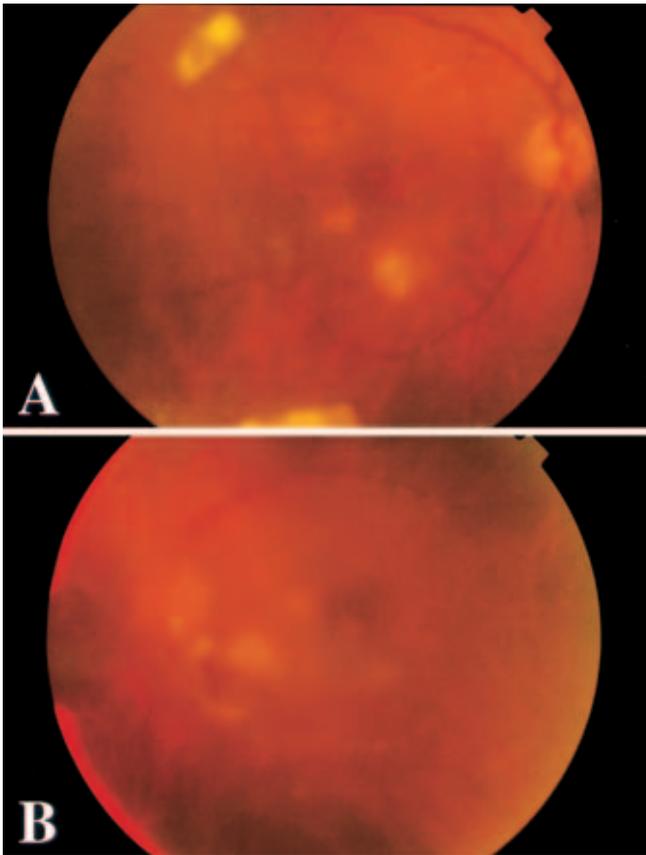


Figure 2. Ophthalmoscopy. The right eye (A) and the left eye (B). Both eyes show several yellowish-white, circumscribed chorioretinal lesions and fluffy, round vitreous opacities.

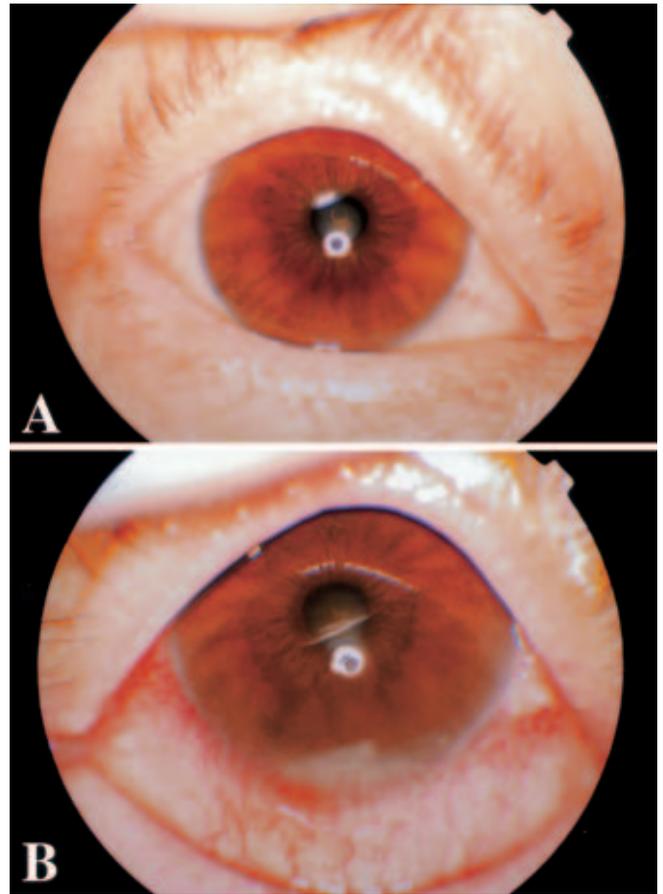


Figure 3. Photographs of the eyes at the recurrence of endophthalmitis. The right eye (A) and the left eye (B). Hypopyon of the left eye is seen.

macrohematuria gradually decreased. The bladder catheter was removed on day 43. Liver failure (total bilirubin up to 16.6 mg/dl, progression of ascites) and renal failure (blood urea nitrogen up to 91.4 mg/dl, creatinine up to 5.7 mg/dl) worsened after admission; however, the infusion of fluids and low-dose dopamine for renal failure, and diuretic therapy combined with albumin infusion for severe ascites were eventually successful. Because of the improvement of the patient's general condition, he was discharged on day 61. At discharge, his corrected visual acuity was 0.5 in the right eye and 0.6 in the left eye. The levels of total bilirubin, blood urea nitrogen, and creatinine were decreased at 1.4 mg/dl, 23.5 mg/dl, and 1.62 mg/dl, respectively.

After discharge, the patient was being treated as an outpatient with fluconazole, 200 mg orally daily, in addition to fluconazole eye drops (Fig. 1). However, in November 2005, endophthalmitis of the left eye relapsed. Fig. 3 shows hypopyon of the left eye (ophthalmoscopic images not available). His corrected visual acuity was 1.5 in the right eye and counting fingers in the left eye. Cataract extraction and vitrectomy of the left eye was performed in December 2005. Vitreous cultures were negative for bacteria and fungi. Post-operatively, the patient was treated with fluconazole, 200 mg

intravenously daily, for 2 weeks. Subsequently, he was treated with fluconazole, 200 mg orally daily, for 2 months. As of July 2006, endophthalmitis of the right eye has not relapsed. His corrected visual acuity has improved to 1.5 in the right eye and to 0.6 in the left eye. Renal function has deteriorated after this serious event (mean blood urea nitrogen, 31.0 mg/dl; mean creatinine, 2.28 mg/dl). Liver function has improved from Child-Pugh grade C to grade A.

Discussion

There have been only a few reported cases of *C. albicans* endophthalmitis after ESWL (3-5). One serious complication of ESWL is urosepsis, which has an incidence of 0.3% (2). Factors that increase the risk of infection are existing urinary tract infection; perioperative urologic manipulation; infected stones; predisposition for infectious endocarditis; and multiple, large, or complex stones (6). There is no direct evidence that ESWL caused candidemia in the present case. However, the patient complained of symptoms of candidemia shortly after ESWL, suggesting the causal relationship between ESWL and candidemia. Furthermore, neither an intravenous access device nor a prosthetic device was used.

The use of multiple antibiotics for chronic cystitis might induce *Candida* colonization of the gastrointestinal tract; however, stool cultures were negative for the pathogen (7). Therefore, we consider that ESWL was the biggest factor for candidemia in this case. We speculate the following pathogenic mechanism of candidemia. In the present case, chronic cystitis was considered to predispose to upper urinary tract infection. At the time of ESWL, candiduria might have developed because of the use of multiple antibiotics (7). There might even have been incorporation of *Candida* colonies into the ureteral stone, which could have liberated *Candida* after disintegration. Under these putative conditions, the mechanical trauma to the ureter during ESWL might have occurred, resulting in *C. albicans* dissemination into the blood stream.

Administration of antibacterial agents before ESWL to prevent infectious problems after the procedure has been useful in patients with bacterial urinary tract infections before ESWL (8). The results suggest that administration of antifungal agents before ESWL might be helpful for preventing fungemia in patients with funguria. In addition, the placement of urinary catheters can contribute to the development of urinary tract infections (9). Recently, novel urinary catheters with anti-infective surface activity have significantly reduced the risk of catheter-associated urinary tract infections for short-term catheterization (10). However, the best prophylaxis is minimizing the duration of urinary catheterization.

Infection is a common complication of liver cirrhosis and is a major cause of death in patients with cirrhosis (11). Various factors that increase the risk of infection in patients with cirrhosis have been reported (12): decreased opsonin function, an impaired complement system, leukocyte dysfunction, decreased antibodies, endotoxin, and tumor necrosis factor. Hassner et al (13) have demonstrated that monocyte functions, as measured with phagocytosis and the killing of *Candida pseudotropicalis* and *C. albicans*, are significantly decreased in patients with cirrhosis. Another study has shown that polymorphonuclear leukocytes from patients with cirrhosis display lower basal functional activity than control cells in phagocytic activity against a clinical strain of *C. albicans* and chemotaxis (14). Thus, patients with cirrhosis are susceptible to fungal infections. Liver cirrhosis is often associated with neutropenia. Generally, neutropenic patients are at higher risk for development of candida infections (15). However, neutropenia was not observed in the present case. Therefore, a cause for the susceptibility to *Candida* infection might be a leukocyte dysfunction.

Diabetes has been reported to be an underlying disease in patients with urinary tract infections due to *C. albicans* (7). In fact, Greenwald et al (5) have reported a patient with type 2 diabetes and *Candida* endophthalmitis after ESWL. The above findings suggest that liver cirrhosis is another underlying disease.

In the present patient, hepatorenal failure developed after

candidemia. A recent study has shown that renal failure is common in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis and it is strongly correlated with mortality (16). Future studies should be performed to determine the relationship between fungemia and renal failure in patients with cirrhosis.

Endophthalmitis is a sight-threatening ocular infection that frequently develops in patients with fungemia; prospective studies have shown that endophthalmitis develops in 28% to 37% of patients with candidemia (17). Furthermore, Menezes et al (18) have shown that the presence of *Candida* endophthalmitis leads to a high mortality rate (77%) in patients admitted to intensive care units. Krishna et al have shown that some patients without *Candida* endophthalmitis on initial ophthalmologic examination develop *Candida* endophthalmitis within 2 weeks (19). It is possible that the present patient had developed endophthalmitis before the ophthalmologic examination. Therefore, periodic ophthalmoscopic examination should be performed for the early diagnosis of metastatic endophthalmitis in patients with fungemia, even if the patients do not complain of blurred vision.

Fluconazole has been shown to be effective in the treatment of *Candida* endophthalmitis (1). Recent studies have suggested that fluconazole efficacy rates (400 mg daily) are not different from those of conventional amphotericin B for the treatment of candidemia (15). We changed fluconazole to micafungin during our patient's hospitalization because fluconazole did not seem to significantly improve the inflammatory response. Furthermore, the rapid deterioration of renal function in this case was a reason for cessation of treatment with fluconazole because this agent is primarily cleared by the kidneys (15). Fluconazole achieves high concentrations in the vitreous humor but has fungistatic effects and is not always active against all *Candida* species; in contrast, micafungin has fungicidal effects and is active against many *Candida* species, including fluconazole-resistant *C. albicans* (20-22). We should have conducted sensitivity tests of the isolates for the two antifungal agents in the present case. Moreover, we should have frequently monitored the *Candida* antigen titer and the level of serum β -D-glucan in addition to the inflammatory response for evaluation of the therapeutic effect of fluconazole. Mochizuki et al have reported that micafungin, 150 to 300 mg daily, is effective in treating *Candida* endophthalmitis (23). Micafungin is primarily cleared by the liver (23). We speculate that if a higher dose of micafungin had been administered with the improvement of liver function for longer than the actual 46 days, the relapse of endophthalmitis of the left eye could have been prevented, although intravenous administration of this agent restricts its use to inpatients. Recently, voriconazole and liposomal amphotericin B, antifungal agents with strong activity against a broad-spectrum of fungi, have been introduced into clinical practice. Further studies are required to establish regimens of antifungal agents, including novel

ones, for moderate-to-severe *Candida* endophthalmitis.

Vitreotomy may be combined with administration of antifungal agents if *Candida* endophthalmitis is complicated by moderate-to-severe vitreitis (1). The long-term fluconazole therapy might be a contributing factor in slight deterioration of renal function of this case after discharge. If vitrectomy had been performed immediately after improvement of the patient's general condition, duration of therapy might have been shorter and adverse effects of the antifungal agent could have been minimized.

In the present case, vitreous cultures were negative for *C. albicans*. A recent study has shown the usefulness of the detection of *C. albicans* DNA in vitreous samples for diagnosing *C. albicans* endophthalmitis (24). This molecular biological approach may help establish a definite diagnosis of *Candida* endophthalmitis, even in culture-negative patients.

The reason why a severe bladder hemorrhage occurred in this patient remains unclear. A possible explanation is that the hemorrhage might have been caused by *Candida* cystitis. Previous studies have described cases of severe *Candida* cystitis (25). Furthermore, the bleeding tendency due to decompensated liver cirrhosis might predispose to hemorrhage

from the fragile bladder mucosa.

In summary, we have reported a rare case of *C. albicans* endophthalmitis associated with hepatorenal failure after ESWL in an elderly man with liver cirrhosis. Clinicians should be aware that fungemia complicated by endophthalmitis can be caused by ESWL. There might be a risk of such complications among patients with cirrhosis in an immunocompromised state. Periodic ophthalmoscopic examinations should be performed for the early diagnosis of endophthalmitis in patients with fungemia. In the treatment of patients with fungal endophthalmitis, sensitivity tests of isolates for antifungal agents should be conducted. The *Candida* antigen titer and the level of serum β -D-glucan should be frequently monitored for evaluation of the therapeutic effect of antifungal agents. In cases of fungal endophthalmitis associated with hepatic and/or renal dysfunction, it is of key importance that dosages of antifungal agents are adjusted for those particular patients. Furthermore, clinicians should take into account the possibility that early vitrectomy may be effective for the treatment of moderate-to-severe fungal endophthalmitis associated with such complications.

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