Combined Surgical and Medical Therapy for Candida Prosthetic Endocarditis in a Patient with Repaired Tetralogy of Fallot

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Summary

Candida prosthetic endocarditis (CPE) is an uncommon and fatal complication in adults with congenital heart disease. The current guidelines for the management of fungal endocarditis recommend a combination of surgical and medical therapy. However, it still remains uncertain when surgical management in CPE patients should be performed. Therefore, the prognosis of CPE patients is very poor. Here we report a case of CPE in a 31-year-old woman who had undergone surgical repair for tetralogy of Fallot during childhood and pulmonary valve replacement at the age of 21 years. She underwent re-pulmonary valve replacement after being sufficiently sterilized with a 5-week course of antifungal medical therapy, leading to clinical improvement. In CPE patients, it is necessary to perform surgical therapy while suppressing the activity of fungi as much as possible.

Key words: Case reports, Infective endocarditis, Antifungal agents, Fluconazole, Pulmonary valve

Infective endocarditis (IE) is a severe complication in patients with congenital heart disease. Candida IE accounts for only 1%-2% of all cases of IE, but it is often fatal. Recent hospital mortality rates remain very high (> 50%). The European Society of Cardiology guidelines for the management of IE recommend combined antifungal administration and surgical valve replacement. However, these guidelines do not describe clearly when we should perform surgical intervention to improve CPE patients’ survival during the course of treatment. Here we report a case of IE due to Candida albicans in a patient with repaired tetralogy of Fallot (TOF). She was successfully managed with a 5-week course of antifungal therapy followed by pulmonary valve replacement.

Case Report

A 31-year-old woman who had undergone intracardiac TOF repair at the age of 10 was admitted to a nearby local hospital with a 2-month history of intermittent high-grade fever. Her medical history indicated that she had undergone bioprosthetic valve implantation and left pulmonary artery angioplasty at the age of 21 owing to increasing pulmonary regurgitation and stenosis of the left pulmonary artery. Right heart catheterization at the age of 30 showed mild pulmonary stenosis (pressure gradient, 32 mmHg). Laboratory results on admission revealed an elevation of the serum C-reactive protein (CRP) level (4.7 mg/dL); the while white blood cell count remained normal. Two sets of serial blood cultures grew C. albicans. Transthoracic echocardiography showed vegetation with a size of 8 mm on the right ventricular outflow tract (RVOT; Figure 1) and a thickened leaflet in the pulmonary valve. Thus, she was diagnosed with IE due to C. albicans. The results of the abdominal and pelvic computed tomography showed no abnormalities, and she had no endophthalmitis. There were no obvious symptoms other than those in the heart, although transthoracic echocardiography on day 5 after admission indicated that a portion of the vegetation had detached and elicited a small pulmonary embolism. Transesophageal echocardiography showed no obvious perivalvular abscess; therefore, we considered that emergent surgical treatment was not necessary and chose medical therapy. There were no immunosuppressive condition and malnutrition. The infection route of C. albicans is unknown.

Treatment with liposomal amphotericin B (L-AMB, 200 mg/day) was initiated, but the patient’s serum creatinine levels increased from 0.46 to 1.15 mg/dL owing to renal dysfunction. The treatment was stopped on day 8. She was transferred to our institution on day 12 for a more intensive treatment.
After admission to our hospital, L-AMB therapy was resumed. Subsequently, nausea and vomiting worsened, and the renal function deteriorated further. Serum creatinine increased to 1.24 mg/dL. Because *C. albicans* detected in her blood culture showed a high sensitivity to all antifungal agents, L-AMB was replaced with micafungin (150 mg/day) and fluconazole (400 mg/day). In response to this combined antifungal therapy, her body temperature, CRP level, kidney function, and hemodynamics stabilized, but her brain natriuretic peptide (BNP) level remained high (300-400 pg/mL) and exertional dyspnea persisted (Figure 2).

At day 40, we surgically removed her prosthetic pulmonary valve. Additionally, the posterior wall of the RVOT, ventriculo-infundibular fold, and pledgets on the RVOT, which had vegetation according to the surgical findings, were resected. In the pathological diagnosis, a 6-mm brown vegetation was observed on the section of the RVOT lumen (Figure 3). After surgical therapy, the patient’s BNP level rapidly decreased (30 pg/mL). She was discharged from our hospital after a 6-week course of antifungal therapy following the operation. Lifelong suppressive oral fluconazole therapy was recommended.

**Discussion**

There seem to be two factors that helped us in treating our patient. First, sufficient sterilization with antifungal therapy followed by surgical therapy successfully treated our CPE patient. Next, switching the regimen of antifungal therapy from L-AMB to a new antifungal drug combination, micafungin and fluconazole, was effective in the patient with adverse events caused by L-AMB.

*Candida* IE is a rare but often fatal disease. Despite aggressive antifungal and surgical therapy, the mortality rates range from 30% to 80%.1,3-7) Investigations comparing the clinical outcomes of medical therapy versus those of combined medical and surgical therapy demonstrated that patients with fungal endocarditis treated with antifungal agents alone tend to have a mortality rate higher than patients treated with a combination of surgery and antifungal agents.5,8-11) Thus, the current guidelines recommend combined medical and surgical therapy for fungal endocarditis.5,8) However, some recent studies have reported that even in patients who have been treated with combined medical and surgical therapy, the prognosis of CPE is very poor.4,13-15) The International Collaboration on Endocarditis-Prospective Cohort Study reported that the overall mortality was high, with 36% mortality in the hospital and 59% at 1 year.15) In previous studies, higher mortality even after surgical and antifungal combination therapy was associated with refractory or persistent candidemia.4,15,16) Surgical therapy under insufficient control of in-

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**Figure 1.** Transthoracic echocardiogram shows vegetation (yellow arrow) on RVOT.

**Figure 2.** Changes in BNP and CRP during hospitalization.
flammation seemed to have a poor outcome.

It still remains uncertain when surgical management of CPE patients should be performed, but we should avoid a surgical therapy under active inflammation. In CPE patients with stable hemodynamics, antifungal therapy should be administered first; thereafter, at some point or another, surgical excision of the infected material should be considered. In our patient, repeat blood cultures remained negative, and the fungus was sterilized by a combination therapy with antifungal agents. We finally decided to perform surgical treatment under sterilized conditions owing to the persistent symptoms of heart failure with the high BNP level. We considered that vegetation on the RVOT could not be completely sterilized by medical therapy alone, and that inflammatory cytokines were always supplied by vegetation. Therefore, chronic heart failure persisted until vegetation was removed by surgical treatment. From this successful case, we suggest that in CPE patients, surgical therapy while in a state after sufficient sterilization with antifungal therapy is useful.

In a meta-analysis of therapy for Candida IE, antifungal monotherapy was associated with poorer outcomes. L-AMB has long been the first-line treatment for C. albicans, and fluconazole has been the standard for concomitant drugs. However, prolonged L-AMB administration is associated with adverse events. In 2003, the first echinocandin caspofungin was approved as therapy for invasive candidiasis and was expected to be as effective as L-AMB. Recently, several studies have found that echinocandin therapy is generally better tolerated than L-AMB.

There is little experience with echinocandin in treating CPE; therefore, we examined the literature to review the clinical cases of CPE that were treated with a new antifungal drug (an echinocandin anti-fungal agent). The Table summarizes the details of case reports and small case series of CPE that were treated with echinocandin. Nineteen patients were treated with echinocandin, of which 12 were cured. Of these, nine were treated with combination therapy; these patients did not die owing to CPE.

In our case, a micafungin and fluconazole combination antifungal therapy was used to replace L-AMB, on the RVOT could not be completely sterilized by medical therapy alone, and that inflammatory cytokines were always supplied by vegetation. Therefore, chronic heart failure persisted until vegetation was removed by surgical treatment. From this successful case, we suggest that in CPE patients, surgical therapy while in a state after sufficient sterilization with antifungal therapy is useful.

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which had caused drug-induced renal dysfunction, nausea, and vomiting. Subsequently, the patient’s renal dysfunction and gastrointestinal symptoms improved. After initiating the combination antifungal therapy, repeat blood cultures remained negative, and the CRP remained low. Some reports have indicated that long-term oral fluconazole therapy is appropriate after prolonged intravenous therapy.\textsuperscript{12,23,27} and we decided to continue oral fluconazole in our patient. As in this case, in CPE case with adverse events such as renal dysfunction caused by L-AMB, combination therapy with micafungin and fluconazole is effective preoperatively.

For the treatment of CPE, it is necessary to administer sufficient antifungal therapy while taking into account the condition of the patients and the optimal timing for surgical therapy. Sufficient sterilization with antifungal therapy followed by surgical therapy successfully treated our CPE patient.

Here we describe an important case of a patient with CPE who was successfully managed with pulmonary valve replacement following sufficient sterilization with a 5-week course of antifungal therapy. In this patient, sufficient antifungal medical therapy could be performed preoperatively because micafungin and fluconazole combination therapy instead of L-AMB was used. The accumulation of data from additional cases is necessary to establish standard guidelines for the optimal timing of surgical intervention for CPE.

Disclosures

Conflicts of interest: None.

References