Candida Prosthetic Valve Endocarditis Cured by Caspofungin Therapy without Valve Replacement

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A 64-year-old woman with a mechanical mitral valve prosthesis developed late-onset Candida endocarditis. Blood cultures grew Candida glabrata and Candida krusei. Transesophageal echocardiography demonstrated vegetations on the valve. The patient was not medically fit for valve replacement, but her condition was successfully treated with 6 weeks of intravenous caspofungin therapy.

Case report. A 64-year-old white woman, who had been a resident of Nigeria for >20 years, had a medical history that included permanent atrial fibrillation and a mechanical mitral valve replacement (29-mm model 500DM29; ATS Medical) implanted in the United Kingdom in 1985 because of rheumatic mitral valve disease. She was given the anticoagulate warfarin and used a finger-prick home testing system to monitor the prothrombin time.

In December 2003, she developed a painful swollen left calf, which was initially treated as cellulitis but was subsequently diagnosed as a spontaneous calf hematoma. The prothrombin time was markedly elevated at 176 s, and the patient had a hemoglobin level of 6.6 g/dL and a WBC count of 13.7 × 10⁹ cells/L. She received a transfusion of 2 units of blood and was given vitamin K. Subsequently, she developed abdominal pain, hematemesis, and acute renal failure and required transfer to the United Kingdom by air ambulance for further treatment.

At admission to the hospital in the United Kingdom, the patient was hypotensive and anuric (creatinine level, 532 μmol/L; urea level, 50 mmol/L), but the bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels were normal. A large left-calf hematoma was confirmed by ultrasonography and was managed conservatively. CT scans revealed a right pleural effusion, bibasal atelectasis, a small amount of ascites, and blood within the colon. Esophagogastroduodenoscopy revealed mild gastric erosions, which were treated with lansoprazole therapy.

Although the patient was not febrile at admission, sepsis was considered in the differential diagnosis. Blood for culture was obtained, and intravenous cefuroxime and metronidazole therapy was started empirically. The abdominal pain and vomiting subsided with conservative management. However, 24 h after the patient was admitted to the hospital, her body temperature began to spike to >38°C, and additional blood for culture was obtained.

The blood cultures performed on the day after the patient was admitted to the hospital in the United Kingdom yielded a Candida species after 5 days of incubation. Additional blood for culture was obtained, and intravenous fluconazole therapy was initiated. Three days later, the initial isolate has been identified as Candida glabrata, and the cultures of blood obtained 6 days after admission also yielded a Candida species. The MICs for the C. glabrata isolate were as follows: fluconazole, 32 mg/L; itraconazole, 4 mg/L; voriconazole, 1 mg/L; flucytosine, <0.125 mg/L; amphotericin B, 0.5 mg/L; and caspofungin, 1.0 mg/L. Because of these MICs and the presence of continuing renal impairment, fluconazole was replaced with intravenous caspofungin (a 70-mg loading dose and then 50 mg daily). The organism growing on the culture of blood obtained 6 days after admission was identified as Candida krusei. The MICs for the C. krusei isolate were as follows: itraconazole, 0.5 mg/L; voriconazole, 0.5 mg/L; flucytosine, 4.0 mg/L; amphotericin B, 0.5 mg/L; and caspofungin, 2.0 mg/L. The identification of both Candida isolates and the corresponding MICs were confirmed by the Health Protection Agency Mycology Reference Laboratory (Bristol, United Kingdom). Caspofungin MICs were established using a broth microdilution assay, in accordance with the methodology of the NCCLS.

Transesophageal echocardiography revealed multiple, small, mobile vegetations on the atrial aspect of the mechanical mitral valve ring (figure 1) and a small paraprosthetic leak. Using Duke clinical criteria [1], we diagnosed definite endocarditis
on the basis of 1 major criterion (an echocardiogram finding positive for endocarditis) and 3 minor criteria (fever; predisposition; and a positive blood culture result not satisfying the major criteria). At this stage, the patient was not medically fit for valve replacement, and therefore the therapeutic strategy was to attempt cure with drug therapy alone.

One week later, the bilirubin level rose to 40 mg/L, and the alkaline phosphatase level rose to 230 IU/L, but the aspartate transaminase level had improved to 60 IU/L. Acute hepatitis C virus (HCV) infection was determined by detection of HCV RNA and a subsequent rise in the level of hepatitis C antibodies. Hepatitis B virus and HIV serologic test results were negative. The source of HCV was presumed to be the blood transfusions the patient had received in Nigeria.

Two days later, the patient experienced further abdominal pain and distension and vomiting similar to that seen at presentation, and clinical examination suggested peritonitis. An abdominal CT scan showed free air and fluid within the peritoneal cavity. Emergency laparotomy was performed; a section of perforated necrotic small bowel was excised, and a defunctioning ileostomy was formed. Histological examination of the resected small-bowel tissue revealed evidence of cytomegalovirus ileitis, with mucosal ulceration and ischemia.

After treatment with caspofungin was started, blood culture results were negative. Caspofungin therapy was stopped after 6 weeks. No other antifungal agents were used. A transesophageal echocardiogram, performed 3 weeks later, demonstrated complete resolution of the vegetations. There was no growth on several sets of blood cultures performed after the caspofungin therapy was stopped, including cultures performed 10 months after the completion of treatment.

The patient underwent prolonged rehabilitation and was discharged from the hospital after 4 months. Six months after discharge, she remained healthy and underwent reversal of the ileostomy.

Discussion. Candida species are an uncommon but increasing cause of infective endocarditis, accounting for 1%–6% of cases [2]. The increasing incidence of fungal endocarditis over the past 20 years has been ascribed to changes in drug therapy and surgical techniques. The use of prosthetic devices, long-term intravenous catheters, broad-spectrum antibiotics, and immunosuppression are all risk factors for Candida endocarditis [2–5].

Candida endocarditis has a crude mortality rate of >50%, despite treatment [2, 3]. The disease often occurs in patients with multiple comorbidities, so the attributable mortality is difficult to assess. Optimal management of the disease requires a high index of suspicion and the prompt use of appropriate antifungal agents [2, 3, 6]. Valve replacement combined with drug therapy is thought to offer an improved outcome, especially when a prosthetic valve is affected. However, there is no evidence from clinical trials to support this practice.

In this case, both C. glabrata and C. krusei were isolated from blood cultures, which suggests that the endocarditis was caused by these species.
by 2 different *Candida* species. Although uncommon, polymicrobial *Candida* endocarditis has been reported previously [2, 3]. The source of the infection in our patient was unclear, but intravascular devices placed in the patient at the Nigerian hospital or the colitic bowel may have been involved.

Antifungal resistance among *Candida* species is uncommon [6–9]. However, *C. krusei* and *C. glabrata* may express intrinsic resistance and acquired resistance, respectively, to fluconazole, and they may also be less susceptible to amphoterericin B [6, 8, 10, 11]. Thus, there is a need for other systemically active agents with fungicidal activity against drug-resistant strains.

Caspofungin is an echinocandin with potent fungicidal activity against many species of *Candida* [11, 12]. Caspofungin has been shown to be as effective as and less toxic than amphoterericin B in the treatment of invasive candidiasis [13]. Caspofungin and other echinocandins have been shown to exhibit potent in vitro activity against fluconazole-resistant *Candida* species [12, 14, 15]. To our knowledge, the present report is the first description of successful treatment of *Candida* prosthethic valve endocarditis with caspofungin therapy alone.

**Summary.** We describe a case of *Candida* endocarditis involving a mechanical prosthetic mitral valve successfully treated with caspofungin therapy alone. Although valve replacement is generally recommended for cases of *Candida* prosthetic valve endocarditis, valve replacement was not required for cure in this case. Caspofungin has potent fungicidal activity against many species of *Candida* [16, 17], including those resistant to other antifungals, and it is less toxic than amphoterericin B. In certain cases, successful treatment of *Candida* prosthetic valve endocarditis may be achievable by use of caspofungin therapy alone. Caspofungin may be of benefit in the treatment of *Candida* prosthetic valve endocarditis for patients who are not medically fit for valve replacement, particularly if either *C. glabrata* or *C. krusei* are isolated.

**Acknowledgments**

We thank Dr. Liz Johnson (Health Protection Agency Mycology Reference Laboratory; Bristol, United Kingdom), for confirming the identity and antifungal susceptibilities of the *Candida* isolates and for determining the caspofungin MICs.

**Potential conflicts of interest.** All authors: no conflicts.

**References**