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## CASE REPORT

# Arteriovenous graft infection caused by *Candida glabrata*: A case report and literature review



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The infection rate of arteriovenous (AV) grafts is high, but fungal etiology is rare. Only five cases of graft infection due to *Candida albicans* (*C. albicans*) or *C. tropicalis* have been described in the literature. Herein, we report the first case of AV graft infection caused by *C. glabrata*. A 60-year-old woman on maintenance hemodialysis for end-stage renal disease was admitted because of intermittent fever, for 10 days. Upon physical examination, tenderness over the AV graft site was noticed. Blood culture yielded *C. glabrata* and her clinical symptoms improved after she was treated with micafungin for 1 month. However, *C. glabrata* candidemia reoccurred 5 weeks later. Cure was achieved after removal of the AV graft and anidulafungin treatment. Pus was observed in the removed graft, from which *C. glabrata* was isolated. The outcome of our case and patients from the literature review suggest that removal of the infected graft is important for treatment success of AV graft *Candida* infection.

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## Introduction

In the hemodialysis population, infection is second to cardiovascular disease in causing morbidity and mortality.<sup>1</sup> The infection rates of permanent hemodialysis vascular access [including arteriovenous (AV) fistula and

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polytetrafluoroethylene (PTFE) AV graft] range from 11% to 35%.<sup>2</sup> The most common pathogens in AV graft infection are *Staphylococcus aureus* (*S. aureus*), coagulase-negative *Staphylococcus*, Gram-negative rods, and *Enterococci*.<sup>3</sup> Fungal infections are rare and the optimal treatment strategy was not defined. Only five cases have been reported to have *Candida* AV graft infection and the causative pathogens were *C. albicans* and *C. tropicalis*.<sup>4–6</sup> We reported the first case of AV graft infection due to *C. glabrata* and performed a review of cases of *Candida* AV graft infection in the literature.

## Case report

A 60-year-old Taiwanese woman receiving regular hemodialysis was admitted to hospital for fever without an obvious infection source. She had a history of end-stage renal disease (ESRD), type 2 diabetes mellitus, hypertension, congestive heart failure NYHA II/VI, and gastric ulcer. She had received hemodialysis with the right forearm native AV fistula before. Because of occlusion of the native fistula, it was removed in December 2008. Hemodialysis was then performed via the left forearm PTFE AV graft, which was removed because of graft infection caused by methicillin-resistant *S. aureus* (MRSA) in December 2009. A new right forearm AV graft was then created in March 2010.

Five months after the right forearm graft creation, she presented to the hospital with intermittent fever, accompanied by chills for 10 days, especially after hemodialysis. On physical examination, there was no local heat, swelling, erythematous change, or drainage over the graft site, but mild tenderness was noticed. She had clear breath sounds and no cardiac murmur, abdominal pain, or lymphadenopathy. Her white blood cell count was 3700/mm<sup>3</sup> with 73% neutrophils and her C-reactive protein (CRP) level was 10.8 mg/L. We collected three sets of blood cultures on the day of admission and gave intravenous vancomycin for suspicion of AV graft infection, due to her previous history of MRSA graft infection. Her fever persisted after a 5-day course of vancomycin treatment. All three blood cultures yielded *C. glabrata*. The patient had not received any antifungal agent for at least 1 year before admission. We treated the patient with intravenous micafungin 100 mg/day for *C. glabrata* candidemia and she became afebrile 5 days after the initiation of micafungin. A repeat blood culture after 6 days of micafungin treatment revealed no growth of *C. glabrata*. Transesophageal echocardiogram (TEE) was performed for candidemia and revealed no visible intracardiac vegetation. She was treated with micafungin for 1 month, to attain a normal-range CRP level and then discharged.

Five weeks later, fever recurred and she had tenderness and swelling with erythematous changes over the graft site (Fig. 1). She was admitted again and received micafungin 100 mg/day. *C. glabrata* was isolated from blood cultures again and the susceptibility testing revealed susceptible dose dependency (SDD) to fluconazole and itraconazole (MICs = 16 µg/mL and 0.25 µg/mL, respectively) by the method of ATB FUNGUS 3 (bioMérieux, Marcy-l'Etoile, France).<sup>7</sup> The isolate was susceptible to 5-flucytosine, voriconazole, and amphotericin B. Her fever persisted after



Figure 1. Erythema over the AV graft site.

14 days of micafungin treatment. The susceptibility results for echinocandins were not obtained until 2013, when a commercial system (Sensititre YeastOne, Trek Diagnostic Systems, East Grinstead, UK) based on the microbroth dilution method was available in the hospital. Besides the same susceptibility results being obtained for fluconazole, itraconazole, voriconazole, 5-flucytosine, and amphotericin B as the ATB FUNGUS 3 kit revealed, the isolate was susceptible to caspofungin, micafungin and anidulafungin (MICs = 1 µg/mL, 2 µg/mL, and 2 µg/mL, respectively).

TEE was performed again and still showed no evidence of intracardiac vegetation, whereas an ophthalmologist consultation suggested neither Roth's spots nor endophthalmitis, and infective endocarditis were excluded. Ten sets of blood cultures were positive for *C. glabrata* during the 36 day follow-up period. The patient had fever intermittently during the period, but she hesitated in undergoing surgery for removal of the AV graft, despite the fact that the AV graft was considered as the only infection focus. Removal of the AV graft was finally performed under the patient's consent and pus in the lumen of the AV graft was observed. The culture of the removed graft also yielded *C. glabrata*. Anidulafungin 100 mg/day was started 3 days before removal of the AV graft and continued for a month. The antifungal treatment was discontinued after her CRP level fell to within the normal range. After the graft removal, the patient became afebrile and the subsequent blood cultures documented eradication. No further *C. glabrata* infection occurred within 1 year of follow-up.

## Discussion

The characteristics of five other cases of AV graft *Candida* infection in literature and this case are summarized in Table 1. All six cases used PTFE graft when AV graft *Candida* infection occurred. Use of PTFE grafts and graft revisions had been identified as risk factors for vascular access site infection.<sup>8</sup> The use of PTFE grafts resulted in the absence of the endogenous cellular components which help to combat infection in native vessels.<sup>9</sup> Although the infection rate of AV grafts due to bacteria is higher than the rate of native AV

**Table 1** Clinical characteristics of patients with arteriovenous (AV) graft *Candida* infection

Case	Year <sup>Ref</sup>	Age/sex	Clinical presentation	Culture site and organism	Underlying condition that caused hemodialysis	Removal of AV graft	Antifungal therapy	Outcome
1	1987 <sup>4</sup>	67/M	Draining fistula	Wound: <i>C. albicans</i> , <i>E. faecalis</i>	No data	Yes	Amphotericin B	Died (autopsy result: no <i>Candida</i> infection)
2	1991 <sup>8</sup>	65/M	Fever, hypotension	Blood: <i>C. albicans</i>	Acute tubular necrosis	Yes	Amphotericin B and 5-flucytosine	Died (persistent candidemia)
3	1993 <sup>8</sup>	52/F	Erythema, draining fistula	Wound and blood: <i>C. tropicalis</i> , <i>C. albicans</i>	Polycystic kidney disease	Yes	Amphotericin B	Cured
4	1994 <sup>8</sup>	54/M	Draining ulcer, non-functional fistula	Hematoma and blood: <i>C. tropicalis</i>	Focal sclerosing glomerulonephritis	thrombectomy and partial fistula removal initially	Fluconazole	Relapsed
5	2008 <sup>7</sup>	63/F	Knee swelling and pain, fever	Graft, synovial fluid and blood: <i>C. albicans</i>	Hypertension	No Yes	Fluconazole Fluconazole Fluconazole	Cured Relapsed Cured
6	2011 [This study]	60/F	Fever, tenderness Fever, tenderness Erythema	Graft and blood: <i>C. glabrata</i>	DM, hypertension	No Yes	Micafungin Anidulafungin	Relapsed Cured

*C.* = *Candida*; *E.* = *Enterococcus*.

fistula infection,<sup>10</sup> there is no report to compare the *Candida* infection rates between AV graft and native fistula cases. Our results revealed that all AV graft *Candida* infection cases used PTFE grafts.

The clinical manifestations of six AV graft *Candida* infection cases varied. Four of the six cases (Nos. 1, 3, 4, and 6) had signs and symptoms of AV graft infection, which included drainage found in AV graft sites in three patients (Nos. 1, 3, and 4), erythematous change over graft sites in two patients (Nos. 3 and 6), and a draining ulcer over a nonfunctional graft (No. 4). Only one case had a nonfunctional graft when candidemia occurred. Moreover, one case presented with septic shock, but had no obvious local infection signs. The above indicates that localized symptoms or signs of infection over the graft site vary and can be absent in *Candida* AV graft infection. In contrast, fever, pain, tenderness, redness, diffuse, or localized swelling, and serous or purulent discharge over the graft site are common in those having bacterial infection of AV access.<sup>3</sup>

The diagnosis of AV graft *Candida* infection is mainly confirmed by the culture of the graft. Five of the six *Candida* graft infection cases had *Candida* species isolated from blood cultures (Table 1). Blood culture reveals a valuable tool to identify the causative pathogen for such cases. All of the six patients received antecedent antibacterial agents, which indicates that fungal etiology is not commonly considered and is not empirically treated in clinical practice. Our report alerts clinicians to consider AV access site as the possible source of candidemia.

Without complete AV graft removal, three patients (Nos. 4, 5, and 6) had temporary clinical improvement with the initial antifungal treatment. All of the three cases had recurrent candidemia. Cure was only achieved after entire AV graft removal in combination with antifungal therapy. Among three patients (Nos. 1, 2, and 3) who received antifungal therapy and graft removal, one attained clinical success, but two had a fatal outcome. Of the two mortality cases, only one case died of persistent candidemia. He was a liver transplant recipient under immunosuppressant therapy and was the only case with septic shock as the initial presentation (No. 2). The other one died of his underlying conditions and lacked evidence of disseminated *Candida* infection by postmortem autopsy (No. 1). With AV graft removal and antifungal treatment, mortality due to *Candida* infection only occurred in one liver transplant recipient presenting with septic shock.

For AV graft infection related bacteremia, surgical exploration and removal of the infected graft material, combined with antibiotic therapy, are often necessary for complete resolution.<sup>11</sup> However, no treatment guidelines have been proposed for candidemia caused by AV graft *Candida* infection. In the first episode of *C. glabrata* candidemia of our case, the antifungal treatment stopped when the CRP level was within the normal range, however, recurrence occurred without removal of the AV graft. Procalcitonin (PCT) has been described as a marker of bacterial sepsis, but the role of invasive fungal infection (IFI) is controversial. In one study for proven or probable IFI,<sup>12</sup> PCT was elevated in fewer than half of invasive candidiasis episodes in the early phase of IFI, and the sensitivity and specificity rates are low. The erythrocyte sedimentation rate (ESR) is a biomarker of high sensitivity

and low specificity for tissue inflammation. There are many factors which elevate the ESR, including various infectious diseases, hematologic and neoplastic diseases, collagen diseases, renal diseases, and miscellaneous diseases.<sup>13,14</sup> No previous report about applying ESR in AV graft *Candida* infection was reported. Our case had ESRD, which may interfere with the ESR value. The above revealed the limited roles of PCT and ESR in the management of AV graft *Candida* infection.

Experience from cases 4–6 revealed that removal of the AV graft is crucial when relapse of *Candida* AV graft infection occurred. *C. glabrata* is more prone to be resistant to azole drugs when compared to *C. albicans* and *C. tropicalis*,<sup>15</sup> although there is no comparison of the susceptibility results between the species of *Candida* isolates from the AV graft. Our *C. glabrata* AV graft infection case demonstrated that *Candida* species in fungal AV fistula infection is not limited to azole susceptible species, like *C. albicans* and *C. tropicalis* (Table 1). For AV graft infection caused by *Candida* species not fully susceptible to azole class drugs, our case report revealed that echinocandins could be effective.

In conclusion, we report the first case of *C. glabrata* AV graft infection that was treated effectively with echinocandins, after the AV graft was removed. The outcome of our case, and patients from the literature review, suggest that removal of the infected graft is important for treatment success of AV graft *Candida* infection.

## Consent

For the patient who died, her son signed a written consent to agree to the academic report of his mother's *Candida* infection.

## Conflicts of interest

All authors declare no financial conflict of interest.

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H.L.H., W.T.W. and P.L.L. prepared the manuscript. Y.H.C. and P.L.L. provided laboratory support. C.Y.L. and Y.T.C. cared for the patients and advised on the clinical aspects of the case report. All authors read and approved the final version of the manuscript.

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