

Successful Treatment of *Malassezia furfur* Endocarditis

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The first reported case of *Malassezia furfur* endocarditis in an adult patient is presented. The unique microbiological aspects of this organism, as well as the difficulties inherent in its antifungal susceptibility testing, are discussed.

Keywords. *Malassezia furfur*; endocarditis; adult; antifungal agents; fungal diseases.

Fungal organisms remain an uncommon but important cause of endocarditis. Gould et al. [1] note that from 2% to 5% of cases of endocarditis are attributable to fungal organisms, predominantly *Candida albicans* (25%), nonalbicans *Candida* species (25%), and *Aspergillus* species (25%). Catheter-associated fungemia with *Malassezia furfur* has been reported in bone marrow transplant patients [2–4] as well as in neonates [4–6]. In this report, we describe the first adult patient proven to have endocarditis due to *M. furfur*, and detail his successful treatment. The methods of identification for this organism, as well as the role of antifungal susceptibility testing, are also discussed.

CASE REPORT

The patient is a 33-year-old man who presented with a 3-week history of fever and 1 day of a “numb right foot.” His medical history was remarkable for a melanoma on his back, excised a month before admission, and injection drug use. He was febrile, and cardiac auscultation noted a soft holosystolic murmur. His right foot was slightly pale, compared with the left, with diminished but palpable pulses. He had a hemoglobin of 9.7 g/dL, but the remainder of his laboratory studies, including tests for hepatitis B, hepatitis C, and HIV, were unremarkable. A computed tomography arteriogram demonstrated a large embolus at the right iliac artery bifurcation, as well as additional emboli in both popliteal arteries.

Blood cultures were obtained, and he was prescribed intravenous ceftriaxone and vancomycin. He was taken for emergency embolectomy, which removed large amounts of “cheesy” thrombus from his right iliac and popliteal arteries. Gram stain of the right iliac thrombus revealed yeast forms, so intravenous fluconazole was added to his regimen. Due to the presence of thrombus in both lower extremities, a cardiac source of his embolus was suspected, so a transthoracic echocardiogram was performed, which showed mild aortic stenosis, mild to moderate aortic regurgitation, and trace mitral regurgitation. A transesophageal echocardiogram was recommended but was refused by the patient.

On the third day of admission, cultures from the iliac artery thrombus grew a nonalbicans species of yeast, and anidulafungin was substituted for fluconazole. Two days later, the organism was presumptively identified as *Malassezia furfur*. Identification was based upon growth dependence on lipid supplementation of the media (olive oil, in this case), colony morphology, growth at 40°C, catalase positivity, and microscopic morphology. This case took place in 2010, before Matrix Assisted Laser Desorption/Ionization - Time of Flight (MALDI-TOF) and sequencing methods of identification were commonly available. Voriconazole was added to his regimen at a dose of 3 mg/kg intravenously (IV) every 12 hours after 2 loading doses of 6 mg/kg, based on the manufacturer’s recommended dosing range of 3–4 mg/kg every 12 hours for invasive candidemia in non-neutropenic hosts. The organism was forwarded to the laboratory now known as the UT Health San Antonio Fungus Testing Laboratory for susceptibility testing, but due to the absence of a standardized methodology for this particular yeast (see the “Discussion”), it could not be performed. The patient remained febrile and eventually agreed to undergo transesophageal echocardiography. This demonstrated a bicuspid aortic valve, moderate to severe aortic regurgitation, and 2 aortic valvular masses. Aortic valve replacement was recommended, but he declined to undergo the procedure. Liposomal amphotericin B, 5 mg/kg IV every 24 hours, was substituted for the anidulafungin, and the voriconazole was continued, given the uncertainty regarding the most appropriate antifungal therapy for an invasive infection caused by this organism.

With unremitting fevers, he consented to undergo valve replacement, performed on his 23rd hospital day. At operation, he was noted to have 2 aortic valve vegetations and underwent pulmonary autograft replacement of the aortic valve, reimplantation of the right and left coronary ostia, and pulmonary valve replacement with a pulmonary homograft (Ross procedure). His admission blood cultures, negative through 21 days, were subcultured to Remel Sabouraud Dextrose agar (Lenexa, KS, USA) overlaid

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with Bertolli Extra Virgin Olive Oil (Salove North America Corp, Lyndhurst, NJ, USA). After 72 hours, pinpoint colonies appeared, subsequently identified as *Malassezia furfur*. Pathologic examination of the aortic valve demonstrated yeast with pseudohyphae formation (Figure 1), and also yielded *M. furfur* in culture.

Postoperatively, his liposomal amphotericin B was held due to a rising serum creatinine. Voriconazole was continued throughout the remainder of his hospital stay, and he was discharged on hospital day 28 on voriconazole, 200 mg by mouth, twice daily. He remained on this agent for at least 2 months after hospital discharge, when he was lost to follow-up. Eighteen months later, he was coincidentally admitted for an unrelated problem. At that time, his cardiac examination and transthoracic echocardiogram were both unremarkable.

DISCUSSION

Malassezia furfur is a yeast and is considered part of the normal human flora, with a predilection for colonizing the scalp, chest,

and back; it is found on up to 90% of adolescents and adults [4]. Although the patient described in this report did have injection drug use as a risk factor for endocarditis, it seems more likely that his infection arose as a complication of his melanoma excision, given the location of his cancer (upper back). *M. furfur* has long been recognized as the causative agent of the skin condition pityriasis versicolor. The organism has lipophilic growth requirements (present in the oily skin in the regions it colonizes), as it cannot synthesize medium- and long-chain fatty acids. Standard blood culture bottles typically don't contain enough fatty acids to support its growth [5]. One technique used to recover *M. furfur* involves use of isolator tubes, with subsequent subculture to media supplemented with olive oil, as was done in our laboratory. The organism is identified by its unusual growth requirements, production of catalase, growth in various concentrations of Tween, esculin hydrolysis, and appearance on microscopy. *M. furfur* buds repeatedly from the same end of the parent yeast, forming "collarettes," 6 µm longest measurement (best appreciated in culture).



Figure 1. Gomori methenamine silver stain of the excised aortic valve from our patient (630× magnification). Note the numerous oval fungi and pseudohyphae, which give the organism its characteristic “spaghetti and meatballs” appearance on microscopic examination.

Antifungal susceptibility testing of *Malassezia furfur* is problematic. Broth microdilution, recommended by the Clinical & Laboratory Standards Institute (CLSI) as a standard method for other fungal organisms, is not considered valid due to the organism's lipid requirement. Miranda et al. [7] determined antifungal susceptibilities using modified Leeming-Notman medium, which contained 3% olive oil. Nakamura et al. [8] used a urea broth microdilution method (*Malassezia* species produce urease, and the presence of split urea can be measured photometrically using phenol red), and Gupta et al. [9] utilized an agar dilution method to determine susceptibilities. The data, in sum, found *M. furfur* to be generally susceptible to itraconazole, voriconazole, and ketoconazole, with low minimum inhibitory concentrations (MICs), with fluconazole's being somewhat higher. Results for terbinafine showed more variability. Finally, data presented by Velegraki et al. [10], obtained using a combination of broth microdilution and Etest, suggest that amphotericin B would appear to be a less reliable agent to use against *M. furfur*, with a mean amphotericin B MIC₁₀₀ (range) of 1 (0.12–64) µg/mL; it is the only bloodstream isolate considered resistant, with an MIC₁₀₀ of 2 µg/mL.

Surgical management is generally recommended up front in cases of fungal endocarditis [11]. Amphotericin B has been advocated as the antifungal of choice, but nephrotoxicity may limit its use, even with lipid formulations of the drug. As experience with triazole compounds grows, these may eventually supplant amphotericin B. Considering the aforementioned susceptibility data for *Malassezia furfur*, triazoles would appear to be a better treatment option than amphotericin, although we will likely never see clinical trial data in this area, given the rarity of the disease. Duration of therapy after valve surgery is unclear. In fungal endocarditis due to other pathogens, some recommend chronic suppression with an oral agent to prevent late relapse.

There has only been 1 prior case of endocarditis due to *Malassezia furfur* reported in the literature [4]. This was in a premature infant who had echocardiographic evidence of endocarditis of the right atrium in the setting of repeatedly positive blood cultures. The patient died of bronchopulmonary dysplasia 2 months after completing a 6-week course of amphotericin B and 5-flucytosine. Our case illustrates the first successful combined medical/surgical approach to this serious infection.

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