The Brief Case: *Scopulariopsis* Endocarditis—a Case of Mistaken Takayasu's Arteritis

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CASE

A 37-year-old Japanese woman with a past medical history of aortic valve replacement secondary to a congenital aortic aneurysm and presumed Takayasu's arteritis treated with prednisone (60 mg daily) presented to the inpatient service with shortness of breath, abdominal pain, and leg and foot pain. The patient had a 9-month history of repeated emboli and fevers. Due to the concern for an unidentified source of the emboli, a computed tomography angiography (CTA) of the chest was conducted, revealing a moderately sized pseudoaneurysm arising from the posterior margin of a previously performed ascending aortic graft and filling defects concerning for thrombi in the distal ascending aorta/proximal aortic arch near the graft anastomosis. The patient was started empirically on broad-spectrum antimicrobials consisting of intravenous vancomycin (750 mg every 12 h [q12h]), piperacillin-tazobactam (3.37 g q8h), and voriconazole (200 mg q12h).

The patient underwent thrombectomy and resection of ascending aortic graft tissues, portions of which were submitted for histopathological and microbiological analysis. Histopathologic examination of the ascending aortic tissue and left iliac artery embolus and thrombus utilizing hematoxylin and eosin (H&E) stain, Gomori methenamine silver (GMS) stain, and periodic acid-Schiff stain (PAS) revealed numerous septate hyphae with dichotomous branching (Fig. 1). Based on this finding, voriconazole therapy was continued and converted to oral voriconazole (360 mg q12h) postextubation to cover suspected aspergillosis. The diagnosis of Takayasu's arteritis was dismissed as the etiology of the patient's aneurysm, and the patient's regimen of prednisone was discontinued. Blood cultures were negative throughout her hospitalization.

After 3 days of incubation at 30°C, mold growth was observed on brain heart infusion agar and Sabouraud dextrose agar with chloramphenicol. The colony surface was at first white and glabrous and then became powdery and light brown with a light tan periphery (Fig. 2). The reverse was tan with a brownish center. Microscopic examination of tape preparations from the mold colony revealed septate hyphae giving rise to short conidiophores which bore annellides mostly arranged in brushlike groups. Conidia were 5 to 8 μ m in size, round, light brown in color, and with truncated bases (Fig. 2). Based on the colony and microscopic morphologies, the identification was most consistent with *Scopulariopsis brevicaulis*. Definitive species-level identification based on molecular testing was beyond the scope of this study; accordingly, the final identification was made at the genus level.

Following reporting of these findings, the antibacterial therapy was discontinued after a total of 4 days and intravenous amphotericin B (65 mg q24h) was added to the

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For answers to the self-assessment questions and take-home points, see page 2872 in this issue (<https://doi.org/10.1128/JCM.02480-16>).

FIG 1 Histopathological examination of left iliac artery embolus and thrombus demonstrating narrow (range, 2 to 5 μm), septate hyphae with dichotomous branching. (A) Hematoxylin and eosin stain (H&E) (black arrows indicate the hyphae). (B) Grocott-Gomori's methenamine silver stain (GMS). (C) Periodic acid-Schiff stain.

antifungal regimen pending antifungal susceptibility data. The isolate was immediately sent to a reference laboratory for susceptibility testing due to the intrinsic highly drug-resistant nature of this organism.

Eighteen days after the mold was identified, the antifungal MIC results were received and reported as follows: amphotericin B, 4 $\mu\text{g}/\text{ml}$; micafungin, 0.5 $\mu\text{g}/\text{ml}$; posaconazole, 1 $\mu\text{g}/\text{ml}$; voriconazole, 2 $\mu\text{g}/\text{ml}$; isavuconazole, 2 $\mu\text{g}/\text{ml}$. These results

A

B

FIG 2 *Scopulariopsis brevicaulis* colony and cellular morphology. (A) Light brown powdery colony with a light tan periphery on Sabouraud dextrose agar after 5 days of incubation. (B) Septate hyphae giving rise to short conidiophores bearing annelides mostly arranged in bushlike groups. The conidia are 5 to 8 μm in size, round, and light brown in color. They are uniquely shaped, appearing truncated at the base and forming chains resembling lightbulbs in a chain (unstained; $\times 500$ magnification).

prompted treatment with delayed-release oral posaconazole (300 mg daily) and intravenous micafungin (100 mg daily). After a 78-day hospital stay, the patient was discharged on long-term antifungal therapy with delayed-release oral posaconazole (200 mg daily). She completed her antifungal therapy 6 months after being discharged. Serial CTA imaging follow-up at 4 months and 12 months postoperatively demonstrated a stable aortic root and ascending thoracic aorta and stable aortobiiliac bypass graft with no signs of complications.

DISCUSSION

Scopulariopsis species include both hyaline and phaeoid fungi that belong to the ascomycete family *Microascaceae*, order *Microascales* (1). Traditionally, *Microascus* and

Scopulariopsis were referred to as teleomorph and anamorph, respectively. Since 1 January 2013, this dual nomenclature has no longer been permitted. As a consequence, the designation *Microascus brevicaulis* is no longer used, and this organism is now solely called *Scopulariopsis brevicaulis* (1). Members of the genus *Scopulariopsis* are saprobic, are commonly isolated from soil, air, plant debris, and moist environments, and are found worldwide (2). These microorganisms are keratinolytic molds that have been associated with onychomycosis and, in rare instances, have been the culprits responsible for more-severe tissue infections, including otomycosis, keratitis, prosthetic-valve endocarditis, sinusitis, pneumonia, brain abscess, and subcutaneous and bone invasion in immunocompetent and immunosuppressed patients (2, 3). Of all the *Scopulariopsis* spp., *Scopulariopsis brevicaulis* is the most commonly encountered in all clinical presentations and anatomic locations (2–4). Moreover, *Scopulariopsis brevicaulis* was considered a species different from *S. stercorearia* and *S. koningii* since the latter two taxa exhibited smooth conidia. A recent study by Sandoval-Denis et al. confirmed the synonymy of these mentioned species by phylogenetic analysis (1).

Fungal endocarditis is a rare disease associated with high morbidity and mortality. Unfortunately, the incidence of fungal endocarditis has increased in the recent past, likely due to more-frequent use of cardiovascular prosthetic devices (5). Fungal endocarditis is most prevalent in patients who are immunocompromised, intravenous drug abusers, recipients of prolonged antibiotic therapy, recipients of parenteral nutrition, and recipients of prosthetic heart valves and in those who have undergone reconstructive cardiac surgery (6). The diagnosis of fungal endocarditis is often challenging to make clinically due in part to inconsistent and nonspecific clinical presentations. While blood cultures remain the most important indication of the much more common entity of bacterial endocarditis, they have a limited role in the diagnosis of fungal endocarditis since less than 50% of reported cases demonstrated positive blood culture results (6, 7). Of these positive cultures, yeast were much more likely to be isolated than molds. Histopathological examination also has limitations since many molds look very similar microscopically, making it difficult to identify the organism to the genus and species levels. Therefore, isolation of fungi in culture is vital for definitive identification, which is often necessary for guiding appropriate antifungal therapy. In addition, the identification of an unusual mold should immediately prompt susceptibility testing since susceptibility patterns have not been well established for many infrequently isolated molds.

Few cases of *Scopulariopsis* endocarditis have been reported in the literature (2, 4, 5). Notably, all cases have been associated with *Scopulariopsis brevicaulis*. This microorganism is known to be intrinsically resistant to broad-spectrum antifungal agents such as amphotericin B, flucytosine, itraconazole, voriconazole, and terbinafine (3). Therefore, it is especially important that prompt antifungal susceptibility testing is performed for the selection of the optimal antifungal regimen in cases of invasive infections. It is also recommended to use long-term suppressive therapy with antifungals after medical and surgical treatment of fungal endocarditis in general due to a high relapse rate, as well as a protracted delay in treatment response (4, 6).

In this case, the patient initially presented with left-foot pain and was admitted for concern of embolic phenomena in the extremities. The differential diagnosis included endocarditis and severe peripheral vascular disease. At that time, no clinical evidence of acute or critical limb ischemia was present. In addition, blood cultures were negative and transesophageal echocardiography (TEE) did not show evidence of endocarditis. Arterial Doppler tests suggested significant peripheral vascular disease, and CTA imaging showed extensive diffuse peripheral disease, bilaterally. Given these findings and the patient's age and demographics, the patient was initially diagnosed with Takayasu's arteritis. After a 5-day hospital stay, she was discharged with planned vascular and rheumatology follow-up for further work-up.

A day after being discharged, she was readmitted due to concern for an unforeseen source of emboli. Due to a history of multiple thrombotic emboli from an unknown source, a CTA of the chest was performed as part of her work-up and revealed a

pseudoaneurysm associated with a previous aortic graft. Examination of thrombectomy and resected tissues from her aortic graft resulted in the diagnosis of hyalohyphomycosis and presumptive aspergillosis, based on the presence of narrow (range, 2 to 6 μm), septate, nonpigmented hyphae. While these are features most frequently associated with *Aspergillus* species, they are also common to other hyaline fungal pathogens such as *Fusarium* spp. and *Scedosporium* spp., as well as *Scopulariopsis* spp. Additionally, phaeoid fungi, especially if sparsely pigmented, cannot be entirely ruled out. It is important that stains traditionally used for fungal identification, including GMS and PAS, may obscure pigmentation, and sparsely pigmented hyphae may not be obvious on H&E staining. Use of Fontana-Masson staining may be helpful to confirm lack of pigmentation. The hyphae of mucoraceous molds are also hyaline but are typically much broader (5 to 25 μm) and have sparse or no septae.

The isolation and identification of this mold were vital to ensuring the selection of appropriate antifungal treatment. The high rates of resistance of these fungi to the most commonly used drugs for the prophylaxis, and first-line treatment, of systemic mold infections, such as amphotericin B and voriconazole, make this type of infection difficult to treat and, consequently, usually fatal. Due to the dearth of *in vitro* susceptibility data available for these fungi, the appropriate therapy for infections by *Scopulariopsis* spp. is nonstandardized. As demonstrated in this case, even with the unavailability of interpretative MIC breakpoints, antifungal susceptibility testing can be useful for guiding the selection of the best antifungal regimen. However, the susceptibility testing results must be interpreted with caution.

In conclusion, *Scopulariopsis* endocarditis is a rare disease that is challenging to treat due to its resistance to broad-spectrum antifungal agents. The isolation and identification of *Scopulariopsis* spp. should immediately prompt antifungal susceptibility testing to select the best antifungal regimen. The patient's successful outcome should be attributed to a multidisciplinary intervention that involved a combined medical and surgical approach that ultimately led to the resection of infected tissue, cardiac reconstruction, identification of the mold, and an aggressive long-term antifungal treatment strategy.

SELF-ASSESSMENT QUESTIONS

1. Which risk factor is associated with fungal endocarditis?
 - A. Asian ethnicity
 - B. Young age (≤ 40 years)
 - C. Aortic valve replacement
 - D. Female gender
2. What histopathological features are indicative of hyalohyphomycosis?
 - A. Broad, pigmented, septate hyphae
 - B. Broad, hyaline hyphae with sparse septations
 - C. Narrow, septate hyphae without melanin pigmentation
 - D. Narrow, pigmented, septate hyphae
3. The following statement is true regarding the antifungal susceptibility profile of *Scopulariopsis brevicaulis*.
 - A. Always susceptible to micafungin and posaconazole
 - B. Multiresistant to broad-spectrum antifungal agents
 - C. Pan-susceptible to commonly tested antifungal agents
 - D. Resistant only to amphotericin B

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