

## Diagnostic Importance of Hyphae on Heart Valve Tissue in Histoplasma Endocarditis and Treatment With Isavuconazole

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A patient who never resided in an endemic area for dimorphic fungi was diagnosed with *Histoplasma capsulatum* endocarditis. His diagnosis was suggested by yeast and hyphae on cardiac valve tissue pathology. Isavuconazole was an optimal therapeutic option due to renal dysfunction and anticoagulation with warfarin for mechanical valve replacement.

**Keywords.** fungal endocarditis; *Histoplasma capsulatum*; histoplasmosis; hyphae; isavuconazole.

### CASE

A previously healthy 56-year-old male construction worker from rural Georgia presented with 1 year of subjective fevers, malaise, and dyspnea. He was in a monogamous relationship with his wife and denied history of travel outside Georgia or animal exposure. He had fever, systolic and diastolic murmurs, and hepatosplenomegaly. Transesophageal echocardiogram revealed severe eccentric aortic insufficiency, an aortic root fluid collection, and a large aortic vegetation.

His serum creatinine was 2.36 mg/dL, white blood cell count was  $3.5 \times 10^9/L$  with normal differential, hemoglobin was 8.5 g/dL,

and platelet count was  $96 \times 10^9/L$ . HIV polymerase chain reaction and fourth-generation screen were negative. Blood cultures were obtained, and empiric ceftriaxone and intravenous vancomycin were administered. He underwent mechanical aortic valve replacement and aortic root reconstruction. Intraoperatively, a  $4 \times 2$ -cm aortic valve vegetation was found with extension of abscess into the annulus and myocardium.

Pathologic examination of the excised aortic valve showed fungal endocarditis with different-sized yeasts, some in clusters, and hyphae (Figure 1). After visualization of fungal elements on tissue pathology, the patient was treated with liposomal amphotericin; however, due to progressive renal insufficiency, he was transitioned to itraconazole. Due to commitment to warfarin after mechanical valve replacement and corrected QT interval (QTc) prolongation, he was transitioned from itraconazole to isavuconazole. Five days after surgery, his aortic valve cultures were positive for a mold. Seven days postoperation, urine *Histoplasma* antigen results were positive (1.02 ng/mL; reference:  $\leq 0.10$  ng/mL), and 9 days postsurgery, the serum *Histoplasma* qualitative immunodiffusion results were positive. His aortic valve fungal cultures were ultimately identified as *H. capsulatum*. The isolate was sent to a reference laboratory for susceptibility testing and, though susceptibility results were not available until after the patient was discharged, the MIC to isavuconazole was  $\leq 0.03$  ug/mL. Sequencing of the internal transcribed spacer region of the rDNA amplified from the formalin-fixed, paraffin-embedded tissue block was also positive for *H. capsulatum*; however, these results were not available until after the culture results. Several months after cardiothoracic surgery, he was recovering well on isavuconazole with plans to remain on this for the duration of his life.

### DISCUSSION

*Histoplasma capsulatum* is one of the most common thermally dimorphic fungi, and though classic areas of endemicity along the Ohio and Mississippi River Valleys have been described, there is increasing recognition of histoplasmosis outside of these areas [1, 2]. *H. capsulatum* is a rare cause of infectious endocarditis, with only 58 previously described cases [3, 4]. In this case, yeast and hyphae were seen in excised cardiac valve tissue before results were available by fungal culture, urine *Histoplasma* antigen, and serological and molecular testing. In tissue sections, *H. capsulatum* is usually seen as phagocytosed clusters of yeasts; however, endocarditis is the exception to the rule as the intracellular yeasts can show hyphal structures more typical of the histopathology of *Candida* spp. or hyaline molds [5].

There are limited data to guide *H. capsulatum* endocarditis treatment, and no specific recommendations in the 2007 Infectious Diseases Society of America Histoplasmosis

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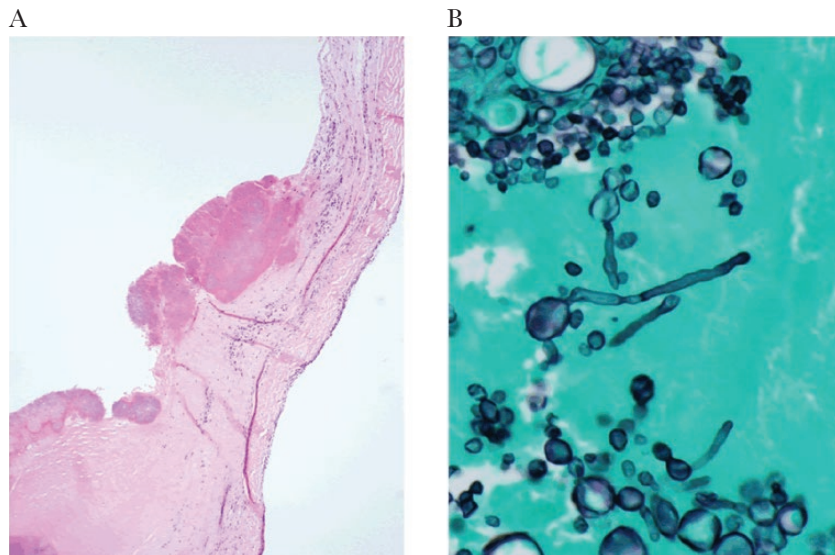
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**Figure 1.** (A) Hematoxylin and eosin stain of the aortic heart valve with vegetation (bright pink material in center; original magnification 8x). (B) Grocott methenamine silver stain of heart valve showing yeasts (round structures of different sizes) and hyphae (elongated structures coming out of the yeasts; original magnification 200x).

Guidelines or the 2015 joint IDSA/American Heart Association Infective Endocarditis Scientific Statement. Expert opinion recommendations include surgical debridement or valve replacement followed by an initial period with amphotericin, then a prolonged or lifelong course of itraconazole [4]. Although an off-label use, isavuconazole may be effective treatment for *H. capsulatum* endocarditis. It does not appear to interact with warfarin, which may be important for patients undergoing mechanical valve replacement, and, where other azoles can cause QTc prolongation, isavuconazole has been associated with QTc interval shortening. Isavuconazole also does not require renal dose adjustment.

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