Endovascular Infections Caused by *Histoplasma capsulatum*

*A Case Series and Review of the Literature*

Christopher Ledtke, MD; Susan J. Rehm, MD; Thomas G. Fraser, MD; Nabin K. Shrestha, MD; Carmela D. Tan, MD; E. Rene Rodriguez, MD; J. Walton Tomford, MD; Anil Jain, MD; Bruce Lyle, MD; Douglas Johnston, MD; Joseph Sabik, MD; Steven M. Gordon, MD; David van Duin, MD, PhD

**Context.**—Endovascular infection is an uncommon but devastating manifestation of histoplasmosis, which is often diagnosed late in disease.

**Objectives.**—To evaluate the clinical and pathologic characteristics of patients with endovascular infections caused by *Histoplasma capsulatum*.

**Design.**—All cases of patients with documented endovascular histoplasmosis at a single tertiary care center in an endemic region during the period 1993–2010 were reviewed.

**Results.**—Patients presented with a subacute febrile illness and a history of endovascular devices. All patients had positive *Histoplasma* serology. Routine bacterial culture results were negative for all patients. In addition to yeast forms typical of histoplasmosis, pathologic findings also revealed mycelial forms in 4 of 5 patients. Inflammation was scant. Urinary antigen detection was positive in 4 of 5 patients and *Histoplasma* blood culture results were positive for 3 of 5 patients. Four patients were treated with a combination of surgical and medical therapy, which consisted of amphotericin B followed by itraconazole; these 4 patients had complete resolution of symptoms and no documented relapse. One patient died before planned surgery.

**Conclusions.**—*Histoplasma capsulatum* endovascular infections are clinically characterized by a subacute febrile illness with negative bacterial cultures in patients with prosthetic endografts or valves. Noninvasive diagnostics are often the initial clue to the diagnosis. Combined medical and surgical treatment is associated with survival. On histopathologic examination both mycelial and yeast forms are often observed, with absent to minimal tissue inflammatory reaction.


---

*Histoplasma capsulatum* var *capsulatum*, hereafter referred to as *H. capsulatum*, is a thermally dimorphic fungus that is endemic in certain areas in the Americas, notably the Mississippi and Ohio River valleys in the United States and Rio de Janeiro State in Brazil, and occurs in microfoci elsewhere. Most infections result in no or self-limited symptoms. When symptomatic, histoplasmosis most commonly causes a subacute pulmonary illness that is self-limiting. Endovascular histoplasmosis, including *H. capsulatum* infective endocarditis, is a rare manifestation of infection. It is an infrequent cause of native and prosthetic valve endocarditis, endarteritis, infected aortic aneurysms, and endovascular graft infections.

Endovascular histoplasmosis has also been diagnosed by pathologic assessment and analysis of an embolic event. Here, we report the clinical presentation as well as diagnostic and histopathologic findings of 5 cases of confirmed *H. capsulatum* endovascular infections at the Cleveland Clinic (Cleveland, Ohio).

**MATERIALS AND METHODS**

Case definition: A patient was considered to have *H. capsulatum* endocarditis if there was evidence of valvular vegetations with fungal forms consistent with *H. capsulatum* noted on histopathologic specimen and/or positive cultures for *H. capsulatum* from explanted tissue.

Case ascertainment: Case finding was carried out through (1) a review of International Classification of Diseases, 9th revision (ICD-9) codes; (2) positive *H. capsulatum* cultures from any site; (3) positive serology results (titer of 1:32 or greater on yeast or mycelial complement fixation); (4) a review of all patients with pathology specimens positive for *H. capsulatum*, taken from any site; and (5) a query of 21 infectious disease physicians in the department.

The study period involved patients seen at our facility between January 1993 and September 2010. A review of the electronic medical record for each patient was carried out and only those with endovascular involvement were included in the study. Data collected for each patient included demographics, comorbidities, description of endovascular involvement, serology, culture data, pathologic findings, treatment, clinical outcomes, and mortality (Table). Of note, one of these patients...
Figure 1. Case 1. A, Low-power view of the resected porcine bioprosthetic valve with overlying vegetation on the arterial/concave side. B, Endocarditis showing no inflammatory reaction in the tissue valve. Case 2. C, Section of the aortic Dacron graft (arrows) and intraluminal vegetation shows no conspicuous inflammatory component. D, The graft (arrow) is covered with neointima and surrounded by fibrous tissue without inflammatory reaction. E, Vegetation consists of fibrin with few macrophages as noted in the lower portion. Note the pale areas within the vegetations representing aggregates of fungal organisms in the top portion of B and E (hematoxylin-eosin, original magnifications ×40 [A and C], ×400 [B and E], and ×200 [D]).
was previously reported as a part of a case series on fungal endocarditis.  

### Case Reports

We selected 2 representative patients, whose histories are discussed below.

**Patient 1.**—A 67-year-old white woman from Ohio with a past medical history of rheumatic heart disease complicated by mitral stenosis and transient ischemic attacks received a porcine Carpentier-Edwards mitral valve replacement 13 years before presentation. Approximately 6 months before presentation, she began experiencing night sweats and intermittent fevers. She was seen by a local physician who drew routine blood cultures and performed an echocardiogram, which revealed a thickened mitral valve without vegetations. Blood culture results were negative. She was treated empirically with vancomycin and gentamicin without improvement. Her exposure history was significant only for residence in a heavily wooded area.

The patient then developed pain and a mass in her right groin. She was found to have a femoral artery pseudoaneurysm and was referred to our facility. She underwent resection of a common femoral artery pseudoaneurysm with right common femoral artery to superficial femoral artery bypass. Intraoperative findings revealed a pseudoaneurysm that arose from the right common femoral artery and contained thrombus material surrounded by inflamed tissue. The superficial femoral artery adherent to the posterior wall of the pseudoaneurysm was occluded with a thrombus. Histopathology examination revealed rare fungal organisms consisting of yeast and hyphal elements within the organizing thrombus located in the superficial femoral artery. There was focal mild acute inflammation in the arterial wall but no evidence of vascular invasion. Fungal organisms were not seen in the pseudoaneurysm, which showed only old thrombus contained by chronically inflamed fibroadipose tissue. Shortly after surgery, the patient developed shortness of breath. A 1.3-cm mass attached to the posterior leaflet of the mitral valve was seen on transesophageal echocardiography. She underwent successful replacement of her mitral valve. Examination of the extracted bioprosthetic valve revealed devitalized porcine valve with rare mononuclear cells on the surface of the leaflets (Figure 1, A and B). The fibrin vegetations contained a small amount of mononuclear cells, rare neutrophils, and abundant yeast forms consistent with *Histoplasma* species. In addition, hyphal forms were noted within the vegetations. Intraoperative fungal cultures of the valve grew *H* *capsulatum*, which was confirmed with molecular sequencing. After initial treatment with amphotericin B, she was given oral itraconazole for lifelong suppressive therapy.

**Patient 2.**—A 31-year-old white man from Indiana with Marfan syndrome had valve-sparing aortic root and ascending aortic replacement with a woven Dacron graft, performed at our institution 11 years before presentation. The patient had recurrent fevers 4 months before presentation and was evaluated at an outside hospital and thought to have cholecystitis. He underwent a laparoscopic cholecystectomy and was given oral ciprofloxacin and metronidazole empirically. However, he remained persistently febrile. Exposure history was significant only for outdoor activities (camping, fishing, hiking) in rural areas of Indiana. He had routine blood cultures drawn, which yielded negative results, and underwent a transsthoracic echocardiogram, which was unremarkable. He was referred to our facility for further evaluation.

Serology for *H* *capsulatum*, obtained for the evaluation of fever of unknown origin, revealed mycelial and yeast complement fixation titers of 1:512 with a positive M and H band on immunodiffusion. A transesophageal echocardiogram revealed a small mobile echodensity within the aortic graft. Cardiac magnetic resonance imaging revealed a 1.5-cm linear density within the ascending aortic graft, suggestive of vegetation versus thrombus. The patient underwent graft extraction and replacement with distal homograft implant. Pathologic findings showed a synthetic vascular graft with fibrotic neointima and luminal thrombus containing fungal yeast and hyphal forms (Figure 1, C through E). Intraoperative cultures grew *H* *capsulatum*, which was confirmed with DNA sequencing. The patient was treated with a course of amphotericin B and subsequently given oral itraconazole for lifelong suppressive therapy.

### Results

We identified 5 patients with *H* *capsulatum* endovascular infections during the study period. All cases were confirmed with pathologic analysis of specimens. In all patients, disease manifested as a prolonged febrile illness. The median time from symptom onset to diagnosis was 6 months (range, 3 to 12 months) with the median time from initial medical evaluation to diagnosis being 3.5 months (range, 1 to 8 months). The median age was 62 years; 4 of 5 patients were older than 55 years. All patients were white. Three patients were male. Four of 5 patients responded to combined medical and surgical treatment. One patient died shortly after diagnosis. All patients had involvement of prosthetic endovascular material. The median time from implant of material to infection was 4 years (range, 1 to 13 years).
DNA (University Histoplasma capsulatum is found in a mycelial form in soil at environmental temperatures and converts to a yeast form during mammalian infection.20 Temperature is thought to be the primary determinant of phase in H capsulatum through pathways involving the transcriptional regulators Ryp1, Ryp2, and Ryp3.21–23 In fact, transition from mycelial to yeast form is a major virulence determinant for H capsulatum. Studies have shown that H capsulatum can be grown as mycelial forms in vivo at 37°C, after certain chemical treatments.24 Mycelial forms in human tissue were first noted in a necrotic lung specimen in 1940 by Arthur Humphrey.25 The presence of mycelial forms may be related to an altered microenvironment producing unusual conditions of nutrition or oxygenation.26,27 Mycelial forms associated with endovascular infections were originally noted in 1955.27,28 It is not clear why mycelial forms are so common in endovascular infections, during which necrosis and lack of nutrients are less likely to play a role. Clinically, the presence of mycelial forms in vivo has the potential to cause diagnostic confusion and delay. Because hyphal forms are rarely encountered in tissue, a correlation between complement fixation titers and immunodiffusion result patterns has not been established in the literature.

The vegetations consisted of fibrin with large aggregates of yeasts and only mild chronic inflammatory cell infiltrates, predominantly macrophages. Of note, there was absence of acute inflammatory reaction to the infectious process in the bioprosthetic valves or synthetic vascular graft. Tissue necrosis was absent. A combination of yeast (Figure 2, A through D) and mycelial forms (Figure 1, E) was observed in 4 of 5 samples submitted for pathologic examination. Typical, small oval yeasts morphologically consistent with Histoplasma (Figure 2, A and C) were admixed with variably sized large round forms (Figure 2, B and D). The hyphal elements were segmented with short straight or branched forms (Figure 2, E). The fungal morphology, particularly the presence of large yeasts and hyphae, did not correlate with antifungal therapy before surgery.

Serologic results were positive for all patients; the median peak mycelial complement fixation titer was 1:1024. The median peak yeast complement fixation titer was 1:512. Immunodiffusion test result was positive for all 5 patients. Four of 5 patients had positive M and H bands, 1 patient had positive H band alone. Urinary antigen (Miravista Diagnostics, Indianapolis, Indiana) was positive for 3 of 4 patients. Embolic events were diagnosed in 3 of 5 patients, with brain emboli occurring in 2 patients and vascular emboli occurring in 2 patients, including 1 patient with coronary and renal artery embolization confirmed at autopsy (patient 4). All patients had specimen culture results confirmed with DNA gene probe for H capsulatum. Universal fungal polymerase chain reaction analysis performed on excised valve tissue from 2 patients confirmed the presence of H capsulatum DNA (University of Washington Medical Center, Seattle, Washington).

Initial antifungal treatment for all patients was amphotericin B. This course was followed by oral itraconazole for 3 of 4 survivors. The fourth survivor could not tolerate itraconazole and was treated with 4 g of amphotericin B and close follow-up. The patient did not have a recurrence during his remaining years of life.

**COMMENT**

*Histoplasma capsulatum* most commonly causes disease of the respiratory tract. Other common manifestations of histoplasmosis include disseminated disease and mediastinal disease such as mediastinal fibrosis and granulomatous mediastinitis. Endovascular and cardiac infections are rare but well established. *Histoplasma capsulatum* should be considered in the differential diagnosis of bacterial culture–negative endovascular infections, particularly for those patients who currently reside or have resided in endemic areas, or who have high-risk hobbies (e.g., spelunking) or occupations (e.g., excavation).

As in other causes of endovascular infection involving prosthetic material, surgical excision should be pursued. In our series, all survivors underwent surgical resection. In contrast, in only 10 of 43 case reports reviewed by Bhatti et al19 was surgical intervention mentioned. In the subset of 8 patients with implantable prosthetic material, survival was noted in 3 patients, all of whom underwent surgical extraction.18,19

In addition to decreasing the burden of infection and repairing mechanical lesions, surgery provides a sample for definitive diagnosis through fungal tissue stains, fungal culture, and nucleic acid amplification of tissue. These tissue samples obtained during surgery most frequently provided the evidence supporting the diagnosis in prior reports as well as in our series.19 As previously reported in endovascular *H capsulatum* infections, we noted that mycelial forms were often present on pathology slides of involved tissue. *Histoplasma capsulatum* is found in a mycelial form in soil at environmental temperatures and converts to a yeast form during mammalian infection.20 Temperature is thought to be the primary determinant of phase in *H capsulatum* through pathways involving the transcriptional regulators Ryp1, Ryp2, and Ryp3.21–23 In fact, transition from mycelial to yeast form is a major virulence determinant for *H capsulatum*. Studies have shown that *H capsulatum* can be grown as mycelial forms in vivo at 37°C, after certain chemical treatments.24 Mycelial forms in human tissue were first noted in a necrotic lung specimen in 1940 by Arthur Humphrey.25 The presence of mycelial forms may be related to an altered microenvironment producing unusual conditions of nutrition or oxygenation.26,27 Mycelial forms associated with endovascular infections were originally noted in 1955.27,28 It is not clear why mycelial forms are so common in endovascular infections, during which necrosis and lack of nutrients are less likely to play a role. Clinically, the presence of mycelial forms in vivo has the potential to cause diagnostic confusion and delay. Because hyphal forms are rarely encountered in tissue, a correlation between complement fixation titers and immunodiffusion result patterns has not been established in the literature.

<table>
<thead>
<tr>
<th>Peak Mycelial CF Titer</th>
<th>Peak Yeast CF Titer</th>
<th>Peak Urinary Antigen, ng/mL</th>
<th>Pathologic Findings</th>
<th>Antifungal Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1024</td>
<td>1:512</td>
<td>3.1</td>
<td>Yeasts and hyphal forms on valve and superficial femoral artery thrombus</td>
<td>Amphotericin B lipid complex, 8 g, now treated with lifelong itraconazole 200 mg QD</td>
<td>Alive at 5 months</td>
</tr>
<tr>
<td>1:512</td>
<td>1:512</td>
<td>1.58</td>
<td>Yeasts and hyphal forms on aortic graft</td>
<td>Amphotericin B 1.9 g, ongoing maintenance therapy with itraconazole 400 mg BID</td>
<td>Alive at 7 months</td>
</tr>
<tr>
<td>1:512</td>
<td>1:64</td>
<td>6.5</td>
<td>Yeasts and hyphal forms on aortic valve and graft</td>
<td>Amphotericin B 2 g, now treated with lifelong itraconazole 100 mg QD</td>
<td>Alive at 10 years</td>
</tr>
<tr>
<td>1:2048</td>
<td>1:512</td>
<td>2.46</td>
<td>Yeasts and hyphal forms on aortic valve, septic emboli to RCA, LIMA graft to LAD, kidney, and brain</td>
<td>Died while taking amphotericin B lipid complex, 5 mg/kg/d</td>
<td>Died before surgery</td>
</tr>
<tr>
<td>1:2048</td>
<td>1:2048</td>
<td>Not assessed</td>
<td>Yeast forms on aortic valve</td>
<td>Amphotericin B 2.4 g, did not tolerate itraconazole</td>
<td>Recovered, died 8 years later of unrelated causes</td>
</tr>
</tbody>
</table>
Noninvasive diagnostics such as fungal serology, fungal blood cultures, and urinary antigen testing were useful methods among our patients for suggesting endovascular histoplasmosis preoperatively. However, the high percentage of positive test results for our patients may be associated with the timing of these tests, that is, relatively late in the course of disease.

In summary, endovascular histoplasmosis is a rare but serious disorder and should be considered among patients with the appropriate exposure history who present with bacterial culture-negative endovascular infections and for patients with prosthetic cardiac valves or vascular grafts who present with fever of unknown origin. Serologic testing may provide a clue to diagnosis and shorten the delay in this uncommon diagnosis. Serology, urinary antigen, and fungal blood cultures should be obtained if endovascular *H. capsulatum* infection is suspected, and these tests in combination may suggest a microbial diagnosis before surgical intervention. The pathologic features of *Histoplasma* endovascular infections are notable for bland-looking fibrinous vegetations with scant inflammatory cells and absent to minimal tissue inflammatory reaction. In contrast to other sites of infection, the presence of hyphae and variably sized large spherical forms of yeasts, in

**Figure 2.** Pathology of endovascular histoplasmosis. A, Tissue section of fibrinous vegetation showing large aggregates of yeasts (2–4 μm in diameter) with basophilic cytoplasm. B, In other areas, the organisms appear as larger, round, empty-looking yeast forms. The large clear spaces represent fixation artifact in which the yeast cytoplasm contracts and the capsule does not, thus giving the impression of empty spaces. C, Typical round to oval yeasts are shown. D, Marked variation in size of the fungal organisms with large spherical and bizarre shapes (up to 30 μm in diameter) is frequently observed in this case series. This example is not in the setting of current antifungal therapy. E, Hyphal forms are also present within these active lesions. Inset shows yeast form with germ tube formation (hematoxylin-eosin, original magnifications ×400 [A and B]; Grocott methenamine silver, original magnifications ×600 [C through E] and ×1000 [inset]).
addition to the usual small oval yeasts, is commonly observed in endovascular Histoplasma infection.

References