

Central Nervous System Histoplasmosis Related to Bioprosthetic Endocarditis

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ABSTRACT

Endocarditis caused by *Histoplasma capsulatum* is a rare occurrence. Involvement of the central nervous system by *Histoplasma* is also relatively uncommon. This paper reports a case of a 62-year-old woman with a past medical history significant for a myocardial infarct 5 years prior which necessitated coronary artery bypass graft surgery, prosthetic aortic valve replacement 4 years prior, and sarcoidosis, diagnosed 1 year prior, which was treated with methotrexate. She presented with fevers, generalized weakness, night sweats, and chest and throat pain. An echocardiogram done as part of her evaluation showed a vegetation on her prosthetic aortic valve. *H. capsulatum* was identified on blood cultures, and she was started on antibiotics. She expired shortly thereafter. At autopsy, a diagnosis of *Histoplasma* endocarditis was confirmed with evidence of embolic disease involving kidneys and digits of the hand. Hilar lymph nodes showed evidence of the fungus. Examination of the brain showed multiple widespread microscopic foci of macrophages, lymphocytes, and microglial cells with associated *Histoplasma* organisms, highlighted on Gomori methenamine silver staining. This paper will discuss central nervous system involvement by *Histoplasma*.

Key words: Brain, endocarditis, histoplasmosis, prosthetic aortic valve

INTRODUCTION

Histoplasma capsulatum endocarditis infection is a rare cause of endocarditis. In two reviews of the literature, only 15 cases (6%) were identified out of a total of 270 endocarditis cases encountered in a 30-year period,^[1] and two cases (1%) were identified out of 152 in a series of cases encountered during a 6-year period of time.^[2] In prosthetic heart valves, three cases were noted in one series of 21 patients (14%), reported over an 18-year period of time.^[3] We report an unusual case of a woman with a prosthetic aortic valve who developed *Histoplasma* endocarditis and at autopsy was found to have multiple microabscesses with *Histoplasma*, due to embolic disease.

CASE REPORT

The patient was a 62-year-old female with a past medical history of hypertension, hyperlipidemia, headaches, aortic

valve replacement 4 years prior for aortic stenosis, and myocardial infarct 5 years prior requiring coronary artery bypass graft surgery. Additional prior surgical history included an appendectomy at age 19 years, splenectomy at age 38 years for spherocytosis, and a vaginal hysterectomy at age 40 years. She had been recently diagnosed with sarcoidosis a year prior and was being treated with methotrexate.

She most recently presented with complaints of generalized weakness, night sweats, and intermittent fevers of 3 months duration. Chest and throat pain precipitated a visit to the emergency room, where an elevated troponin level and electrocardiogram study suggestive of myocardial infarct was noted. A plan to do a cardiac catheterization was canceled due to a high fever and an echocardiogram was done instead, which was reported to show a mobile mass on her prosthetic aortic valve with questionable fistula and a possible aortic valve abscess. A subsequent electrocardiogram showed a sinus rhythm with first-degree atrioventricular block, occasional

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premature atrial and ventricular complexes and evidence of an antero-septal infarct of undetermined age. Blood cultures were sent and demonstrated evidence of *H. capsulatum*; the patient was started on vancomycin, ceftriaxone, rifampin, and amphotericin. Before she was able to go to surgery, the patient expired after several episodes of ventricular tachycardia.

An autopsy was performed and showed evidence of *Histoplasma* endocarditis involving the bioprosthetic aortic valve. Septic emboli were noted in the right coronary artery, internal mammary artery graft, left kidney, and second and fourth fingers on the left hand. Overall, there was cardiomegaly (heart weight 520 grams) with left ventricular hypertrophy. A remote myocardial infarct was found involving the intraventricular septum accompanied by and acute subendocardial infarct in the basal interventricular septum and multiple foci of healing microinfarcts in the left ventricle. A 3.2 cm thrombus was noted in the right atrium. Hilar lymph nodes showed evidence of histoplasmosis as well as non-necrotizing granulomas consistent with sarcoidosis.

Histologic sections of the brain showed multiple microscopic collections of macrophages, benign appearing lymphocytes, and microglial cells [Figure 1]. Gomori methenamine silver and Ziehl Neelsen stains were performed looking for evidence of microorganisms. Gomori methenamine silver staining showed multiple small intracytoplasmic structures within macrophage cytoplasm, morphologically consistent with *Histoplasma* organisms [Figure 2]. Mycobacterial organisms were not noted on the Ziehl–Neelsen staining. In addition, a 0.4 cm focus of hemorrhage was noted in the left parietal lobe cortex, and focal acute neuronal necrosis was observed in the Sommer sector region of both hippocampi.

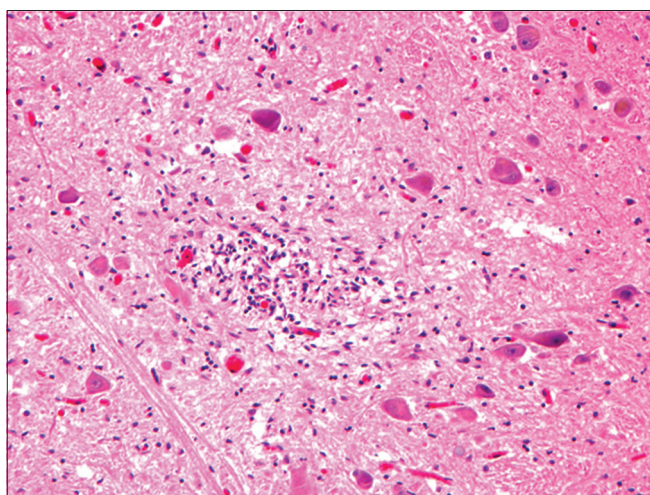


Figure 1: A small collection of macrophages, benign lymphocytes and microglial cells situated within the medulla of the brain stem (hematoxylin and eosin, original magnification $\times 200$). Multiple such lesions were seen scattered throughout the brain and brain stem

DISCUSSION

A variety of fungal organisms can cause infections in the central nervous system; the most commonly encountered of these include *Aspergillus* species and *Cryptococcus neoformans*.^[4] *H. capsulatum* is a dimorphic fungus which is known to be endemic to the Ohio Mississippi River Valley as well as certain locations in other parts of the world including Latin American, Africa, and Asia. Disease in humans is caused by inhalation of aerosolized mycelia from contaminated animal droppings and soil. In humans, the organism usually assumes a single budding yeast form that is readily phagocytosed by macrophages. In an immunocompetent host, the organism may be asymptomatic or cause mild lower respiratory symptoms. In an immunosuppressed host, as was the current patient, infection is more likely to lead to more severe symptoms and disseminated disease.^[4,5]

Central nervous system involvement in patients with disseminated disease may be seen in anywhere from 10 to 20% of cases, with the most common manifestation being meningitis.^[4,6] Other manifestations of central nervous system infection include encephalitis, myelopathy, and solitary mass-like lesion or abscess resembling neoplasms.^[4,6,7] Cases may also present as infarcts or small microabscesses secondary to septic emboli from endocarditis, as happened in the current case.^[1-4] Not surprising, symptoms attributable to central nervous system involvement are highly dependent on the nature of the underlying pathology and the extent and location of disease involvement. Immunosuppression is a major risk factor for the development of disease; this includes immunosuppressed states in the setting of AIDS, solid organ transplant, stem cell transplant and with the use of immunosuppressive agents like methotrexate, which the

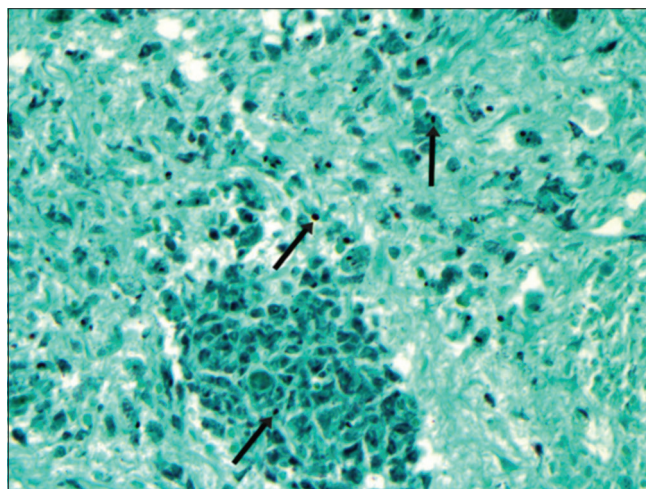


Figure 2: Gomori methenamine silver staining highlighting multiple small organisms (arrows) morphologically consistent with *Histoplasma* (original magnification $\times 400$)

current patient was taking for her sarcoidosis. About half of all central nervous system infections are associated with disseminated disease, as was evident in this case.^[4] According to Wheat *et al.*, central nervous system involvement can be seen in up to a quarter of patients who have disseminated disease, implying that not all patients with central nervous system involvement are symptomatic.^[6] The patient in the current case demonstrated no symptoms related directly to her central nervous system involvement.

In 2014, Riddell *et al.* reported on a series of 14 cases of *H. capsulatum* endocarditis; all patients in this series were male, and 10 patients had an infected prosthetic aortic valve.^[8] Four patients had neurologic symptoms including stroke and/or altered mental status, consistent with embolic disease in the brain. At 6 months follow-up, three patients had died. Wheat *et al.* reported a mortality rate of 25% overall in patients with central nervous system involvement by histoplasmosis.^[6] Response to antifungal agents is generally poor, and there is a lack of evidence-based guidelines defining what might be the most effective treatment strategy.^[4]

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