Fungal Infection of a Ventriculoperitoneal Shunt: Histoplasmosis Diagnosis and Treatment

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Key words
- Amphotericin B
- Histoplasmosis
- Ventriculoperitoneal shunt

Abbreviations and Acronyms
5-FC: Flucytosine
CNS: Central nervous system
CSF: Cerebrospinal fluid
MRI: Magnetic resonance image
VP: Ventriculoperitoneal
WBC: White blood cell

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■ BACKGROUND: **Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum,* commonly found in the Americas, and *Histoplasma duboisii,* located in Africa. In the United States, *H. capsulatum* is prevalent in the Ohio and Mississippi river valleys. In rare circumstances, central nervous system (CNS) histoplasmosis infection can be caused by shunt placement. We present a case report of a 45-year-old woman in whom CNS histoplasmosis developed after having a ventriculoperitoneal (VP) shunt placed for communicating hydrocephalus. A review of the literature on fungal infections after CNS shunt placement as well as treatment options for this subset of patients was undertaken.**

■ METHODS: **The PubMed database current to 1958 was filtered and limited to English-language articles. Fifty-eight articles were selected for review based on evidence of information regarding the fungal organism responsible for shunt infection, symptoms, treatment, and/or outcomes. Also included in this review is our case study.**

■ RESULTS: **A thorough analysis of the PubMed database revealed 58 reported cases of CNS shunt–related fungal infections in the English-language medical literature as well as 7 therapeutic agents used to treat patients in whom post-shunt fungal infections developed.**

■ CONCLUSIONS: **We describe the steps in diagnosis of histoplasmosis after shunt placement, provide an effective therapeutic regimen, and review the present understanding of CNS fungal infections. The medical literature was surveyed to compare and analyze various CNS fungal infections that can arise from shunt placement as well as treatments rendered.**

INTRODUCTION

Histoplasmosis is a dimorphic fungal disease that can be caused by either *Histoplasma capsulatum* or *Histoplasma duboisii* (25). The former is endemic to North America and South America, more prevalent in the Ohio and Mississippi river valleys. Each year, thousands of people in the endemic areas of North America are infected, with <1% becoming symptomatic (29). *H. duboisii*, on the other hand, is endemic to Nigeria and Niger (73).

Histoplasma is a fungus that exists as a dormant soil saprophyte in a hyphal phase. When inhaled, histoplasma may form small infectious yeast-like cells called micronidia within the human reticuloendothelial system (63, 72). Depending on the inoculum fraction and the immune status of the individual, the infection may present acutely or may develop insidiously with presentation of symptoms over a span of months to years (8). During the pathogenic phase, the fungi are capable of hematological dissemination from the pulmonary system to various organs. Common sites include the liver, spleen, and gastrointestinal tract (15, 29). The majority of infected organs show few to no symptoms; however, CNS and cardiac involvement increase the risk of complications (29). CNS dissemination is limited to the meninges, the spinal cord, and the brain. Patients may present with subacute or chronic meningitis, spinal or focal brain lesions, strokes, and encephalitis (75). Clinically, this pattern of dissemination is recognized in 10% to 20% of histoplasmosis cases (74). In the same study, Wheat et al. found that fever occurred in almost every case of disseminated CNS histoplasmosis (n = 104), as well as other neurological findings such as a depressed level of consciousness in 28.8%, headaches in 24%, cranial nerve deficits in 19.2%, and seizures in 13.5%.

In addition to *H. capsulatum*, other fungal organisms known to disseminate to the CNS include *Candida* species (38), *Cryptococcus neoformans* (34), and *Aspergillus* species (28). Persistent chronic meningitis and parenchymal lesions are classic examples of ways in which chronic histoplasmosis with CNS involvement may present. On the other hand, primary CNS fungal infection after shunt placement is rarely reported (57). Here we present a 45-year-old woman in whom CNS histoplasmosis developed due to the placement of a ventriculoperitoneal (VP) shunt for the treatment of communicating hydrocephalus. We discuss the presenting symptoms, the diagnosis of the infectious agent, and an effective treatment regimen. Furthermore, we survey the current medical literature to develop a consensus

regarding symptoms, outcomes, and efficacious treatment for shunt-related fungal infections.

CASE REPORT

Ms. S. is a 45-year-old woman who upon initial presentation suffered from persistent headache, neck stiffness, unsteady gait, and poor memory. A thorough history and physical was completed, and no clinical evidence of systemic illness or infection was noted. The patient did not report having spent time in an area endemic to histoplasmosis and was not noted to be immunocompromised. The patient did not complain of fevers, chills, or fatigue. Given her worsening condition, a computed tomography scan of the head was completed, which revealed moderately dilated bilateral third and fourth ventricles consistent with communication hydrocephalus. A magnetic resonance image (MRI) with and without contrast was obtained, and did not show evidence of infection, tumors, or other ominous pathology. A lumbar puncture was performed in a clinical setting, and an opening pressure of 25 was noted. Cerebrospinal fluid (CSF) cytology, cell count, protein, glucose, and culture remained negative. Preoperative white blood cell (WBC) and clotting examination results were within normal limits.

After a thorough clinical evaluation, it was decided that the patient was suffering from communicating hydrocephalus and would benefit from elective placement of a VP shunt. Immediately after placement, the patient recovered well and felt alleviation of headache and mild restoration of gait. Unfortunately, on postoperative day 2, Ms. S. began experiencing fever of 103.4°F, reduced appetite, fatigue, and nausea. Her physical examination included photophobia, nuchal rigidity, and an unstable gait. It was suspected that the patient was suffering from meningitis, and to narrow the differential, a lumbar puncture was performed. Laboratory results of her CSF showed CSF WBC 17, lymphocytic pleocytosis, protein of 80, and hypoglycorrhachia of 24. At the time, Gram stain was positive for lymphocytes; however, no organisms were seen. The infectious disease team was consulted and broad-spectrum antibiotics were started; however, the patient continued to decompensate.

It was our suspicion that the VP shunt was contaminated and required removal. After operative removal, the VP shunt tip was sent for culture and a diagnosis of histoplasmosis infection was made less than 24 hours after the shunt tip began to culture (*H. capsulatum*). In our case, no hematological markers were used to diagnose the infection—rather, a positive instrumentation culture identified the organism.

Initially Ms. S. was treated with 300 mg itraconazole twice daily; however, she reported significant side effects, including nausea and lethargy. The CNS pleocytosis persisted, and for that reason, intravenous Abelcet (Enzon Pharmaceuticals, Inc., Piscataway, New Jersey, USA), the lipid complex form of amphotericin B, was administered. The patient was continued on intravenous Abelcet at 5 mg/kg/day. A repeat lumbar puncture revealed significant improvement of the pleocytosis and elevation of the low glucose levels, although the CNS protein levels remained elevated. The patient also noted nausea related to the required potassium supplementation taken orally with Abelcet. The fever and headache had been relieved, and the patient continued Abelcet therapy for 6 months.

A final lumbar puncture was performed to track treatment efficacy. The CSF was clear and colorless with normal WBCs, red blood cells, protein, and glucose. On physical examination no papilledema, pronator drift, unsteady gate, or nuchal rigidity was observed. Therapy was then switched from Abelcet to oral itraconazole 200 mg 3 times daily. An MRI with and without contrast obtained at follow-up showedd a slight interval increase in the size of the lateral ventricles with evidence of transependymal flow, likely related to the original presenting hydrocephalus.

The patient continued antifungal therapy at the discretion of the infectious disease team. Lumbar punctures were performed to track treatment efficacy, and the patient eventually underwent an uncomplicated placement of a ventriculoperitoneal shunt.

METHODS

The PubMed database current to 1958 was filtered using the search terms histoplasmosis in CNS, fungal infections with VP shunts, shunt-related fungal infections, histoplasmosis, and brain histoplasmosis. This search was also limited to English-language articles and human studies only. A thorough analysis of the PubMed database revealed 58 reported cases of shunt-related fungal infections in the English-language medical literature. Thirty-three articles were selected for review based on evidence of information regarding the fungal organism responsible for shunt infection, symptoms, treatment, and/or outcomes (Table 1). The mean patient age from our literature search was 28.3 years (4 ages were not documented), and the patients' ages ranged from 1 month to 79 years. A slightly higher proportion of men (28 of 52, 53.8%) than women were affected by shunt-related fungal infections. Ventriculoperitoneal shunts (41 of 54, 75.9%) were also more commonly the source of infection than ventriculoatrial (VA) shunts (7 of 54, 13.0%). Other shunts infected in decreasing order were external ventricular shunts (n = 4), a cystoperitoneal shunt (n = 1), and a lumbar drain (n = 1). Of the fungal species that could colonize shunts, the prominent agent responsible was *Candida* species (42 of 56, 75.0%). For other fungal organisms, *C. neoformans* had the next highest incidence of infection (8 of 56, 14.3%) followed by *H. capsulatum* (2 of 56, 3.57%). Each of the following was reported only once in shunt-related infections: *Aspergillus* species, *Blastomyces dermititidis*, *Coccidioides immitis*, and *Paecilomyces variotii* (Table 1).

In regard to common presenting symptoms, emesis (11 of 43, 25.6%), headaches (10 of 43, 23.3%), and fevers (24 of 43, 52.2%) were most prevalent. Amphotericin B was preferentially used to treat the variety of fungal infections seen in shunts (43 of 48, 89.6%). Also frequently used were 5-flucytosine (12 of 48, 25.0%) and fluconazole (10 of 48, 20.8%). Other notable drugs were itraconazole (n = 2), ketoconazole (n = 2), and gentian violet (n = 1). The only drugs used without concomitant amphotericin B administration were fluconazole (n = 4), itraconazole (n = 1), and gentian violet (n = 1). The intravenous route was the most common administered form of amphotericin B (42 of 43, 97.7%), followed by an intraventricular method (9 of 42, 21.4%), then intrathecal (6 of 42, 14.3%), and lastly through an Ommaya (1 of 42, 2.38%). With respect to outcomes, improvement occurred in 76.5% (40 of 51)