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An instructive case of CNS *histoplasmosis* in an immunocompetent host

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ABSTRACT

Histoplasma capsulatum is a dimorphic endemic fungus which infects both immunocompetent and immunocompromised hosts. Isolated CNS *histoplasmosis* is a rare presentation with increased risk in individuals with impaired cellular immunity, however not all patients with this condition are immunocompromised. We report a case of isolated CNS *histoplasmosis* in an otherwise healthy immunocompetent patient who was initially treated with Liposomal Amphotericin B followed by oral Voriconazole and later Itraconazole with significant improvement in clinical status.

1. Introduction

Histoplasma capsulatum is a fungal infection commonly seen in immunocompromised, especially transplant and HIV patients, however its occurrence in immunocompetent patients has long been reported prior to the AIDS epidemic. The clinical presentation in immunocompetent patients can range from a benign subclinical course to life threatening meningitis.

H. capsulatum is a dimorphic fungus which is present worldwide in distribution, but is endemic to many parts of North and Latin America. **A vast majority of exposed individuals in endemic areas have a mild self remitting illness which goes undiagnosed and only a few patients (< 1%) develop clinically apparent infection mainly acute respiratory symptoms and rarely produce CNS symptoms which might range from acute meningitis to stroke to ring enhancing lesions to chronic meningitis**.

CNS involvement in *histoplasmosis* is either a manifestation of disseminated infection or an isolated focal infection. CNS involvement has been reported in 5–10% of cases of disseminated *histoplasmosis*, but isolated CNS *histoplasmosis* is rare. The risk of developing CNS *histoplasmosis* is increased in individuals with impaired cellular immunity, but not all patients with this condition are traditionally immunocompromised [1,2]. We report an instructive case of Isolated CNS *histoplasmosis* in an otherwise healthy immunocompetent patient who presented with headaches and altered mental status.

2. Case

A 35 year old Caucasian male was admitted on day 0 with complaints of altered mental status (short term memory loss), weakness, headaches, vomiting for 3 day. Patient had been recently admitted to an outside hospital 2 weeks ago with Upper Extremity weakness, dysarthria and was diagnosed with pontine stroke secondary to small vessel vasculitis after initial work up. He improved with steroids, therefore was discharged to a skilled nursing facility for rehabilitation on tapering doses of steroids. Patient completed last dose of prednisone 2 day prior to this admission when he started experiencing above symptoms.

On physical examination his temperature was 100.2 °F, heart rate 106, Respiratory rate 18, Blood pressure 138/82 mm Hg, oxygen saturation of 99% on room air. On general examination he was awake, alert, oriented to person, but not to place or time. Pupils were equal round and reactive to light and accommodation. Heart sounds were regular, well heard, with no murmurs or rubs, lungs were clear to auscultation, abdomen was obese, non-tender with normal bowel sounds. On neurological exam Cranial nerves were intact, with no facial asymmetry, no aphasia or dysarthria, no nuchal rigidity, strength was 5/5 in all extremities; sensations both to light, deep touch were intact. On cerebellar exam there was Left more than Right appendicular ataxia, but no gait ataxia.

His laboratory work up on day 0 included WBC 15.7 k/cmm, H/H 15.8/45.9 g/dl/% platelet count of 195 k/cmm, neutrophils 88%, Lymphocytes 5%, monocytes 5%. CMP was within normal limits. HIV serology was negative. CSF was done on day 1, was clear and colorless with WBC's of 330/mm^3, RBC's 0/mm^3, neutrophils 65%, lymphocytes 24%, Protein 320 mg/dl, glucose 2 mg/dl, gram stain on CSF and culture were negative. Work up included HSV PCR,

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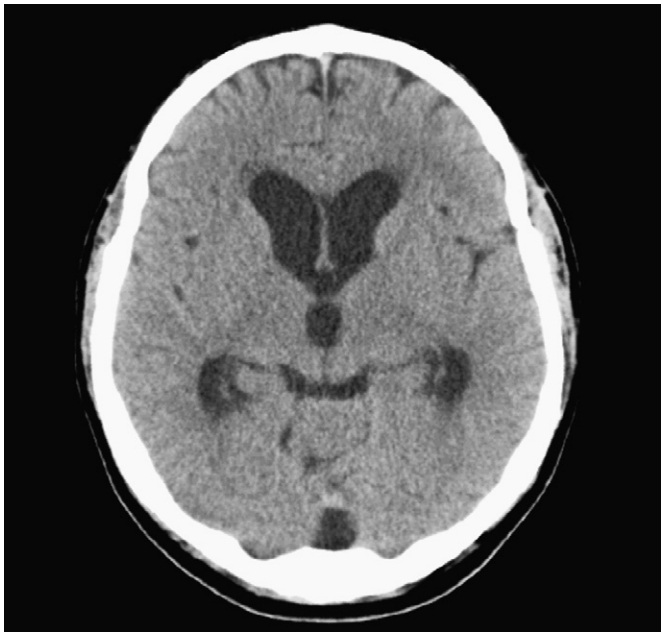

Fig. 1. CT Brain showing communicating hydrocephalus.

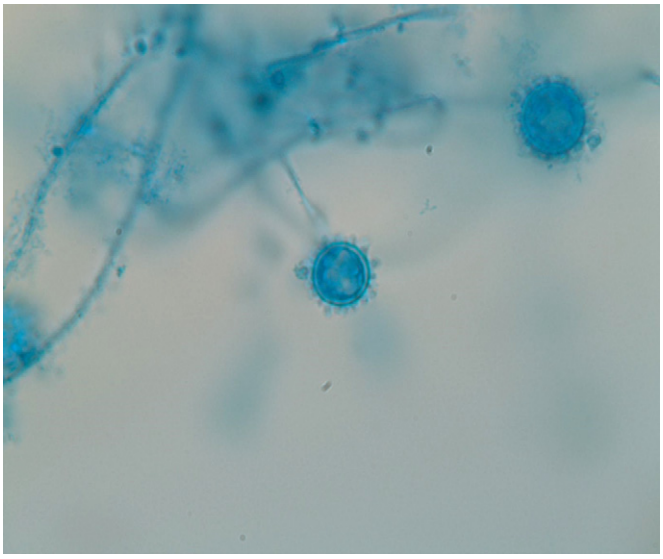

Fig. 2. Fungal culture showing classic macroconidia (tuberculate), grown on medium at room temperature.

Enterovirus PCR, Cryptococcal Ag, VDRL on CSF which were negative; Westnile virus serology, Arboviral serology, Coccidioides serology, Lyme Antibody, Toxoplasma serology in serum which were negative and Quantiferon which was indeterminate. Subsequent CSF analysis done on day 3, 8, 14, 15, 16 and 17 showed persistent CSF pleocyctosis with neutrophilic predominance but with improving WBC count and hypoglycorrhachia.

Imaging on day 0 included CXR which was normal and CT of his brain without contrast which showed communicating hydrocephalus (Fig. 1) followed by MRI of Brain with and without contrast on day 1 which showed recent infarct superimposed on remote infarcts of the Pons and Communicating hydrocephalus.

Further work up on day 14 included Urine HPA (<0.6 ng/ml) which was low positive, Serum HPA <0.6 ng/ml (low positive), a negative Serum Anti-Histoplasma Antibody but a CSF HPA which was highly positive at >39 ng/ml. Patient was diagnosed with CNS *histoplasmosis*. Fungal cultures of CSF were positive for *H. capsulatum* on day 22 (Fig. 2). Blood and bone marrow fungal cultures were negative.

Patient had waxing and waning mental status in the hospital l due to worsening hydrocephalus, requiring placement of an External ventricular device followed by Ventriculoperitoneal shunt on day 19. He was initially treated with 2 weeks of Liposomal Amphotericin *B* at a dose of **3 mg/kg/day** starting from day 14th of admission followed by Voriconazole at **200 mg orally twice daily** along with tapering doses of prednisone. Although initially planned to treat patient with 4–6 weeks of Liposomal Amphotericin B duration was shortened to 2 weeks due to development of nephrotoxicity. Patient's mental status and weakness improved while on treatment and was discharged to a nursing home for rehabilitation on prolonged course of Voriconazole on day 37.

Patient followed up at the infectious diseases clinic on day 120 and periodically thereafter and was noted to have neurological improvement both subjectively and objectively. Due to development of skin rash with Voriconazole nearly 330 day (11 months) into treatment and due to the persistence of Lymphocytic predominant leucocytosis in the CSF along with elevated protein and low but improving glucose levels on follow up, Voriconazole was switched to oral Itraconazole **at a dose of 200 mg orally twice daily** after 11 months of Voriconazole. Patient was continued on Itraconazole to date (day 540) due to persistant but improving CSF parameters. Last CSF analysis performed almost 540 day into treatment showed WBC 28/mm^3, RBC 2/mm^3, Protein 208 mg/dl, Glucose 50 mg/dl, Neutrophils 3%, Lymphocytes 84% and Monocytes 13%. Repeat Fungal culture starting from day 25 of admission was negative. Patient had complete resolution of symptoms and repeat CSF HPA which was done around day 180 was non-detectable. Follow up MRI of the brain on day 270 showed decompressed hydrocephalus with normal ventricular size and no new ischemic brain lesions.

3. Discussion

H. capsulatum is a dimorphic fungus, present worldwide in distribution, but mostly endemic to many parts of North America, especially seen along the Ohio and Mississippi river valleys. CNS *histoplasmosis* is most commonly a manifestation of disseminated disease and Isolated CNS *histoplasmosis* is a rare presentation especially in immunocompetent patients.

Although CNS *histoplasmosis* is increased in individuals with impaired cellular immunity, about 20–30% of patients with this condition are immunocompetent. The most common manifestation of CNS *histoplasmosis* is chronic meningitis which is characterized by basilar meningeal involvement that can lead to communicating hydrocephalus. Less common presentations include Acute Meningitis, Encephalitis, small ring-enhancing lesions throughout the brain and spinal cord (with and without meningeal involvement), larger more typical brain abscesses and stroke due to infected emboli.

Symptoms range from headache, mental status changes, cranial nerve palsies, behavioral changes and ataxia. CSF changes with meningitis are similar to those noted for other fungal meningitides and tuberculous meningitis. White blood cells usually range between 50 and 500 cells/μl, which are predominantly mononuclear. CSF Protein is usually elevated with modestly low glucose [2].

The diagnosis of Isolated CNS *histoplasmosis* could be difficult with negative Urine HPA misleading the diagnosis. The sensitivity of HPA which is around 90% in urine and 80% in the serum of patients with disseminated *histoplasmosis* is predicted to be much

less with isolated CNS *histoplasmosis*. HPA is found in the CSF of 25–50% of patients with chronic meningitis caused by *histoplasmosis*. Higher antigen values in the CSF sample than in serum or urine samples is consistent with antigen production in the CNS, rather than passive diffusion from the serum in the presence of a breakdown of the blood brain barrier or contamination of the CSF with blood caused by a traumatic lumbar puncture [1]. CSF cultures may be positive in only 10–30% of cases [3]. There is no single test with high sensitivity, which supports the use of multiple tests.

Optimal treatment for CNS *histoplasmosis* is unclear. No prospective studies with an evidence based approach are available. Polyene antifungal and Azoles are the available options. IDSA (Infectious Diseases society of America) guidelines recommend Liposomal Amphotericin B at a dose of 5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks followed by Itraconazole 200 mg 2 or 3 times daily for at least 1 year and until resolution of CSF abnormalities, including HPA [4].

Liposomal Amphotericin B achieves higher concentrations in brain tissue than does the standard deoxycholate formulation and is associated with less toxicity and improved survival [3,5]. Itraconazole is the recommended azole but its poor tolerance and variable bioavailability makes it less desirable.

Fluconazole is associated with high failure rates due to resistance associated with reduction in susceptibility of cytochrome P450-dependent enzymes 14α-demethylase (CYP51p) and 3-ketosteroid reductase to Fluconazole [6]. Newer azoles including Voriconazole and Posaconazole have promising outcomes in treatment of *histoplasmosis*. Voriconazole has been shown in several reports to have successful treatment outcomes for the treatment of CNS *histoplasmosis* [6–8]. In patients who received previous Fluconazole therapy there is a risk of cross resistance to Voriconazole.

Antifungal therapy is recommended for up to 12 months in immunocompetent patients. Despite appropriate therapy there is risk of failure and relapse which warrants long term suppressive therapy [3].

Conflict of interest

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