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Case report

A fungal nightmare: A rare and deadly presentation of disseminated histoplasmosis

Amal Naji *, Martin Baxter, Alex Kumi, Jan Camille Ozaeta, Nicole Onuoha, Danhely Cruz-Vasquez, Olawole Akinboboye, John-Paul Papadopoulos, Zola Nlandu

Department of Internal Medicine, Piedmont Athens Regional, GA, USA

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ABSTRACT

Histoplasma capsulatum is a dimorphic fungus commonly associated with localized pulmonary disease but can often spread to various organs causing disseminated histoplasmosis. Once the disseminated disease reaches the central nervous system (CNS), mortality rates increase significantly and can reach up to 40 %. The prognosis is frequently determined by adequate and timely diagnosis. Treatment often includes amphotericin B for a total of 4–6 weeks followed by itraconazole for at least 1 year. Herein, we present the case of a 65-year-old male who initially presented with worsening headaches and was later found to have disseminated histoplasmosis.

Introduction

Histoplasmosis is the most prevalent endemic mycosis in the United States [1]. It is caused by Histoplasma Capsulatum, a dimorphic soil-based fungus, found mainly in the Mississippi and Ohio river valleys [2]. Although the majority of those exposed to H.capsulatum develop a subclinical infection, host immunodeficiency is often associated with a more morbid clinical course. Localized infection primarily affects the lungs and can cause disseminated granulomatous infection, with considerable morbidity and mortality [3]. We present a case of a seemingly healthy middle-aged male with recent travel to the Midwest, who initially presented with headache that has been worsening for the past few months. Later in the admission, patient had altered mental status and was found to have disseminated histoplasmosis. The patient eventually developed obstructive hydrocephalus and catastrophic brainstem and basal ganglia infarcts which ultimately led to his death. Herein, we discuss his presentation and the multi-specialty approach to investigation and treatment.

Case presentation

A 65-year-old male construction-worker with a past medical history of atrial fibrillation status post cardioversion, coronary artery disease and primary hypertension presented to our facility complaining of worsening headaches.

One month prior to his most recent presentation, he had presented to our facility with intractable headaches and lethargy, and subsequent computed tomography (CT) brain scan revealed a 1 cm hypodensity in the cerebellum. He was later evaluated by an oncologist, who ordered CT chest, abdomen and pelvis to evaluate for metastasis. The pan-CT revealed numerous sub centimeter cysts in the liver, a cyst in the spleen and one in the kidney, none of which were suggestive of malignancy. He was discharged with a plan for outpatient positron emission tomography (PET) scan, which subsequently showed a tiny left adrenal nodule with mild-moderate hypermetabolic activity. In the interim, he was prescribed dexamethasone, which provided relief for a brief period. However, a week later, symptoms recurred with increased severity leading to representation to hospital.

During this admission, the patient was initially able to provide most of his history and mainly complained of nausea and vomiting with poor oral intake. His labs were remarkable for leukocytosis with a white blood cell (WBC) count of 18,100/uL, normocytic anemia with hemoglobin of 10 g/dL, and hyponatremia (121 mmol/L). Hepatic panel showed aspartate aminotransferase(AST) of 22 U/L and Alanine aminotransferase (ALT) of 53 U/L. Later during admission, he had an acute decompensation with altered mentation, fevers, and inability to protect airway. Patient was intubated and then transferred to the intensive care unit (ICU) team. In the ICU, the patient was noted to have absent brainstem reflexes as well as prominent anisocoria, which prompted a neurology and neurosurgery evaluation. At first, osmotic demyelination syndrome was considered among the possible differential diagnoses; however, it was thought to be less likely. Therefore, lumbar

* Correspondence to: Piedmont Athens Regional Medical Center, 1199 Prince Avenue, Athens, GA 30606, USA.
E-mail address: amal.naji@piedmont.org (A. Naji).

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puncture and bronchoscopy were performed. The cerebrospinal fluid (CSF) studies revealed 535 cells/mm3 nucleated cells with a differential of 6 % lymphocytes and 89 % neutrophils, > 200 mg/dl protein, and 17 mg/dl glucose. A meningitis/encephalitis biofire panel that includes common organisms involved in CSF infections was ordered and was unremarkable. Moreover, CSF fungal culture was ordered and did not show any growth. HIV screen was negative. Patient was thought to be a diagnostic dilemma because his clinical picture did not fit any of the typical infectious, malignancy or autoimmune diagnosis. Workup was done to rule out aspergillus, toxoplasma, cysticercosis, coccidioides, tuberculosis, toxoplasmosis, and HSV. He was also started on broad spectrum antibiotics and acyclovir. Patient's mental status continued to deteriorate and he was therefore placed on the RIPE regimen to cover for possible tuberculosis meningitis, though he did not have significant risk factors. After discussion with the patient's family, a decision was made to proceed with a bronchoscopy and bronchoalveolar lavage n the 9th day of ICU admission. His bronchoalveolar lavage cytology revealed growth of budding yeast. Therefore, histoplasma serum serology and urine antigen tests were ordered. The antibodies were unremarkable but the urine antigen tested positive. At this time, empiric treatment for tuberculosis was discontinued. He was started on liposomal amphotericin B for disseminated histoplasmosis. Eventually, the patient passed away (Fig. 1).

Imaging

CT head without contrast on admission revealing a peripherally hyperdense centrally cystic right cerebellar lesion measuring 11 × 9 mm with no extra-axial collection (Fig. 2). An MRI of the brain 3 days following revealed interval development of areas of restricted diffusion along the posterior limbs of the internal capsules (right greater than left), right thalamus and patchy areas of restricted diffusion in the pons along with additional interval development of mild hydrocephalus and layering fluid in the occipital horns. A repeat MRI of the brain several days later revealed extensive restricted diffusion with mild ventriculomegaly associated mild enhancement along the surface of the lateral ventricles (Fig. 3) along with evidence of hydrocephalus (Fig. 4) and diffuse decreased caliber of the intracranial arterial vasculature clinically suspicious vasospasm.

Discussion

Disseminated histoplasmosis, caused by the dimorphic fungus Histoplasma Capsulatum, primarily affects individuals in regions with high exposure rates, such as the Ohio and Mississippi River valleys [4–6]. While the majority exposed to low levels of histoplasma remain asymptomatic, the clinical presentation varies based on the extent of exposure and host characteristics [4].

Histoplasma resides in soil and bird or bat droppings, often leading to pulmonary infections when inhaled. For those who develop symptoms, they may range from mild to severe pneumonia. Dissemination can occur, affecting various organs, including the central nervous system, where it can be fatal. CNS histoplasmosis is a rare occurrence however when present is often associated with a mortality rate of up to 20–40 % and a relapse rate of 50 % [7–9]. Therefore, early diagnosis is essential to positively affect the clinical outcome.

Interestingly, our patient did not have evidence of prior diagnosis of immunosuppression. Moreover, his symptoms were very nonspecific leaving the entire medical team in a diagnostic dilemma. Prior to presentation, he had workup for metastatic disease and was started on dexamethasone by an oncologist. However, his clinical course eventually became more complex, and the patient was completely obtunded. He was later found to have multiple brain lesions. By the time a diagnosis of histoplasmosis was made, the patient had evidence of hydrocephalus and then cerebral vasospasm. Eventually, the patient passed away.

Upon reviewing the literature, several case reports have emphasized on the common misdiagnosis of disseminated histoplasmosis as a primary hematologic malignancy [10]. This misdiagnosis frequently delays detection and ultimately worsens prognosis. Therefore, attention to details and the identification of unique features of disseminated histoplasmosis is key to saving a patient's life. Of interest, 80 % of the cases involve adrenal glands [11,12]. Moreover, CNS lesions often present as multiple ring enhancing lesions. These ring-enhancing lesions were seen on the CT brain images of our patient. The presence of multisystem involvement especially in the appropriate demographic setting should prompt physicians to consider histoplasmosis among the possible diagnoses [8]. However, histoplasmosis is frequently missed because it is not a common diagnosis. Our case demonstrates the importance of a comprehensive evaluation because histoplasmosis was not among our differential diagnoses initially. However, we ordered further investigations to confirm the diagnosis after the BAL grew budding yeasts.

When suspecting histoplasmosis, clinicians frequently order histoplasma urine antigen tests because it is a rapid test that often results in a few hours to days. Despite the high sensitivity and specificity associated with this test, the gold standard remains culture followed by histopathology. In our case, the patient had a positive histoplasma urine antigen however diagnosis was confirmed by bronchoalveolar lavage and cerebrospinal fluid culture [13,14].

The prognosis of disseminated histoplasmosis is dependent on the timing of the diagnosis and initiation of treatment. Early initiation of treatment is often associated with a survival rate as high as 74 %. In the presence of CNS involvement, treatment frequently includes liposomal amphotericin B for a total of 4–6 weeks followed by itraconazole for at

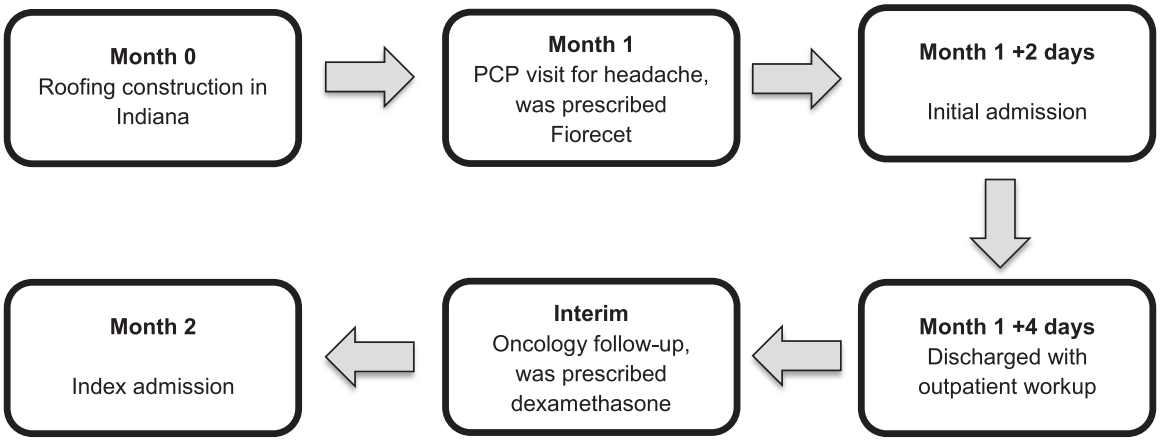

Fig. 1. Timeline of clinical presentation.

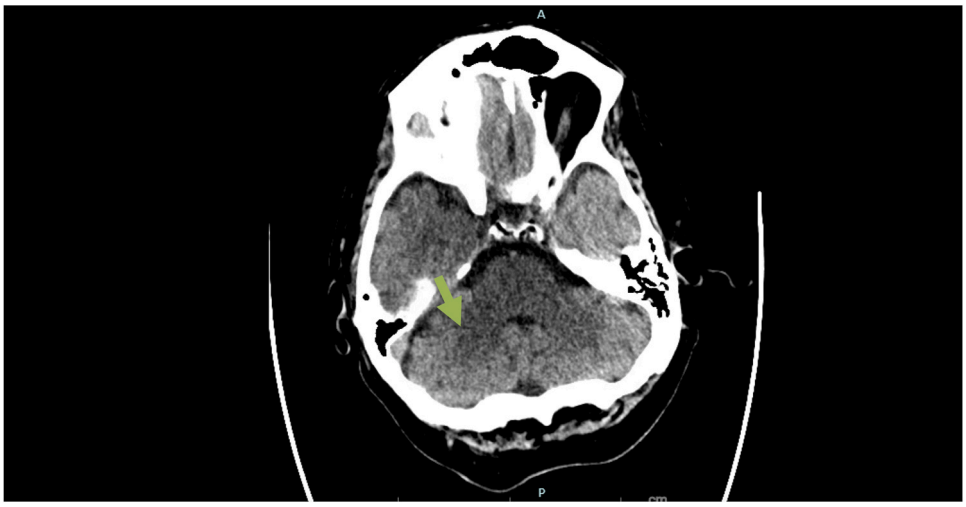

Fig. 2. CT head WO contrast revealing an indeterminant centrally cystic right cerebellar lesion.

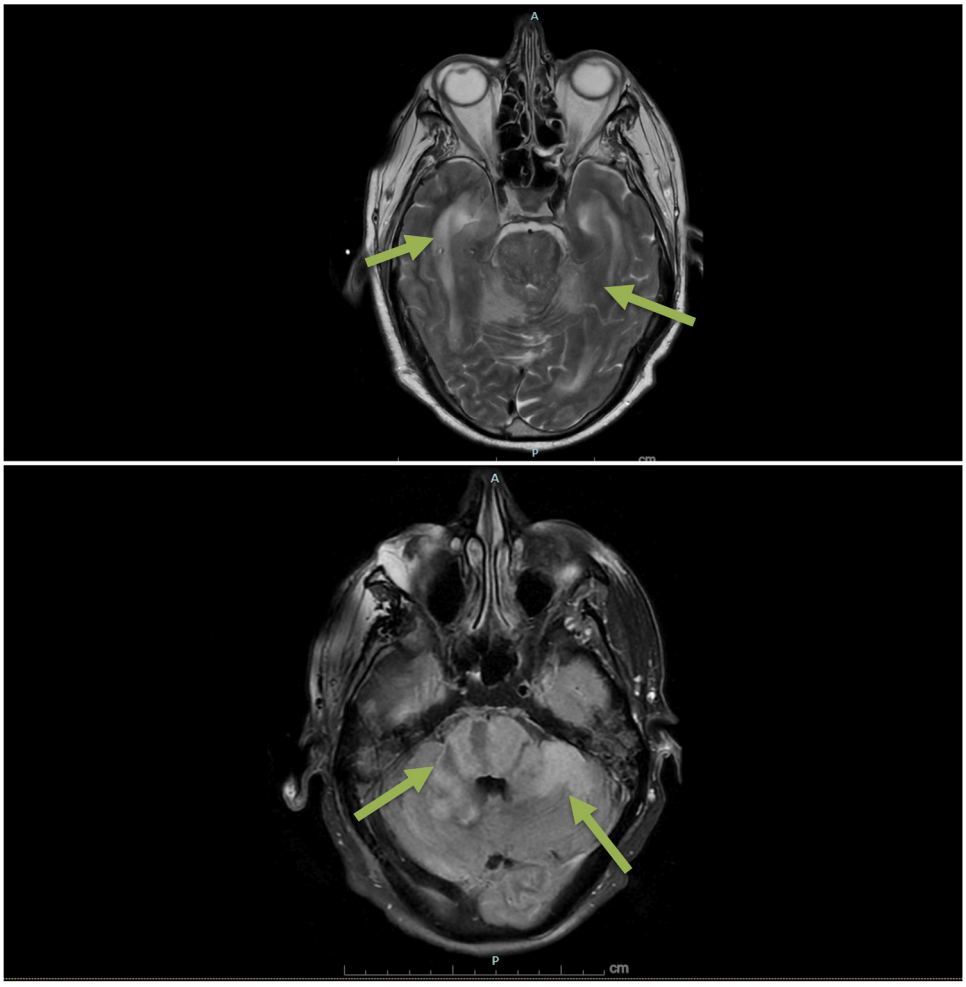

Fig. 3. T2 a brain MRI with and without contrast revealing extensive restricted diffusion.

least one year. Studies have also shown that several patients achieve complete recovery and are able to regain normal functional statuses if treatment is initiated promptly. Only 14 % of the patients that were adequately treated had severe functional impairment at follow-up, and these patients were mostly immunocompromised [10,15,16]. Therefore, we present this case to increase physician awareness and recognition of this disease in order to ensure early initiation of treatment.

Conclusion

In conclusion, disseminated histoplasmosis is commonly misdiagnosed. Early initiation of treatment plays a crucial role in improving

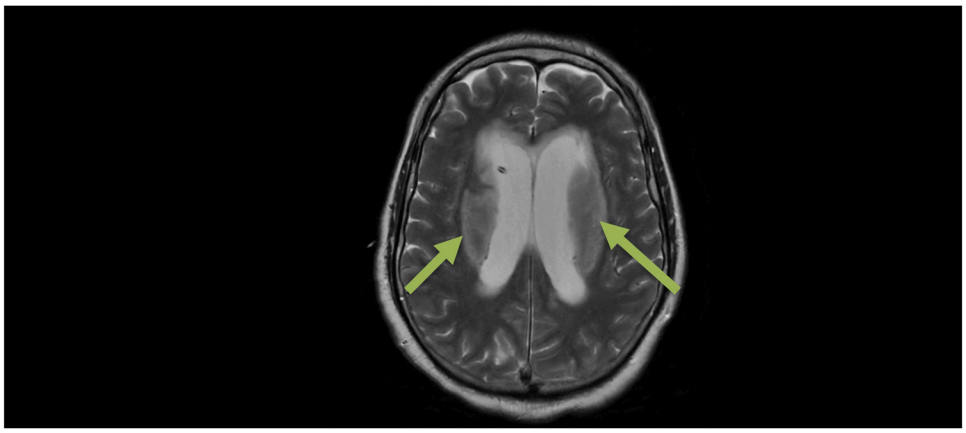

Fig. 4. MRI brain revealing evidence of hydrocephalus.

the survival rate. We presented a rare case of an older adult male who presented with an atypical clinical picture and was later found to have disseminated histoplasmosis.

CRediT authorship contribution statement

Olawole Akinboboye: Resources, Conceptualization. **John-Paul Papadopoulos:** Writing – review & editing, Supervision. **Zola Nlandu:** Writing – review & editing, Supervision. **Amal Naji:** Writing – review & editing, Writing – original draft, Conceptualization. **Martin Baxter:** Writing – original draft. **Alex Kumi:** Writing – original draft. **Jan Camille Ozaeta:** Writing – original draft. **Nicole Onuoha:** Writing – original draft, Conceptualization. **Danhely Cruz-Vasquez:** Resources, Conceptualization.

Authors statement

We, the authors of the manuscript titled "A Fungal Nightmare: A Rare and Deadly Presentation of Disseminated Histoplasmosis "hereby submit this work for consideration for publication in ID Cases.

Our research contributes to the field of infectious diseases by describing a rare case of disseminated histoplasmosis.

We confirm that this manuscript is original and has not been published previously, nor is it currently under consideration for publication elsewhere. All authors have contributed significantly to the conception, design, data acquisition, analysis, and interpretation, and have approved the final version of the manuscript for submission.

We have followed all ethical guidelines and regulations regarding the conduct of research involving human subjects and/or animals and have obtained all necessary approvals and informed consent where applicable.

We believe that our work will be of interest to the readership of ID Cases and will contribute to the dissemination of knowledge in the field of infectious diseases.

Consent

Verbal informed consent was obtained from the patient's wife for publication of this case report and accompanying images.

Ethical approval

None needed.

Funding

None.

Conflict of Interest

None.

Declaration of Competing Interest

All authors have no competing interests to declare.

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