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Case Report

Atypical presentation of progressive disseminated histoplasmosis in a patient recently diagnosed with AIDS

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ABSTRACT

Opportunistic infections, including progressive disseminated histoplasmosis (PDH), may have variable and surprising presentations in patients with AIDS. This can be either a primary infection or reactivation of a latent infection. Latent infections may occur due to being unmasked by the immune reconstitution inflammatory syndrome after the initiation of combined antiretroviral therapy. PDH can be difficult to diagnose in patients with AIDS due to its variable presentation and many overlapping symptoms with other opportunistic infections. Serum and urine antigen testing are highly sensitive and typically used as the initial diagnostic test to workup suspected PDH. However, negative antigen and antibody tests do not rule out *Histoplasmosis capsulatum* infection and suspicion should remain high for PDH in the right clinical context. A definitive diagnosis may require biopsy-proven narrow-based budding yeast. We present an interesting patient with AIDS who presented with worsening cognitive decline and was ultimately diagnosed with PDH based on biopsy histopathology in the setting of negative antigen and antibody testing.

Introduction

Histoplasmosis capsulatum is a fungus responsible for causing progressive disseminated histoplasmosis (PDH), one of the most common endemic mycoses in the HIV/AIDS population [1]. Although relatively benign to the immunocompetent population, patients who are immunosuppressed can present with severe disseminated disease [2].

The diagnostic workup for suspected infection begins with serum and urine antigen testing [3]. If suspicion remains high but noninvasive testing is negative, a tissue biopsy is obtained from the anatomic site of concern. The presence of narrow-based budding yeast from a biopsy can confirm the diagnosis [2]. In this report, we describe a unique case of PDH in a patient with AIDS based on the hard palate and lymph node biopsies in the setting of negative antigen and antibody tests.

Case summary

A man aged 62 years who was living in Detroit, Michigan presented to the emergency department for 3 months of worsening fatigue, cognitive decline, and recurrent falls. At this time, he was diagnosed with HIV. Initial clusters of differentiation 4 (CD4) count was 82 cells/μl and his HIV viral load was 1,896,419 copies/ml. Workup included magnetic resonance imaging (MRI) of the brain and spine, computed tomography (CT) of the chest, and an X-ray of the spine. MRI showed mild atrophic and periventricular white matter changes. CT chest showed a nonspecific 0.9 × 0.8-cm mediastinal lung nodule, and a mildly enlarged 1.3-cm right hilar lymph node. Sputum qualitative real-time polymerase chain reaction (PCR) was positive for *Pneumocystis jirovecii*, and the patient was started on trimethoprim-sulfamethoxazole. Also, a β-D-glucan assay was >500 pg/ml, indicating a likely fungal infection. *H. capsulatum* urine antigen was negative. He started combined antiretroviral therapy (cART) with bictegravir, emtricitabine, and tenofovir alafenamide. A month after starting cART, he presented back to the emergency department. Per his wife, his fatigue and cognitive decline worsened despite his adherence to cART. In addition, she

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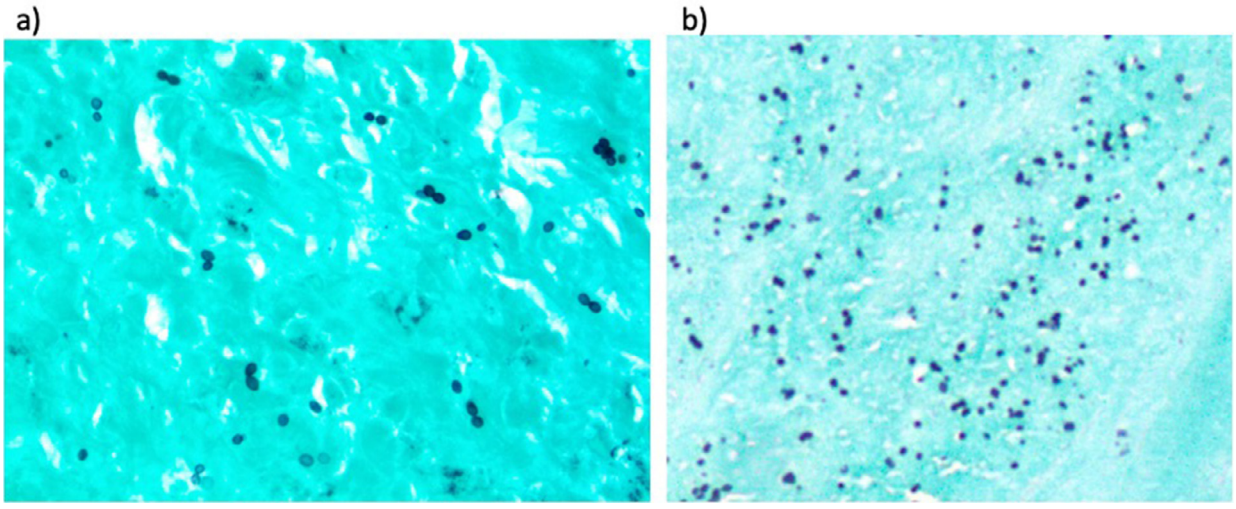

Figure 1. Methenamine silver stain showing budding yeast forms from the biopsies of the (a) oral palate and (b) retropharyngeal lymph node.

confirmed that he spent several months in Mexico City, Mexico in the last 2 years for his work as an engineer. It was unknown if he had exposure to pigeons or bats. He was admitted to the infectious disease floor for further evaluation.

Upon admission, a broad workup was initiated to determine if his symptom progression was due to HIV-associated opportunistic infections, including HIV encephalopathy. The repeat CD4 count was 233 cells/µl, and his HIV viral load was 902 copies/ml. A neurologic exam revealed diffusely brisk reflexes, but normal muscle strength in all four extremities. He was drowsy and unable to follow commands or answer questions. An examination of the oral cavity revealed a right-sided, friable, irregular-appearing mass of the hard and soft palates, which prompted a biopsy.

On day 3, the patient became acutely confused and developed nuchal rigidity and photophobia, prompting further radiologic evaluation. Diffusion-weighted brain MRI revealed diffuse high signal intensity, central and parietal lobe atrophy, and mild ventriculomegaly, due to either vasculitis or meningitis. There was no leptomeningeal enhancement, masses, or fluid collection. CT of the head showed a subacute stroke in the right basal ganglia, but CT angiography was unremarkable. CT of the neck revealed a left-sided necrotic retropharyngeal lymph node, which prompted a second biopsy. Cerebrospinal fluid (CSF) analysis from a lumbar puncture showed an opening pressure of 12 cm water, glucose of 58 mg/dl, elevated protein of 161.2 mg/dl, and elevated total cell count of 10 per mm^3, with 82% lymphocytes. CSF was negative for cryptococcus antigen, cytomegalovirus PCR, herpes simplex virus (HSV) PCR, John Cunningham virus (JCV), West Nile virus, bacterial growth cultures, acid-fast bacillus growth cultures, and fungal growth cultures.

On day 7, results from the palate and retropharyngeal lymph node biopsies revealed budding yeast forms consistent with *H. capsulatum*, prompting a diagnosis of PDH (Figure 1). Thus, amphotericin B liposome 200 mg (3 mg/kg) was started intravenously, given every 24 hours. *H. capsulatum* serum and urine antigen were obtained but returned negative. CSF from the lumbar puncture 3 days ago was also tested for *H. capsulatum* antigen but was negative. Serum yeast and mycelial fixation antibody tests were also negative.

The patient finished a 4-week course of amphotericin on day 36 and was discharged to a skilled nursing facility, with a 6-month course of itraconazole. He showed little improvement in his mental status despite treatment. Additional workup during his hospital course was negative for *Mycobacterium tuberculosis, Treponema pallidum, Chlamydia trachomatis, Neisseria meningitidis, Toxoplasma gondii* serology, HSV, Epstein-Barr virus, varicella zoster virus, HSV1, HSV2, West Nile Virus, JCV, and hepatitis C. A total of 2 days after discharge, a fungal PCR from the original oral biopsy came back positive for *H. capsulatum* DNA. Yet, fungal cultures from the same sample and blood cultures never showed any signs of growth.

Discussion

This is a unique case of PDH in a patient with AIDS, presenting with altered mental status and cognitive decline that progressively worsened after initiating cART. Although uncommon, there are reports of similar patient presentations in the literature [2,4].

Due to the patient's vague presentation and immunocompromised status, the infectious disease team had an extensive differential diagnosis and workup for opportunistic infections. Antigen assays are commonly relied upon for diagnosing *H. capsulatum* in acutely ill patients due to their rapid availability within 1-2 days. However, antigen and antibody testing were persistently negative in this patient. This was unexpected, as urine and serum antigen tests have sensitivities of 95-100% and 83-92% and specificities of 99% and 100%, respectively, in patients with AIDS with PDH [1,2,5]. Furthermore, yeast and mycelial fixation antibody tests have a sensitivity of 72.8-94.3% and a specificity of 70-80% [4]. The negative repeat *H. Capsulatum* antigen and serology testing were perplexing in our patient's case. However, it must be emphasized that the palate and retropharyngeal lymph node biopsies showing narrow-based budding yeast confirmed the diagnosis [4,6]. Interestingly, one study found that patients with AIDS or an immunocompromised status were more likely to have oral manifestations as the initial presentation of PDH [7].

One hypothesis behind our patient's clinical picture is based on immune reconstitution inflammatory syndrome (IRIS) [8,9]. IRIS in a patient with AIDS is the unexpected clinical deterioration due to paradoxically worsening or unmasking of an infection upon cART initiation. Our patient was diagnosed with PDH 1 month after starting cART. His CD4 count increased from 82 to 233 cells/µl, and his viral load dropped from 1,896,419 to 902 copies/ml. We hypothesize that *H. capsulatum* infection was unmasked as cART led to the increased quantity and response of macrophages, T cells, and cytokines against *H. capsulatum*. This led to a massive inflammatory response that correlates with the findings in his lymph nodes, oral cavity, and central nervous system (CNS) [8]. We pos-

tulated that his encephalopathy was due to his own overactive immune response. Hence, despite appropriate therapy, his mental status did not improve [10]. Interestingly, one study found an increased incidence of PDH within 2 months of starting cART compared with both untreated patients and those on cART for longer than 6 months [11]. Another study describes similar patients with atypical neurologic findings that worsened despite medical treatment who were diagnosed with CNS-IRIS due to JCV and *Cryptococcus* organisms [12]. However, it should be emphasized that suspicion for *H. capsulatum* infection and risk of IRIS is not a reason to delay starting cART [13]. Uniquely, this is the first case of a patient with AIDS presenting with CNS-IRIS due to an unmasked *H. capsulatum* infection.

Conclusion

PDH can have a widely variable presentation, making it difficult to diagnose in patients with AIDS who are at risk for a variety of opportunistic infections. Negative urine and serum antigen tests do not rule out the disease, and *H. capsulatum* should remain in the differential diagnosis in the right clinical context. As seen in our patient, CNS manifestations may be the presenting symptoms of IRIS due to the unmasking of the *H. capsulatum* infection. In summary, a high index of suspicion for IRIS secondary to *H. capsulatum* should be maintained in patients started on cART.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Andrew J. Stefan: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. **Erica S. Herc:** Writing – review & editing, Supervision. **Smitha Gudipati:** Writing – review & editing. **Indira Brar:** Writing – review & editing. **Alyssa Vitale:** Resources, Visualization. **Zain Tariq:** Writing – review & editing, Supervision, Project administration.

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Ethical approval

Patient confidentiality was upheld, no patient identifiers were used, and no experimental investigations were performed. Therefore, ethics approval was not sought for this case report.

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