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Bilateral adrenal histoplasmosis in an immunocompetent man from Texas

Colin J. Rog*, Daniel G. Rosen, Francis H. Gannon

Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA

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ABSTRACT

Disseminated histoplasmosis affecting the adrenal gland(s) of immunocompetent adults is a very rare infection. Here, we present a case of bilateral adrenal histoplasmosis in an immunocompetent, 62-year-old gentleman from Texas along with a brief review of the published literature. Given the risk of patient decompensation secondary to adrenal insufficiency and the wide availability of effective treatments, adrenal histoplasmosis must be considered even in immunocompetent adults who acquire adrenal masses.

1. Introduction

Histoplasma capsulatum is a dimorphic fungus with a world-wide distribution. In the United States, it is most prevalent in the moist Ohio and Mississippi River Valleys and is especially common in soils enriched with bird droppings or bat guano, bird roosts, and caves [1]. *Histoplasma* infects humans by a variety of mechanisms (fomites, direct inoculation, solid organ transplant, sexual contact), but most commonly, microconidia, or spores, are inhaled into the alveoli. In the warm, moist environment found there, the spores germinate and convert to yeast forms. Inciting an immune response, the yeasts are taken up by alveolar macrophages. It is within macrophages that *Histoplasma* replicates, using the reticuloendothelial system as highway to disseminate to regional lymph nodes other organs of the body. Immune signaling works to the advantage of the invading fungi when infected macrophages acutely induce a cytokine response that draws even more macrophages and monocytes toward infectious *Histoplasma* spores [1–3]. Within approximately two weeks, a T cell-mediated response should result in clearance of *Histoplasma* spores and organisms; when this does not take place, like in the context of immunosuppression, progressive dissemination can and often does occur [2].

Although very uncommon, cases of disseminated histoplasmosis have been reported in immunocompetent patients. In this extraordinarily rare subset, however, involvement of the adrenal gland, either unilaterally or bilaterally, is not uncommon. In fact, the adrenal gland is the most common organ involved in disseminated *Histoplasma* infections of immunocompetent individuals, and adrenal involvement may serve as the only demonstrable site of active fungal disease in these patients [4,5]. Furthermore, adrenal histoplasmosis must be followed particularly carefully due to the possibility of advancing to the point of causing adrenal insuffiency – the most common cause of death in patients with disseminated *Histoplasma* infection [6,7].

2. Case

The patient was a 62-year-old HIV-negative gentleman with relevant past medical history of essential hypertension, Hepatitis C, and 40 pack-years of cigarette smoking who initially presented with 2–3 months of low grade fevers in the evenings, drenching night sweats, fatigue, 30 pounds of unintentional weight loss, and loss of appetite. Suspecting malignancy, an abdominal CT was performed, and it showed a right adrenal lesion with central hypodensity and peripheral enhancement (Day 0). On Day +21, CT abdomen with adrenal protocol demonstrated enlargement of the right lesion and interim development of a lesion on the left. Measurements were 2.6×4.3×4.2 cm on the right and 2.9×1.3×2.7 cm on the left at that time (Fig. 1). This was followed by FDG PET/CT on Day +28 which demonstrated intense FDG avidity and average Hounsfield units of 31–36, making metastatic disease highly likely. The initial diagnosis was secondary adrenal malignancy of unknown primary.

Anticipating image-guided needle biopsy, pheochromocytoma was ruled out based on absence of hypertensive spells and normal urine metanephrines. The right mass was biopsied on Day +71 under CT guidance. Grossly, the material was necrotic and hemorrhagic, but microscopy showed epithelioid histiocytes and caseating granulomas (Fig. 2a and b), and PAS and trichrome stains showed intracellular organisms morphologically consistent with *Histoplasma* species (Fig. 2c and d). Other stains and cultures, including those for AFB, were negative. He was subsequently diagnosed with adrenal histoplasmosis and started on itraconazole 200 mg TID for three days followed by BID for an indefinite duration on Day +91.

Further investigation revealed that besides serving about 6 months in Thailand during the Vietnam War era, the patient had not traveled outside of the southern United States. He was working as superintendent overseeing maintenance of pipes at the time of diagnosis, but

* Corresponding author.

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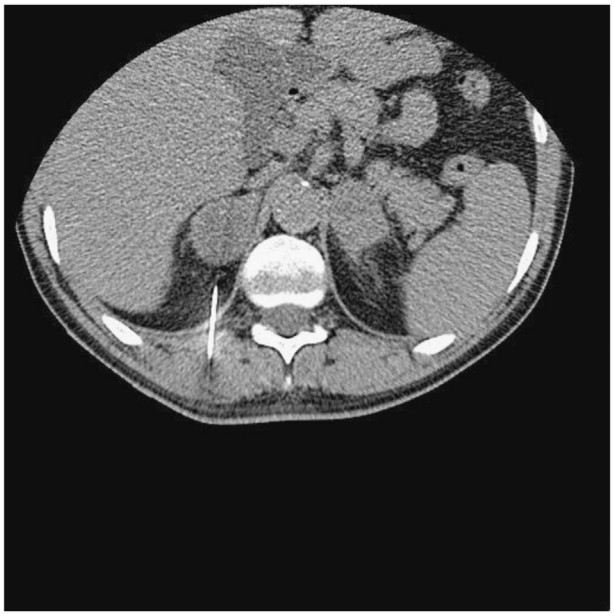

Fig. 1. Abdominal CT.

he denied any exposure to bird or bat droppings. Furthermore, he denied alcohol and IV drug use, unsafe sex, incarceration, or known TB contacts. He also denied cough, dyspnea at rest or on exertion, and changes in the color of his skin. With the exception of low grade fever and completely asymptomatic orthostasis (140 s/80 s lying down vs 120 s/70 s standing), vitals, physical examination, and relevant labs (CBC with differential, BMP, AM cortisol, and ACTH stimulation) were all within normal limits, ruling out adrenal insufficiency secondary to inflammatory adrenal destruction.

The patient tolerated the medication well with no side effects, his symptom began to resolve, and he started to gain weight slowly. However, follow-up CT with adrenal protocol performed roughly 6 months after initial biopsy demonstrated that while the right lesion remained stable, the one on the left had enlarged to 2.3×1.7×3.5 cm. Again fearing that adrenal malignancy of unknown primary was clouding the clinical picture, biopsy of the left lesion was taken on Day +244, which showed the same results as the initial biopsy of the right adrenal lesion. Other workup, including tumor markers and renin-to-aldosterone ratio, was negative. Although contingency plans were developed should the itraconazole fail, the patient remained on his previously prescribed regimen for two years due to risk of relapse on discontinuation. So far, he remains symptom-free for almost 9 months off itraconazole.

3. Discussion

In order to better understand this diagnosis into a global context, an extensive literature search was performed. All English language publications documenting cases of unilateral or bilateral adrenal histoplasmosis in immunocompetent adult patients were included and totaled just 17.

In total, 73 cases have been reported in the past 10 years - 56 in

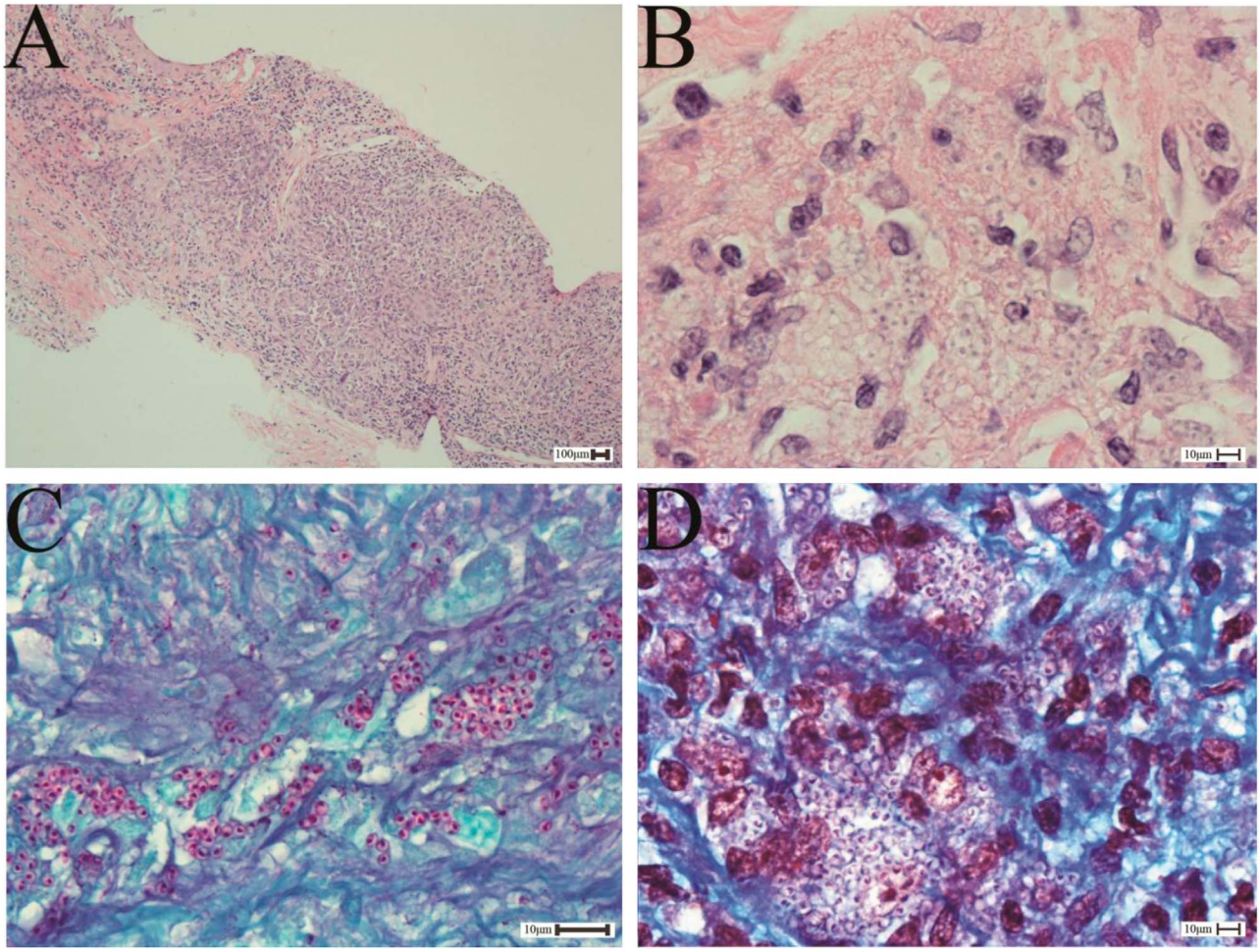

Fig. 2. a – H & E 10×, 2b – H & E 40×, 2c – PAS 100×, 2d – Trichrome 40×.

men, 4 in women, and 13 of unknown gender. Of the men, ages ranged from 31 to 87 years with a mean of 57.2 years. Of the women, ages ranged from 28 to 63 years with a mean of 42.3 years. 48 cases (65.8%) were found bilaterally, 12 cases (16.4%) were found unilaterally, and 13 cases (17.8%) lacked proper documentation to make this determination. These statistics seem to dispute previously held notion that adrenal histoplasmosis is most often found unilaterally [8]. In 33 cases (~45%), clinical and laboratory findings were consistent with a diagnosis adrenal insufficiency. 32 patients (43.8%) were treated with itraconazole alone, 6 patients (8.2%) were treated with amphotericin B alone, 20 patients (27.4%) were treated with a combination of itraconazole and amphotericin B, 1 patient (1.3%) received adrenalectomy, 1 patient (1.3%) was not treated, and 13 cases (17.8%) lacked documentation of treatment. Outcomes were, on the whole, quite promising. 57 patients (78.1%) lived, 2 patients (2.7%) died of complications of the infection, 1 patient (1.3%) died of complications of multidrug resistant *Pseudomonas aeruginosa* pneumonia before treatment for histoplasmosis could be administered, and 13 cases (17.8%) lacked documentation of outcome.

Of note, only one other case was found from the United States (Central Texas). All others were reported from tropical locales such as India, Brazil, and Thailand. Texas is considered a non-endemic region for *Histoplasma*, and the incidence of this infection in any of its clinical manifestations in adults sixty-five years old or older is only 2.7–3.06 per 100,000 in the state [9].

By far, the most common clinical manifestation of *Histoplasma* infection in humans is an asymptomatic or self-limiting pneumonitis reminiscent of a mild influenza in 90–95% of cases [1,3,5]. Hilar lymphadenopathy is common and is often accompanied by fever, headache, cough, and myalgias [1,5].

In the other 5–10% of cases, primary cutaneous or disseminated disease occur, and the clinical presentation is very different. The liver, spleen, lymph nodes, bone marrow, and adrenal glands are some of the most common organs involved, resulting in a wide variety of presentations and syndromes. Symptoms often include fatigue, weight loss, anorexia, fever, nausea, and vomiting [7,8]. Adrenal involvement is particularly common, especially in immunocompetent patients [5]. The cause of *Histoplasma* tropism for the adrenal gland is unclear, but it is hypothesized that the glucocorticoid-rich adrenal cells and the relative scarcity of reticuloendothelial cells contribute [9,10]. Adrenal involvement also presents a unique danger; chronic infection causes the adrenal glands to atrophy and calcify, which can result in adrenal insufficiency. Symptoms of adrenal insufficiency include fever, malaise, orthostatic hypotension, nausea, vomiting, hyperkalemia, hyponatremia, eosinophilia, hyperpigmentation, and night sweats and must be recognized and addressed immediately with glucocorticoid and mineralocorticoid therapy to prevent severe, life-threatening complications [7,11–13]. However, this syndrome is uncommon [4,14,15]. This is due to the fact that disseminated disease usually causes patients to seek medical attention much earlier than the time needed for the 90% destruction of both adrenal glands necessary for the manifestation of clinical adrenal insufficiency [16].

If a localized focus of infection can be identified, the gold standard is ultrasound-guided fine needle aspiration cytology (USG-FNAC). In order to find localized foci for USG-FNAC, CT is by far the most sensitive and most commonly utilized imaging method. Often, adrenal involvement will be seen as adrenal enlargement with central hypodensity indicative of necrosis and hemorrhage, enhancing internal septations, and peripheral rim enhancement [5,7]. May Graunwald Giemsa stains can be performed on air-dried smears, Papanicoulaou stain is often used on alcohol-fixed smears, periodic acid Schiff (PAS) and Gomori-Grocott methenamine silver (GMS) are used to identify fungal elements, and Ziehl Neelsen stain is used to identify the presence of acid fast bacilli [12,13]. Common findings indicative of *Histoplasma* infection microscopically include granulomatous inflammation with caseous necrosis (mononuclear cell infiltrates and multinucleated giant cells), oval or spherical hyaline granules measuring 2–4 μm in diameter, or uninucleate, intracellular (in macrophages) or extracellular yeasts with single buds attached at narrow bases measuring 3–5 μm in diameter and often occurring in clusters as well as positive *Histoplasma* cultures [7,8,12,13]. Furthermore, given that mycobacteria and fungi are the most common microorganisms to disseminate, cultures should be prepared for these two groups of organisms from the aspirate [12,13]. If no localized focus can be identified, other methods for detecting disseminated *Histoplasma* include bone marrow aspiration and biopsy [2].

At the top of the list of differential diagnoses for unilateral or bilateral adrenal masses found on imaging are primary tumor or metastases, *M.* tuberculosis, and non-Hodgkin lymphoma. However, histoplasmosis, other fungal infections (blastomycosis, paracoccidioidomycosis, cryptococcosis, and coccidioidomycosis), sarcoidosis, subacute adrenal hemorrhage, and adrenal abscess must also be considered [3,8,17,18].

For moderate to severe disseminated infections, the Infectious Disease Society of America recommends liposomal amphotericin B followed by itraconazole, although itraconazole therapy alone is often sufficient for milder cases [1,17]. It is widely recognized that a prolonged treatment of at least 1 year is necessary due to *Histoplasma*'s adeptness at persisting latently within the human body [8]. Given the risk of severe patient decompensation secondary to adrenal insufficiency the wide availability of effective treatments for this unique infection, adrenal histoplasmosis must be considered even in immunocompetent adults who acquire unilateral or bilateral adrenal masses.

Conflict of interest

There are none.

Acknowledgements

There are none.

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