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Bilateral adrenal histoplasmosis in an immunocompetent man from Texas

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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

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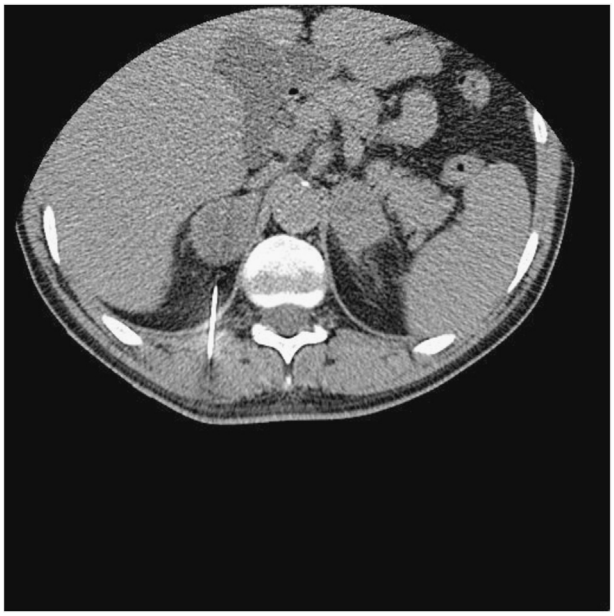

Fig. 1. Abdominal CT.

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

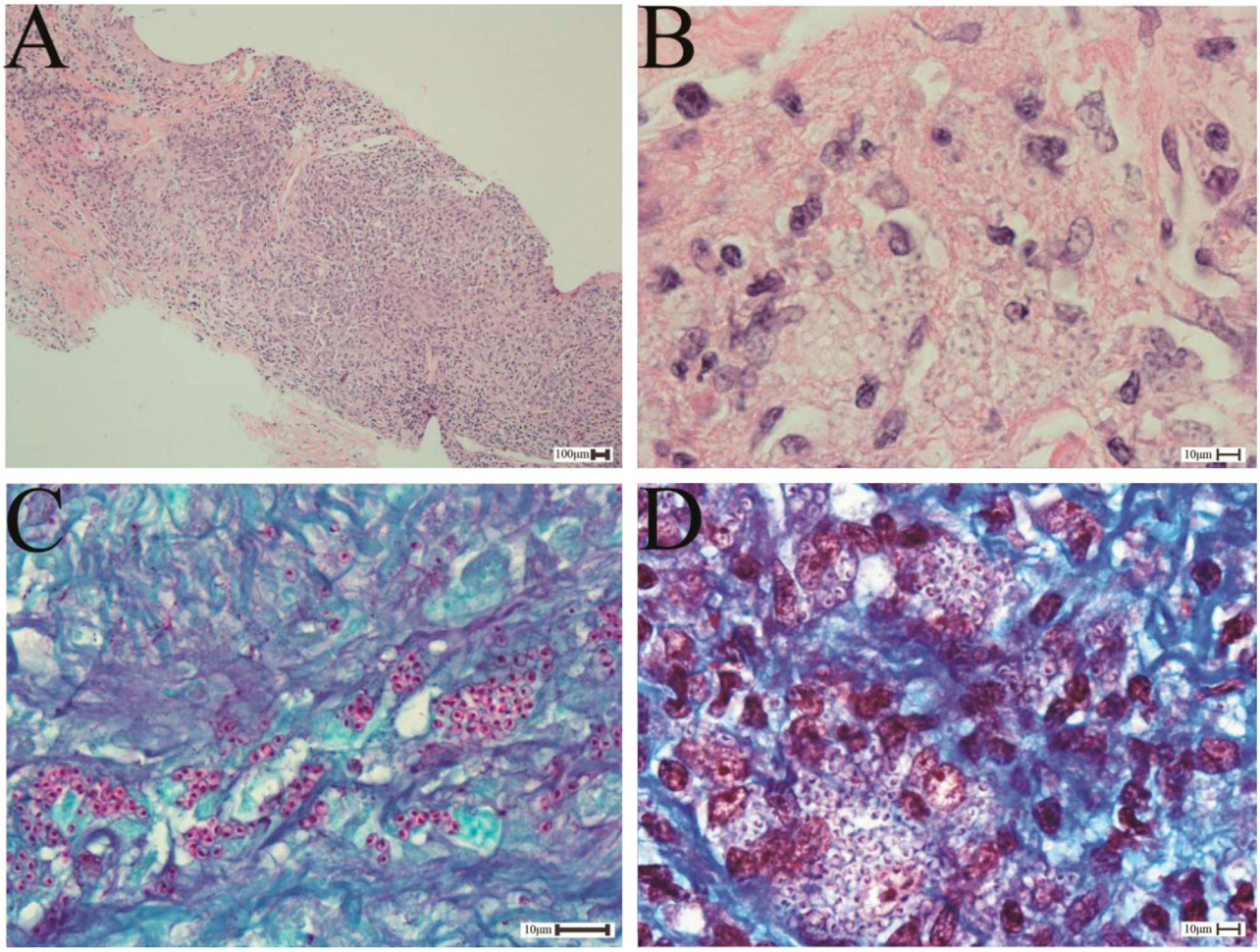

Fig. 2. a – H & E 10×, 2b – H & E 40×, 2c – PAS 100×, 2d – Trichrome 40×.