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An Unusual Case of Adrenal Histoplasmosis in A 63-Year-Old Immunocompetent Man Who Presented with Bilateral Adrenal Hyperplasia

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Abstract:

A 63-year-old man presented with abnormal thyroid function tests, fatigue and unintentional weight loss. Thyroid disorder was excluded with repeat labs. Further investigation discovered a left lung nodule on a chest X-ray and bilateral large adrenal masses on computed tomography scan of abdomen and pelvis. Detailed Laboratory investigations were negative for a functional mass or adrenal insufficiency. Biopsy of adrenal gland revealed Histoplasma capsulatum. He was treated with liposomal Amphotericin B followed by Itraconazole for three months followed by improvement in fatigue and weight loss. Histoplasma capsulatum is an opportunistic pathogen and has a high susceptibility to disseminate in immunosuppressed patients. It is rare for histoplasmosis to involve adrenal glands in immunocompetent patients. Adrenal insufficiency in patients with Histoplasmosis is a predictor of increased risk for morbidity and mortality. With the availability of effective treatment and risk of adrenal insufficiency, adrenal dissemination should be considered when a patient is diagnosed to have disseminated histoplasmosis, even in the absence of adrenal insufficiency symptoms.

Keywords: Histoplasmosis; adrenomegaly; adrenal incidentaloma; immunocompetent; dimorphic fungus; amphotericin B

Introduction

Histoplasma capsulatum is a dimorphic fungus with world-wide distribution. In the United States, it is most prevalent in the moist Ohio and Mississippi River Valleys.[1] H. capsulatum mostly affects immunocompromised patients but it has been reported in immunocompetent individuals as well involving the adrenal glands. Adrenal insufficiency if present in disseminated histoplasmosis can lead to increased risk for morbidity and mortality.

Case Presentation:

A 63 year old retired car mechanic was referred to our Endocrinology clinic for questionable hyperthyroidism with abnormal thyroid function tests. He had initially presented to his primary care physician with the non-specific complaints of increased sweating, fatigue, polyuria, polydipsia, and an unintentional weight loss of approximately ten pounds. Laboratory investigations revealed abnormal thyroid function tests with a TSH of 1.7 mIU/L, and a Free T4 of 2.02ng/dL that prompted the Endocrinology referral. He had no significant family history except for diabetes and kidney disease in his siblings. He smoked two packs of cigarettes a day for the past fifty years and consumed alcohol daily. He had no known drug allergies. On review of systems, he had dark tarry stools, reduced libido, and difficulty getting erections in addition to fatigue and weight loss. On physical examination, his blood pressure was 139/75 mm Hg, heart rate was 91 beats per minute and his temperature was 98.7 degrees Fahrenheit. His body mass index was 22.30 with a weight of 151 pounds and a height of 69 inches. On general exam, he was awake, alert and oriented without distress. His thyroid gland was not palpable, chest was clear to auscultation, heart was regular without murmurs, and his abdomen was soft and non-tender without masses. He had no edema, cyanosis or clubbing in extremities. His neurological examination revealed 2+ bilateral deep tendon reflexes. Repeat thyroid function tests were ordered and he was asked to return to the Endocrinology clinic in two weeks.

On follow-up visit 2 weeks later, he was still complaining of fatigue along with the new complaints of dizziness and further weight loss of four pounds. Repeat thyroid function tests were in the normal reference range. He was sent back to his primary care physician with recommendations to screen for lung cancer and other occult malignancy in lieu of unexplained weight loss and his smoking history. His chest X-ray by his primary care revealed a 1cm nodule in the left upper lung. Computed tomography of abdomen and pelvis was also performed when he started to complain about abdominal pains. It showed bilateral adrenal lesions 5.0 -5.7cm in size. He was sent back to the Endocrinology service. He did not have hypertension, paroxysmal anxiety attacks, palpitations or any symptoms suggestive of pheochromocytoma. Detailed laboratory investigations in the Endocrinology clinic including comprehensive metabolic panel, complete blood count, morning aldosterone levels and renin activity, 1-mg dexamethasone suppression test, 24- hour urine cortisol, catecholamines and metanephrines and cortrosyn stimulation tests were negative for primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma or primary adrenal malignancy. A probable diagnosis of lung cancer with bilateral adrenal gland metastasis was suspected and he was referred to the interventional radiologist for the adrenal gland biopsy. Cytopathology results were consistent with the diagnosis of H. capsulatum. A hospital admission was co-ordinated with the hospitalist service and the Infectious disease specialist. He was admitted to the hospital where Liposomal Amphotericin B was administered intravenously for 2 weeks followed by Itraconazole 200mg oral twice daily as an outpatient. Three months later, the patient had improved overall and had gained ten pounds. His chest Computed tomography revealed few additional lung nodules with no change in size of previously discovered nodules. Itraconazole 200mg oral twice daily treatment was continued for two years as per Infectious disease specialist recommendations. He was followed in the Endocrine clinic annually for approximately two and a half years. During this time, he continued to improve and his adrenal work up remained negative for adrenal insufficiency.

Discussion:

We report a case of bilateral adrenomegaly with histoplasmosis in a 63-year-old immunocompetent patient, who responded well to antifungal treatment. Histoplasma capsulatum is a dimorphic fungus with world-wide distribution. In the United States, it is most prevalent in the moist Ohio and Mississippi River Valleys [1] H. capsulatum generally affects immunocompromised patients and is uncommonly reported in immunocompetent individuals. Disseminated histoplasmosis is a rare complication but affects the adrenal glands in 80 % cases. However, the incidence of hypoadrenalism amongst these groups of patients is extremely rare and was reported as 7 to 20 % [2].

H. capsulatum appears to be strongly associated with the droppings of certain bird species as well as bats [3]. Spores containing H. capsulatum can be found in soil contaminated with birds' and bats' droppings. Human infection occurs after the fungus (in the form of microconidia or hyphal fragments) is inhaled, travels through the respiratory system, and reaches the alveoli [4]. The microconidia are converted to the yeast form upon ingestion by the alveolar macrophages where they replicate and then spread to the regional lymph nodes, and throughout the reticuloendothelial system. A cytokine response is induced by the infected macrophages and draw more macrophages and monocytes to fight the organism, and these coalesce together to form granuloma. Within two weeks, the T-cell mediated immune response is complete and results in the clearance of the organism. Failure of this results in the progressive spread of infection to other organs [5]. In most patients inhalation of H. capsulatum leads to a self-limited pulmonary infection. In immunocompromised, it may lead to chronic pulmonary infection or disseminated disease [6].

Less commonly, disseminated histoplasmosis can be seen in an immunocompetent host. Common clinical manifestations include fever, malaise, fatigue, anorexia, weight loss, and respiratory symptoms [7]. Most common organs involved are liver, spleen, and bone marrow, and gastrointestinal tract. Remarkably, the adrenal glands are involved in disseminated histoplasmosis, with bilateral adrenal involvement being common [8]. Although rare, adrenal histoplasmosis may advance to the point of causing adrenal insufficiency. It is important that adrenal histoplasmosis is followed carefully, as adrenal insufficiency is the leading cause of death in patients with disseminated Histoplasma infection [9].

Our patient with bilateral adrenal hyperplasia due to Histoplasmosis presented with non-specific symptoms of fatigue and weight loss. The clinical presentation of disseminated histoplasmosis usually resembles other chronic infections or malignancy as presented in this case. Differential diagnoses of tuberculosis, sarcoidosis, histoplasmosis, adrenal haemorrhage, lymphoma, and metastatic carcinoma should be considered [10]. Pulmonary infection which is caused by Inhalation of H. capsulatum is usually asymptomatic with no consequences. Nevertheless, the reactivation of infection can occur in immunocompromised states. Once infected, the latency period might last up to 60 years [11].

Computed tomography of the abdomen showed 5.0-5.7 cm bilateral adrenal lesions. Our initial impression was metastatic adrenal malignancy probably due to smoking-related lung cancer. However, fine needle aspiration cytology (FNAC) of the lesions revealed the presence of yeast cells. Fortunately, we were able to detect and treat the infection in our patient before he could experience any complications such as adrenal insufficiency. Our patient responded well to IV liposomal amphotericin B for 2 weeks and then with oral Itraconazole 200mg twice daily for 2 years to prevent relapse of infection. Usually, patients with adrenal histoplasmosis present with bilateral adrenal enlargement, have normal configuration, central hypo density due to necrosis or haemorrhage and peripheral enhancement on the CT scan.9 However, bilateral adrenomegaly with the same characteristics may also be seen in lymphoma, adrenal haemorrhage, metastatic or disseminated infections such as tuberculosis, cryptococcosis, aspergillosis or blastomycosis.9 Performing a cytopathological evaluation as soon as possible can help in diagnosis of the infection at the earliest, and therefore the treatment can be started immediately so that the life threatening consequences can be prevented.

Although hypoadrenalism is rare in disseminated histoplasmosis even with adrenal involvement in immunocompetent individuals, we should monitor carefully for any warning signs and symptoms. Kauffman demonstrated that only 12 out of 58 elderly patients with histoplasmosis were found with adrenal involvement, but

none of them had adrenal failure [12].

These findings were consistent with our patient. In a study of 40 patients with adrenal histoplasmosis, eight patients had normal cortisol levels at the time of diagnosis while two patients developed adrenal insufficiency after one year despite the treatment [13]. It is important to closely monitor patients with serum cortisol levels during every follow-up visit to prevent fatal outcomes. In another study of 242 patients with adrenal histoplasmosis during 1971 to 2012, most of the reported patients were from countries which are not previously considered to be heavily endemic for histoplasmosis. Furthermore, 41.3 % of patients with adrenal involvement developed adrenal hypofunction [14]. As modern technology illuminates more cases of adrenal histoplasmosis, the global boundaries of endemicity need to be redefined.

Conclusion:

Disseminated histoplasmosis may present with non-specific symptoms in immunocompetent patients and heightened suspicion is required for the diagnosis. Disseminated histoplasmosis can involve adrenal glands and is related to high risk of morbidity and mortality with adrenal insufficiency. This uncommon and potentially lethal disease is treatable with appropriate diagnostic work up and timely intervention with anti-fungal medications.

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