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Case report

Bilateral adrenal histoplasmosis presenting as adrenal mass mimicking malignancy in an immunocompetent patient

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ABSTRACT

We report a case of a 78-year-old immunocompetent man who presented with worsening fatigue and lethargy for one month. He had also been complaining of cough and SOB for two months which had been attributed to his underlying COPD and possible pneumonia. CT showed bilateral pleural effusions, ground-glass opacities, cirrhosis, splenomegaly and bilateral adrenal masses which was highly suspicious for malignancy. After pheochromocytoma was ruled out, EUS-FNA guided biopsy was performed on the left adrenal gland. Histology was positive for yeast cells, with fungal staining (PAS) revealing narrow-based budding compatible with Histoplasma. The patient was treated with amphotericin and itraconazole. Our case is unique as he presented with hepatosplenomegaly, which is reported in less than a quarter of cases. Although typically a diagnosis in immunocompromised patients, a high index of clinical suspicion is required to diagnose disseminated histoplasmosis in an immunocompetent patient. The gold standard for diagnosis is fungal tissue culture. However results may take up to weeks. EUS-FNA guided biopsy of adrenal glands can aid in early definitive diagnosis and management.

Introduction

Histoplasmosis, a dimorphic saprophytic fungus, is transmitted via inhalation of the microconidia spores found in soil enriched with nitrogen from bird and bat droppings [1,2]. Disseminated disease can affect almost all systems, with a high incidence in the lungs, reticuloendothelial system, central nervous system, gastrointestinal tract, kidneys, and adrenal glands [3]. There are two forms, acute infection seen in infants and immunocompromised hosts, and chronic infection seen in older adults. Disseminated histoplasmosis is diagnosed via isolation of *Histoplasma* from extrapulmonary sites. The gold standard for diagnosis is isolation of *H. capsulatum* on culture or identification of yeast on histopathology, with antigen testing available for a more rapid diagnosis and serology also available. There is a lack of information on the prognosis of disseminated histoplasmosis in the medical literature.

Case presentation

A 78-year-old male with a history of hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease, gastroesophageal reflux disease, presented to Emergency Room (ER) with worsening fatigue, night sweats, and 20 lb weight loss for the past month. He reported that two months before arrival, he started experiencing cough and shortness of breath which was attributed to his underlying COPD and possible pneumonia. Despite appropriate management, the patient's health continued to worsen which prompted him to present to the ER. He denied any prior history of fungal infections, or travel to Histoplasmosis endemic areas. He resided in northern Texas. He had served in the Vietnam War.

On admission, he was tachypneic and tachycardic. Physical examination revealed sinus tachycardia, trace bilateral edema, and bilateral diffuse wheezing. His admission labs were significant for elevated ESR. His pneumonia workup including COVID-19 PCR and sputum culture came back negative.

A computerized tomography (CT) scan of his abdomen and pelvis showed lobulated liver contour, splenomegaly, and bilateral adrenal masses that were absent on previous imaging a year ago. Adrenal glands had thickened irregular capsule, irregular margins, and nodular surface

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concerning for adenoma versus metastatic disease (Fig. 1). The right adrenal mass measured 4.6 × 3.4 cm, abutting right hemidiaphragm, liver, and inferior vena cava (32.3 HF pre-contrast), and the left adrenal mass measured 4.1 × 3.2 cm (33.1 HF pre-contrast). It was labeled "highly suspicious for metastatic disease." CT chest showed mildly prominent mediastinal lymph nodes, mild biapical bronchiectasis and atelectasis, interval improvement in bilateral lower lobe groundglass opacities from a year prior, and tree-in-bud clusters in the medial left lower lobe and superior lingula which were absent a year ago.

Further workup revealed negative HIV immunoassay. Nonalcoholic fatty liver disease score was –0.24 (indeterminate) and Fibrosis-4 score was not reliable given his age. Endocrinology was consulted for evaluation of the adrenal mass. Lab work showed normal dehydroepiandrosterone sulfate, 24-hour urine metanephrines, plasma metanephrines, and AM serum cortisol levels. ACTH stimulation test failed to demonstrate appropriate rise in cortisol levels. He continued to endorse fatigue and night sweats and was started on 0.1 mg fludrocortisone and hydrocortisone twice daily.

Gastroenterology was consulted for EUS guided adrenal gland biopsy. After ruling out pheochromocytoma our patient underwent EUS guided biopsy of the left adrenal gland which showed a 4.2 × 3.2 mm left adrenal heterogenic, hypoechoic mass. The mass was predominantly solid with a few small non-echoic necrotic and hyperechoic areas (Figs. 2,3) with well-defined borders and an intact interface was seen between the mass and adjacent structures suggesting a lack of invasion. A fine needle biopsy (FNA) with Doppler ultrasound was performed. Tissue was sent for further histology and fungal workup which turned out to be negative for malignant cells and interestingly showed yeast cells. Fungal staining (PAS) revealed narrow-based budding compatible with Histoplasma on Grocott's Methenamine Silver stain (Fig. 4). The smear was negative for acid-fast bacillus. Later his infectious lab work turned out to be positive for urine and serum Histoplasma antigen.

The patient was started on 2 weeks of liposomal amphotericin B and transitioned later to itraconazole 200 mg daily. On follow up a few months later, he was doing well and has repeat imaging pending.

Discussion

Incidental adrenal mases are now increasingly diagnosed on computed tomography of abdomen. According to one study the incidence of adrenal incidentaloma is 2–5% of the general population. Of these 2% are malignant and up to 10% have endocrine abnormalities [4,5].

H. capsulatum can involve almost any system but has a predilection for pulmonary involvement in immunocompetent patients. Patients with impaired immune systems, hematologic malignancies, advanced age, and chronic medical illnesses are especially susceptible to disseminated histoplasmosis [6,7]. Likely factors that predisposed our patient to adrenal histoplasmosis despite immunocompetent status was advanced age and chronic medical illnesses. Disseminated histoplasmosis with

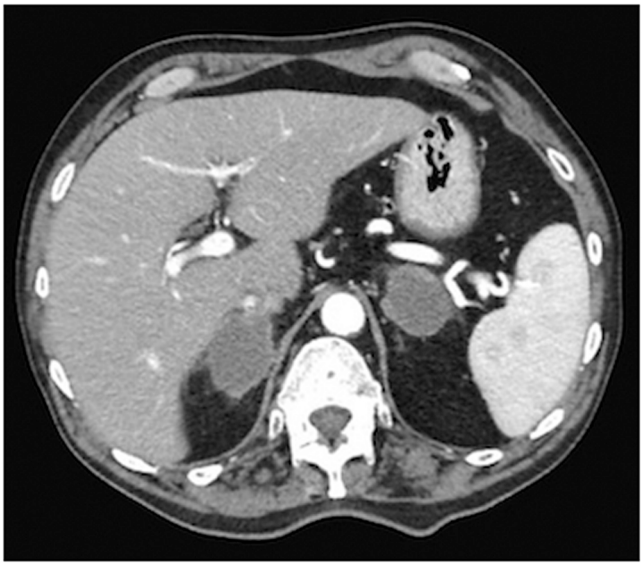

Fig. 1. Bilateral adrenal masses on abdominal CT - An abdominal CT image showing the bilateral adrenal masses with thickened irregular capsules, irregular margins, and nodular surface concerning for adenoma vs metastatic disease.

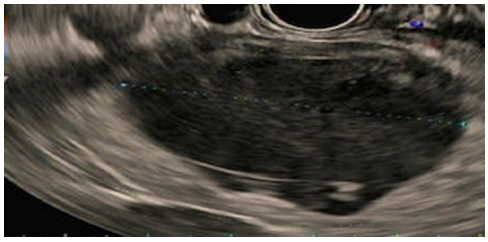

Fig. 2. Endoscopic ultrasound image of left adrenal mass - An endoscopic ultrasound image showing the 4.2 × 3.2 mm left adrenal mass.

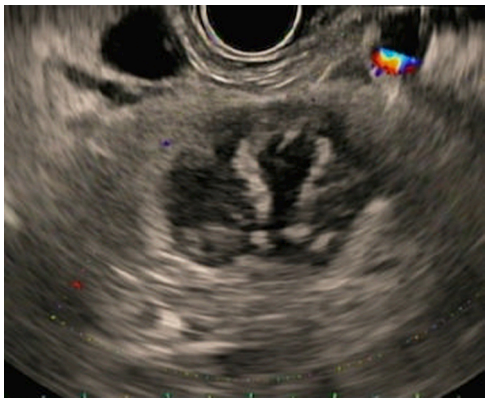

Fig. 3. Endoscopic ultrasound image of left adrenal mass - An endoscopic ultrasound image showing the 4.2 × 3.2 mm left adrenal mass which was heterogenic and predominantly solid with a few small non-echoic necrotic and hyperechoic areas.

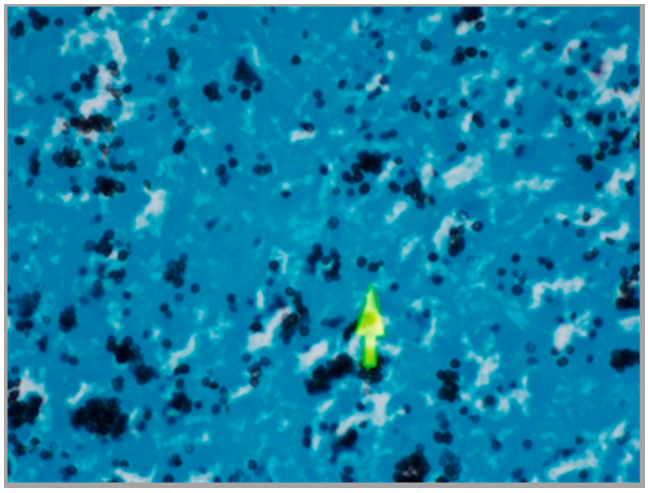

Fig. 4. PAS stain - Cell block section containing clusters of yeasts (size 2–4 μm) showing narrow-based budding (arrow) compatible with Histoplasma species (GMS stain X600).

adrenal gland involvement presents with several months of constitutional symptoms and bilateral or unilateral adrenal masses on imaging. The differential diagnosis of bilateral adrenal masses is extensive and includes tuberculosis, adrenal metastasis, adrenal adenomas, fungal etiologies, etc. [8–10].

In contrast to the normally seen bilateral symmetric enlargement of the adrenal glands in histoplasmosis our patient had bilateral thickened irregular capsules, irregular margins and nodular surface more concerning for adenoma vs metastatic disease which led the differential diagnosis of fungal infection lower on the list. Histoplasmosis may be suspected on radiology but imaging features are not sensitive and can be seen in other disseminated diseases such tuberculosis, cryptococcosis, lymphoma, and metastasis to adrenal glands [11]. Gold standard diagnostic method is fungal tissue culture, but results may not be available for several weeks. For this reason, patients with a high index of suspicion for malignancy are often referred for percutaneous biopsy. EUS or percutaneous FNA biopsy of adrenal tissue, utilized in conjunction with rapid onsite cytopathologic evaluation, can be helpful in the diagnosis of Histoplasmosis as it yields positive results in most of the cases.

Once the diagnosis of histoplasmosis is confirmed, treatment involves liposomal amphotericin B followed by itraconazole for acute or disseminated histoplasmosis of moderate to severe disease. For patients in which adrenal insufficiency is suspected, treatment with corticosteroids can be started without a complete laboratory diagnosis of blood cortisol level and low ACTH-stimulated cortisol responses similar to our patient [12]. Reversal of adrenal dysfunction has been described after prolonged antifungal treatment [13].

On a systematic review of randomly selected studies regarding adrenal histoplasmosis case series or case reports from the past 20 years, 2003 – 2023, the majority of patients were male (86.4%), half were immunocompromised (50%), roughly half had adrenal insufficiency (51.3%) (Table 1). Our patient fits into the majority demographics based on this systematic review, as he was male, not immunocompromised, and was found to have adrenal insufficiency. It worth noting that an interesting feature of our case was that our patient had hepatomegaly, which was noted in only 24.3% of cases. A minority of cases (40.5%) had involvement of other sites including hepatosplenomegaly.

This case illustrates the importance of maintaining a high index of suspicion for disseminated histoplasmosis with adrenal involvement in any patient who presents with constitutional symptoms and bilateral adrenal gland enlargement, regardless of immunocompetent status. It is imperative for the clinician to keep in mind that there are two forms of disseminated histoplasmosis, an acute infection seen in infants and immunocompromised hosts, and a chronic infection seen in older adults. It is important to remember to test for adrenal insufficiency in patients diagnosed with disseminated histoplasmosis who have adrenal involvement. EUS FNA guided biopsy of adrenal glands can aid in early definitive diagnosis and management.

Author contribution

G. Moon wrote the article, revised the article for intellectual content, approved the final article, and is the article guarantor. M. Nadeem, S. Usiukiewicz, and M. Jamil reviewed the literature and were involved in the investigation. E. Idrisov and A. Weston were involved in the investigation. R. Sawh MD provided the images and descriptions. All authors contributed to the article.

Ethical approval

Patient information was anonymized to the full extent of our ability.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Table 1
Case report/case series of adrenal histoplasmosis during the time period from 2003 to 2023.

Reference	Age	Gender	Immunocompromised Status	Geographic Location	Imaging findings	Adrenal Insufficiency
[14]	42	M	N		Bilateral adrenal gland homogeneous enlargement	Y
[15]	85	M	N		Bilateral adrenal masses	Y
[16]	69	M	Y (Hep B)	Louisiana	Right adrenal mass	N
[17]	63	M	Y (Hep C, post liver and renal transplants)	Midwest	Multifocal pneumonia in bilateral lungs, calcified granulomas, bilateral adrenal masses	Y
[18]	56	M	Y (HIV untreated)		Left maxilla soft tissue mass, bilateral adrenal gland enlargement	Y
[19]	57	M	Y (T2DM)		Bilateral hypodense adrenal masses	Y
[20]	62	M	Y (Hep C)	Texas	Bilateral adrenal masses	N
[21]	71	M	N	Canada	Bilateral adrenal masses	Y
[22]	50	F	Y (T2DM)	Ecuador	Bilateral adrenal masses, rectal mass, hepatosplenomegaly	Y
[23]	72	M	N	Philippines	Bilateral adrenal masses, left apex fibrosis	Y
[24]	75	M	Y (T2DM)	Malaysia	Bilateral adrenal masses	N
[25]	73	M	N	India	Bilateral adrenal masses, central tongue lesion, hepatosplenomegaly	N
[26]	Median age 56.2	M (8/8)		India	Bilateral adrenal enlargement (8/8), hepatosplenomegaly (4/8), periportal and portocaval lymphadenopathy (1/8)	3/8
[27]	72	F	Y	Ontario, Canada	Bilateral adrenal masses, scarring in the lung apices, a calcified granuloma anteriorly in the right lower lobe of the lung and a 1.1-cm area of decreased attenuation in the left lobe of the liver	Y
[28]	42	M	Y (T2DM)	Sri Lanka	Bilateral adrenal masses, hepatosplenomegaly, enlarged para-aortic lymph nodes	Y
[29]		M (9/11)	Y (T2DM in 4/11 and pulm TB in 2/11)	India	Unilateral or bilateral adrenal enlargement	4/11
[30]	45	M	Y (T2DM)	India	Bilateral small nodular lung lesions with central cavitation in some lesions and bilateral diffusely enlarged adrenal glands	Y
[31]	60	M	Y (T2DM)	India	Bilateral enlarged adrenal glands, hepatosplenomegaly	N
[32]	56	M	N	India	Bilateral enlarged adrenal glands, hepatosplenomegaly	N
[32]	38	F	Y (TB)	India	Bilateral adrenal gland enlargement	Y

Declaration of Competing Interest

There are no conflicts of interest to disclose.

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There are no acknowledgements to disclose.

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