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Case Report

Bilateral Adrenal Nodules in the Setting of Disseminated Fungal Infection: An Important Consideration for Appropriate Management of Adrenal Pathology

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ABSTRACT

Background/Objective: Increased utilization of cross-sectional imaging has led to a rise in diagnosis of incidental adrenal lesions. Physicians in many clinical settings are increasingly faced with addressing these incidental lesions by initiating the correct workup, diagnosis, and long-term follow-up plan. Our objective was to demonstrate the importance of maintaining a broad differential and completing a thorough workup in determining the correct treatment plan for patients with bilateral adrenal lesions.

Case Report: We present 2 patients who recently completed chemotherapy for lymphoma, found to have new bilateral adrenal lesions on postchemotherapy imaging. Urine antigen and/or adrenal biopsy was performed to confirm the diagnosis of disseminated fungal infection. This diagnosis has major implications on the treatment plan, which includes antifungal therapy instead of surgical management or additional chemotherapy. Cross-sectional imaging after initiation of antifungal treatment demonstrated decreasing size of nodules.

Discussion: A broad differential is critical when working up and developing treatment plans for adrenal nodules, specifically considering a fungal etiology in the setting of immunosuppression or primary extra-adrenal malignancy.

Conclusion: Incidentally found adrenal lesions are becoming more common, and in turn, the obligation for appropriate management of adrenal pathology not only falls to medical and surgical endocrinologists but also to general practitioners. It is prudent to consider atypical etiologies including disseminated fungal infection prior to surgical excision or initiation of chemotherapy as those treatment strategies would not benefit select patients.

Introduction

The incidence of adrenal tumors has increased 10-fold in the past 20 years with approximately 4% of patients noted to have incidental adrenal nodules on cross-sectional imaging.[1,2] Up to three fourths of adrenal incidentalomas are benign, nonfunctional adenomas, and earlier detection of these lesions has resulted in well-established guidelines for management.[2,3] Differential diagnoses for an incidentally discovered adrenal nodule is broad and includes adenoma, nodular hyperplasia, pheochromocytoma, adrenal carcinoma, metastasis from other primary malignancy, cystic lesion, myelolipoma, hemangioma, adrenal hemorrhage, and lymphoma. Narrowing the differential starts with biochemical workup to evaluate for aldosterone, cortisol, or catecholamine hypersecretion. Cross-sectional imaging utilizing adrenal protocol allows for evaluation of contrast washout on delayed phase to further characterize adrenal nodules. The role of adrenal biopsy is debated and thought to rarely aid in diagnosis, with some studies reporting

Abbreviations: CT, computed tomography; FNA, fine needle aspiration.

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minimal benefit with serious biopsy-related complications.[4,5] Biopsy can be useful for indeterminate nonfunctioning adrenal masses where results will change management, such as those with a potential infectious etiology.[2,6–8] Here, we present 2 patients with bilateral adrenal nodules in the setting of immunosuppression related to treatment for extra-adrenal malignancies, found to have disseminated fungal infections.

Case Report

The first patient (patient A) was a 77-year-old woman diagnosed with stage IV diffuse large B cell lymphoma status post 6 cycles of R-CHOP chemotherapy who was noted to have bilateral enlarging adrenal nodules on posttreatment cross-sectional imaging. Of note, these nodules were not present on her initial imaging at the time of lymphoma diagnosis. The left adrenal nodule, measuring 2.8 × 1.4 cm, was first noted on imaging during chemotherapy treatment. Posttreatment positron emission tomography/computed tomography (CT) identified bilateral adrenal abnormalities including increased size of the left-sided mass measuring 2.6 × 2.0 cm and concern for right adrenal hemorrhage. Repeat imaging 4 months later demonstrated enlargement of the left adrenal nodule to 3.7 × 2.2 cm with heterogeneous enhancement and a right-sided nodule measuring 2.6 cm (Fig. 1). She subsequently underwent biochemical workup including normal levels of dehydroepiandrosterone, aldosterone, renin, adrenocorticotropic hormone, urinary cortisol, and plasma metanephrine/normetanephrine (Table). The dexamethasone suppression test resulted in a cortisol level of 2.2 μg/dL with an elevated midnight cortisol level. The patient was referred to endocrine surgery for further evaluation and discussed at multidisciplinary tumor board, where the recommendation was to obtain CT-guided adrenal biopsy. Initially, the biopsy results returned nondiagnostic, and therefore, adrenalectomy was discussed. Prior to surgery, however, a urine histoplasmosis antigen test was performed and returned elevated at 6.7 ng/dL (normal, <0.2 ng/dL), which prompted repeat review of the adrenal biopsy. Upon further review by microbiology, intracellular yeast consistent with *Histoplasma capsulatum* was noted. She was referred to infectious disease and diagnosed with disseminated histoplasmosis. Treatment with itraconazole was initiated. Follow-up cross-sectional imaging 8 months after initiation of antifungal therapy demonstrated a decreased size of bilateral adrenal nodules.

The second patient (patient B) was a 52-year-old man with a history of gastric primary diffuse B cell lymphoma. He underwent 6 cycles of R-CHOP chemotherapy and on posttreatment positron emission tomography/CT was noted to have new bilateral adrenal nodules. The right adrenal nodule measured 1.0 × 0.9 cm, and the left adrenal nodule measured 1.9 × 1.1 cm

Highlights

- Fungal infection should be on the differential in patients with bilateral adrenal lesions
- Diagnosis of fungal adrenal lesions radically changes management from chemotherapy or surgery to antifungals
- Adrenal biopsy is useful for nonfunctioning adrenal masses where results will change management

Clinical Relevance

Disseminated fungal infection should be a consideration in patients with bilateral adrenal nodules in the setting of immunosuppression. Diagnosis of fungal adrenal lesions substantially alters management from initiation of chemotherapy or surgical resection to infectious disease consultation and antifungal therapy.

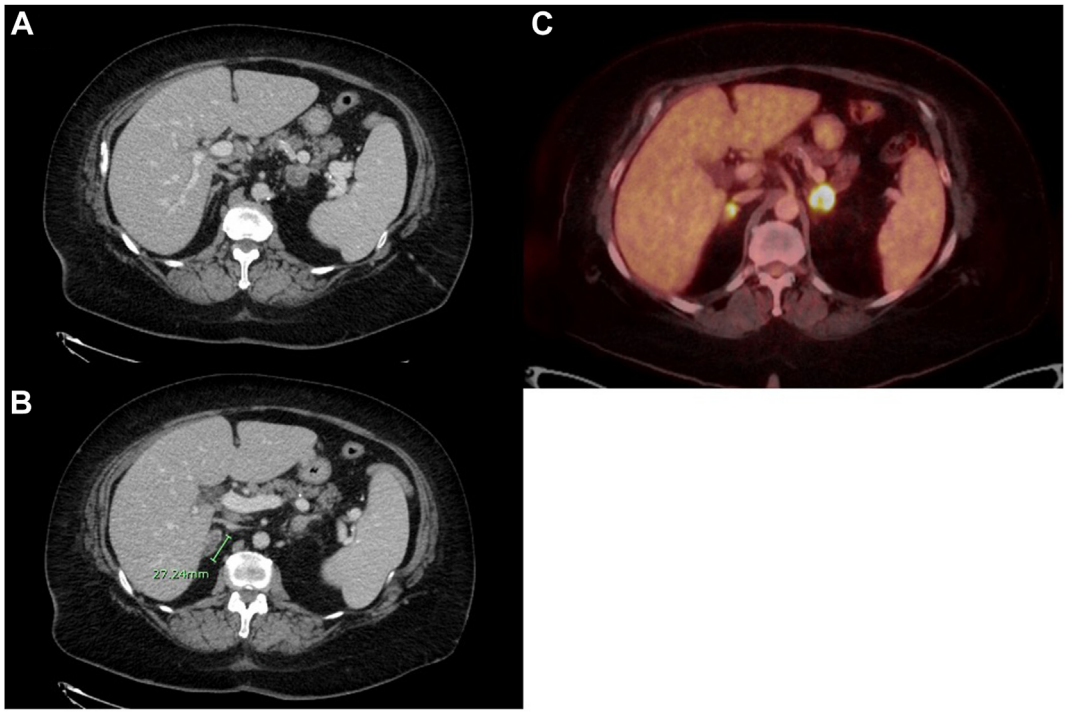

Fig. 1. Postchemotherapy cross-sectional imaging for patient A demonstrating bilateral adrenal nodules. *A*, Right adrenal nodule measuring 2.6 cm. *B*, Left adrenal nodule measuring 3.7 x 2.2 cm. *C*, Positron emission tomography/computed tomography showing bilateral fluorodeoxyglucose-avid adrenal lesions.

Table
Biochemical Workup of Patients A and B

Biochemical workup	Patient A	Patient B	Normal range
Aldosterone	17 ng/dL	…	0-31 ng/dL
Cortisol, salivary (8 AM)	0.654 μg/dL	…	0.025-0.600 μg/dL
Cortisol, random serum	21.2 mCg/dL	18.5 mCg/dL	4-25 mCg/dL
Cortisol, urinary	29 μg/24 h	…	6-42 μg/24 h
DHEA sulfate	37 mCg/dL	273 mCg/dL	35-430 mCg/dL
Metanephrine, plasma	<0.01 nmol/L	…	0.00-0.49 nmol/L
Normetanephrine, plasma	0.71 nmol/L	…	0.00-0.89 nmol/L
Potassium	3.7 mmol/L	5.0 mmol/L	3.5-5.5 mmol/L
Renin	34.2 μg/mL	…	2.5-45.7 μg/mL
Sodium	142 mmol/L	140 mmol/L	135-145 mmol/L
Histoplasma, urine	6.7 ng/mL	…	<0.5 ng/mL
Blastomyces antigen	…	0.94 ng/mL	<0.20 ng/mL
Blastomyces antibody	…	4.0 EIA	<0.9 EIA

Abbreviations: DHEA = dehydroepiandrosterone; EIA = enzyme immunoassay.

(Fig. 2). Biochemical workup was limited at outside institution and only included normal dehydroepiandrosterone and cortisol levels. The left-sided nodule increased in size on repeat imaging, which prompted CT-guided fine needle aspiration (FNA) biopsy. Tissue examination showed thick-walled organisms with broad-based budding consistent with Blastomyces (Fig. 3). There was no evidence of lymphoma in the tissues suggesting that the nodules were related to disseminated fungal infection as opposed to primary disease progression. Urine Blastomyces antigen and serum antibody confirmed the diagnosis of disseminated blastomycosis. He was referred to infectious disease and started on antifungal therapy but was shortly thereafter lost to follow-up. No additional imaging of the adrenal glands was obtained following initiation of antifungal treatment. Of note, this patient was not evaluated for pheochromocytoma, and as discussed in subsequent sections, it is essential to rule out catecholamine secretion prior to biopsy.

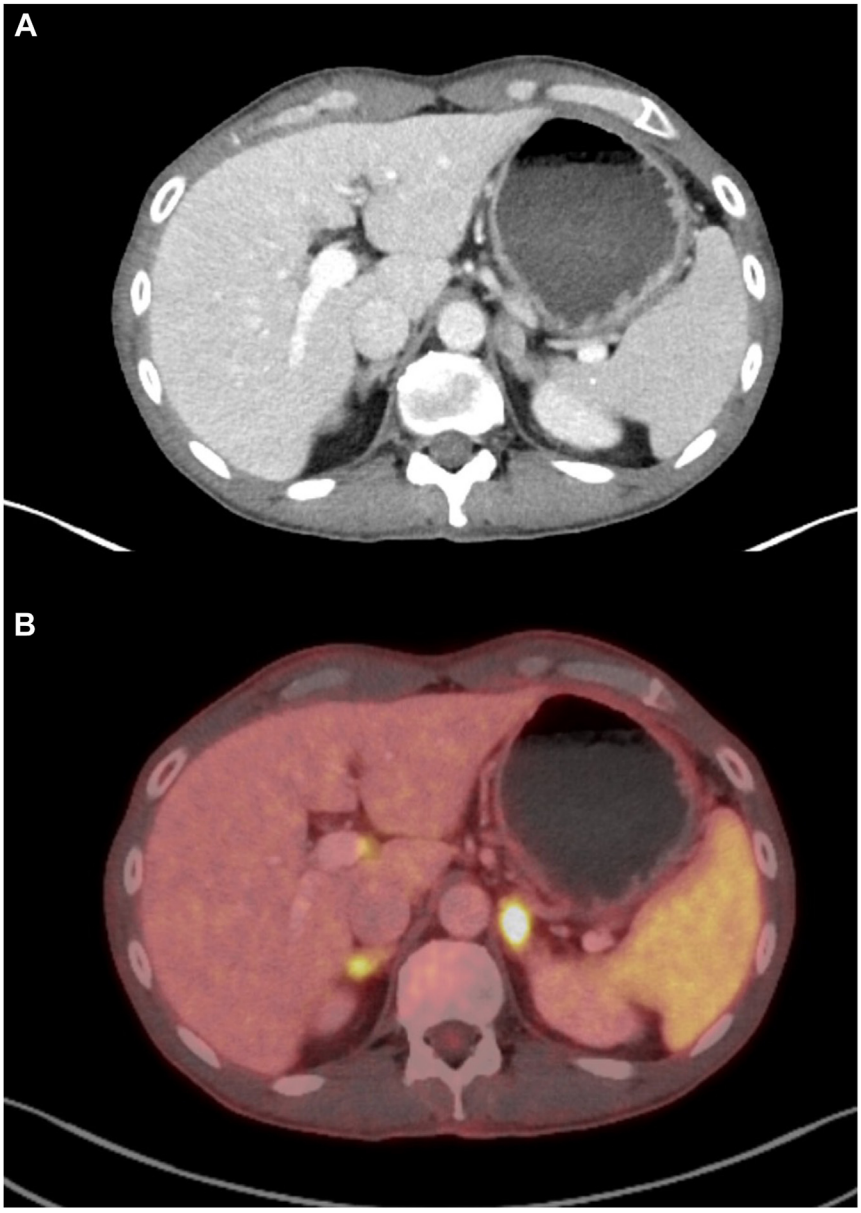

Fig. 2. Postchemotherapy cross-sectional imaging for patient B demonstrating bilateral adrenal nodules. *A*, Right adrenal nodule measuring 1.0 × 0.9 cm and left adrenal nodule measuring 1.9 × 1.1 cm. *B*, Positron emission tomography/computed tomography demonstrating fluorodeoxyglucose-avid bilateral adrenal nodules.

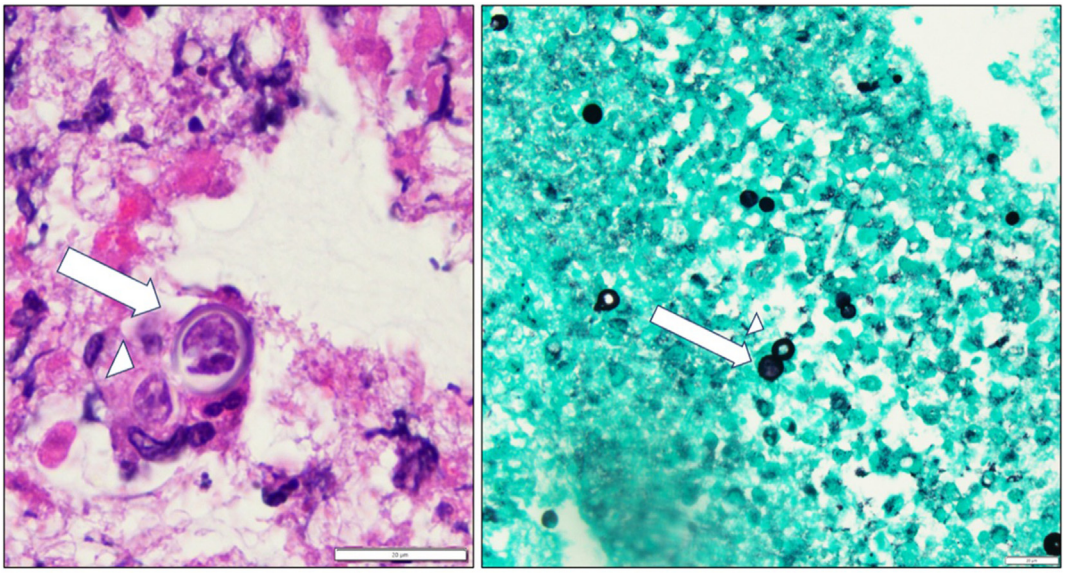

Fig. 3. Fine needle aspiration of adrenal nodule demonstrating large, circular, broad-based budding yeasts. Material aspirated from the left adrenal nodule was initially stained via Diff-Quik and Papanicolaou (neither shown), revealing acute and granulomatous inflammation with scattered budding organisms morphologically consistent with *Blastomyces* species. Later, a cell black was generated and stained via hematoxylin and eosin (left) and Gomori methenamine silver (right) accentuating the morphologic features already described. Arrow, parent cell; Arrowhead, budding progeny cell. Bars, 20 μm.

Discussion

Increased utilization of cross-sectional imaging has led to a rise in identification of incidental adrenal nodules, necessitating a foundation of knowledge regarding workup and triage of adrenal pathology in many emergency departments and primary care physicians.[9] Despite well-established principles of adrenal pathology management, only a minority of patients with adrenal tumors undergo optimal workup for hormone excess.[2] Narrowing the differential for an adrenal incidentaloma involves obtaining a detailed medical and family history, clinical assessment, biochemical workup, and imaging studies. Although only 3% of all adrenal incidentalomas are malignant, it is essential to identify and triage these patients to expedite oncologic resection for optimal outcomes.[6] Adrenal biopsy is typically unnecessary in the workup of an adrenal mass given the specificity and sensitivity of adrenal protocol imaging in characterizing an adrenal mass; however, there are circumstances in which it can be useful in directing next steps of management.[2] The algorithm for characterizing adrenal lesions includes evaluating the Hounsfield units and contrast enhancement washout. Majority of benign adenomas are lipid-rich; however, the small percentage of benign adenomas that are lipid-poor tend to have contrast washout of >50% on 15-minute delayed enhanced images.[10] Adrenal biopsy is indicated to further classify an adrenal mass if it is deemed nonfunctional on biochemical testing and is lipid-poor (>10 HU) with <50% washout on delayed images and the patient has a known primary extra-adrenal malignancy.[10] Biopsy in this setting is utilized to rule out metastatic disease. In the absence of primary extra-adrenal malignancy, further imaging with nuclear scintigraphy or surgical resection may be warranted for final diagnosis.[10] Adrenal biopsy may not necessarily be required in immunocompromised patients with bilateral adrenal lesions because fungal etiology should be high on the differential and prompt further investigation with urine fungal antigen testing prior to pursuing biopsy. As with any procedure, adrenal FNA carries significant risk, including bleeding, pneumothorax, or even seeding of a tumor along the biopsy tract in cases of malignancy.[4,11] Adrenal biopsies in patients with pheochromocytoma can lead to life-threatening complications including hemorrhage, capsular disruption and tumor seeding, hypertensive crisis, myocardial infarction, arrhythmia, stroke, or death. With approximately 5% incidentalomas found to be pheochromocytoma, comprehensive biochemical testing should performed be rule this out prior to biopsy to avoid life-threatening sequelae.[5] The indication and utility of adrenal biopsy was demonstrated with our patients; however, patient A was ultimately diagnosed with urine fungal antigen testing because the biopsy was nondiagnostic.

Infectious causes of bilateral adrenal lesions include fungus and mycobacterium. Histoplasmosis is the most common endemic fungal infection in the United States, with the Ohio and Mississippi Valleys having the highest rates of infection (Fig. 4).[12,13] Similarly, Blastomyces is hyperendemic in areas near the Great Lakes, along the Mississippi and Ohio rivers.[14] Both dimorphic fungi are found in the soil, which, when disrupted (eg, construction or demolition), yields aerosolization of infectious conidia enabling inhalation. The majority of Histoplasma infections are asymptomatic, although the infection can be severe in the immunocompromised. Dissemination through the reticuloendothelial system occurs during acute infection involving various organs, including potentially the adrenal gland.[13] Dissemination is more common with Blastomyces, occurring in 25% to 40% of symptomatic infections. Although clinically disseminated histoplasmosis is less frequently diagnosed,[14] Goodwin et al[15] found that in a series of 84 patients with disseminated histoplasmosis, 82% had adrenal involvement at autopsy. For pulmonary and disseminated blastomycoses, urine antigen tests have a reported sensitivity of 93% and specificity of 79%.[14] Cross-reaction between Histoplasma and Blastomyces antigens commonly confounds interpretation. Our first patient underwent adrenal biopsy that was nondiagnostic; however, subsequent rereview after positive urine histoplasmosis antigen testing confirmed the presence of the fungus. Microscopic aspirate review often begins with the Wright-Giemsa-based Diff-Quik stain, wherein pear-shaped, 2- to 4-μm, narrow-based budding Histoplasma yeasts exhibit an intense violet nuclear hue ringed by a deep blue outer envelope with polar pallor (Fig. 5). Circular, 10- to 15-μm, broad-based budding Blastomyces yeasts also stain violet exhibiting a characteristic double-refractile cell wall (Fig. 3). To further

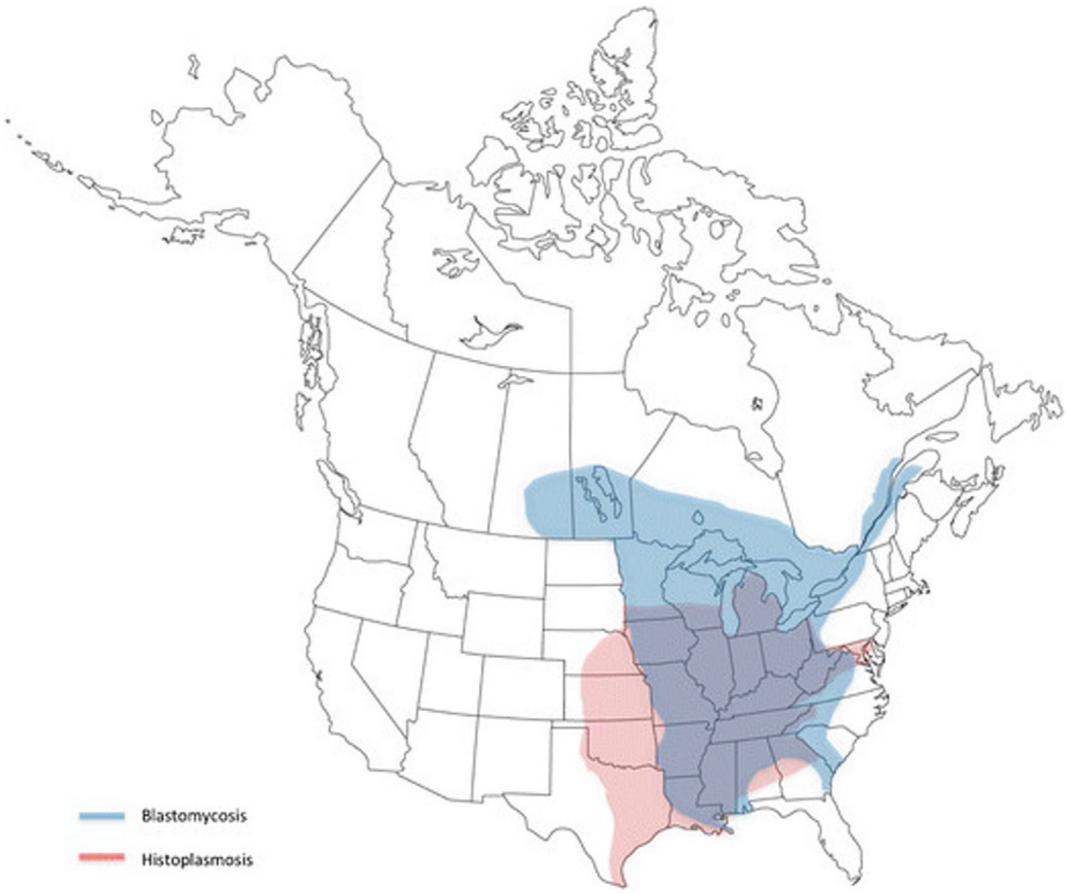

Fig. 4. Map of distribution of Blastomyces (blue) and Histoplasma (red).[12]

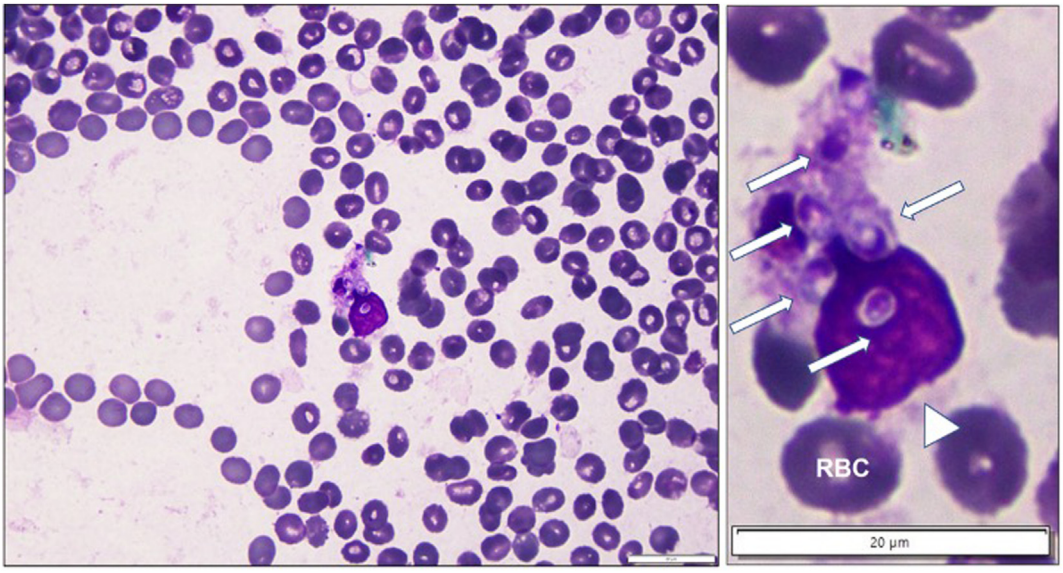

Fig. 5. Fine needle aspiration of adrenal mass demonstrating small, intraphagocytic yeasts. Material aspirated from the left adrenal mass was stained via a modified Wright-Giemsa method (Diff-Quik). Upon review, the specimen was hypocellular consisting primarily of contaminating blood, although adipose tissue and groups of benign adrenocortical cells were present. Small (3.2 × 2.5 µm), pyriform yeasts (arrows) were noted within phagocytic cells (arrowhead). These features were consistent with those expected for *Histoplasma capsulatum* yeasts. Bars, 20 µm. *RBC* = red blood cell.

assess, a nonroutine histochemical stain, Gomori methenamine silver or periodic acid-Schiff, is frequently employed. These staining methods are involved and usually occur hours to days after the initial cytopathologic review. Ultimately, fungal culture and broad range polymerase chain reaction may confirm diagnosis. When evaluating bilateral adrenal lesions, awareness of the risks of fungal infection prompts rigorous review of biopsies and pursuit of ancillary testing (culture, antigen/antibody, and polymerase chain

reaction). Management with antifungals and follow-up with an infectious disease specialist should follow diagnosis.

This report highlights 2 patients with bilateral adrenal nodules consequent to disseminated fungal infection, a relevant clinical scenario that is not well described in the literature. A notable limitation of this series is the lack of appropriate biochemical workup for the second patient prior to adrenal biopsy. Care occurred at an outside facility without referral to an endocrine surgeon or medical endocrinologist. Per our review, pheochromocytoma was not ruled out prior to FNA, which is recommended to mitigating risk of hypertensive crisis. Herein lies one of the many knowledge gaps inherent to appropriate evaluation of adrenal masses as they become more commonly encountered.

Conclusion

Earlier detection of adrenal tumors from increased utilization of cross-sectional imaging has led to well-established guidelines for managing adrenal lesions. This includes thorough history, biochemical testing, adrenal-specific imaging, and, in selected instances, adrenal FNA biopsy. We discuss 2 cases of bilateral adrenal lesions discovered in the setting of disseminated fungal infection, demonstrating how management vastly changes with correct diagnosis. It is important to consider atypical etiology for adrenal pathology and complete a comprehensive workup, including urine fungal antigen and serum antibody testing in addition to adrenal biopsy in these scenarios. This is a valuable consideration for all practitioners given an increased rate of incidentally discovered adrenal lesions.

Disclosure

The authors have no conflicts of interest to disclose.

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