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Case Report

Primary Adrenal Insufficiency due to Cryptococcus With Persistent Adrenal Enlargement and Insufficiency

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ABSTRACT

Background/Objective: Infiltrative fungal infections are an unusual cause of primary adrenal insufficiency (AI). Our objective is to present a long-term follow-up of a patient with AI due to cryptococcal adrenalitis.

Case Report: A 47-year-old woman presented in January 2004, with 50-lb weight loss, nausea, emesis, and headache with diplopia. During the 6 months prior to her presentation the patient had multiple admissions for evaluation of recurrent nausea and emesis. Prior to the most recent of these admissions, the patient developed a headache; evaluation of her cerebrospinal fluid revealed the presence of *Cryptococcus*, and she was treated with a 2-week course of amphotericin B. Physical examination demonstrated a temperature of 101.1 °F, heart rate of 110 bpm, and blood pressure of 94/65 mm Hg. She appeared ill and was underweight with dry mucous membranes and photophobia. Laboratory tests revealed random cortisol of 0.5 μg per dL. CT imaging showed bilateral adrenal gland enlargement and fine needle aspiration of the adrenal gland revealed encapsulated budding yeast. Stress dose intravenous glucocorticoids were administered and switched to oral hydrocortisone and fludrocortisone because the patient clinically improved with a second course of amphotericin B. Further evaluation in 2017 revealed persistently enlarged adrenal glands, positive cryptococcus antigen, and low IgG levels.

Discussion: Our literature review noted few publications of AI caused by disseminated cryptococcus with no long-term follow-up of these cases beyond a 1- to 4-year time frame.

Conclusion: Patients with AI due to disseminated fungal infection need long-term follow-up to assess for resolution of adrenal enlargement and evaluation of immunocompromised status.

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Introduction

Primary adrenal insufficiency (AI) due to disseminated fungal infection such as *Cryptococcus neoformans* is uncommon and the mortality rate is high; rates of 35% to 40% are observed in the acute 3 months following diagnosis of cryptococcal meningoencephalitis[1]. Cryptococcus infection typically occurs in the lungs and further infiltration to other organs is atypical in immunocompetent patients. Although infrequent, it can involve other organs including the liver, lymph nodes, peritoneum, adrenal glands, eyes, and skin lesions.[1-3] The case presented is unique in that the patient's medical care spans more than a decade. The records from 2004 were obtained by the first author from hospital documents kept on file by the patient. None of the authors had an established doctor-patient relationship with the patient at the time of diagnosis of AI. Recent records evaluating persistent adrenal gland enlargement and immunodeficiency were provided by the patient's endocrinologist and the second author.

Case Report

A 47-year-old woman presented in January of 2004 with a 50 lb weight loss, nausea, emesis, and headache with diplopia. The patient had been in good health before the onset of symptoms

Abbreviations: ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CSF, cerebrospinal fluid; CT, computed tomography; CVID, common variable immunodeficiency; FNA, fine needle aspirate; GERD, gastroesophageal reflux disease; IgG, immunoglobulin G.

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with a past medical history of tonsillectomy and Hashimoto's thyroiditis controlled on levothyroxine 50 mcg daily. The patient had multiple admissions in the preceding 6 months due to fatigue, myalgias, nausea, emesis, anorexia, abdominal pain, and loose stools. During prior hospitalization, the patient was diagnosed with cryptococcal meningoencephalitis and received a 2-week course of intravenous amphotericin B and oral fluconazole 400 mg daily. Prior hospitalizations included upper endoscopy consistent with gastritis and abdominal imaging with ultrasonography noting biliary sludge, no cholelithiasis or biliary obstruction, and right suprarenal mass measuring 5 × 2.1 × 5.1 cm without further documentation of additional abdominal imaging.

Physical examination was notable for temperature of 101.1 °F, heart rate of 110 bpm, blood pressure of 94/65 mm Hg, respiratory rate of 16 bpm, and 98% oxygen saturation on room air. The patient appeared ill and was underweight with dry mucous membranes and mild photophobia. Laboratory tests included sodium 133 mEq per L (135-146 mEq per L), potassium 5.3 mEq per L without hemolysis (3.5-5.3 mEq per L), blood urea nitrogen 22, creatinine 1.0 (baseline 0.6), glucose 83 mg per dL, thyroid stimulating hormone 1.550 (0.45-5.0 UIU per mL), and HIV negative. Cerebrospinal fluid was obtained by lumbar puncture and revealed a negative bacterial panel, and the results were positive for encapsulated yeast with *C. neoformans* antigen testing +1:4 titer. Gastroenterology testing including stool ova and parasite testing, stool leukocyte, and *Clostridium difficile* testing was negative. The morning serum cortisol concentration at 4:30 AM was 0.5 μg per dL, adrenocorticotropic hormone 764 pg per mL (10-60 pg per mL), aldosterone <0.2 ng per dL, and renin 25 ng per mL per hour, and anti-adrenal antibody negative. The patient was treated with IV hydrocortisone 100 mg every 8 hours and titrated down with ongoing improvement in clinical status. The patient was switched to oral hydrocortisone 10 mg daily in the morning, 5 mg in the afternoon, and Florinef 0.15 mg daily. Computed tomography (CT) scan of abdomen with contrast noted right adrenal gland 4.4 × 2.0 cm and left adrenal gland 3 × 2.1 cm. Original images from 2004 are not available for review. Cytopathology from the right adrenal biopsy with CT-guided fine needle aspiration (FNA) demonstrated *Cryptococcus neoformans* without evidence of malignancy. Upon diagnosis of disseminated cryptococcus one month after first treatment with amphotericin B, the patient received an additional 2-week course of intravenous amphotericin B and was then placed on continuous fluconazole 200 mg daily.[2] Consultation with Infectious Disease in 2004 did not result in clear etiology as to the cause of disseminated cryptococcus in an immunocompetent patient. Records from this consultation were not available for review.

In 2017, at the age of 61 years, the patient moved and established care with a different endocrinologist. The patient continued Florinef 0.15 mg daily, switched to prednisone 5 mg daily, and remained on fluconazole 200 mg daily. Updated CT imaging demonstrated persistent enlargement of adrenal glands with the right adrenal gland at 4.13 × 2.45 cm and the left at 3.64 × 2.12 cm (Fig. 1 through 3). Recent updates in medical history were notable for recurrent *Cl. difficile* infection treated with multiple courses of oral vancomycin and resolved after fecal microbiota transplantation. The patient had also required hospitalization once for bacterial pneumonia after diagnosis of primary AI. A second consultation with Infectious Disease was pursued. Additional laboratory tests indicated persistent infection with positive serum *Cryptococcus* antigen and low IgG with subsequent diagnosis of common variable immunodeficiency (CVID). Upon diagnosis of CVID, subcutaneous IgG therapy was started. The patient continued to require both glucocorticoid and mineralocorticoid replacement at physiologic levels with clinical episodes of Addisonian crisis during times of acute illness requiring intramuscular or intravenous glucocorticoids.

Highlights

- Adrenal gland biopsy is not often needed. Consider use where diagnosis of infectious etiology or new metastatic disease may directly affect patient care
- Diagnosis of disseminated fungal infection as etiology of primary adrenal insufficiency warrants further evaluation for underlying immunodeficiency
- Reassessment for recovery of adrenal function should be considered following treatment of infectious process causing primary adrenal insufficiency

Clinical Relevance

Disseminated fungal infections are a known cause of primary adrenal insufficiency. This case presents a patient with no prior known immunocompromised status presenting after recent diagnosis of Cryptococcus meningitis. Additional laboratory testing and abdominal imaging identified primary adrenal insufficiency with bilateral adrenal gland enlargement. This is an unusual case in that long-term follow-up of more than a decade is presented. Consideration of when to pursue adrenal gland biopsy is reviewed as well as additional testing for underlying immunodeficiency patients with disseminated *Cryptococcus neoformans*.

Discussion

We describe the case of a previously healthy middle-aged woman with recent cryptococcal meningoencephalitis with diagnosis of AI following recurrence with disseminated fungal infection. Appropriate diagnosis and treatment with glucocorticoids and mineralocorticoids prevented this patient from experiencing continued volume depletion with inability to compensate for acute illness, which could have directly led to death. Screening for AI with 8:00 AM cortisol is advised, although in the acutely ill hospitalized patient random cortisol can be helpful to assess the ability of the adrenal glands to respond to the acute stressor requiring hospitalization. When the suspicion of AI in a hospitalized patient is high, treatment with glucocorticoids should not be delayed given increased morbidity and mortality. In the case presented, the incidental finding on abdominal ultrasonography of a 5.1 cm suprarenal mass appeared to have gone unnoticed and without dedicated CT adrenal imaging until readmission with diagnosis of disseminated *C. neoformans*.

While there are myriad causes of bilateral adrenal gland enlargement, in the case presented, the finding of low attenuation on CT was concerning for an infiltrative disease process. FNA biopsy is not routine, although it can be helpful to tailor effective treatments in patients with infectious etiology or potentially metastatic disease.[4,5] Pheochromocytoma should be excluded before pursuing FNA, and this procedure is of limited value in assessing for primary adrenal malignancy.[6] In the case presented, adrenal FNA was pursued in determining the etiology of bilateral adrenal gland enlargement because evidence of disseminated cryptococcus would directly impact treatment decisions. Although there have been no randomized controlled trials of antifungal therapy for central nervous system or disseminated

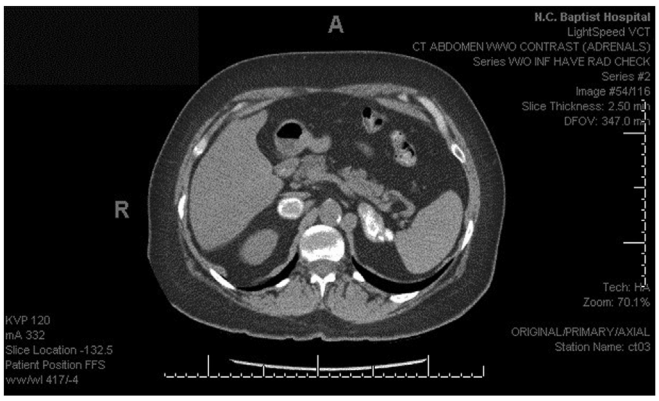

Fig. 1. Computed tomography scan of abdomen noting bilateral adrenal enlargement.

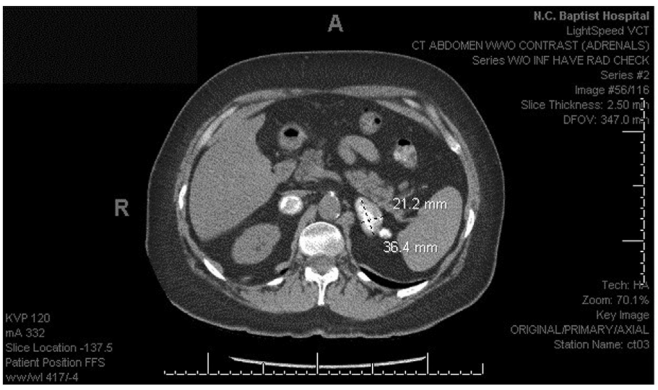

Fig. 3. Computed tomography scan abdomen with the largest cross-section of the left adrenal gland measuring 3.64 × 2.12 cm.

cryptococcus in solid organ transplant recipients, treatment recommendations are largely based on this population. Guidelines recommend treatment with liposomal amphotericin B or amphotericin B lipid complex plus 5-flucytosine followed by fluconazole for consolidation and maintenance. Maintenance therapy with fluconazole is typically for a minimum of 6 to 12 months duration.[2,7]

The literature on cryptococcal infection leading to primary AI is sparse, because there have been case reports, but no large case series. The first case report[4] was published in 1948 with few additional publications until the last five years.[8-11] A small case series published in 2018 reviewed 7 cases of primary AI caused by infiltrative disease of bilateral adrenal glands, which included one case with disseminated cryptococcus. The patient in this review underwent evaluation for recovery of adrenal function 4 months after antifungal therapy and was found to have persistent AI.[12] Treatment with amphotericin B is typically effective, although in 3 case reports, where it was ineffective for cryptococcal adrenalitis, adrenalectomy was pursued.[13-15] Additional data on adrenal involvement are observational from autopsies. While the review by Salyer et al[16] demonstrated that adrenal involvement was common with disseminated cryptococcus with 11 of 41 cases positive for adrenal lesions, another autopsy review noted only 1 case out of 13 with adrenal involvement.[17] Normalization of adrenal gland size following antifungal treatment has not been thoroughly evaluated in the literature. A case report by Muraoka et al,[4] of a 24-year-old individual with disseminated cryptococcus and adrenal enlargement, noted that the adrenal glands decreased to normal size on CT imaging 6 months after treatment with amphotericin B and fluconazole.

Nineteen years after diagnosis, the patient remains on daily fluconazole and monthly subcutaneous IgG therapy for CVID with persistently elevated cryptococcal antigen level and bilateral adrenal gland enlargement. Regarding the diagnosis of CVID, this disorder has extreme heterogeneity characterized by hypogammaglobinemia and increased risk of infections. Defects occur at three cellular levels with over 42 identified genetic mutations. Patients with CVID often have varying degrees of clinical symptoms even amongst patients with similar immunologic abnormalities. Age of onset is of clinical significance, because pediatric-onset and adult-onset patients present differently, adults typically with bronchitis, arthritis, and fatigue.[18] It is remarkable in the patient presented that no other significant infections have occurred aside from the recurrent *Cl. difficile* infection and one hospitalization for bacterial pneumonia.

In patients with bilateral adrenal disease, it is not always clear if treatment of the underlying cause will result in recovery of glucocorticoid production. In cases where primary AI is secondary to a destructive disease process such as malignancy, recovery is unusual. In cases where etiology is infectious, reassessment for recovery of adrenal function may be considered because there are reports of regaining adrenal function, although this is not a common outcome[12]. We propose that in patients with primary AI due to disseminated cryptococcus, long-term follow-up is necessary to assess for resolution of adrenal gland enlargement and recovered ability to produce glucocorticoids.

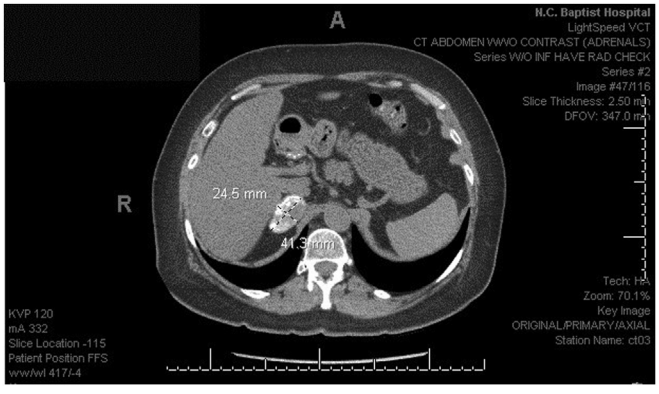

Fig. 2. Computed tomography scan of abdomen with the largest cross-section of the right adrenal gland measuring 4.13 × 2.45 cm.

Disclosure

Catherine E. Price discloses that she is the daughter of the patient presented who has provided informed consent for publishing the case report. The educational efforts of the patient's initial endocrinologist greatly contributed to further pursuits in medicine and a subsequent career in Endocrinology. No financial disclosures. The other authors have no multiplicity of interest to disclose.

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Author Contributions

All authors made individual contributions to authorship. C.P. was involved in obtaining copies of original records from 2003-2004 because the case was never presented previously as well as the writing and manuscript submission. J.A. contributed in writing and editing. C.B. was involved in the management of this patient upon establishing care in 2017 and pursued a second opinion consultation with Infectious Disease. C.B. was also involved in the writing of this manuscript. All authors reviewed and approved the final draft.

Informed Patient Consent for Publication

The patient has provided signed informed consent.

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