Case Report

Histoplasmosis: An Unusual Cause of Adrenal Insufficiency

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A B S T R A C T

Objective: Adrenal insufficiency (AI), if not diagnosed in a timely manner, can lead to fatal outcomes. Here we describe an unusual case of AI secondary to disseminated histoplasmosis (DH) and the importance of being aware of the association of infections and AI.

Methods: A 56-year-old Hispanic man with untreated HIV infection presented for the evaluation of left upper jaw swelling and pain. A brain magnetic resonance imaging scan revealed a 4-cm soft-tissue mass in the left maxilla. Biopsy of the mass was consistent with histoplasmosis. He was also noted to have hyponatremia and hyperkalemia, which raised the suspicion of AI. Laboratory investigation showed a baseline cortisol level of 7 mg/dL (normal, 7-23 mg/dL) and adrenocorticotropic hormone level of 86 pg/mL (normal, 7-69 pg/mL). His 60-minute cortisol level after a 250-mg cosyntropin stimulation test was 9 mg/dL (normal, 7-23 mg/dL). Computed tomography of the chest incidentally noted bilateral adrenal enlargement. An adrenal biopsy was not pursued due to the high index of clinical suspicion of DH as the etiology of AI.

Results: He was diagnosed with adrenal histoplasmosis because of the evidence of AI and bilateral adrenal enlargement in the setting of DH. He was started on glucocorticoid replacement for primary AI and continues to be on glucocorticoids even after 5 years of diagnosis. DH frequently involves the adrenal gland (80%) and can present as adrenal enlargement but does not always cause primary AI.

Conclusion: Our case demonstrates the importance of being vigilant about infections like histoplasmosis as a potential cause of AI. Delay in treatment in such cases could result in life-threatening consequences.

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Introduction

When Thomas Addison first described adrenal insufficiency (AI) in 1855, infections were a common cause. 1 Mycobacterium tuberculosis infection still remains an important cause of AI in the developing world. 2,3 However, more recently, the most common etiology of AI in adults is autoimmune disease (80%) and in children is congenital adrenal hyperplasia (72%). 4 In a literature review of cases of adrenal histoplasmosis over the last decade, 72 cases were reported worldwide, of which only 3 patients originated from U.S. 5 Hence, in developed countries, there tends to be a lower suspicion for infectious causes as an etiology for AI. We describe a patient with untreated HIV infection who developed primary adrenal insufficiency (PAI) from disseminated histoplasmosis (DH).

Case Report

A 56-year-old Puerto Rican man with untreated HIV infection and hypertension presented to the emergency department from his dentist's office for evaluation of swelling and pain of the left upper jaw, difficulty in swallowing, weight loss of about 9 kg, and nonproductive cough for a duration of 3 months. On examination, his blood pressure was 147/95 mm Hg, heart rate was 116 beats/min, respiratory rate was 16 breaths/min, and temperature was 97.8 °F. The patient had oral thrush, palpable cervical lymph nodes, and a mass in the posterior maxillary region near the upper left molars. A generalized maculopapular rash was noted on the upper chest and back. His HIV viral load was 162,500 copies/mL and the CD4 count was 27 cells/µL. Magnetic resonance imaging of the brain with and without gadolinium contrast showed a 3.9 × 2.5 × 4.3-cm soft-tissue mass in the posterior aspect of the left maxilla with erosion into the maxillary sinus. Biopsy of the mass showed sheets of...
of granulomatous tissue with plump macrophages containing well-demarcated fungal spores consistent with histoplasmosis. Computed tomography (CT) of the chest for the evaluation of cough showed hilar lymphadenopathy with an incidental finding of bilateral adrenal gland enlargement, with the left gland measuring 4.8 × 3.7 cm and right gland measuring 4.7 × 2.3 cm (Fig. 1).

Laboratory testing during hospitalization showed persistent hyponatremia and mild hyperkalemia. A 250-μg cosyntropin stimulation test was performed because of suspected AI. The baseline cortisol was 7 μg/dL (normal, 7-23 μg/dL) and adrenocorticotropic hormone was 86 pg/mL (normal, 7-69 pg/mL). The 60-minute cortisol level after cosyntropin injection showed a suboptimal response at 9 μg/dL. This was consistent with the diagnosis of primary adrenal insufficiency (PAI). Laboratory results are listed in Table 1. He did not undergo adrenal biopsy, given the high index of clinical suspicion of DH as the etiology of AI; 21-hydroxylase antibody levels were undetectable.

Mineralocorticoid and glucocorticoid replacement therapy was started with fludrocortisone 0.1 mg once daily and prednisone 7-23 mg once daily. This was consistent with the diagnosis of primary adrenal insufficiency (PAI). Laboratory results are listed in Table 1. He did not undergo adrenal biopsy, given the high index of clinical suspicion of DH as the etiology of AI; 21-hydroxylase antibody levels were undetectable.

Table

| Serum laboratory investigation | Reference range | May 2, 2015 | March 21, 2019 |
|-------------------------------|-----------------|------------|---------------|
| Adrenocorticotropic hormone    | 7-69 pg/mL      | 86         | ...           |
| Aldosterone                   | 4-31 ng/dL      | <3         | ...           |
| Cortisol, 0 min               | 7-23 μg/dL      | 7          | 9.4           |
| Cortisol, 30 min after        | 7-23 μg/dL      | 9          | ...           |
| 250 μg cosyntropin             | 7-23 μg/dL      | 9          | 12.1          |
| Renin                         | 0.5-4.0 ng/mL/h | 0.6        | ...           |
| Sodium                        | 137-144 mEq/L   | 126        | 140           |
| Potassium                     | 3.6-5.1 mEq/L   | 4.9        | 4.4           |
| Glucose                       | 75-200 mg/dL    | 98         | ...           |
| Creatinine                    | 0.6-1.2 mg/dL   | 0.9        | 0.7           |

Histoplasmosis is a common fungal infection caused by the dimorphic fungus *Histoplasma capsulatum* in the endemic areas of the world like the midwestern U.S. and Central America. Of note, our patient was born in Puerto Rico and relocated to the northeastern U.S. more than 20 years ago. The inhalation of histoplasma spores commonly results in asymptomatic infection or presents as mild and self-limiting pneumonitis. Histoplasmosis can be severe and is mostly seen in immunocompromised patients. It is thought to be more common because of defective underlying cellular immunity. This can lead to progressive disseminated disease and involvement of various organs, including the adrenal gland. Other opportunistic infections that are commonly seen in patients with HIV infections and can disseminate to involve the adrenals include cytomegalovirus, *Mycobacterium avium* and *intracellulare*, etc. Our patient had a very low CD4 count of 27 cells/μL at the time of this episode, which may have led to infection with histoplasmosis. The dissemination of histoplasmosis occurs through the reticuloendothelial system and can affect the adrenal gland in many ways, including extracapsular perivasculitis, granulomatous inflammation, and the destruction of the adrenal glands. Al usually is a result of extensive destruction of both the adrenal glands by infection. Chronic infection can also lead to atrophy and calcification, leading to a higher risk of development of PAI. DH
Adrenal histoplasmosis, although rare, should be considered as a differential diagnosis in patients presenting with bilateral adrenal gland enlargement and primary AI, especially in areas where histoplasmosis is endemic. It is also important to monitor patients with adrenal histoplasmosis and have a low threshold to screen patients for PAI in the future. Our case demonstrates the importance of being vigilant about this association as a delay in treatment could result in life-threatening consequences.

Conclusion

Adrenal histoplasmosis, although rare, should be considered as a differential diagnosis in patients presenting with bilateral adrenal gland enlargement and primary AI, especially in areas where histoplasmosis is endemic. It is also important to monitor patients with adrenal histoplasmosis and have a low threshold to screen patients for PAI in the future. Our case demonstrates the importance of being vigilant about this association as a delay in treatment could result in life-threatening consequences.

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Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Leelarathna L, Powrie J, Carroll P. Thomas Addison’s disease after 154 years: modern diagnostic perspectives on an old condition. QJM. 2009;102:569–573.
2. Paolo Jr WF, Nosanchuk JD. Adrenal infections. Int J Infect Dis. 2006;10:343–353.
3. Gupta P, Bhalla A, Sharma R. Bilateral adrenal lesions. J Med Imaging Radiat Oncol. 2012;56:636–645.
4. Betterle C, Morlin L. Autoimmune Addison’s disease. Endocr Dev. 2011;20:161–172.
5. Koene R, Catanese J, Sarosi GA. Adrenal hypofunction from histoplasmosis: a literature review from 1971 to 2012. Infection. 2013;41:757–759.
6. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007;20:115–132.
7. Wahab NA, Mohd R, Zainudin S, Kamaruddin NA. Adrenal involvement in histoplasmosis. EXCLI J. 2013;12:1–4.
8. Goodwin RA, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. Medicine. 1980;59:1–33.
9. Larbcharoensub N, Boonsakan P, Aroonroch R, et al. Adrenal histoplasmosis: a case series and review of the literature. Southeast Asian J Trop Med Public Health. 2011;42:920–925.
10. Rog CJ, Rosen DG, Cannon FH. Bilateral adrenal histoplasmosis in an immunocompetent man from Texas. Med Mycol Case Rep. 2016;14:4–7.
11. Herndon J, Nadeau AM, Davidge-Pitts CJ, Young WF, Bancos I. Primary adrenal insufficiency due to bilateral infiltrative disease. Endocrine. 2018;62:721–728.
12. Alloio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2014;172:115–124.
13. Borstein SR, Alloio B, Airt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:364–388.
14. Benevides CFL, Durães RO, Aquino R, Schiavon LdL, Narciso-Schiavon JL, Buzoletti FdC. Bilateral adrenal histoplasmosis in an immunocompetent man. Rev Soc Bras Med Trop. 2007;40:230–233.
15. Rozenblit AM, Kim A, Tuva J, Wenig BM. Adrenal histoplasmosis manifested as Addison’s disease: unusual CT features with magnetic resonance imaging correlation. Clin Radiol. 2001;56:682–684.
16. Singh M, Chandy DD, Bharani T, et al. Clinical outcomes and cortisol reserve in adrenal histoplasmosis—a retrospective follow-up study of 40 patients. Clin Endocrinol. 2019;90:534–541.