Case Report

Persistence of histoplasma in adrenals 7 years after antifungal therapy

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ABSTRACT

Adrenal histoplasmosis is an uncommon cause for adrenal insufficiency. The duration of treatment for adrenal histoplasmosis is not clear. Existing treatment regimens advocate antifungals given for periods ranging from 6 months to 2 years. We report here a rare case who showed persistence of histoplasma in adrenal biopsy 7 years after being initially treated with itraconazole for 9 months. This calls for a prolonged therapy with regular review of adrenal morphology and histology in these patients.

Key words: Addison's disease, antifungal therapy, histoplasma

Introduction

Histoplasmosis is the most common systemic mycosis, characteristically affecting the reticuloendothelial system, blood, and its components.[1,2] Body's defense mechanisms including both cellular and humoral immunity prevent the affliction by histoplasma. Impaired cellular immunity as in uncontrolled diabetes, AIDS or malignancy could result in invasion and dissemination of the histoplasma.

Adrenals are a common site of invasion by the histoplasma. In overwhelming acute invasion by the histoplasma, the presentation is usually a catastrophic event such as an acute adrenal crisis.[3] However, chronic forms present as subtle features of adrenal insufficiency such as lethargy, hyperpigmentation, weight loss, and gastrointestinal symptoms. Treatment of adrenal histoplasmosis includes antifungals given over a variable period of 6 months to 2 years. However, whether prolonged antifungal treatment can totally eradicate histoplasmosis is unclear. We report here a case whereby the patient diagnosed as adrenal histoplasmosis was treated with 9-month itraconazole therapy and was continued on steroid replacement. There was no regression in the adrenal size and an adrenal biopsy performed 7 years later revealed persistence of histoplasma.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.111679

Case Report

A 50 year old male, a diagnosed case of Addison's disease, presented to the Endocrine clinic of this hospital for reevaluation. His clinical history dated 7 years back when he presented with complaints of hyperpigmentation and weight loss for 10 months. There had been no history of tuberculosis in the past. A diagnosis of primary adrenal insufficiency was made (ACTH 743 pg/ml, post-ACTH cortisol 4.8 mcg/dl, PRA 24.7 ng/ml/h (1.3-3.95) and aldosterone 16.6 ng/dl (4-31) and the patient initiated on glucocorticoids and mineralocorticoids. Both the adrenals were enlarged on CT imaging (rt adrena l6.8 × 3.2 cm and Lt adrenal – 5.8 × 4.0 cm). Adrenal biopsy revealed numerous tiny unstained elliptical yeast-like bodies, some of them showing budding. These were Periodic Acid Schiff stain positive [Figure 1]. He received itraconazol 400 mg daily for 9 months which was then stopped and the patient continued on steroid replacement therapy. Hyperpigmentation, appetite, and weight gradually improved while on therapy. He had developed diabetes for the past 2 years and had been receiving oral hypoglycemics.

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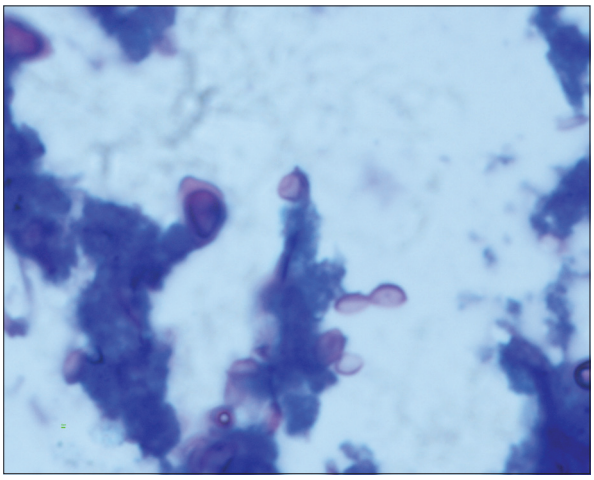

Figure 1: Adrenal biopsy shows numerous tiny unstained elliptical yeast-like bodies (staining positive with Periodic Acid – Schiff stain), some of them showing budding (×1000)

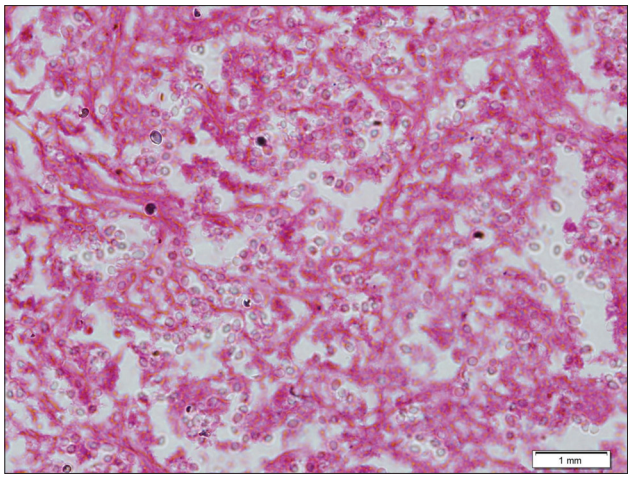

Figure 2: Adrenal biopsy 7 years after initial therapy shows numerous spores of histoplasma capsulatum that stain positive with the PAS stain (×400)

Present evaluation revealed a 75 kg male with no cutaneous striae; blood pressure was 151/93 mm Hg. Investigations revealed a normal hemogram with ESR-40, and normal liver and kidney function tests and Thyroid Function Tests, ACTH 19.5 pg/ml and post-ACTH cortisol levels 4.3 mcg/dl after 1 day of missing the steroid preparation. HIV serology was negative. A repeat CT imaging revealed bilaterally enlarged adrenals with no significant change in either the size or the morphology of the adrenals when compared to the previous CT imaging. Repeat adrenal biopsy revealed necrotic tissue with numerous spores of histoplasma capsulatum that stained positive with the PAS stain and Grocott methanamine silver stain [Figure 2].

Discussion

Histoplasmosis is an infectious granulomatous disease caused by dimorphic fungus Histoplasma Capsulatum.[1,2] Humans get infected by airborne spores of birds or bat's excreta.[1,2] The fungus has a predilection for the reticuloendothelial system mainly lymph nodes, spleen, and liver.[3] The disease may be classified as acute, chronic, and disseminated.[4] Majority of cases infected with Histoplasma remain asymptomatic. Most symptomatic patients present with variety of self-limited manifestations, the most common being influenza like syndrome and fever.[5] The chronic form of the disease is mainly localized to the lung and manifests with tuberculosis like picture and sequelae.[4] Disseminated histoplasmosis is rare occurring mostly in acute rather than chronic forms; however, the frequency of dissemination in acute histoplasma infections is 1:2000.[6] Most patients who develop acute infection are immunocompromised. An acute rapidly fatal course with diffuse reticuloendothelial involvement characterizes the infection in infants and others who are severely immunosuppressed, while a chronic course with focal organ distribution is more typical in nonimmunocompromised individuals.[6,7]

Adrenal involvement in histoplasmosis could be either a part of disseminated form in immunosuppressed patients or may occur as a localized adrenal disease. The disseminated forms present as acute adrenal crisis along with multisystem involvement. Godwin *et al*. reported acute adrenal crisis in 7% of patients presenting with disseminated histoplasmosis.[6] However, subtle or chronic forms of adrenal insufficiency due to focal adrenal involvement may be more common. Sarosi *et al*. reported around 50% adrenal involvement in patients presenting with various forms of histoplasmosis.[8] CT features of adrenal histoplasmosis vary depending on the stage of the disease. Typically, it includes bilateral adrenal masses with peripheral enhancement and central hypodensities, with calcification seen in the healing phase.[9] These changes are usually bilateral and symmetrical and the shape of adrenal gland is usually preserved.

Treatment of histoplasmosis involves systemic antifungal therapy – ketoconazole or itraconazole for mild to moderate forms and Amphotericin B for severe infections. The duration of therapy is unknown with therapy given for adrenal forms for a period ranging from 6 months to 2 years.[10] Mukherjee *et al*. reported two immunocompetent patients with histoplasmosis who were treatment with oral itraconazole 200 mg daily for 6 months and 18 months respectively.[11] While the adrenal function was normal 9 years after therapy in the first patient, the second patient continued to have enlarged adrenals 18 months after therapy.

The present case received itraconazole for 9 months. However, there was no reduction in the adrenal size and

histoplasma could still be demonstrated in the adrenal biopsy 7 years later. It is unclear whether steroid overdose, development of diabetes or patient's own immune status was responsible for persistence of histoplasma. Whether histoplasma could remain in dormant, latent or subclinical forms for prolonged periods is not known. Desmet *et al*.[12] reported an immunocompetent patient who developed a reactivation of a latent histoplasma infection, presenting as subacute progressive disseminated histoplasmosis acquired during a previous stay in Africa more than 10 years before.[12] Johnston *et al*.[13] reported a patient with chronic disseminated histoplasmosis who was followed after successful treatment with amphotericin B for 10 years until his death from chronic obstructive airways disease. Necropsy showed that Histoplasma organisms could still be identified in the adrenal and pancreatic abscesses, though none appeared viable on electron microscopy.

In conclusion, this was a rare case of adrenal histoplasmosis who showed persistence of histoplasma in the adrenal lesions 7 years after itraconazole therapy. This calls for a more aggressive and prolonged therapeutic approach in these patients.

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Cite this article as: Kothari D, Chopra S, Bhardwaj M, Ajmani AK, Kulshreshtha B. Persistence of histoplasma in adrenals 7 years after antifungal therapy. Indian J Endocr Metab 2013;17:529-31.

Source of Support: Nil, **Conflict of Interest:** None declared.