Addison's disease due to *Histoplasma duboisii* infection of the adrenal glands

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ABSTRACT

داء النوسجات يحدث نتيجة للإصابة بفطر النوسجة المغمدة. الإصابة بداء النوسجة المنتشر وقصور الغدة الكظرية نتيجة للإصابة بهذا الفطر من الأمور التي يندر حدوثها في الإنسان الطبيعي. نصف هنا حالة لرجل يبلغ من العمر خمسون عاماً من غرب السودان، يشكو من ضعف عام، وتقيء، وإسهال لمدة سبعة أشهر. اجري فحص سريري ومخبري شُخص بموجبة داء أديسون نتيجة لإصابة الغدة الكظرية بفطر النوسجة المغمدة. تم علاج المريض بالحقن الوريدي بالهيدروكورتيزون وحبوب البردنسلون والأتراكونازول.

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. In the normal individual, both disseminated histoplasmosis and symptomatic adrenal histoplasmosis are rare. Herein, we describe the case of a 50-year-old gentleman residing in western Sudan who presented with a 7-month history of generalized body weakness, easy fatigue, and frequent attacks of vomiting and diarrhea. Physical examination and laboratory investigations confirmed the diagnosis of Addison's disease due to *Histoplasma capsulatum* var *duboisii* infection of the adrenal glands. He was treated with intravenous hydrocortisone, followed by oral prednisolone and itraconazole.

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Two forms of histoplasmosis infect humans: the classic histoplasmosis caused by *Histoplasma capsulatum* var *capsulatum* and the more geographically restricted African histoplasmosis due to *Histoplasma capsulatum* var *duboisii*. Both diseases are endemic in Africa though the African form is the predominant form. Herein, we report a patient from Sudan who had Addison disease caused by *Histoplasma capsulatum* var *duboisii*. As far as we are aware adrenal disease caused by *Histoplasma capsulatum* var *duboisii* has not been described before.

Case Report. A 50-year-old patient residing in western Sudan presented with a 7-month history of generalized body weakness, easy fatigue, frequent attacks of vomiting, and diarrhea, loss of appetite, and reported that he lost approximately 15% of his total body weight. He was treated at his local hospital on several occasions for hypotension and presumed malaria infection without improvement. He had a family history of goiter and a personal history of goiter for the past 20 years and was not on long term medications. On physical examination he was ill, pale with a temperature of 37.6^{0}C, pulse rate of 110/min, blood pressure of 90/60 mm Hg with postural hypotension and he weighed 75 kilograms with a height of 180 cm. He had hyperpigmented palm creases and buccal mucosa. Neck examination showed a multinodular goiter with no retrosternal extension or audible bruit and no cervical lymphadenopathy. Examination of his cardiopulmonary system, abdomen, and nervous system were unremarkable. Laboratory investigations are shown in **Table 1**. These showed a low hemoglobin, normal white blood cell count with absolute eosinophilia, elevated erythrocyte sedimentation rate, elevated serum urea, and a low sodium concentration and a normal potassium level. He had normal thyroid function tests. Human immunodeficiency virus (HIV) serology was negative. The serum cortisol was low with a grossly elevated adrenocorticotrophic hormone (ACTH) level. His chest x-ray was clear and sputum was negative for acid-fast bacilli. Ultrasonography of the thyroid gland showed an enlarged right lobe with a huge cyst and fine needle aspiration of the thyroid gland showed features consistent with multinodular goitre. Abdominal computerized axial

tomography (CT) scan showed a well circumscribed capsular enhancing rounded septated cystic lesion on the right adrenal region and a similar pyramidal shaped lesion in the left supra renal region. Histopathology of CT guided biopsy of the adrenal gland showed fungal hyphae and spores consistent with *Histoplasma capsulatum* var *duboisii* (**Figure 1 & 2**). He received intravenous hydrocortisone 100 mg QID for 48 hours followed by oral prednisolone and was then maintained on prednisolone 7.5 mg daily and itraconazole 200 mg daily for 6 months. Two weeks after hospital admission, his fever subsided, vomiting and diarrhea stopped, and 2 months after discharge from the hospital his weight increased to 82 kilograms. Palmer and buccal pigmentation improved, and his complete blood count and blood chemistry normalized.

Discussion. African histoplasmosis involves the skin, subcutaneous tissues, lymph nodes, and bones, and rarely the lungs, and other internal organs.[1,2] Approximately 70% of patients develop a localized disease. Disseminated infection affects 2-5 or more sites in the body. In disseminated histoplasmosis, involvement of the adrenal glands occurs in 80% of patients and 5-10% develop clinical adrenal insufficiency.[3] Biopsy of the adrenal gland in this patient showed several multinucleated giant cells containing budding yeasts. The yeasts were oval with single nuclei, had thick capsules, measured 8-15 microns and were budding. The buds were joined to the parent cell by a narrow base. The fungus stained red with Periodic acid-Schiff (PAS) stain and black with Gomori Methenamine silver (**Figure 1 & 2**). As observed in this case, *Histoplasma capsulatum* var *duboisii* is usually larger and is found in giant cells in comparison with *Histoplasma capsulatum* var *capsulatum*, which is found in histiocytes. Difficulty may also be experienced with *Blastomyces dermatitidis* infection which is found in the same geographical area in Africa.[4] In this case, the yeasts are always spherical, the single bud is formed on a large base and the numerous nuclei contrast with the single nucleus of *Histoplasma capsulatum* var *duboisii.* The portal of entry of *Histoplasma capsulatum* var *duboisii* is not definitely known. The fungus enters the human body most probably via the respiratory tract, even if the presence of or the sequel to a primary pulmonary infection cannot

Table 1 - Laboratory investigations in a 50-year old gentleman with Addison's disease due to *Histoplasma duboisii*.

Test	Normal range	Patient values
Hemoglobin concentration	138-172 g/L	71 g/L
White blood cell count	4-11 x 10^9/L	6.1 x 10^9/L
Eosinophil count	0.04-0.4 x 10^9/L	0.55 x 10^9/L
Platelet count	140-350 x 10^9/L	666 x 10^9/L
ESR	5-10 mm/Hr	81 mm/Hr
Serum urea	2.5-6.7 mmol/L	7.1 mmol/L
Serum Na	135-146 mmol/L	126 mmol/L
Serum K	3.5-5.0 mmol/L	4.1 mmol/L
TSH	0.3-3.5 mU/L	1.4 mU/L
T_3	1.2-3.1 mmol/L	2.8 mmol/L
T_4	60-160 mmol/L	120 mmol/L
Serum cortisol (AM)	171-536 mmol/L	46.45 mmol/L
Serum cortisol (PM)	64-327 mmol/L	48.36 mmol/L
ACTH level	9-32 mcg/L	1360 mcg/L
Fasting blood glucose	4.5-5.6 mmol/L	6.0 mmol/L
HIV test		Negative
Sputum for AAFB		Negative

TSH - thyroid stimulating hormone, T3 - triiodothyronine, T4 - thyroxine, ACTH - adrenocorticotrophic hormone, HIV - human immunodeficiency virus, AAFB - alcohol acid fast bacilli, Na - sodium, K - potassium, ESR - erythrocyte sedimentation rate

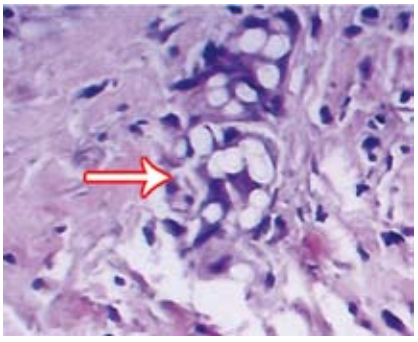

Figure 1 - Multinucleated giant cells containing thick-walled budding yeasts of *Histoplasma duboisii* (hematoxylin and eosin x 40).

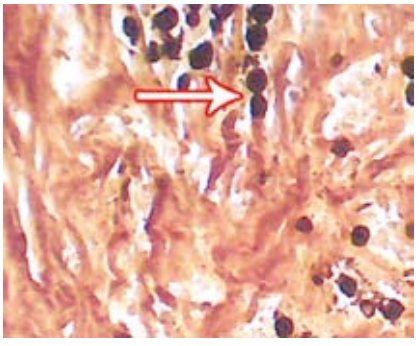

Figure 2 - Several budding yeasts of *Histoplasma duboisii* staining black with Gomori methenamine silver. Note the bud attached with a narrow base which is characteristic (Gomori methenamine silver x 40).

be demonstrated.[5] Differential diagnosis of infectious agents causing Addison's disease includes *Mycobacterium tuberculosis*,[6] *Histoplasma capsulatum*,[3] *Blastomyces dermatitidis*,[4] *Cryptococcus neoformans*,[7] *Pneumocystis carinii*,[8] *Paracoccidioidomycosis*,[9] *Coccidioides immitis*.[10] Another cause of Addison's disease to be considered is acquired immunodeficiency syndrome.[11]

Tuberculosis (TB) was the most common cause of Addison disease in the past, and still may be a major consideration in areas where TB is common. It tends to involve both the adrenal cortex and the medulla, however, medullary involvement may not have any major consequences. Tuberculosis of the adrenal glands usually is a tertiary disease due to the hematogenous spread of infection to the adrenal glands, as clinical evidence of the primary infection is not always present. The diagnosis is based on the result of microbiological (culture or smear) or demonstration of acid-fast bacilli on histological section by Ziehl-Nielsen stain.[6] Adrenal insufficiency in patients with the acquired immunodeficiency syndrome is a well-recognized condition with an estimated incidence of 5-8%. Adrenal pathology most frequently results from infection with *Cytomegalovirus*, other less common causes include *Mycobacterium Avium* intracellulare infection, *Pneumocystis Carnii*, *Cryptococcus neoformans*, *Toxoplasmosis*, *Histoplasma Capsulatum*. These organisms can all by distinguished by their morphology in the tissues and by culture. Adrenal function in acquired immunodeficiency syndrome patients can also be inhibited as a result of polyclonal B cell activation and the production of anti-adrenal cell antibodies.[11] Human immunodeficiency virus test was however, negative in this patient. Itraconazole is a synthetic triazole antifungal agent that slows fungal cell growth by inhibiting CYP450- dependent synthesis of ergosterol, a vital component of fungal cell membranes, causing cellular components to leak resulting in fungal cell death. It is used in a dose of 200 mg daily for 3-6 weeks in pulmonary histoplasmosis and for 6-12 months for all manifestations of histoplasmosis.

In conclusion, in developing countries, patients presenting with Addison's disease should be carefully investigated for infectious causes including histoplasmosis.

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