

# ADRENAL HISTOPLASMOSIS: A CASE SERIES AND REVIEW OF THE LITERATURE

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**Abstract.** Adrenal histoplasmosis is an uncommon mycotic disease typically caused by *Histoplasma capsulatum*. The objective was to determine the clinicopathological findings in adrenal histoplasmosis. Pathological records were searched from the database at the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University from 1993 to 2008 for cases of adrenal histoplasmosis. The keywords were "histoplasmosis" and "adrenal gland". Adrenal histoplasmosis was diagnosed by histopathology and Gomori-Grocott methenamine silver staining. *Histoplasma capsulatum* was confirmed by tissue culture and/or serology. The authors report seven cases of adrenal histoplasmosis in immunocompetent patients. The mean age at diagnosis was 67 years. All patients presented as chronic fatigue syndrome. The onset of symptoms ranged from one to three months. Addison's disease was found in adrenal histoplasmosis in one case (14.3%). The computed tomography revealed adrenal nodules measuring 1.2 to 7.8 cm in diameter. The histopathology showed granulomatous inflammation with caseous necrosis. Culture of adrenal tissue from two patients revealed *Histoplasma capsulatum*. Serum *Histoplasma* antibodies were positive in four cases. A cure was accomplished in 6 out of 7 cases (85.7%). The patients were followed up for 2.5 to 16.5 years.

**Keywords:** histoplasmosis, mycosis, adrenal gland, chronic fatigue syndrome, adrenal insufficiency

## INTRODUCTION

Histoplasmosis is an uncommon opportunistic infection in the general population, and is more prevalent in immunocompromised patients (Deepe, 2005).

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Among non-AIDS patients who develop systemic mycosis, the histoplasmosis occurs in 0.65% of cases (Larbcharoensub *et al*, 2007). *Histoplasma* spp spreads from the lungs to the adrenal glands by hematogenous route. Diagnosis relies largely on biopsies, with histopathologic and microbiologic confirmation of fungal organisms in infected tissue (Deepe, 2005). There are few epidemiological data regarding adrenal histoplasmosis in Thailand (Roubsanthisuk *et al*, 2002). In this paper, we present 7 cases of histopathologically

and microbiologically verified adrenal histoplasmosis at Ramathibodi Hospital, Mahidol University.

## MATERIALS AND METHODS

This was a retrospective study of adrenal histoplasmosis diagnosed histopathologically at the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, between January 1993 and December 2008. All cases were seronegative for human immunodeficiency virus (HIV).

Adrenal tissue was formalin-fixed, embedded in paraffin, sectioned at 4  $\mu$ m and stained with Hematoxylin and Eosin (H&E) before examination. Fungal morphology was delineated using Gomori-Grocott methenamine silver (GMS), and Periodic Acid Schiff (PAS) to detect adrenal histoplasmosis. Information obtained from the medical records included age, gender, underlying predisposing risk factors for the disease, clinical manifestations, preoperative adrenal function and microbiologic studies. The present study was approved by the committee on human research at the Faculty of Medicine, Ramathibodi Hospital (ID05-51-38).

## RESULTS

Of the seven cases identified as having adrenal histoplasmosis, the mean age was  $67 \pm 10.6$  years and 5 (71.4%) were men. All patients were Thai immunocompetent individuals, who presented with chronic fatigue, weight loss, anorexia, and fever. The history of symptoms ranged from one to three months. Four cases (Patients 1-4) were considered to have primary adrenal insufficiency and underwent adrenocortical function testing. In one case (Patient 4), the adrenal function test revealed primary

adrenal insufficiency. All cases were examined for adrenal neoplasm and underwent abdominal computed tomography (CT) to identify the adrenal gland; 6 of 7 cases (85.7%) had bilateral adrenal masses (Fig 1, Patient 2) and one had a unilateral right adrenal mass. The adrenal masses were 1.2 to 7.8 cm in diameter. All cases were eventually diagnosed by needle biopsy (Patients 1-4, 7) or adrenalectomy (Patient 5, 6). The histopathology showed granulomatous inflammation with caseous necrosis within the lesion. The sections of the adrenal glands showed oval hyaline granules 2 to 4  $\mu$ m in diameter, and uninucleate intracellular and extracellular yeast. The yeast had single buds attached by a relatively narrow base and were often clustered. Culture of adrenal tissue obtained in two patients (Patients 1, 2) revealed *Histoplasma capsulatum*. Serum *Histoplasma* antibodies were positive in four cases (Patients 3-6). In one case (Patient 7), the patient had systemic histoplasmosis involving the gastrointestinal tract, bone marrow, and spleen.

Clinical management depended on the clinical situation of the individual cases. Antifungal drugs itraconazole, and/or amphotericin B were given in 6 out of 7 cases (Patients 1-5, 7). One case (Patient 6) was treated with adrenalectomy without antifungal medication. The treatment resulted in cure in 6 out of 7 cases (Patients 2-7). These patients were followed up for 2.5 to 16.5 years. Two patients (Patients 1, 5) died of pneumonia. An autopsy was performed on one case (Patient 1) which revealed bronchopneumonia with persistent bilateral adrenal histoplasmosis.

## DISCUSSION

Many pathogens are known to affect the adrenal gland in both immunocompe-

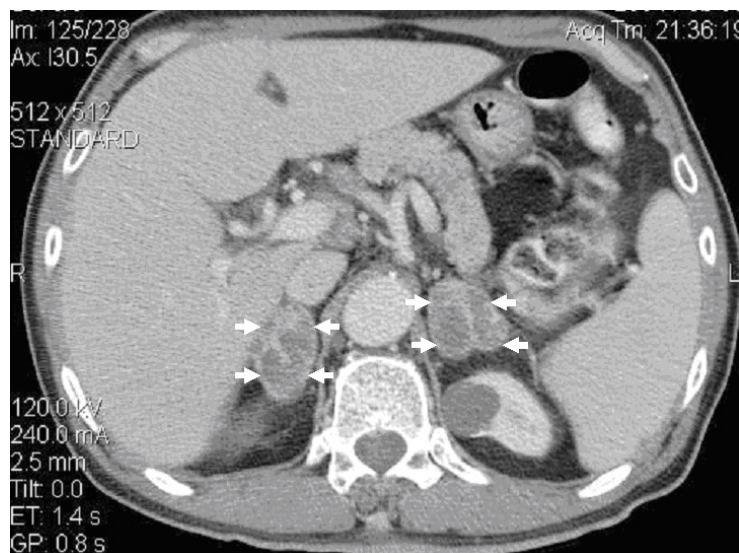


Fig 1—CT image. Noncontrasted CT shows bilateral adrenal masses (patient No 2).

tent and immunocompromised individuals. Adrenal infection is most frequently caused by hematologic dissemination. Most patients had symptoms, clinical signs, laboratory and radiological features resembling adrenal neoplasms. *Mycobacterium tuberculosis* is the most common bacterial pathogen associated with adrenal destruction (Paolo and Nosanchuk, 2006). Fungal infection is an uncommon disease of the adrenal gland. Most reported cases have involved *Histoplasma* spp (Wilson *et al*, 1984; Rozenblit *et al*, 2001; Roubsanthisuk *et al*, 2002; Vijayanathan *et al*, 2003; Paolo and Nosanchuk, 2006; Benevides *et al*, 2007; Carvalho *et al*, 2007; Kauffman, 2007).

Adrenal histoplasmosis has a wide spectrum of clinical manifestations, including chronic fatigue, weight loss, anorexia, and fever. Duration of the presenting symptoms is highly variable, ranging from one to six months (Rozenblit *et al*, 2001; Roubsanthisuk *et al*, 2002; Benevides *et al*, 2007). Patients with adrenal histo-

plasmosis have many of the same symptoms as those with the chronic fatigue syndrome. Adrenal histoplasmosis may diminish intracellular perforin by depressing T lymphocyte and natural killer cell function, causing chronic fatigue (Zhou *et al*, 2001; Maher *et al*, 2005). Primary adrenal insufficiency/Addison's disease occurs in 5-71% of adrenal histoplasmosis cases and is the commonest cause of death (Sarosi *et al*, 1971; Wilson *et al*, 1984; Paolo and Nosanchuk, 2006). These

patients exhibit fever, malaise, orthostatic hypotension, nausea, and vomiting. Hyperkalemia, hyponatremia and eosinophilia are present. Addison disease typically occurs with extensive destruction of both adrenal glands by infection. In early stages of destruction, it typically presents as chronic fatigue syndrome.

The typical CT findings of adrenal histoplasmosis are bilateral symmetrical adrenal enlargement with low-density areas of necrosis and hemorrhage (Doppman *et al*, 1982; Wilson *et al*, 1984; Rozenblit *et al*, 2001; Vijayanathan *et al*, 2003; Paolo and Nosanchuk, 2006; Benevides *et al*, 2007; Carvalho *et al*, 2007; Kauffman, 2007). The adrenal glands tend to maintain their normal configuration. The differential diagnosis of these CT findings includes tuberculosis, aspergillosis, cryptococcosis, blastomycosis, and penicilliosis (Mootsikapun and Srikulbutr, 2006; Paolo and Nosanchuk, 2006). Hence, the diagnosis of adrenal histoplasmosis cannot be made radiologically. Therefore,

Table 1  
Clinical and pathological findings of 7 patients with adrenal histoplasmosis.

	1	2	3	4	5	6	7
Patient no.	87	69	66	48	70	63	66
Age (years)	Male	Male	Male	Female	Male	Female	Male
Sex	Fatigue for 1 month	Fever, and fatigue for 1 month	Fatigue, and fever for 1 month	Fatigue, and hyperpigmentation for 3 months	Fatigue for 1 month	Fatigue for 2 months	Fatigue for 3 months
Chief complaint	HTN, chronic atrial fibrillation, COPD, BPH	DM	HTN, BPH hyperlipidemia,	HTN, DM, CRF	HTN, ischemic heart disease, CVA, BPH	Non-Hodgkin lymphoma, remission	HTN, DM, CRF
Underlying disease	5 kg in 5 months	5 kg in 1 month	5.5 kg in 1 month	30 kg in 2 months	26.5 kg in 3 months	5.3 kg in 1 month	19 kg in 6 months
Weight loss	5.5x3.5x6.4	3.7x2.7x4.1	6.0	4.8x2.6x3.0	6.5x5.7x7.8	2.4x4.0x3.8	4.0x5.0
Tumor size of the right adrenal gland (cm)	1.2x1.2x1.2	3.9x4.0x4.7	6.0x5.13	4.9x2.7x5.0	2.0x2.0x4.2	No	4.0x5.0
Tumor size of the left adrenal gland (cm)	22.8	13.1	16.7	198	Not performed	Not performed	Not performed
ACTH (pg/ml) stimulation test at 0 minute (normal: 0-71 pg/ml)	27.1	21	17.5	Not performed	Not performed	Not performed	Not performed
ACTH (pg/ml) stimulation test at 30 minutes	27.2	24.5	17.2	Not performed	Not performed	Not performed	Not performed
ACTH (pg/ml) stimulation test at 60 minutes	Not performed	Not performed	Not performed	Not performed	0.9	1.5	Not performed
Overnight 1 mg dexamethasone suppression test ( g/dl)	<i>H. capsulatum</i>	<i>H. capsulatum</i>	No growth	No growth	No growth	Contaminate	No growth
Tissue culture <i>Histoplasma</i> antibodies	Not performed	Not performed	Positive	Positive	Positive	Positive	Negative
Treatment	Biopsy followed by amphotericin B and itraconazole	Biopsy followed by amphotericin B and itraconazole	Biopsy followed by itraconazole	Biopsy followed by itraconazole and corticosteroid maintenance	Adrenalectomy follow by itraconazole and corticosteroid maintenance	Adrenalectomy, no follow medication	Biopsy followed by itraconazole
Status	Death 1 year after diagnosis due to pneumonia	Alive 6.5 years	Alive 4.5 years	Alive 16.5 years	Not performed	Alive 6 years	Alive 2.5 years

HTN, hypertension; COPD, chronic obstructive pulmonary disease; BPH, benign prostatic hyperplasia; DM, diabetic mellitus, CRF, chronic renal failure; CVA, cerebrovascular accident; ACTH, adrenocorticotrophic hormone

a high index of suspicion is essential, in immunodepressed cases. Immunocompetent hosts may also develop adrenal histoplasmosis (Hage and Wheat, 2008).

Characteristic histopathology demonstrates fungal elements and tissue reactivity. Histoplasmosis typically results in a localized mononuclear cell infiltrate developing granulomata with multinucleated giant cells. Yeast in tissue sections show uninucleate hyaline spherules or ovules 2 to 4  $\mu$ m in diameter (Deepe, 2005). Yeasts have a single bud attached by a narrow base and are often clustered. Using the GMS procedure, yeast may be detected in areas of caseating necrosis in the histoplasma obtained by needle biopsy or from an adrenalectomy specimen. Other laboratory tests, such as serology, complement fixation, a precipitation test, latex particle agglutination test, agar-gel double immunodiffusion test and radioimmunoassay have also been used (Kauffman, 2007). However, the gold standard for a definite diagnosis of histoplasmosis is tissue culture (Hage and Wheat, 2008).

The majority of individuals with histoplasmosis recover spontaneously and do not require specific therapy. Supportive treatment is often recommended for symptomatic acute histoplasmosis. However, chronic and severe acute infections must be treated. Adrenal histoplasmosis should be treated like disseminated histoplasmosis. Patients who are not severely ill can be treated with oral itraconazole, 200 mg bid. Patients with severe infection should be treated initially with amphotericin B at a dosage of 0.7 to 1 mg/kg daily or the lipid formulation of amphotericin B at a dosage of 3 to 5 mg/kg daily. Continuing amphotericin B throughout the entire course of therapy is no longer the standard of care. For almost all patients, as their condition improves,

generally within a few weeks, therapy is switched to oral itraconazole at a dosage of 200 mg bid (Wheat, 1997; Deepe, 2005; Kauffman, 2007).

This study offers the unique opportunity to assess the clinicopathology of adrenal histoplasmosis over a sixteen-year period at Ramathibodi Hospital. The frequent clinical manifestations observed in these patients was chronic fatigue. The authors emphasize the importance of microbiological studying the specimen to diagnose mycosis, and in particular to differentiate it from penicillosis, which is endemic in Thailand.

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