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## CASE REPORT

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# Fine Needle Aspiration Biopsy in the Diagnosis of Disseminated Histoplasmosis of the Adrenal Glands

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### ABSTRACT

*Disseminated histoplasmosis is a rare and potentially fatal disease caused by the dimorphic soil fungus *Histoplasma capsulatum*. This report is of a 66-year-old man who was initially diagnosed with a tooth abscess that was revealed to be histoplasmosis at biopsy. Subsequently, this patient presented with histoplasmosis of the vocal cords and hypoadrenalism. Computed tomography-guided biopsy accurately diagnosed the presence of bilateral adrenal histoplasmosis and he was successfully treated with itraconazole.*

**Key Words:** Adrenal, Computed tomography, Histoplasmosis

### INTRODUCTION

*Histoplasma capsulatum* is a dimorphic fungus that grows in its mycelial form in soil enriched by bat and avian droppings — hence the name ‘bird fever’ given to the infection. *Histoplasma capsulatum* infection develops when infectious spores are inhaled into the lungs where they transform into pathogenic yeast-phase organisms. Histoplasmosis has been diagnosed on all continents but endemic areas with the highest concentration of cases are found in the eastern part of the USA and most of Latin America. The endemicity of histoplasmosis in Southeast Asia is not well studied. By 1970, 13 patients from 7 countries in Asia had culturally confirmed histoplasmosis.<sup>1</sup> Except for 1 patient in Japan, all the others were from Southeast Asia, including Indonesia, Malaysia, Thailand, and Vietnam. By 1972, another 48 patients from South and Southeast Asia had been reported.

The disease exists in 3 forms. Acute or primary histoplasmosis causes flu-like symptoms. Most patients who are infected recover without any medical intervention. Chronic histoplasmosis affects the lungs and can be

fatal. Disseminated histoplasmosis affects many organ systems in the body and is often fatal. Bilateral adrenal involvement is a rare presentation of disseminated histoplasmosis. As it is an opportunistic pathogen, there is higher susceptibility of dissemination for immunodeficient or immunosuppressed patients.

During the past 2 years, several patients with disseminated histoplasmosis have presented with bilateral adrenal enlargement on computed tomography, with a positive tissue diagnosis after computed tomography-guided fine needle aspiration biopsy (FNAB).

### CASE REPORT

A 66-year-old man first presented 7 years previously with vague abdominal discomfort. Computed tomography (CT) of the abdomen revealed a mass in the left lobe of the liver, a biopsy of which revealed only granulomatous inflammation. A definitive diagnosis of histoplasmosis was made after biopsy of a mandibular lesion for which this patient presented with a tooth abscess. He was treated with ketoconazole but defaulted follow-up after several months. Six months later he presented with severe weight loss and a repeat CT scan showed bilateral adrenal masses. A random serum cortisol was reported to be normal. After this he was lost to follow-up.

In January 1997, the patient attended an ear nose and throat surgeon for a hoarse voice and was found to have

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Submitted: 23 December 2003; Accepted: 3 April 2003.

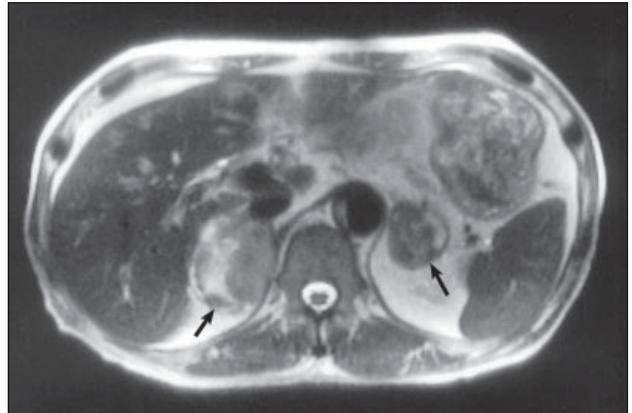


**Figure 1.** Enhanced computed tomography scan showing bilateral adrenal enlargement with speckles of calcification within the glands (arrows) and a granulomatous lesion in the liver (arrow head).

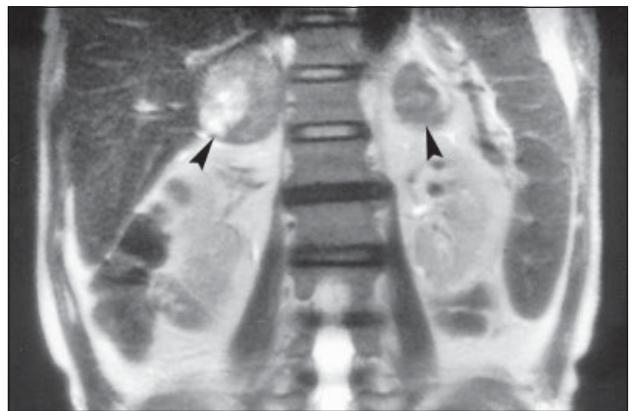
a vocal cord lesion. Histology of the lesion confirmed histoplasmosis. However, he defaulted treatment again.

This patient was readmitted to a private hospital in 1998 with Addisonian crisis. At examination, he was hyperpigmented, dehydrated, hypotensive, hypoglycaemic, and hyponatraemic. He was resuscitated with intravenous hydrocortisone succinate, glucose, and saline. Chest and abdominal X-rays were normal. A pre- and post-contrast CT scan subsequently performed showed further enlargement of the adrenal glands with speckled areas of calcification (Figure 1). The right suprarenal mass measured 5.2 cm x 4.7 cm and the left suprarenal mass measured 3.5 cm x 3 cm. Minimal enhancement was seen after intravenous contrast administration. The CT features were considered to be compatible with the clinical diagnosis of bilateral adrenal histoplasmosis. He was given cortisone acetate and fludrocortisone and referred to the endocrine clinic at the University Malaya Medical Center.

CT-guided percutaneous FNAB of the left adrenal gland was performed using a 22 gauge needle. Special stains revealed abundant budding yeasts consistent with *Histoplasma capsulatum*. A short Synacthen test confirmed hypoadrenalism with a basal of  $134 \times 10^3$  pmol/L and a peak of  $307 \times 10^3$  pmol/L (normal value,  $>550 \times 10^3$  pmol/L). An adrenocorticotrophic hormone level taken at baseline was raised at 32.56 pmol/L (normal range,  $<26$  pmol/L), in keeping with adrenal hypofunction. An HIV test was negative. Magnetic resonance imaging was attempted but the patient was claustrophobic so only 2 sequences were completed. The axial and coronal T-2 weighted images showed bilateral adrenal gland enlargement with high signal intensity centres suggestive of areas of necrosis (Figures 2 and 3). The



**Figure 2.** T-2 weighted axial image showing bilateral adrenal enlargement with a high intensity centre suggestive of necrosis (arrows). [Time of recovery, 4.4 milliseconds; time of echo, 90 milliseconds; flip angle, 150°].



**Figure 3.** T-2 weighted coronal image showing bilateral adrenal enlargement with the same high signal intensity centre indicating the presence of necrosis (arrowheads). [Time of recovery, 4.4 milliseconds; time of echo, 90 milliseconds; flip angle, 150°].

patient was treated with itraconazole 200 mg daily for 9 months and has shown significant symptom improvement during follow-up.

## DISCUSSION

Histoplasmosis usually starts as a pulmonary infection, which is asymptomatic or is associated with mild influenza-like symptoms.<sup>2</sup> Most cases subside without sequelae. This primary histoplasmosis is not contagious. Sometimes histoplasma spores continue to live in the lungs and the illness progresses to chronic histoplasmosis, which can take months or years. The symptoms of chronic histoplasmosis resemble those of tuberculosis with fluid-filled lung cavitation and atelectasis. This is a serious disease that can be fatal.<sup>3</sup> The rarest form of this disease is disseminated histoplasmosis (DH), whereby the cells disseminate haematogenously to multiple sites. Sometimes the disease remains dormant for many years. A weakened immune

system will result in disease reactivation.<sup>2</sup> The adrenal glands are the most commonly involved organs in disseminated histoplasmosis, frequently resulting in adrenal insufficiency.<sup>2</sup> The disease may also affect the spleen, liver, and bone marrow.

The organism has a particular predilection for the adrenal cortex, causing adrenal enlargement in as many as 79% of infected individuals and adrenal insufficiency in approximately 40% of these patients.<sup>4</sup> CT scan may suggest the diagnosis of active adrenal histoplasmosis, the most common appearance being that of symmetrically enlarged glands that retain normal adrenal contours and have low attenuation centres (probably due to caseous necrosis) and peripheral contrast enhancement. Adrenal calcification is usually not seen in the acute phase of the disease, but may develop during the healing process.<sup>2</sup>

Hypoadrenalism or Addison's disease is a rare hormonal disorder that affects approximately 1 to 2 per 100,000 people.<sup>5</sup> It affects men and women similarly and occurs in all age groups, including children. Hypoadrenalism is usually caused by an autoimmune reaction of the body (idiopathic) or adrenal destruction (neoplasm, tuberculosis, amyloidosis, inflammatory necrosis, or fungal infections such as histoplasmosis), or is iatrogenic (trauma with haemorrhage into the adrenal glands, surgery, discontinuation of steroids, ketoconazole, or other drugs).<sup>5</sup>

Serological tests (complement fixation or immunodiffusion) for *Histoplasma* may be falsely negative in 34% of patients with DH and tissue stains are frequently negative (54%).<sup>4</sup> Absolute confirmation of disseminated histoplasmosis (DH) may be obtained antemortem only by culture or biopsy of involved material. Bone marrow culture is the diagnostic procedure of choice.<sup>4</sup> FNAB of the adrenal glands, however, has emerged as a safe, accurate, and inexpensive diagnostic procedure. This and other reports indicate the value of percutaneous FNAB for revealing the responsible organism. FNAB is usually performed under CT guidance from the prone, posterior approach using 20 to 22 gauge needles.<sup>2</sup> Complications such as infection, haemorrhage, or pneumothorax are rare.<sup>4</sup>

A high index of clinical suspicion for this patient led to the biopsy that demonstrated the pathognomonic features of DH — large number of yeast form within the macrophages.<sup>6,7</sup> Adrenal insufficiency, however, did

not develop in this patient until therapy with ketoconazole had begun. This may be coincidental, as Dismukes et al described adrenocortical insufficiency only after prolonged therapy with ketoconazole.<sup>8</sup> This patient had been treated with ketoconazole for 6 months in 1996, when he presented with a tooth abscess, and again in 1998 when he was diagnosed with histoplasmosis of the vocal cords. Since January 1999, this patient was given itraconazole, which led to complete clinical remission. However, the CT findings did not change and the patient now has adrenal hypofunction that is being treated with fludrocortisone and cortisone acetate.

This patient's clinical presentation and disease course illustrate several important points, as follows:

- antemortem diagnosis of DH is clinically challenging and common diagnostic measures may be unreliable<sup>7</sup>
- clinical diagnosis of DH may be facilitated by the detection of bilateral adrenal enlargement on CT scan
- confirmation of DH rests upon culture or biopsy of infected material<sup>9</sup>
- CT-guided adrenal biopsy is an accurate means of diagnosis with a low risk
- the true prevalence of histoplasmosis in this region is poorly documented and pockets of endemicity probably exist throughout Southeast Asia.<sup>1</sup>

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