

# Histoplasmosis Presenting with Progressively Worsening Backache— A Case Report

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## Abstract

**Introduction:** Bilateral adrenal enlargement is often the result of disseminated malignant disease, and this diagnosis is particularly likely in a patient with severe weight loss. We describe a case with bilateral adrenal enlargement presenting with progressively worsening backache as a prominent symptom. **Clinical Picture:** A 55-year-old man presented with intermittent low back pain which was progressively worsening, fever, anorexia, low back pain and a 10-kg weight loss. He had underlying diabetes mellitus and ischaemic heart disease. He gave a history of travel to caves for worship. Clinically, the most significant findings included nodular lesions in the anterior fauces and left palatoglossal region. Computed tomographic scan revealed bilateral adrenal masses. Biopsies were taken from the palatal nodules, which revealed histiocytes with numerous histoplasma organisms. **Treatment:** He was commenced on itraconazole 200 mg daily for a period of 9 months. There was a dramatic initial response with settling of his fever and this was followed by subjective improvement in his well-being. **Outcome:** He is presently on follow-up and has completed 9 months of itraconazole therapy with resolution of all his symptoms and has gained about 10 kg of weight.

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**Key words:** Bilateral adrenal masses, Histoplasmosis, Itraconazole, Low back pain, Palatal nodules

## Case Report

A 55-year-old man presented with intermittent low back pain of 2 months' duration which was progressively worsening, fever, anorexia and a 10-kg weight loss. He has travelled several times in the past few years to caves in Kuala Lumpur for worship. Past history of significance was a myocardial infarction in 1995, for which he was on treatment which included anticoagulation therapy, and also diabetes mellitus for which he was on oral hypoglycaemic therapy. During the period of current illness, he saw general practitioners but with no improvement in his well-being, despite being treated with antibiotics. He was lethargic, the blood pressure was 160/100 mmHg on lying and 150/90 mmHg on standing. He also had lower back tenderness, which was progressively becoming more severe. Other notable clinical features were clubbing of his fingers which was a feature since childhood, nodules in the anterior fauces and left palatoglossal area, background

diabetic retinopathy and a palpable liver of 2 cm below the right costal margin. Haematological concentrations were haemoglobin, 13.7 g/dL; white cell count, 8500/dL with neutrophils, 76%; lymphocytes, 21%; basophils, 2% and eosinophils, 1%; platelet, 275 x 10<sup>9</sup>/L and erythrocyte sedimentation rate of 62 mm/h. Biochemistry analysis revealed urea, 5.5 mmol/L; sodium, 129 mmol/L; potassium, 4.3 mmol/L; creatinine, 169 mmol/L; random blood sugar, 9.2 mmol/L; albumin, 35 g/dL; globulin, 42 g/dL; bilirubin, 20 mmol/L; 5-fold elevated alkaline phosphatase of 508 mmol/L and 3-fold elevated alanine transaminase at 105 mmol/L.

The chest radiograph was normal and abdominal ultrasound showed an enlarged liver with no focal lesions. Ultrasound also detected a suprarenal mass measuring 3 cm on the right side. Echocardiography revealed a dilated heart with an impaired ejection fraction of 33%. There were no vegetations seen on all the valves. A smear for

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acid-fast bacilli was negative and the Mantoux test was 10 mm.

Abdominal computed tomography (CT) showed bilateral adrenal masses measuring 8 x 4 x 2.5 cm on the right side and 6 x 3.3 x 1.8 cm on the left side (Fig. 1). There were no calcifications seen. CT of the thorax did not reveal any mediastinal mass or lymphadenopathy. Serum HIV antibody was negative.

Twenty-four hour urine cortisol level was 404 nmol (normal range 79 to 590 nmol); 0900 hour level was 412 nmol and 0000 hour level was 317 nmol, both of which fell within the normal range.

A dental review was carried out and biopsies of the nodules seen were carried out. Histology results confirmed the presence of mixed inflammatory cells and histiocytes with numerous histoplasma organisms. A diagnosis of disseminated histoplasmosis was made.

The patient was commenced on itraconazole 200 mg daily and his fever settled within 48 hours. He was clinically

better and his appetite improved.

He remained well and there was no evidence of adrenal insufficiency or recurrence of histoplasmosis on follow-up after 9 months of therapy. Subsequent cortisol levels, checked every 2 months on clinic follow-up, were also normal. Serial CT scans showed a progressive reduction in the size of the lesions. The adrenal size reduced to 4 x 3 x 2 cm on both sides (Fig. 2).

The patient gained weight whilst on treatment, his oral nodular lesions disappeared and his liver function normalised. The backache, which was the predominant symptom, completely disappeared, and has remained absent 6 months after completion of therapy.

### Discussion

Histoplasmosis is due to a saprophytic dimorphic fungus that grows well in soil fertilised by bird or bat droppings. Our patient could have acquired the infection from bat droppings when he visited the caves for worship. Most infections are acquired by inhalation of spores of *Histoplasma capsulatum* and are asymptomatic, but large aerosol inhalations produce an acute self-limiting illness with patchy pneumonitis and hilar lymphadenopathy. Chronic progressive pulmonary disease and acute or chronic forms of disseminated histoplasmosis are unusual and often associated with abnormal host defence mechanisms.<sup>1</sup> This includes those with AIDS, organ transplantation and the use of corticosteroids or immunosuppressants. Our patient had no obvious defect in immunocompetence except for the fact that he was diabetic.

Pathologically, there is proliferation of the organisms within the cells of the reticuloendothelial system. Few organisms are found in cases with the chronic form of disseminated histoplasmosis in contrast to the acute type usually seen in infants and in patients with AIDS.

The most characteristic lesion in chronic disseminated histoplasmosis is oropharyngeal ulcer, which occurs in almost 70% of the more chronic cases.<sup>2</sup> The tongue and buccal mucosa are the most common sites, although they may be found on the larynx, lip, hard and soft palate and pharynx. The ulcers are usually painful and often have rolled edges suggesting malignancy. Most of them are chronic and persistent. Biopsy of these ulcers is the usual diagnostic test leading to the diagnosis. In biopsy material, the organism may be difficult to detect on haematoxylin and eosin but easily seen with Wright's stain and best identified with Gomori's methenamine silver stain.

Definitive diagnosis requires a positive culture or histological demonstration of typical intracellular yeast-like organism in involved tissues. Biopsies of oropharyngeal ulcers, liver or bone marrow are frequently confirmative.<sup>1</sup>

Adrenal disease in histoplasmosis ranges from isolated

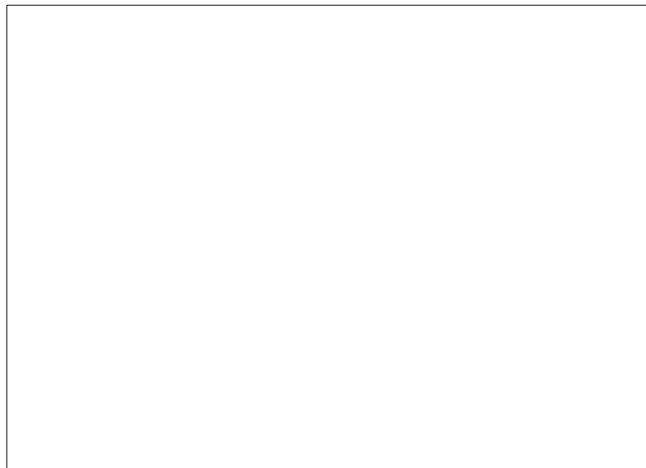


Fig. 1. High resolution CT scan of the adrenal glands. Well-defined bilateral adrenal masses can be seen.

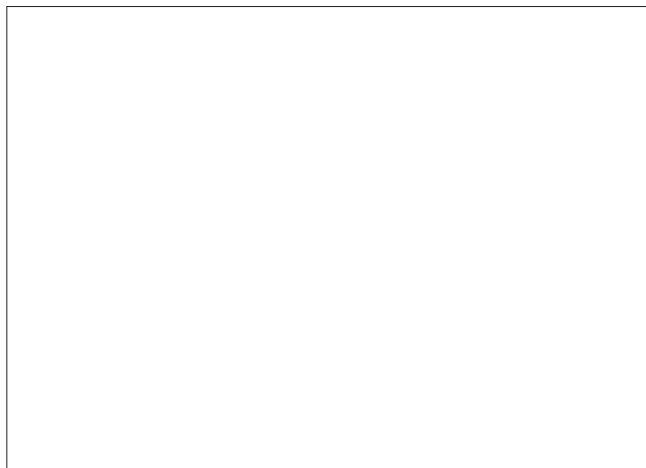


Fig. 2. Post treatment scan revealed some evidence of resolution.

cortical foci of parasitised macrophages to a more generalised infection with extensive infarction, caseation and massive swelling of underlying adrenal tissue. The latter change is associated with adrenal insufficiency.

In disseminated histoplasmosis, pulmonary involvement is variable and may be absent but liver enlargement is a prominent feature. Goodwin et al<sup>2</sup> found the incidence of Addison's disease to be 7% in their review, although the incidence of adrenal involvement has been reported to be as high as 50% by Sarosi et al.<sup>3</sup>

Histoplasmosis must be remembered as a cause of bilateral adrenal masses.<sup>4</sup> Similar sporadic cases will continue to appear. Chronic disseminated histoplasmosis with adrenal masses is therefore a prime example of an uncommon, unpredictable, but curable disease.

In our patient, several differential diagnosis had been considered including that of tuberculosis of the adrenals, bilateral adrenal haemorrhage as he was on anticoagulation and bilateral pheochromocytoma.

Before the advent of azoles, amphotericin B was the treatment of choice for patients with histoplasmosis.<sup>5</sup> Both ketoconazole and itraconazole are effective alternatives to amphotericin B in both forms of histoplasmosis.<sup>6</sup> These azoles can be administered orally and are associated with lesser side effects. Itraconazole, which is a triazole, has far greater preferential affinity for fungal as compared with mammalian cytochrome P-450 enzymes compared with ketoconazole which is an imidazole.<sup>7</sup> Therefore, it does not affect synthesis of adrenal hormones in humans compared with ketoconazole.<sup>7</sup> Itraconazole is effective in AIDS associated histoplasmosis.<sup>7</sup> For the majority of patients without AIDS who have chronic histoplasmosis, itraconazole is well tolerated. However, for the severely ill patients with or without AIDS, amphotericin B is the preferred initial treatment. For AIDS patients with disseminated histoplasmosis, induction therapy with amphotericin B followed by itraconazole maintenance therapy has been shown to be safe and effective in preventing relapses of disseminated histoplasmosis.<sup>8</sup>

The diagnosis of histoplasmosis relies on the physician's alertness to the presence of disease. Travel history to Southeast Asia should alert one to the possibility of this diagnosis, in view of the reporting of this disease with some frequency from this region. It seems reasonable to question whether the disease is endemic. Pockets of endemicity probably exist throughout Southeast Asia.<sup>9</sup> The true prevalence of histoplasmosis in its various clinical forms in Southeast Asia is poorly documented and a high index of suspicion will constantly be needed to diagnose this condition early and to administer appropriate treatment.

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