

## Disseminated histoplasmosis mimicking miliary tuberculosis: a case report

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### Abstract

A 35-year-old Chinese man who was known to have insulin-dependent diabetes mellitus was admitted for fever and weight loss. During his hospital stay, he fell to his death from his ward at the twelfth floor. The clinical features, radiological findings and gross organ changes at autopsy closely simulated miliary tuberculosis. Histology, however, revealed extensive necrosis of the adrenal glands, lungs, spleen, kidneys and thyroid associated with the presence of *Histoplasma capsulatum* organisms. This case highlights the similarity both clinically and pathologically between histoplasmosis and tuberculosis and emphasizes the need to be aware of this infection in a nonendemic area among patients with a compromised immune system.

**Key words:** Histoplasmosis, granulomatous inflammation, tuberculosis, diabetes mellitus.

### INTRODUCTION

Depression of cellular immunity can predispose to various fungal infections including candidiasis, aspergillosis, nocardiosis and histoplasmosis. Conditions implicated as causes of immune depression include cancer chemotherapy, thymic dysplasia, corticosteroid therapy and more recently, human immunodeficiency virus (HIV) infection. In such patients, a high index of suspicion should be kept of the rarer infections that they are prone to. Histoplasmosis is one such infection. Diagnosis of this infection can be difficult because the clinical features are usually protean and frequently simulate other granulomatous infections. Furthermore, the organisms themselves can be difficult to recognise in histological sections.

We report a case of disseminated histoplasmosis in a diabetic patient which clinically mimicked tuberculosis. The diagnosis was clarified only on histological examination of post mortem material. This case emphasises the need for greater clinical awareness of the condition particularly in view of the high mortality associated with the disseminated form of this infection.

### CASE REPORT

A 35-year-old Chinese man was admitted to the University Hospital, Kuala Lumpur for fever, loss of appetite, loss of weight, polyuria and polydipsia of one month's duration. He was a vagabond from Jinjang, Kuala Lumpur and had

two previous admissions four years earlier both for diabetic ketoacidosis.

On admission, the patient was pale, thin and emaciated. He had a blood pressure of 100/70 mmHg and a pulse rate of 108 per minute. There was a low grade fever. Occasional crepitations were heard at the lung bases. Both the liver and spleen were enlarged. Dental hygiene was poor but there were no oral ulcers or skin lesions.

Routine haematological tests were within normal limits. The random blood sugar level was elevated (21.6 mmol/L). There was also glycosuria, ketonuria and a metabolic acidosis. The blood urea and electrolyte levels were: urea 4.5 mmol/l, sodium 136 mmol/l, potassium 3.3 mmol/l and chloride 103 mmol/l. The serum creatinine level was 84 µmol/l. Blood cultures failed to grow any organism and serological tests for typhoid, typhus and dengue fever were negative. The chest radiograph showed numerous tiny miliary shadows on which a clinical suspicion of tuberculosis was aroused. Liver function tests showed mild elevation of liver enzymes. Sputum examination failed to demonstrate any acid fast bacillus on staining and the outcome of cultures for tuberculosis was being awaited.

The patient was treated with insulin injections and his diabetes improved. Extensive dental caries required dental referral and extractions were done.

Eleven days after admission, he was found dead on the ground floor of the hospital tower

block, presumably having jumped from his ward on the twelfth floor. The Mantoux test was not yet ready for reading at the time of death. The HIV antibody status of this patient was not known. A coroner's autopsy was performed.

#### Autopsy findings

The autopsy examination revealed a markedly emaciated body with extensive injuries and fractures involving the head, chest wall, thoracic and abdominal organs consistent with the fall. In addition, both lungs were **consolidated** and heavy. Their external and cut surfaces revealed numerous confluent, yellowish white caseous nodules of about 2 mm. diameter each (Fig. 1). The hilar lymph nodes were not enlarged.

The right adrenal gland contained nodular yellowish necrotic lesions. The left adrenal gland was macerated by the trauma, but the remaining tissue also showed extensive **necrosis**. The enlarged liver and spleen were lacerated but did not show any other gross pathology.

Other visceral organs examined did not show any gross lesions. No culture of the tissues was attempted.

#### Histology

The most striking changes were seen in the adrenal glands. These showed extensive areas of necrosis with numerous intracellular and **ex**-tracellular yeast cells at the periphery (Fig. 2). There was very little inflammatory reaction to

the necrosis. The yeast cells were ovoid, measuring about 4  $\mu\text{m}$  in their long axis and each exhibited a peripheral halo. The Gomori **met**-hemine silver (GMS) stain demonstrated budding in some yeast cells which were typical of *Histoplasma capsulatum* (Fig. 3).

Sections of the lungs showed many **poorly**-formed epithelioid **granulomas** with large areas of central caseous necrosis. There was minimal lymphocytic reaction and Langhan's type giant cells were not present. Moderate numbers of *Histoplasma capsulatum* organisms were found within the epithelioid cells.

Similar organisms were also found in the kidneys, thyroid and spleen, with the former two showing granulomatous lesions as well. In addition the spleen exhibited marked depletion of lymphoid cells and marked distension of **sinu**-soids by histiocytes. The liver revealed numerous tiny granulomatous lesions although no fungal organism was found. No acid fast bacilli were demonstrable in all these organs. The **mediast**-inal lymph nodes were depleted of lymphoid follicles.

#### DISCUSSION

Although histoplasmosis was first discovered by Darling and later described in detail by Parsons *er al.*' more than 80 and 40 years ago respectively, a high mortality rate associated with missed diagnosis of disseminated histoplasmosis is still **common**.<sup>2</sup> Thus pathologists and physicians alike must be aware of this

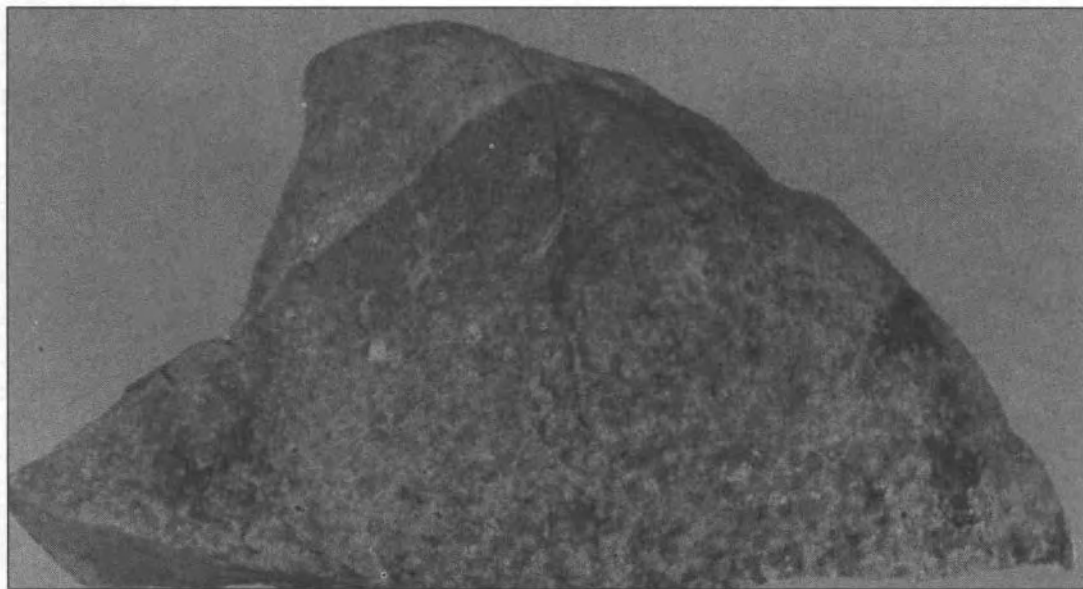


FIG. 1: Gross appearance of upper lobe of left lung showing numerous tiny necrotic nodules.

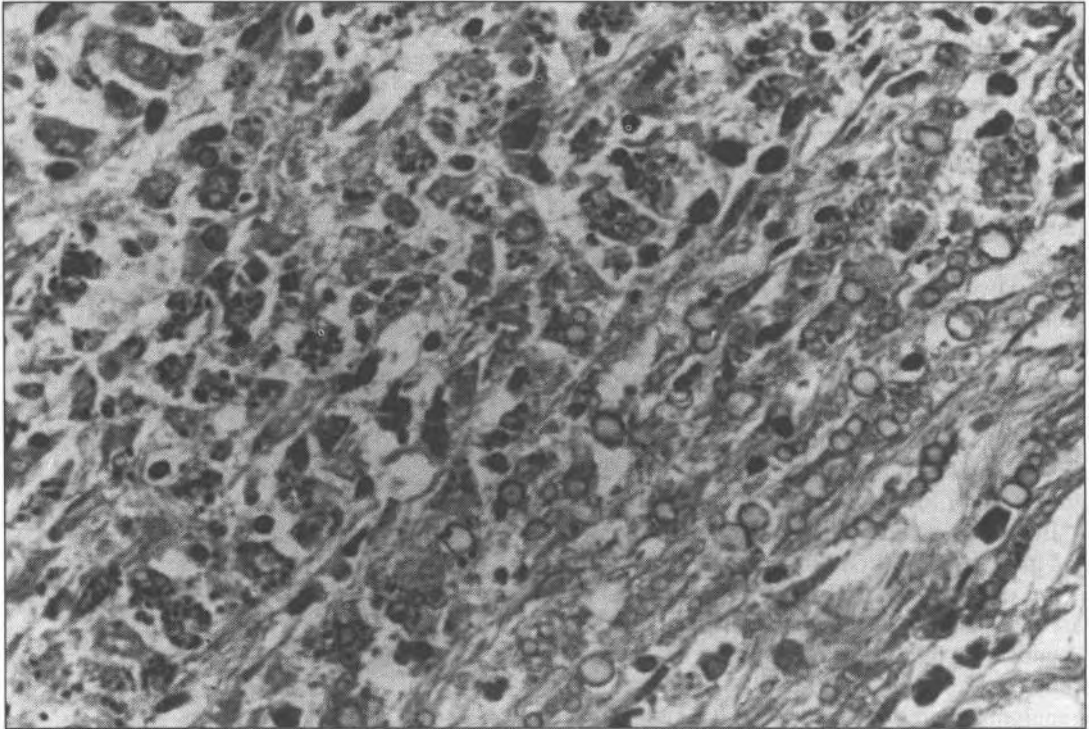


FIG. 2: Photomicrograph of right adrenal gland showing groups of yeast cells within the cytoplasm of necrotic macrophages and parenchymal cells. Extracellular forms are seen at lower right field. Note the poor inflammatory response to the organism. H&E X 300.

disease and the diagnostic methods available in order to lower its mortality rate. Furthermore, with the expected increase in incidence of the acquired immune deficiency syndrome (AIDS) in Malaysia in the future, the incidence of histoplasmosis is likely to increase. Hence, there is a further need for greater awareness among health care workers of this infection. Immune deficiency associated with diabetes mellitus probably had played a part in the susceptibility of this patient to the infection.

This infection, whether in the form of chronic pulmonary disease or the disseminated forms, closely simulate tuberculosis clinically<sup>1,3,4,5</sup> and sometimes also in histological sections. The histological diagnosis is hampered by the fact that the organisms are frequently very scarce. Because of their small size, they are also very difficult to identify. Special techniques such as the Gomori's methenamine silver method or periodic acid Schiff reaction are required to demonstrate the yeast forms in tissue sections.

Diagnosis is usually dependent on isolation or identification of the organisms,<sup>2,6</sup> or, more recently, on detection of specific antibody or antigen in the serum or urine. Rapid diagnosis have also been achieved in certain centres with the application of immunofluorescence and

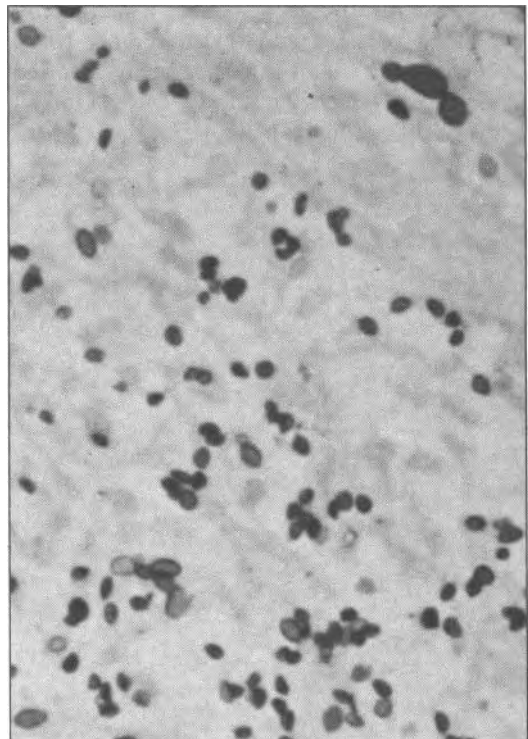


FIG. 3: Section of right adrenal gland showing numerous yeast cells, some with budding characteristic of *Histoplasma capsulatum*. Gomori's methenamine silver X 300.

immunoperoxidase techniques on tissue sections." Although isolation of **the fungus** was **not** carried out in this case, a diagnosis of disseminated histoplasmosis can be made with certainty because of the characteristic yeast cells found in **tissue** sections. In histological sections, other infections that need to be distinguished from histoplasmosis are tuberculosis, torulopsis, leishmaniasis, candidiasis and cryptococcosis.<sup>8,9</sup>

Goodwin *et al.*<sup>3</sup> classified histoplasmosis by considering the clinical and pathological features. The intermediate duration of illness, presence of weight loss, hepatosplenomegaly and focal destructive lesions, especially in the adrenal glands, place our patient into the subacute **disseminated form** according to Goodwin's classification.

Because tuberculosis is common in Malaysia, it is invariably the first differential diagnosis in a case of this nature. However, whenever acid fast bacilli cannot be demonstrated or isolated, a diagnosis of histoplasmosis should be considered. Steroids should not be given in any **granulomatous** disease unless histoplasmosis had been excluded, as it has been reported that this frequently results in a fatal outcome.<sup>10</sup>

This patient had very severe **adrenal** gland involvement. Antemortem findings suggestive of adrenal insufficiency include a marginally low blood pressure and serum sodium level. Goodwin *et al.*<sup>3</sup> in an extensive study reported adrenal involvement at autopsy in 82% of all forms of disseminated histoplasmosis.

## REFEWENCES

1. Parson RJ, Zarafonitis CJD. Histoplasmosis in Man: report of seven cases and a review of seventy-one cases. *Arch Int Med* 1945; **75**: 1.
2. Sathapatayavongs B, Batteiger BE, Wheat J, Slama TG, Wass JL. Clinical and laboratory features of disseminated histoplasmosis during two large urban outbreaks. *Medicine (Baltimore)* 1983; **62**: 263-70.
3. Goodwin RA, Shapiro JL, Thurman GH, Thunnan SS, Des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. *Medicine (Baltimore)* 1980; **59**: 1-33.
4. Johnston AW, Postlethwaite R, Ewen SWB *et al.* Disseminated histoplasmosis. *J Inf* 1984; **9**: 79-82.
5. Chin TH, McGarry T, Cooper S *et al.* Disseminated histoplasmosis in the acquired immunodeficiency syndrome. *Arch Int Med* 1987; **147**: 1181-4.
6. Wheat J, French MLV, Kohler RB, Zimmerman SE, Smith WR, Norton JA, Eitzen HE, Smith CD, Slama TG. The diagnostic laboratory tests for histoplasmosis. Analysis of experience in a large urban outbreak. *Ann Int Med* 1982; **97**: 680-5.
7. Wheat LJ, Kohler RB, Tewan RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. *N Engl J Med* 1986; **314**: 83-8.
8. Klatt EC, Cosgrove M, Meyer PR. Rapid diagnosis of disseminated histoplasmosis in tissues. *Arch Pathol Lab Med* 1986; **110**: 1173-5.
9. Binford CH, Connor DH. Pathology of Tropical and extraordinary Diseases, Washington DC, Armed Forces Institute of Pathology, 1976 vol 2. pp 578-80.
10. Taylor GD, Fanning EA, Ferguson JP *et al.* Disseminated histoplasmosis in a nonendemic area. *Can Med Assoc J* 1985; **133**( 15): 763-5.