Addison’s Disease Due to Histoplasma capsulatum

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SUMMARY

A case of disseminated Histoplasma capsulatum infection, with concomitant adrenal cortical insufficiency, occurring in a 53-year-old Coloured male, is described. The patient presented with weakness, weight loss and an ulcer on his tongue. Examination showed hypotension, generalized lymphadenopathy, hepatosplenomegaly, and caseation and cavitation of the upper lobe of the left lung. Treatment consisted of intravenous hydrocortisone, saline and amphotericin B, until his death in a state of acute shock 10 days later. A total of 382 mg of amphotericin B was administered in divided doses, through an indwelling inferior vena cava catheter. Postmortem examination showed hepatomegaly, splenomegaly, acute dilatation of the stomach, ileus, submucosal intestinal haemorrhages and caseation and cavitition of the upper lobe of the left lung. A tubular thrombus was found in the inferior vena cava, with no evidence of pulmonary embolization. Both kidneys were normal. The adrenals were enlarged and practically replaced by caseous material. Histoplasma capsulatum was later cultured from the lung and adrenal tissues.


Since Simson and Barnetson described the first case of systemic histoplasmosis in South Africa in 1942, the reported cases have increased to 7. Funston et al. recently published a full review of the series and added another case report. The purpose of this report is to document a further case.

CASE REPORT

A 53-year-old Coloured male presented at Addington Hospital, Durban, with a 7-month history of weight loss (of about 8 kg), weakness, and an ulcer on his tongue.

For the previous 18 years he had been employed at Mooirivier as a handyman, frequently working in cellars infested with bats, or on farms where he came into contact with poultry. He had never been in any caves. Before this, he had for 10 years been a sailor, predominantly on vessels plying between South Africa and the Far East. For the past 18 years the patient had taken 3-4 tots of cane spirit daily, and he smoked 40 cigarettes per day.

With the onset of the symptoms 7 months before admission, the patient had what he described as ‘severe influenza’. One week later he noted a hard, painless tumour on his tongue. After a biopsy of this tumour, it was reported as consisting of granulomatous tissue, but no fixed diagnosis was made at that time. A second biopsy of the lesion was done 5 months later and histoplasmosis was diagnosed.

Clinical Findings

Clinically the patient appeared emaciated and weak. He was 190 cm tall and weighed 56 kg. His blood pressure was 90/60 mmHg, and his temperature 39°C. There was generalized lymphadenopathy, the glands being firm but not tender. The liver was palpable 1 cm below the costal margin and the spleen could just be felt during deep
inspiration. The chest was emphysematous, but no clubbing of the fingers or toes was noted. Neurological examination was normal.

There was an oval ulcer about 3 x 2 cm in size and 0.5 cm deep in the midline of the posterior third of the tongue, with ragged and firm edges somewhat undermined, but not indurated. The base of the ulcer was red and uneven, with patches of necrotic tissue present. The surrounding tissue appeared normal. Both the submandibular and jugular groups of glands were bilaterally enlarged and firm, but not tender. The patient spoke with difficulty and had excessive ptyalism.

**Laboratory Investigations**

Cerebrospinal fluid and bone marrow were examined histologically and cultured for the presence of histoplasmosis, but both yielded negative results.

The haemogram, sputum and repeated X-ray examinations of the chest were normal. The erythrocyte sedimentation rate was 27 mm in the first hour (Westergren). The blood urea was initially 38 mg/100 ml. Serum proved to be anticomplementary to the histoplasmosis complement fixation test (mycelial phase antigen). The tuberculin and histoplasmin skin tests were negative. The urinary 17-ketosteroid and 17-hydroxyketosteroid values were 1.7 mg/24 hours and 0.8 mg/24 hours, respectively. The direct van den Bergh reaction was positive, the serum bilirubin 14 mg/100 ml, the alkaline phosphatase 29 KA units and the flocculation tests abnormal. Total serum protein was 5.2 g/100 ml (serum albumin 2.2 g/100 ml, serum globulin 3.0 g/100 ml and A/G ratio 0.7:1). Serum electrolytes were: sodium 118, chlorides 88 and potassium 5.7 mEq/litre. A 24-hour urine specimen (330 ml) contained a sodium concentration of 11.8 mEq/litre, potassium 20.4 and chlorides of 21.0 mEq/litre.

**Therapy**

A diagnosis of systemic histoplasmosis with adrenal insufficiency was made, and treatment with intravenous hydrocortisone and saline commenced. Despite the poor urine excretion, it was decided to treat the patient with amphotericin B. A fine polythene catheter was inserted into the inferior vena cava via the inguinal region, through which daily doses of amphotericin B were infused. The catheter was irrigated with a mixture of 10 000 units of heparin in 1 litre of 5% dextrose in water after each dose.

As expected the patient reacted severely during the infusions with rigors and pyrexia. His blood urea rose to 118 mg/100 ml. The rigors were appreciably diminished by the administration of promethazine.

On the 8th day of treatment the patient developed blood-stained diarrhoea and severe abdominal pain. The abdomen was diffusely tender, and at this stage the hyperpigmentation of the elbows and buccal mucosa became more noticeable. The region around the inguinal insertion of the catheter was mildly septic and signs of right-sided basal pneumonia were noted. Repeated X-ray examinations of the chest were normal. At this stage the possibility of a septic embolus arising from the inferior vena caval catheter was considered and the catheter was therefore removed on the 10th day. That night the patient collapsed suddenly. When seen, he had no perceptible blood pressure and despite vigorous attempts at resuscitation, died 30 minutes later.

At postmortem examination the liver weighed 2.1 kg and the spleen weighed 225 g; both showed areas of caseation. There was acute dilatation of the stomach, and an ileus with submucosal haemorrhages was present. Caviation and caseation of the upper lobe of the left lung and bilateral terminal bronchopneumonia, were found. The inferior vena cava contained a tubular thrombus, about 15 cm long with pus around the site of entry of the catheter in the right inguinal region. No signs of peritonitis were present.

![Fig. 2. Tubular thrombus in the inferior cava seen at autopsy.](image)

The adrenal glands weighed 20 g and appeared caseated. Hardly any normal adrenal tissue could be found. The kidneys appeared normal macroscopically and microscopically. *Histoplasma capsulatum* was subsequently cultured from both the lung and the adrenals.
Fig. 3. Section of adrenal tissue showing intracellular and extracellular yeast forms of Histoplasma capsulatum (H. and E. x 960).

DISCUSSION

Systemic spread of Histoplasma infection is uncommon. During the 1964 epidemic in Iowa, only one patient out of the estimated 6,000 infected persons, developed the disseminated form. The adrenal is apparently one of the organs most commonly affected. It is estimated that approximately 90% of the adrenal cortex has to be destroyed before signs and symptoms of adrenal cortical insufficiency appear.

Crispwell et al. reviewed a series of 68 autopsy cases of Histoplasma capsulatum, 36 of which had involvement of the adrenals. Only 15 of these 36 cases had clinical features indicative of possible adrenal insufficiency. The authors added another 4 cases with proved adrenal involvement, 3 of which had been correctly diagnosed and effectively treated, and one case coincidentally discovered at autopsy. Sarosi et al. more recently found evidence of adrenal involvement in 27 of 54 cases with disseminated Histoplasma capsulatum.

The diagnosis of Addison's disease in this particular case was based on both clinical and biochemical criteria. The patient died in a state of acute shock 10 days after admission, despite immediate commencement of vigorous therapy of intravenous saline and 1 g of hydrocortisone.

The administration of amphotericin B was facilitated by the placement of an indwelling inferior vena caval catheter. A surprise finding at the postmortem was that of a tubular thrombus. No evidence of pulmonary emboli was found, despite the presence of suggestive lung signs. Reaction to therapy with amphotericin B is difficult to evaluate. The usual total dose is 1400 - 1600 mg and this patient had only received 382 mg up to the time of death.

Initial rigors and fever that follow with the commencement of therapy are well documented. The frequently reversible azotaemia that may occur with amphotericin B is a greater limiting factor. Blood urea of this patient rose from 38 mg/100 ml to 118 mg/100 ml. A less common complication is gastro-intestinal bleeding, and it is difficult to distinguish this from the bleeding occurring as a result of uraemic enterocolitis.

It is remarkable that all the previous South African cases (with the exception of one case, a boy of 13 years) occurred in Whites. The present case is apparently the first Coloured case reported. As far as can be determined, this is also the first reported case with adrenal failure due to extensive adrenal cortical involvement, although Murray and Brandt refer to caseation and necrosis of the right adrenal occurring in one of their patients. It is well known that steroids suppress inflammatory reaction, therefore general adrenal cortical involvement was not surprising.

It was difficult to pinpoint the origin of the infection. It seems from his history that infection occurred during the last year of his life, since no history of previous lung disease was obtained. It is well known, however, that infection can exist in a subclinical form, and this could have occurred during any of his seafaring trips, or at any other time as a result of his occupation, which brought him into contact with droppings from bats and poultry. If this was the case, it is not known whether the final illness was an acute exacerbation or a reinfection. The negative serology was unhelpful, as these tests are known to be negative often in acutely ill patients. Natal is a known source of Histoplasma capsulatum. Repeated X-ray examinations of the lungs were normal, despite the presence of extensive cavity formation and caseation. Even re-examination of the X-ray plates, after the postmortem results were known, showed no radiological abnormalities, apart from the terminally occurring bronchopneumonic changes.

The ulcer of the tongue was a prominent characteristic, as also mentioned by other authors.

Enlargement and dysfunction of the liver can apparently be ascribed to a combination of histoplasmosis and the excessive use of alcohol.

REFERENCES