DISSEMINATED HISTOPLASMOSIS PRESENTING AS A NON-HEALING TONGUE ULCER

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ABSTRACT

A 51-year old man presented with a persistent tongue ulcer, fever, cervical lymphadenopathy and hepatomegaly. The diagnosis was initially thought to be tuberculosis. This led to the initiation of antituberculous chemotherapy to which the patient failed to respond. The correct diagnosis of histoplasmosis was made after the detection of *Histoplasma capsulatum* on further review of the tongue ulcer biopsy specimen. He responded to treatment with amphotericin B.

Keywords: Chronic disseminated histoplasmosis, tongue ulcer

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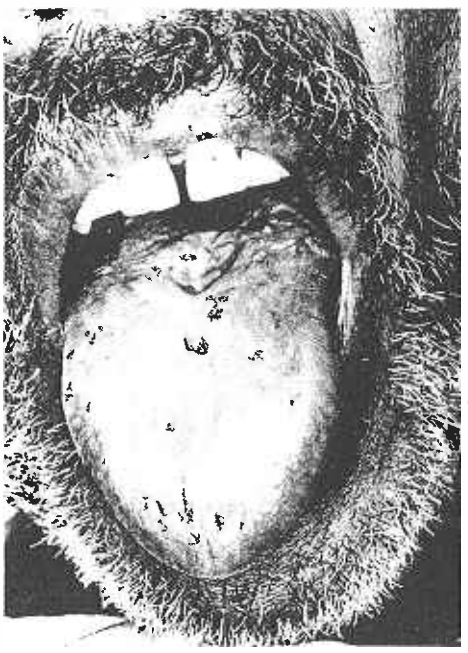
INTRODUCTION

Disseminated histoplasmosis is a rare systemic fungal infection. The most characteristic lesion in chronic disseminated histoplasmosis is an oropharyngeal ulcer. This report describes a case of disseminated histoplasmosis presenting with a non-healing tongue ulcer. The diagnosis was initially overlooked because the clinical picture of the patient's illness resembled closely that of tuberculosis which is endemic in Malaysia. The failure to identify the causative organism on initial histology of the tongue biopsy also contributed to the delay in making the correct diagnosis.

CASE REPORT

The patient was a 51-year old Indian railway station master in Chemor in the state of Perak. He and his family stayed in quarters next to the railway station which was infested with bats and littered with bat droppings. He had never travelled abroad. He first presented to our surgical service with a painful tongue ulcer of 9 months' duration. He had a low grade fever and suffered loss of appetite accompanied by a weight loss of 8 kg. There were no respiratory symptoms. Six months earlier he was found to have diabetes mellitus and treatment was commenced with chlorpropamide. The other members in his family were well.

Fig 1
Ulcer on dorsal surface of the tongue



Examination revealed a fairly well built man with a low grade pyrexia. He did not have pallor, jaundice or other cutaneous stigmata of chronic liver disease. His blood pressure was 130/80 mm Hg and there was no postural

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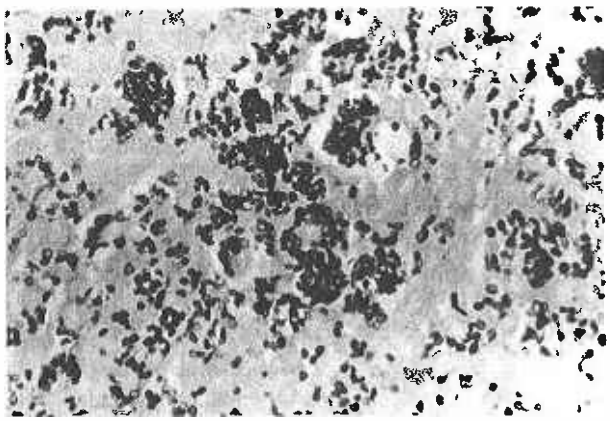
hypotension. A tender superficial ulcer measuring 2 x 2 cm with irregular everted edges was present on the dorsal surface of the middle third of his tongue. The floor was erythematous and the base was indurated (Fig 1). There was enlargement of his right submandibular and right upper deep cervical lymph nodes which were discrete, firm, mobile and nontender. Chest examination revealed no abnormality. The liver was enlarged with a vertical span of 14 cm. It was smooth, firm and non-tender. The spleen was not palpable. The rest of the examination was normal.

Investigations showed a normal haemoglobin level and normal total white cell count. However, the eosinophil count was slightly elevated at 553 x 10^6/l and the erythrocyte sedimentation rate was 68 mm in the first hour. Serum electrolyte levels were normal. Liver function tests were normal except for an elevated alkaline phosphatase of 251 IU/l. Urinalysis revealed no abnormality. Chest X-ray was normal. The Mantoux test with 1 tuberculin unit was negative. Serology for syphilis was also negative. Wedge biopsy of the edge of the tongue ulcer and excision biopsy of the enlarged right upper deep cervical lymph node showed the presence of multiple epithelioid granulomata without caseation necrosis. Staining for acid-fast bacilli (AFB) and fungi was negative.

Fig 2
Section shows numerous macrophages with *Histoplasma capsulatum* within the cytoplasma. Gomoris methenamine silver stain x 800.



A working diagnosis of tuberculosis with underlying diabetes mellitus was made and a trial of antituberculous chemotherapy was commenced with daily rifampicin 600 mg, isoniazid 300 mg and ethambutol 1200 mg. Despite treatment for a month the patient continued to be febrile and his liver became progressively larger. He was then referred over to us. The antituberculous drugs were discontinued and a liver biopsy was performed which revealed nonspecific hepatitis without any evidence of granuloma formation. Culture of the liver biopsy specimen for fungus and *Mycobacterium tuberculosis* was negative. The Kveim test was negative. A bone marrow biopsy was normal and no AFB or fungus were cultured. The adrenal glands were found to be enlarged on CT scanning, the right adrenal measuring 4.25 cm while the left was 3.58 cm in length. There were no cystic changes and no calcification of the adrenals. Plasma cortisol at 0800 hr was 533 mmol/l (normal 138-690 mmol/l). His serum calcium and 24 hour urine calcium were not elevated.

Additional sections and review of the earlier tongue ulcer biopsy showed the presence of fungal bodies of *Histoplasma capsulatum* on staining with Gomori's methenamine silver stain and PAS/D (Fig 2). Serum HIV antibody was negative.

The patient was treated with amphotericin B and a total of 2 gms were administered over a two month period. His fever settled. He felt better and started to put on weight while on treatment. The tongue ulcer gradually healed and the enlarged liver became smaller. On follow-up, 8 months after completion of therapy, there was no clinical evidence of adrenal insufficiency or recurrence of histoplasmosis.

DISCUSSION

Histoplasma capsulatum is a dimorphic fungus. It grows well in the mycelial form in moist surface soil enriched by bird or bat droppings. Our patient could have acquired the infection from the bat droppings around his residence.

Clinically, histoplasmosis manifests as several distinct syndromes depending on the host immunocompetence and response as well as the size of the inocula. Disseminated histoplasmosis has been associated with immunocompromised states (1). In recent years it has been recognised as an important AIDS-associated opportunistic infection and AIDS should be sought as a cause of inadequate host immunocompetence in patients presenting with this disease (2). The case reported here has no obvious defect in immunocompetence except for the fact that he was a 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 histoplamosis in contrast to the acute type usually seen in infants and patients with AIDS.

According to Goodwin (3) the most characteristic lesion in chronic disseminated histoplasmosis is an oropharyngeal ulcer which occurs in almost 70% of the more chronic cases. The tongue and buccal mucosae are the most common sites of these ulcers 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 stain but easily seen with Wrights stain and best identified with Gomori's methenamine silver stain. In general, many heavily parasitized macrophages can be found in the centre of the lesion or at the base of the ulcer and small number of phagocytes with fewer organisms can be found at the margins. In some of the chronic cases of disseminated histoplasmosis in Goodwin's series tuberculoid granulomata were observed in the periphery of the lesions.

In disseminated histoplasmosis tuberculoid granulomata are in general absent. They are found only in cases at the mildest end of the disease spectrum in which the infection is low grade and relatively few organisms are found and there is near normal tissue response, implying near normal immunocompetence (3).

In disseminated histoplasmosis, pulmonary involvement is variable and may be absent but liver enlargement is a prominent feature. Goodwin et al (3)

found the incidence of Addison's disease to be 7% in his review of 84 cases of disseminated histoplasmosis although the incidence of adrenal involvement has been reported as high as 50% by Sarosi et al (4). The normal blood pressure, blood electrolyte levels and plasma cortisol suggest significant adrenal reserve in our patient although his adrenal glands were found to be enlarged on CT scan.

Definitive diagnosis requires a positive culture or histological demonstration of typical intracellular yeast-like organisms in involved tissues. Biopsies of oropharyngeal ulcers, liver or bone marrow are frequently confirmative (3, 5).

The clinical presentation of this case closely mimicked that of tuberculosis which is endemic and more common in this region. This close resemblance had caused the correct diagnosis of disseminated histoplasmosis being overlooked initially. The same problem had been encountered by others (6,7). The failure to demonstrate the causative organism on initial histology had also contributed to the delay in diagnosis. The importance of eliminating diseases other than tuberculosis even when tuberculoid granulomata have been identified on histology needs to be emphasized. Additional sections of all available biopsy material should be attempted to identify the organism; especially if clinical suspicion of histoplasmosis is high. It is also important to send fresh biopsy specimen for special cultures.

For many years the standard drug treatment for histoplasmosis had been intravenous amphotericin B. In recent years ketoconazole and itraconazole have been shown to be effective in treating the chronic disseminated form of the disease (8-10). These azoles can be administered orally and are associated with lesser side-effects.

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