The Ulster Medical Journal, Volume 71, No. 2, pp. 147-149, November 2002.

Case Report

Histoplasmosis as a presentation of Human Immunodeficiency Virus Infection

F M Carey, S P Quah, R Orr, M McBride

Accepted 12 August, 2002

Opportunistic fungal infections account for a significant amount of morbidity associated with HIV disease. In Northern Ireland approximately 10% of our HIV positive patients have acquired their disease in foreign climes, particularly sub-Saharan Africa and the United States of America. This, coupled with increasing travel in general abroad, increases the likelihood of them acquiring opportunistic infections not often encountered in the United Kingdom. We report here a case of localised oral histoplasmosis without evidence of disseminated disease in a patient who had just been diagnosed as having HIV infection. Reactivation of latent histoplasma infection occurred as a result of previous exposure in South Africa following gradual depletion of his immune function by HIV infection.

CASE REPORT

History

A 51 year old heterosexual male presented to our department in May 2000. He had been diagnosed with palatal histoplasmosis one week previously in South Africa prompting a HIV test which returned as positive. He had immediately flown back home to Northern Ireland for treatment. His symptoms started in 1996 when he developed recurrent mouth ulcers and overgrowth of his gums. This persisted and in 1999 he developed a cough, intermittently productive of green sputum, recurrent fevers, and boils in the axillae and groins. In January 2000 his symptoms had increased in severity to such an extent that they were affecting his ability to eat and drink. He was unable to expectorate sputum because of pain in his mouth. He attended both his general practitioner and dentist over the following months where he was diagnosed as having recurrent chest infections and blocked sinuses respectively. He failed to respond to antibiotic treatment. Upon referral to an oral surgeon in April a palatal biopsy revealed histoplasmosis infection. A subsequent HIV test was positive.

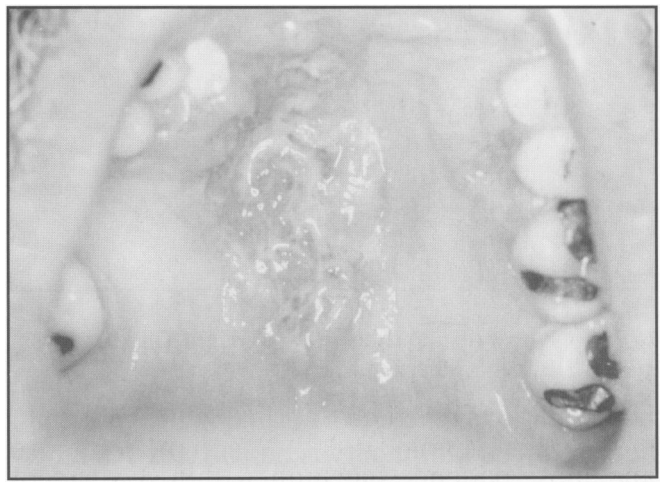

Fig 1. Necrotic ulcerated lesion on the hard palate.

Since leaving the United Kingdom in the 1960s he had lived and worked in different African countries, finally settling in South Africa. He had had multiple heterosexual encounters which included professional sex workers.

Examination revealed a well looking man with an ulcerated necrotic area on the roof of his mouth (figure 1). A raised nodule 0.5 cm in diameter was present on the dorsum of the right hand. The rest of the examination was unremarkable.

Department of GenitoUrinary Medicine, Royal Victoria Hospital, Belfast.

F M Carey, MRCGP, Specialist Registrar

S P Quah, MRCP, Specialist Registrar

R Orr, MRCP

M McBride, FRCP, Consultant

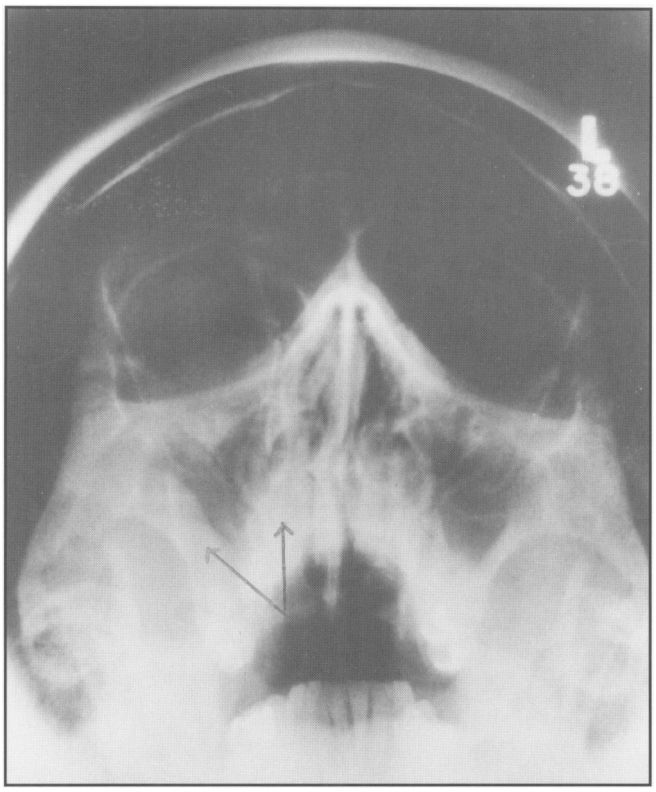

Fig 2. X-ray of maxillae showing right sided mucosal antral thickening.

Investigations revealed a normal white cell count but a reduced lymphoctye count –0.9 x 10 /L (1.5 – 3.5). His CD4 count was 0.06 x 10^9 /L (0.5 – 1.6). Confirmatory HIV testing was positive. Microscopy of sputum showed occasional pus and epithelial cells. Culture of sputum, blood and a swab of the palatal ulcer showed no growth. Analysis of urine for histoplasma antigen was negative. A chest radiograph was normal but a radiograph of facial bones showed maxillary antral mucosal thickening of the lateral wall (figure 2). Histology of a palatal biopsy obtained from South Africa showed an inflammatory infiltration of mainly histiocytes in the subepithelial stroma with areas of necrosis. PAS staining revealed small fungal organisms lying within the cytoplasm of the histiocytes (figure 3). Biopsy of the lesion on the hand showed it to be molluscum contagiosum.

Treatment with intravenous amphotericin B encapsulated in lysosomes at a dose of 0.5mg/kg was given for two weeks. Thereafter oral antifungal treatment in the form of itraconazole 200mg daily was the commenced. Prophylaxis for *pneumocystis carini* infection with cotrimoxazole was changed to dapsone 100 mg daily following development of a widespread maculopapular rash. His cough settled within the

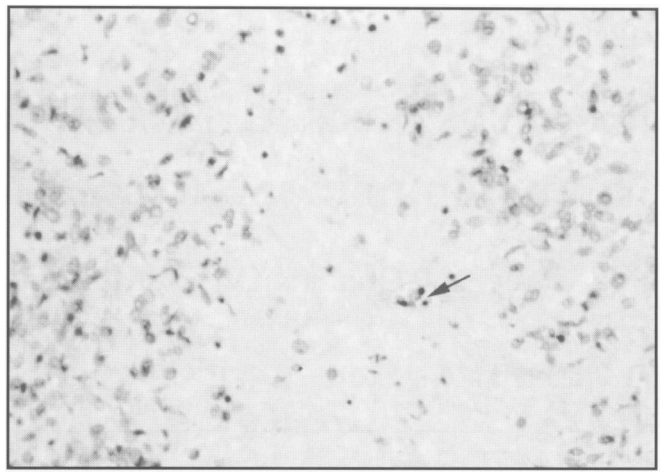

Fig 3. Palatal biopsy with PAS staining showing a granuloma with a necrotic centre in which small fungal organisms of histoplasma may be seen (x 40).

first week and the palatal lesions had gradually regressed. Repeat blood investigations showed his CD4 count to have increased to 0.11 x 10/L. After discussion with the patient an antiretroviral regime was chosen and commenced.

DISCUSSION

This 51 year old man had symptoms suggestive of oral histoplasmosis for four years prior to a definitive diagnosis. This led to the diagnosis of co-existent HIV infection. He responded very well to antifungal treatment. Attempts to diagnose infection at other sites (for example, paranasal sinuses) were not undertaken as his response to treatment was so prompt.

Histoplasma capsulatum is a dimorphic fungus, distributed worldwide between latitudes 45 north and 30 south of the equator. It is endemic in certain areas of north and south America, where it remains a major health problem.[1] It is acquired by inhalation of fragments of the mycelial form which are deposited in the pulmonary alveoli and converted to the yeast form at body temperature. CD4 T lymphocytes are crucial to the host's defence, hence the susceptibility of immunocompromised individuals.[2]

In immunocompetent individuals 90% of infections are asymptomatic. In HIV positive patients histoplasmosis usually presents as a disseminated infection and is categorised as an AIDS defining illness in such patients. It has been reported as the second or third most frequent opportunistic infection in HIV positive patients living in endemic areas.[2]

The pattern of clinical presentation is varied – fever, weight loss, respiratory complaints, lymphadenopathy, hepatosplenomegaly, skin and oral lesions [3] and central nervous system involvement can occur with 5 - 10% of patients presenting with symptoms of septic shock.[4]

Blood tests may show anaemia, neutropenia or thrombocytopenia reflecting bone marrow involvement with the fungus. Liver function tests may be abnormal.

Diagnosis is based on culture of the fungus from blood, sputum or other clinical specimens. Histopathological examination of biopsy material (eg. lung, skin), bone marrow aspirate or lavage fluid may also be diagnostic.

Detection of anti-histoplasma antibodies in serum by either immunodiffusion techniques or a complement fixation test yields a sensitivity of 70-80%. However 30-50% of immuno-compromised individuals fail to develop detectable titres of antibody.

Detection of histoplasma antigen in the urine or serum yields sensitivities of 90 and 50% respectively. It is useful in immunocompromised patients and allows serial monitoring to assess response to therapy, however it is not widely available.[5]

Treatment with amphotericin B at a dose of 0.5 to 1.0 mg/kg for a total dose of 0.5 to 1.0 gm gives a response rate of 85-90%. Amphotericin B encapsulated in liposomes is being increasingly used as it causes fewer adverse reactions. Itraconazole orally at a dose of 400 mg daily showed a response rate of 85%, however patients with severe life threatening illness or central nervous system involvement were excluded from this study.[2]

Suppressive therapy with itraconazole a dose of 200 to 400 mg daily has been shown to be highly effective in preventing relapse whether initial treatment was with amphotericin B or itraconazole. Amphotericin B given by weekly or biweekly infusion resulted in 85-90% relapse free survival but may require an indwelling intravenous catheter. Long term continuation of maintenance treatment is recommended.[3]

Future therapies may include chloroquine which has been shown to greatly augment the ability of human macrophages to inhibit the intracellular growth of histoplasma yeasts. Nikkomycin Z is highly active against Histoplasma capsulatum in vitro. It has been shown to treat murine histoplasmosis successfully but has not yet been trialed in humans. A vaccine, made from the glycoprotein yeast wall, has been shown to confer protective immunity in mice against experimental infection. A human vaccine may be of benefit in the immunocompromised patient or military personnel in endemic areas, or those exposed to histoplasma occupationally.

The incidence of HIV infection in Northern Ireland continues to rise with a significant number of patients originating from Africa and America. Travel to distant climes, is increasing. It is very likely that in the future more cases of fungal infection, previously viewed as exotic, will be seen by doctors and dentists here.

REFERENCES

1. Wheat J. Histoplasmosis: experience during outbreaks in Indianapolis and review of the literature. *Medicine* 1997; **76**: 339-54.
2. McKinsey D S, Spiegel R A, Hutwagner L, *et al.* Prospective study of histoplasmosis in patients infected with human Immunodeficiency virus: incidence, risk factors, and pathophysiology. *Clin Infect Dis* 1997; **24**: 1195-203.
3. Wheat J. Histoplasmosis in the acquired immunodeficiency syndrome. *Curr Top Med Mycol* 1996; **7(I)**: 7-18.
4. Eisig S, Boguslaw B, Cooperband B, Phelan J. Oral manifestations of disseminated histoplasmosis in the acquired immunodeficiency syndrome: a report of two cases and review of the literature. *J Oral Maxillofac Surg* 1991; **49**: 310-3.
5. Corti M E, Cendoya C A, Soto I, *et al.* Disseminated histoplasmosis and AIDS: clinical aspects and diagnostic methods for early detection. *AIDS Patient Care & STDs* 2000; **14**: 149-54.