

Disseminated histoplasmosis successfully treated with amphotericin B

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SYNOPSIS A 61-year-old woman presented with malaise, intermittent fever, weight loss, and epigastric pain. *Histoplasma capsulatum* was eventually isolated from a liver biopsy and from the bone marrow and the patient was successfully treated with amphotericin B.

Disseminated histoplasmosis is very rarely seen in Great Britain; there have been only 11 reported cases, with positive cultures in eight (Macleod, Murray, Davidson, and Gibbs, 1972). All but two of the patients died. We present here a case of active disseminated histoplasmosis diagnosed by culture and successfully treated with amphotericin B.

Clinical Report

Mrs E.W.S., a 61-year-old housewife, had travelled extensively since 1935, spending five years in Malaya during the Second World War, and shorter periods in Australia, Nigeria, and South Africa more recently. She was admitted to St Thomas' Hospital on 16 June 1971 with a six-month history of malaise, weight loss, and intermittent fever. She also complained of epigastric pain and flatulence. The only abnormal physical findings were a persistent low-grade pyrexia and an enlarged, tender liver. The only abnormalities revealed on initial investigation were an ESR (Westergren) of 15 to 29 mm/hr, a serum amino-aspartate transferase of 85 iu/l (normal range 25-65 iu/l), and an alkaline phosphatase of 20 KA units/100 ml (normal range 4-13 KA units/100 ml). Chest radiography and white count were normal. A liver biopsy was performed on 29 June, and histology showed non-caseating giant cell granulomata but no acid-fast bacilli nor fungi were seen. The biopsy material was not cultured. Tuberculosis was strongly suspected and therapy was begun with isoniazid, para-aminosalicylic acid, and streptomycin. After three weeks these drugs were stopped as the fever continued unabated and her symptoms remained unaltered. A further liver biopsy showed unchanged histology. The specimen was

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cultured on Lowenstein-Jensen slopes and in nutrient broth (incubated for 23 days with aerobic and anaerobic incubation of each subculture for five days), but all cultures were sterile.

Sarcoidosis was then considered as a possible diagnosis and treatment with prednisone begun. Within two days the fever settled and she felt markedly better. She was discharged from hospital on 17 August but was readmitted three weeks later still apyrexial but very easily tired. Within one week fever and malaise returned and a herpetic rash developed on the buttocks (varicella zoster on electron microscopy). A laparotomy was performed on 19 October: the only abnormal finding was an enlarged granular liver and a wedge biopsy of this showed granulomatous hepatitis. Culture media on this occasion included Sabouraud agar on which after about two weeks' incubation at 22°C two colonies of *Histoplasma capsulatum* appeared. Both histoplasmosis and coccidioidin skin tests were negative but antibody studies on the patient's serum showed a titre of 1:128 in the histoplasma complement-fixation test. *H. capsulatum* was also grown from the bone marrow. The liver biopsy was then stained by Grocott's modification of Gomori's methenamine silver technique and occasional yeast forms of the fungus were demonstrated. Careful examination of many methenamine silver preparations of the previous liver biopsies revealed occasional histoplasma in two of the three specimens but they were not identifiable with the periodic acid-Schiff stain (PAS) or on haematoxylin and eosin sections.

A diagnosis of disseminated histoplasmosis was made and treatment with intravenous amphotericin B started on 17 November. She tolerated the drug well and a total of 3 g was given over 21 weeks. A

further liver biopsy showed a few irregular granulomata but no histoplasma was seen or cultured. She was discharged home on 15 April, 1972, afebrile but still complaining of tiredness.

One month later she was readmitted with increasing malaise, ankle oedema, and a tender enlarged cervical lymph node. The lymph gland was removed: histology showed numerous histoplasma on silver staining, and culture yielded one colony of *H. capsulatum*. It was now concluded that the patient had uncontrolled disseminated disease but both bone marrow and liver biopsy culture were sterile and the liver histology was normal. The histoplasma complement-fixation test was now negative. A further 0.65 g of amphotericin B was given and there has been no further evidence of infection following her discharge from hospital in July 1972.

Discussion

The few patients with disseminated histoplasmosis reported from Great Britain have all been infected abroad. It seems possible that this patient acquired the primary infection in Malaya during the war since the organism is known to occur there. Ponnampalam (1963) isolated *H. capsulatum* from the soil of a bat-infested cave in central Malaya; he also investigated 227 adult patients admitted to hospital in Kuala Lumpur with respiratory symptoms and found 10.5% had a positive histoplasmin skin test and 19.8% had a positive histoplasma complement-fixation test (Ponnampalam, 1964). If infection did occur in Malaya, it was 25-30 years before the disease became manifest, but in two of the cases of disseminated histoplasmosis described by Macleod *et al* (1972) the patients had lived in England for 16 and 18 years since travelling abroad. However, our patient could have acquired the infection in South Africa, where she visited diamond mines, Nigeria, where there were several dust storms, or Australia.

Although histoplasmosis is a disease of protean manifestations, fever, malaise, and loss of weight are described as presenting symptoms in the majority of patients with disseminated disease (Reddy, Gorelick, Brasher, and Larsh, 1970; Macleod *et al*, 1972; Smith and Utz, 1972). Hepatomegaly is said to be common: of the 26 patients with progressive disseminated histoplasmosis described by Smith and Utz (1972), 16 had hepatomegaly and in 21 the liver function tests were abnormal. Adrenal insufficiency caused by granulomatous replacement of the gland is also common in histoplasmosis. Although this patient did show an abnormal response to adrenocortical stimulation it seems most likely that this was an effect of the long-term administration of

prednisone as when this was finally discontinued she suffered no ill effects. The absence of any pulmonary signs is not unusual in cases presenting after a long latent period.

The diagnosis was finally made by culture of the liver biopsy. Silverman, Schwarz, Lahey, and Carson (1955) recommend liver biopsy as a useful diagnostic aid in histoplasmosis and Smith and Utz (1972) reported a positive culture or stain from five out of eight patients who had a liver biopsy. However Reddy *et al* (1970) did not find liver involvement particularly common in their series. Bone marrow culture, positive in this patient, is recommended by several authors: Smith and Utz (1972) found positive bone marrow cultures in 70% of 23 patients and Reddy *et al* (1970) in 65% of 23 patients. Blood culture is also recommended by Reddy *et al* (1970) who found 52% positive. Although several blood cultures were performed in our patient, no subcultures were incubated for more than five days. Our experience showed that prolonged culture is necessary to grow the fungus and that silver stains are mandatory to demonstrate it in histological preparations. Even with silver staining it may be difficult to find the fungus although a textbook view is that histoplasma '... can usually be recognized with ease in the disseminated form of the disease, since the fungus cells can readily be seen with the haematoxylin and eosin stain' (Emmons, Binford, and Utz, 1970). In the liver biopsies in this case, the organism was only demonstrable in methenamine silver preparations, but in the lymph node biopsy, in which there were many organisms, it was possible to recognize its presence on haematoxylin- and eosin-stained slides. Although the morphology of *H. capsulatum* may be characteristic in histological preparations, definitive identification of the fungus should come from its isolation and characterization in culture.

It is known that the histoplasmin skin test is often negative in disseminated histoplasmosis and this was the case in our patient. However she had a histoplasma complement-fixation titre of 1:128 and it is interesting that only nine of 26 patients with disseminated histoplasmosis reported by Smith and Utz (1972) had a complement-fixation titre of 1:32 or more.

Before the introduction of amphotericin B, disseminated histoplasmosis carried a very high mortality. It is difficult to assess the total dose required to treat the disease; Rogers (1967) recommends a total dose of 2 g, whereas Smith and Utz (1972) quote doses ranging from 0.95 g to 5.9 g. Our initial treatment of 3 g of amphotericin B was considered adequate but in view of the local recurrence a further course was given, and she received a

total of 3.65 g. Success of therapy can be judged by inability to culture the fungus from the bone marrow or liver and by the clinical condition of the patient. The side effects of amphotericin B are well known but apart from a raised blood urea during treatment she tolerated the drug very well.

This case is interesting, not only because of the rarity of the disease in Great Britain but also because of the successful treatment. The following points are worth making: first, the unusual causes of non-caseating hepatic granuloma should always be considered in patients who have travelled outside the UK, no matter how long before the onset of symptoms. Secondly when a liver biopsy specimen is obtained from patients with unexplained pyrexia, cultures should always be set up and should be incubated both at 22°C and 37°C for at least three weeks. Thirdly, silver stains are essential for the demonstration of histoplasma in histological sections; PAS is inadequate.

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