Disseminated histoplasmosis in an English patient with diabetes mellitus

A JARIWALLA, B R TULLOCH, H FOX, J KELLY, R DAVIES

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Summary

Histoplasma capsulatum is not endemic in Britain. We report a case of disseminated histoplasmosis in an English man who had not ventured out of northern Europe for 30 years. The disease presented as painful mouth ulcers and hepatosplenomegaly six months after he had developed maturity-onset diabetes. The origin of the infecting fungus may have been from within the United Kingdom or alternatively it may have existed as an intraoral saprophyte for over 30 years.

Introduction

A patient who had not left northern Europe for over 30 years presented with persistent oral ulceration and maturity-onset diabetes. Histological examination of the mouth ulcers suggested a diagnosis of histoplasmosis.

Case report

The patient, a 55-year-old English credit director, was born in Sheffield but had spent most of his life in the Manchester area. In August 1975 he noticed polyuria and nocturia, and over the subsequent six months lost 15 kg in weight despite maintaining a good appetite. Five weeks before admission in April 1976 he complained to his dentist of a painful sublingual ulcer that restricted eating. The discomfort was exacerbated by dry biscuits, and persisted despite treatment with metronidazole and carbenoxolone sodium pellets. He was referred to hospital for further investigation. Previous ill health was limited to an episode of jaundice 15 years previously which had cleared after two weeks of bed rest. Apart from a trip to northern France, travel abroad had been restricted to war service with the RAF in South Africa, India, and Burma, the patient having returned to the United Kingdom in 1946. He smoked 26 cigarettes a day and drank little alcohol. The family history included maturity-onset diabetes developing in his mother at 83 years.

He was fit and remained afebrile during his initial hospital confinement. There were xanthelasmata above both eyelids but no tendon xanthomata. There was no lymphadenopathy. Blood pressure was 140/70 mm Hg lying and standing. A ragged ulcer measuring 1·5 × 1 cm extended from the lingual gingiva to the root of the tongue, being surrounded by a rolled edge (fig 1). The liver was enlarged 8 cm below the costal margin but was smooth and non-tender. The spleen was enlarged to 6 cm. The results of neurological examination were normal.

Investigations showed: haemoglobin 13·4 g/dl; white cell count 2·5 × 10^9/l (2500/mm^3), (neutrophils 74%, lymphocytes 20%, monocytes 6%). There was no appreciable eosinophilia. Erythrocyte sedimentation rate was 18 mm in one hour. Platelet count was 13·9 × 10^9/l (139 000/mm^3), reticulocytes less than 1%. The Mantoux test gave a negative result at a titre of 1/10 000. Blood sugar (fasting) was 10·8 mmol/l (194·6 mg/100 ml), with glycosuria 2%, no ketonuria. The following investigations gave negative results: bone marrow biopsy; tests for rheumatoid factor and antinuclear factor; Widal, Kahn, and Wassermann tests. Concentrations of serum creatinine, calcium, phosphate, bilirubin, albumin, globulin, thyroxine, creatinine, phosphokinase, serum iron, urea, electrolytes, and cholesterol were normal; protein electrophoresis, total binding capacity, lipoprotein profile, electrocardiogram, and barium meal examination showed nothing abnormal.

Chest *x*-ray examination showed no hilar lymphadenopathy or calcification. A liver scan confirmed hepatosplenogomegaly. The sputum showed histocytes but no malignant cells, acid-fast bacilli, yeasts, or fungi. The serum γ-glutamyltransferase was 120 IU/l (normal < 65 IU/l), alkaline phosphatase 173 IU/l (normal < 100 IU/l). Plasma cortisol was 344 nmol/l (12·5 μg/100 ml), rising to 785 nmol/l (28·4 μg/100 ml) after tetracosactrin stimulation. Results of histoplasma skin test and histoplasma complement fixation test were weakly positive and negative, respectively.

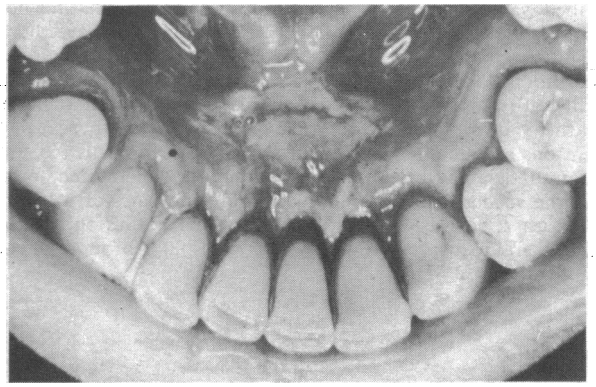

FIG 1—View of ulcer in lingual sulcus spreading towards frenulum linguae.

BIOPSY FINDINGS

A piece of partially ulcerated squamous epithelium and underlying connective tissue was obtained from the mouth ulcer. The epidermis showed hyperplasia at the ulcer margin. In the subepidermal region many of the histocytes were mixed with plasma cells and occasional giant cells (fig 2). Within the histocytes, and particularly within those in the dermal papillae, there were many rounded eosinophilic structures surrounded by a clear halo (fig 3). These gave a positive reaction to staining with periodic acid and methamine silver (fig 4) but a negative reaction when stained with mucicarmine.

The liver biopsy specimen showed many intraparenchymal non-caseating tuberculoid granulomata (fig 5). There was no disturbance of hepatic architecture, nuclear vacuolation was not seen, and there was no steatosis. No organisms were seen in the biopsy specimen.

CLINICAL PROGRESS

The glycosuria responded satisfactorily to a 140 gram, 6·3 MJ (1500 kcal) diet. A course of amphotericin B was given twice weekly

University of Manchester, Departments of Medicine and Pathology, The Royal Infirmary, Manchester M13 9WL

A JARIWALLA, BM, MRCP, medical registrar
B R TULLOCH, MSC, MRCP, senior lecturer in medicine (present appointment: associate professor of medicine, University of Texas, Houston, USA)
H FOX, MD, FRCPATH, reader in pathology
J KELLY, MB, BAO, lecturer in pathology

Turner Dental Hospital, Manchester

R DAVIES, BDS, PHD, senior lecturer in periodontology

by slow intravenous infusion, doses increasing stepwise from 5 mg to 50 mg. Blood count, electrocardiogram, and renal function were carefully monitored. After three weeks' treatment the mouth ulcer disappeared, but liver and spleen size increased by a further 3-4 cm. The enlargement of these two organs regressed over the next two months until the spleen became impalpable; the liver edge was just palpable after three months' treatment. A total of 2·5 g amphotericin-B was administered.

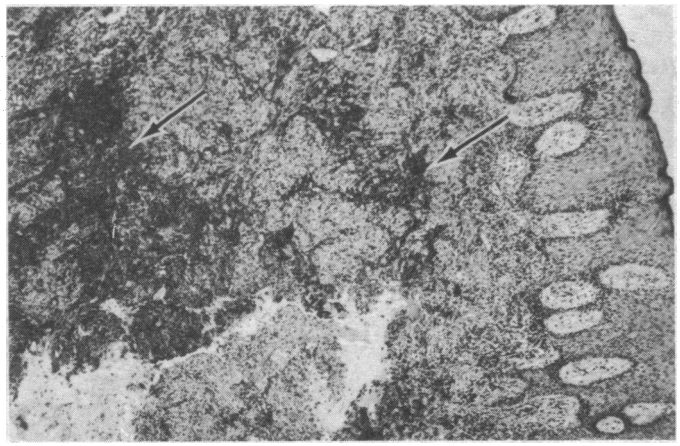

FIG 2—Low-power view of oral lesion showing area immediately adjacent to ulcer. (Haematoxylin-eosin ×35.)

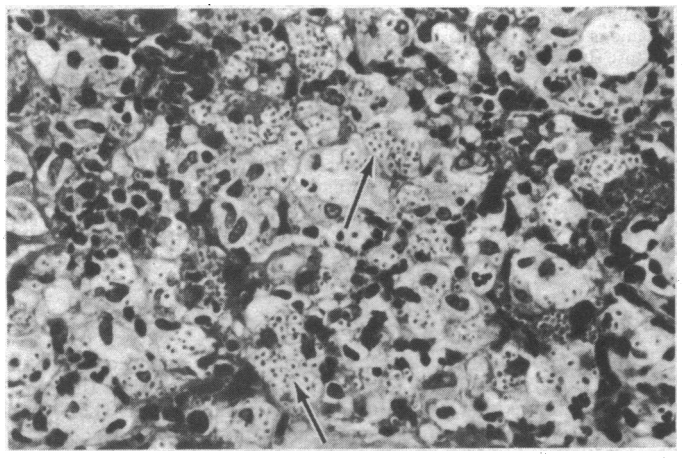

FIG 3—High-power view of oral lesion showing rounded organisms in dermal histiocytes. (Haematoxylin-eosin ×210.)

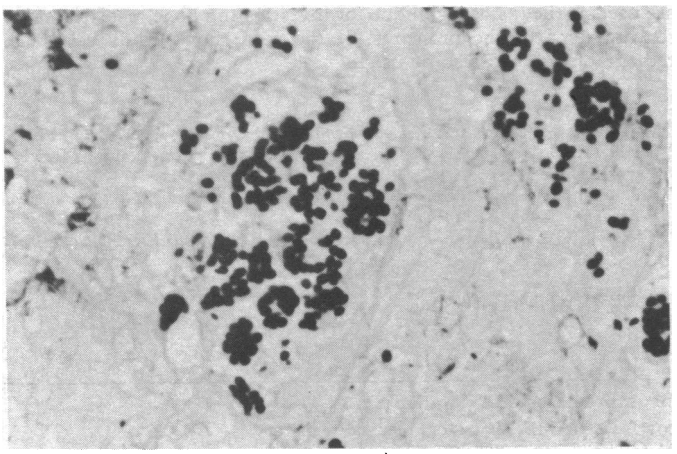

FIG 4—Organisms in dermal histiocytes stained with methamine silver. (×336.)

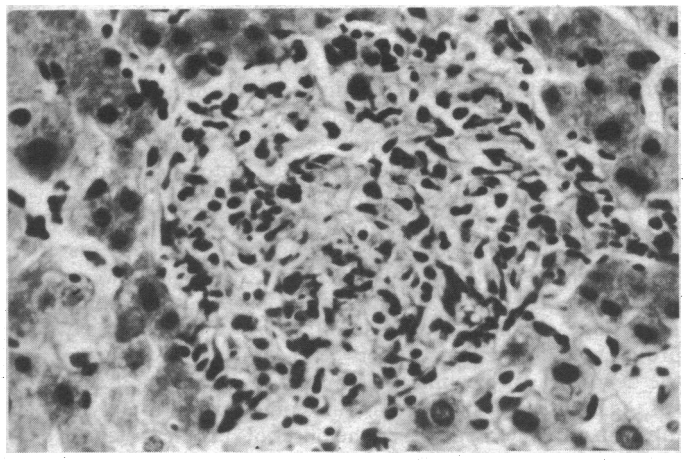

FIG 5—Liver biopsy specimen showing intraparenchymal noncaseating granuloma. (Haematoxylin-eosin ×210.)

Discussion

The diagnosis of histoplasmosis in this patient rested principally on the histological findings. The nature of the cellular reaction was typical of histoplasmosis, while the morphology, intracellular site, and tinctorial qualities of the organisms were characteristic of *H capsulatum*; in particular the staining reactions of the organisms excluded cryptococcosis and leishmaniasis. No organisms were seen in the hepatic granulomata and these showed no specific distinguishing features. Hepatic granulomata are not, however, a feature of uncomplicated diabetes mellitus and in the presence of oral histoplasmosis it appeared reasonable to attribute the hepatic lesions to disseminated histoplasmosis—a condition known to produce granulomata of this type. Because of the extreme rarity of histoplasmosis in Great Britain, however, it was thought advisable to seek further opinion and a colleague visiting the United States showed the sections to several pathologists working in endemic areas. All agreed that the appearances of the oral ulcer were typical of histoplasmosis.

In endemic areas histoplasmosis presents in three principal forms.

Primary exposure, characterised by fever, rigors, and pulmonary infiltrates that usually clear spontaneously, occasionally leaving scattered fine areas of calcification visible on chest *x*-ray pictures.

A chronic granulomatous form, with granulomata of the lungs or alimentary tract.

Rare, progressive systemic histoplasmosis has been reported to show a predilection for the very young and the late middle-aged, particularly men, in whom the nature of the disease varies with the degree of primary inoculation and the ability to mount a cellular response.[1 2]

In older men there is a high incidence of chronic bronchitis and smoking, and about 60% present with mucocutaneous lesions.[3] Causes of diminished cellular immune response include glucocorticoids, immunosuppressants, sarcoidosis, and disseminated carcinoma.[1] In our patient the ulcer appeared some six months after he had developed diabetes mellitus, which might have provided metabolic conditions that predisposed to infection by facultative pathogens.

ORIGIN OF THE ORGANISM

H capsulatum is a saprophytic fungus endemic in areas such as the United States (particularly the Mississippi and Ohio river valleys), Africa, the Mediterranean, and the Middle East.[4] It is not known to occur in the United Kingdom. After summarising the geographical characteristics of the Mississippi valley—summer temperatures of 10-21°C, rainfall 76-127 cm

per year—Knight considered that some areas of the United Kingdom, including the temperate west counties, north Wales, and north-west Cheshire may have sufficient warmth and humidity to harbour the yeast in fertile environments.[5] These tend to be soil infested with animal matter—chicken coops, starling roosts, and caves rich in bat guano. Seven years before admission our patient killed a bat that entered his room in a nineteenth century Somerset house, but no febrile illness followed this event. He otherwise denied hobbies or activities that could lead to exposure to potentially infected material. Closer questioning about his wartime exploits, however, revealed several visits to the Elephanta caves outside Bombay in 1945. The implication of bat infection at this source would presume a 30-year interval between acquiring the organism and the development of clinical symptoms. Presumably if this were so, the fungus was during this prolonged interval a symbiotic inhabitant of the mouth, and the onset of diabetes mellitus provided a favourable environment for its proliferation and dissemination. The alternative to this rather convoluted theory is to assume that the patient contracted histoplasmosis as an opportunistic infection in England after developing his diabetes mellitus.

We are grateful to the sister and the staff of ward M2, Manchester Royal Infirmary, the Department of Oral Medicine, the Dental Hospital, and to Professor P H Adams for permission to report this case.

Requests for reprints should be addressed to B R Tulloch, Endocrine Section, Department of Medicine, University of Texas, Houston 77025, USA.

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SHORT REPORTS

Detection of bone metastases in carcinoma of bronchus

At diagnosis lung cancer is at least as frequently a systemic as a regional disease.[1] Bone metastases have been found at necropsy in over one-third of cases.[2] It is reasonable to try to exclude such metastases before treatment. We have compared the value of three techniques for detecting bone metastases—namely, measurement of serum alkaline phosphatase concentrations, plain radiography, and radioisotope scanning.

Methods and results

We examined the records of 100 consecutive patients with carcinoma of the bronchus who had undergone investigation for bone metastases. Sixty patients had bone pain and 40 were investigated for assessment of tumour spread before a course of chemotherapy or radiotherapy.

Bone metastases were thought to be present in 44 patients. Of these, 20 had squamous-cell carcinoma, 14 oat-cell carcinoma, and 10 adenocarcinoma. Bone metastases were confirmed histologically in six patients, by subsequent radiographs in 17 patients, and the remaining 21 patients had severe, persistent, localised bone pain before death. The other 56 patients had no evidence of bone metastases at death or after 18 months' follow-up. Of the 44 cases of bone metastases, 40 had been investigated because of bone pain.

In all cases serum alkaline phosphatase was measured, and plain radiography and a bone scan were performed. Radiographs were taken of painful areas, of regions that had been positive at scanning, or for a skeletal survey, and were reported without knowledge of the bone-scan result. The scans were performed on a Scintomat 2 machine (Siemans) with the use of 99-Tc-labelled polyphosphate. The whole spine, pelvis, and upper femora were examined routinely, and other areas as indicated. Scans were reported by other observers without access to radiographs.

The results are summarised in the table. The serum alkaline phosphatase concentration (normal 35 IU/l) was raised in half the patients with bone metastases. In only 10 cases was it raised by more than 10%. It was raised in 11 patients with no bone metastases; this was due to liver metastases in nine patients, and Paget's disease in two patients.

Plain radiographs detected six of the cases of bone metastases due to squamous-cell carcinoma, four of those due to adenocarcinoma, and seven of those due to oat-cell carcinoma.

Bone scans detected 19 out of 20 metastases due to squamous-cell carcinoma, all 10 cases due to adenocarcinoma, but only eight of the 14 cases due to oat-cell carcinoma. The scan was positive in seven cases in which radiographs were negative and sites were symptom-free. The duration of symptoms in patients with positive scans was raised from two days to seven months, but seven patients had symptoms for one week or less. In six cases the scan was equivocal and *x*-ray pictures showed degenerative disease. Abnormal findings on two scans were correctly identified as being due to Paget's disease, and this was confirmed by plain radiography.

Results of investigations for bone metastases in 100 cases of carcinoma of the bronchus

Technique	True-positive (n = 44)	True-negative (n = 56)	False-positive	False-negative
Serum alkaline phosphatase estimation	22	22	11	45
Plain radiography	17	56	0	27
Radioisotope bone scanning	37	56	0	7

Comment

Estimation of serum alkaline phosphatase was a poor technique for isolating bone metastases. Plain radiography detected less than half the cases of bone metastases. Radiographs cannot usually show bone metastases until they are 1-1·5 cm in diameter, and 50% bone calcification has occurred.[3 4]

Most patients with positive scans had symptoms, but some had pain only for a short period and others had positive scans in sites that were symptom-free. Hence bone scans may be useful in detecting otherwise unobtrusive bone metastases. We suggest that bone scans are used as the major technique for investigating bone metastases due to carcinoma of the bronchus. If the scan shows equivocal areas, radiography should also be used.

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Brompton Hospital, London SW3
S J WILLIAMS, MB, MRCP, medical registrar
M GREEN, MD, MRCP, consultant physician
I H KERR, FRCP, FRCR, consultant radiologist