Sarcoidosis possibly predisposing to disseminated histoplasmosis

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In Europe most authors consider that histoplasmosis due to *Histoplasma capsulatum* is a rare imported fungal disease that is only diagnosed when it appears in the disseminated form. Such a presentation is very unusual in areas where it is endemic.¹ This paradox is explicable because in most cases infection is localised, so that in endemic areas cases of dissemination represent a very small proportion of the total; where histoplasmosis is not endemic but is seen among those who have lived or travelled in regions where it is endemic, disseminated disease may present many years after their return and represents a large proportion of confirmed cases. Underlying immunosuppression has been reported in 44% of patients with disseminated disease²; predisposing factors include haematological malignancy, use of immunosuppressive drugs (corticosteroids, cytotoxic drugs), or immunologically depressive disease such as AIDS,³ systemic lupus erythematosus, and diabetes mellitus.⁴

When dissemination occurs it predominantly affects the lungs, the adrenal glands, and the reticuloendothelial system, but may also affect other organs, such as the pharynx, liver, and the central nervous system, leading to the peculiar aspects that have been described.⁵ The effects may be confused with those of other systemic diseases, such as tuberculosis and connective tissue diseases. The diagnosis becomes particularly difficult when systemic diseases such as these predispose to dissemination of histoplasmosis. We report a case of fatal subacute histoplasmosis developing in a patient with probable sarcoidosis.

Case report

The patient was a 49 year old caucasian who had lived for 15 years in the Ivory Coast (Yamousoukro) without any history of disease. Three years after his return to France (Lyon) he became ill. He was admitted elsewhere in June 1984 with weakness, anorexia, and weight loss of 3 kg over four months. Physical examination revealed only a palpable liver edge. The chest radiograph showed a miliary type infiltrate sparing the bases together with hilar adenopathy (fig 1). Needle biopsy of enlarged peribronchial lymph nodes showed non-specific inflammation. Despite cultures negative for *Mycobacterium tuberculosis*, the patient was treated with isoniazid ethambutol and rifampicin for two months, without success. Indeed, weight loss continued and a pyrexia of 37-38.5°C was noted, as well as painful hoarseness with

visible ulceration of the right tonsil. Biopsy of this lesion and of a peribronchial lymph node showed non-caseating granulomas with giant cells. Bronchoalveolar lavage fluid containing 40% lymphocytes together with twice the normal concentrations of angiotensin converting enzyme in serum and lavage fluid suggested sarcoidosis.

Antibiotics were stopped and the patient was discharged for personal reasons without treatment. He was admitted as an emergency in September 1984 with shock: acute adrenal insufficiency was suspected because of dehydration and hyperkalaemia (6.2 mmol/l) and was confirmed by a plasma cortisol concentration of less than 5 µmol/l). Rehydration and replacement steroid treatment were rapidly instituted but the patient's condition was poor: the weight loss over three months was over 10 kg, and painful hepatomegaly and two small peribuccal ulcers were noted. Investigations for possible infections were performed without any positive results and acute sarcoidosis was diagnosed, although the miliary shadowing had disappeared. High dose corticosteroids (80-100 mg prednisone/day) were administered for 15 days after a liver biopsy, which showed granulomatous hepatitis. This treatment had no effect on the patient's progress. A biopsy specimen of the skin ulcer, after haematoxylin and eosin staining, showed numerous intracellular and extracellular yeasts 3-5 µm in diameter, strongly suggesting *H capsulatum* (fig 2). Treatment with amphotericin B was started in increasing doses but by this time the patient had become comatose. Cerebrospinal fluid was sterile and contained 1.20 g/l protein and 0.8 mmol/l glucose. Despite intensive resuscitation the patient died three days later.

Fig 1 Chest radiograph taken in June 1984 showing miliary mottling sparing the bases, with hilar adenopathy.

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Fig 2 Skin biopsy specimen showing the intracellular and extracellular yeasts (arrows). (Haematoxylin and eosin; scale in micrometres.)

Postmortem histological examination using a yeast specific silver stain showed adrenal glands, liver, kidney, and thyroid to be affected, confirming dissemination of the disease. Unfortunately, the central nervous system could not be examined. Cultures of blood and cerebrospinal fluid remained negative, but microimmunodiffusion studies on blood drawn two weeks before death were positive for precipitins against the H and M antigens of histoplasmin.

Discussion

Two types of pathogenic histoplasma have been described: *H duboisii*, 12–15 μm in diameter, is endemic in West and Central Africa and leads to chronic dissemination in skin, bones, and the reticuloendothelial system. *H capsulatum*, easily differentiated by its smaller size (3–5 μm), is endemic in the same countries but also in the United States and Central America, where it was first described. Infection usually produces an influenza like illness, which is often undiagnosed. Reactivation can occur as a progressive disseminated form; this is included among the granulomatous diseases, which also include sarcoidosis, syphilis, disseminated coccidioidomycosis and chronic berylliosis.⁶ Thus disseminated histoplasmosis has often been found to mimic sarcoidosis, thereby resulting in delayed diagnosis.⁷ This may have been the case here but another possibility must be considered, especially since despite detailed investigation we found no immunosuppressive condition that might explain the reactivation in our patient. Thus for three reasons we suggest that active sarcoidosis was the underlying disease. Firstly, the illness had begun with weakness and weight loss months before the pharyngeal symptoms appeared and negative conversion of the tuberculin skin test reactivity (which had

been positive three years before) was observed in June 1984. Secondly, if the miliary shadowing had been due to disseminated histoplasmosis it would not have decreased as the disease progressed. Thirdly, we performed hexamine-silver staining on sections of the node biopsy specimens from both June and September 1984 and no *H capsulatum* was found, even though the same method disclosed organisms in sections of the tonsillar biopsy specimen of September 1984. The possibility of histoplasmosis in the presence of underlying sarcoidosis has been suggested by several authors⁸; possibly the systemic T cell defect that occurs in active sarcoidosis⁹ might account for the reactivation of yeasts dormant inside the primary complex. It is also possible that corticosteroid treatment contributed to the acute presentation of the disease.¹

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