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Miliary tuberculosis and disseminated aspergillosis

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Summary

A patient with concurrent miliary tuberculosis and disseminated aspergillosis is described.

Introduction

An association between *Aspergillus* infection and tuberculosis has long been recognized (Virchow, 1856; Lapham, 1926). *Aspergillus* is generally considered a harmless secondary saprophyte. A patient is described who developed concurrent miliary tuberculosis and disseminated aspergillosis, and whose clinical features suggested that both infections contributed to his illness.

Case report

A 42-year-old labourer presented with an 11-day history of an influenza-like illness. Six months and 1 month previously he had suffered two similar but milder episodes of illness, from which he recovered spontaneously. Otherwise he had been physically fit. On examination he was pale and ill. He had a temperature of 38°C, a membranous tonsillitis and a palpable liver and spleen (both one inch below the costal margin).

Initial investigations showed haemoglobin 11 g/dl; leucocyte count $1.7 \times 10^9/l$; neutrophils 7%; lymphocytes 90%; monocytes 2%; platelet count 70×10^9 ; serum albumin 34 g/l; globulin 29 g/l; bilirubin 9 $\mu\text{mol/l}$ (0.5 mg/dl); aspartate transaminase 45 i.u./l; alkaline phosphatase 119 i.u./l (17 KAu.); IgG 7.8 g/l; IgA 2.1 g/l; IgM 1.0 g/l. Bone marrow aspirate was hypocellular. Blood, CSF, urine and throat swab were sterile. Tuberculin

test (1 : 10 000), Australia antigen, WR and Paul-Bunnell were negative. Chest X-ray was normal.

After obtaining cultures of blood, urine and faeces, he was treated with gentamycin and flucloxacillin without benefit. On the fourth day, after a lumbar puncture, he started treatment with streptomycin, isoniazid and ethambutol. Forty-eight hours later his temperature fell to normal, but after a further 48 hours he again developed a remittent pyrexia. During the next 10 days his condition deteriorated. Serum albumin fell to 26 g/l, alkaline phosphatase rose to 258 i.u./l (36 KAu.) and aspartate transaminase rose to 67 i.u./l. After a total of 13 days' treatment he developed a skin rash and antituberculous therapy was stopped. A trephine biopsy of the iliac crest showed reduced haemopoietic cells with increased lymphocytes, suggesting the possibility of lymphosarcoma. On the twenty-eighth day, exploratory laparotomy revealed small nodules up to 0.8 cm in diameter in the liver and spleen. Liver biopsy, lymph node biopsy and splenectomy were performed.

Following the histology report he started amphotericin intravenously and ethambutol, isoniazid and rifampicin orally. At the same time the original specimen of bone marrow grew acid-fast bacilli. Although his temperature started to settle, he remained desperately ill and died suddenly 5 days later.

Biopsy and post-mortem findings

Histology of the liver and spleen showed granulomas consisting of round collections of histiocytes

FIG. 1. A characteristic granuloma in the spleen showing central histiocytes and necrosis with a peripheral cuff of inflammatory cells consisting mainly of plasma cells. Note the absence of epithelioid cells and giant cells (Haematoxylin and eosin $\times 200$).

FIG. 2. Branching septate fungal hyphae characteristic of *Aspergillus* in the centre of a granuloma (periodic acid Schiff $\times 410$). The inset shows the abundant tubercle bacilli present in some granulomas (Ziehl Nielsen $\times 410$).

and polymorphonuclear cells cuffed by a rim of plasma cells with a few lymphocytes and fibroblasts. The histiocytes did not have epithelioid characteristics and giant cells were absent (Fig. 1). In the larger granulomas of the spleen there was central necrosis and branching septate fungal hyphae resembling *Aspergillus* in the necrotic zones (Fig. 2). In the small granulomas abundant acid-fast bacilli were demonstrated in the areas of viable histiocytes (Fig. 2—inset). In some granulomas both *Aspergillus* and acid-fast bacilli were seen.

The lack of epithelioid and giant cells, together with the negative tuberculin reaction and the numerous acid-fast bacilli indicated non-reactive tuberculosis (Anderson, 1971). The lymph node contained small non-necrotic granulomas.

At post-mortem granulomas identical to those described above were found in the lungs, liver and cervical lymph nodes. *A. fumigatus* was cultured from the lungs and typical human *Mycobacterium tuberculosis* from the lungs, liver and lymph nodes. The bone marrow showed marked depletion of haemopoietic cells, but plasma cells and lymphocytes were plentiful. Lymph nodes from several regions which were free from granulomas showed reactive changes but the nodal architecture was preserved and there was neither evidence of depletion of paracortical lymphocytes nor of lymphoma.

Discussion

Both acid-fast bacilli and aspergilli were demonstrated in the granulomas and clearly there had been blood stream spread of both organisms from the pulmonary lesion. Clinically, miliary tuberculosis had been suspected because of the combination of unexplained fever and pancytopenia. After a brief improvement, the patient's condition deteriorated despite continued anti-tuberculous therapy. Since patients with miliary tuberculosis of the 'cryptic' type generally develop a normal temperature within 1 week (Proudfoot *et al.*, 1969), the authors believe that the patient's initial improvement was a genuine response to antituberculous therapy and his subsequent deterioration was a result of *Aspergillus* infection.

The classification of *Aspergillus* infections has been discussed by Finegold, Will and Murray (1959) who categorize them as primary or secondary, either of which may be localized, invasive or disseminated. In these terms, the patient had secondary disseminated aspergillosis, to which pancytopenia, the use of antibiotics and active tuberculosis may all have been predisposing factors. Although the bone marrow suggested possible lymphosarcoma, this was not confirmed by the histology of the liver

biopsy, spleen, lymph node biopsy or post-mortem findings. The cause of the pancytopenia remains uncertain.

The most common form of infection complicating tuberculosis is the intracavity aspergilloma, where the infection is generally considered saprophytic (Hinson, Moon and Plummer, 1952; Villar, Pimentel and Costa, 1962; Riley and Tannenbaum, 1962). Locally invasive *Aspergillus* infections have also been described complicating tuberculosis, often following pneumonectomy (Barlow, 1954; Golebiowski, 1958; Kelmenson, 1959). Disseminated forms of aspergillosis are recognized with increasing frequency in patients with haematological, malignant and other diseases (Finegold *et al.*, 1959; Gowing and Hamlin, 1960; Young *et al.*, 1970), but although tuberculosis is often listed as one such predisposing cause, the authors have been unable to find a similar recorded case of combined disseminated aspergillosis and miliary tuberculosis.

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