Thorax 1987;**42**:818–20

Sarcoidosis in two patients with cystic fibrosis: a fortuitous association?

T J COOPER, A J DAY, P H WELLER, D M GEDDES

From the Department of Thoracic Medicine, London Chest Hospital, London, and the Institute of Child Health, University of Birmingham

ABSTRACT Two cases of cystic fibrosis complicated by sarcoidosis are described. Possible pathogenetic interactions between the two diseases are discussed. The diagnosis of sarcoidosis in patients with chronic pulmonary inflammation is difficult, and if overlooked may lead to inappropriate treatment.

Sarcoidosis has not been reported previously in cystic fibrosis. We here describe two patients, the first of whom had florid multisystem disease.

Case reports

CASE 1

An 11 year old boy with cystic fibrosis presented in October 1979 with weight loss, sore eyes, arthralgia, facial swelling, increasing cough, and dyspnoea. His height and weight were on the 3rd centile, and examination showed him to have finger clubbing, axillary lymphadenopathy, bilateral parotid swelling, acute iridocyclitis, mild hepatomegaly, sternal bowing, and pulmonary crackles in the right upper zone. Soon after birth he had had persistent respiratory symptoms and a positive result in a sweat test at three months had confirmed cystic fibrosis. He had required continuous antibiotic treatment, with physiotherapy, until six years of age, when he was treated intermittently.

A chest radiograph showed bilateral hilar enlargement and interstitial shadowing. A Mantoux test (1:1000) gave a negative result. Right axillary node biopsy revealed three nodes with the classical epithelioid cell granulomas of sarcoidosis. He started treatment with prednisolone, with improvement, but had episodic malaise and lymphadenopathy on low doses. In October 1980 he had further investigations after referral to a tertiary centre. Here he had a positive Kveim test result, confirmed by biopsy, while taking a dose of 5 mg of prednisolone. Results of autoantibody tests for antinuclear and rheumatoid factors were negative. Complement C3 and C4 levels were normal, and the platelet aggregation test for immune complexes gave a negative result, as did complement fixation tests for various respiratory pathogens. A skin test for *Aspergillus fumigatus*, however, yielded a weakly positive response. From September 1981 his sputum culture consistently showed *Pseudomonas aeruginosa*. He became increasingly unwell from May 1983, with recurrent fever, lethargy, parotid and submandibular pain, and pain and stiffness in his ankles. He lost weight and his erythrocyte sedimentation rate (ESR) rose to 60–70 mm in one hour. A chest radiograph showed interstitial shadowing with scattered infiltrates in the right lung field. Radiographs of the hands and wrists were normal. Serum γ-glutamyl transpeptidase activity was raised (80 IU/l, compared with 3–24 IU/l for boys of this age), and the serum immunoglobulin IgE was increased (1·38 g/l). Progressive renal impairment was indicated by a rise in serum creatinine to 209 µmol/l (2·36 mg/100 ml); serum calcium concentrations were 2·17–2·18 mmol/l (8·68 mg/100 ml) (24 hour urinary excretion not determined after inadequate sampling). The ^{51}Cr EDTA slope clearance was 36 ml/min, and a DTPA nephrogram showed poor function bilaterally with no obstruction. Vesicoureteric reflux was excluded, and renal biopsy showed considerable interstitial fibrosis, numerous sclerosed glomeruli, cellular infiltration, and tubular atrophy. It was later stated that features of the biopsy material indicated sarcoidosis as the cause of the chronic renal failure. After the alternate day dose of prednisolone had been increased to 20 mg there was some clinical improvement, with reduction of serum creatinine to 156 µmol/l (1·76 mg/100 ml) and of the ESR to 6 mm in one hour. In late 1985 he remained well; the chest radiograph showed some

Address for reprint requests: Dr D M Geddes, London Chest Hospital, London E2 9JX.

Accepted 30 March 1987

cavitation in the left lung field, and serum creatinine and γ glutamyl transpeptidase concentrations were 138 μmol/l (1·56 mg/100 ml) and 64 IU/l respectively.

CASE 2

A 15 year old boy with cystic fibrosis presented in October, 1981, with fever, lethargy, arthralgia, and worsening cough and dyspnoea. Examination showed axillary lymphadenopathy, swelling of the right knee, and pulmonary crackles in the left lower and right upper zones. He had had meconium ileus at birth, and a positive result in the sweat test at two months. Subsequently he had lost time at school with recurrent respiratory symptoms, but avoided admission to hospital until 1979, when he experienced severe exacerbations with persistent *Pseudomonas aeruginosa* in sputum culture.

A chest radiograph with tomography showed bilateral hilar enlargement with diffuse interstitial shadowing and peribronchial thickening. A Kveim test biopsy showed sarcoid granulomas. Serum angiotensin converting enzyme was increased at 62 (normal range 16–52) nmol/ml/min. Serial sputum and early morning urine cultures were negative for tubercle bacilli. Aspergillus precipitins were not found, and the results of complement fixation tests for respiratory viruses, *Chlamydia psittaci, Coxiella, Mycoplasma,* and *Legionella* were negative. Concentrations of serum immunoglobulins IgG and IgM were raised, and complement C3 and C4 levels were normal. Urinary calcium excretion was normal at 3·42 mmol/24 h. The right knee was aspirated, producing 130 ml of turbid synovial fluid. Treatment with prednisolone 15 mg daily was started, and this resulted in appreciable radiological resolution of the hilar enlargement by February 1982. By late 1985 he had had no apparent recurrence of sarcoidosis.

After the diagnosis of sarcoidosis in this second patient, serum angiotensin converting enzyme was assayed in patients with cystic fibrosis during 20 consecutive admissions for infective exacerbations. In each case the concentration was found to be in the normal range.

Discussion

Sarcoidosis has not previously been described in patients with cystic fibrosis. The incidence of cystic fibrosis in Britain (1 in 2000 live births[1]) and of sarcoidosis (2–4 per 100 000/y[2]) would render the chance occurrence of both diseases in the same patient rare. A pathogenic interaction may thus exist, and possibly sarcoidosis is being overlooked in patients with cystic fibrosis who have frequent exacerbations of respiratory symptoms.

There are several possible ways in which a pathogenic interaction between sarcoidosis and cystic fibrosis might occur. Possibly sarcoid granulomas develop in response to immune stimulation by antigens derived from microorganisms or some other source. Consequently cystic fibrosis might predispose to the development of sarcoidosis either through the presence of a foreign material in the lung or as a result of an altered immunological reaction, or some combination of the two. A microbial cause for sarcoidosis has not been fully established, but there is evidence implicating both mycobacteria and viruses in a possible synergistic role.[3,4] Both viruses and bacteria (although not mycobacteria) are common in lung infection in cystic fibrosis, in which synergism has also been cited, with rise in antibodies to *Pseudomonas,* in relation to respiratory syncytial viral infection.[5] Alternatively, granulomas can be evoked by carbohydrates, lipids, and inert macromolecules that are not derived from microorganisms.[6] Some diseases with immune characteristics similar to sarcoidosis have tissue changes that are considered to be induced by the presence of glycoproteins and polypeptides.[7–9] Certain glycoproteins and polypeptides are generated to excess by monocyte-macrophage hyperactivity in cystic fibrosis, and it is argued that these are responsible for aberrant immune responses.[10] Possibly therefore some persisting antigenic material collects in the lungs of patients with cystic fibrosis, either as a result of infection or conceivably as a secondary response to the as yet unknown biochemical defect, and this may lead on to granuloma formation.

The most likely pathogenetic mechanism, however, is an altered immune response in cystic fibrosis secondary to chronic infection. Chronic immune stimulation in cystic fibrosis leads to hyperimmunoglobulinaemia and circulating immune complexes similar to those seen in sarcoidosis.[1,11–13] Antigen presentation may be potentiated in cystic fibrosis by progressive tissue damage and defective bronchial mucosal surfaces.[11] With persistence of antigen and in the presence of excessive antibody, large antigen-antibody complexes may form that are resistant to digestion by phagocytic cells.[14] Antigen-antibody complexes are known to cause granulomas in animals,[14] and deposits of immunoglobulin and complement have been found in sarcoid granulomas and in various tissues in cystic fibrosis.[12,15] Immune complexes were not found in our patients, but may have been responsible for the renal impairment in the first case and the knee joint effusion in the second.

Although evidence is insufficient to allow conclusions about pathogenesis, the coexistence of the two conditions is probably not fortuitous, and is of clinical importance. Fever, malaise, and deteriorating

lung function with hilar node enlargement and diffuse radiographic shadowing are features of both cystic fibrosis and sarcoidosis. It would therefore be very easy for the features of sarcoidosis to be masked by the lung disease of cystic fibrosis, and a second diagnosis would be unlikely to be considered. Diagnosis by pulmonary histology would be impeded by the potential hazards of transbronchial biopsy in cystic fibrosis, and by the presence of various inflammatory changes in any lung tissue. A Kveim biopsy or examination of other extrapulmonary tissue is therefore advisable if sarcoidosis is suspected. Hilar lymphadenopathy and a substantial rise in serum angiotensin converting enzyme concentration occur more frequently in the sarcoidosis of childhood than in the adult disease. Serum angiotensin converting enzyme was not found to be increased in 20 consecutive patients admitted for exacerbations in cystic fibrosis. Finally, as the sarcoidosis in both of the reported patients responded to corticosteroid treatment after antibiotics had been ineffective, it is important that this diagnosis should be considered in cystic fibrosis, particularly if there is unexplained deterioration.

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