CASE STUDY

Familial extensive idiopathic bilateral pleural fibrosis


ABSTRACT: The authors report three sisters with bilateral isolated apical pleural fibrosis of unknown origin, which did not respond to empirical antituberculosis therapy and oral corticosteroids. The disease evolved in an unrelenting fashion producing pleural fibrosis at the lung bases and leading to the death of two sisters and to lung transplantation in the other. There was no history of other familial disease or consanguinity. The particular features of these cases and the differences from other reports of apparently cryptogenic pleural fibrosis are outlined. Eur Respir J 1999; 14: 971–973.

Bilateral pleural fibrosis is rare, usually occurring after pleural effusions caused by infectious diseases, particularly tuberculosis, or in association with systemic connective tissue disorders, various drugs, and most commonly, asbestos exposure [1]. Few cases of apparently idiopathic pleural fibrosis have been reported [2–5]. This report describes three young sisters with isolated progressive bilateral pleural fibrosis of unknown origin, who developed respiratory failure leading to death in two cases and bilateral lung transplantation in the other.

Case reports

Patient 1

In September 1983, a 23 yr old nonsmoking female was admitted to hospital with bilateral apical pneumothoraces. The previous medical history included pulmonary tuberculosis in 1977 which healed after antituberculous treatment given for 12 months, initially with a 3 month course of oral corticosteroids. Between 1979 and 1983, the patient developed a dry cough and dyspnoea on exertion. A chest radiograph in 1981 had shown mild retraction of the right upper lobe and nodular opacity in the left upper lung, but no pleural thickening (fig. 1a). The patient worked as a secretary and did not take any medication. She had had no exposure to mineral dust. Clinical examination was unremarkable except for the presence of kyphoscoliosis. Chest radiography demonstrated bilateral apical pulmonary parenchyma appeared normal, but the size of pulmonary arteries was increased. An electrocardiogram and echocardiography confirmed pulmonary arterial hypertension. Laboratory investigations were within the normal range and no autoantibodies were present. Pulmonary function testing showed a severe restrictive pattern (total lung capacity (TLC) 20% of predicted) and arterial hypoxaemia (oxygen tension in arterial blood (PaO₂) 7.98 kPa (60 mmHg) breathing air). A further course of antituberculosis therapy and oral corticosteroids (40 mg of prednisone for 3 months) was given with no improvement. Subsequent progress was marked by spontaneous resolution of the pleuropneumothoraces but the pleural fibrosis increased (fig. 1b) and the patient developed rapidly progressive respiratory failure with right heart failure leading to death in November 1984. Autopsy was not performed.

Patient 2

In June 1990, the 28 yr old sister of the first patient was evaluated for dry cough and dyspnoea on exertion. She had never smoked, and her prior medical history was unremarkable. She worked as a cashier and took no medication. She had never had exposure to asbestos. Clinical examination was normal except for the presence of kyphoscoliosis. A chest radiograph showed bilateral apical pleural thickening and retraction of the right upper lobe, which was confirmed by computed tomography (CT).

Fibreoptic bronchoscopy was normal and extensive evaluation for infectious agents was negative. Laboratory investigations were normal. Pulmonary function tests demonstrated a restrictive pattern (TLC 40% predicted) and arterial hypoxaemia (PaO₂ 8.25 kPa (62 mmHg) breathing air). The patient received empirical antituberculosis therapy and oral corticosteroids with no improvement. Chest radiography showed progression of the pleural thickening towards the lung bases. In April 1992, a recurrent right apical pneumothorax led to thoracotomy for pleural symphysis.

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Light microscopic examination showed extensive pleural fibrosis. The immediately adjacent lung parenchyma was also involved by the fibrotic process but lung tissue distant from the pleura was normal. No granulomatous lesions or asbestos bodies were detected. The patient died in December 1992 from respiratory failure. Autopsy was not performed.

**Patient 3**

In February 1992 the third sister, 29 yrs old, sought medical advice although she was asymptomatic. She was a nonsmoker, with no previous medical history and worked as a telephone operator. Clinical examination was normal with no kyphoscoliosis. No drug use or mineral dust exposures were reported. A chest radiograph showed bilateral apical pleural thickening, which was confirmed by computed tomography (fig. 2). Thoracic magnetic resonance imaging (MRI) demonstrated bilateral pleural thickening predominantly at the apex and no mediastinal fibrosis. There was no retroperitoneal fibrosis on an abdominal CT scan. Laboratory tests were normal. Fibreoptic bronchoscopy was normal and an extensive search for infectious agents, including mycobacteria, was negative. Transbronchial lung biopsy was not contributory. Pulmonary function tests demonstrated a restrictive pattern (TLC 50% pred). Human leukocyte antigen (HLA) typing showed that the patient was HLA B7. She was given oral corticosteroids for 9 months together with colchicine for the first 3 months with no improvement of lung function. Right thoracotomy was performed in November 1993, revealing a roughened right upper lobe, surrounded by a dense and sclerotic membrane involving the visceral pleura, delimiting a network through which herniations of the lung were observed. Histology showed regular thickening of the pleura and the immediately contiguous lung parenchyma by a dense collagen network devoid of inflammatory cells.

**Fig. 2.** Thoracic computed tomography from patient 3 performed while she was asymptomatic, showing bilateral apical pleural thickening more marked on the left side (arrow heads.)

**Fig. 1.** a) Chest radiograph from patient 1 performed in 1981, 3 yrs after the end of treatment for pulmonary tuberculosis, showing mild right upper lung retraction and a small nodule in the upper left lung but no pleural thickening. b) Chest radiograph from the same patient taken in January 1984, showing pleural fibrosis more marked on the left side.

Fig. 3. Histopathological features of lung tissue obtained from patient 3 at the time of bilateral lung transplantation. The pleura was thickened by a dense fibrotic process devoid of inflammatory cells that extended modestly into the interlobular septa and to the immediately adjacent lung parenchyma but spared the lung tissue distant from the pleura. Similar appearances were observed throughout both lungs. Haematoxylin-eosin-safranin stain, internal scale bar=250 μm.
Discussion

These three nonsmoking sisters developed progressive bilateral pleural fibrosis of unknown origin that resulted in the death of two of them and led to lung transplantation in the third. An extensive search failed to detect any evidence of the common causes of pleural fibrosis. In particular, the patients had never taken any drugs associated with pleural fibrosis (i.e., ergotamine, methysergide, procainamide, bromocriptine, practolol), and had no evidence of collagen vascular diseases [1]. Although a history of pulmonary tuberculosis was present in the first patient, it is believed that tuberculosis could not account for her pleural fibrosis, since the process occurred long after the pulmonary tuberculosis was healed, and she did not respond to the combined antituberculosis and corticosteroid therapy. Furthermore, the other two sisters had no history of tuberculosis and no granulomatous lesions were observed in pleural specimens obtained by surgical biopsy. Similarly, occult exposure to asbestos is very improbable in these patients. Although apical predominance of pleural fibrosis has been reported in some workers exposed to asbestos, the present cases are clearly different in that no pleural plaques were seen on thoracic imaging, and above all, there was no evidence of asbestos accumulation in lung biopsies from patients 2 and 3 [6, 7].

Several features of these three patients are noteworthy. Firstly, the pleural fibrosis was not preceded by a pleural effusion as is usually the case [1]. Secondly, the fibrosing process was initially apical with subsequent spread to the lung bases, which contrasts with the basal predominance of most cases of diffuse pleural fibrosis [1, 2]. Thirdly, the occurrence of apical pneumothorax in two cases was surprising in the context of pleural thickening. This was probably due to the disruption of the lung parenchyma resulting in herniations through the pleural fibrotic network, as was observed in patient 3 at the time of surgery. Finally, histopathological analysis in patients 2 and 3 demonstrated that the fibrosis process extended to the adjacent lung parenchyma but spared lung tissue distant from the pleura.

Very few cases of apparently cryptogenic pleural fibrosis have been reported [2–5]. Buchanan et al. [2] described four patients with predominant basal fibrosing pleuritis who improved after pleural decortication. All four patients were HLA B44 positive, a phenotype not seen in the single patient reported here in whom HLA typing was performed. Oliver and Neville [3] reported two patients with progressive apical pleural fibrosis of unknown origin. Their second case was similar to the present one but gave a history of contact with tuberculosis and extensive occupational exposure to asbestos. More recently, Hayes et al. [4] described two HLA-B44 siblings, with consanguineous parents, who developed bilateral fibrosing pleuritis in association with Fanconi's syndrome. In the current cases, no other familial diseases were identified, the parents were not consanguineous, and the remaining siblings (two brothers, 35 and 22 yrs old and a 40 yr old sister) are free of pleuropulmonary disease.

In summary, the three patients reported here appear to be unique. The factors which resulted in the development of severe bilateral pleural fibrosis remain to be identified.

References