Simultaneous occurrence of pulmonary interstitial fibrosis and alveolar cell carcinoma in one family

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ABSTRACT The coexistence of interstitial pulmonary fibrosis and alveolar cell carcinoma is well known. The familial occurrence of a combination of these two entities, however, is very rare. We present a family of which five members had diffuse interstitial pulmonary fibrosis. Three of them had in addition alveolar cell carcinoma. In a sixth family member, evidence of alveolar cell carcinoma was present without proven interstitial fibrosis. An autosomal dominant trait is suggested as the mode of inheritance of both interstitial fibrosis and alveolar cell carcinoma in this family.

In 1970, Driessen and Scherpenisse,¹ reported on two brothers with alveolar cell carcinoma (ACC) and diffuse interstitial fibrosis (DIPF). In the same family a female cousin had pulmonary fibrosis but without carcinoma. Since then we have seen other members of this family who have been affected by both conditions. The only other study we could find reported on identical twin brothers who presented with ACC, almost at the same time.² We were unable to find other reports on familial occurrence of both ACC and DIPF. This fact stimulated the present report as a sequel to the study of Driessen and Scherpenisse.¹

Patients

PATIENT 1

This 37-year-old man (fig 1, case III-1), a building surveyor, was seen for the first time in 1958 because of gradually increasing dyspnoea on exertion. For two years he had been followed in another hospital because of pulmonary fibrosis of unknown origin. His mother had a chronic cough. One of his uncles had died of a "pulmonary tumour" (pedigree case II-7).

On physical examination the base of the right lung appeared dull to percussion and breath sounds were diminished in this area. There were no crackles or wheezes. Peripheral clubbing of the

digits without cyanosis was noted. The erythrocyte sedimentation rate was 30 mm in the first hour. Haemoglobin was 17.6 g/dl. A chest radiograph (fig 2) showed diffuse fine reticulo-nodular shadowing and a dense mass in the right lung. The fine markings had been visible in 1954.

Lung function studies (table) showed a restrictive defect. While staying in hospital for further analysis, the patient became hemiplegic because of a spinal tumour, which at operation appeared to be a metastasis of an alveolar cell carcinoma (ACC). Shortly thereafter he died. Necropsy revealed diffuse infiltration of the lungs with ACC and extensive alveolar and peribronchial fibrosis (fig 3).

PATIENT 2

The brother of patient 1 (fig 1, case III-2), office clerk, was 31 years old when he was referred to our clinic. At mass screening radiography he was found to have diffuse pulmonary mottling. For the previous three years he had noticed increasing dyspnoea on exertion and recurrent bronchial infections. On physical examination peripheral clubbing without cyanosis and basal crackles were noted. ESR was 12 mm the first hour. Haemoglobin was 17.3 gr/dl. A chest radiograph showed an irregular, patchy, reticulonodular pattern throughout both lungs without signs of consolidation. Pulmonary function studies showed a restrictive defect (table 1). No diagnosis could be made after extensive investigation, including

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Fig 1 Family pedigree.

transbronchial biopsy. Histological examination of lung tissue obtained by open lung biopsy disclosed marked fibrotic thickening of the alveolar septa, peribronchial fibrosis, smooth muscle hypertrophy, squamous cell metaplasia, and hyperplasia of mucus secreting cells in the bronchial mucosa. Many areas showed a gradual change to frank mucus-producing carcinoma, lining alveolar spaces.

Fig 2 Chest radiograph of patient 1, pedigree case III-1.

A diagnosis of pulmonary fibrosis with ACC was made. Five months later the patient died.

PATIENT 3

This 48-year-old housewife (fig 1, case III-6) was a cousin of patients 1 and 2.

In 1962 she was investigated for upper abdominal complaints and an hiatus hernia was found. At that time a chest film was normal except for increased markings in the lower lungs. In 1968 she was admitted to the pulmonary department because of dyspnoea on exertion for about one year and productive cough. Her father had died of a "lung tumour" (fig 1, case II-7). The chest radiograph showed a diffuse increase in interstitial markings, suggestive of diffuse interstitial fibrosis (fig 4) and pulmonary function tests showed a restrictive defect (table 1). Extensive investigation did not reveal a cause for the illness, nor any evidence of autoimmune-, systemic-, or organic dust disease. Open lung biopsy showed peri-bronchial and interstitial fibrosis with metaplastic changes and cuboidal hyperplasia of alveolar cells (fig 5). The picture was very similar to the one found in the lungs of her two cousins though there were no signs of ACC. The patient was treated with oral corticosteroids. Her pulmonary condition seemed stable for a number of years. In 1970 she underwent a hemi-colectomy for adenocarcinoma. From 1973 until her death from cerebral hemorrhage in 1976, she was admitted to hospital several times

Table 1 Lung function data of affected family members

Patient	VC (% pred) (l)	FEV ₁ (% pred) (l)	FEV ₁ /VC (%)	RV/TLC (% pred) (%)	Lung compliance l/kPa (% pred)	TlCO mmol/min/kPa (% pred)
1	1.6 (37)	1.2 (38)	74	29 (125)	ND	ND
2	2.0 (51)	1.6 (55)	81	25 (108)	0.92 (41)	ND
3	2.2 (63)	1.8 (120)	83	29 (111)	0.51 (16)	3.4 (45)
4	1.8 (56)	1.4 (64)	78	33 (126)	0.76 (23)	4.4 (53)
5	ND	ND	ND	ND	ND	ND
6 August 75	4.2 (78)	3.7 (95)	88	26 (100)	1.43 (58)	7.9 (62)
6 August 78	3.4 (58)	3.1 (65)	91	27 (128)	0.75 (28)	5.6 (45)

VC=vital capacity; FEV₁=forced expiratory volume over one second; FEV₁/VC %=FEV₁ expressed as a percentage of the VC.; RV=residual volume; TLC=total lung capacity; RV/TLC %=RV expressed as a percentage of the TLC; TlCO=carbon monoxide transfer factor: (% pred)=percentage of the predicted value in brackets; ND=not done.

Fig 3 Lung biopsy of patient 1, showing alveolar cell carcinoma. H and E, original magnification $\times 140$.

Fig 4 Chest radiograph of patient 3, pedigree case III-6.

because of severe respiratory insufficiency. No necropsy was performed but during her lifetime there never were any radiographic or clinical signs of ACC.

PATIENT 4

This 49-year-old housewife (fig 1, case III-9) was a sister of patient 3. She was always in good health until early in 1978 when she developed a mild, non-productive cough and malaise. A chest film disclosed dense infiltration in both lower lobes. She had never smoked and did not take any drugs. Some weeks later the radiograph showed increase of both lobar densities. On admission to hospital she did not appear acutely ill nor dyspnoeic. There were no signs of finger clubbing or cyanosis. Fine crackles were present, and dullness on percussion was heard in both lower quadrants.

Fig 5 Lung biopsy of patient 3 showing septal fibrosis with cuboidal hyperplasia of air spaces. H and E, original magnification $\times 80$.

ESR was 31 mm, haemoglobin 15.4 gr/dl, white cell count $7800/\text{mm}^3$, with $440/\text{mm}^3$ and later $1287/\text{mm}^3$ eosinophils. Laboratory work-up for autoimmune and systemic diseases was negative. No rises of any anti-viral antibody titres, nor evidence of organic dust disease were found. Circulating immune complexes, determined as previously described,³ were slightly increased. A chest film showed dense infiltrations, predominantly on the right side. On tomography, an air-bronchogram was visible in the consolidated right lower lobe. No diagnosis could be obtained by transbronchial and needle biopsy. At thoracotomy the right lung felt stiff and granular. A mass was palpable in the lower lobe, from which a biopsy was taken. Microscopic examination showed a typical ACC, infiltrating the lung. There was scattered interstitial fibrosis (fig 6). The patient died in December 1978, after being treated unsuccessfully with various anti-tumour agents and high dose corticosteroids. Post-mortem studies of the lung showed the same picture as in the biopsy, with patchy interstitial and peribronchial fibrosis of both lungs and multiple areas of ACC. No metastases were found.

PATIENT 5

This 25-year-old housewife (fig 1, case IV-4) was the daughter of patient 3. In 1975 she was admitted to hospital because of enlarged cervical and supraclavicular nodes. For several months she had complained of malaise, non-productive cough, and fatigue.

Seven weeks before admission, a few blood streaks appeared in her sputum. Three weeks before admission she noticed a swelling in the right upper side of the back. The patient did not smoke and took no drugs, nor was there any known exposure to organic dusts. Lymph nodes were easily palpable in the right and left side of the sternomastoid muscles and in the supraclavicular fossa. Fixed to the right ninth rib posteriorly a tumour was felt. The chest radiograph showed a homogeneous mass at the right hilum and atelectasis of the posterior part of the right upper lobe.

ESR was 90 mm in the first hour, haemoglobin 12.9 gr/dl, haematocrit 39%, white cell count $12\cdot400/\text{mm}^3$ with a normal differential. Histological examination of an excised supra-clavicular lymph gland disclosed malignant cells, compatible with a large cell carcinoma of the lung. A PAS stain was negative. Transbronchial biopsy from the right upper lobe revealed atypical cells with vacuolised cytoplasm, big nuclei, and nucleoli. The most likely diagnosis was an ACC or large cell carcinoma. The patient died suddenly on the tenth day in hospital. Necropsy was not permitted.

PATIENT 6

This 21-year-old office clerk (fig 1, case IV-5) was the son of patient 3, and brother of patient 5. He attended for the first time in 1975. For some years he had experienced slowly increasing dyspnoea on exertion. Until 1975 he played in the local football team. He had allergic rhinitis and an occasional

Fig 6 Lung biopsy of patient 4 showing alveolar cell carcinoma developing in fibrotic areas. H and E, original magnification $\times 80$.

productive cough. He did not take drugs, nor smoke. There was no evidence of systemic collagen disorders. Physical examination showed no dyspnoea at rest, clubbing or cyanosis. At both lung bases some fine inspiratory crackles were heard. ESR was 3 mm in the first hour, haemoglobin 15.4 gr/dl, haematocrit 43%, white cell count 6800/mm³ with a normal differential. Circulating immune complexes were not significantly increased and tests for autoimmune or systemic disease were negative. His chest film showed a diffuse reticular pattern, very suggestive of interstitial fibrosis. Pulmonary function studies (table 1) showed a restrictive ventilatory defect and a decreased transfer factor for carbon monoxide. Extensive clinical investigation did not provide a diagnosis.

Microscopical examination of tissue obtained by open lung biopsy revealed severe peribronchiolar fibrosis with lymphocyte infiltration and scattered emphysematous bullae. Bronchiolar epithelium showed metaplastic changes, but there were no signs of tumour. Immunofluorescent studies for IgG, IgA, IgM, and complement (C3) were negative. It was decided to treat him with azathioprine (150 mg) and prednisolone (20 mg). His pulmonary condition seems stable at present apart from some intercurrent respiratory infections.

Discussion

The familial occurrence of ACC, with or without pulmonary fibrosis, has been reported only twice

before. Driessen and Scherpenisse¹ reported on patients 1, 2, and 3 of the present study. Joishy *et al*² observed identical male twins having ACC, with nearly synchronous onset and with metastasis to the brain, but without pulmonary fibrosis. The coexistence of interstitial pulmonary fibrosis and carcinoma of the lung, especially alveolar cell carcinoma, is well known.⁴⁻¹² Beaver and Shapiro⁴ mentioned seven cases of ACC in which the tumour was intimately associated with areas of fibrosis. They suggested that cuboidal epithelial metaplasia of the alveoli, a histological feature often seen in fibrotic lesions, could represent a pre-cancerous phase of cellular growth. They also noted that the increasing incidence went parallel with and was probably related to the reported increasing incidence in pulmonary fibrosis. This view was supported by Spain,⁵ who presented 12 cases of ACC, with co-existing fibrosis, which was mostly diffuse, sometimes of focal nodular type. Also Meijer and Liebow⁶ pointed to the fact that atypical proliferation with marked hyperplasia and metaplasia of bronchial alveolar cells represents a premalignant condition. This atypical proliferation may be conceived of as a regenerative process after damage to the lung by various agents. This process may lead ultimately to fibrosis. At present, no studies are available providing insight into the incidence of ACC in patients with fibrotic lung disease. Other malignant pulmonary tumours are also prone to develop in the fibrotic lung and adenocarcinoma, oat cell carcinoma, epidermoid carcinoma, and large cell anaplastic carcinoma

have been reported.⁶⁻⁸ In these series, however, no cases of familial origin, nor familial fibrosis were reported.

At least 13 families with familial interstitial pulmonary fibrosis have been described in the last 20 years.^{1 13-24} Bonanni *et al*¹⁷ suggested an immunological factor, because of eosinophilia and raised levels of gamma globulin. In this study, and the ones by Hughes¹⁶ and Adelman,¹⁹ the autosomal dominant trait was demonstrated as the mode of inheritance. A striking fact in the reported cases is the great difference in the clinical features and in the age at which the pulmonary fibrotic disease started.¹⁶ Sometimes other abnormalities were seen in association with the familial fibrosis, such as rheumatoid arthritis, oculocutaneous albinism, and a platelet function defect.²²⁻²⁴

In the family at issue, five patients had confirmed pulmonary fibrosis, and three of them had ACC as well. A fourth patient with probably a large cell carcinoma or ACC had no radiological evidence of pulmonary fibrosis, though this does not exclude it absolutely. Epler *et al* showed that, in a series of 458 patients with histologically proven diffuse infiltrative lung diseases, the pre-biopsy chest radiograph was normal in about 10%.²⁵

A specific cause for the fibrosis was not found in any of the patients in the present study. Our findings suggest that the fibrosis is of a familial, hereditary origin, transmitted as an autosomal dominant trait. There may be a common aetiological background both for the tumour and for the fibrosis, possibly of genetic origin. HLA studies of the family were not performed, and this hypothesis can therefore not be tested. The fact that the incidence of tumours other than ACC, was fairly high in the other members of the family (table 2) suggests that an inherited gene (or genes) renders this family more susceptible to them.

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Table 2 Other tumours in the family

Patient pedigree number	Age (yr)	Tumour	Histologically confirmed
II-4	?	Intestine	no
II-7	47	Lung	no
III-3	66	Squamous cell ca lip	yes
III-4	58	Pancreas	yes
III-6	50	Adeno-ca colon	yes
III-8	33	Seminoma testis	yes

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