

## Chronic extrinsic allergic alveolitis in a family with idiopathic pulmonary fibrosis: the importance of histological diagnosis

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*Chronic extrinsic allergic alveolitis in a family with idiopathic pulmonary fibrosis: the importance of histological diagnosis. P.L.J. van Valenberg, J-W.J. Lammers, H.A. van den Hout, J. Molema, C.L.A. van Herwaarden.*

**ABSTRACT:** We report a patient who presented with progressive exertional dyspnoea, chronic cough and radiographic signs of interstitial lung disease. Since several of his family members were known to have familial idiopathic pulmonary fibrosis he was also suspected to suffer from this disease. After thorough investigation, including histological examination of lung biopsies obtained by thoracoscopy, a diagnosis of chronic extrinsic allergic alveolitis was made.

Current knowledge of familial idiopathic pulmonary fibrosis is discussed. This case report underlines the importance of a histological diagnosis in interstitial lung disease.

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Idiopathic pulmonary fibrosis (IPF) is a disease of unknown origin. The diagnosis IPF is made by exclusion of other interstitial lung diseases, such as pneumoconiosis, sarcoidosis, collagen-vascular disease, drug-induced pneumonitis and extrinsic allergic alveolitis. Although clinical presentation, radiographic findings and pulmonary function abnormalities may suggest the existence of IPF, microscopic examination of lung tissue remains mandatory for correct diagnosis and management.

Familial occurrence of IPF is rare; until now 41 families have been described in the literature [1-9]. We describe another family with IPF, of which one member was seen because of progressively increasing dyspnoea and radiographic abnormalities, which appeared to be caused by a different interstitial lung disease.

### Case report

A 48 yr old farmer was well until six months before he visited our out-patient clinic because of fatigue, progressive exertional dyspnoea and chronic cough. He produced small amounts of white sputum. He was a nonsmoker. His family history was remarkable.

### Family history

One of the patient's sisters had recently died of idiopathic pulmonary fibrosis at the age of 38 yrs. She presented 9 months earlier with progressive exertional

dyspnoea and cough. At that moment she was 32 weeks pregnant. Physical examination revealed only fine crackles over the lower zone of the right lung. Laboratory findings were unremarkable, except for an erythrocyte sedimentation rate (ESR) of 67 mm·h<sup>-1</sup>. A chest X-ray showed bilateral reticulonodular markings, especially in the lower lung zones. Lung function measurements showed a restriction without obstruction (predicted values are placed between brackets as mean±sd): total lung capacity (TLC) 3.0 l (5.8±0.6 l), vital capacity (VC) 1.7 l (4.2±0.4 l), forced expiratory volume in one second (FEV<sub>1</sub>) 1.5 l (3.5±0.4 l). The CO-diffusion capacity was decreased to 60% of predicted. Histological examination of transbronchial lung biopsies was not conclusive. Because of rapid clinical deterioration prednisone, 40 mg daily, was started. A caesarean section was carried out in the 34th week of her pregnancy and she gave birth to a healthy daughter. Shortly afterwards, an open lung biopsy was performed. Histologically, there was extensive interstitial fibrosis, compatible with an advanced stage of idiopathic pulmonary fibrosis. Immunosuppression was increased but she died a few months later.

The patient's brother, a 42 yr old plasterer, was seen at our out-patient clinic with progressive exertional dyspnoea and cough of four months duration. A diagnosis of idiopathic pulmonary fibrosis was based on clinical presentation, laboratory investigations, lung function abnormalities, chest radiography, bronchoalveolar lavage (BAL) findings, and histological examination of transbronchial lung biopsies. Initial improvement on prednisone, 60 mg daily, was followed by a rapid clinical deterioration and he died 6

months after the diagnosis was made. Autopsy demonstrated end-stage pulmonary fibrosis.

The youngest member of the family, a 34 yr old woman, wanted to be investigated to determine whether she also suffered from idiopathic pulmonary fibrosis. Physical examination and laboratory investigations were normal. The chest X-ray, however, showed a fine reticulonodular pattern in the lower lung zones. Lung function tests demonstrated a restrictive pattern with decreased lung compliance and an impaired diffusion capacity during exercise. BAL fluid analysis revealed a slightly increased cell count with normal differentiation, transbronchial lung biopsies showed no abnormalities. An open lung biopsy to confirm the diagnosis IPF was refused. One year after these initial investigations her lung function has deteriorated slightly further.

Two other brothers and one sister have no complaints, whereas one younger brother died of leukaemia at the age of 18 yrs. Both parents are still alive and healthy. The mother of the patient's father and two of her sisters died relatively young, around 40 yrs of age, due to an undefined pulmonary disease. A genealogical tree of this family is given in figure 1.

Physical examination of our patient revealed clubbing of the hands and feet and fine crackles over both lower lung fields. Laboratory investigation demonstrated a normal ESR and angiotensin converting enzyme (ACE), the anti-nuclear factor (ANF) was positive but anti-ds deoxyribonucleic acid (DNA) and rheumatoid-factors were negative. Serum gammaglobulin was increased to  $19.1 \text{ gr}\cdot\text{l}^{-1}$  (polyclonal). The enzyme-linked immunosorbent assay (ELISA) reaction on *Aspergillus fumigatus* was weakly positive with a titre of 1:160, the precipitation-reaction showed two lines. Serology for *Micropolyspora faeni* was positive with an ELISA titre of 1:160 and four precipitation lines. A chest X-ray showed a reticulonodular pattern in the lower zones of both lungs (fig. 2).

The lung function was restricted with a slight but reversible obstruction: TLC  $5.5 \text{ l}$  ( $7.3 \pm 0.7 \text{ l}$ ), VC  $4.3 \text{ l}$  ( $5.0 \pm 0.5 \text{ l}$ ), FEV<sub>1</sub>  $2.7 \text{ l}$ , after inhalation of  $400 \mu\text{g}$  salbutamol,  $3.2 \text{ l}$  ( $3.5 \pm 0.5 \text{ l}$ ). The lung compliance was decreased to  $1.3 \text{ l}\cdot\text{kPa}^{-1}$  ( $3.4 \text{ l}\cdot\text{kPa}^{-1}$ ). The incremental maximal exercise test with a step-by-step increase in workload of  $10 \text{ W}$  every minute, was symptom limited because of dyspnoea at a workload of  $130 \text{ W}$ . The heart frequency reached  $120 \text{ beats}\cdot\text{min}^{-1}$ . The arterial oxygen tension ( $\text{PaO}_2$ ) decreased from  $11.3 \text{ kPa}$  at rest to  $8.6 \text{ kPa}$  during maximal exercise, whilst the arterial carbon dioxide tension ( $\text{PaCO}_2$ ) increased from  $5.3$  to  $5.5 \text{ kPa}$ . The base-excess decreased from  $+1.9$  to  $-4.4 \text{ mmol}\cdot\text{l}^{-1}$ . Transbronchial lung biopsies showed no abnormalities. BAL fluid analysis, however, revealed an increase in total cell count to  $17.4 \times 10^6 \cdot \text{ml}^{-1}$  ( $0.10$ – $0.15 \times 10^6 \cdot \text{ml}^{-1}$ ), with 24% lymphocytes (<12%), 59% macrophages (85%), 14% polymorphonuclear granulocytes (1–2%) and 3% plasma cells (0%). Because of the family history there was a suspicion of IPF but some findings did not support the diagnosis, such as the positive serology for *M. faeni* and *A. fumigatus*,

and the cell-differentiation of the BAL fluid. These findings, together with the occupation of the patient, indicated extrinsic allergic alveolitis. A thoracoscopy was performed. The lung surface showed a fine nodular aspect and histological examination of lung biopsies showed extensive subpleural fibrosis, a chronic alveolitis with interstitial fibrosis and several giant-cell granulomata in the interstitium (fig. 3). The diagnosis chronic extrinsic allergic alveolitis was confirmed and, because of persistent complaints, treatment was started with prednisone,  $60 \text{ mg}$  daily, which dose was slowly tapered down to  $10 \text{ mg}$ . Now, almost 4 yrs later, the patient has remained clinically and radiographically stable (fig. 4), and his lung function tests have not changed.

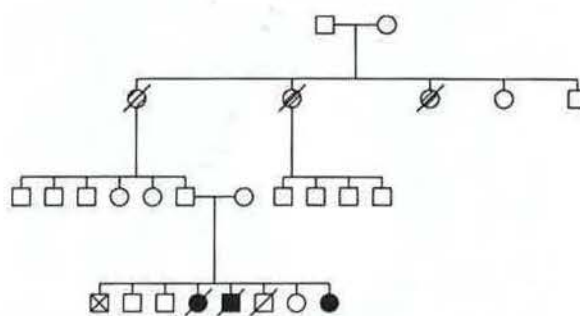


Fig. 1. - Genealogical tree. □: male; ○: female; ⊠: case subject with chronic extrinsic allergic alveolitis; ■ and ●: deceased patients with idiopathic pulmonary fibrosis (IPF); ●: female with IPF; ⊘: female suspected of having died from IPF; ⊠: male died of leukaemia.



Fig. 2. - Chest X-ray, showing reticulonodular pattern in the lower zones of both lungs, before start of therapy.

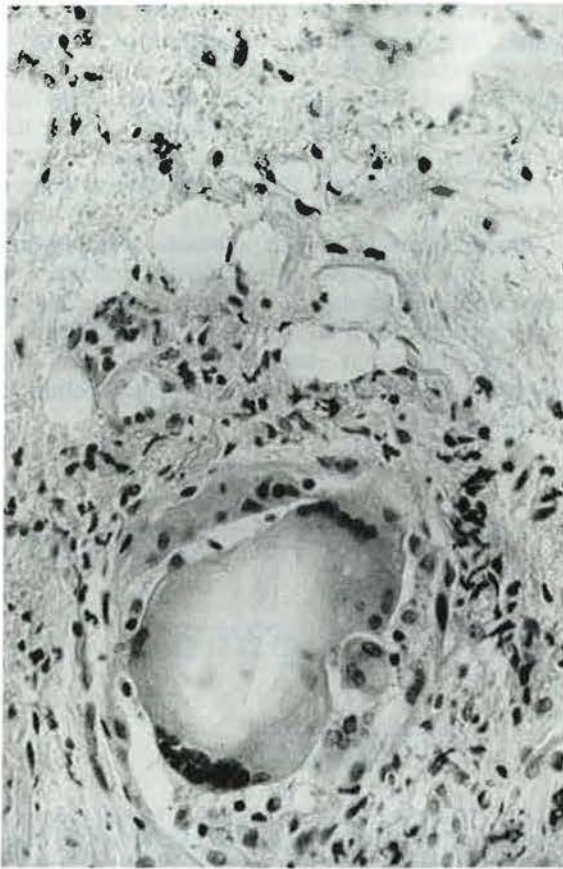


Fig. 3. - Lung biopsy showing signs of chronic alveolitis with fibrosis and a giant-cell granuloma in the interstitium.



Fig. 4. - Chest X-ray, after therapy, although less inflated, showing an essentially unchanged pattern.

## Discussion

We have described a patient who appeared to have a chronic extrinsic allergic alveolitis in a family with IPF. When the patient presented himself with complaints of progressive exertional dyspnoea and chronic cough the diagnosis IPF was considered, mainly because of his family history. IPF is usually diagnosed by exclusion of other interstitial lung diseases. Histological confirmation of the clinical diagnosis seems imperative [1] but it is not always possible to obtain lung tissue, especially in an advanced stage of the disease. Lung biopsies obtained with bronchoscopy and thoracoscopy tend to be too small for a correct diagnosis and some degree of submucosal and subpleural fibrosis is often present but is non-conclusive [1, 10]. Only when specific abnormalities are found, such as granulomata, malignancies, infections or typical findings of histiocytosis X, can a diagnosis be made with these techniques [10, 11]. Preferably, an open lung biopsy is performed to establish the diagnosis and to assess the degree of alveolitis and fibrosis, which may be helpful to estimate the prognosis [10, 11]. Cell counts and differentiation in BAL fluids are not diagnostic, but may indicate the presence of an interstitial lung disease. Until now, BAL mainly remains an investigational tool for the study of interstitial lung diseases [11].

Of the members described in this family, the diagnosis in the first sister was eventually made by open lung biopsy. In the brother, the histology of trans-bronchial biopsies was compatible with IPF, which was confirmed at autopsy. The youngest sister, with only a clinical diagnosis of IPF, has until now refused to undergo an open lung biopsy procedure. Finally, the subject of this case report presented with the same complaints as his family members with IPF. The fact that, as a farmer, he had positive serology tests for *M. faeni* and *A. fumigatus*, does not imply that he has an extrinsic allergic alveolitis. Of persons exposed to organic inhalational antigens, only 5-20% develop an allergic alveolitis, whereas approximately one half of the remaining asymptomatic subjects show an immune response, manifested by BAL lymphocytosis or positive serum precipitins [4]. Thoracoscopy was performed, since the patient refused an open lung biopsy procedure. Subpleural fibrosis and alveolitis with interstitial fibrosis and also several giant-cell granulomata were found in the interstitium. Granulomata have never been described in IPF [1]. This made the diagnosis of chronic extrinsic alveolitis certain, and the clinical course of the patient confirms the diagnosis, since after 4 yrs of follow-up his clinical situation is unchanged.

The family history of the patient revealed a familial occurrence of IPF. As yet, this family included, 42 families with this disease have been described in the literature. Reviewing these cases, there appear to be two different modes of inheritance. Firstly, an autosomal recessive pattern appearing mainly in small children, who usually do not become older than a few

months of age. This has now been described in four different families [7-9]. Secondly, an autosomal dominant inheritance pattern, with varying penetrance, has been described in 37 families [1-9]. The clinical picture of familial IPF is completely identical to non-familial IPF [1]. Patients generally present at a younger age, 20-40 yrs, in comparison to non-familial IPF (50-70 yrs), but a great variation in age of presentation is possible [1]. At a younger age of presentation the course of the disease appears to be more aggressive [2]. The genetic defect is unknown. There is no clear association with human leucocyte antigen (HLA)-typing [12], but there may be a defect in chromosome 14 [13, 14]. Subclinical alveolitis is supposed to be present in 50% of asymptomatic first degree relatives [3].

To our knowledge there has not, as yet, been a report of a patient with chronic extrinsic alveolitis in a family with IPF. This diagnosis could only be made by histological examination of lung tissue. This case report, therefore, illustrates the need for a histological diagnosis of interstitial lung diseases, in a family with known IPF.

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