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Management of a patient with familial idiopathic pulmonary fibrosis

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Abstract. Idiopathic pulmonary fibrosis (IPF), the most common subtype of idiopathic interstitial pneumonia, is a chronic progressive lung disease with a very high mortality. Usually diagnosis is established in adults older than 50 years and most cases are considered to be sporadic. Individuals with a familial form of IPF have at least one affected member in the same primary biological family and account for less than 5% of total patients. Sporadic and familial IPF are clinically and histologically indistinguishable from one another, although some familial forms appear to develop at an earlier age and exhibit different patterns of gene transcription. This case study describes the early clinical course of a patient diagnosed with a familial form of IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30 Suppl 1: 48-51)*

Key words: familial, genetics, idiopathic pulmonary fibrosis, management, pirfenidone

Introduction

Although familial cases of idiopathic pulmonary fibrosis (IPF) exist, they account for less than 5% of patients (1). Familial IPF is defined as a form that affects two or more members of the same primary biological family. The familial aggregation and the fact that pulmonary fibrosis with a histological 'usual interstitial pneumonia' (UIP)-pattern develops in other rare inherited disorders is indicative of a genetic predisposition to IPF. Mutations of the surfactant proteins C (SP-C) and A (SP-A2) have been identified in familial pulmonary fibrosis (2, 3). Both surfactant proteins are expressed exclusively by type II alveolar epithelial cells, suggesting that dysfunction of these cells may play a relevant role in pulmonary fibrosis (4). Other studies identified components of the telomerase complex to be associated with familial pulmonary fibrosis (5, 6). Interestingly, alterations in the telomere region are also a common finding in patients with sporadic IPF (7). The effects of mutations in surfactant and telomerase encoding genes reveal potential pathways of IPF pathogenesis including endoplasmic reticulum stress, cellular senescence, DNA-repair response and others (4). However many studies on apparent 'familial IPF' have the limitation that affected family members often demonstrate a different type of idiopathic interstitial pneumonia (1). In sporadic IPF a plethora of different factors – inter alia cytokines and profibrotic molecules – has been suggested to be involved in the pathogenesis. The current model of disease development assumes that, in genetically predisposed individuals, IPF manifests as an aberrant response to an alveolar epithelial injury (e.g. smoking or respiratory infections). Experimental

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treatment approaches the aim to attenuate lung epithelial injury or to target the complex activation of fibroblasts. Currently pirfenidone is the only substance licensed for the treatment of mild-to-moderate IPF in the EU and Japan. This case study describes the early clinical course of a patient diagnosed with a familial form of IPF.

Case Report

Medical history

Following the death of his 76-year-old father two months previously from IPF, this 49-year-old male patient, a social worker, self-referred himself for screening having complained of episodes of shortness of breath upon severe exertion over the past year. He had no history of cough or expectoration, had never smoked and had no other significant previous medical history. There was no suggestion of connective tissue disease, allergy or exposition to asbestos.

Clinical examination

The patient was 189 cm in height and 96 kg in weight and had a body mass index (BMI) of 26.9 kg/m^2. Clinical examination revealed discrete, right-sided basal inspiratory crackles, but the patient was otherwise normal except for appearing to be decidedly nervous with a high level of anxiety.

Diagnosis

Lung function testing showed mild pulmonary restriction with a total lung capacity (TLC) of 74.6%, an inspiratory vital capacity (IVC) of 74.8% of predicted and a slight reduction in diffusing capacity of the lung for carbon monoxide (DL_{CO}) of 66.6% of predicted. Autoimmune serology and serum precipitins were negative. Analysis of bronchoalveolar lavage (BAL)-fluid showed a neutrophilia and a slightly raised eosinophil percentage. High resolution computed tomography (HRCT) demonstrated reticular changes in the lower part of the lung with a subpleural distribution, but without honeycombing or ground-glass changes (Figure 1). These findings led to a radiological diagnosis of a

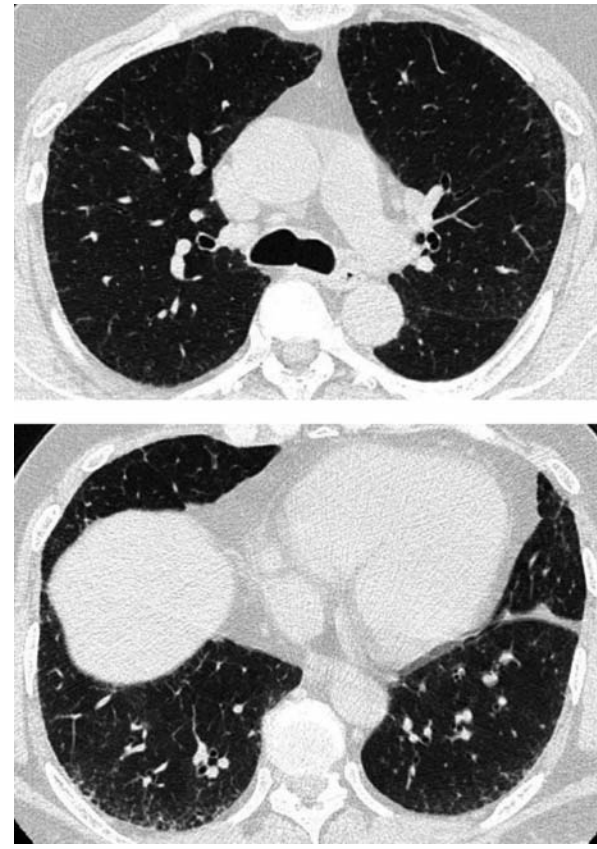

Fig. 1. HRCT images showed reticular changes in the lower part of the lung with a subpleural distribution, no honeycombing or ground-glass changes

'possible' usual interstitial pneumonia (UIP). As the patient did not consent to a video-assisted thoracoscopy, a transbronchial cryobiopsy was offered as an alternative. Findings from multiple cryobiopsy samples taken from the right upper and lower lobe showed an alveolar-septal fibrosis as well as fibroblast foci confirming a histopathological pattern of 'definite' UIP (Figure 2). Given the clinical history, IPF was diagnosed and a likely familial form was suspected.

Treatment

After expressing a particular desire for treatment, the patient was prescribed treatment with pirfenidone in June 2012. In addition, and in consideration of the patient's apparent significant psychological burden, a direct referral to the clinical psychologist was also implemented.

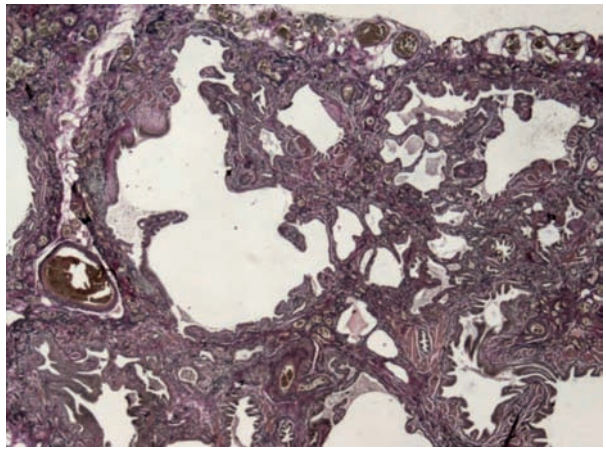

Fig. 2. HE staining of a transbronchial cryobiopsy sample showing a 'definite' UIP pattern

Outcomes

As of November 2012, the patient demonstrated good medication compliance, and complained of no relevant adverse effects except for slight gastrointestinal discomfort. No exacerbations or infections were reported. Lung function testing and chest x-ray results were stable. However, as the patient acknowledged ongoing coping problems, participation in psychological group therapy was arranged once weekly. At the beginning of 2013, psychosomatic rehabilitation was organised.

Discussion

This case study of a patient with apparent familial IPF raises important questions regarding the management of such patients that remain unanswered in current treatment guidelines (1). For example, what would be the natural course of familial IPF in this patient? What are the treatment options for patients with familial IPF? And, is there a role for the early introduction of pirfenidone in familial IPF?

Given the limited symptoms and mild functional impairment in this case, we discussed the option of a watch-and-wait approach. Furthermore, we informed the patient of the possible opportunity for future trial recruitment. However, the patient expressed a strong wish for immediate therapy so that, in conjunction with the national German guidelines for IPF (8), pirfenidone was prescribed. Such a therapeutic approach can undoubtedly be discussed as controversial, as recently done by Raghu (9) and Jenkins (10). Furthermore, it is unclear from the current management guidelines if, and when, pulmonary rehabilitation and/or palliative care should be implemented in patients with familial IPF. In our opinion, a multi-disciplinary approach, with an initial focus on psychotherapy is crucial in this case of familial IPF.

While genetic studies in familial IPF have provided useful insights into the pathogenesis of IPF, genetic testing in patients with either familial or sporadic IPF is not currently advised as part of the clinical evaluation (1). Clearly, further functional studies that confirm their significance and studies investigating other mutations, associations, and gene–environment relationships are needed. Based on current early medical trials in the field of IPF, future expensive treatments are to be expected. As seen in the growing field of targeted therapy in oncology, the likelihood of an individual's positive response to an IPF therapy should ideally be predictable prior to therapy induction. It is to be hoped that the translation of ongoing basic science research into clinical practice can be realised in order to enable a personalised diagnosis, treatment and prognosis in IPF.

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