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Case report

Familial idiopathic pulmonary fibrosis in a young female

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ABSTRACT

Idiopathic pulmonary fibrosis is a chronic interstitial lung disease of unknown cause. In the past years there have been observations of clustering of pulmonary fibrosis in families, indicating the disease can be inherited. The most commonly identified mutations are mutations involving proteins from the telomerase complex and the surfactant system, where the mutations from the surfactant protein system are less identified. We report a rare care of familial IPF in a young female at the age of 34 years, in whom genetic testing shows two different heterozygous variants for the surfactant protein system as a probable cause of her interstitial lung disease.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrotic interstitial lung disease of unknown cause. IPF is a progressive and irreversible disease, and mainly affects adult men with a mean age of 66, with a smoking history. The etiology of the disease is still under investigation, and it is suggested that a combination of genetics and environmental factors may play an important role. In the past years, there have been observations of familial clustering of pulmonary fibrosis, indicating that the disease can be hereditary [1,2]. The prevalence of interstitial lung disease (ILD) in a first-degree relative of a patient with IPF is approximately 2–20% [2,3]. Familial IPF affects mainly men, and the age of onset is often younger than in sporadic IPF, approximately 55 years [4]. We report a rare case of a young woman with an early onset of familial IPF at the age of 34 years.

1.1. Case report

A 34-year old Polish female was referred to The Danish Center of Interstitial Lung Diseases in 2011 on the suspicion of lymphangioleiomyomatosis (LAM). She had dyspnea at exertion and dry cough, and since her teenage years she had nail clubbing. She was a smoker with eight pack years and had a family history of lung disease. There was no suspicion of autoimmune or connective tissue disease or occupational or environmental exposure relevant for interstitial lung diseases.

At referral, her pulmonary function showed a forced expiratory volume (FEV1) of 3.14 L (104%), forced vital capacity (FVC) of 3.7 L (107%), FEV1/FVC ratio 84% and a diffusion capacity for carbon monoxide (DLCO) of 56% of predicted. The distance at a six-minute walk test (6MWT) was 480 m without desaturation. High resolution computed tomography (HRCT) of the lungs showed cystic changes and non-specific discrete fibrosis with an upper lobe predominance (Fig. 1). LAM, Langerhans cell histiocytosis and emphysema were suspected. Bronchoscopy with bronchial lavage showed a normal cytological differential count without any CD1-alfa positive cells, and a transbronchial biopsy was non-diagnostic. The patient underwent a surgical lung biopsy, described as chronic lymphocytic inflammation and non-specific fibrosis. Fig. 2 shows the histology of the patient's lung biopsy from lingula in the left lung.

Supplementary immunological tests for LAM and histiocytosis were negative. Non-specific interstitial pneumonia (NSIP) and hypersensitivity pneumonitis were discussed as possible diagnosis but no other investigations could support this. The final diagnosis was emphysema, and, as requested by the patient, she was sent back to the referring hospital.

In 2015, the patient was again referred due to progressive dyspnea. Still no specific diagnosis could be made, but she was followed at the specialist unit due to the progressiveness of the lung disease. During the following 18 months, her pulmonary function was slowly declining. In May 2017, FEV1 was 2.11 (72%), FVC 2.39 (71%) and DLCO 21%. 6MWT was 482 m with significant desaturation from 97% to 77%. A new HRCT showed progressive cystic changes in the upper lobes,

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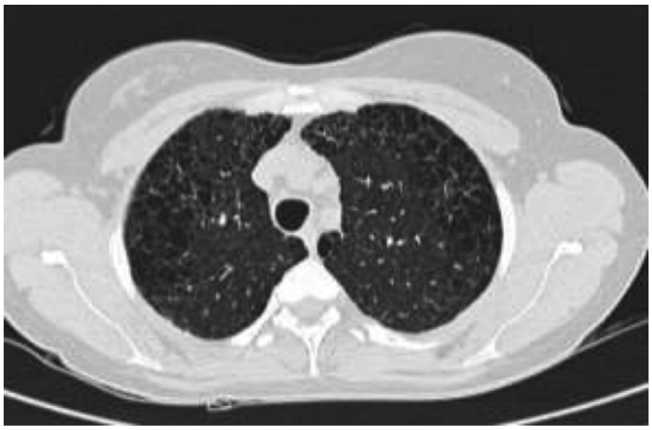

Fig. 1. Inspiratory high resolution computed tomography (HRCT) images showing upper lobe predominant cysts. There is no traction bronchiectasis or reticulation.

traction bronchiectasis and ground glass opacities (GGO) (Fig. 3a, b and 3c).

Upon questioning, she told that all male family members had grey hair at age of 40–50 years old but there was no family history of liver cirrhosis or bone marrow failure. Her father died at the age of 58 due to rapid progression of an interstitial lung disease.

Fig. 4a and b shows the fibrotic changes seen in his HRCT-scan.

He did not accept invasive examinations to further clarify the diagnosis. Her grandfather, aunt and uncle also died of lung diseases and they were all reportedly smokers. The patient's family tree is shown in Fig. 5.

A diagnosis of Familiar Interstitial Pneumonia (FIP) was made based on the patient's family history, the HRCT, progression and review of the histology. Antifibrotic therapy with pirfenidone and lung transplantation evaluation was initiated. Genetic screening was carried out with sequencing and CNV analyses of the coding regions of *ABCA3, AP3B1, BLOC1S3, CSF2RA, DTNBP1, ELMOD2, HPS1, HPS3, HPS4, HPS5, HPS6, MUC5B, NKX21, SFTPA1, SFTPA2, SFTPB, SFTPC, SFTPD, TERC* and

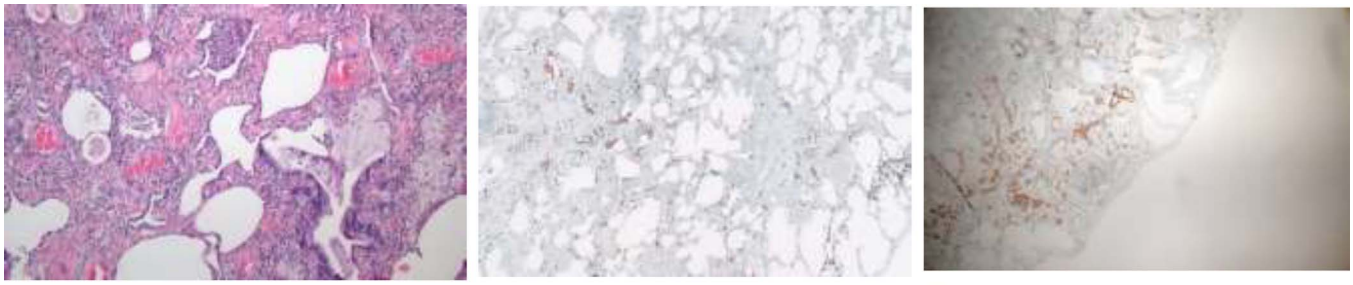

Fig. 2. 2a: Honeycombing fibrosis, lymphocytic inflammation and macrophages in the alveoli (hematoxylin-eosin, 100×).**2b**: Interstitial fibrosis and alveolar macrophages positive for CD68 (40×). **2c**: Heterogeneous fibrosis with smooth muscle hyperplasia (smooth muscle actin, 40×).

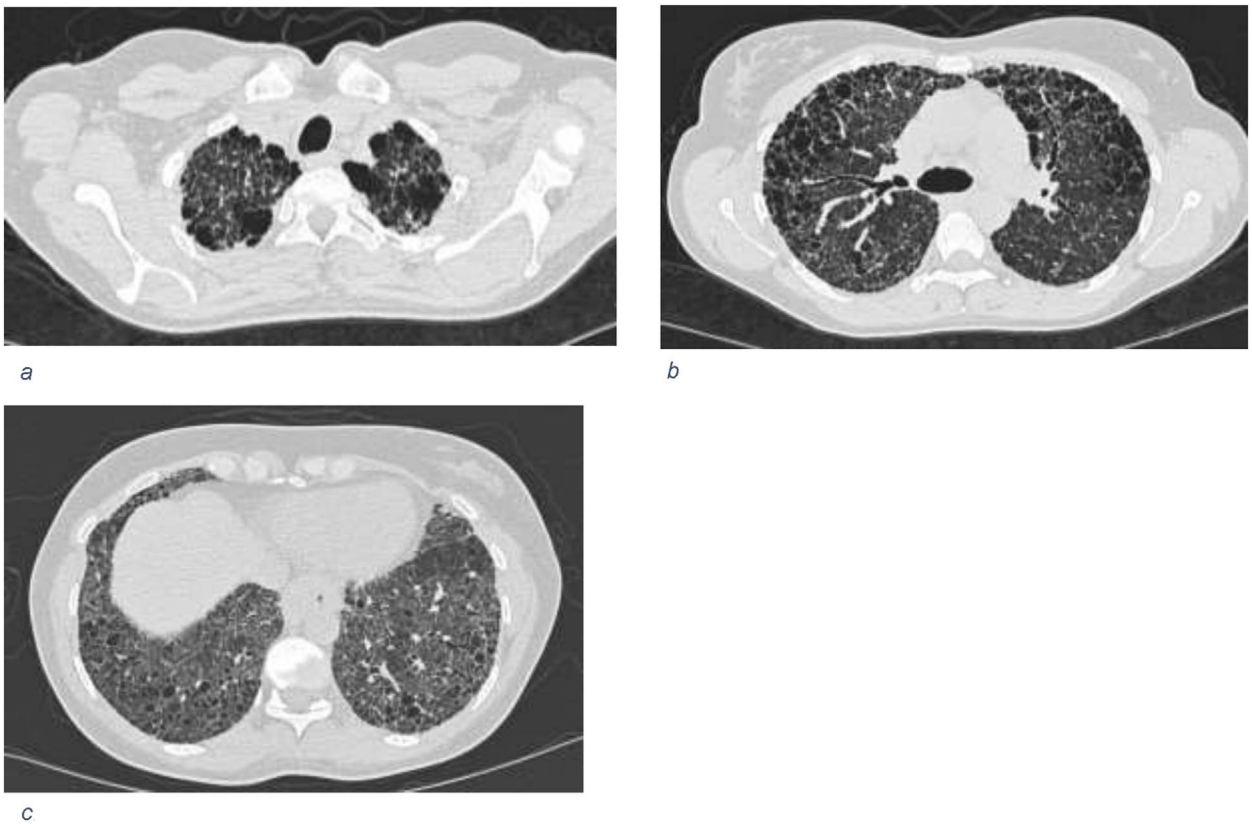

Fig. 3. 3a: Inspiratory HRCT images of upper lobe showing progression of cysts. **3b**: Inspiratory HRCT images at the level of carina showing progression of cysts, tractions bronchiectasis and fine reticulation. **3c**: Inspiratory HRCT images of lower lobes showing honeycombing (progression of the cysts in multiple layers).

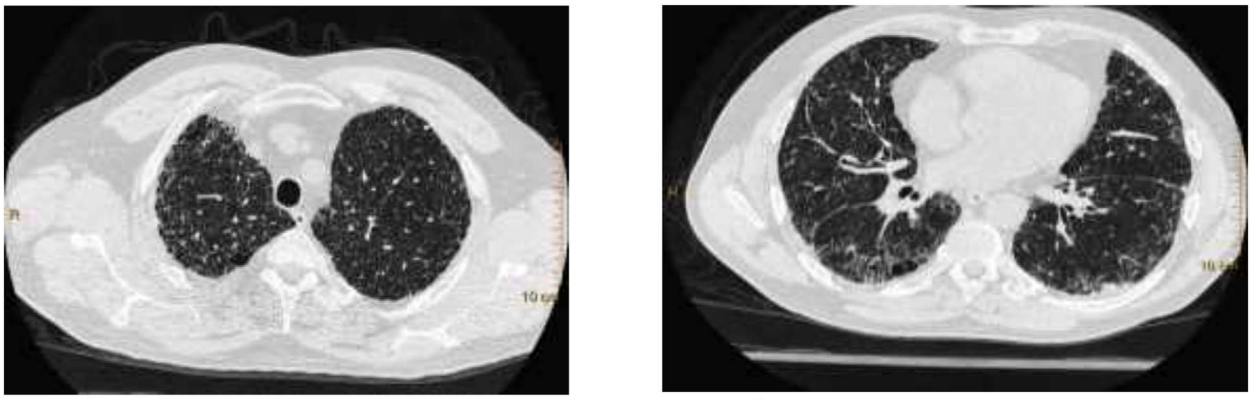

Fig. 4. 4a: Inspiratory HRCT images of the upper lobe showing cysts and fine reticulation.**4b**: Inspiratory HRCT images of the lower lobe showing fine reticulation, cysts and traction bronchiectasis.

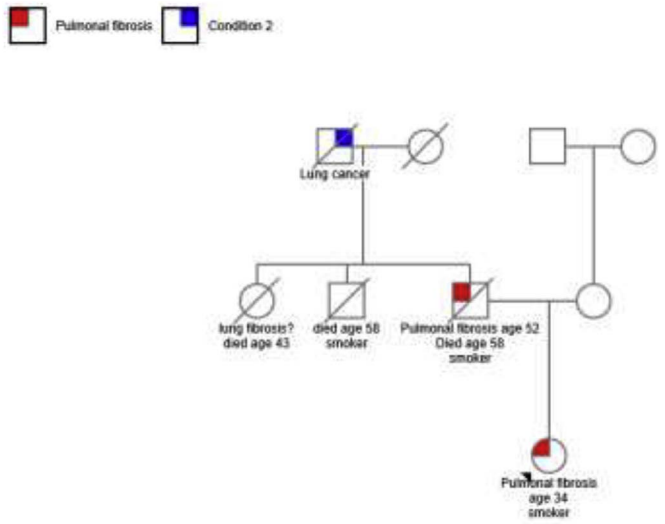

Fig. 5. Family tree.

Table 1
The mutations detected in the patient.

Heterozygous c.977T > C (p.Leu326Pro), Exon 9	*ABCA3*
Heterozygous c.671C > A (p.Thr224Asn), Exon 6	*SFTPA1*

TERT. A variant of unknown significance was identified in *ABCA3* and a variant of unknown significance was identified in *SFTPA1* (Table 1).

2. Discussion

In the past 10 years, pathogenic variants in genes associated with the telomerase complex and surfactant systems have been identified to be associated with familial pulmonary fibrosis. Considering the telomerase complex, the two most commonly involved genes are *TERT* and *TERC*, where pathogenic variants in *TERT* have been detected in approximately 15% of the familial IPF cases [2].

Pathogenic variants in genes coding surfactant protein are less often identified. Surfactant is a protein secreted by type II epithelial alveolar cells and the main types are surfactant proteins (SP)-A, SP-B, SP-C and SP-D, where the corresponding genes are *SFTPA, SFTPB, SFTPC* and *SFTPD*. *SFTPC* is the most commonly involved gene, wherein pathogenic variants have been described to segregate with autosomal dominant transmission of disease, with intrafamilial and interfamilial age range from birth to 72 years [2–4].

Mutations in *SFTPA* are extremely rare – there are two isoforms of SP-A, SP-A1 and SP-A2 and only few cases of families with *SFTPA2* mutations have been reported. The transmission was autosomal dominant with the phenotype of early pulmonary fibrosis and lung cancer [4–6]. In 2016, Nathan et al. completed a study investigating 12 families with IPF and lung cancer. They reported the first case of a pathogenic variant in *SFTPA1* in heterozygous state to be associated with pulmonary fibrosis [7]. Our patient is heterozygous for a variant of unknown significance in *SFTPA1*, which has not been described before. In order to elucidate the full significance of the found mutations, the genetic results from her family members would be needed.

Mutations in the adenosine triphosphate binding cassette A3 (*ABCA3*) gene have been associated with autosomal recessive interstitial lung disease. ABCA3 is known to be related to the processing and secretion of SP-C. Homozygous *ABCA3* mutations have been reported in children with ILD, but in a large family, combined pulmonary fibrosis and emphysema (CPFE) has also been reported to be associated with *ABCA3* mutations [2,3]. Our patient was heterozygous for the variant c.977T > C (p.Leu326Pro), which has not been described in literature before and the significance is uncertain. Furthermore, a variant affecting the other ABCA3 gene was not identified.

The result of our patient's genetic test shows that mutations in the *ABCA3* and *SFTPA1* genes may be significant.

Our case shows the diagnostic challenges in very rare diseases such as FIP. Our patient had symptoms for 6 years before the diagnosis of FIP was made, despite the thorough examinations she underwent. The early onset of pulmonal fibrosis before the age of 45, a family history of both IPF and lung cancer, and the fact that neither the patient nor her family members had extrapulmonal manifestations, is supportive of a surfactant-related disorder [8]. Both the variants of unknown significance were detected in surfactant protein genes. It was not possible to make segregation analyses because all other affected family members are deceased.

Physicians must consider FIP also in younger patients with a family history of fibrotic lung disease even if the radiologic and histopathologic pattern is non-specific for a clear pattern. A clear family history must be weighted heavily, more information of the family history sought and all clinical findings, even those with a non-specific pattern, should be evaluated in this context in order to secure an early diagnosis. Careful follow up is necessarily to diagnose progression of the disease and to start relevant treatment.

Genetic investigations should be considered in all patients with FIP. Even though the significance of a mutation is not known at the moment, future research may result in individual risk stratification with respect to prognosis, risk of progression and treatment response.

Conflicts of interest

None.

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