FAMILIAL IDIOPATHIC PULMONARY FIBROSIS IN THREE LEBANESE SIBLINGS
Case report with long-term follow-up

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ABSTRACT : This is the first report of a familial cluster of idiopathic pulmonary fibrosis (IPF) in Lebanon. This rare variant of IPF has an autosomal dominant mode of inheritance with variable expressivity, and is commonly associated with a mutation of the surfactant protein C gene. The patients are younger at diagnosis but have otherwise identical clinical, radiological, and histological features as the more common non-familial cases. IPF is an invariably fatal disease with no effective treatment. Lung transplantation remains the only chance for more prolonged survival and must be considered in young patients.

The true prevalence of idiopathic pulmonary fibrosis is not known. According to an epidemiologic report from the US, there are up to 20 cases per 100,000 individuals with a male to female ratio of 1.5 to 1 [1]. Only about 0.5 to 2% of all cases of IPF are thought to have a genetic basis [2]. We describe three siblings from a village in southern Lebanon who were evaluated and followed up at the American University of Beirut Medical Center (AUBMC) for chronic respiratory complaints between 1989 and 2002. All three were diagnosed with pulmonary fibrosis by open lung biopsy. The patients gave no history of exposure to chemical or environmental fibrogenic agents. A literature review shows no previously reported cases of familial IPF in Lebanon. To date, about 110 families have been reported to have this disease worldwide [3-6].

CASES

Case # 1
A 35-year-old woman, nonsmoker, with no significant prior medical history presented to AUBMC in 1989 complaining of progressive shortness of breath, cough, and chest pain of one year duration. She had been started on antituberculosis medication for suspected tuberculosis by a physician elsewhere. Physical examination revealed end-expiratory wheezes and basilar crackles. Chest X-ray revealed a pneumothorax and generalized fibrosis in all lung fields (Fig. 1). Pulmonary function tests revealed a restrictive pattern. Blood tests were normal except for positive ANA and RA latex tests. An open lung biopsy showed interstitial pneumonitis with fibrosis consistent with usual interstitial pneumonitis (UIP) (Fig. 2). The patient was placed on oral steroids for several months with some symptomatic improvement, however, she later discontinued treatment and experienced progressive respiratory deterioration. She died in 1994 at the age of 40.


FIGURE 1. CXR with generalized fibrosis.
**Figure 2**

**Left**: Low magnification showing a patch of interstitial fibrosis (*arrows*) with relatively normal lung tissue in the right upper corner (*H & E stain, x 20*).

**Right**: Higher magnification showing an area of fibrosis with a fibroblastic focus denoting the presence of active disease (*black arrow*) and an adjacent lymphocytic infiltrate (*white arrow*) (*H & E stain, x 100*).

**Figure 3**

CXR with bilateral reticulonodular infiltrates.

**Figure 5**

CXR with diffuse interstitial infiltrates.
**Figure 4**

**Above**: A peripheral focus of prominent interstitial fibrosis with subpleural cystic change (H & E stain, x 20).

**Below**: Expansion of the interstitium by fibrosis and chronic inflammation on the right with less involved alveolar septa on the left. (H & E stain, x 100)

**Figure 6**

**Above**: An area of extensive fibrosis with slightly dilated alveolar spaces in the upper part of the field (H & E stain x 20).

**Below**: A fibrotic area with a lymphoid follicle in the lower right. (H & E stain x 100)
Case # 2
In 1994, the patient’s sister presented to AUBMC at the age of 25 with abnormal chest X-ray findings (Fig. 3). An open lung biopsy from the right upper and middle lobes revealed wide areas of interstitial fibrosis with chronic inflammation in both lobes, also consistent with UIP (Fig. 4). Her condition worsened progressively and she died in 2003 at the age of 34.

Case # 3
In 1996, their 33-year-old brother presented with symptoms of fatigue, cough, and dyspnea on exertion of one year’s duration. Chest X-ray revealed diffuse interstitial infiltrates (Fig. 5). An open lung biopsy revealed pulmonary fibrosis and interstitial pneumonitis with a pattern that is consistent with UIP (Fig. 6). Most of the left lower lobe biopsy and all of the lingular sample were involved. He died in 1999 at the age of 36 while waiting for lung transplantation.

The clinical presentations of all three cases are summarized in Table I.

**DISCUSSION**

Idiopathic pulmonary fibrosis (IPF), also termed cryptogenic fibrosing alveolitis or usual interstitial pneumonia (UIP), is a rare disease of unknown etiology. The pathogenesis of IPF stipulates that there is an injury to the lung parenchyma which results in the formation of immune complexes. These complexes stimulate alveolar macrophages to produce a variety of factors including chemotactic factors that attract neutrophils into the interstitium. The inflammatory cells, together with activated resident cells are thought to release polypeptide mediators that stimulate fibroblast proliferation and matrix collagen synthesis [7-8]. There is mounting evidence that there are genetic influences that are also involved in the pathogenesis of IPF. The evidence includes the existence of familial clusters, and the recent discovery of cases with mutated surfactant proteins [9-10]. These genetic influences could play a role by altering surfactant proteins, by affecting the immunological response to injury, or by modulating collagen metabolism in the lung [11-12]. Genetically altered pulmonary surfactant is now proven to play a role in the pathogenesis of some interstitial lung diseases, particularly in familial cases of IPF.

Pulmonary surfactant, a complex mixture of phospholipids and proteins present in alveolar lining fluid, contains proteins designated as surfactant proteins A, B, C, and D [13]. Mutations in surfactant protein C (SP-C) have been well documented in familial IPF, but are rare in sporadic cases [3, 13-15]. These mutations may lead to the production of structurally abnormal proSP-C or SP-C protein. In severe lung disease, there may be complete absence of SP-C and proSP-C [1, 4, 6]. The pattern of inheritance of familial IPF suggests an autosomal dominant inheritance with variable expressivity [3, 10, 14, 20]. Patients with either sporadic or familial forms of IPF invariably die within 6 to 8 years after diagnosis. Conventional treatment with steroids has been unsatisfactory in altering the natural history of the disease. Somatic cell gene therapy, which has played a role in the man-
agement of some monogenic human disorders, is ineffec-
tive in IPF. This is probably because the disease is poly-
genic and involves complex interactions between genetic
susceptibility and environmental factors. Experiments in
animal models attempted at reducing the expression of
transforming growth factor-β (TGF-β), the most impor-
tant growth factor involved in inflammatory fibrosis, and
at enhancing fibrinolytic activity. Epigenetic approaches
using antisense oligonucleotides to suppress collagen
synthesis have also been tried, but no gene therapy yet
exists for IPF [7]. Lung transplantation, despite its major
medical complications [16], remains the only therapeutic
option shown to improve survival in IPF [17], and it must
be considered early on in younger patients [18].

Patients with sporadic IPF are usually 50 to 70 of age
at the time of diagnosis [19], while familial cases are
usually younger. Apart from this and the common occur-
rence of SP-C gene mutations, familial cases are indis-
tinguishable from non-familial cases [21].

CONCLUSION

This is the first documented familial cluster of idiop-
athic pulmonary fibrosis in Lebanon. It includes three
siblings with similar clinical courses, radiographic
pictures, and histopathologic features. The occurrence
of familial cases of IPF has stimulated the search for spe-
cific genetic mutations, and is beginning to unravel some
molecular aspects in the pathogenesis of IPF in general.
Mutations in SP-C gene were identified in some, but not
all, patients with IPF. Further insight into the molecular
basis of IPF is necessary in order to develop new modal-
ities of treatment. Currently, the only effective treatment
available is lung transplantation.

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