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REPORT OF FOUR CASES OF FAMILIAL IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

A 25 year old male and his 46 year old aunt presented with shortness of breath and a dramatic response to steroids. The other two patients are sisters with more advanced disease. One of these responded partially to steroids, while the other died within 4 months of treatment. The genetic basis and pathogenesis are discussed.

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INTRODUCTION

Familial fibrosing alveolitis or idiopathic pulmonary fibrosis (IPF) was first described by Sandos in 1907, and almost 30 years later the non-familial cases were described by Hamman and Rich. Both familial and non-familial cases are identical clinically.[1,9] The familial cases are transmitted in an autosomal dominant manner with incomplete penetrance.[2,3]

HLA, immunoglobulins (Gm) and antitrypsin (P_1) loci are polymorphic and hence quite suitable for evaluation of studies to determine the genetic basis of diseases. HLA is located on chromosome 6, while Gm and P_1 are located on chromosome 14.

Studies on HLA-A, HLA-B and HLA-DR suggest that they are not important in transmission of IPF, while studies on Gm and P_1 loci suggest the IPF gene locus is located on chromosome 14 and that the disease is transmitted in an autosomal dominant manner.[4] Studies on siblings also seem to suggest similar transmission.[9]

Although over 100 agents have been identified as the causative agents of IPF, including many dusts, the causative agent remains unknown in over 2/3 of the cases.[1]

There is an ongoing controversy involving the terminology of chronic lower respiratory diseases since the description by Hamman and Rich. These include cirrhosis of the lung, chronic interstitial pneumonia, fibrocystic pulmonary dysplasia, idiopathic interstitial pneumonitis, idiopathic pulmonary fibrosis, and fibrosing alveolitis, among others.[5]

Liebow's description of desquamative interstitial pneumonitis and studies by Carrington[7] demonstrating good clinical response to steroids has further contributed to the controversy.

European investigators and workers at NIH consider DIP and IPF as variants of the same disease while others consider these as two separate entities.[8]

MATERIALS AND METHODS

The four patients were seen at Imam Reza Medical Center over a 6 year period (Table I). All patients had chest X-rays, routine pulmonary function tests and arterial blood gas estimations (Table II). The patients had transbronchial lung biopsies after stabilization of the acute condition. Pulmonary lavage studies were not performed nor was gallium-67 scanning performed, as these were not available. One of the patients, a 55 year old female, died within 4 months of initial admission. Autopsy was not performed.

CASE REPORTS

Case 1: A 27 year old well nourished male weighing 85 kgs was admitted with shortness of breath, dizziness and cough which followed a flu-like syndrome 10 days previously. He developed increasing dyspnea on exercise and cyanosis. He was a salesman and an ex-smoker, having smoked 10-15 cigarettes per day for 7 years but had quit smoking two years prior to the present illness. The patient had three brothers, all of whom were in good physical condition. On examination the patient was cyanotic with sinus tachycardia and had a few fine bibasilar crepitations. There was no

glycoprotein. PDGF is not only chemotactic for mesenchymal cells but also stimulates the fibroblasts to enter the cell cycle at G phase. MDGF is also chemotactic for neutrophils.[15] The increased numbers of neutrophils in the alveolus are not reflected by a rise in neutrophils in the peripheral blood.

The neutrophils are the most damaging cels, for they produce superoxide anions and other substances including proteases, collagenases and elastase. The superoxide anions damage the alveolar type I cells which constitute 80% of the alveolar cells. If the damage is mild these can be replaced by type II cells which transform to type I cells. The proteases damage the alveolar wall matrix and the collagenases cleave the type I collagen which is a major component of the alveolar skeletal structure.

The elastase produced by the neutrophils damages the basement membrane. The alveolar macrophages besides producing MDGF and PDGF, also produce fibronectin, a glycoprotein which is also chemotactic for fibroblasts. Fibronectin signals the fibroblasts to enter the cell cycle and together with MDGF and PDGF, causes fibroblasts to proliferate, resulting in fibrosis.

In early stages when the basement membrane has not yet been damaged, there may be recovery but when the basement membrane has also been damaged there is increased fibrosis as described above.

DISCUSSION

Chronic lower respiratory disorders are best evaluated by clinical examination, pulmonary function tests, bronchial lavage using five 20 ml sterile saline to lavage the bronchi, gallium 67 scan and lastly biopsy.

Vital capacity reflects well the total lung volume while the diffusing capacity reflects the status of the alveolar capillary bed.[12]

Although transbronchial biopsy is the method of choice in confirming diagnosis of sarcoidosis, it is considered less than ideal in IPF for sometimes it gives a false negative result.

Bronchial lavage has a good prognostic value especially when more than 10% of the cells are neutrophils and the gallium 67 scan is positive. There is usually a marked deterioration of the patients within 6 months, as compared to patients with less than 10% of neutrophils and a negative scan.

The unaffected family members of patients with familial idiopathic pulmonary fibrosis have increased numbers of activated macrophages in the lavage fluid but over a few year follow-up no cases with IPF have yet developed.[9]

Cigarette smoking worsens this condition as smoking not only activates the alveolar macrophages but also increases their number and as the macrophages have a life span of months to years the damage may continue for some time even after cessation of smoking. It should be noted that patient number one was an ex-smoker.

In the cases presented here the detailed family workup has not yet been worked out. However patient number one is said to have three healthy brothers. Perhaps lavage evaluation of those siblings may be helpful.

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