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Case report

The inter-connection between fibrosis and microvascular remodeling in idiopathic pulmonary fibrosis: Reality or just a phenomenon

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ABSTRACT

Background: Idiopathic pulmonary fibrosis is the most frequent interstitial disease with the worst prognosis. It is characterized by an uncontrolled fibrosis which is difficult to manage. The pathogenesis of this disease remains unclear with many theories resulting in multiple target therapies. The relation between fibrosis and vascular remodeling has been debated in the literature with different results that may seem contradictory.

Aim: We target to evaluate the connection between fibrosis and vascular remodeling in usual interstitial pneumonia.

Material and methods: 26 cases of idiopathic pulmonary fibrosis were reviewed by 2 pathologists and the diagnosis of UIP was retained according to the American Thoracic Society's criteria. Fibrotic changes and vascular remodeling were evaluated blindly. The fibrotic changes were classified as severe, intermediate and mild. Vascular occlusion was graded in 4 grades extending from medial hypertrophy (grade 1) to plexiform lesions of the vascular wall (grade 4).

Results: We noticed that severe degrees of fibrosis were correlated with severe grades of vascular obstruction. In fact, our 26 cases were classified as severe fibrosis in 11 cases with grade IV vascular lesions in 6 cases, intermediate fibrosis in 12 cases with grade II vascular lesions in 8 cases and mild fibrosis in 3 cases with grade I vascular lesions in all cases.

Conclusion: Many theories have been reported concerning the UIP's pathogenesis. Recently, many authors reported that the primum movens of these lesions was an epithelial/endothelial injury which induces uncontrolled fibrosis and microvascular remodeling using different pathways. This puts emphasis on the necessity of multi-target therapies in order to improve the management of this fatal disease.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most frequent interstitial disease which is classified among idiopathic interstitial diseases (IIDs). This entity is a fibrosing disease characterized by the worse prognosis due to its difficult management. In fact, the only efficient treatment of this entity is the lung transplantation. Its better management depends on the knowledge of its complex pathogenesis. IPF is a clinical denomination and the histological correlation is usual interstitial pneumonia (UIP) which is characterized by a heterogeneous architecture determined by the succession of normal and fibrotic areas. Microvascular remodeling is a common phenomenon which is frequently reported in UIP. This phenomenon in association to other factors, deals with the development of a pulmonary hypertension (PH) which is associated with a poor survival [1,2]. Many authors tried to assess the interconnection between parenchymal fibrosis and vascular remodeling. We tried to explore this relationship among 26 cases of UIP diagnosed in our department of Pathology. We tried to emphasize on the fact that more effective therapeutics may be discovered if both phenomenon will be more integrated.

2. Materials

26 patients with the diagnosis of IPF/UIP were included in this

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study. All the cases were diagnosed on surgical lung sample according to the American Thoracic Society/European Respiratory Society International multidisciplinary consensus classification of the idiopathic interstitial pneumonias (IIP). All slides were reviewed by 2 pathologists. UIP was defined by alternating areas of normal parenchyma and injured parenchyma characterized by alveolar collapse, honeycombing and severe organizing fibrous airspace wall [3] (Fig. 1). Similarly to the article of Parra and coworkers, we evaluated the fibrosis using a semiquantitative manner [4]. Grade I was attributed to minimal fibrotic lesions defined as alveolar collapse with relatively normal lung parenchyma. Grade II lesions were characterized by moderate organizing fibrosis of the wall with fibroblast foci. Grades III and IV were defined by severe fibrosis of the wall with honeycombing and foci of actively proliferating fibroblasts and myofibroblasts (Fig. 2).

In order to grade the vascular remodeling, we also used the criteria of Parra and colleagues. It was evaluated by a semiquantitative analysis for different level of vascular obstruction. Grade I defined isolated hypertrophy of the arterial media. Grade II corresponded to proliferative intimal lesions. Total occlusion of the arterial lumen defined grade III and grade IV was characterized by plexiform lesions (Fig. 3).

3. Results

- Baseline characteristic: Between 2006 and 2010, 32 surgical biopsies were performed in order to explore ILDs. Among these cases, 80.6% (26 cases) were classified as UIP, 19.35% (6 cases) were classified as NSIP. We focused on the 26 cases of UIP. Our study was about 6 women and 20 men with a median age of 56.76 (range 37–75).
- Diagnostic criteria: To retain the diagnosis of UIP, all the items follow were present in all cases: a heterogenous architecture, honeycombing cysts, fibroblastic foci. Besides, the diagnosis of UIP was retained only after a correlation with clinical and radiological findings.
- Morphological results: The different grades of vascular obstruction were correlated with parenchymal changes. In fact, grades III and IV were observed in heavily fibrotic pulmonary parenchyma. Minimal fibrosis was noted in 3 cases with grade I. In all cases, vascular remodeling was of grade I. Intermediate fibrosis was noticed in 12 cases. 2 cases were classified as grade I, 8 cases were classified as grade II and 2 cases were classified as grade III. Severe fibrosis was noted in 11 cases. One case was classified as grade I, 1 case was classified as grade II, 3 cases were classified as grade III and 6 cases were classified as grade IV.

4. Discussion

Pulmonary fibrosis is refractory to treatment and induces a high mortality rate. It represents a heterogeneous group of lung disorders dealing with the progressive and irreversible destruction of lung architecture and death from respiratory failure [5]. IPF is of unknown etiology and is characterized by a heavy fibrosis dealing with a life expectancy of 2–6 years after diagnosis [6]. Many pathogenic theories have been reported within the last decade. Initial theories supposed that chronic inflammation played a key-role [7]. Then, many authors supposed that this theory wasn't convincing based on the finding that consisted in the presence of epithelial cell injury and abnormal wound repair in the absence of preceding inflammation [8]. Besides, intrinsic defects in the wound healing response involving lung epithelial cells and fibroblasts have supposed to play a major role in the pulmonary fibrosis's pathogenesis [9]. Finally, based on the multiplicity of the theories, many authors supposed that the pathogenic events must be more complex [10]. Vascular remodeling is a known phenomenon in IPF dealing with pulmonary hypertension whose prevalence in

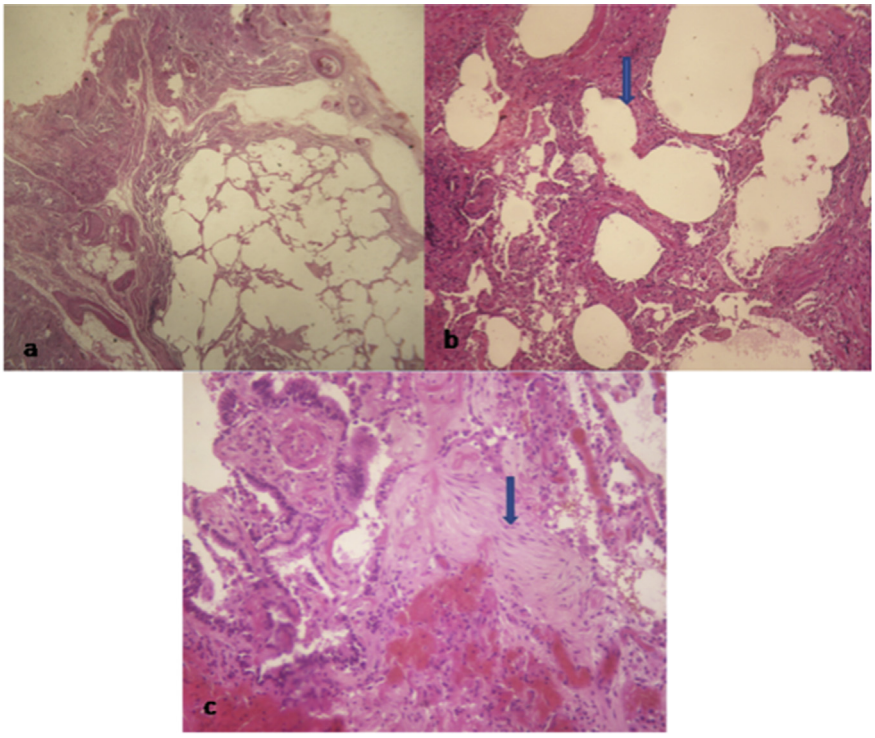

Fig. 1. Diagnostic criteria of usual interstitial pneumonia: a/ alternating areas of relatively normal parenchyma and fibrosing areas with alveolar collapse. b/ honeycombing areas. c/ Fibroblast foci within alveolar wall.