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Anti-parietal cell autoimmunity is associated with an accelerated decline of lung function in IPF patients

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ABSTRACT

Background: Autoantibodies against lung epithelial antigens are often detected in patients with Idiopathic Pulmonary Fibrosis (IPF). Anti-Parietal Cell Antibodies (APCA) target the H+/K+ATPase (proton pump). APCA prevalence and lung H+/K+ATPase expression was never studied in IPF patients.

Methods: We retrospectively collected clinical, lung function and imaging data from APCA positive patients (APCA+IPF) and compared them with APCA negative IPF patients matched on the date of diagnostic assessment. H+/K+ATPase expression was assessed with immunohistochemistry and PCR.

Results: Among 138 IPF patients diagnosed between 2007 and 2014 and tested for APCA, 19 (13.7%) APCA+ patients were identified. APCA+IPF patients were 16 men and 3 women, mean age 71 years. The median titer of APCA was 1:160. A pernicious anemia was present in 5 patients and preceded the fibrosis in 3 cases. With a mean follow up of 31 months, 2 patients had an exacerbation and 7 patients died. As compared with 19 APCA- IPF patients, APCA+IPF patients had a less severe disease with better DLCO (57% vs 43% predicted), preserved PaO_2 (85 ± 8 mmHg vs 74 ± 11 mmHg), a lower rate of honeycombing on HRCT (58% vs 89%), but they experienced an accelerated decline of FVC (difference 61.4 ml/year; p = .0002). The H+/K+ATPase was strongly expressed by hyperplastic alveolar epithelial cells in the fibrotic lung.

Conclusion: Anti-parietal cell autoimmunity is detected in some IPF patients and is associated with an accelerated decline of lung function. Anti-parietal cell autoimmunity may promote lung fibrosis progression.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease, characterized by abnormal fibroproliferation leading to chronic respiratory failure and death. The etiology of IPF is unknown, but a repeated injury to the alveolar epithelium from an unknown trigger, a persistent immuno-inflammatory phase and a dysregulated tissue repair are generally considered as important mechanisms for IPF development [1,2]. Gastroesophageal reflux is particularly frequent in IPF and may contribute to repeated alveolar epithelium injury and lung fibrosis progression [3]. Anti-reflux therapy, including proton pump inhibitors and anti-reflux surgery, have been suggested to influence the progression of lung function decline and exacerbation rate in IPF patients [4,5] although this remains a matter of debate in the absence of any direct evidence from randomized trials [6,7]. Interestingly, recent observations indicate that proton pump inhibitors may have antifibrotic activities by directly suppressing proinflammatory cytokines, profibrotic proteins, and proliferation of lung fibroblasts [4].

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Abbreviation list

6-MWT	6 Minutes Walk Test
ALAT	Asociación Latino Americana de Tórax
ANA	AntiNuclear Antibodies
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
Anti-CCP	Antibodies against Cyclic Citrullinated Peptide
Anti-MCV	Antibodies against Mutated Citrullinated Vimentin
APCA	Anti-Parietal Cell Antibodies
ATS	American Thoracic Society
(hs)ATP4A and B	*Homo sapiens* ATPase H+/K Transporting Alpha and Beta subunit (encoding genes)
BAL	Broncho-Alveolar Lavage
BMI	Body Mass Index
DLCO	diffusion capacity of the lung for carbon monoxide
ELISA	Enzyme-Linked ImmunoSorbent Assay
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in 1 s
FITC	Fluorescein IsoThioCyanate
FVC	Forced Vital Capacity
GERD	Gastroesophageal Reflux Disease
H+/K+-ATPase	Hydrogen/potassium ATPase (proton pump)
HRCT	High-Resolution Computed Tomography
IPF	Idiopathic Pulmonary Fibrosis
IL-10	Interleukin 10
JRS	Japanese Respiratory Society
MCV	Mean Corpuscular Volume
mRNA	messenger RiboNucleic Acid
MRC	Medical Research Council
PaO_2	Partial pressure of arterial oxygen
PH	Pulmonary Hypertension
qPCR	quantitative Polymerase Chain Reaction
SD	Standard Deviation
SEM	Standard Error of the Mean
TGF-β 1	Transforming Growth Factor beta 1
TLC	Total Lung Capacity
TNF-α	Tumor Necrosis Factor alpha
UBC	Ubiquitin C
UIP	Usual Interstitial Pneumonia

Several observations suggest that an autoimmune response is involved in the pathogenesis of IPF [8]. First, Evidence for immune activation in IPF pathogenesis is supported by the recent identification of a signature of 52 genes expressed by peripheral blood mononuclear cells significantly associated with transplant-free survival in IPF patients [9,10]. Decreased expression of genes belonging to the co-stimulatory signal during T cell activation was evidenced, in particular, CD28, ICOS, LCK, and ITK, in a sub-group of patients with shorter transplant free survival. Second, B cells aggregates are often observed in IPF lungs, organized with activated T lymphocytes and mature dendritic cells, suggesting intense antigen-presentation activity in the lung parenchyma [11,12]. Third, circulating CD4 T cells from IPF patients exhibit typical characteristics of activation. Indeed, they produce cytokines helping autoantibody production by B cells, and also fibrogenic mediators such as IL-10, TGF-β 1 or TNF-α [13,14]. Fourth, CD4 T cells purified from lymph nodes from IPF patients proliferate when cultured with autologous lung tissue protein extracts [13]. Fifth, a global impairment of regulatory Tcells has been described in IPF which could participate in the development of auto-immune responses [15]. Finally, potentially pathogenic immune complexes have been found in the sera, bronchoalveolar lavage, and pulmonary parenchyma of IPF patients [16–18]. The responsible antigen(s) remain(s) to be identified, but several studies point to the alveolar epithelial cell as a possible target of autoimmunity in IPF, as circulating autoantibodies directed toward epithelial cells have been detected by different groups [18–25] including our group [26].

Autoimmune gastritis is an organ-specific autoimmune disease characterized by anti-parietal cell autoimmunity targeting the hydrogen/potassium ATPase (H^+/K^+-ATPase) proton pump [27]. The H^+/K^+-ATPase proton pump is a membrane-bound enzyme located in the parietal cells of the stomach that is responsible for exchanging hydrogen ions into the gastric lumen to produce hydrochloric acid. Anti-Parietal Cell Antibodies (APCA) are directed against the alpha and possibly the beta subunits of H^+/K^+-ATPase proton pump [28,29]. APCA are also detected in 20% of patients infected with *Helicobacter pylori* although no pathogenic link has been clearly demonstrated [29]. Interestingly, the H+/K+-ATPase proton pump is expressed by the human airway epithelium, particularly in the seromucinous glands [30,31], but its expression in the IPF lung was never evaluated specifically.

We hypothesized that anti-parietal cell autoimmunity could be involved in IPF pathophysiology. The aim of this study was 1) to detect the presence of H+/K+-ATPase targeted autoimmunity through the detection of APCA in IPF patients; 2) to describe the characteristics of APCA-positive IPF patients, as compared to a matched control group of APCA-negative IPF patients; and 3) to characterize the expression of the H+/K+-ATPase proton pump in the IPF lung.

2. Materials and methods

2.1. Selection of patients

The criteria for inclusion in the study were 1) a diagnosis of IPF and 2) a positive APCA search. Among 310 patients with IPF diagnosed in our center between April 2007 and December 2014, 138 were tested for APCA detection during the diagnostic autoimmune assessment. IPF diagnosis was given in agreement with ATS/ERS/JRS/ALAT guidelines [32] after a careful multidisciplinary discussion. For each APCA+ patient, we identified from our database one control patient, who was the next consecutive patient diagnosed with IPF and a negative search for APCA (APCA-patients). All patients gave their informed consent and the study was approved as an observational study by the Institutional Review Board of the French learned society for respiratory medicine - Société de Pneumologie de Langue Française (CEPRO 2012–016).

2.2. Data collection

One physician (GB) used a standard form to retrospectively collect the data from electronic medical files. These included epidemiological and clinical characteristics, tobacco smoke history, blood tests and autoantibodies detection results, and lung function tests at diagnosis and during follow-up. When patients were lost to follow-up, survival information was obtained through the interrogation of municipalities of birth, as permitted under French law.

2.3. APCA antibodies detection

The semi-quantitative analysis of serum APCA was done by indirect immunofluorescence on mouse stomach with a FITC-*anti*-human serum anti-immunoglobulin (G,A,M) (BIO-RAD, Marnes la Coquette, France). A positive result was defined by an APCA titer 1:80 or higher [33,34].

2.4. Radiographic and histopathological data analysis

High-resolution computed tomography (HRCT) scans were reviewed and scored in a standardized manner by a thoracic radiologist