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Prevalence and clinical significance of circulating autoantibodies in idiopathic pulmonary fibrosis

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KEYWORDS
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Summary
Background: The clinical significance of circulating autoantibodies in idiopathic pulmonary fibrosis is unclear. The objective of this study was to determine the frequency and clinical significance of circulating autoantibodies in idiopathic pulmonary fibrosis.
Methods: We measured an extensive panel of autoantibodies (including rheumatoid factor, anti-cyclic citrullinated peptide, and anti-nuclear antibodies by immunofluorescence) associated with connective tissue disease or vasculitis in a cohort of well-characterized patients with idiopathic pulmonary fibrosis ($n = 67$). The prevalence of circulating autoantibodies was compared between idiopathic pulmonary fibrosis patients and healthy controls ($n = 52$). We compared the clinical characteristics of patients with and without circulating autoantibodies, and analyzed the relationship between autoantibody positivity and transplant-free survival time.

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Results: Positive autoantibodies were found in 22% of patients with IPF and 21% of healthy controls. There were no differences in the types of autoantibodies found between patients with idiopathic pulmonary fibrosis and healthy controls. Among patients with idiopathic pulmonary fibrosis, there were no significant differences in clinical characteristics between those with and without circulating autoantibodies. The presence of circulating autoantibodies was associated with longer transplant-free survival time on adjusted analysis, however the significance varied depending on which statistical model was used (HR 0.22—0.47, *p* value 0.02—0.17).
Conclusions: The frequency of circulating autoantibodies in patients with idiopathic pulmonary fibrosis is no different compared to healthy controls, but may be associated with longer survival.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease of unknown etiology characterized by usual interstitial pneumonia (UIP) pattern on histopathology or radiology.[1] Central to the diagnosis of IPF is the exclusion of a defined connective tissue disorder (CTD), as a UIP histopathologic and radiologic pattern can be seen in patients with CTD, in particular among those with rheumatoid arthritis and scleroderma.[2—6]

Published guidelines suggest that all patients with suspected IPF be screened with rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), and anti-nuclear antibody (ANA) testing, even in the absence of CTD symptoms. Further, it is recommended that those patients with positive screening results be carefully evaluated for an occult CTD, often in consultation with a rheumatologist.[1,7] Importantly, circulating autoantibodies have been described in patients with IPF who have no evidence of a defined CTD.[2,8—10] However, the clinical relevance of these circulating autoantibodies remains unknown.

In this study, we investigated the frequency and clinical significance of commonly measured circulating autoantibodies in a well-characterized cohort of patients with IPF. We sought to determine if the frequency and type of circulating autoantibodies in patients with IPF differed from two control populations, healthy, age-similar controls and patients with undifferentiated connective tissue disease (UCTD). In addition, we examined whether patients with IPF and circulating autoantibodies comprised a distinct clinical phenotype and whether the presence of circulating autoantibodies in IPF influenced survival.

Materials and methods

Study population

Patients with IPF seen between October 2005 and May 2010 were identified from an ongoing cohort study of interstitial lung disease (ILD) at the University of California San Francisco (UCSF). Signs and symptoms of CTD were systematically and prospectively collected on all patients. This Institutional Review Board-approved cohort included informed consent for the use of clinical data and banked serum for future studies. Patients were included in the current study if they had a diagnosis of IPF based on the previous guidelines and had banked serum available.[11]

The primary control population was healthy volunteers, ages 50—80 years old. We also identified all patients in the UCSF database who had banked serum available and a diagnosis of undifferentiated connective tissue disease-associated (UCTD) ILD. Patients were given a multidisciplinary diagnosis of UCTD-ILD if they have at least one clinical manifestation suggestive of a CTD (e.g. Raynaud's, arthralgias, dry eyes and mouth), at least one positive serology, and absence of sufficient American College of Rheumatology criteria for a defined CTD.[12]

Radiological evaluation

Available chest high-resolution computed tomography (HRCT) scans for patients with IPF were re-evaluated by a thoracic radiologist blinded to the clinical course and autoantibody status of all patients. UIP pattern (yes or no) was identified based on current criteria.[1]

Autoantibody profile

An extensive autoantibody evaluation was performed on banked serum from all patients. The laboratory was blinded to the diagnosis and other clinical features of all patients. ANA by immunofluorescence assay (IFA) and RF by nephelometry were performed by the UCSF Clinical Laboratory according to standard protocols. Additional autoantibody testing was performed using the BioPlex™ 2200 System (Bio-Rad Laboratories, Hercules, CA). This system is an FDA-cleared fully-automated random-access analyzer, which employs multiplexed fluoromagnetic bead technology to simultaneously perform measurements of multiple autoantibodies in a single sample.[13] The following circulating autoantibodies were tested using the BioPlex system: anti-cyclic citrullinated peptides (CCP), Smith (Sm), ribonucleoprotein (RNP), SmRNP, Scl-70, Jo-1, anti-Ro (SS-A), anti-La (SS-B), double stranded deoxyribonucleic acid (dsDNA), chromatin, ribosomal P, centromere B, proteinase 3 (PR3), myeloperoxidase (MPO), and glomerular basement membrane (GBM).