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Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA

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Abstract

The purpose of this study was to identify rheumatoid arthritis (RA)-related autoantibodies in subjects with interstitial lung disease (ILD) and no articular findings of RA, supporting the hypothesis that RA-related autoimmunity may be generated in non-articular sites, such as the lung. This was a retrospective chart review utilizing clinic databases of patients with ILD to identify cases with lung disease, RA-related autoantibody positivity, and no clinical evidence of articular RA. Four patients with ILD, RF, and anti-CCP positivity and no articular findings of RA were

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identified. All four patients were male with a mean age at time of diagnosis of ILD of 70 years old. All had a history of smoking. Three patients died within 2 years of diagnosis of ILD and never developed articular symptoms consistent with RA; the final case met full criteria for articular RA several months after stopping immunosuppressive treatment for ILD. RF and anti-CCP can be present in smokers with ILD without clinical evidence of articular RA and in one case symptomatic ILD and autoantibody positivity preceded the development of articular RA. These findings suggest that RA-specific autoimmunity may be generated due to immunologic interactions in the lung and may be related to environmental factors such as smoking.

Keywords

Anti-cyclic citrullinated peptide (anti-CCP) antibodies; Interstitial lung disease; Rheumatoid arthritis; Rheumatoid arthritis pathogenesis; Rheumatoid factor (RF)

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by articular and extra-articular involvement, as well as the presence of autoantibodies including rheumatoid factor (RF) and highly RA-specific anti-cyclic citrullinated peptide (anti-CCP) antibodies [1].

RF and anti-CCP antibodies have been shown to be present prior to the appearance of clinical symptoms of arthritis and the combination of RF and anti-CCP positivity is highly specific for the disease [1, 2]. The presence of autoantibodies prior to articular manifestations of RA suggests that the initial immune dysregulation in RA occurs years before symptomatic disease onset, although the site where this initial immune dysregulation occurs is unknown. However, several factors including the association of inhaled environmental agents such as tobacco smoke and silica dust with the development of RA and the high prevalence of lung disease in early RA suggest that the lung may be the site of initial RA-related immune dysregulation [3–5]. The purpose of this study was to identify individuals with symptomatic lung disease and RA-related autoantibodies but no clinical evidence of articular RA, supporting the hypothesis that RA-specific autoimmunity may be generated in the lung in the absence of articular disease.

Materials and methods

Study design

This was a retrospective chart review to identify patients with symptomatic lung disease, RA-related autoantibody positivity, and no clinical evidence of articular RA.

Study population

Patients were identified using clinic databases of from National Jewish Health (NJH) and clinics affiliated with the University of Colorado Denver School of Medicine between January 2003 and December of 2007 with a diagnosis of ILD based on clinical, radiographic, and/or histologic evidence. Initial inclusion criteria for this study included: (1)

diagnosis of ILD and (2) RF positivity, as RF was performed routinely as part of an ILD evaluation in these subjects, followed by anti-CCP testing if RF was positive. After these inclusion criteria were applied, patients were excluded if they had an established diagnosis of RA simultaneously or prior to development of pulmonary symptoms. Patients were additionally excluded if chart review identified any of the following: (1) positivity for any articular, nodule, or radiographic criteria for RA, based on the 1987 Revised ACR Criteria for RA; (2) diagnosis or symptoms suggestive of lupus, scleroderma, Sjogren's syndrome, or a known etiology for lung disease (such as sarcoidosis); and (3) a diagnosis of mycobacterial infection, as active tuberculosis has been associated with RF and/or anti-CCP positivity [6, 7]. Additional information obtained included the specific type of ILD, age at diagnosis of ILD, sex, smoking status, silica dust exposure, pulmonary radiographic findings, lung pathology, and lung disease treatment and outcome.

Autoantibody testing

RF was tested by two methodologies including latex agglutination and nephelometry, with cutoff levels for positivity of titers ≥1:40 (latex agglutination) or levels >15 IU/mL (nephelometry). Anti-CCP testing was performed by ELISA assay using either the INOVA Diagnostics, QUANTA Lite™ CCP2 kit (San Diego, CA, USA), with a level ≥20 U/mL considered positive, or the Axis-Shield DIASTAT™ kit (Dundee, Scotland, United Kingdom), with a level >5 U/mL considered positive.

Institutional/ethical approval

Approval for the study was obtained from the institutional review boards of the participating sites.

Results

We identified 14 subjects with ILD, RF positivity, follow-up anti-CCP testing, and no evidence of articular RA at the time of initial diagnosis of ILD and antibody positivity. These subjects all had RF testing done as part of a routine evaluation for ILD and testing was not driven by the presence of joint disease. No subjects had anti-CCP testing done in absence of RF testing and none were positive for anti-CCP and negative for RF.

Of these 14 cases with ILD, ten were RF positive only and four cases were positive for RF and anti-CCP. All four of these RF and anti-CCP positive cases were male, with a mean age at diagnosis of ILD of 70 years old (range 67– 75). These four cases were smokers, although the fourth case had quit approximately 20 years prior to onset of lung symptoms; none had significant dust exposure. Cases 1–3 had their ILD classified as idiopathic pulmonary fibrosis (IPF) based on clinical history and chest imaging, and no lung biopsy was performed. The fourth case had a diagnosis of non-specific interstitial pneumonitis (NSIP) made from open lung biopsy. The three cases with IPF died of their lung disease within 2 years of diagnosis despite therapy with corticosteroids and/or other immunosuppressive agents, and none were noted to develop articular symptoms. The fourth case underwent treatment for ILD with a 12-month course of daily oral cyclophosphamide and tapering prednisone, and had improvement in lung findings and symptoms. Approximately 6 months

after cessation of therapy, he developed definite synovitis classifiable as RA by ACR criteria and was treated with a combination of methotrexate and etanercept for his articular symptoms and he had no worsening of lung disease over 3 years of follow-up. For cases 1–3, RF levels at the time of ILD diagnosis were 1:1,280 and 1:320 (latex agglutination) and 120 IU/mL (nephelometry), respectively; for case 4, the initial RF level was 390 IU/mL (nephelometry). In cases 1–3, the anti-CCP levels were 28, 35, and 71 U/mL (INOVA). In case 4, the anti-CCP level was >200 U/mL (Axis-Shield).

Discussion

A proposed model for the development of RA is that interactions between genetic and environmental factors lead to the initial development of RA-related immune dysregulation. Once tolerance to self-antigens has been broken, there is then a period of asymptomatic autoimmunity, evidenced by circulating autoantibodies, followed by the eventual development of clinically apparent RA. Supporting this model are the known genetic and environmental factors associated with increased risk for RA and known pre-arthritis positivity for RF and anti-CCP in subjects who eventually develop articular RA [2, 5, 8]. However, it is unknown where the initial genetic and environmental interactions leading to RA may occur. Several factors lead to the hypothesis that the lung is the site of initial RA-related immune dysregulation including: (1) the association of HLA alleles containing the shared epitope, smoking, and the development of anti-CCP positive RA [9]; (2) the known high prevalence of lung disease even in early RA [3, 4]; and (3) the association of RF and anti-CCP positivity with extra-articular manifestations of RA including lung disease [10]. In support of this hypothesis, we have identified four smokers with ILD and RF and anti-CCP positivity but no articular findings for RA, with one case developing articular RA after presenting with lung disease.

Symptomatic lung disease and RF positivity preceding the development of clinically apparent articular RA is not a new finding [11]. However, the lack of specificity of RF for RA makes it difficult to support mechanistic arguments for the initiation of RA-related immunity in the lung on the basis of RF positivity alone [12]. In contrast, the high specificity of anti-CCP antibodies for RA (>97%), especially with concomitant RF positivity, suggests that anti-CCP and RF positivity in patients with ILD and no clinically apparent articular RA is related to RA-specific immunologic dysregulation [1]. As such, while speculative, it is reasonable to hypothesize that in these four smokers with ILD and RA-specific antibodies interactions in the lung between genetic and environmental factors such as tobacco smoke, or other factors perhaps related to smoking such as infections, may have led to localized lung injury and immune responses and subsequent development of ILD and generation of RA-related autoantibodies. Additionally, supporting an assertion that RA-related autoimmunity may be generated in the lungs, a recent study has shown increased levels of citrullinated proteins in cells lavaged from the lungs of smokers, suggesting that smoking (or smoking-related factors such as infections) may lead to increased levels of citrullinated antigens in the lung, perhaps setting the stage for anti-citrullinated protein autoimmunity [13].

Study limitations

Due to the small numbers of cases identified, we were unable to associate the presence or levels of RA-related antibodies and specific types of ILD or prognosis, and there was no genetic information available to test hypotheses about genetic associations with smoking and RA-related autoantibodies. Also, these cases may have had subtle articular RA at the time of their ILD diagnosis that was missed on evaluation, or suppressed by treatments for their lung disease. Finally, it is possible that RA-related autoantibodies in the three cases that did not develop articular RA are non-specific responses to chronic immune dysregulation in the lung.

Conclusions

RA-specific autoantibodies can be identified in smokers with ILD and no findings of articular RA. These findings support the hypothesis that RA-specific autoimmunity may be generated in the lung in the absence of articular disease and may be related to environmental factors such as smoking. Further studies are needed to explore the relationship between lung disease and the generation of RA-related autoimmunity. In particular, bronchoscopy with lavage or lung biopsy in subjects with lung disease and RA-related antibodies but no articular findings of RA or similar studies in subjects with early articular RA are needed to explore further the role of citrullination and inflammation in the lung in relationship to RA-related autoantibody generation.

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