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BRIEF REPORT

Airways Abnormalities and Rheumatoid Arthritis–Related Autoantibodies in Subjects Without Arthritis: Early Injury or Initiating Site of Autoimmunity?

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Objective. **To evaluate the presence of pulmonary abnormalities in rheumatoid arthritis (RA)–related autoantibody–positive subjects without inflammatory arthritis.**

Methods. **Forty-two subjects who did not have inflammatory arthritis but were positive for anti–cyclic citrullinated peptide antibodies and/or ≥2 rheumatoid factor isotypes (a profile that is 96% specific for RA), 15 autoantibody-negative controls, and 12 patients with established seropositive early RA (<1-year duration) underwent spirometry and high-resolution computed tomography (HRCT) lung imaging.**

Results. **The median age of autoantibody-positive subjects was 54 years, 52% were female, and 38% were ever-smokers; these characteristics were not significantly different from those of autoantibody-negative control subjects. No autoantibody-positive subject had inflammatory arthritis based on joint examination. HRCT revealed that 76% of autoantibody-positive subjects had airways abnormalities including bronchial wall thickening, bronchiectasis, centrilobular opacities, and air trapping, compared with 33% of autoantibody-negative controls ($P = 0.005$). The prevalence and type of lung abnormalities among autoantibody-positive subjects were similar to those among patients with early RA. In 2 autoantibody-positive subjects with airways disease, inflammatory arthritis classifiable as articular RA developed ~13 months after the lung evaluation.**

Conclusion. **Airways abnormalities that are consistent with inflammation are common in autoantibody-positive subjects without inflammatory arthritis and are similar to airways abnormalities seen in patients with early RA. These findings suggest that the lung may be an early site of autoimmune-related injury and potentially a site of generation of RA-related autoimmunity. Further studies are needed to define the mechanistic role of lung inflammation in the development of RA.**

Multiple studies have identified a "preclinical" phase of seropositive rheumatoid arthritis (RA) during which the levels of circulating RA-related autoantibodies are elevated prior to the onset of symptomatic inflammatory arthritis (1). Lung disease has also been identified in early symptomatic RA as well as prior to the onset of articular symptoms of RA (2–4), perhaps because the lung is an early target of systemic RA-related autoimmunity, or because the lung is potentially a site for the generation of RA-related autoimmunity due to initial autoimmune responses in the lung. This latter possibility is a consideration because elevations of circulating autoantibody levels prior to the onset of clinically apparent RA suggest that RA may be generated at an extraarticular site (5). To examine the relationship between RA-related autoimmunity and inflammation-related lung abnormalities in the absence of clinically apparent inflammatory arthritis, we evaluated the lungs of subjects without inflammatory arthritis who were positive for RA-related autoantibodies and compared

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Table 1. Characteristics of the study participants*

Variable	Autoantibody-positive cases (n = 42)	Autoantibody-negative controls (n = 15)	Early RA patients (n = 12)
Age, median (IQR) years	54 (43–62)	53 (41–67)	53 (40–59)
Female sex	22 (52)	9 (60)	8 (67)
Non-Hispanic white race	37 (88)	13 (87)	10 (83)
≥1 shared epitope allele†	22 (52)	8 (53)	6 (86)‡
Ever smoked	16 (38)	3 (20)	5 (42)
Pack-years, median (range)	7 (3–19)	1 (1–25)	20 (16–41)
Chronic lung disease§	8 (19)	1 (7)	6 (50)
Diagnosis by health care provider			
Pneumonia	18 (43)	2 (13)	5 (42)
Acute bronchitis	18 (43)	6 (40)	1 (8)¶
Joint symptoms#	21 (50)	8 (53)	Not assessed
≥1 tender joint (68-joint count)	8 (19)	2 (13)	Not assessed
Inflammatory arthritis	0 (0)	0 (0)	Not assessed
Autoantibody prevalence		Not applicable	
Anti–CCP-2 or anti–CCP-3.1	30 (71)		12 (100)
Any anti-CCP and any RF isotype	16 (38)		11 (92)
≥2 RF isotypes	20 (48)		12 (100)
IgM-RF	18 (43)		11 (92)
IgG-RF	24 (57)		9 (75)
IgA-RF	10 (24)		9 (75)

* Except where indicated otherwise, values are the number (%). All of the patients with early rheumatoid arthritis (RA) fulfilled the 1987 American College of Rheumatology criteria for the classification of RA and were rheumatoid factor (RF) and anti–cyclic citrullinated peptide 3.1 (anti–CCP-3.1) positive. In this group, the median onset of arthritis symptoms prior to the lung study was 9 months, and the median time since diagnosis was 5 months. Ten of these patients were receiving prednisone, 8 were receiving methotrexate, 4 were receiving hydroxychloroquine, and 2 were receiving nonsteroidal antiinflammatory agents only. IQR = interquartile range.

† The methodology used for determining shared epitope status is provided in ref. 6.

‡ Shared epitope allele status was determined in 7 of 12 patients.

§ Includes self-reported history of asthma, chronic bronchitis, or emphysema as diagnosed by a health care provider prior to the lung study (or the diagnosis of RA) and ascertained after study enrollment. Among the patients with early RA, 3 had a prior diagnosis of asthma and 3 had a prior diagnosis of emphysema.

¶ $P = 0.039$ versus autoantibody-positive cases.

The presence of joint symptoms was based on the results of a standardized questionnaire performed at the time of the lung study, ascertaining subject-reported current or prior pain, stiffness, or swelling in any of 68 joints.

the findings with those in autoantibody-negative subjects and seropositive patients with early RA.

PATIENTS AND METHODS

Study subjects. This study utilized the Studies of the Etiology of Rheumatoid Arthritis (SERA) project, a prospective cohort established to investigate the natural history of RA development. The SERA project is described elsewhere (6). Briefly, probands with RA are identified, and their first-degree relatives without RA are recruited for prospective study. Additionally, RA-related autoantibody–positive subjects without inflammatory arthritis are recruited into SERA through community health fair screening. Once enrolled, SERA subjects undergo a standardized joint assessment (symptom evaluation and a 68-joint examination) and testing for the following antibodies: RF isotypes IgM, IgA, and IgG (Quanta Lite enzyme-linked immunosorbent assay [ELISA]; Inova Diagnostics), anti–cyclic citrullinated peptide 2 (anti–CCP-2) (Diastat kit; Axis-Shield), and anti–CCP-3.1 (IgA/IgG ELISA; Inova Diagnostics). A cut-off for positivity for each RF isotype was established using a level that was positive in <5% of 491 blood donor controls. The cutoffs for anti–CCP-2 and anti–CCP-3.1 positivity were >5 units and ≥20 units, respectively.

For this lung study, autoantibody-positive subjects were recruited from 2 SERA study sites (Denver and Los Angeles). These subjects did not have inflammatory arthritis and were positive for anti–CCP-2 or anti–CCP-3.1 and/or ≥2 RF isotypes; this profile was 96% specific for established RA when tested in 200 SERA probands with RA and 200 blood donor controls, and is therefore likely to reflect true RA-related autoimmunity. Autoantibody-negative subjects were recruited as controls from the Denver SERA site and frequency-matched to the autoantibody-positive subjects for age, sex, race, and smoking history. To limit the inclusion of individuals exposed to radiation, the number of controls studied with high-resolution computed tomography (HRCT) was based on attaining 80% power to detect a ≥35% difference in the prevalence of lung abnormalities between autoantibody-positive and autoantibody-negative subjects (α =

Table 2. Results of the pulmonary evaluations*

Variable	Autoantibody-positive cases (n = 42)	Autoantibody-negative controls (n = 15)	P†	Early RA patients (n = 12)	P‡
Spirometry					
FEV_1/FVC <70% predicted	5 (12)	0 (0)	0.311	4 (33)	0.098
$FEF_{25–75\%}$ <70% predicted	13 (31)	2 (13)	0.187	6 (50)	0.307
HRCT					
Any airways disease (all subjects)§	32 (76)	5 (33)	0.005	11 (92)	0.421
Bronchial wall thickening	21 (50)	2 (13)	0.015	10 (83)	0.041
Bronchiectasis	6 (14)	1 (7)	0.662	2 (17)	1.000
Centrilobular opacities	10 (24)	1 (7)	0.256	6 (50)	0.148
Air trapping	29 (69)	1 (7)	0.000	10 (83)	0.474
Airways disease, never smokers	19/26 (73)	4/12 (33)	0.033	6/7 (86)	0.652
Airways disease, no history of chronic lung disease¶	22/31 (71)	5/14 (36)	0.047	5/6 (83)	1.000
Airways disease, Denver participants only	22/31 (71)	5/15 (33)	0.025	11/12 (92)	0.237
Airways disease, no joint tenderness	26/34 (76)	5/13 (38)	0.020	–	–
Parenchymal disease#	4 (10)	1 (7)	1.000	5 (42)	0.019
Nodules	4 (10)	0 (0)	0.564	3 (25)	0.175
Alveolar infiltrates (ground-glass opacities)	0 (0)	1 (7)	0.263	2 (17)	0.046
Lung fibrosis	0 (0)	0 (0)	1.000	0 (0)	1.000
Spirometry in subjects with airways disease identified by HRCT					
FEV_1/FVC <70% predicted	4/32 (13)	0/5 (0)	–	4/11 (36)	–
$FEF_{25–75\%}$ <70% predicted	12/32 (38)	0/5 (0)	–	6/11 (55)	–

* Values are the number/number assessed (%). For spirometry, predictive values were calculated according to the Third National Health and Nutrition Examination Survey. Obstructive disease is defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <70% of predicted; measurement of the reduced forced expiratory flow, midexpiratory phase ($FEF_{25–75\%}$) may be more sensitive for airways disease and obstruction compared with FEV_1/FVC measurements.

† Autoantibody-positive cases versus autoantibody-negative controls.

‡ Autoantibody-positive cases versus patients with early rheumatoid arthritis (RA).

§ Includes 1 or more of the following: bronchial wall thickening, bronchiectasis, air trapping, or centrilobular nodularity (the latter indicates small airways disease/inflammation). Of note, air trapping occurs when small airways disease results in obstruction of airways outflow and subsequent overdistension of the alveoli on expiration, which is seen on high-resolution computed tomography (HRCT) imaging as increased air density.

¶ Chronic lung disease as assessed by questionnaire at the time of the lung study visit and includes 1 or more of the following, diagnosed by a health care provider: emphysema, asthma, or chronic bronchitis.

Includes 1 or more of the following: ground-glass opacities/alveolar infiltrates, parenchymal nodules, and lung fibrosis.

0.05). Patients with early RA were recruited from the University of Colorado clinics. These patients fulfilled the 1987 American College of Rheumatology (ACR) criteria for the classification of RA (7), were positive for RF and anti–CCP-3.1, had received a diagnosis of RA <1 year prior to enrollment, and had no clinical history of RA-related lung disease.

Lung study protocol. All subjects completed a standardized questionnaire regarding possible prior lung disease and underwent spirometry and HRCT lung imaging. SERA subjects also underwent joint symptom assessment and a 68-joint examination by a trained examiner. HRCT was performed using multidetector scanners, with helical supine inspiratory acquisition contiguous (5-mm) reconstructed images as well as 1-mm images reconstructed every 20 mm with high-resolution algorithms. Supine expiratory 1-mm axial images were obtained every 40 mm. Finally, prone inspiratory images were obtained with 1-mm collimation every 40 mm. HRCT images were reviewed by 2 chest radiologists who were blinded to each subject with regard to each subject's autoantibody and disease status. Abnormalities were defined and scored using standard criteria (8), and the subjects were classified as having the presence or absence of 1) airways disease (1 or more of the following: bronchial wall thickening, bronchiectasis, centrilobular opacities [representing bronchiolar disease], and abnormal air trapping) or 2) parenchymal disease (1 or more of the following: ground-glass opacities/alveolar infiltrates, nodules, and interstitial lung disease/fibrosis). After their initial independent interpretations, the radiologists reached a consensus on discrepant findings while still blinded to autoantibody/disease status; these final interpretations were used for the analyses.

Statistical analysis. Nonparametric testing was used to compare findings between groups, and kappa statistics were used to determine interobserver agreement for HRCT interpretations.

Ethics considerations. Institutional review boards at the participating institutions approved all study protocols.

RESULTS

Characteristics of the study participants. Fifty-six autoantibody-positive SERA subjects were eligible; 42 (75%) of these subjects agreed to participate. Eighteen autoantibody-negative subjects were contacted, and 15 (83%) were enrolled in the study. Twelve (80%) of 15 patients with early RA who were eligible for inclusion agreed to participate. The primary reasons that subjects declined to participate were concerns regarding

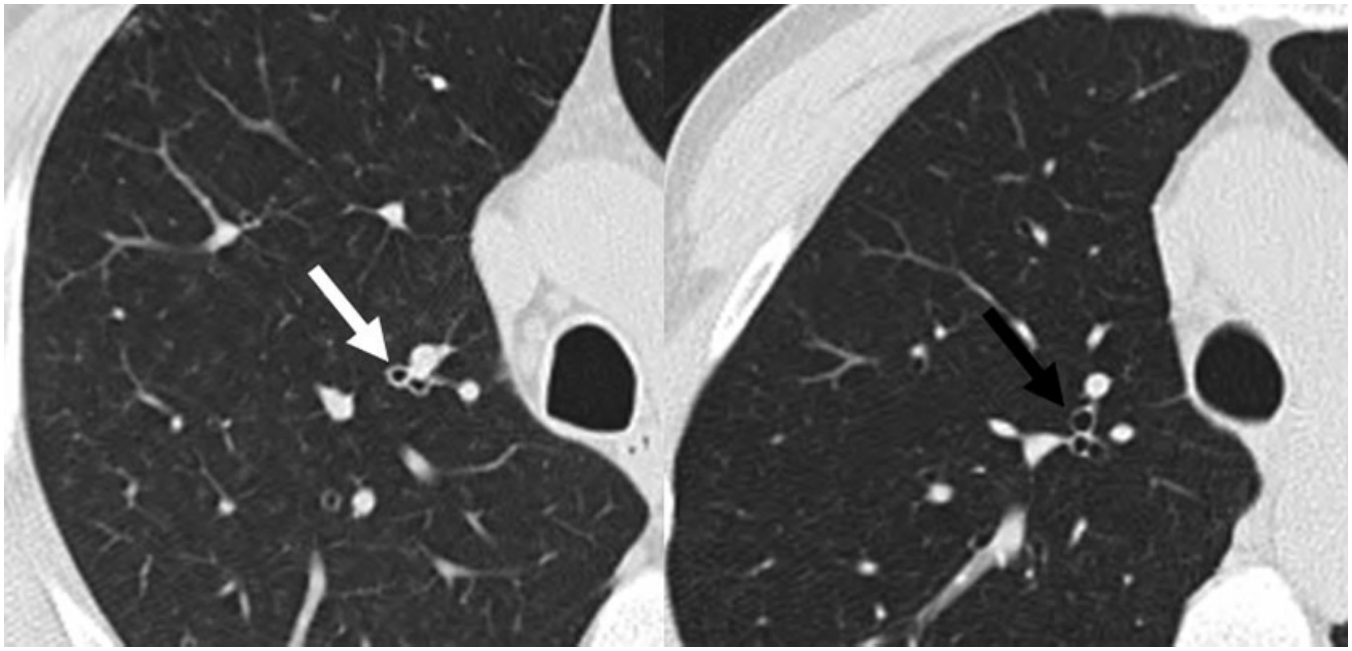

Figure 1. High-resolution computed tomographic images demonstrating bronchial wall thickening. Images were obtained from similar lung anatomic levels in a subject positive for anti–cyclic citrullinated peptide antibodies and rheumatoid factor isotypes IgM and IgA) (left), and from an autoantibody-negative control (right), who were matched for age, sex, and smoking status. The image on the left shows bronchial wall thickening (**white arrow**). In contrast, the image on the right shows a normal-appearing thin-walled bronchus (**black arrow**).

imaging-associated radiation and the possibility of discovering non–RA-related findings (e.g., lung cancer); only 1 autoantibody-positive subject participated in the study to learn more about an existing lung problem.

The characteristics of the study participants are shown in Table 1. There were no significant differences between autoantibody-positive subjects and autoantibody-negative control subjects in terms of age, sex, race, smoking status, or self-reported history of health care provider–diagnosed chronic lung disease, bronchitis, or pneumonia. When compared with the autoantibody-positive subjects, the patients with early RA had a higher rate of chronic lung disease diagnosed prior to the onset of RA, although the difference was not significant.

Results of joint examinations. At the time of lung evaluation, 50% of autoantibody-positive subjects and 53% of autoantibody-negative control subjects self-reported current or prior pain, stiffness, or swelling in at least 1 joint; in all subjects, these symptoms were attributed to 1 of the following (as diagnosed by a health care provider): prior injury, osteoarthritis, fibromyalgia, or hemochromatosis. All but 2 of the SERA subjects underwent simultaneous joint and lung evaluation, and none had evidence of synovitis. Neither of the 2 subjects (both of whom were autoantibody positive) who were not examined at the time of the lung study had reported joint symptoms during telephone interviews using the standardized SERA joint questionnaire (6), and 1 had undergone a joint examination at a research visit 6 months previously, with normal results.

HRCT and spirometry. The results of HRCT and spirometry are shown in Table 2. HRCT demonstrated airways abnormalities in significantly more autoantibody-positive subjects than autoantibody-negative control subjects (76% versus 33%; $P = 0.005$); representative images showing airways thickening are presented in Figure 1. Significant differences in the prevalence of airways abnormalities between autoantibody-positive and autoantibody-negative subjects persisted even after subgrouping by smoking status, site of study (Denver versus Los Angeles), history of chronic lung disease, and presence of joint tenderness. Airways abnormalities were present in 11 (92%) of 12 patients with early arthritis; this prevalence was not significantly different from that in autoantibody-positive subjects ($P = 0.421$). Pulmonary parenchymal abnormalities were most prevalent in the patients with early RA. Among autoantibody-positive subjects, there were no significant associations between subject-related characteristics as listed in Table 1 (including specific autoantibodies) and HRCT findings (data not shown), although the majority of

subjects with abnormal results of spirometry also had HRCT evidence of airways disease (Table 2). After initial individual reviews, the 2 chest radiologists agreed on 59 (85.5%) of 69 interpretations, with a kappa value of 0.68.

Followup after the lung study. In 2 autoantibody-positive subjects with airways abnormalities on HRCT, joint symptoms consistent with inflammatory arthritis developed ~13 months after the lung study. In both of these subjects, RF-positive, anti-CCP–positive RA (according to the 1987 ACR criteria) was subsequently diagnosed.

DISCUSSION

Here, we identified airways abnormalities in a high proportion of subjects who had circulating RA-related autoantibodies but did not have inflammatory arthritis. We did not obtain lung tissue from these autoantibody-positive individuals, although historically, biopsy specimens obtained from patients with established RA and similar HRCT findings have shown significant airways inflammation (2). Therefore, we believe that the airways abnormalities seen in this study are due to inflammatory changes. Of note, the results of spirometry were not significantly different between autoantibody-positive and autoantibody-negative subjects, although this was not unexpected, because HRCT is a more sensitive measure for airways disease (9).

However, although we believe that the airways abnormalities seen in these subjects are due to inflammation, the relationship between this inflammation and circulating RA-related autoantibodies is unknown. It may be that these abnormalities are unrelated to autoantibody status, or that circulating RA-related autoantibodies generated outside the lung have targeted the airways. Alternatively, in the context of the hypothesis that RA-related autoimmunity is initiated at an extra-articular site (5), these findings of airways inflammation may indicate that RA-related autoimmunity is initially generated in the lungs. This possibility is supported by the association of inhaled factors (including smoke and dust) with an increased risk of RA (10) as well as by the known immunobiology of the lung, where inflammation and adaptive immune responses can develop in response to inhaled factors. In particular, Rangel-Moreno et al identified collections of organized lymphatic tissue termed "inducible bronchus associated lymphatic tissue" (iBALT) in the lungs of patients with established RA and lung disease (11). Importantly, those investigators also demonstrated that plasma cells within iBALT from patients with RA and lung disease were reactive to the Fc portions of IgG and to citrullinated fibrinogen, suggesting that RF and anti–citrullinated protein antibodies (ACPAs) were being generated in the lungs, although the initial trigger for the generation of iBALT and these autoantibodies was not identified (11). Furthermore, the observed RF production in the lungs of patients with cystic fibrosis, which likely is due to chronic infection–related inflammation, supports the notion that the lung is a potential site of generation of RA-related autoimmunity (12).

Thus, in a model in which RA-related autoimmunity is initiated in the lung, an environmental factor such as smoking or infection may trigger airways inflammation and local generation of autoantigens, similar to what was demonstrated by Makrygiannakis et al, who observed elevated levels of citrullinated proteins in lung samples from smokers (13). Subsequently, autoreactive cells and autoantibodies such as ACPAs may develop within the lung (10); local inflammation in the lung may also result in RF production (4), which is a possible explanation for the high concordance of elevated levels of ACPA and RF in patients with established RA. Once autoimmune factors develop, they may transmit from the lung to the circulation via regional lymphatics or translocation, and circulating autoimmunity may later trigger the inflammatory arthritis that is characteristic of RA.

Based on this hypothetical model of RA development, the airways abnormalities seen in this study suggest that the lungs of autoantibody-positive subjects may harbor biologic factors that initially generate RA-related antibodies. However, there are important caveats to these findings and resultant speculations regarding the initiation of RA in the lungs. First, the concept that RA is generated outside the joints is speculative, although data identifying RA-related elevations in autoantibody levels prior to the onset of clinically apparent inflammatory arthritis (1,5) support the possibility that RA may indeed be generated outside the joints. Second, it is uncertain that the autoantibody-positive subjects in this study truly had preclinical RA, because classifiable RA developed in only 2; however, the presence of RA-related autoimmunity regardless of progression to future symptomatic inflammatory arthritis is still relevant to understanding the pathogenesis of RA. Third, if extraarticular development of RA does occur, the lung may not be the only site, because data suggest that other sites such as the periodontal region may be involved in RA pathogenesis (14). Fourth, it is possible that the elevated autoantibody levels observed in the current

study are nonspecific factors associated with chronic lung inflammation or infection (4,15). Fifth, it is possible that the autoantibody-positive subjects and patients with early RA were inadvertently enriched with factors that may affect their airways, including smoking and/or preexisting lung disease, or that the autoantibody-negative control subjects had healthier lungs than is typical. The subjects were not selected based on lung disease, however, and the prevalence of lung disease in the patients with early RA and the autoantibody-negative subjects is not atypical based on published findings (2,16). Finally, the autoantibody-positive subjects may have subtle joint inflammation that is undetectable by physical examination, suggesting that their observed lung abnormalities are not occurring in the absence of synovitis. However, in a preliminary study, we observed no evidence of synovitis on contrasted magnetic resonance imaging of the dominant-side metacarpophalangeal joints, wrists, and metatarsophalangeal joints of a subset of 15 of the autoantibody-positive subjects with lung abnormalities (data not shown).

Airways abnormalities in RA-related autoantibody–positive individuals without apparent inflammatory arthritis suggest that the lung is an early target, or potentially a site of initial generation, of RA-related autoimmunity. These findings suggest the need for additional studies to evaluate the mechanisms by which the lungs may be involved in early RA development. Such studies may include serial assessments examining the progression of lung abnormalities and circulating autoimmunity in relation to the development of inflammatory arthritis, tissue sampling to define the biology of lung injury and inflammation in relation to potential generation of RA-related autoantibodies, and examination of genetic and environmental factors that may be associated with potential pulmonary generation of RA-related autoimmunity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Deane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Demoruelle, Simonian, Sachs, Pedraza, Harrington, Petersen, Derber, Norris, Holers, Deane.

Acquisition of data. Demoruelle, Weisman, Lynch, Sachs, Pedraza, Harrington, Kolfenbach, Striebich, Pham, Strickland, Petersen, Parish, Derber, Holers, Deane.

Analysis and interpretation of data. Demoruelle, Weisman, Simonian, Lynch, Sachs, Harrington, Kolfenbach, Strickland, Parish, Derber, Holers, Deane.

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