16 **LUNG ABNORMALITIES IN SUBJECTS WITH ELEVATIONS OF RHEUMATOID ARTHRITIS-RELATED AUTOANTIBODIES WITHOUT ARTHRITIS BY EXAMINATION AND IMAGING SUGGEST THE LUNG IS AN EARLY AND PERHAPS INITIATING SITE OF INFLAMMATION IN RHEUMATOID ARTHRITIS**

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Background/objectives Elevations of serum autoantibodies (Abs) prior to joint symptoms suggest that rheumatoid arthritis (RA) may be initiated outside of the joints. This site is unknown, although several factors suggest that it may be the lungs including the association of inhaled factors such as smoking with RA. Our purpose herein was to evaluate a hypothesis that the lung is a site of initiation of RA-related autoimmunity

by comparing lung findings in RA-related Ab+ subjects at risk for future RA but without current inflammatory arthritis (IA) to Ab- controls and patients with established early RA.

Materials/methods 45 Ab+ cases without IA on 68 joint exam were identified from the Studies of the aetiology of RA project, a prospective study of preclinical RA. These cases were positive for Abs >96% specific for future RA: anti cyclic citrullinated peptides (CCP2) (Axis-Shield) or CCP3.1 (INOVA, San Diego, CA, USA), and/or ≥ 2 rheumatoid factor (RF) isotypes (IgA, M, G) (INOVA) (N=9 CCP2+; N=25 CCP3.1+; N=11 RFs+ only). Additionally, 16 Ab-sera controls (frequency matched to Ab+ cases on age, sex and smoking) and 12 patients with early RF/aCCP2+ RA (<1 year) were selected. All subjects underwent high-resolution CT (HRCT) of the lungs, interpreted in a blinded fashion by two chest radiologists according to established criteria (Fleischner Society; Hansell, *et al* 2008). To evaluate for synovitis not detected on joint exam, a subset of Ab+ cases underwent contrasted MRI of the metacarpophalangeals, wrists and metatarsophalangeals, scored for synovitis by two joint radiologists using the outcome measures in rheumatoid arthritis clinical trials/rheumatoid arthritis MRI scoring system protocols.

Results 45 Ab+ cases were a mean age of 54, 56% female and 33% smokers (no significant differences from Ab-controls). 77% of Ab+ cases had airways disease on HRCT including bronchial wall thickening, bronchiectasis, centrilobular opacities and air trapping, compared to 31% of Ab-controls ($p<0.01$). Of the 30 Ab+ cases that were never smokers, 70% had airways disease compared to 3/12 (25%) of never smoking controls ($p=0.01$). No Ab+ case had evidence of IA on joint exam at time of lung evaluation, and additionally, 15 Ab+ cases with abnormal lungs that underwent joint MRI had no synovitis by imaging. One Ab+ subject with airways disease developed RA by 1987 criteria (Arnett, *et al* 1988) ~13 mos. after lung study. Finally, 9/12 (75%) of early RA subjects (mean age 50, 58% female, 42% smokers) studied in parallel had radiographically indistinguishable airways abnormalities when compared to the Ab+ cases ($p>0.5$).

Conclusions Airways abnormalities are present in a high proportion of RA-specific Ab+ cases without IA (examination or MRI), and these lung abnormalities are similar to those in patients diagnosed with early RA. This suggests that there is a continuum of lung injury during the development of RA, and that lungs are either a site of RA-related autoimmune-mediated injury during the presymptomatic phase of disease, or more likely a site of initiation of RA-related autoimmunity perhaps due to external factors beyond smoking that generate local inflammation, especially since the airways interact substantially with the environment. Prospective studies are ongoing to evaluate the generation of RA-specific in the lungs, and to follow the evolution of autoimmunity and IA in these subjects.