Lung consolidation and mediastinal lymphadenopathy in patients with early anti-citrullinated protein antibody-positive rheumatoid arthritis

Sirs,

Because pulmonary disorders influence a patient's choice of treatments, it is important for clinicians to determine factors related to pulmonary involvement in patients with rheumatoid arthritis (RA). However, few reports show associations between lung lesions and anti-citrullinated protein antibody (ACPA)-positive RA. We aimed to determine lung field characteristics of patients with early RA who were ACPA-positive.

We enrolled 74 patients with early RA, within half one year of disease onset, between 2014 and 2017 at our institution. We excluded three patients because they exhibited bacterial pneumonia or underwent a non-thin section chest computed tomography (CT). All patients underwent chest CT within a few months of their first visit to our department. CT findings were blindly reviewed by two experienced thoracic radiologists who achieved good consensus. CT abnormalities were defined and scored using standard criteria (1). We compared clinical profiles between patients with early RA who were ACPA-negative and ACPA-positive.

Results are summarised in Table I. The ACPA-positive group had a significantly higher frequency of RF positivity ($p<0.0001$). No significant between-group differences were observed for patient characteristics, medications, or disease activities at baseline. CT scans showed no significant between-group differences in airway lesions. The ACPA-positive group had more consolidation and mediastinal lymphadenopathy than the ACPA-negative group (both $p<0.05$). Multivariate analyses showed that high disease activity (simple disease activity index [SDAI] scores >26) (odds ratio [OR] 11.91, $p<0.005$) and ACPA-positivity (OR 14.95, $p<0.05$) predicted lung consolidation. Multivariate analyses also showed two independent factors that predicted mediastinal lymphadenopathy: smoking history (OR 5.46, $p<0.05$) and ACPA-positivity (OR 10.60, $p<0.05$). Our subgroup analysis showed that high disease activity (defined by SDAI scores >26) at RA onset was significantly related to the number of parenchymal abnormalities ($p<0.05$), especially lung consolidation ($p<0.005$) only in the ACPA-positive group. Most patients in the ACPA-negative group, either with or without high disease activity, did not exhibit lung consolidation.

A previous report showed that patients with early RA who were ACPA-positive exhibited significantly higher frequency of parenchymal lesions on CT, immunologically-active cells and citrullinated proteins in bronchial tissue (2, 3). In our study, patients with early RA who were ACPA-positive had higher instances of lung consolidation on CT, suggesting that this specific finding might relate to ACPA-positivity. This finding also reflects autoimmune responses, including ACPA production. Interestingly, our subgroup analysis showed that patients with early RA who were ACPA-positive had significantly more lung consolidation on CT, especially when they had high disease activity at RA onset. This suggests a correlation with autoimmune response severity (that induces ACPA production), between the lung and joint synovia. Mediastinal lymphadenopathy, where a regional lymph nodes composed of lung tissue develop abnormalities, occurred more frequently in patients with early RA who were ACPA-positive, compared to patients who were ACPA-negative. This finding also suggests that early autoimmune responses (that involve ACPA production) begin within the lung tissue. Our analysis also showed that patients with early RA and a smoking history had a significantly higher frequency of mediastinal lymphadenopathy. Smoking exposure has a large impact on patients with RA and ACPA-positivity, but not those who are ACPA-negative (4-6). Thus, a smoking history was associated with severe autoimmune responses inducing ACPA production in lung tissues, in patients with early RA.

Lung tissue may be the primary organ where autoimmune responses featuring ACPA production take place. Additionally, lung consolidation (detected via CT) may be associated with high disease activity in patients with early RA who are ACPA-positive.

Table I. Participant characteristics at baseline and chest CT findings in patients with early RA (univariate analysis).

Variables	ACPA-negative (n=26)	ACPA-positive (n=45)	*p*-value
Patient characteristics			
Age (years)	65.5 (54.5–77.5, n=26)	64.0 (56.0–73.0, n=45)	0.500
Disease duration (months)	2.5 (2.0–4.0, n=26)	2.0 (1.0–3.0, n=45)	0.150
Male gender	10/26 (38.5%)	17/45 (37.8%)	1.000
Smoking history	11/26 (42.3%)	16/45 (35.6%)	0.618
Medication			
Concomitant prednisolone (+)	3/26 (11.5%)	4/45 (8.9%)	0.701
Concomitant methotrexate (+)	2/26 (7.7%)	3/45 (6.7%)	1.000
Laboratory finding			
RF positivity	7/26 (26.9%)	42/45 (93.3%)	<0.001 x 10-1
Clinical disease activity			
SDAI	24.9 (13.8–32.8, n=24)	18.4 (9.8–26.8, n=42)	0.096
DAS28-CRP	4.3 (3.3–5.4, n=24)	4.0 (3.1–4.8, n=42)	0.113
DAS28-ESR	5.1 (4.3–6.0, n=24)	4.8 (4.0–5.5, n=42)	0.236
Airway abnormalities			
Bronchial wall thickening	8/26 (30.8%)	15/45 (33.3%)	1.000
Bronchiectasis	16/26 (61.5%)	28/45 (62.2%)	1.000
Centrilobular small nodules	19/26 (73.1%)	30/45 (66.7%)	0.607
Air trapping	12/26 (46.2%)	15/45 (33.3%)	0.318
The number of airway abnormalities	2.0 (1.0–3.0, n=26)	2.0 (1.0–3.0, n=45)	0.535
Parenchymal abnormalities			
Emphysema	6/26 (23.1%)	15/45 (33.3%)	0.427
Fibrosis	6/26 (23.1%)	21/45 (46.7%)	0.075
Ground glass opacity	10/26 (38.5%)	21/45 (46.7%)	0.621
Consolidation	1/26 (3.9%)	10/45 (22.2%)	0.046
Nodule	10/26 (38.5%)	17/45 (37.8%)	1.000
Intrapulmonary lymph node (ILN)	3/26 (11.5%)	13/45 (28.9%)	0.141
Nodule excluding ILN	7/26 (26.9%)	7/45 (15.6%)	0.354
The number of parenchymal abnormalities	1.0 (0.0–2.0, n=26)	2.0 (0.0–3.0, n=45)	0.141
Other findings			
Atelectasis	1/26 (3.9%)	1/45 (2.2%)	1.000
Lymphadenopathy	11/26 (42.3%)	20/45 (44.4%)	1.000
Axillary lymphadenopathy	11/26 (42.3%)	14/45 (31.1%)	0.440
Mediastinal lymphadenopathy	1/26 (3.9%)	11/45 (24.4%)	0.045

Data are reported as median (interquartile range, number) or number (percentage). Variables were compared using Fisher's exact test or Mann-Whitney U-test.

RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; SDAI: Simple Disease Activity Index; DAS28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Y. Endo[1], *MD*
T. Koga[1], *MD, PhD*
S. Tsutsui[2], *MD, PhD*
K. Ashizawa[3], *MD, PhD*
S. Kawashiri[1], *MD, PhD*
A. Kawakami[1], *MD, PhD*

[1]Department of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan;
[2]Department of Radiology, Japan Community Healthcare Organization (JCHO), Isahaya General Hospital, Isahaya, Japan;
[3]Department of Clinical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Letters to the Editors

Please address correspondence to:
Dr Tomohiro Koga,
Department of Immunology and
Rheumatology, Unit of Advanced
Preventive Medical Sciences,
Graduate School of Biomedical Sciences,
Nagasaki University,
1-7-1 Sakamoto,
Nagasaki 852-8501, Japan.
E-mail: tkoga@nagasaki-u.ac.jp

Competing interests: none declared.

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