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Autoantibody profiles and their association with blood eosinophils in asthma and COPD

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ACT, Asthma control test; ANA, Antinuclear antibodies; ANCA, Anti-neutrophil cytoplasmic autoantibodies; BMI, Body mass index; CAT, Chronic obstructive pulmonary disease assessment test; CCP, Cyclic citrullinated peptide; COPD, Chronic obstructive pulmonary disease; ECB, Eosinophil counts in blood; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity; IgE, Immunoglobulin-E; IQR, Interquartile range; MPO, Myeloperoxidase; PR3, Proteinase 3; RF, Rheumatoid factor; SD, Standard deviation

ABSTRACT

Background: Autoimmune involvement in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD) has been proposed, and autoantibodies are a hallmark of autoimmunity. This study aimed to compare the autoantibody profiles of asthma and COPD, and the relationship between autoantibodies and features of these diseases.

Methods: We recruited 110 asthma patients and 92 COPD patients for a prospective study. Six autoantibody types were evaluated: antinuclear antibody, anti-cytoplasmic antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibody, myeloperoxidase–anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) and proteinase 3-ANCA. Other clinical data were also recorded concurrently.

Results: An antinuclear antibody titre of $\geq 1:160$ presented only in asthma but not in COPD (10% vs. 0%, $p = 0.0002$). Eosinophil counts in blood were negative predictors of antinuclear antibody in asthma. Conversely, eosinophil counts in blood and immunoglobulin-E levels of ≥ 100 IU/mL were positively associated with rheumatoid factor in asthma but not in COPD. There was no relationship between antinuclear antibody or rheumatoid factor and disease severity.

Conclusions: It is possible that asthma tends to involve autoimmunity associated with antinuclear antibody more frequently than COPD because asthma is the more robust factor for antinuclear antibody positivity. Antinuclear antibody and rheumatoid factor are associated with eosinophilic responses, but they do not work as biomarkers for disease severity.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases that are characterised by respiratory symptoms and airflow limitation caused by airway inflammation.^{1,2} The

pathogenesis of asthma and COPD is poorly understood. Asthma is not considered as a single disease, and its heterogeneity has been increasingly emphasised by cluster analysis classification.^{3,4} Although cigarette smoking is the main risk factor for COPD, most smokers do not develop COPD,⁵ and therefore it is likely that factors other than smoking are necessary for the development of COPD.^{6,7}

Autoimmune involvement in the pathogenesis of both asthma and COPD has been proposed, and autoantibodies are a hallmark of autoimmunity.^{7–10} It was reported that the prevalence of antinuclear antibodies (ANAs) was higher in asthma and COPD patients

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than in healthy controls^{11–14} and rheumatic symptoms, cold sensitivity and Raynaud's phenomenon were more common among patients who presented with ANA in asthma.¹¹ In addition, ANA is more prevalent in non-atopic asthma than atopic asthma, and autoimmunity has been proposed as a component of the pathogenesis of non-allergic asthma.¹⁵ Thus, autoimmunity may contribute to the pathophysiology of asthma and COPD, and may impair pulmonary function.

To the best of our knowledge, it is unclear whether asthma and COPD have distinct autoantibody profiles. In addition, it is not completely understood what disease parameters are associated with the presence of autoantibodies. Therefore, an assessment of autoantibody profiles may help to better characterise asthma and COPD. Here, we conducted a prospective study to compare the autoantibody profiles of asthma and COPD and assess the relationship between autoantibodies and disease features.

Methods

Study design and patients

We conducted a prospective observational study. One hundred and ten asthma and 92 COPD outpatients aged ≥ 20 years who were being treated at Shinko Hospital, Kobe, Japan, between July 2015 and March 2016 were recruited. A diagnosis of asthma was supported by clinical findings, including patient history and clinical course (for example, repeated paroxysmal dyspnoea, wheezing and cough, and a prompt response to anti-asthma medication), the existence of atopic disposition and environmental antigen-specific anti-IgE antibodies, the reversibility of airflow obstruction on spirometry and exclusion of other cardio-pulmonary diseases. A diagnosis of COPD was based on a history of smoking, occupational or environmental exposure, and obstructive lung disease with a forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) $< 70\%$. All patients were stable at the time of their inclusion, and patients who experienced collagen vascular diseases, other respiratory diseases or malignancy and who received daily systemic corticosteroids and/or immunosuppressants were excluded. All participants gave written informed consent and patient anonymity was preserved using methods approved by the Ethics Committee. The study was approved by the Institutional Review Board of Shinko Hospital (approval number: 1503).

Blood test

Using blood samples taken from the recruited patients (8 mL per patient), we evaluated complete blood cell counts, cell differentiation, IgE and levels of six autoantibody types: ANA, anti-cytoplasmic antibodies, rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, myeloperoxidase–anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) and proteinase 3-ANCA (PR3-ANCA). Operators were blinded as to the groups they analysed. ANA levels were evaluated using a Premune Hep20-10FANA kit (Euroimmun, Luebeck, Germany). ANA was fluorescently labelled and then visualised under a fluorescence microscope. The fluorescence pattern of ANA was determined along with the cytoplasmic fluorescence pattern of anti-cytoplasmic antibodies (technical support was provided by Toshiharu Saito). ANA titres of $\geq 1:160$ were considered to indicate ANA-positive samples.¹⁶ RF levels were evaluated using an N-assay TIA RF kit (Nit-tobo, Tokyo, Japan) and levels > 15 U/L were considered to indicate RF-positive samples. The anti-CCP antibody was evaluated using the Architect anti-CCP antibody (Abbott Laboratories, Abbott Park,

IL, USA), and levels ≥ 4.5 U/mL were considered to indicate anti-CCP-positive samples. MPO-ANCA and PR3-ANCA levels were examined using an MPO-ANCA test (BS) and a PR3-ANCA test (BS) (Medical & Biological Laboratories, Nagoya, Japan), respectively, and a level of ≥ 3.5 U/mL was considered to indicate MPO-ANCA- or PR3-ANCA-positive samples. Blood IgE was examined using an ImmunoCAP Total IgE kit (Phadia, Uppsala, Sweden) and levels of ≥ 100 IU/mL were considered to be high levels of IgE, in accordance with a previous report.¹⁷

Questionnaires

All patients completed questionnaires to assess patient demographics and smoking status. We also checked for previous episodes of respiratory hospitalisation or unscheduled hospital visits caused by chest symptoms within a year prior to inclusion in the study, and these were defined as exacerbations of asthma/COPD < 1 year. An asthma control test (ACT) for asthma patients and a COPD assessment test (CAT) for COPD patients were performed concurrently with the blood test and pulmonary function tests. The ACT is a validated questionnaire with five questions, which is used to assess if a patient has controlled asthma.¹⁸ The ACT scale ranges from 5 (poor control of asthma) to 25 (complete control of asthma). The CAT is a questionnaire that is designed to measure the impact of COPD on a person's life.¹⁹ The CAT scale ranges from 0 to 40, with higher scores indicating worse symptoms and control.

Pulmonary function tests

Pulmonary function tests were conducted by trained operators, in accordance with American Thoracic Society/European Respiratory Society guidelines,²⁰ using a CHESTAC-8800 system (Chest, Tokyo, Japan).

Main outcome measures

The primary objective of the analyses was to compare the prevalence of each autoantibody between asthma and COPD. The secondary objective was to find the predictors of the presence of each autoantibody in asthma and COPD.

Statistical analyses

Statistical analysis was performed using JMP 9 software (SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as numbers (%), means (standard deviation [SD]) or medians (interquartile range [IQR]) depending on the distribution. Comparisons between asthma and COPD groups were performed using a Student's *t*-test, Mann–Whitney *U* test, chi-square test and Fisher's exact test, as appropriate. The distribution frequency of ANA titres between asthma and COPD was compared using a chi-square test. Gender bias in ANA positive patients was analysed using Fisher's exact test. Predictors of the presence of ANA and RF were evaluated using a univariate logistic regression analysis, but other autoantibodies were not evaluated because of statistical instability owing to their low prevalence. Comparisons of disease severity including ACT, CAT, exacerbations of asthma/COPD < 1 year, and FEV₁% predicted between ANA or RF positive and negative groups were performed using a Mann–Whitney *U* test and Fisher's exact test. Eosinophil counts in blood (ECB) between ANA or RF-positive and negative groups were compared using a Mann–Whitney *U* test. A *p*-value of < 0.05 was deemed statistically significant.

Results

Patients

We included 110 asthma and 92 COPD patients in the study. The clinical characteristics of the patients are shown in Table 1. Age, sex, body mass index (BMI), smoking history, ECB, the levels of blood IgE and pulmonary function were significantly ($p < 0.05$) different between the asthma and COPD groups.

Autoantibody profiles

The autoantibody profiles of the groups are shown in Table 2. ANA was prevalent in the asthma group only and no one demonstrated an ANA titre of $\geq 1:160$ in the COPD group (10% vs. 0%, $p = 0.0002$). Seventy-six per cent (84/110) of asthma and 87% (80/92) of COPD patients presented with an ANA titre of $<1:40$. Furthermore, 6% ($n = 7$) of asthma and 8% ($n = 7$) of COPD patients presented with an ANA titre of $1:40$, and 7% ($n = 8$) of asthma and 5% ($n = 5$) of COPD patients presented with an ANA titre of $1:80$. The distribution frequency of ANA titres was significantly ($p = 0.02$) different between the asthma and COPD groups (Fig. 1). There was no significant difference in ANA positivity between females and males in asthma (9/64 (14%) vs. 2/46 (4%), $p = 0.1$). Various fluorescence patterns were observed, including homogeneous, speckled, centromere, nucleolar, granular and dense fine-speckled 70 patterns, in the asthma group. Furthermore, more than two fluorescence patterns could overlap. Twelve (11%) asthma patients and nine (10%) COPD patients were positive for RF. The prevalence of anti-cytoplasmic antibodies and the anti-CCP antibody was low, and no patient demonstrated the presence of ANCA. In addition, no patient who was positive for autoantibodies presented with articular symptoms, dry mouth, dry eye, Raynaud's phenomenon or other cutaneous lesions suggesting connective tissue diseases.

Predictors of ANA and RF

High ECB were negative predictors of ANA in asthma (Table 3). Conversely, high ECB and high levels of IgE were positively associated with RF in asthma but not in COPD (Table 4). There was no relationship between ANA or RF and disease severity, as predicted using different criteria including the ACT, CAT, exacerbations in <1

Table 2

Prevalence of autoantibodies in asthma and COPD.

	Asthma, n = 110	COPD, n = 92	p Value
ANA, n (%)	11 (10)	0 (0)	0.0002
Homogeneous	4 (4)	N/A	N/A
Speckled	5 (5)	N/A	N/A
Centromere	2 (2)	N/A	N/A
Nucleolar	5 (5)	N/A	N/A
Peripheral	0 (0)	N/A	N/A
Granular	2 (2)	N/A	N/A
Nuclear membrane	0 (0)	N/A	N/A
DFS 70	3 (3)	N/A	N/A
Others	4 (4)	N/A	N/A
Anti-cytoplasmic antibodies, n (%)	2 (2)	1 (1)	1.0
RF, n (%)	12 (11)	9 (10)	0.8
Anti-CCP antibody, n (%)	4 (4)	3 (3)	1.0
MPO-ANCA, n (%)	0 (0)	0 (0)	N/A
PR3-ANCA, n (%)	0 (0)	0 (0)	N/A

COPD, chronic obstructive pulmonary disease; ANA, antinuclear antibodies; N/A, not available; DFS, dense fine speckled; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; MPO, myeloperoxidase; ANCA, anti-neutrophil cytoplasmic autoantibodies; PR3, Proteinase 3. Fluorescence patterns could overlap.

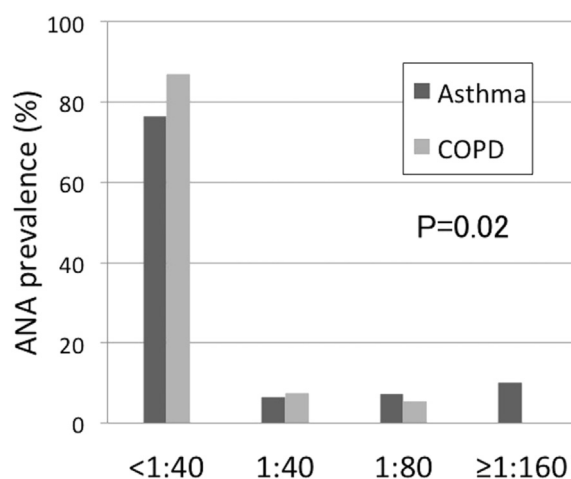


Fig. 1. Distribution frequency of antinuclear antibody titres was significantly different between the asthma and chronic obstructive pulmonary disease groups.

Table 1

Baseline characteristics.

	Asthma, n = 110	COPD, n = 92	p Value
Age, mean (SD), years	65 (14)	73 (9)	<0.0001
Female, n (%)	64 (58)	9 (10)	<0.0001
BMI, mean (SD), kg/m ²	23.8 (4.5)	22.3 (2.9)	0.005
Smoking history			
Current smokers, n (%)	14 (13)	18 (20)	0.2
Former smokers, n (%)	49 (45)	72 (78)	<0.0001
Pack-years, median (IQR)	5 (0–28)	57 (39–82)	<0.0001
ACT, mean (SD)	22 (4)	N/A	N/A
CAT, mean (SD)	N/A	11 (7)	N/A
Exacerbations <1 year, n (%)	26 (24)	17 (18)	0.4
Blood test			
Eosinophils, mean (SD), %	5.2 (3.5)	3.5 (2.5)	<0.0001
IgE, median (IQR), IU/mL	157 (53–492)	95 (24–376)	0.02
Pulmonary function test			
FEV ₁ /FVC, % (SD)	70 (15)	52 (12)	<0.0001
FEV ₁ , mean (SD), % predicted	80 (22)	62 (23)	<0.0001

COPD, chronic obstructive pulmonary disease; SD, standard deviation; IQR, interquartile range; ACT, asthma control test; N/A, not available; CAT, COPD assessment test; IgE, immunoglobulin-E; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity.

Table 3

Predictors of antinuclear antibodies in asthma.

	OR	95% CI	p Value
Age, per year	1.01	0.96–1.06	0.7
Female	3.60	0.87–24.41	0.08
BMI, per kg/m ²	0.94	0.78–1.08	0.4
Smoking history, per pack-year	1.01	0.98–1.03	0.5
ACT, per score	1.09	0.93–1.38	0.3
Exacerbations <1 year	1.24	0.26–4.69	0.8
Eosinophils, per %	0.75	0.53–0.97	0.02
IgE ≥ 100 IU/mL	0.48	0.13–1.69	0.2
FEV ₁ % predicted, per %	1.01	0.98–1.04	0.5

COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; ACT, asthma control test; CAT, COPD assessment test; IgE, immunoglobulin-E; FEV₁, forced expiratory volume in 1 s.

year, or FEV₁% predicted (Table 5). The ANA-positive group showed significantly lower ECB than the ANA-negative group in asthma (median, IQR: 2.9%, 1.6%–4.3% vs. 4.4%, 2.7%–7.5%, $p = 0.03$) (Fig. 2A). Conversely, the RF-positive group showed significantly higher ECB than the RF-negative group in asthma (median, IQR: 7.3%, 4.4%–10.6% vs. 3.9%, 2.5%–6.5%, $p = 0.02$) (Fig. 2B).

Table 4
Predictors of rheumatoid factor.

	Asthma			COPD		
	OR	95% CI	p Value	OR	95% CI	p Value
Age, per year	1.02	0.97–1.07	0.5	1.00	0.92–1.08	0.9
Female	1.50	0.44–5.92	0.5	1.17	0.06–7.70	0.9
BMI, per kg/m ²	0.93	0.79–1.07	0.4	0.86	0.64–1.13	0.3
Smoking history, per pack-year	1.00	0.97–1.03	0.8	0.99	0.97–1.01	0.4
ACT, per score	1.08	0.93–1.36	0.4	N/A	N/A	N/A
CAT, per score	N/A	N/A	N/A	0.92	0.80–1.02	0.1
Exacerbations <1 year	0.62	0.09–2.55	0.5	0.52	0.27–3.16	0.5
Eosinophils, per %	1.21	1.03–1.42	0.02	0.98	0.70–1.26	0.9
IgE ≥100 IU/mL	7.91	1.45–147.43	0.01	4.14	0.94–28.93	0.06
FEV ₁ % predicted, per %	0.99	0.96–1.02	0.4	1.01	0.97–1.04	0.7

COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; ACT, asthma control test; N/A, not available; CAT, COPD assessment test; IgE, immunoglobulin-E; FEV₁, forced expiratory volume in 1 s.

Table 5
Relationship between ANA or RF and disease severity.

	ANA+	ANA–	p Value	RF+	RF–	p Value
Asthma	(n = 11)	(n = 99)		(n = 12)	(n = 98)	
ACT, mean (SD)	23 (3)	21 (4)	0.4	23 (3)	21 (4)	0.4
Exacerbations <1 year, n (%)	3 (27)	23 (23)	0.7	2 (17)	24 (24)	0.7
FEV ₁ , mean (SD), % predicted	84 (27)	80 (22)	0.6	75 (26)	81 (22)	0.4
COPD				(n = 9)	(n = 83)	
CAT, mean (SD)	N/A	N/A	N/A	8 (6)	11 (7)	0.2
Exacerbations <1 year, n (%)	N/A	N/A	N/A	1 (11)	16 (19)	1.0
FEV ₁ , mean (SD), % predicted	N/A	N/A	N/A	65 (28)	62 (23)	0.8

ANA, antinuclear antibodies; RF, rheumatoid factor; ACT, asthma control test; FEV₁, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; N/A, not available.

Discussion

The principal results of this study are the followings. (1) An ANA titre of ≥1:160 presented only in asthma and not in COPD. (2) ECB are negative predictors of the presence of ANA in asthma. (3)

Conversely, high ECB and high levels of IgE are positively associated with RF in asthma but not in COPD. (4) There is no relationship between ANA or RF and disease severity. (5) The prevalence of anti-cytoplasmic antibodies and anti-CCP antibody is low, and the prevalence of ANCA is extremely low. Overall, it is possible that asthma tends to involve autoimmunity associated with ANA more frequently than COPD because asthma is the more robust factor for ANA positivity, and our results concerning ANA and ECB could indicate a distinct pathogenesis in asthma.

The prevalence of ANA in asthma and COPD has been reported previously. Szczeklik *et al.* reported that ANA at a titre of ≥1:40 was present in 55% of patients with aspirin-induced asthma, 41% of those with intrinsic asthma, 39% of those with atopic asthma, and 11% of healthy subjects, with the difference between each group and the healthy subjects being statistically significant.¹¹ Moreover, Núñez *et al.* showed that the prevalence of an ANA titre of ≥1:160 was significantly higher in COPD patients than in control subjects (34% vs. 3%, $p < 0.01$).²¹ Bonarius *et al.* also reported that significantly more COPD patients than control subjects were positive for ANA at a titre of ≥1:80 (44% vs. 22%, $p = 0.001$).¹³ In this study, it was surprising that ANA at a titre of ≥1:160 was present only in asthma but not in COPD, despite other authors reporting high titres of ANA in COPD patients. It is known that female sex correlates to ANA positivity,²² and there were more females in the asthma group. However, there was no significant difference in ANA positivity between females and males in the asthma group, and hence gender bias cannot explain our results. Given that patients with Japanese ethnicity were recruited to our study, we speculate that ethnic differences may also have played a role.

Autoimmunity has been proposed as a contributory factor in the pathogenesis of non-allergic asthma¹⁵ and our findings regarding the inverse relationship between ECB and ANA in asthma are consistent with this idea. High ECB indicate T helper type 2 (Th2)-driven inflammation in asthma.²³ Although it is poorly understood whether ANA has any pathophysiological significance in asthma or if it is a nonspecific marker of an ongoing autoimmune response, one intriguing interpretation of our results is that asthma with reduced ECB tends to involve autoimmunity, as represented by ANA, but not Th2-driven eosinophilic inflammation.

Several reports have described the association of RF with eosinophils. It has been shown that ECB are significantly higher in asthma patients who are positive for RF than in those who are negative for RF.²⁴ Moreover, RF levels are correlated with ECB in a

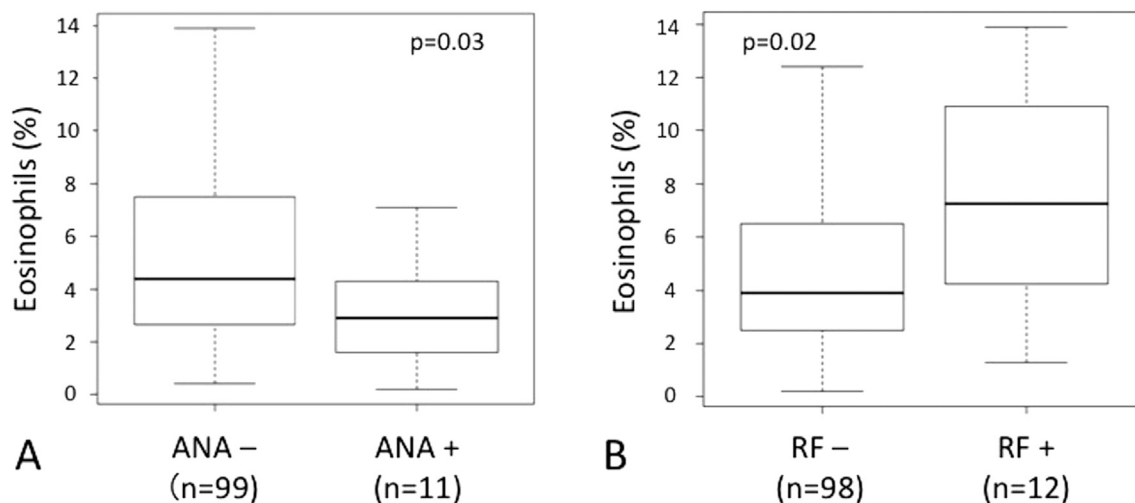


Fig. 2. (A) Antinuclear antibodies (ANA)-positive group showed significantly lower levels of eosinophils compared with the ANA-negative group in asthma. (B) The rheumatoid factor-positive group showed significantly higher levels of eosinophils in asthma.

patient with chronic eosinophilic pneumonia.²⁵ It is possible that RF levels reflect the activity of allergic disorders. However, Rintisch *et al.* showed that RF-producing congenic rats, which had been immunised with ovalbumin, and with experimental allergic bronchitis developed a significantly increased number of eosinophils in bronchoalveolar lavage fluid as well as increased total IgE in their blood, compared with controls.²⁶ Therefore, RF itself may contribute to the eosinophilic inflammatory pathway.

Sigari *et al.* reported that eight (14%) patients with wood-smoke-induced COPD, four (7%) patients with tobacco-induced COPD and two (4%) patients from a healthy control group were positive for the anti-CCP antibody. However, they compared only the levels of anti-CCP antibody among these groups and it was not described whether the anti-CCP antibody positivity significantly differed between the COPD and control groups.²⁷ In our study, only three (3%) COPD patients were positive for the anti-CCP antibody. Although smoking is considered a risk factor for both rheumatoid arthritis (RA) and COPD,^{28,29} it was difficult to confirm an association between the presence of the anti-CCP antibody, which is a useful diagnostic biomarker for RA,³⁰ and COPD status in our study. In addition, no patient presented with MPO-ANCA or PR3-ANCA in this study, so ANCA positivity can be considered as extremely rare in asthma and COPD.

Although ANA profiling studies have previously been conducted for asthma and COPD, our study is unique in several respects. First, autoantibodies were investigated in a comprehensive fashion by evaluating ANA, anti-cytoplasmic antibodies, RF, anti-CCP antibody and ANCA. Second, we included ECB and blood IgE as covariates of the Th2 response. Third, we compared asthma with COPD because they are similar in terms of both being obstructive airway diseases and a higher ANA prevalence has been previously reported in both. However, we did not evaluate healthy controls and it is unclear whether the prevalence of each autoantibody is higher in asthma and COPD groups than in healthy controls. The prevalence of ANA at a titre of $\geq 1:160$ accounts for 2.8% of the Japanese general population,²² so the 10% ANA positivity in our asthma patients appears to be higher than that of Japanese healthy controls. In addition, no patient who was positive for autoantibodies presented with articular symptoms, dry mouth, dry eye, Raynaud's phenomenon or other cutaneous lesions suggesting connective tissue diseases. However, we did not perform further examination for autoimmune diseases. It would be required to study whether the autoantibody positive asthma and COPD patients have developed the autoimmune diseases. Finally, it might have been difficult to detect the relationship between the presence of autoantibodies and disease severity because of the small size of this study. In a large epidemiological study with 3257 healthy participants, it was found that levels of autoantibodies were inversely correlated with FEV₁/FVC and predicted FEV₁.³¹ It may be possible to confirm the relationship between the presence of autoantibodies and worsening lung function in asthma and COPD if a larger sample of subjects can be recruited.

In conclusion, it is possible that asthma tends to involve autoimmunity associated with ANA more frequently than COPD because asthma is the more robust factor for ANA prevalence, compared with COPD. ANA and RF are associated with eosinophilic responses in asthma, but they do not function as biomarkers for disease severity.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KT and HM designed the study and wrote the manuscript. All authors contributed to data collection. KT, HM and YS performed the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

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