A case of anti-Th/To antibody-positive interstitial lung disease and pulmonary arterial hypertension that does not meet the classification criteria of systemic sclerosis. Comment on the article by Moschetti *et al.*

Sirs,

We read with great interest the article by Moschetti and colleagues analysing the long-term follow-up of pulmonary involvement in patients with anti-Th/To antibody (ATA)-positive systemic sclerosis (SSc) (1). Their study revealed that 40% of ATA-positive SSc patients developed interstitial lung disease (ILD), although none of the 13 ATA-positive SSc patients developed pulmonary arterial hypertension (PAH) (1). In contrast, Suresh *et al*. reported that 23% of ATA-positive SSc patients developed PAH (2). ATAs were reported not only in SSc patients, but also in idiopathic pulmonary fibrosis patients without SSc (3). Therefore, the relationship between ATAs and pulmonary involvement remains unclear. Here, we report an ATA-positive patient who did not meet the classification criteria for SSc, but who developed PAH 11 years after being diagnosed with ILD. We compare the frequencies of ILD and PAH in ATA-positive patients in the literature.

An 81-year-old Japanese woman had been diagnosed with ILD at age 70 from physical examinations, including chest radiographs. Eleven years after that diagnosis, chest radiographs and high-resolution computed tomography scans showed cardiomegaly and worsening of the ILD (Fig. 1 A-B). Pulmonary function tests revealed a forced vital capacity (FVC) 79.5% of predicted, a diffusing capacity for carbon monoxide (DLCO) 34.2% of predicted, and an FVC/DLCO ratio of 2.3. Transthoracic echocardiography revealed an elevated right ventricular systolic pressure (RVSP) of 52 mmHg (Fig. 1 C). The present case fulfilled the following items for which a right-sided heart catheterization (RHC) is recommended: signs of pulmonary hypertension (PH), an FVC/DLCO ratio of >1.6, and/or a DLCO >60% of predicted (4). RHC showed pre-capillary PH with a mean pulmonary artery pressure of 25 mmHg, a pulmonary artery wedge pressure of 6 mmHg, a cardiac output of 3.74 L/min via thermodilution, and a pulmonary vascular resistance of 6.9 Wood units. Based on the Nice Classification (5), she had relatively good pulmonary function test results for group 3, and negative results for groups 2 and 4 based on the catheter findings, leading to a diagnosis of group 1. Since her serum showed a nucleolar pattern in indirect immunofluorescence studies, we suspected ATAs. Our in-house enzyme-linked immunosorbent assay using recombinant hPop1 and Rpp25 (6), which are major epitopes for ATAs, showed her serum to react to both. This study was approved by the ethics committees of Nagoya University Hospital and Ichinomiya Municipal Hospital, and conducted in accordance with the Declaration of Helsinki. The patient gave written informed consent to participate.

Although she had puffy fingers and nailfold capillary microscopic abnormalities, no other symptoms such as skin thickening, Raynaud's phenomenon, or gastrointestinal involvement were observed. She did not meet the 2013 classification criteria for SSc (7), with a score of 6. She was treated with oral prednisolone 30 mg/day. After 2-week follow-up, improved RVSP to 40 mmHg was shown on transthoracic echocardiography. During our half-year observation period, no exacerbation of the skin manifestations was found.

We searched PubMed for articles on the relationship between ATAs and pulmonary involvement up to October 2023. The frequencies of ILD and PAH in ATA-positive SSc patients reported previously in the literature are summarised in Table I. The variability in data among the cohorts may

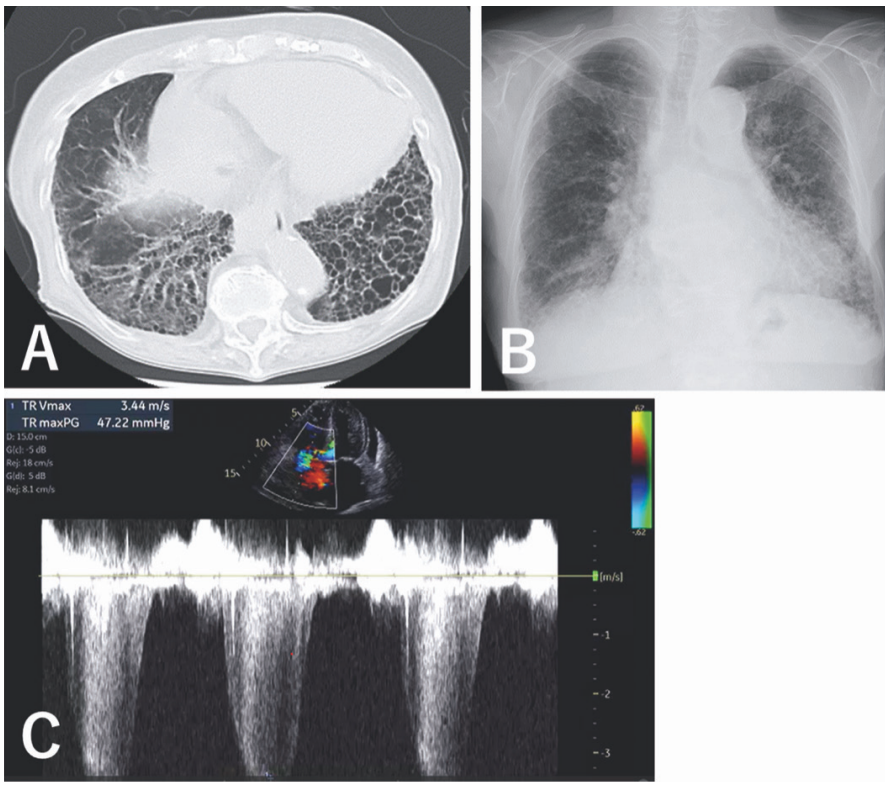

Fig. 1. Radiologic images and echocardiography.
A. High-resolution computed tomography scan shows ground-glass opacities, mainly in the lower lobes of the lungs.
B. Chest radiograph shows cardiomegaly and reticular shadows in both lower lung fields.
C. Transthoracic echocardiogram shows increased tricuspid regurgitation pressure gradients.

Table I. Frequencies of ILD and PAH in ATA-positive SSc patients reported in selected large SSc patient cohorts in the literature.

SSc patient cohort	ATA (+) patients/ all SSc patients	ILD (+) patients/ ATA (+) patients	PAH (+) patients/ ATA (+) patients	Reference
Italy	13/608 (2.1 %)	4/10* (40 %)	0/13 (0 %)	(1)
US	204/3613 (5.6 %)	103/204 (54 %)	47/204 (23 %)	(2)
Japan	6/249 (2.4 %)	4/6 (67 %)	0/6 (0 %)	(6)
Japan	7/203 (3.4 %)	2/7 (29 %)	1/7 (14 %)	(8)
Italy	8/216 (3.7 %)	3/8 (38 %)	0/8 (0 %)	(9)
Canada and US	8/202 (4.0 %)	4/8 (50 %)	0/8 (0 %)	(10)
Total	246/5091 (4.8%)	120/243 (49.4%)	48/246 (19.5%)	

The search term was 'anti-Th/To' OR 'pulmonary involvement' OR 'interstitial lung disease' OR 'pulmonary hypertension'. Articles with cohorts of only limited or diffuse cutaneous SSc patients and of under 200 cases were not used. Cohorts in which pulmonary hypertension and pulmonary arterial hypertension were not differentiated were excluded. *Three other cases were excluded because detailed information was unavailable.
TA: anti-Th/To antibody; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.

be due to differences in ethnicities, observation periods, physical examination methods, and disease definitions. In the aggregated data of all patients in the cohorts, the frequency of ILD was higher than that of PAH. According to our literature search, none of the ATA-positive patients who did not meet the 2013 classification criteria for SSc presented with both ILD and PAH. However, our case emphasised a long-term pulmonary involvement risk in an ATA-positive patient.

Acknowledgements
We would like to thank Dr Yuta Nakagawa for performing the cardiac catheterisation diagnostic test.

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Competing interests: none declared.

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