Anti-EJ antibody-positive antisynthetase syndrome developed pulmonary arterial hypertension 7 years after the onset of disease: the necessity of periodic evaluation

Sirs,

Antisynthetase syndrome (ASS) is a heterogeneous systemic autoimmune disease characterised by the association between anti-aminoacyl-transfer RNA (anti-ARS) antibodies and distinct clinical subsets. These include interstitial lung disease (ILD), nonerosive arthritis, Raynaud's phenomenon, and the skin changes of "mechanic's hands" (1). Pulmonary hypertension (PH) was confirmed in 7.9% of ASS patients (2), and the 3-year survival rate was reported to be 58% (1). Anti-glycyl (EJ) antibody, a rare subset of anti-ARS, was found in 1-5% of ASS patients (3,4), and the aetiology and prognosis have not been elucidated. Herein, we describe a case of anti-EJ antibody-positive ASS that developed pulmonary arterial hypertension (PAH) 7 years after the onset of ILD.

The patient was a 76-year-old Japanese man who had been diagnosed with ASS at the age of 69, requiring glucocorticoid, tacrolimus, and nintedanib treatment. Written consent was obtained from the patient. The Institutional Research Ethics Board does not require board review for a single case report when the patient's privacy is protected.

Non-specific interstitial pneumonia (Fig. 1A-B), "mechanic's hands", and anti-EJ antibodies were observed at disease onset. Seven years after disease onset, he presented with a 3-month history of exertional dyspnoea and oedema of the lower extremities. On examination, he was afebrile, and his skin was intact. He required oxygen supplementation of 3 L/min at rest and 5 L/min on exertion. His 6-min walking distance was 130 m. Chest radiographs and computed tomography showed cardiomegaly and no extensions in interstitial pneumonia (Fig. 1C-D). Pulmonary function tests revealed a forced vital capacity (FVC) of 61.4% predicted, diffusing capacity for carbon monoxide (DL_{CO}) of 24.0% predicted, and an FVC/DL_{CO} ratio of 2.5. This ratio of >1.6 generally predicts isolated PH in patients with ILD (5). Transthoracic echocardiography revealed a tricuspid regurgitation pressure gradient of 46 mmHg, dilated right ventricular with diffuse hypokinesis, and small left ventricular cavity with a flattened septum ("D-shape") and normal wall motion (Fig. 1E). No perfusion defects were detected by a perfusion scan (Fig. 1F). Right heart catheterisation confirmed pre-capillary pulmonary hypertension with a mean pulmonary artery pressure of 29 mmHg

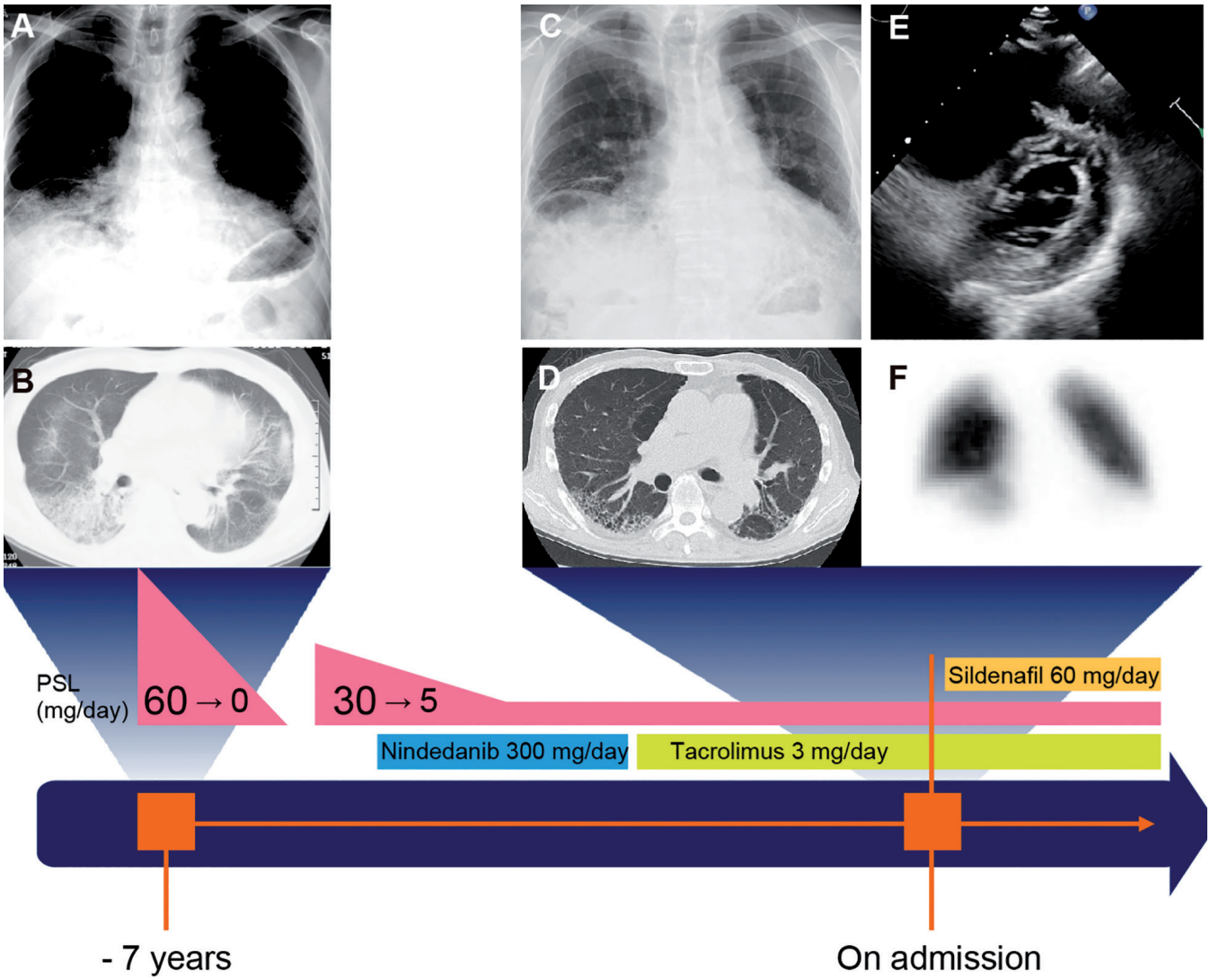

Fig. 1. Clinical course with radiologic images, echocardiography, and perfusion scan.
A. Chest radiograph showing cardiomegaly and reticular shadows in both lower lung fields. **B**. CT scan demonstrating ground-glass opacities mainly in the lower lobes. **C**. Chest radiograph showing cardiomegaly. **D**. High-resolution CT scan demonstrating signs of interstitial fibrosis and traction bronchiectasis mainly in the lower lobes. **E**. Transthoracic echocardiogram showing a small left ventricular cavity with flattened septum. **F**. Perfusion scan demonstrating no perfusion defects.

and pulmonary artery wedge pressure of 9 mmHg, cardiac output of 3.4 L/min via thermodilution, and pulmonary vascular resistance of 5.8 Wood units. He was diagnosed with PAH and right heart failure, and we initiated sildenafil 60 mg daily. During the 1-month follow-up, he was able to perform all instrumental activities of daily living on an oxygen supplementation of 0.5 L/min at rest and 3 L/min on exertion.

Anti-ARS antibodies include anti-Jo1, anti-PL12, anti-PL7, and anti-EJ, as well as numerous others, each corresponding to a unique amino-acyl transfer RNA synthetase complex (1). PH in patients with ASS is associated with decreased survival (2). ASS-associated PH (ASS-PH) was observed in mainly anti-Jo1 antibody-positive ASS, and the aetiology comprises several different factors, including PAH, left heart disease, and ILD. PH secondary to ILD can be the predominant cause of ASS-PH (2), but the association between ILD and secondary PH is not fully understood. ASS-PH can develop and progress independently of the occurrence and progression of ILD. Cavagna *et al*. reported that two cases of anti-Jo1 antibody-positive ASS with stable ILD developed PAH 6-7 years after the onset of ASS (6). Both patients achieved clinical improvement through sildenafil monotherapy. A case of anti-Jo1 antibody positive ASS-PAH by Chatterjee *et al*. progressed irrespective of ILD activity (7). Anti-EJ antibody-positive ASS commonly shows isolated ILD at the onset of the disease (4) and frequent relapse (8). In anti-EJ antibody-positive ASS, although concomitant ILD may be a trigger for PH, the prognosis pattern of PH is unknown. This case highlights that clinicians need to maintain heightened vigilance for PAH in ASS patients, independently of ILD extension, disease activity, and duration. As recommended in patients with systemic sclerosis, periodic evaluation for PAH may benefit in a specific subset of ASS patients.

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