

[ CASE REPORT ]

## Wild-type Transthyretin Amyloidosis with Diffuse Alveolar-septal Amyloidosis Diagnosed by a Transbronchial Lung Biopsy

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### Abstract:

A 69-year-old man visited our pulmonary medicine department for dyspnea. Chest computed tomography (CT) revealed ground-glass opacity bilaterally in the lungs. Upon performing a transbronchial lung biopsy (TBLB), organizing pneumonia was diagnosed. His electrocardiogram revealed low voltage, and the cardiac ultrasound revealed hypertrophy of the interventricular septum. The patient had bilateral carpal tunnel syndrome, and amyloidosis was suspected. Congo red stain was added to the lung biopsy specimen. Amyloid deposition of transthyretin (ATTR) was positive, mutations with amino acid changes were not observed in the *TTR* gene. Wild-type ATTR Amyloidosis (ATTRwt amyloidosis) was diagnosed using a TBLB. Chest CT after treatment with steroids revealed diffuse alveolar-septal amyloidosis.

**Key words:** wild-type transthyretin amyloidosis, transthyretin, cardiomyopathy

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### Introduction

In wild-type amyloid deposition of transthyretin (ATTR) amyloidosis (ATTRwt amyloidosis), wild-type transthyretin (TTR) without genetic mutations becomes an amyloid precursor protein (1). Amyloid fibrils are formed by dissociation, misfolding, and polymerization of the tetramer; TTR is then deposited in the tissues, such as the myocardium, tendon, lung, and peripheral nerves, resulting in their dysfunction. Wild-type TTR deposition leads to sporadic amyloid disease and ATTRwt amyloidosis, which occurs in the elderly (2). A skin biopsy, subcutaneous liposuction, and gastrointestinal biopsy are usually recommended for the diagnosis of amyloidosis; however, the diagnosis rate is not suitably high at present (3-6).

Tafamidis, TTR tetramer stabilizers, have been reported to improve the prognosis of cardiac symptoms of ATTRwt amyloidosis (7); therefore, the early diagnosis of ATTRwt amyloidosis is important.

We herein report a case of wild-type TTR amyloidosis with diffuse alveolar-septal amyloidosis diagnosed by a transbronchial lung biopsy (TBLB).

### Case Report

A 69-year-old man had been diagnosed with atrial fibrillation and cardiogenic cerebral infarction 1 month earlier and been prescribed anticoagulants. He did not show any consequences of the cerebral infarction. He was aware of his dyspnea on exertion and had a dry cough one week before admission. He had bilateral carpal tunnel syndrome for which surgery had been performed 10 years ago. No significant contributory family history was noted. He had a smoking history of 80 pack-years.

His vital signs were as follows: body temperature, 36.9°C; blood pressure, 139/91 mmHg; heart rate (HR), 107/min; respiratory rate, 16/min, and oxygen saturation, 96% (room air). Inspiratory crackles were audible in the lungs bilaterally. His blood test results revealed leukocytes, 8,100/ $\mu$ L

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**Table. Laboratory Data.**

TP	6.8 g/dL	WBC	8,500 / $\mu$ L	ANA	<40
Alb	3.7 g/dL	Neutro	71.7 %	PR3-ANCA	<1.0
AST	35 U/L	Lym	15.0 %	MPO-ANCA	<1.0
BUN	14.3 mg/L	Eo	3.0 %	KL-6	979 U/mL
Cre	0.83 mg/dL	Hb	13.3 g/dL	SP-A	71.0 ng/mL
Na	137 mEq/L	MCV	92.7	B-D-glucan	<6.0
K	4.7 mEq/L	Plt	338 $\times$ 10 <sup>3</sup> / $\mu$ L	M protein	-
Cl	103 mEq/L	CRP	1.08 mg/dL	BJP in urine	-
				$\kappa/\lambda$ ratio	1.3

ANA: anti-nuclear antibody, BJP: Bence-Jones protein



**Figure 1.** Chest radiograph (A) and chest computed tomography (B) of the patient.

(neutrophils, 68.3%; lymphocytes, 20.4%; and eosinophils, 2.6%), C-reactive protein, 1.08 mg/dL; KL-6, 979 U/mL, and brain natriuretic peptide, 233 pg/mL. M protein, and Bence Jones protein were not detected by immunoelectrophoresis (Table).

Chest radiography revealed cardiomegaly and an infiltration shadow in the right lung field (Fig. 1A). Chest computed tomography (CT) revealed multiple infiltrative and ground-glass opacities in the lungs bilaterally (Fig. 1B). An electrocardiogram (Fig. 2A) revealed HR of 118/min, atrial fibrillation, low potentials on limb induction, and poor-R wave progression on V1-3 wave. Echocardiography (Fig. 2B, C) revealed a hypertrophic myocardium with high echogenicity. Bronchoscopy was performed to identify the cause of the clinical and infiltrative shadows. The TBLB specimen of the lower lobes of the right lung showed poly-poidal organizing lesions protruding into the alveolar spaces (Fig. 3A); organizing pneumonia (OP) was diagnosed and treatment with steroids was initiated.

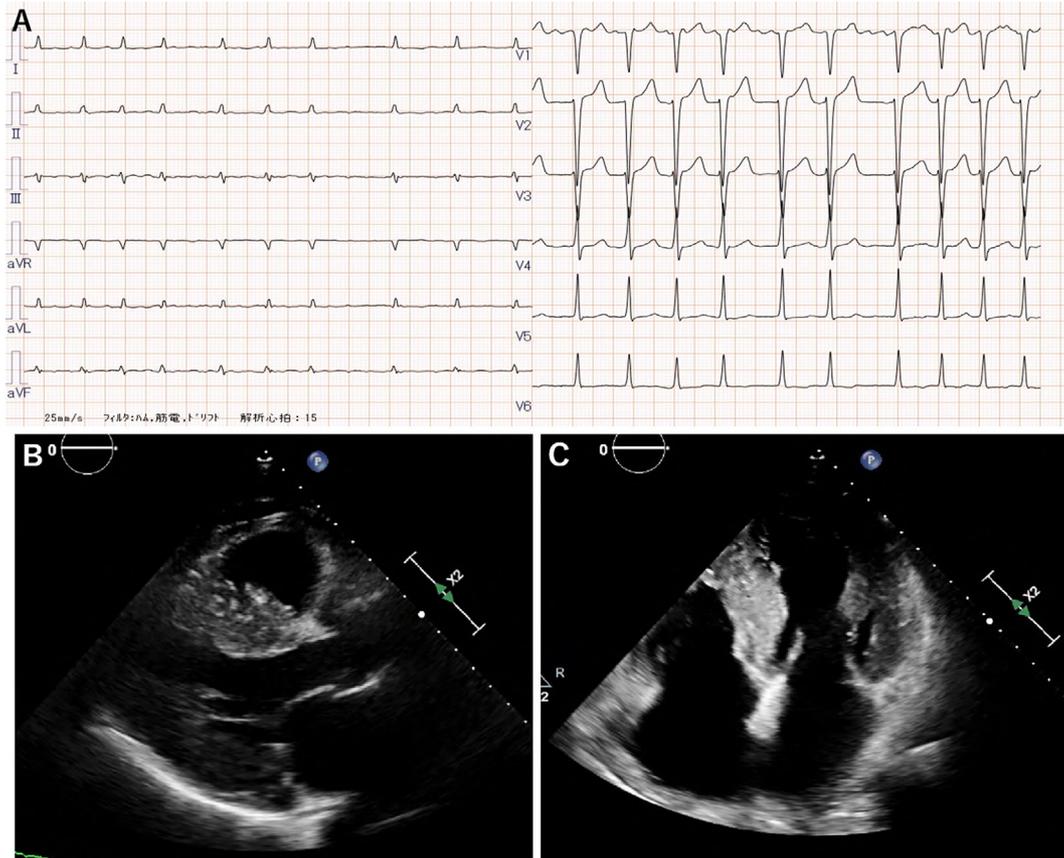
However, cardiac amyloidosis was also suspected owing to the presence of a hypertrophic myocardium with low potentials on electrocardiographic limb guidance and a medical history of bilateral carpal tunnel syndrome. A biopsy of the stomach, duodenum, and skin was performed; however, amyloid deposition was not observed. Therefore, Congo red stain was added to the TBLB specimens, which were stained positive (Fig. 3B, C), and polarized light microscopy re-

vealed apple green birefringence amyloid deposits (Fig. 3D) and diffuse amyloid deposits in the alveolar septum (Fig. 3B). Technetium 99m pyrophosphate scintigraphy revealed the strong accumulation of technetium pyrophosphate in the inferior wall (Fig. 4); amyloid deposition of TTR was positive and mutations with amino acid changes were not observed in the TTR gene. Based on the above findings, ATTRwt amyloidosis was diagnosed by TBLB, so we planned to administer tafamidis.

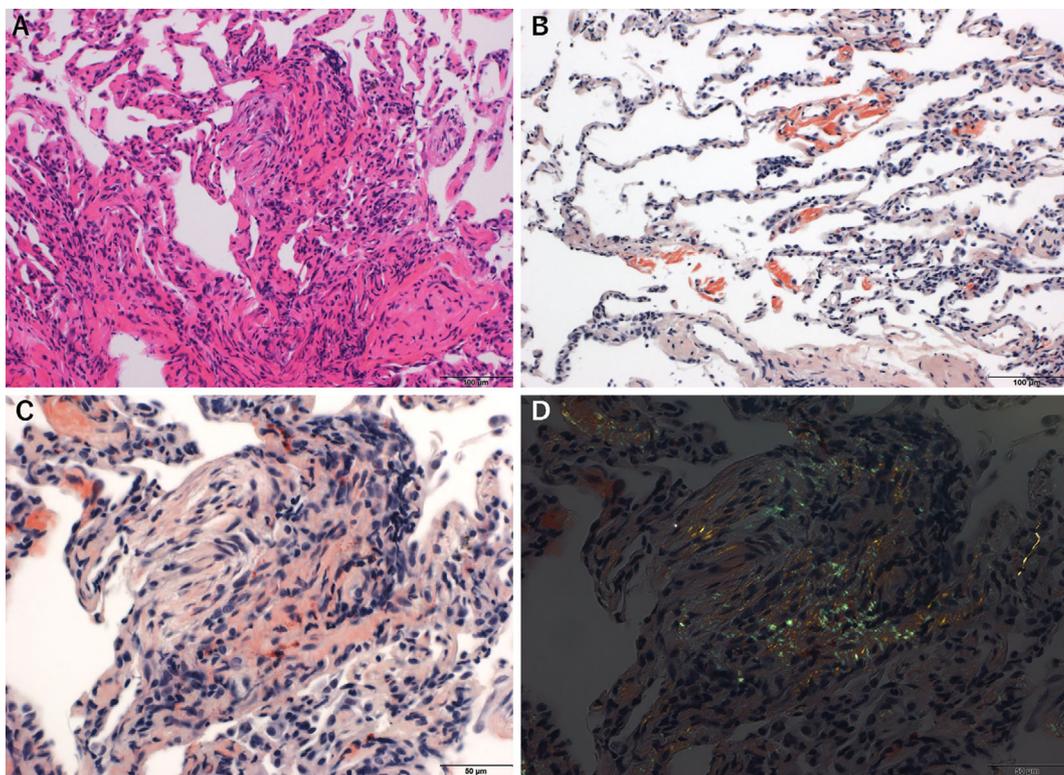
Chest CT following treatment using steroids for OP revealed residual ground glass opacity under the pleura (Fig. 5), and pathology of the biopsied TBLB specimens revealed amyloid deposition in the alveolar septum; thus, we construed a diagnosis of diffuse alveolar-septal amyloidosis.

## Discussion

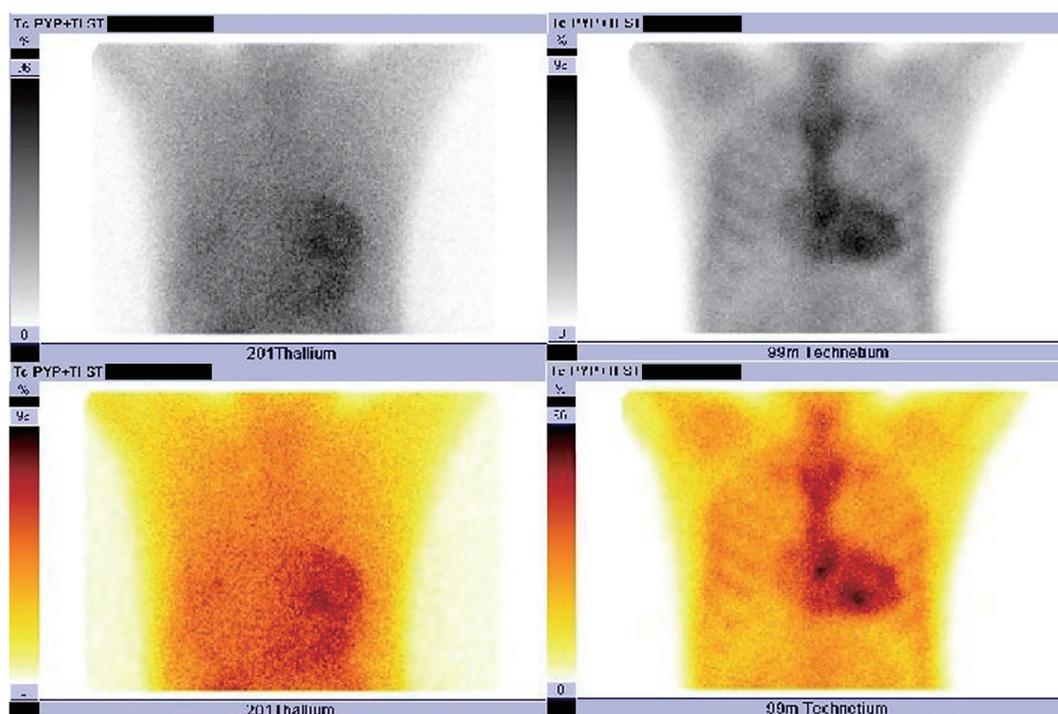
We herein report a case of ATTRwt amyloidosis, that was diagnosed by the development of OP and TBLB. ATTRwt amyloidosis is a systemic form of amyloidosis that occurs when wild-type TTR without genetic mutations becomes an amyloid precursor protein. Amyloid fibrils are formed by dissociation, misfolding, and polymerization of the tetramer, which is deposited in tissues and causes functional impairment. TTR-derived amyloid deposits are mainly found in the myocardium, lung, kidney, gastrointestinal tract, abdominal wall fat, joints, and ligaments, and occur in carpal tunnel



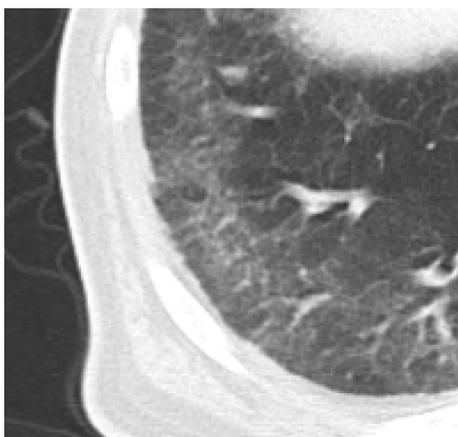
**Figure 2.** Electrocardiogram (A) and cardiac ultrasound (B, C) of the patient. LVDD 52 mm, LVDS 41 mm, IVSth 16 mm, PWth 14 mm, E/e' 22.2, EF 42%. LVDD: left ventricular diastolic dimension, LVDS: left ventricular systolic dimension, IVSth: interventricular septum thickness, PWth: posterior wall thickness, EF: ejection fraction



**Figure 3.** Pathological findings in the biopsied transbronchial lung biopsy specimens (A). Congo red staining (B, C) and apple green birefringence (D).



**Figure 4.**  $^{99m}\text{Tc}$  pyrophosphate scintigraphy. Accumulation of technetium pyrophosphate in the inferior wall.



**Figure 5.** Chest computed tomography following treatment with steroids for organizing pneumonia.

syndrome, scoliosis, cardiomegaly, arrhythmia, and heart failure (8). Bilateral carpal tunnel syndrome is a symptom appearing early in the course of ATTRwt amyloidosis. The mean time to heart failure in patients with ATTRwt amyloidosis with carpal tunnel syndrome is approximately 6.9 years (9). In the present case, the patient had been diagnosed with bilateral carpal tunnel syndrome 10 years ago, indicating evidence for the diagnosis of ATTRwt. The median overall survival period from the definitive diagnosis to follow-up is approximately 3.5 years. However, in 2018, the discovery of tafamidis, a TTR-stabilizing agent, reportedly improved the prognosis of ATTRwt amyloidosis (9).

To our knowledge, there has only been one report of ATTRwt amyloidosis associated with OP, and we presumed

that these two entities were only weakly related (10). We therefore believe that OP is associated with worsening ATTRwt amyloidosis.

Pulmonary amyloidosis is classified into diffuse alveolar-septal amyloidosis, nodular pulmonary amyloidosis and tracheobronchial amyloidosis. Diffuse alveolar-septal amyloidosis is usually caused by systemic amyloid light chain (AL) amyloidosis, whereas nodular pulmonary amyloidosis and tracheobronchial amyloidosis usually present with localized AL amyloidosis. In diffuse alveolar-septal amyloidosis, amyloid deposits are found in the alveolar septal and vascular walls (11, 12). To our knowledge, this is the first reported case of ATTRwt amyloidosis with diffuse alveolar-septal diagnosed using an immunohistochemical analysis of TBLB samples and a genetic analysis of a blood sample. In ATTRwt, the diagnosis rates of a skin biopsy, subcutaneous liposuction, and gastrointestinal biopsy are 14-15%, 63-73%, and 38%, respectively (3-6). A TBLB has reportedly resulted in the diagnosis of pulmonary amyloidosis in 14 cases (13), and has also proven useful in the diagnosis of pulmonary amyloidosis.

**The authors state that they have no Conflict of Interest (COI).**

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