

Case report

A case of wild-type transthyretin amyloidosis associated with organizing pneumonia

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Abstract

An 81-year-old man was referred to our hospital with bilateral multiple patchy opacities on chest radiography. His chief complaints were a few months' history of intermittent mild cough and slightly yellow sputum. Chest computed tomography (CT) showed non-segmental air-space consolidations with ground-glass opacities. Amyloid deposition with organizing pneumonia (OP) was seen in transbronchial lung biopsy (TBLB) specimens from the left S8. Three months later, the infiltration originally seen in the left lower lobe was remarkably diminished, and new infiltrations in the lingual and right lower lobes were detected on chest CT. Amyloid deposition with OP was seen in TBLB specimens from the left S4. Transthyretin was detected following immunohistochemical examination. The presence of wild-type transthyretin (ATTRwt) was proven using genetic analysis. The present report describes a rare case of ATTRwt amyloidosis associated with OP.

Key words: pulmonary amyloidosis, transthyretin, senile amyloidosis, organizing pneumonia

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Introduction

Amyloidoses are rare diseases that result from extracellular deposition of amyloid, a fibrous material derived from various proteins that self-assemble in a highly-ordered ab-

normal β -pleated sheet conformation^{1–3}. Although systemic light chain (AL) amyloidosis is the most common type of systemic amyloidosis, wild-type transthyretin amyloidosis (ATTRwt; or senile systemic amyloidosis [SAA]) is increasingly being diagnosed³.

The true incidence of ATTRwt amyloidosis in elderly people remains unknown. Some studies have reported cardiac amyloid deposits of this type in 16–25% of individuals older than 80 years at autopsy^{3,4}. As ATTRwt amyloidosis is asymptomatic in many cases, the antemortem diagnosis of ATTRwt amyloidosis is relatively rare^{4,5}. Here, we report a rare case of ATTRwt amyloidosis with organizing pneumonia (OP) that was diagnosed using transbronchial lung biopsy (TBLB) and genetic analysis of a blood sample. The patient provided a written informed consent to us to share these findings.

Case Report

An 81-year-old man with no smoking history was referred to our hospital because of a few months' history of intermittent mild cough and slightly yellow sputum. Bilateral multiple patchy opacities were seen on the chest radiography (Figure 1a), and non-segmental air-space consolidations with ground-glass opacities were seen on the chest computed tomography (CT) (Figure 1b and c). Mediastinal or hilar lymph node enlargement was not detected on chest CT. His past medical history included hypertension, hyperlipidemia, and coronary artery stenosis, for which he was taking medications. He had a younger brother who was diagnosed with lung cancer, and an older brother who was diagnosed with cerebral apoplexy. The patient presented with the following vital signs: temperature, 36.8°C; pulse rate, 85 beats/min; blood pressure, 131/84 mmHg; and oxyhemoglobin saturation, 95% in normal room air. The findings of the systemic examination, including chest auscultation, were normal.

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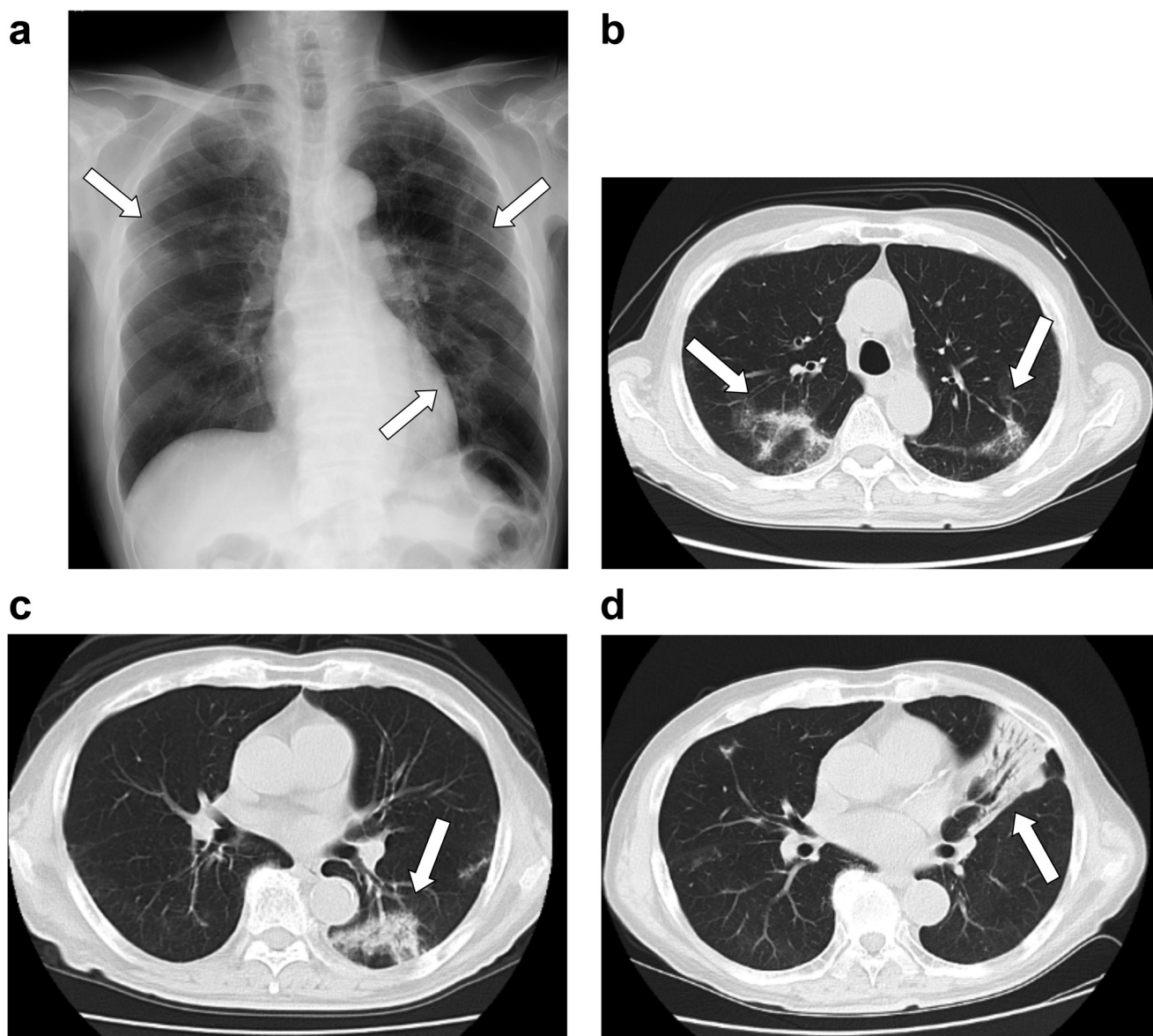


Figure 1 Chest X-ray film showing bilateral multiple patchy opacities (a). Computed tomography (CT) scans showing bilateral multiple non-segmental air-space consolidations with ground-glass opacities (b, c). A CT image showing air-space consolidation with air bronchogram in the left S4 (d).

The blood test results demonstrated an increase in the percentage of eosinophils (white blood cells, $6300/\text{mm}^3$ [normal range, $4000\text{--}9000/\text{mm}^3$]; eosinophils, 9.2%), fibrinogen (651 mg/dL [normal range, $200\text{--}400\text{ mg/dL}$]), C-reactive protein (3.28 mg/dL [normal range, $0.0\text{--}0.3\text{ mg/dL}$]), alkaline phosphatase (503 IU/L [normal range, $115\text{--}359\text{ mg/dL}$]), and serum calcium (10.6 mg/dL [normal range, $8.7\text{--}10.3\text{ mg/dL}$]). In addition, the patient presented with mild anemia (hemoglobin, 11.6 g/dL [normal range, $13.0\text{--}17.5\text{ g/dL}$]), low serum albumin (3.0 g/dL [normal range, $4.0\text{--}5.0$

mg/dL) and mild proteinuria ($15\text{--}29\text{ mg/dL}$ [normal range, $<14\text{ mg/dL}$]). Tests for rheumatoid factor, anti-nuclear antibody, and anti-neutrophil cytoplasmic antibody all yielded negative findings. We also obtained negative findings for β -D-glucan, cryptococcal antigen, and aspergillus antigen. The IgG, IgA, and IgM concentrations were 1416 mg/dL (normal, $870\text{--}1700\text{ mg/dL}$), 626 mg/dL (normal, $110\text{--}410\text{ mg/dL}$), and 69 mg/dL (normal, $35\text{--}220\text{ mg/dL}$), respectively. The levels of tumor markers, including carcinoembryonic antigen (CEA), squamous cell carcinoma-associated

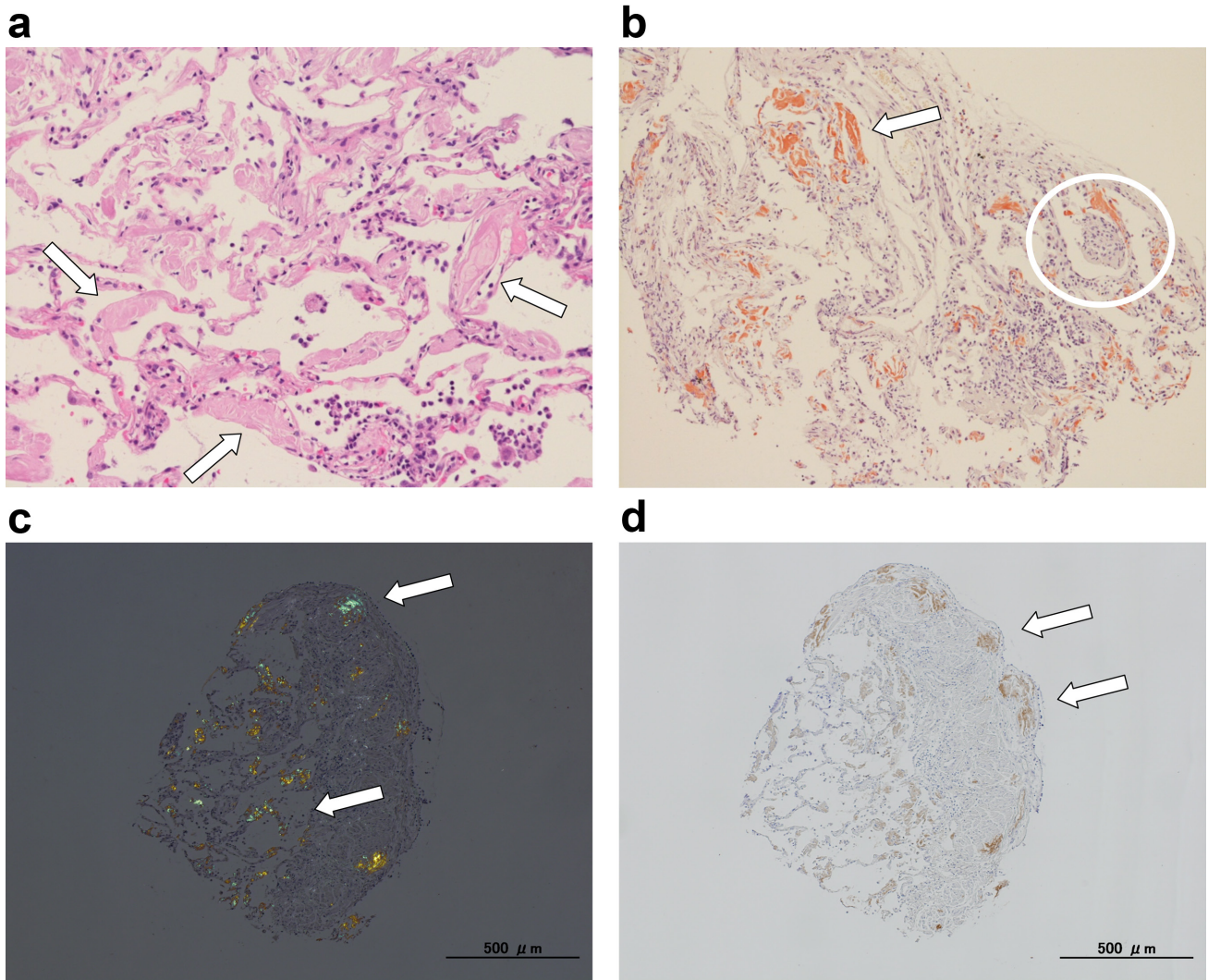


Figure 2 The biopsy specimens from the transbronchial lung biopsy of the left S8 revealing amorphous eosinophilic deposits (hematoxylin and eosin staining) (a). The eosinophilic deposits are positive for direct fast scarlet staining (arrow), and the white circle highlights a Masson body (b). The eosinophilic deposits are identified using apple green birefringence when stained with Congo red and viewed under polarized light (c). Immunohistochemical staining with anti-transthyretin is positive (d).

antigen (SCC), and pro-gastrin releasing peptide (ProGRP), were all within the normal range. In addition, all sputum cultures, including those for acid-fast bacilli, showed negative findings.

A transbronchial lung biopsy (TBLB) of the left S8 region that demonstrated consolidation on radiography was performed. The biopsy specimens demonstrated diffuse eosinophilic deposits in alveolar wall, and some of the alveolar spaces contained Masson bodies, which was consistent with organizing pneumonia (OP) (Figure 2a and b). As the eosinophilic deposits were positive for direct fast scarlet staining, and identified by apple-green birefringence when stained with Congo Red and examined under polarized light, the eo-

sinophilic deposits were demonstrated to be amyloid (Figure 2b and c). After oxidation with permanganate solution, the direct fast scarlet staining did not disappear, indicating that the amyloid was of the non-amyloid A protein-derived type. In additional examinations, blood immunological electrophoresis showed normal findings, and Bence-Jones protein was not detected by urine immunological electrophoresis. Afterwards, the patient was conservatively managed without any further treatment, as his condition spontaneously improved. Three months later, the infiltration seen in the left lower lobe was remarkably diminished, and new infiltrations in the lingual and right lower lobes were detected on CT (Figure 1d). TBLB of the area demonstrating

consolidation in the left S4 was performed, and the biopsy specimens showed diffuse amyloid deposition with OP pattern again. Immunohistochemical examination of the TBLB specimens revealed transthyretin-derived amyloid (Figure 2d), and the presence of wild-type transthyretin was proved by genetic analysis of transthyretin (TTR) using his blood sample. Therefore, he was diagnosed with ATTRwt amyloidosis, also known as senile systemic amyloidosis, associated with OP.

We performed a systemic examination because ATTRwt amyloidosis could affect the heart and lungs, and the stroma of the vascular wall of various organs^{4,5}. Duodenal and gastric biopsy specimens taken during upper gastrointestinal endoscopy, rectal biopsy specimens taken during colonoscopy, and a bone marrow needle biopsy specimen did not reveal amyloidosis. In the neurological examinations, brain magnetic resonance imaging (MRI) revealed no significant findings, but a nerve conduction velocity test of the sural nerve revealed mild depression. On ultrasonic cardiography, mildly increased left ventricular wall thickness and a punctate high-echo lesion of the ventricular septum were suspected. However, at the time of diagnosis, no clear evidence of cardiac amyloidosis was detected using cardiovascular MRI and no cardiac dysfunction was found using ultrasonic cardiography (ejection fraction of 61.4%).

He was conservatively managed as an outpatient, and the non-segmental air-space consolidation on the chest CT spontaneously disappeared. However, at his two-year follow-up, decreased left ventricular systolic function (ejection fraction of 39.9%) was found on ultrasonic cardiography and was followed up carefully by a cardiologist.

Discussion

We present a case of amyloidosis, in which the development of OP and TBLB led to a diagnosis of ATTRwt amyloidosis. In our case, although the details were unclear, we suspected that OP was cryptogenic organizing pneumonia (COP) or secondary OP related to respiratory infection. Moreover, as there were no reports that described the association between ATTRwt and development of OP, we thought that the development of OP was not associated with pulmonary amyloidosis. Although ATTRwt amyloidosis is increasingly being diagnosed, the antemortem diagnosis of this form of amyloidosis is relatively rare^{4,5}. To the best of our knowledge, this is the first reported case of ATTRwt amyloidosis diagnosed using the immunohistochemical examination of TBLB samples and genetic analysis of a blood sample.

Pulmonary amyloidosis is characterized by extracellular deposition of a specific histochemical substance called amy-

loid in the pulmonary tissues^{1,4,6-8}. Amyloid includes various proteins in a β -pleated sheet configuration that makes the proteins resistant to proteolysis^{1-3,9}. Amyloidosis can be classified as localized or systemic amyloidosis^{1,2,10}. Consequently, pulmonary amyloid deposition is also divided into an organ-restricted type and a type that is a part of systemic amyloidosis^{6,11}. Pulmonary amyloidosis may present as either a nodular parenchymal form (parenchymal nodules), a diffuse interstitial form (diffuse interstitial damage), a tracheobronchial form (submucosal deposits in the airways), or as a pleural effusion associated with pleural amyloid deposition^{7,8,11}. The present patient may be classified as having the diffuse interstitial form of pulmonary amyloidosis, which is the least common form of pulmonary amyloidosis and is seen much more commonly as a part of systemic amyloidosis⁸.

Although pulmonary involvement in systemic amyloidosis is common, as amyloidosis is relatively rare disease, the detection of amyloid deposition in pulmonary tissues is rare^{1,2,10}. Systemic amyloidosis can be subclassified as immunoglobulin light chain amyloidosis (AL amyloidosis), reactive amyloidosis (AA amyloidosis), familial amyloidosis (FAP, mainly a variant transthyretin amyloidosis), senile systemic amyloidosis (SAA, also known as wild-type ATTR amyloidosis), and dialysis amyloidosis^{2,4}. The most common form of systemic amyloidosis is AL amyloidosis, and AL-type amyloidosis is the most common form of pulmonary amyloidosis in both systemic and localized forms^{2,9}. However, in our case, the amyloidosis was classified as the ATTRwt type of systemic amyloidosis. An antemortem diagnosis of ATTRwt amyloidosis is relatively rare, and transthyretin amyloid deposition in TBLB specimens is extremely rare^{4,5,9}.

The incidence of ATTRwt amyloidosis, also referred to as senile systemic amyloidosis, is expected to increase with the recent increase in the life expectancy^{4,5}. In a recent study in the United Kingdom, ATTRwt amyloidosis represented 6.4% of amyloidosis cases in 2009–2012³. ATTRwt amyloidosis is the most common systemic amyloidosis in elderly people, and it mainly affects the heart and lungs, and the vascular wall and stroma of various organs^{4,5}. Although approximately 20% of individuals older than 80 years were found to have amyloid deposition in the heart at autopsy, as ATTRwt amyloidosis is not easily recognized by physicians, there are likely to be many undiagnosed elderly patients with ATTRwt amyloidosis³⁻⁵. Cardiac involvement is the leading cause of morbidity and mortality in amyloidosis, and it is a dominant feature in patients with ATTRwt amyloidosis³. Atrial fibrillation and progressive chronic heart failure are major clinical features of patients with ATTRwt¹². Therefore, in patients with ATTRwt amyloidosis, careful follow-

up of cardiac amyloidosis using cardiovascular MRI, ultrasonic cardiography, and the serum concentration of brain natriuretic peptide (BNP) would be necessary.

In summary, we have described a rare case of pulmonary ATTRwt amyloidosis with OP. When transthyretin amyloid deposits are discovered in the TBLB specimens of an elderly patient, systemic evaluation, including assessment of the cardiac function, is required. Our report provides further insight into the clinical significance of ATTRwt amyloidosis for physicians.

Conflicts of Interest: The authors state that they have no conflicts of interest.

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