Spontaneous Resolution of Multiple Nodular Pulmonary AA Amyloidosis

Hirotoshi Fukatsu 1,2, Haruka Miyoshi 2 and Kuniharu Ishiki 2

Abstract

A 62-year-old man presented with a two-week history of dry cough. A chest computed tomography (CT) showed three nodular masses of soft tissue density without calcification or cavitory formation in the right lung. F-18 fluorodeoxyglucose PET/CT scan revealed high FDG uptake in two out of three pulmonary nodules. Transbronchial lung biopsy specimens consisted of amorphous eosinophilic deposits that were demonstrated to be amyloid because they were positive for Congo Red staining. After oxidation with permanganate solution, the Congo Red staining disappeared, indicating that this amyloid was amyloid A protein-derived type. There was no evidence of any systemic diseases. We diagnosed the patient as having multiple nodular pulmonary AA amyloidosis. The patient was conservatively managed without treatment, and the pulmonary nodules disappeared spontaneously three months later.

Key words: pulmonary AA amyloidosis, spontaneous resolution, FDG PET-CT

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Introduction

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of an abnormal protein formed by amyloid fibrils. Although the deposition of amyloid can be localized, restricted to one organ or site in the body, or systemic in various organs and tissues throughout the body, pulmonary involvement is relatively rare (1). Pulmonary amyloidosis can take a variety of forms; traditionally it is separated into nodular, tracheobronchial, and diffuse alveolar septal forms (2-6). Nodular pulmonary amyloidosis comprises single or multiple nodules characterized by central deposition associated with minor inflammatory infiltration by lymphocytes, plasma cells, and multinucleated histiocytes (7). Patients with nodular pulmonary amyloidosis usually are asymptomatic and have no underlying systemic diseases (2). In addition, the pulmonary nodules have been reported not to regress but to typically display slow growth over years (2-5). However, there have been few reports describing spontaneous resolution of pulmonary localized amyloidosis (8, 9). We herein describe a case report of spontaneous resolution of pulmonary localized AA amyloidosis.

Case Report

A 62-year-old man presented with a two-week history of dry cough. His chest X-ray from another hospital showed multiple nodules in the right lung. He was admitted to our institution for further examination of pulmonary nodules. He had no other symptoms and no relevant past medical history. In addition, he was a non-smoker and had no family history of pulmonary, hematological or collagen disease. A physical examination of the heart, lungs, and abdomen revealed no abnormal findings. In addition, there was no cervical, axillary, or inguinal lymphadenopathy. Neurological examinations also revealed no focal or sensory abnormal findings. Laboratory examinations are shown in Table 1. Complete blood count, blood urea nitrogen, and serum creatinine were within normal ranges. Aspartate aminotransferase, alanine transaminase, and C-reactive protein (CRP) were slightly elevated [34 IU/L (normal, 10-27), 40 IU/L (5-33), and 1.82 mg/dL (0.00-0.60), respectively], and serum amyloid A (SAA) was within normal range [5.3 μg/mL (0.0-8.0)]. Anti-

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nuclear antibody was positive (X 80, speckled), and serum rheumatoid factor was positive [35 IU/mL (0-20)]. Anti-SS-A and anti-SS-B were negative.

Tumor markers, including CEA, CA19-9, SCC, and ProGRP, were within normal ranges. Blood immunological electrophoresis showed a normal pattern. Proteinuria and Bence-Jones protein were not found by urine immunological electrophoresis. Sputum culture including tuberculosis was negative. A chest computed tomography (CT) showed three nodular masses of soft tissue density without calcification or cavitary formation (Fig. 1). These varied in size from 0.5 to 3 cm in diameter, were well demarcated and were situated in the right lung. In addition, neither hilar nor mediastinal lymph nodes were swollen. As the multiple lung nodules raised suspicions of metastatic lesions from a hidden malignancy, F-18 fluorodeoxyglucose (18FDG) PET-CT was performed to characterize the nodules and to detect possible lesions of a primary malignancy. 18FDG PET-CT scan revealed high FDG uptake in two out of three pulmonary nodules, and the maximum standardized uptake value (SUVmax) was 6.72 (Fig. 2). However, there was no hypermetabolic lesion indicative of a primary malignancy seen throughout the entire body except for the chest. Bronchoscopy was performed and bronchoalveolar lavage was negative for acid fast bacilli, nocardia, and fungi. Transbronchial lung biopsy (TBLB) for two nodules with FDG uptakes was performed, and the biopsy specimens consisted of amorphous eosinophilic deposits that were demonstrated to be amyloid because they were positive for Congo Red staining (Fig. 3). After oxidation with permanganate solution, the Congo Red staining disappeared, indicating that the amyloid was amyloid A protein-derived type (Fig. 4). Upper gastrointestinal endoscopy and colonoscopy revealed no remarkable findings. In addition, duodenal and rectal biopsy specimens did not reveal amyloidosis, although kidney biopsy and the aspiration biopsy of bone marrow and subcutaneous fat were not performed. There was no evidence of any systemic diseases and in particular no evidence of myeloma. We diagnosed the patient as having pulmonary localized AA amyloidosis. The patient was conservatively managed without treatment. Af-

### Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Component</th>
<th>WBC 7200 /µL</th>
<th>TP 7.2 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC 471 ×10⁶ /µL</td>
<td>15.5 g/dL</td>
<td>7.2 g/dL</td>
</tr>
<tr>
<td>Ht 45.0%</td>
<td>34 IU/L</td>
<td>40 IU/L</td>
</tr>
<tr>
<td>Hb 15.5 g/dL</td>
<td>40 IU/L</td>
<td>40 IU/L</td>
</tr>
<tr>
<td>Platelets 23.5 ×10⁴ /µL</td>
<td>336 IU/L</td>
<td>206 IU/L</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>BUN 12 mg/dL</td>
<td>Cr 0.73 mg/dL</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>IgA 214 mg/dL</td>
<td>IgM 143 mg/dL</td>
</tr>
<tr>
<td>Occult blood</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>BJ protein</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>β2-MG 61 µg/L</td>
<td>(.5)</td>
<td>(.5)</td>
</tr>
</tbody>
</table>

**Figure 1.** A chest CT showed three nodular masses of soft tissue density without calcification or cavitary formation.
terward, dry cough and laboratory findings improved one month later. In addition, the pulmonary nodules disappeared spontaneously three months later (Fig. 5). After six months, primary diseases which caused secondary amyloidosis were not observed and chest CT showed no recurrence of the pulmonary nodules.

Discussion

Primary pulmonary amyloidosis is a localized form confined to the lung parenchyma, and it is the most commonly observed among the localized forms of amyloidosis (4, 10, 11). Pulmonary amyloidosis occurs in three patterns, which have been described as tracheobronchial, nodular, and diffuse parenchymal forms (3, 4). The parenchymal form is also called the alveolar septal form.

In pulmonary nodular amyloidosis, the nodules have been reported to have sharp and lobulated margins in a peripheral or subpleural location (5, 12). The size of the nodules varies from micronodular to 15 cm in diameter. Moreover, these lesions are commonly located in the outer one-third of the lungs (5, 12). The differential diagnosis includes primary or metastatic neoplasm and granulomatous disease. Although 18F-FDG PET has been recently reported to increase diagnostic accuracy in the differentiation of benign and malignant lesions, 18F-FDG PET-CT versus contrast-enhanced CT revealed lower specificity in lesion characterization (13, 14). In fact, several reports have described positive findings for pulmonary amyloidosis that raised the possibility of the presence of a malignancy (15, 16). Therefore, pulmonary amyloidosis should be added as a possible false-positive when pulmonary malignancy is suspected (15, 16). In the present case, multiple nodules were observed in the right lung, which suggested they were metastatic lesions. In addition, 18F-FDG PET-CT in our case showed high uptakes, although the location of the primary lesion remained uncertain. Therefore, TBLB was performed, allowing us to diagnose these lesions as localized pulmonary AA amyloidosis. Although one of three nodules in the present patient did not show high FDG uptake, it may be because the nodule was too small to be detected by 18F-FDG PET-CT.

AA amyloidosis is mainly associated with long-standing infections or noninfectious inflammation and less frequently with cancer, mainly renal cell carcinoma and Hodgkin’s disease (17). However, it has been reported that 23 of 374 patients (6%) presenting with AA amyloidosis had clinically covert inflammation disease that could not be characterized (18). In the present case, although ANA and RF were not within normal ranges, there were no findings indicating collagen diseases including rheumatoid arthritis. Therefore, the cause of AA amyloidosis was not detected, even during the follow-up period, and we thus diagnosed this patient as having primary pulmonary AA amyloidosis.

AA amyloid is a unique non-immunoglobulin protein gen-
nerally recognized as a reactive or secondary systemic amyloidosis because it is usually a complication of any disorder associated with a sustained acute phase, chronic inflammation, infection, and neoplastic disorders (17, 18). AA fibrils are derived from cleavage fragments of the circulating acute phase reactant, SAA. SAA is an apolipoprotein of high-density lipoprotein (HDL), which like CRP is synthesized in the liver under the transcriptional regulation of cytokines including IL-1, IL-6, and TNF-α. The circulating concentration of SAA tends to parallel that of the much more frequently measured CRP. A sustained high plasma level of SAA is a prerequisite for the development of AA amyloidosis. Therefore, the treatment of AA amyloidosis is aimed at controlling the underlying inflammation disorders to reduce the SAA level. If the treatment of the underlying disease can maintain the SAA concentration below 10 mg/L, the deposition of amyloid can be prevented, the lesions can regress, and long-term survival can be significantly improved (18).

In the present case, there were no underlying conditions suggestive of systemic diseases, and pulmonary amyloidosis spontaneously resolved without treatment. Although several cases with secondary amyloidosis have been reported to completely resolve with adequate treatment, there have been few cases to show spontaneous resolution with pulmonary amyloidosis (22). To the best of our knowledge, three cases including the present case of spontaneous resolution of pulmonary amyloidosis have been reported, as shown in Table 2 (8, 9). All patients were male and the types of pulmonary amyloidosis were varied. The type of amyloidosis in our case was AA, whereas the others were unknown.

The present case did not exhibit any clinical or laboratory evidence of systemic diseases, including rectal and gastrointestinal biopsy specimens, although bone marrow aspiration was not performed. On the other hand, it has been reported that subcutaneous fat aspiration was a sensitive and specific method for excluding systemic amyloidosis (23, 24). However, as systemic amyloidosis does not spontaneously resolve, we considered the present case to be different from systemic amyloidosis, although we did not perform subcutaneous fat aspiration.

In conclusion, we report a rare case of multiple localized pulmonary AA amyloidosis with high FDG uptake. This case showed a spontaneous resolution without treatment; and clinicians should bare in mind that localized nodular pulmonary amyloidosis can resolve spontaneously.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Gender</th>
<th>Type of amyloidosis</th>
<th>Type of pulmonary involvement</th>
<th>Time to resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doshi A</td>
<td>41</td>
<td>Male</td>
<td>N/A</td>
<td>diffuse alveolar septal</td>
<td>one year</td>
</tr>
<tr>
<td>Hof DG</td>
<td>39</td>
<td>Male</td>
<td>N/A</td>
<td>tracheobronchial</td>
<td>N/A</td>
</tr>
<tr>
<td>Our case</td>
<td>62</td>
<td>Male</td>
<td>AA</td>
<td>multiple nodular</td>
<td>three months</td>
</tr>
</tbody>
</table>

N/A: Not available

References

18. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history