Pulmonary Localized AA Type Amyloidosis with Cyst-like Structures and Marginal Zone B-cell Lymphoma of the MALT Type Coexisting Independently in the Left upper Lung

Naoki Yanagawa, Shin-ya Ogata and Teiichi Motoyama

Abstract

A 77-year-old man was found to have an abnormal shadow on chest X-ray. Chest CT indicated four lesions in both lungs. One was located in the left S1+2. The others were located in the left S3, right S8 and S9, and those had cyst-like structures. The tumor in S1+2 showed diffuse proliferation of atypical lymphocytes, which were positive for CD20. The diagnosis of pulmonary mucosa-associated lymphoid tissue lymphoma was made. The tumor in S3 was composed of eosinophilic amorphous deposits. The diagnosis of amyloidosis was confirmed by polarized light examination. After oxidation with permanganate solution, the Congo red staining disappeared.

Key words: pulmonary amyloidosis, AA (amyloid-associated) type amyloidosis, pulmonary MALT lymphoma

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Introduction

Amyloid is a pathological fibrillar proteinaceous substance, deposited between cells in various tissues and organs of the body in a wide variety of lesions. Amyloidosis can be either systemic amyloidosis or localized amyloidosis. The former is involved in several organ systems, the latter is limited to a single organ (1). Three forms of pulmonary amyloidosis have been recognized in the literature: namely diffuse alveolar septal, nodular, and tracheobronchial (2). The most common form is nodular amyloidosis, a rare condition with a good prognosis that usually presents in older individuals as asymptomatic nodules identified on routine chest X-rays. The cause of pulmonary nodular amyloidosis is uncertain, although it has been hypothesized that it represents a reaction to chronic inflammatory disorders (e.g., tuberculosis, HIV infection), or connective tissue diseases (2-5). Amyloidosis is also associated with systemic lymphoproliferative disorders and plasma cell dyscrasias (2, 5, 6). On the other hand, primary pulmonary lymphoma is rare, accounting for only 0.34% of all lymphomas, for 3-4% of extranodal lymphoma and 0.5-1% of primary pulmonary malignancies (7). Most primary lymphomas of the lung arise from the mucosa-associated lymphoid tissue (MALT) of the bronchus, which are called low grade marginal zone B-cell lymphoma of MALT. MALT lymphoma is considered to be associated with autoimmune disorders or other chronic inflammatory processes (8). MALT lymphoma sometimes may contain amyloid deposits, but this finding is extremely rare; it has been reported in only 18 cases (3, 6, 8-14). This report presents a case of pulmonary AA (amyloid-associated) type amyloidosis with cyst-like structures and MALT lymphoma coexisting independently in the left upper lobe.

Case Report

An abnormal shadow was observed on a chest X-ray in the lung of a 77-year-old man during a routine health screening. He had no symptoms, and his prior history showed no anomalies. He had smoked 20 cigarettes/day for the last 56 years. A physical examination also indicated...
Figure 1. Chest CT showed four mass lesions in the left upper lung and the right lower lung. One was located in S1+2, 40 mm in diameter, with irregular margins (a). The other lesions were located in the left S3 (b), right S8 (c), and right S9 (d), ranging in diameter from 8-16 mm, with cyst-like structures.

nothing unusual. A laboratory examination showed that his C-reactive protein (CRP) was slightly elevated (0.8 mg/dL), IgM was high (404 mg/dL), IgG was upper limit of normal (1,590 mg/dL), and serum amyloid A protein was high (40.2 μg/L). Serum rheumatoid factor, anti-nuclear antibody, anti-SS-A antibody, and anti-SS-B antibody were negative. Bence-Jones protein was not found by urine immunological electrophoresis. A chest X-ray showed an ill-defined mass in the left upper zone. Chest CT indicated total four mass lesions in the left upper lung and the right lower lung (Fig. 1). One was located in the left S1+2, 40 mm in diameter, with irregular margins (Fig. 1a). The other lesions were located in the left S3 (Fig. 1b), right S8 (Fig. 1c), and right S9 (Fig. 1d), ranging in diameter from 8-16 mm, and with cyst-like structures. No mediastinum lymphadenopathy was recognized, and PET (positron emission tomography)/CT revealed no abnormalities except for the S1+2 mass. Gastro-duodenoscopy and colonoscopy showed no abnormal findings. A lung biopsy specimen was obtained under CT guidance from the left S1+2 mass, and a MALT lymphoma was suspected. A transbronchial lung biopsy was performed on the left S3 mass, and a nodular amyloidosis was diagnosed. Therefore, a left upper lobectomy was performed. The subaortic, subcarinal, and left hilar lymph nodes were also sampled.

The resected tissue specimens were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with routinely Hematoxylin and Eosin staining saffron. Special stains (Congo red including oxidation with permanganate solution and Direct Fast Scarlet), and polarized light examination were also performed. Immunohistochemical staining of the formalin fixed paraffin-embedded sections was performed using the labeled streptavidin-biotin method (Nichirei, Tokyo, Japan). The antibodies used are listed in Table 1. There were two tumor lesions in the resected left upper lung (Fig. 2a). The tumor in S1+2 was 40×28×46 mm in size, whitish to grayish in color, with irregular margins. The tumor in S3 was 17×14×22 mm in size, pale whitish in color, with a cavity. These tumors were separated. Microscopically, the tumor in S1+2 showed diffuse proliferation of atypical small to medium sized lymphocytes featured like centrocyte-like cells (CCL cells) or monocytopid B-cell with an active germinal center, which infiltrated into the bronchiole and presented the features of lymphoepithelial lesions (Fig. 2b). The lymphoepithelial lesions were found more clearly by immunohistochemical staining for cytokeratins (AE1+AE3) (Fig. 2c). The atypical lymphoid cells were positive for CD 20 (Fig. 2d), CD79α, bcl-2, and kappa light chain, and negative for CD3, CD5, and cyclin D1. In this area, amyloid deposits were not found. On the other hand, the tumor of S3 was composed of eosinophilic amorphous deposits. Those deposits had apple green birefringence under polarized light examination. Congo red staining (Fig. 2e) and Direct Fast Scarlet staining were positive, and a diagnosis of amyloidosis was confirmed. After oxidation with permanganate solution, the Congo red staining disappeared. The material was positive for amyloid A, but negative for either kappa or lambda light chain, suggesting that this amyloidosis is AA
type. Cyst-like lesions corresponded to dilated bronchioles infiltrated by amyloidosis (Fig. 2f). No tumor cells were observed in the lymph nodes.

**Discussion**

Primary pulmonary lymphoma is rare, accounting for only 0.34% of all lymphomas, for 3-4% of extranodal lymphoma and 0.5-1% of primary pulmonary malignancies (7). Most primary lymphomas of the lung arise from the mucosa-associated lymphoid tissue (MALT) of the bronchus, which are called low grade marginal zone B-cell lymphoma of MALT. Microscopically, MALT-type primary pulmonary lymphoma is defined as a lesion containing: a) proliferation of small lymphoid cells analogous to the marginal zone cells of Peyer’s patches or spleen follicles, centrocyte-like cells and small lymphocytes, plasmacytes or monocyteid cells; b) a lymphoepithelial lesion showing lymphoid cell migration from the marginal zone to the bronchiolar epithelium; c) reactive follicular hyperplasia; and d) rare blastic cells; in particular, a) and b) are important findings (7). Since the present case also has findings of a) and b), we consider it agrees with the common diagnostic criteria of MALT-type lymphoma.

Localized amyloid deposition arising from an extranodal marginal zone lymphoma is very rare with a frequency of less than 1% (3). Only 18 cases have been reported (3, 6, 8-14), and the deposited amyloids were AL (amyloid light chain) type in almost all of those cases. AL is derived from plasma cells and contains immunoglobulin light chains. This deposition is associated with some form of monoclonal B-cell proliferation and is known as primary amyloidosis (1). It is not known how lymphoproliferative disorders (monoclonal B cell dyscrasia, including plasmacytoma, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, and MALT lymphoma) produce AL amyloid. It is thought to be due to an overproduction of immunoglobulin from lymphoproliferative disorders and an excretory block of immunoglobulin (6). However, in the present case, AA (amyloid-associated) type localized amyloidosis and MALT lymphoma independently coexisted in the left upper lobe. AA amyloidosis is a unique nonimmunoglobulin protein, and is generally recognized as reactive or secondary systemic amyloidosis because it is usually a complication of any disorder associated with a sustained acute phase response, chronic inflammation, infection, and neoplastic disorders (2). AA fibrils are derived from cleavage fragments of the circulating acute phase reactant, SAA (serum amyloid-associated protein). SAA is an apolipoprotein of high density lipoprotein (HDL) (15), which, like CRP is synthesized in the liver under the transcriptional regulation of cytokines including IL-1, IL-6 and TNF-1α (16). 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. Most cases of AA amyloidosis are based on chronic inflammation (rheumatoid arthritis, Sjögren’s syndrome, and Crohn’s disease) and their association with lymphoma is rare (1, 2, 17). In the present case, depositing amyloids were not stained by antibodies to kappa and lambda light chains, but were stained by those to amyloid A. These results suggest that the deposited amyloid in this case was not produced by lymphoma cells. On the other hand, it has been reported that MALT lymphoma may occur as an acquired lymphoproliferative lesion in cases of chronic inflammation and autoimmune disorders, such as rheumatoid arthritis, Sjögren’s syndrome, and systemic lupus erythematosus (4, 12, 13). MALT of the stomach is considered to be associated with a continuous infection of Helicobacter pylori. In the current case, serum rheumatoid factor, anti-nuclear antibody, anti-SS-A

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**Table 1. Antibodies and Results of Immunohistochemistry**

<table>
<thead>
<tr>
<th>Antibody (Clone)</th>
<th>Source</th>
<th>Source</th>
<th>S1+2 tumor</th>
<th>S3 tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid A(mcl1)</td>
<td>DakoCytomation, Glostrup, Denmark</td>
<td>-</td>
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<tr>
<td>Bcl-2(124)</td>
<td>DakoCytomation, Glostrup, Denmark</td>
<td>+</td>
<td>-</td>
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<tr>
<td>CD3(PS1)</td>
<td>Nichirei, Tokyo, Japan</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD5(4C7)</td>
<td>Nichirei, Tokyo, Japan</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD10(56C6)</td>
<td>Novocastra, Newcastle upon Tyne, UK</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD20 (L-26)</td>
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<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>CD23(1B12)</td>
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<tr>
<td>CD30 (Ber-H2)</td>
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<td>-</td>
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<td>CD79 α (JCB117)</td>
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<td>Cyclin D1(5D4)</td>
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<td>-</td>
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<tr>
<td>Cytokeratin (AE1/AE3)</td>
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<tr>
<td>IgA</td>
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<td>IgG</td>
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<td>IgM</td>
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<td></td>
</tr>
<tr>
<td>Kappa chain</td>
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<td>-</td>
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<td>Lambda chain</td>
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Figure 2. Macroscopic, microscopic, and immunohistochemistry findings. There were two mass lesions in the resected left upper lung. The arrow and arrowhead indicate the mass lesion in S1+2 and in S3, respectively (a). Histopathologically, the mass in S1+2 showed diffuse proliferation of atypical small to medium sized lymphocytes and featured centrocyte-like cells (CCL cells) or monocytoid B-cell with an active germinal center, which had infiltrated into the bronchiole and presented the features of a lymphoepithelial lesion (arrowhead) (b: Hematoxylin and Eosin staining, ×400). These lymphoepithelial lesions were found more clearly by immunohistochemical staining for cytokeratins AE1+AE3 (c: ×400). Immunohistochemically, the atypical lymphoid cells were positive for CD20 (d: ×400). Eosinophilic amorphous deposits found in S3 were stained by Congo red (e: ×200). Cyst-like lesions corresponded to dilated bronchioles infiltrated by amyloidosis (f: Hematoxylin and Eosin staining, ×100)

antibody, and anti-SS-B antibody were negative, and no symptoms of autoimmune disease were found, and overt chronic inflammation was also not found. But we consider that covert chronic inflammation might exist from the laboratory data of IgM and IgG, and AA type amyloidosis and MALT lymphoma arose synchronously and independent of each other.

The mechanism of cyst-like structure formation in pulmonary nodular amyloidosis is uncertain. However, Lantuejoul et al suggest a ball-valve mechanism, which results in air trapped within narrowed airways and is infiltrated either by amyloid deposits and/or malignant lymphoid proliferation (18). Ohdama et al suggest that amyloid deposits within bronchioalveolar structures and around alveolar capillaries could favor an ischemic process leading to disruption of alveolar processes (19). Since two mass lesions which were detected in the right lower lung also had cyst-like structures, we speculate that these lesions were also amyloidosis.
In conclusion, a case of pulmonary AA type amyloidosis with cyst-like structures and MALT lymphoma coexisting independently in the left upper lobe was encountered. Amyloidosis combined with MALT lymphoma is usually the AL type, however in this case it was the AA type.

Acknowledgement

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References