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【 CASE REPORT 】

Nodular Pulmonary Amyloidosis Associated with Sjögren's Syndrome

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Abstract:

Amyloidosis is a rare disease characterized by the deposition of abnormal proteins in extracellular tissues. We herein report a case with instructive radiologic features of nodular pulmonary amyloidosis associated with Sjögren's syndrome. A 67-year-old woman was referred to our department because of an abnormal chest radiograph. Chest computed tomography revealed multiple round cysts accompanied by calcified nodules. The patient was clinically diagnosed with primary Sjögren's syndrome and pathologically diagnosed with nodular pulmonary amyloidosis (light chain, kappa). Although multiple lung cysts have many etiologies, the presence of calcified nodules associated with multiple lung cysts is useful for narrowing down the differential diagnosis.

Key words: pulmonary amyloidosis, Sjögren's syndrome, cyst, calcified nodule

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Introduction

Amyloidosis is a rare disease characterized by the deposition of abnormal proteins in extracellular tissues, resulting in vital organ dysfunction and eventually death (1, 2). The disease can be confined to a single organ (10-20% of cases) or involve multiple organs (80-90% of cases) (1, 3). The respiratory system is involved in approximately 50% of cases, more commonly in the systemic form (4, 5).

Although cystic lung diseases show a wide disease spectrum, associated radiologic findings of ground-glass opacity, nodules, or calcified nodules can aid in reaching a correct diagnosis (6).

We herein report an instructive case of nodular pulmonary amyloidosis associated with Sjögren's syndrome showing multiple lung cysts and calcified nodules.

Case Report

A 67-year-old non-smoking woman was referred to our department because of an abnormal chest radiograph. She had no respiratory symptoms and no preexisting conditions but had had dryness of the mouth and eyes for the past few weeks. There were no abnormalities in her vital signs or physical examination findings. She had no family history of lung disease.

Lung function tests revealed normal spirometry. Chest radiography showed small nodules in both lungs (Fig. 1A). Chest computed tomography revealed multiple round cysts accompanied by calcified nodules, predominantly in the lower lobes (Fig. 1B-D). Laboratory tests showed elevated levels of antinuclear antibody (×160, speckled pattern), rheumatoid factor (153 IU/mL), and positivity of anti-Ro/SSA antibody. No other autoantibodies were detected. No systemic symptoms other than the symptoms of sicca were observed. The patient was clinically diagnosed with primary Sjögren's syndrome based on positivity for rheumatoid factor and anti-Ro/SSA antibodies and the impaired function of the salivary and lacrimal glands.

Bronchoalveolar lavage showed a cell count of 150/μL (macrophages, 82%; lymphocytes, 18%). Bronchoalveolar lavage fluid cultures were negative. A transbronchial lung biopsy revealed no specific diagnosis. A video-assisted tho-

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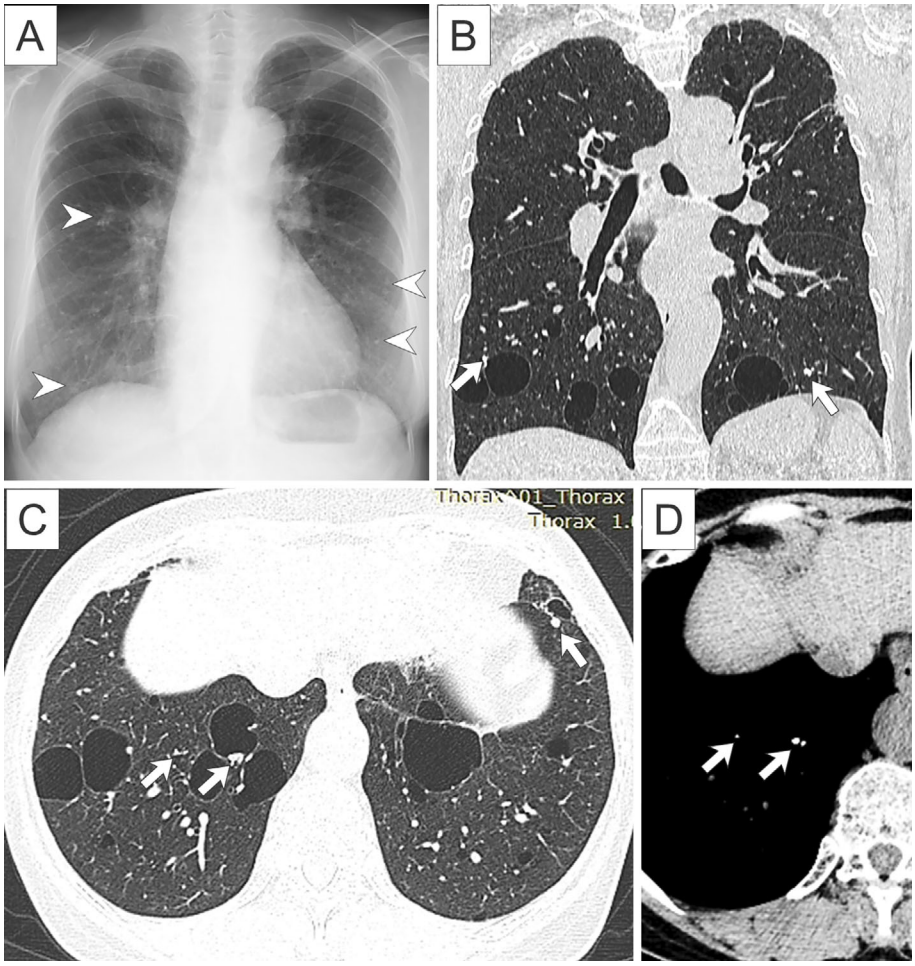

Figure 1. **Chest radiography showing some nodules (arrowheads) (A). Chest high-resolution computed tomography showing multiple cysts and calcified nodules (arrows), predominantly in the lower lobes (coronal view, B; axial view, C-D). Some nodules are present on the wall of the cyst, the others are isolated.**

racoscopic lung biopsy was therefore performed. A biopsy specimen obtained from the left lower lobe (S9), which contained a radiologically separated nodule and cyst, showed small foci of amorphous eosinophilic materials in the walls of small vessels and perivascular interstitium, forming nodular lesions (Fig. 2A, B). Interstitial fibrosis with chronic inflammatory infiltration and enlarged airspaces formed a cyst-like lesion (Fig. 2A, C). The nodule and cystic lesion were located separately from each other (Fig. 2A). The narrowing of the bronchiolar lumen due to the infiltration of mononuclear cells in the peribronchiolar stroma was also observed (Fig. 2D). Congo-red staining of the nodular materials was positive (Fig. 3A). Amyloid deposits were identified in Congo-red-stained specimens based on their apple-green birefringence under a polarized light microscope (Fig. 3B). Immunohistochemistry revealed that the materials were positive for light chain kappa (Fig. 3C). A systemic examination showed no evidence of amyloidosis outside the lungs. There were no major symptoms of systemic amyloidosis, serum immunoglobulin abnormalities, or serum or urine electrophoresis abnormalities. She was therefore diagnosed with nodular pulmonary amyloidosis associated with Sjögren's syndrome. She has been followed up for five years without progression.

We evaluated the nodules on axial images (slice thickness: 1 mm) at 5-mm intervals. A total of 78 nodules were found in all lung fields, and the longest diameter of the nodules was 4.1±1.9 mm (mean ± standard deviation). Calcification was found in 31 of the nodules (39.7%). Fifty-seven cysts were larger than 10 mm; 11 of these (19.3%) had mural nodules.

Discussion

Pulmonary amyloidosis is a rare entity and includes three different clinicopathologic types: diffuse alveolar-septal amyloidosis, nodular pulmonary amyloidosis, and tracheobronchial amyloidosis (7). Pulmonary amyloidosis may be localized or part of systemic amyloidosis (2, 7). Diffuse alveolar-septal amyloidosis is sometimes related to systemic amyloidosis, but nodular and tracheobronchial amyloidosis are usually limited to the lung (7). Diffuse alveolar-septal amyloidosis is symptomatic when amyloid deposits severely affect the alveolar structures, resulting in severe respiratory

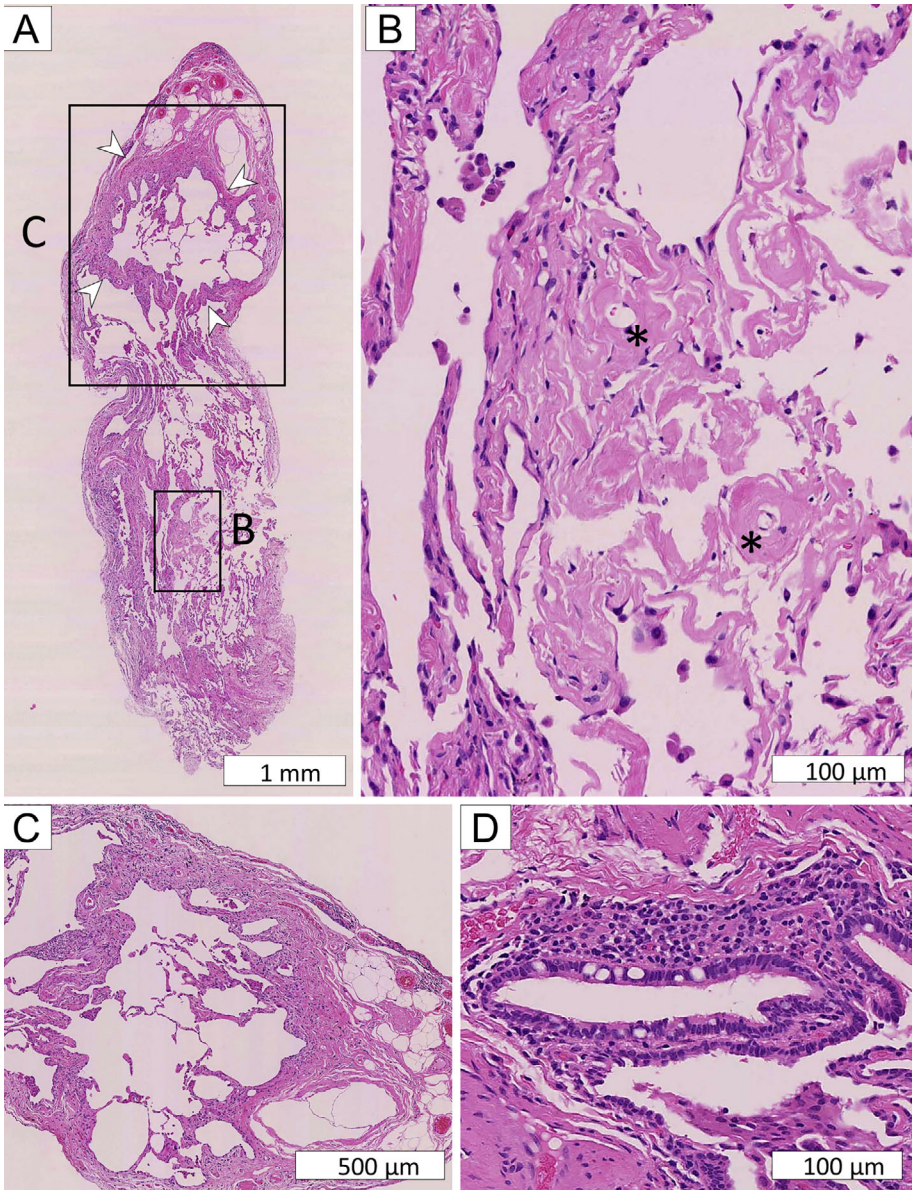

Figure 2. **(A) A Hematoxylin and Eosin staining section (a lower magnification view) showing a cyst-like lesion (arrowheads) and a nodular lesion. (B) A higher-magnification view of the nodular lesion showing amorphous eosinophilic materials in the walls of small vessels (*) and perivascular interstitium (inset of A). (C) An enlarged view of inset C showing interstitial fibrosis with chronic inflammatory infiltration and enlarged airspaces, forming a cyst-like lesion. (D) The infiltration of mononuclear cells in peribronchiolar stroma leads to narrowing of the bronchiolar lumen.**

impairment (2, 7). However, most cases of nodular and tracheobronchial amyloidosis are usually asymptomatic and only require careful follow-up (2, 7).

Nodular pulmonary amyloidosis is usually a localized and incidental finding on chest radiography (2). Currently, many cases of nodular pulmonary amyloidosis are thought to be associated with an underlying lymphoproliferative disease, such as Sjögren's syndrome or extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (2). Nodular pulmonary amyloidosis often shows solitary nodules, but Sjögren's syndrome-associated amyloidosis presents as multiple calcified nodules with multiple cysts (1, 7, 8). Thirty to fifty percent of patients with nodular pulmonary amyloidosis have calcified nodules (1). The amyloid fibrils themselves have an affinity for calcium and are detectable on radiographs; calcification and ossification may occur in both primary and secondary amyloidosis (7, 9). Although radiologic manifestations of nodular pulmonary amyloidosis associated with Sjögren's syndrome may be dramatic, patients with this disease are usually asymptomatic, and their prognosis is excellent without treatment (7, 8).

The cysts and nodules are reported to be located adjacent to each other in amyloidosis associated with Sjögren's syndrome (10, 11), but they were more often located separately in the present case. Jeong et al. examined the CT findings of

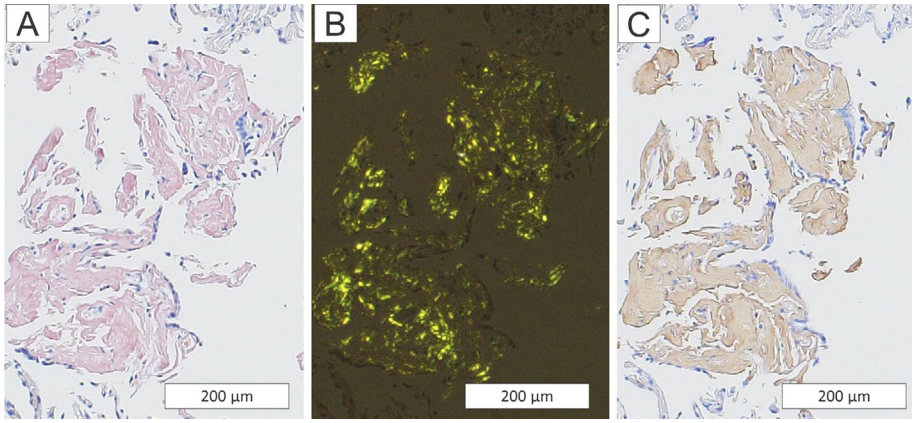

Figure 3. **Congo-red staining of the nodular materials was positive (A). Under a polarized light microscope, Congo-red-stained specimens showed apple-green birefringence (B). Immunohistochemical staining of the materials was positive for light chain kappa (C).**

5 patients with Sjögren's syndrome accompanying pulmonary amyloidosis and lymphoproliferative disease and found that the nodules varied in diameter (mean, 9.9 mm; range, 3-24 mm) (10). However, in the present case, the nodules were relatively small (4.1±1.9 mm). The actual mechanism underlying cyst formation in amyloidosis associated with Sjögren's syndrome is poorly understood; however, it may result from extensive amyloid deposition and the infiltration of inflammatory cells into the bronchial wall, which narrows the airway, acting as a check-valve mechanism and forming cysts with mural nodules (8, 10). In the present case, the amyloid nodule was relatively small and not large enough to involve the airway, which may have resulted in the cyst and nodule not being located adjacent to each other. However, Sjögren's syndrome itself reportedly renders a patient prone to cyst formation, regardless of whether or not it is associated with amyloidosis (12). The pathogenesis of cyst formation in Sjögren's syndrome is thought to be a check-valve mechanism due to airway inflammation or complications of lymphoid interstitial pneumonia (8, 12, 13). Although no pathological findings suggestive of lymphoid interstitial pneumonia were evident, lymphocytic infiltration and plasma cell infiltration in the bronchiolar walls were noted, which corresponded to airway narrowing. Therefore, in addition to amyloidosis, Sjögren's syndrome itself may be related to cyst formation.

Multiple lung cysts have many etiologies, including Birt-Hogg-Dubé syndrome, desquamative interstitial pneumonia, lymphangioleiomyomatosis, lymphoid interstitial pneumonia, *Pneumocystis jirovecii* pneumonia, pulmonary Langerhans cell histiocytosis, cystic metastasis, and amyloidosis (6, 13, 14). However, the presence of calcified nodules associated with multiple lung cysts narrows the differential diagnosis to pulmonary amyloidosis (6). Amyloid deposition can also be seen in lymphoproliferative diseases or malignant tumors, such as lymphoma, mucosa-associated lymphoid tissue lymphoma, carcinoid, squamous cell carcinoma, mucinous invasive adenocarcinoma, and metastatic renal carcinoma (15). Sjögren's syndrome is associated with an increased risk of lymphoma, especially marginal zone B-cell lymphoma and MALT lymphoma (16). Radiological abnormalities of lymphoma include nodules or masses, airspace consolidation, ground-glass attenuation, mediastinal lymphadenopathy, and pleural effusion (12, 17). Therefore, amyloidosis and lymphoma are sometimes difficult to distinguish. Radiologically, cysts rarely appear in lymphoma, and calcified nodules are usually absent in lymphoma (12, 18). However, calcified nodules may be seen when lymphoma is complicated by amyloidosis (15). Therefore, a surgical lung biopsy is required to confidently differentiate these diseases (7, 8).

The present case describes instructive radiologic features of nodular pulmonary amyloidosis associated with Sjögren's syndrome, and clinicians should be aware of these chest computed tomography findings.

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

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