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CASE REPORT

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Pulmonary AL amyloidosis in a patient with primary Sjögren syndrome

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Abstract The condition of a 29-year-old woman with primary Sjögren syndrome (SS) was complicated by amyloid light chains- (AL-) type amyloidosis in the paranasal sinus. She had not complained of respiratory symptoms, but her chest computed tomography (CT) scan revealed bilateral multiple nodular shadows. Lung biopsy specimens using video-associated thoracoscopy showed amyloidoma in a subpleural nodular lesion and amyloid deposits in the interstitial parenchymal walls and pulmonary vessels. Pulmonary AL amyloidosis, presumably related to a chronic inflammatory lymphoproliferative process in SS, has rarely been reported.

Key words Pulmonary amyloidosis · Sjögren syndrome (SS)

Introduction

Sjögren syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands, leading to the clinical symptoms of dry mouth and eyes. In addition to the destruction of exocrine glands, SS can affect the respiratory system at various sites from the trachea to small airways and pulmonary parenchyma. The frequency of lung involvement represented by lymphocytic interstitial pneumonia (LIP) in primary SS cases varies from 9% to 55%,[1] depending on the population studied and the evaluation procedures employed. The association between SS and LIP is well recognized.[2–4] However, pulmonary amyloidosis associated with SS has been considered to be very rare. Here, we describe a primary SS patient with amyloid light chains- (AL-) type amyloidosis complications in the paranasal sinus and lung, presenting multiple nodular pulmonary shadows by chest computed tomography (CT) scan.

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Case report

A 29-year-old Japanese woman was admitted to a nearby hospital in October 1997 because of a bilateral nasal obstruction with occasional episodes of nasal bleeding. A clinical diagnosis of bilateral sinusitis was made by an otorhinolaryngologist. The mucosal biopsy specimens of paranasal sinus by nasopharyngoendoscopy revealed amyloid depositions with inflammatory mononuclear cells (Fig. 1). Apple-green birefringence was seen when histological sections of amyloid deposits stained by Congo red were viewed with polarized light. When these deposits were treated with potassium permanganate before Congo red staining, they were resistant. Immunohistologically, these amyloid deposits showed positive staining of P component, and negative staining of AA protein and β_2 microglobulin. Based on these findings, the deposits were thought to be AL type. The clonality of light chains showed increased staining in the λ chain rather than in κ chain.

Since 1995, the patient had repeatedly experienced dryness of mouth and eyes with swelling of the bilateral parotid glands. Serum anti-SS-A and -SS-B antibodies were both positive, a labial gland biopsy specimen confirmed the diagnosis of Sjögren syndrome, and no amyloid deposits were seen. She was referred to our hospital for an evaluation of amyloidosis associated with Sjögren syndrome in February 1998. A physical examination on admission revealed a body temperature of 36.8°C. Small cervical lymph nodes were palpable, but no skin eruption was observed. On auscultation, fine and coarse crackles were not audible. A ophthalmologic examination showed a decreased tear flow rate by Schirmer's test and corneal erosions suggesting keratoconjunctivitis sicca.

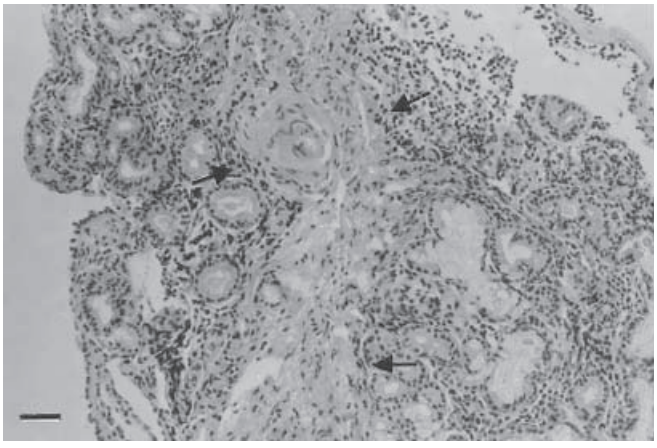

Fig. 1. Mucosal biopsy specimen of paranasal sinus shows amyloid deposits (*arrows*) with inflammatory cells (hematoxylin-eosin stain). *Bar* 100 μm

Peripheral blood counts revealed white blood cells at 4100/μl, a red blood cell count of 3.17×10^6/μl, hemoglobin at 10.3 g/dl, and a platelet count of 140×10^3/μl. Urinalysis was negative for proteinuria and occult blood. Serum blood urea nitrogen (BUN) and creatinine were normal at 10 mg/dl and 0.6 mg/dl, respectively. Serum total protein was 7.5 g/dl, and slightly hypergammaglobulinemia was found: IgG, 1860 mg/dl; IgA, 235 mg/dl; IgM, 107 mg/dl. However, no monoclonal band was detected by immunoelectrophoresis, nor was urinary Bence–Jones protein observed. Plasma cells without dysplasia were less than 5% in the bone marrow smear. C-reactive protein was less than 0.3 mg/dl, and rheumatoid factor was 40 U/ml (normal, <20). Fluorescein antinuclear antibody was positive with a speckled pattern. The enzyme-linked immunosorbent assay (ELISA) indices of antibodies to SS-A and SS-B were both positive, 139 and 22 (normal, <7 and <10), respectively. Anti-ssDNA antibody was positive at 106 U/ml (normal, <25), but anti-dsDNA antibody was negative at less than 10 U/ml (normal, <12). Anti-Sm antibody and anti-RNP antibody were negative. Anti-DNA antibody (RIA) was 4 U/ml (normal, <6) and complement activity (CH50) was 43.3 U/ml (29.0–48.0). Anticardiolipine · β_2-glycoprotein I (GPI) antibody was normal at less than 1.2 U/ml (normal, <3.5).

Coagulation studies showed a prolonged activated partial thromboplastin time (aPTT) at 35.1% (normal, 76%–130%), but a normal prothrombin time at 93.1% (normal, 86%–118%). A cross-mixing test suggested the existence of circulating anticoagulant, and lupus anticoagulant (LA), using the LA confirmation test kit (Gradipore, Australia), was positive, indicating the presence of antiphospholipid antibody. Resting arterial blood gases in room air showed a PaO_2 of 106.9 torr, $PaCO_2$ of 38.5 torr, and HCO_3^- of 25.1 torr. A lung function test showed a normal pattern at %VC of 84% and FEV1.0% of 95%. Electrocardiogram and echocardiogram were normal with no suggestion of cardiac amyloidosis. Neither hepatosplenomegaly nor space-occupying lesions in the liver were detected by abdominal CT.

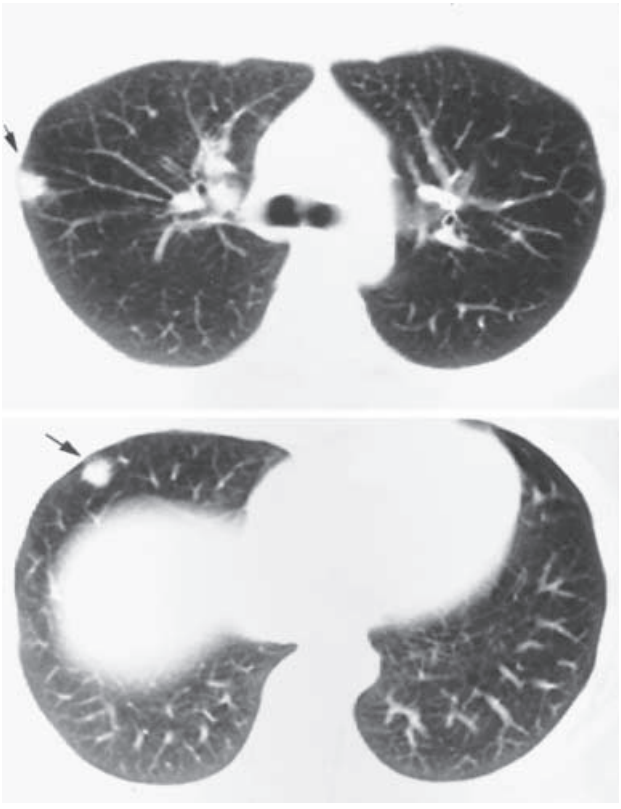

Fig. 2. Chest computed tomography (CT) scan reveals nodular pulmonary lesions but does not detect obvious interstitial shadows (*arrows*)

A chest CT scan revealed approximately ten bilateral nodular shadows about 10–20 mm in diameter in the whole lung without enlargement of mediastinal or pulmonary lymph nodes, although a chest roentgenogram apparently could not detect these abnormalities (Fig. 2). No interstitial shadow in the lung was apparent by chest CT. The patient had not complained of respiratory symptoms such as cough, sputum, or shortness of breath on exertion. On March 30, 1998, a lung biopsy of the right upper lobe (S3a) using a video-associated thoracoscope (VATS) was performed to make a histological diagnosis of pulmonary nodular shadows. The lung biopsy specimens, which showed both a white subpleural lesion and nearby normal lung lesion by VATS, were obtained. The histopathological findings of subpleural nodular tumor-like lesions confirmed amyloidoma, showing eosinophilic amorphismic substance deposits, and invading the alveoli predominantly around the bronchus and vessels (Fig. 3a). The normal appearance of lung tissue from gross observation also indicated that diffuse interstitial parenchymal amyloid depositions in the alveolar septa could be seen together with the lymphocyte infiltration (Fig. 3b). The amyloid deposits were also observed in pulmonary vessels and tracheobronchial walls. Small pulmonary arteries showed endoarterial stenosis by amyloid deposits in their walls (Fig. 3c). Immunohistochemically, these deposits were thought to be AL amyloidosis, resembling the paranasal mucosal biopsy specimens of sinusitis, because of negative

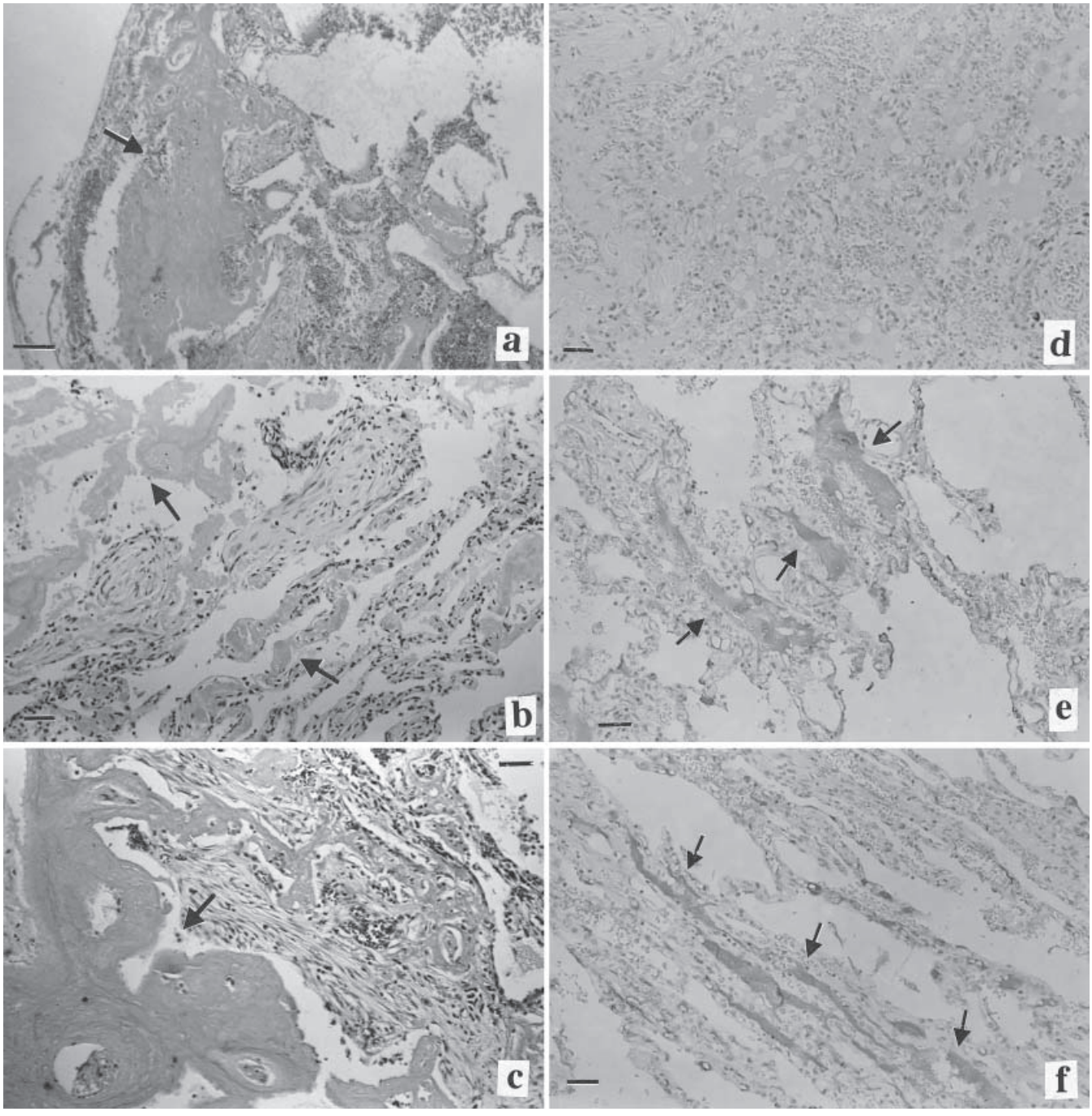

Fig. 3. **a** Lung tissue specimen using video-assisted thoracoscopy (VATS) shows subpleural amyloid deposits (*arrow*) in right upper lobe (hematoxylin-eosin stain). *Bar* 200 μm. **b** Interstitial parenchymal amyloid deposits (*arrows*) are seen (Congo red stain). *Bar* 100 μm. **c** Amyloid deposits (*arrow*) are recognized in the walls of small pulmonary vessels with endothelial stenosis (Congo red stain). *Bar* 100 μm. **d** Amyloid deposits of lung tissue show negative staining by anti-AA protein antibody. *Bar* 100 μm. **e,f** The clonality of light chains is not found in pulmonary amyloidosis. Both anti-κ antibody staining **e** and anti-λ antibody staining **f** are positive (*arrows*). *Bar* 100 μm

staining of anti-amyloid protein A (anti-AA) protein (Fig. 3d). Clonality using anti-κ or anti-λ antibodies could not be found in pulmonary amyloidosis (Fig. 3e,f). The gastroduodenal mucosa and skin biopsy specimens did not have amyloid deposits, suggesting no evidence of generalized involvement.

After lung biopsy, the patient became febrile and complained of right chest pain with increased C-reactive protein (CRP). Three days after lung biopsy by VATS, a chest CT scan revealed patchy opacity in the right lower lobes from which bloody bronchoalveolar lavage fluid was obtained. She was diagnosed with a pulmonary hemorrhage of the right lower lobe (S7, S8), a site different from that of the lung biopsy. Although the cause of the pulmonary hemorrhage was unknown, she was treated with methyl prednisolone (PSL) pulse therapy (1 mg/day, 3 days), followed by

oral administration of PSL at 50 mg/day. The pulmonary hemorrhage slowly disappeared, and the dose of PSL was gradually tapered. She was administered a combination of aspirin and antithrombotic drugs to avoid the risk of pulmonary infarction, based on findings of her stenotic pulmonary vessels and the presence of positive lupus anticoagulant. Three years later, an abnormal nodular shadow revealing pulmonary amyloidosis on a chest CT scan showed almost no remarkable changes or at least no exacerbations.

Discussion

Amyloidosis may be classified into AA type and AL type, based on the bioclinical nature of the deposited fibril. The former, derived protein A, is well known to occur as systemic secondary amyloidosis associated with rheumatoid arthritis, in which the amyloidosis is a major cause of death. The latter form, AL-type amyloid consisting of immunoglobulin light chains, is related to systemic primary types such as myeloma-associated amyloid or with most localized forms. When a localized amyloid is associated with a chronic inflammatory reaction, that amyloid is usually AL. AL amyloidosis is thought to be caused by the deposits of portions of an immunoglobulin light chain produced by a plasma cell proliferative process.[5] In the United States, 75% of amyloidosis is found in the form of primary amyloidosis of the AL type. Such patients do not have multiple myeloma or any other overt B-cell neoplasm.[6] A modest increase in the number of inflammatory cells such as plasma cells in localized lymphoid tissues is suspected to be responsible for the production of the precursor of AL protein that is deposited locally.

In the present case, both paranasal sinus and lung biopsy specimens showed AL-type amyloid deposits immunohistochemically. In the clonality of light chains in amyloid, λ type was increased in paranasal sinusitis, but that clonality was not seen in the lung, and M protein was not detected in either her serum or urine. Therefore, the clonality of light chains was thought to be uncertain, and presumably there was no monoclonality. The patient's amyloid deposits were assumed to be localized in the respiratory tract at present, because tissue impairment-related amyloidosis was not detected in other organs such as skin, heart, kidney, or gastrointestinal tract.

Amyloidoses in the respiratory tract are widely involved in the paranasal cavity, nasopharynx, tracheobronchus, and lung. Pulmonary amyloidoses occur in combination in tracheobronchial, nodular parenchymal, and diffuse parenchymal patterns. The diffuse parenchymal form is characterized by amyloid depositions in the pulmonary interstitium and in the media of small blood vessels.[7,8] In the present case, it was of interest that the confirmation of multiple nodular pulmonary lesions was difficult by chest roentgenogram. Even though asymptomatic for lungs, a chest CT scan should be required for any suspicion of pulmonary amyloidosis.

It is widely acknowledged that SS itself is frequently accompanied by B-cell lymphoproliferative disorders.[9] Therefore, SS may possibly coexist with AL amyloidosis in chronic inflammatory sites, even when there is no evidence of myeloma or plasma cell dyscrasia. Eight case reports describing the association of SS and pulmonary amyloidosis in the English literature were identified.[10–17] The characteristics of these previously reported cases, including the patient under study, are summarized in Table 1. Multiple nodular pulmonary shadows were seen in all patients. In laboratory data, none of them exhibited monoclonal gammopathy. The biopsy specimens diagnosed as pulmonary amyloidosis were obtained by open lung biopsy in five of these patients. There were no cases of systemic amyloidosis suggesting visceral organ impairment such as renal or cardiac failure aside from the respiratory tract. Two cases manifested AL-type and two AA-type amyloidosis, respectively, whereas the remainder were not precisely defined. Differences in clinical characteristics, complications, or prognosis between these AL and AA amyloidosis cases could not be found in the literature because of the small number of cases.

The prognosis for pulmonary amyloidosis differs depending on whether the amyloid is deposited in the diffuse parenchymal interstitium or a multiple nodular amyloid tu-

Table 1. Clinical characteristics of pulmonary amyloidosis in patients with primary Sjögren syndrom (SS)

Case number	Age	Sex	Roentgenographic findings	M protein site	Biopsy type	Amyloid	Therapy	Reference
1	59	F	Multiple nodular, linear	–	Open lung	ND	PSL	10
2	60	F	Multiple nodular, hilar lymphadenopathy	–	TBLB	ND	ND	11
3	46	F	Multiple nodular	–	Open lung	ND	ND	12
4	53	F	Multiple nodular, linear, bullae	–	Open lung	ND	PSL	13
5	58	F	Multiple nodular	–	Open lung	AA	DMSO	14
6	29	F	Multiple nodular	–	Open lung	AA	PSL, CY	15
7	71	F	Multiple nodular	–	Transthoracic needle	ND	PSL	16
8	66	F	Multiple nodular	–	Open lung	AL	PSL, MPH, IFN-α	17
Present case	29	F	Multiple nodular	–	VATS	AL	PSL	

AA, amyloid protein A; AL, amyloid light chains; ND, not decided; PSL, prednisolone; DMSO, dimethyl sulfoxide; CY, cyclophosphamide; MPH, melphalan; IFN-α, interferon-α; TBLB, trans-bronchial lung biopsy; VATS, video-assisted thoracoscopy

mor forms. The interstitial deposit-type amyloidosis shows dyspnea and hemoptysis and usually has a progressively unfavorable course leading to respiratory failure. The optimal treatment for amyloidosis has not yet been established. Prednisolone and alkylating drugs have yielded some benefit in a limited number of patients with nodular amyloidosis. The progression of amyloidosis may be stopped because the chronic inflammatory process of SS in lymphoproliferative disorder was reduced by PSL. Our patient was treated with methyl PSL pulse following orally administered PSL because of a pulmonary hemorrhage of unknown cause. Although the cause of pulmonary hemorrhage was uncertain, it is conceivable that, during the surgical manipulations, the weak vessels to which the amyloid had attached were forcibly pulled apart and torn loose. Otherwise, the autoimmune mechanism underlying SS is similar to other connective tissue diseases such as systemic lupus erythematosus. The patient was treated with glucocorticoid without a combination of alkylating or immunosuppressive drugs, which she had refused because she hoped to become pregnant. We thought that her AL amyloidosis had not progressed during the past 3 years. It is presumed that the effect of PSL could be to suppress the lymphoproliferative process of SS, because the size or number of multiple nodular shadows in her lung were not changed and the arterial blood gas was not exacerbated.

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