Amyloid-associated cystic lung disease in primary Sjögren’s syndrome

Misbah Baqir a, Elizabeth M. Kluka a, Marie-Christine Aubry c, Thomas E. Hartman b, Eunhee S. Yi c, Philippe R. Bauer a, Jay H. Ryu a,*

a Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
b Department of Radiology, Mayo Clinic, Rochester, MN, USA
c Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA

Received 20 August 2012; accepted 10 January 2013
Available online 10 February 2013

KEYWORDS
Amyloidosis;
Cystic lung disease;
Sjögren’s syndrome

Summary
Background: Cystic lung disease can be seen in patients with Sjögren’s syndrome (SS) and is generally thought to be due to lymphocytic interstitial pneumonia.

Methods: Using computer-assisted search we identified patients with primary SS seen at Mayo Clinic, Rochester, MN during a 14-year period from 1997 to 2010 who were diagnosed with pulmonary amyloidosis confirmed on lung biopsy. Clinical records, imaging studies, and pathologic specimens were reviewed to delineate presenting features, diagnostic evaluation, and clinical course.

Results: Eight patients (7 women, 1 man) with primary SS were diagnosed with pulmonary amyloidosis by lung biopsy (7 surgical, 1 bronchoscopic). Their median age was 55 years (range, 32–75 years) and all were nonsmokers. Presenting symptoms included dyspnea and cough but 4 patients presented with radiologic abnormalities in the absence of respiratory symptoms. CT findings included cystic lesions and nodular opacities in all eight patients. PET scan performed in six patients did not reveal 18F-2-deoxyglucose (FDG) uptake except in one nodule with borderline uptake. Lung biopsy demonstrated the presence of amyloid in all patients and was associated with mucosa-associated lymphoid tissue (MALT) lymphoma in three patients. Pulmonary function results were normal in five patients and revealed mild impairment in a mixed pattern in one patient.

Conclusions: We conclude cystic and nodular lung lesions seen in patients with primary SS can represent amyloidosis which can be associated with MALT lymphoma in some of these patients.

© 2013 Elsevier Ltd. All rights reserved.

Abbreviations: FISH, fluorescence in situ hybridization; H & E, hematoxylin and eosin; MALT, mucosa-associated lymphoid tissue; SAA, serum amyloid A; SAP, serum amyloid P; SS, Sjögren’s syndrome.

* Corresponding author. Division of Pulmonary and Critical Care Medicine, Gonda 18 South, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA. Tel.: +1 507 284 2447; fax: +1 507 266 4372.
E-mail addresses: baqir.misbah@mayo.edu (M. Baqir), kluka.elizabeth@mayo.edu (E.M. Kluka), aubry.mariechristine@mayo.edu (M.-C. Aubry), hartman.thomas@mayo.edu (T.E. Hartman), yi.joanne@mayo.edu (E.S. Yi), bauer.philippe@mayo.edu (P.R. Bauer), ryu.jay@mayo.edu (J.H. Ryu).

0954-6111/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.rmed.2013.01.005
Introduction

Sjögren’s syndrome (SS) is a chronic inflammatory disorder characterized by lymphocytic infiltration of exocrine glands resulting in xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement.1–4 Primary SS is distinguished from secondary SS by the absence of an underlying rheumatic condition, e.g., rheumatoid arthritis, and affects 3%–4% of the adult population, primarily women.5 Primary SS is associated with diverse extraglandular manifestations involving the skin, kidney, lung as well as the vascular and nervous systems.4,6

Several pulmonary manifestations can be encountered in patients with primary SS. These include interstitial lung disease, airway disease, lymphoproliferative disease, pleural disease, and, rarely, pulmonary vascular abnormalities.7–9 Cystic lung disease in patients with SS has been usually associated with lymphocytic interstitial pneumonia and follicular bronchiolitis but amyloidosis has occasionally been implicated.8,10 In this study we sought to clarify the relationship between pulmonary amyloidosis and cystic lung disease in patients with primary SS.

Patients and methods

A computer-assisted search of medical records was conducted and identified 8 subjects with primary SS seen at Mayo Clinic, Rochester, MN during a 14-year-period between Jan. 1, 1997 and Dec. 31, 2010. Approval was obtained from the Mayo Foundation Institutional Review Board prior to beginning the study.

All subjects included in this study fulfilled the current consensus criteria for primary SS.1 We identified those who had pulmonary amyloidosis diagnosed on bronchoscopic or surgical lung biopsy and had relevant chest imaging studies available for review. Medical records of these patients were reviewed to extract data regarding age, sex, smoking history, clinical presentation, imaging studies, biopsy procedures, and diagnoses.

The chest imaging studies were reviewed by two experienced readers (TEH, JHR) independently and were evaluated for pulmonary, pleural and mediastinal/hilar abnormalities. The pulmonary abnormalities evaluated included: nodules, reticular opacities, interlobular septal thickening, ground-glass opacities, consolidation, cysts, honeycombing and emphysema. If inspiratory images were available, they were evaluated for the presence of air trapping. When nodules were present they were evaluated for number (solitary, 2–10 and >10), attenuation (solid, semisolid and ground-glass), margins (smooth and irregular), extent (<10%, 10–40% and >40%), lung distribution (unilateral, bilateral asymmetric and bilateral symmetric), axial distribution (central, subpleural and perilymphatic) and cephalocaudal distribution (upper, lower and diffuse). When reticular opacities, interlobular septal thickening, ground-glass opacities, consolidation or emphysema were present they were evaluated for extent, lung distribution, axial distribution and cephalocaudal distribution as outlined above. Additional note was made on the size of the cysts or honeycombing (<5 mm, 6–10 mm, 11–20 mm and >20 mm) based on the predominate size of the cysts or honeycombing. Mediastinal/hilar images evaluated were primarily evaluated for adenopathy, but any other abnormalities noted were recorded. Adenopathy was present if the short axis diameter of a node was >10 mm. Differences in interpretation were settled by consensus.

Pathology specimens were available for current review in five patients, including four wedge biopsies and one transbronchial biopsy. The pathologic information was abstracted from the pathology reports in the other three patients whose wedge biopsies were obtained at another institution and were previously reviewed by us during their clinical evaluation at Mayo Clinic. Hematoxylin and eosin (H & E) and Congo red staining was performed in all cases. Immunohistochemical studies for lymphoma work-up was performed in 7 patients and included antibodies directed against CD3 and CD20 in 7, with kappa and lambda immunoglobulin light chains in 6, and fluorescence in situ hybridization (FISH) for kappa and lambda light chains in one. Immunohistochemistry for amyloid battery including serum amyloid P (SAP) component, serum amyloid A (SAA) protein, transthyretin, beta-2 microglobulin, kappa and lambda immunoglobulin light chains, was performed in two patients and liquid chromatography tandem mass spectrometry in another five. The focus of the histologic review was on the identification of cysts and cause as highlighted by radiologic findings in these patients.

Results

Clinical and laboratory features

Eight patients (seven women, one man) with primary SS were diagnosed with pulmonary amyloidosis by lung biopsy (seven surgical, one bronchoscopic) (Table 1). Their median age was 55 years (range, 32–75 years). Presenting symptoms included dyspnea and cough in four patients and four remaining patients presented with incidental abnormalities noted on chest imaging without respiratory symptoms. All eight patients had sicca symptoms with two patients having enlarged parotid glands.

All patients manifested anti-SS-A/Ro and anti-SS-B/La antibodies. Serum protein electrophoresis revealed biclonal gammopathy in one patient (75F patient on Table 1) but was negative in the remaining seven patients including urine protein electrophoresis that had been performed in five of these seven patients. One symptomatic patient with extensive nodular and cystic lesions (56F on Table 1) was treated rituximab therapy but no specific therapy for amyloidosis or MALT lymphoma was undertaken for the remaining seven patients.

Chest imaging

Chest radiography was abnormal in seven patients and revealed nodular or interstitial opacities but was normal in the remaining patient. Cystic lesions were identified by chest radiography in two of eight patients. Chest CT scanning revealed parenchymal cysts in all eight patients.
In six cases the cysts were bilateral and asymmetric and in two cases the cysts were unilateral. In the unilateral cases, one had only one cyst and the other had only two cysts. In the six bilateral cases, four had lower lung predominance and in two cases the cysts were diffuse. With regard to axial distribution, the cysts were diffuse without a subpleural, central or perilymphatic distribution. In one case the predominant cyst size was \(< 5\) mm, in 4 cases the predominant size was \(6–10\) mm and in 3 cases the predominant size was \(11–20\) mm.

Chest CT scan also revealed two or more nodules in all eight patients (Fig. 2). In four patients the nodules were of mixed attenuation containing solid, semisolid and/or ground glass components. In four remaining cases, only solid nodules were present. The pulmonary nodules varied in size from less than \(5\) mm to greater than \(10\) mm; one of the nodules was cavitated. In one case, several of the larger nodules were partially calcified. The nodule distribution was bilateral and asymmetric in all eight patients with lower lung predominance in five.

Ground-glass opacities were seen in two cases. In both cases, there was a solitary area of ground glass attenuation that involved \(< 10\%\) of the lung. No cases had reticular opacities, interlobular septal thickening, consolidation, honeycombing or emphysema. Additionally, no cases had pleural abnormalities or adenopathy.

On follow-up CT of the four cases with solid nodules, in one case the nodules were stable; in the second case one nodule had cavitated, one had decreased and the rest were stable; in the third case, one had increased and the rest were stable; and in the fourth case, the nodules had increased in number and size over the interval of 68 months. Of the four cases with mixed nodules, one had a decrease in size and number over the long term, but had a mixed response on early follow-up. In the second case, the solid nodules increased or were stable and the semi-solid nodules were stable. In the third case, there was a mixed response, with no overall change. In the fourth case, all nodules were stable. The cavity that was seen on the initial CT in one case had become solid. Of the eight

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of eight patients with primary Sjogren’s syndrome and pulmonary amyloidosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), gender</td>
<td>Smoking</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>56F</td>
<td>Never</td>
</tr>
<tr>
<td>74F</td>
<td>Never</td>
</tr>
<tr>
<td>48F</td>
<td>Never</td>
</tr>
<tr>
<td>53F</td>
<td>Never</td>
</tr>
<tr>
<td>75F</td>
<td>Never</td>
</tr>
<tr>
<td>32F</td>
<td>Never</td>
</tr>
<tr>
<td>58F</td>
<td>Never</td>
</tr>
<tr>
<td>39M</td>
<td>Never</td>
</tr>
</tbody>
</table>

Abbreviations: F = female, M = male, FDG-PET = fluorodeoxyglucose \(^{18}\)F positron emission tomography, NA = data not available.
cases with cysts, one had new cysts develop. Of the previous noted cysts, in six cases the cysts were stable and in two cases the cyst size increased. In the two cases with ground-glass opacities, one was stable and one decreased. In no case did a nodule become a cyst even with the longest followup of 99 months.

PET scan was performed in six patients for assessment of pulmonary nodules and did not reveal 18F-2-deoxyglucose (FDG) uptake except in one nodule with borderline activity (maximal standardized uptake value [SUVmax] 2.2) (Table 1). Pulmonary function results were available in six patients and revealed normal results except mild impairment in a mixed pattern in one patient.

Histopathological findings

The presence of amyloid was confirmed on lung biopsies of all eight patients with Congo red staining (Fig. 3) and by immunohistochemistry or mass spectrometry was determined as AL-kappa type in seven. In three patients amyloid was associated with mucosa-associated lymphoid tissue (MALT) lymphoma, two with kappa light chain restriction and one with lambda light chain restriction in the plasma cells (Figs. 4–6). The amyloid subtype was not specifically assessed in the patient with the lambda light chain restriction in the MALT lymphoma. Of the five patients without MALT lymphoma, follicular bronchiolitis and lymphoid hyperplasia were seen in one patient each while the remaining three patients exhibited amyloid only. The latter group included the patient who was diagnosed by bronchoscopic lung biopsy that demonstrated only amyloid and bronchoalveolar lavage showed no lymphocytes.

Of the seven patients with wedge biopsies, the presence of cysts was recorded in five and identified on histologic review in three, one with lymphoid hyperplasia and two with MALT lymphoma. In one patient, the cyst walls were comprised of the lymphoid infiltrate while for the other two, a mixture of both the lymphoid infiltrate and amyloid. In two of these cases, the cysts appeared to be dilated airways involved by the amyloid. None of the biopsies showed findings characteristic of lymphocytic interstitial pneumonia, i.e., diffuse infiltration of alveolar septa by lymphocytes and plasma cells. In all cases, the nodules could be explained by the amyloid with or without an associated lymphoid infiltrate.

Discussion

In this study of patients with primary SS, we found pulmonary amyloidosis to be associated with cystic lesions and nodules. The association of cysts in the lung with amyloid is of particular interest since pulmonary cysts in patients with SS are generally assumed to be due to lymphocytic interstitial pneumonia and not biopsied. In addition, we found MALToma to be present in nearly one-half of these primary SS patients with pulmonary amyloid.

![Figure 3](image3.png)

**Figure 3** Confluent deposition of eosinophilic amorphous materials in the right half of the field (hematoxylin and eosin, 200×), consistent with amyloid that is supported by sulfated Alcian blue staining (inset, 200×).

![Figure 4](image4.png)

**Figure 4** Cystically dilated spaces surrounded by dense lymphoid infiltrates (hematoxylin and eosin staining, 40× original magnification).

![Figure 5](image5.png)

**Figure 5** Markedly increased B-lymphocytes within the lymphoid infiltrates (anti-CD20 immunostaining, 400×). These B-cells are kappa light-chain-restricted by immunohistochemical method (not shown).
the fragility and destruction of alveolar walls due to thilium. Another proposed mechanism for cyst formation is with bronchiolar epithelial cells rather than alveolar ep-
were also able to demonstrate that the cysts were lined
deposition and lymphoproliferative cell infiltration, they
be related to the benign lymphoproliferative process seen
these patients had SS. Amyloid deposition was believed to
and cysts associated with pulmonary amyloidosis; two of
lesions in patients with primary SS can represent pulmonary
nodule as well as the lung.9,25–28

Sjogren Syndrome is a chronic inflammatory disorder but
is also recognized as a lymphoproliferative disease with
varying presentation from polyclonal lymphocytic infil-
tion of the salivary glands to oligo- or monoclonal B cell
proliferation resulting in clonally derived lymphoprolifer-
ative disorders such as monoclonal gammopathy, light-chain
amyloidosis, and malignant lymphoma.14,15 Pulmonary
involvement in primary SS is being increasingly recognized
and can present with parenchymal, pleural, airway or vas-
cular manifestations.9,16–18 Amyloid deposition in patients
with SS is less well known but has been described to occur in
multiple organs including the skin,19,20 kidney,21 breast,22
tongue,23 lymph nodes,24 as well as the lung.9,25–28

All of our eight patients with SS and pulmonary amyloi-
dosis presented with cysts and nodules on chest imaging
and all of them had AL type amyloid. AL amyloidosis in SS
has most often been reported as localized nodular pulmo-
ary amyloidosis.29,30 For example, Desai and colleagues30
described three patients who manifested lung nodules
and cysts associated with pulmonary amyloidosis; two of
these patients had SS. Amyloid deposition was believed to
be related to the benign lymphoproliferative process seen
in the lung. Lantejoul and colleagues17 reported cystic and
nodular lung lesions in a patient with amyloidosis associ-
ated with MALT lymphoma but without SS. It appears that
cystic lung lesions can be seen with amyloidosis in the
presence or absence of SS or MALT lymphoma.

The mechanism of cyst formation is not fully under-
stood. Some authors have proposed the presence of in-
flammatory cells or amyloid exhibiting ball-valve
mechanism resulting from bronchiolar obstruction.28 In
support of this theory Jeong et al.29 described histopatho-
logic findings in a patient with SS-related pulmonary amyloi-
dosis and cystic lung disease in whom the cyst appeared
to be located distal to bronchioles narrowed by amyloid
deposition and lymphoproliferative cell infiltration, they
were also able to demonstrate that the cysts were lined
with bronchiolar epithelial cells rather than alveolar epithe-
lum. Another proposed mechanism for cyst formation is
the fragility and destruction of alveolar walls due to
interstitial inflammation. Colombat et al.31 have shown the
role of metalloproteinases released by macrophages caus-
ing elastolysis and cystic lung diseases in pulmonary light
chain deposition disease. Additional studies analyzing
larger lung specimens such as those obtained at autopsy or
explants may yield clarification on how cysts form. Multiple
mechanisms may lead to development of cystic lung lesions
in patients with pulmonary amyloidosis associated with SS.
FDG uptake on PET scanning has been described in iso-
lated cases of amyloidosis.32,33 In contrast, FDG uptake is
seen in the majority of MALT lymphomas but depends partly
on the underlying histologic features of the tumor.34–36 In
six of our patients who underwent PET scanning no FGD
uptake was seen in the lung with the exception of one nodule
that exhibited borderline FDG uptake in a patient with
pulmonary MALToma.

There are several limitations to our study including the
retrospective design and a modest number of study sub-
jects. In addition, there was limited follow-up data on the
clinical course of these patients. Additional studies are
needed to define the long-term evolution of cystic and
nodular pulmonary lesions as well as the associated prog-
osis in SS patients with pulmonary amyloidosis.

In summary, we conclude that cystic and nodular lung
lesions in patients with primary SS can represent pulmonary
amyloidosis with or without MALT-type lymphoma. Clinici-
ans need to be aware of diverse causes of cystic lung
lesions in patients with SS.

Disclosure
None for all authors.

Funding
None.

Conflict of interest statement
None declared.

References
for Sjogren’s syndrome: a revised version of the European
criteria proposed by the American-European Consensus Group.
2. Kassan SS, Moutsopoulos HM. Clinical manifestations and early
diagnosis of Sjogren syndrome. *Arch Intern Med* 2004;164(12):
1275–84.
primary Sjogren syndrome: a systematic review. *J Am Med
Assoc* 2010;304(4):452–60.
4. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjogren’s
syndrome: new clinical and therapeutic concepts. *Ann Rheum
community-based study of prevalence and impact. *Br J
Rheumatol* 1998;37(10):1069–76.
Cystic amyloid lung disease in Sjögren’s


