Presentation of Sjogren Syndrome as Nodular Pulmonary Amyloidosis

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Abstract

Sjogren syndrome is an autoimmune disorder that leads to dryness in the eyes and mouth. Nodular pulmonary amyloidosis is a localized amyloid deposition pathology commonly seen with monoclonal lymphoproliferative disorders. We present a patient who came in with dyspnea and was found to have nodular pulmonary amyloidosis on biopsy. Commonly associated lymphoproliferative pathologies were ruled out and on further workup, the patient was found to have Sjogren syndrome. This case demonstrates pulmonary nodular amyloidosis as a rare presentation of Sjogren syndrome in the setting of relatively well-controlled symptoms. Detection of pulmonary nodular amyloidosis should prompt evaluation of associated conditions such as malignancy and autoimmune disorders to guide further management.

Categories: Internal Medicine, Pulmonology, Rheumatology
Keywords: localized amyloid, pulmonary nodular amyloidosis, amyloidosis, pulmonary disease, sjogren’s disease

Introduction

Amyloidosis is a heterogeneous group of disorders associated with the deposition of proteins in an abnormal fibrillar form in tissues [1]. Light chain (AL) amyloidosis and reactive (AA) amyloidosis are the two most common types of amyloidosis. In AL amyloidosis, clonal plasma cells produce light chains (λ or κ) that are amyloidogenic [2]. AA amyloidosis occurs due to increased secretion of serum amyloid A (SAA) protein, a protein produced in inflammatory pathologies [3]. Along with the sustained elevation of SAA, genetic polymorphisms in SAA and the type of autoinflammatory syndrome facilitate conversion to SAA to beta-pleated sheet and deposition in organs [4]. Pulmonary involvement is usually insignificant in systemic amyloidosis, and localized pulmonary amyloidosis is infrequently reported [5]. Isolated pulmonary amyloidosis in Sjogren syndrome is also an uncommon phenomenon. Here we present a patient who was found to have pulmonary nodular amyloidosis with Sjogren syndrome.

Case Presentation

A 78-year-old lady presented to the emergency room with increasing shortness of breath and cough for the past two to three months. The patient had been using lubricant eye drops for the past many years for her dry eyes but did not have any past diagnosis of Sjogren syndrome. The patient had normal vital signs on presentation. Normal breath sounds were heard on auscultation. Complete blood count and basic metabolic profile were unremarkable. Chest x-ray showed multiple nodular lesions in the right lung fields (Figure 1). Computed Tomography (CT) scan of the chest showed numerous bilateral pulmonary nodules, including a spiculated 11 cm-sized mass in the left lower lobe, suspicious of malignancy (Figure 2). Positron emission tomography (PET)-CT scan showed fluorodeoxyglucose (FDG) activity in the lung nodules and FDG avid hilar region (Figure 3). Due to high suspicion of malignancy and for staging and characterization, the patient underwent surgical resection and biopsy of the right upper lobe. Pathologic specimen showed nodular amyloidosis, confirmed on Congo-red stain. Interestingly, there was no evidence of any neoplastic process in the resected specimen, despite high FDG activity on the PET scan.
FIGURE 1: Chest x-ray showing nodular infiltrates in right lung fields
Due to the detection of amyloidosis, further workup was done due to high suspicion of autoimmune disorders. It showed positive antinuclear antibody (ANA) of 1:1280 with a speckled pattern, strongly positive Sjogren’s syndrome A (SS-A)/Ro and Sjogren’s syndrome B (SS-B)/La antibodies, and elevated ribonucleoprotein (RNP) antibodies. (Table 1). The monoclonal protein screen showed polyclonal paraproteinemia with elevated kappa and lambda light chains. There was also a slight isolated Immunoglobulin (Ig) G rise with normal levels of other Igs (Table 2).
Laboratory | Value | Reference range and limits
--- | --- | ---
ANA | 1:1280, speckled | <1:80
CCP, IgG | <0.4 | <0.4
anti ds DNA | negative | negative
C3 complement | 135 mg/dL | 90-230 mg/dL
C4 complement | 24 mg/dL | 10-51 mg/dL
RNP antibody | 3.0 Elisa Units | <1.0 Elisa Units
SM antibody | 0.2 Elisa Units | <1.0 Elisa Units
SS A/Ro antibody | >8.0 Elisa Units | <1.0 Elisa Units
SS B/La antibody | >8.0 Elisa Units | <1.0 Elisa Units
IgA, serum | 316 mg/dL | 70-400 mg/dL
IgM, serum | 103 mg/dL | 40-230 mg/dL
IgG, serum | 1725 mg/dL | 700-1600 mg/dL

**TABLE 1: Autoimmune antibody screen test following the discovery of nodular amyloidosis on biopsy**

ANA: antinuclear antibody; CCP: cyclic citrullinated peptide; Ig: immunoglobulin; ds DNA: double-stranded DNA; RNP: ribonucleoprotein; SM: smooth muscle; SS: Sjogren syndrome

In this scenario, the patient had persistent dry eyes and strongly positive SS-A and SS-B antibodies. Neoplastic processes were ruled out on biopsy, which leaves Sjogren syndrome causing and presenting as nodular pulmonary amyloidosis.

All the possible options including immunomodulators such as rituximab were discussed with the patient for...

Laboratory | Value | Reference range and limits
--- | --- | ---
Free light chains ratio | 2.19 | 0.26-1.65
Kappa light chains | 69.1 | 3.3-19.4 mg/L
Lambda light chains | 31.5 | 5.7-26.3 mg/L
IgG, serum | 1,725 | 700-1,600 mg/dL
IgA, serum | 316 | 70-400 mg/dL
IgM, serum | 103 | 40-230 mg/dL
Protein, Total | 7.4 | 6.58-8.51 g/dL
Albumin | 3.70 | 3.73-5.65 g/dL
Alpha-1 globulins | 0.34 | 0.13-0.45 g/dL
Alpha-2 globulins | 0.90 | 0.37-0.93 g/dL
Beta globulins | 0.81 | 0.69–1.29 g/dL
Gamma globulins | 1.66 | 0.58-1.50 g/dL

**TABLE 2: Monoclonal protein screen performed in the setting of amyloidosis**

Ig: immunoglobulin
the treatment of amyloidosis. After weighing the treatment options with the possible risk of
immunosuppression, particularly in the ongoing coronavirus disease 2019 (COVID-19) pandemic, a decision
was made not to start any treatment. The patient was followed up in the Rheumatology and Hematology
clinic and she remained largely asymptomatic. She has not reported any other occurrence of symptoms since
the initial presentation.

Discussion
Lung amyloidosis has three main histologic presentations described as nodular pulmonary amyloidosis,
tracheobronchial amyloidosis, and diffuse alveolar septal amyloidosis [6]. Nodular pulmonary amyloidosis
usually represents localized AL or AL/heavy chain (AH) amyloidosis [7]. It is usually detected incidentally as
the patients are largely asymptomatic on presentation. On detection, nodular amyloidosis is found to be
isolated but may be present alongside a localized clonal proliferation of B-lymphocytes or plasma cells
secreting light chains [8]. It has also been shown to be associated with an underlying lymphoproliferative
disorder such as mucosa-associated lymphoid tissue (MALT) lymphoma [7].

Due to its frequent association with localized lymphoma and other lymphoproliferative disorders, surgical
excision and biopsy are essential for the diagnosis of amyloidosis and exclusion of localized lymphoma, as
management options vary. In the advent of worsening symptoms and extension of amyloidosis, surgical
excision has been done successfully [9].

Sjogren syndrome is associated with multiple pulmonary disorders, most commonly being interstitial lung
disease, bronchiolitis, chronic obstructive pulmonary disease, and reactive airway disease (Table 3) [10]. The
presence of pulmonary nodular amyloidosis as a presentation of Sjogren syndrome is not widely reported.
<table>
<thead>
<tr>
<th>Type of Lung Involvement</th>
<th>Main Clinical Features</th>
</tr>
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<tbody>
<tr>
<td>Airways disorders</td>
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<tr>
<td>Upper airways inflammation</td>
<td>Dryness in nasal and oropharyngeal mucosa finally leading to atrophy of the submucosal glands of the airway mucosa.</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease and reactive airway disease</td>
<td>Shortness of breath, chronic dry cough, or wheezing due to airway hyperresponsiveness. PFTs allow the distinction of the two patterns.</td>
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<tr>
<td>Bronchiolitis (folicular bronchiolitis, chronic bronchiolitis, and bronchiolitis obliterans)</td>
<td>Traditionally presents with cough and dyspnea. PFT findings may be normal or show either a restrictive or obstructive pattern. It appears as a reticular or reticulo-nodular pattern on HRCT.</td>
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<tr>
<td>Bronchiectasis</td>
<td>Dry cough, isolated dyspnea, and hemoptysis in rare occasions. Patients with bronchiectasis have a higher frequency of respiratory infections and pneumonia.</td>
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<tr>
<td>Parenchymal disease</td>
<td></td>
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<tr>
<td>Interstitial lung disease</td>
<td>Non-productive cough and dyspnea are present in half of patients, the remaining are completely asymptomatic. On auscultation, it is characterized by fine bibasilar end-inspiratory “velcro-like” crackles. The most common ILD pattern is NSIP, followed by UIP, OP, and LIP. In early involvement, it is easy to observe a reduction of DLCO (alveolar inflammation) with a preserved FVC (normal lung volumes).</td>
</tr>
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<td>Lymphoma and pseudolymphoma</td>
<td>Cough, slowly progressive dyspnea, and traditional B symptoms (fever, night sweats, and weight loss) are characteristic of lung lymphoma. Parenchymal radiographic findings are often associated to mediastinal lymphadenopathy and pleural effusions Pseudolymphoma is generally asymptomatic, and it usually appears as a solitary nodule or mass.</td>
</tr>
<tr>
<td>Pulmonary amyloidosis</td>
<td>Cough or dyspnea along with fatigue, weakness, hemoptysis, and pleuritic chest pain. Radiologically, it is characterized by large, calcified, randomly distributed, irregular, smooth-bordered nodules alone, or in association with LIP.</td>
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<td>Sarcoidosis</td>
<td>Asymptomatic or presenting with exertional dyspnea or dry cough. Heerfordt’s syndrome is defined by the characteristic parotid enlargement and the presence of uveitis. Radiographic abnormalities include bilateral hilar lymphadenopathy, pulmonary infiltrates, or fibrosis.</td>
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<tr>
<td>Cystic lung disease</td>
<td>Mostly subclinical. Cysts are usually bilateral with the majority located in the middle lung.</td>
</tr>
<tr>
<td>Pulmonary venous thromboembolism</td>
<td>Characterized by a lack of overt clinical symptoms in the early phase and by exertional dyspnea in more advanced disease. Physical examination could reveal a loud second pulmonary heart sound. PFTs commonly show normal lung volumes with a reduction in DLCO. Transthoracic Doppler echocardiography can be useful for screening for PAH however, RHC is required for definitive diagnosis and to orient between PAH different etiologies.</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension (PAH)</td>
<td></td>
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<tr>
<td>Lymphocytic pleuritis</td>
<td>Rare manifestation in pSS characterized by chest, fever, cough, dyspnea, and exudative pleural effusion.</td>
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<td>Neuromuscular disease with secondary pulmonary involvement</td>
<td>Dyspnea, persistent episodes of chest pain, restrictive syndrome, and the absence of significant interstitial and/or pleural disease.</td>
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**TABLE 3: Pulmonary complications of Sjogren syndrome**


In the current case, the presence of multiple nodular lesions in lung fields with FDG-avid lesions warranted
the workup for malignancy with resection and biopsy. On the pathologic specimen, there was no evidence of neoplastic processes, and amyloidosis was confirmed with the Congo-red stain. With the autoimmune panel results and the presence of xerophthalmia, the association of nodular amyloidosis with Sjögren syndrome was established.

This case report presents an uncommon association of Sjögren syndrome with nodular pulmonary amyloidosis. Further exploration of the pathophysiology of autoimmune disorders and associated inflammation can explain systemic amyloidosis but isolated organ amyloidosis in such conditions is uncommon. Further research and understanding of single-organ amyloid deposition in systemic conditions may provide a suitable explanation.

Conclusions
Isolated nodular pulmonary amyloidosis is a condition most commonly associated with lymphoproliferative malignancies. Along with its evaluation, clinicians also need to consider autoimmune disorders in the differential. Sjögren syndrome is one such condition that can infrequently present as nodular pulmonary amyloidosis. In that setting, management is generally conservative with symptomatic management.

Additional Information

References
5. Gillmore JD, Hawkins PN: Amyloidosis and the respiratory tract. Thorax. 1999, 54:444-51. 10.1136/thx.54.5.444