CHEST

Amyloid-associated Cystic Lung Disease

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BACKGROUND: Amyloid-associated cystic lung disease is rare. It can be associated with collagen vascular disease (CVD). We aimed to describe the clinical, radiology, and pathology findings of this entity.

METHODS: We reviewed the records of subjects having biopsy-proven pulmonary amyloidosis with cystic lung disease demonstrated at high-resolution computed tomography (HRCT). Demographic characteristics, association with CVD and lymphoproliferative disorders, pulmonary function, and pathology results were reviewed. HRCT appearance was analyzed for number, size, distribution, and morphology of cysts and nodules.

RESULTS: Twenty-one subjects (13 female, eight male; median age, 61 years) with cystic pulmonary amyloidosis were identified. The most common pulmonary function patterns were normal (42%) and obstructive (32%). The most common associated CVD was Sjögren syndrome (10 of 12). Nine subjects had no CVD. Cysts tended to be multiple (≥ 10 in 14 of 21, 67%), round (21 of 21, 100%), or lobulated (20 of 21, 95%); thin-walled (< 2 mm in 17 of 21, 81%); and of small (< 1 cm in 21 of 21, 100%) to moderate (1-2 cm in 17 of 21, 81%) size. Peribronchovascular (19 of 21, 90%) and subpleural (19 of 21, 90%) cysts were typically present. Seventeen (81%) subjects had lung nodules, which tended to be numerous (≥ 10 in 10 of 17, 59%; 4-9 in six of 17, 35%). At least one calcified nodule was present in 14 of 17 subjects (82%). Pulmonary mucosa-associated lymphoid tissue lymphoma (MALToma) was diagnosed in seven subjects (33%).

CONCLUSIONS: Amyloid-associated cystic lung disease can occur with or without underlying CVD. Cystic lesions in the lung are commonly numerous, often are peribronchovascular or subpleural, and are frequently associated with nodular lesions that are often calcified. MALToma was a relatively frequent association. CHEST 2016; 149(5):1223-1233

KEY WORDS: amyloidosis; connective tissue disease; interstitial lung disease

ABBREVIATIONS: CVD = collagen vascular disease; GGO = ground-glass opacity; HRCT = high-resolution computed tomography; LIP = lymphocytic interstitial pneumonia; MALToma = mucosa-associated lymphoid tissue lymphoma; PFT = pulmonary function test; RA = rheumatoid arthritis

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Amyloidosis is a group of conditions characterized by extracellular tissue deposition of plasma proteins in an abnormal insoluble fibrillar form. Amyloidosis can be classified according to its etiology, the abnormal proteins involved, or its primary clinical manifestation.[1-3] In 1993, the World Health Organization classified amyloidosis on the basis of the structure of the variable fibrillar protein with subsequent division into primary or secondary disease (Table 1).[4]

Primary amyloidosis is the result of a clonal proliferation of plasma cells (ie, monoclonal gammopathy or myeloma), and the fibrillar protein is a fragment of the immunoglobulin light chain (lambda or kappa) that forms type AL amyloid. Secondary amyloidosis is usually associated with chronic inflammation or neoplasms, and the associated fibrillar protein is amyloid A (type AA). Dialysis-related amyloidosis is characterized by accumulation of amyloid fibrils derived from β2-microglobulin. Senile amyloidosis is associated with amyloid derived from transthyretin. All types of amyloid protein take up Congo red stain and exhibit apple green birefringence at polarized microscopy.[5]

In amyloidosis, the thorax can be affected in several ways, with AL amyloid being the most common.[5] Four different patterns of noncardiac intrathoracic amyloid deposition have been described: tracheobronchial, mediastinal or hilar lymphadenopathy, pleural effusion, and lung parenchymal.[1,2,6-9] When the lung parenchyma is affected, the most common pattern found is nodular or interstitial deposition.[3,7,8,10] Cystic lung disease associated with pulmonary amyloidosis is uncommon and has been described in association with Sjögren syndrome and lymphoproliferative disease such as mucosa-associated lymphoid tissue lymphoma (MALToma).[6,11-14]

In this study, we present our experience over 14 years at the Mayo Clinic of subjects with biopsy-proven pulmonary amyloidosis with cystic lung disease, describing the demographic characteristics, pulmonary function test (PFT) results, and high-resolution computed tomography (HRCT) findings of this condition and the association of cystic pulmonary amyloidosis with underlying collagen vascular diseases (CVDs) and lymphoproliferative disorders. In addition, we compared the clinical and imaging features of pulmonary amyloidosis with cystic lung disease in subjects with CVD-associated amyloidosis with those in subjects without CVD.

Materials and Methods

Study Population and Data Collection

Following approval by the Mayo Foundation Institutional Review Board in Rochester, Minnesota (10-006289), we reviewed the medical records of subjects with biopsy-proven pulmonary amyloidosis who had cystic lung disease at HRCT encountered at Mayo Clinic during a 14-year period (1997-2010). Age, sex, clinical presentation, smoking status, PFT, autoimmune serology test, HRCT, lung biopsy, and protein immunoelectrophoresis results were extracted from the medical record. Pathology reports were examined for type of biopsy specimen and confirmation of amyloid on the basis of hematoxylin-eosin and Congo red staining. Additionally, in cases in which amyloid typing was performed, by means of either immunohistochemistry or liquid chromatography tandem mass spectrometry, the specific amyloid protein was recorded. CVD was

TABLE 1] Classification of Amyloidosis According to the World Health Organization (Modified)[4]

Amyloid Name	Protein Precursor	Syndrome
AA	Serum amyloid A protein	Reactive systemic amyloidosis associated with hereditary or acquired chronic inflammatory disease
AL	Variable monoclonal immunoglobulin light chains Produced systemically Produced locally	Systemic amyloidosis associated with monoclonal gammopathy, myeloma, and so on Amyloidosis localized to the urogenital tract, skin, eyes, respiratory tract, and so on
ATTR	Normal plasma transthyretin	Senile systemic amyloidosis with prominent cardiac involvement Genetically variant transthyretin Autosomal dominant hereditary amyloidosis; familial amyloid polyneuropathy, often with significant cardiac and/or renal amyloidosis
AB2M	β2-microglobulin	Systemic amyloidosis with predominant periarticular involvement associated with renal failure and long-term dialysis
AB	β-amyloid precursor protein	Cerebrovascular and intracerebral plaque amyloid associated with Alzheimer disease
AIAPP	Islet amyloid polypeptide	Amyloid in islets of Langerhans in type 2 diabetes mellitus