The Radiologic Spectrum of Cardiopulmonary Amyloidosis*

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Amyloidosis, either primary or related to other pathologic states, may mimic a variety of disorders and produce a multitude of appearances demonstrable on radiographic examinations of the chest. All intrathoracic tissues and organs may be affected, but the major abnormalities most commonly involve the heart and lungs. The radiographic appearances in ten patients are described and correlated with the underlying gross and microscopic pathologic findings. No specific pattern of pulmonary involvement could be determined, aside from tracheobronchial amyloidosis. The final diagnosis is dependent upon the awareness of the clinical and radiologic spectrum and the final microscopic examination of involved tissue.

Amyloidosis may affect any of the structures within the thorax and in many cases may produce gross pathologic abnormalities that may be demonstrated and evaluated radiologically. The disease may be a final common pathway for a variety of abnormal processes and, therefore, has been associated with various lymphoproliferative disorders, senescence, and a variety of heredofamilial diseases that include medullary carcinoma of the thyroid with multiple endocrine adenomas, various neurologic conditions, and familial Mediterranean fever.1

We have reviewed the radiologic and pathologic findings in ten patients manifesting various aspects of cardiopulmonary amyloidosis. In this report, we have attempted to describe and correlate these features, in order to facilitate recognition and diagnosis of the abnormal process.

**Materials and Methods**

The case histories of 12 patients proven to have amyloidosis within the heart or lungs were reviewed. The initial symptoms were nondescript in most cases, although patients with diffuse pulmonary disease manifested cough and dyspnea. The chest x-ray films showed abnormal findings in ten. Gross or microscopic pathologic materials, or both, were available for confirmation and correlation in each of these patients.

**Results**

The clinical, roentgenographic, and pathologic findings are summarized in Table 1. Most patients were over 50 years of age, and the male/female ratio was 2.3. Widespread amyloidosis was present in seven patients, and localized disease was present in three.

**Radiographic Features**

A spectrum of radiographic findings is seen in pulmonary amyloidosis, regardless of the underlying cause. In order to facilitate the radiologic discussion, the following morphologic classification of types of cardiopulmonary amyloidosis is being utilized: (1) nodular, which may be subdivided into (a) solitary or (b) multiple; (2) diffuse parenchymal (alveolar-septal and interstitial); (3) tracheobronchial, which may be subdivided into (a) solitary or (b) diffuse; (4) mediastinal and hilar adenopathy; or (5) cardiac. Amyloidosis may involve the lung in any of these patterns, and any of these may occur alone or in combination with each other.

When amyloidosis occurs in a nodular form, it may appear as a single mass or as multiple masses (Fig 1 and 2). The majority of the nodular lesions are located peripherally and subpleurally. The nodules are often oval in appearance, although round lesions are not infrequent. In general the lesions are sharply demarcated. Irregular, poorly defined margins have, nevertheless, been described (Fig 3). Solitary nodular lesions measuring between 2 and 6 cm in diameter with generally sharp margins are almost always benign. Most solitary amyloid nodules fit this appearance. The masses may undergo additional superimposed changes, such as cavitation (Fig 3) and calcification. Calcification occurring in a fine stippled or cloud-like appearance has been de-
Table 1—Findings in Ten Patients with Amyloidosis of the Heart or Lungs

<table>
<thead>
<tr>
<th>Case, Sex</th>
<th>Amyloidosis</th>
<th>Major Organs Involved by Amyloid</th>
<th>Principal Radiographic Findings in Chest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), Sex</td>
<td>Degree</td>
<td>Localization</td>
<td>Associated Diseases</td>
</tr>
<tr>
<td>1, 57, M (Fig 1)</td>
<td>First</td>
<td>Local</td>
<td>Lip</td>
</tr>
<tr>
<td>2, 60, F (Fig 2)</td>
<td>First</td>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td>3, 43, M (Fig 3)</td>
<td>First</td>
<td>Local</td>
<td>Bilateral pulmonary lymphocytic interstitial pneumonia</td>
</tr>
<tr>
<td>4, 28, M (Fig 4)</td>
<td>Second</td>
<td>Diffuse</td>
<td>Metastatic nodular carcinoma of thyroid gland</td>
</tr>
<tr>
<td>5, 61, M (Fig 6)</td>
<td>First</td>
<td>Local</td>
<td>Lip</td>
</tr>
<tr>
<td>6, 53, F</td>
<td>First</td>
<td>Diffuse</td>
<td>Lung; heart; tongue; gut</td>
</tr>
<tr>
<td>7, 60, F (Fig 5)</td>
<td>First</td>
<td>Diffuse</td>
<td>Lung; heart; gut</td>
</tr>
<tr>
<td>8, 75, F</td>
<td>First</td>
<td>Diffuse</td>
<td>Lung; heart; muscle; gut; thyroid; bladder</td>
</tr>
<tr>
<td>9, 63, F</td>
<td>First</td>
<td>Diffuse</td>
<td>Tongue; heart; lung</td>
</tr>
<tr>
<td>10, 54, F</td>
<td>First</td>
<td>Diffuse</td>
<td>Kidney; thoracic vertebrae; heart; lung</td>
</tr>
</tbody>
</table>

The cloud-like calcification is not always identified on routine chest x-ray films, and tomographic studies may be required to demonstrate its presence. Identification of calcification is quite significant, since it helps suggest the nature of the lesion. Amyloid lesions without demonstrable calcification cannot be radiographically differentiated from other nodular pulmonary lesions. Certain metastatic lesions that produce amyloid are prone to undergo calcification.

Figure 1. Solitary nodular pulmonary amyloidosis in asymptomatic 57-year-old man. A (left), Oval, sharply defined left perihilar mass. Results of all pertinent laboratory and clinical studies were within normal limits. Pathologic examination showed cystic subpleural intrapulmonary mass abutting on, but not invading, adjacent bronchus. B (right), Septic subpleural intrapulmonary mass that abutted on adjacent bronchus. Microscopic studies revealed multiple areas of deposits of amyloid surrounded by thick fibrous tissue containing occasional foreign-body giant cells, numerous plasma cells and lymphocytes (Hematoxylin and eosin, original magnification × 50).
with subsequent ossification. Medullary carcinoma of the thyroid is a classic example of such a tumor (Fig 4).6

The rate of growth of nodular amyloid is variable, although slow or indolent enlargement is characteristic. Occasionally, the nodule enlarges rapidly and simulates a tumor.5,7 Furthermore, recurrence of a solitary amyloid nodule has been described after a nine-year interval.8 Concomitant mediastinal and hilar adenopathy, as well as pleural disease, may occasionally be present in any of the pulmonary parenchymal forms of amyloidosis.

Almost all of the patients with alveolar-septal and pulmonary interstitial amyloidosis have disseminated disease.9 Four of our cases had interstitial amyloidosis (Fig 2, 3, and 5). Two of these were associated with amyloid of the heart and one with multinodular amyloidosis of the lung (Fig 2). In another patient, progression of the interstitial process continued and was subsequently associated with a chronic lymphocytic interstitial pneumonia (Fig 3). Primary disseminated amyloidosis involving the lung has a significant predilection for pulmonary interstitial involvement, as was noted in most of the cases reported in the literature.

Amyloidosis can involve the tracheobronchial tree, either as a mass or as a diffuse infiltration within the wall.3,10 The majority of solitary masses involve the larynx and subglottic areas and produce obstruction of the airway. Diffuse involvement is far less frequent and usually occurs with cough,5,11 hemoptysis,2 obstruction of the airway,9 or recurrent pneumonia.11 The diagnostic radiographic fea-

**Figure 2.** Bilateral multinodular and interstitial pulmonary amyloidosis in 50-year-old woman complaining of increasing dyspnea and cough. Chest x-ray film reveals multiple small bilateral nodular deposits superimposed upon diffuse linear and reticular infiltration. Biopsy showed nodular amyloid within alveolar septa and walls of vessels. Other studies failed to reveal evidence of involvement of other organs.

**Figure 3.** Cavitating nodular and infiltrating pulmonary amyloidosis associated with chronic lymphocytic interstitial pneumonia in 43-year-old man with malaise, cough, and mild dyspnea of several weeks' duration. A (upper), Chest x-ray film reveals bilateral infiltrations of lower lobes and early infiltration of left upper lobe, as well as poorly defined cavitating nodular infiltration in left lower pulmonary field. B (lower), Excisional biopsy of cavitating lesion demonstrates heavy lymphocytic infiltration surrounding nodules of amorphous amyloid (H and E, original magnification × 50).
usually associated with nodular indentations. In addition, this diagnostic technique may be of use in evaluating the therapeutic results following bronchosopic procedures in which obstructive lesions had been extirpated, resulting in reexpansion of an atelectatic lung.  

An interesting variant of tracheobronchial amyloidosis in 61-year-old man with chronic cough who was admitted for evaluation of persistent lingular infiltrate. Bronchogram demonstrates multiple segmental stenosis of left upper lobar bronchus, as well as of apical posterior and anterior segments, with suggestion of nodulation. Bronchosscopic examination revealed several small nodular deposits within trachea, along with obstructing friable mass at origin of left upper lobe bronchus. Biopsy of lesions showed submucosal deposits of amyloid.

Figure 3C. Patient’s clinical status worsened over the next six years. Recent chest x-ray film shows extensive infiltrates and bullae and blebs in lower lobes. At autopsy, moderate degree of pulmonary fibrosis was present, with multiple subpleural cysts. Microscopic sections revealed areas of parenchymal replacement by lymphocytic infiltration. Nodular collections of lymphocytes surrounding deposits of amyloids were noted in other areas, and appearance was similar to that seen six years previously.

Figure 4. Amyloid-containing medullary carcinoma of thyroid gland metastatic to lung as bilateral nodules in 28-year-old man. He had history of progressive shortness of breath, lethargy, and biopsy-proven medullary carcinoma of thyroid with calcifications and amyloid within gland (arrow). Lungs revealed bilateral diffuse calcified nodules which on biopsy demonstrated metastatic medullary carcinoma with heavy calcification or ossification (or both) of amyloids within individual nodules of tumor. X-ray films reviewed over next four years showed little change.

Figure 5. Alveolar septal and interstitial pulmonary and cardiac amyloidosis in 56-year-old woman who initially had persistent right-sided abdominal pain. Surgery was performed, and biopsy of small bowel demonstrated extensive deposition of amyloid. Chest x-ray film reveals cardiomegaly, bilateral pleural effusions, and bilateral interstitial infiltrates, along with distended pulmonary veins in upper lobe, all thought to be consistent with congestive heart failure. Patient died after surgery, and at autopsy, lungs were diffusely infiltrated with amyloid, especially in alveolar septa. No congestion was noted.

Figure 6. Diffuse obstructive tracheobronchial amyloidosis in 61-year-old man with chronic cough who was admitted for evaluation of persistent lingular infiltrate. Bronchogram demonstrates multiple segmental stenosis of left upper lobar bronchus, as well as of apical posterior and anterior segments, with suggestion of nodulation. Bronchososcopic examination revealed several small nodular deposits within trachea, along with obstructing friable mass at origin of left upper lobe bronchus. Biopsy of lesions showed submucosal deposits of amyloid.
Amyloidosis is diffuse calcification of the trachea and bronchi. This has been reported in over 200 cases and is known as tracheobronchopathia osteoplastica. Although we have not seen this variant in our series, several cases in the literature were noted to have heavily calcifying nodular submucosal amyloid tumors scattered throughout the trachea and main bronchi. This feature has led some authors to believe that the end stage of diffuse tracheobronchial amyloidosis may be tracheobronchopathia osteoplastica.

Cardiac involvement is usual in this form of pulmonary amyloidosis. The radiographic features of infiltrative pulmonary amyloid are strikingly similar to pulmonary congestion (Fig. 5). The actual diagnosis unfortunately is often only realized at autopsy; however, a persisting unchanging pattern of congestive failure should alert one to the diagnosis.

The lungs in this form have a firm "sponge rubber" consistency. Deposition of amyloid occurring within the alveolar septa causes diffuse thickening and distention of the alveoli. More frequently, amyloid is found in the walls of the pulmonary arteries, arterioles, and veins, along with perivascular deposition. Microscopic calcification and even ossification are usually present. Occasionally, alveolar septal amyloid may result in exudation of fluid into the alveolar spaces, thus giving the gross and radiologic appearance of predominant air-space disease.

Mediastinal widening and/or unilateral or bilateral hilar adenopathy due to amyloid have been reported in five cases in the literature. The lesions resemble sarcoidosis, lymphoma, tuberculosis, or metastatic disease. A specific impression of amyloidosis prior to biopsy is not possible in any of these cases without the presence of macroscopic stippled calcification.

Symptomatic individuals with cardiac involvement usually manifest congestive failure, coronary insufficiency, or disturbances in conduction. Chest x-ray films usually show nonspecific cardiomegaly, often accompanied by pulmonary congestion or frank pulmonary deposition of amyloid (Fig. 5). A configuration simulating pericardial effusion ("water-bottle shape") has been noted on conventional x-ray films. Furthermore, the results of right atrial angiographic and cardiac blood-pool isotopic studies have also been misleading in some patients. Pericardial effusion had been suggested, as a result of marked cardiac dilatation and thickening of the chamber walls. In most cases, differentiation can be made by echocardiograms demonstrating marked thickening of the interventricular septum and the absence of fluid. The radiographic demonstration of the epicardial fat or coronary arteries as borderforming structures on the silhouette may be more difficult. Amyloid is seen in varying degrees in 30 to 70 percent of microscopic sections in hearts of individuals over the age of 60 years. Although usually confined to the heart, minimal microscopic evidence of involvement of the pulmonary vessels or septa has also been occasionally noted.

Pathologically, the heart is rubbery and noncompliant, with thickened muscular walls. Endocardial thickening with formation of nodules may be present. The deposition of amyloid may be within the interstitium of the myocardium, subendocardial, and within coronary arteries and around arterioles. Although described as the cause of coronary insufficiency, mechanical occlusion of coronary arteries due to amyloid is rare, and coronary arteriograms are usually normal. Occlusions of microscopic vessels (arterioles) and diffuse replacement of myocardial muscular fibers may account for the ischemic symptoms.

**Discussion**

Amyloidosis is characterized by extracellular deposition of a fibrillar glycoprotein (measuring 50 to 140 Ångstroms in diameter), to which a mucopolysaccharide may be attached. All types of amyloid have the same fibrillar microstructure regardless of etiology. Amyloid is deposited between parenchymal cells and within connective tissue and the walls of blood vessels, resulting in eventual functional impairment of organs. An absence of inflammatory response is the rule, except in pulmonary involvement due to primary and myeloma-associated amyloidosis. Because of the matrix of mucopolysaccharide, cartilaginous metaplasia occurs. Calcification and ossification, especially in the lungs, further complicates the pathologic features.

The diagnosis must be confirmed microscopically, since no laboratory tests allow for a specific diagnosis. In general, the diagnosis of amyloidosis is based upon the demonstration with hematoxylin-eosin stain of amorphous acellular eosinophilic deposits which demonstrate green birefringence when stained with Congo red and viewed through the polarizing microscope. Production of amyloid is the result of an aberration of either synthesis or degradation of immunoglobulins that transpires within reticuloendothelial cells, fibroblasts, or stem cell precursors of plasma cells. This abnormality occurs following antigenic or other sustained stimulation or dyscratic or neoplastic proliferations of these cells. The association with chronic infection, hyperglobulinemic states, plasmacytosis, lymphoproliferative neoplasms, agammaglobulinemia, and immunologic incompetence, as well as immunologic tolerance...
(senile amyloid), thus becomes clarified.13

The occurrence of pulmonary amyloidosis with severe chronic lymphocytic interstitial pneumonia13 in case 3 deserves further comment. Bonner et al19 reported a case of Sjögren’s syndrome in whom rheumatoid arthritic changes were present in the hands, associated with polyclonal macroglobulinemia and 19S-7S cryoglobulin. Bilateral interstitial infiltrates with bullae were present over the lower pulmonary fields on chest x-ray films. Biopsy of the lung revealed diffuse infiltration of plasma cells and lymphocytes in alveolar walls and especially around bronchioles. Adjacent waxy nodules of amyloid were present as well, entrapping small vessels and bronchioles. Lymphocytic interstitial pneumonia has been described in other cases of Sjögren’s syndrome, with or without macroglobulinemia,20 and may be seen in Waldenström’s macroglobulinemia21 and Wegener’s granulomatosis. Amyloidosis is also associated with Waldenström’s macroglobulinemia and may occur without surrounding lymphocytic infiltration.19 Thus, although both processes are related to immunologic hyperreactivity and the altered immunologic state, the coexistence of both processes in our case without other known systemic disease, dissemination of amyloidosis, or macroglobulinemia suggests a “direct” cause-and-effect relationship between the processes. In both of these patients, the extensive infiltrative pattern due to lymphocytic interstitial pneumonia obscured the radiographic identification of the nodular deposits of amyloid.

In most cases a specific diagnosis of amyloidosis within the chest cannot be made based only on radiographic appearances or laboratory findings; biopsy and microscopic examination of tissue, with confirmation using special stains, are required. The exception to this may be in cases of diffuse tracheobronchial amyloidosis where the bronchogram is almost pathognomonic and in cases of nodular pulmonary, tracheobronchial, and mediastinal lymph node amyloidosis in which characteristic calcifications can be visualized. Nevertheless, awareness of the spectrum of radiographic abnormalities produced by amyloidosis as it affects the various organs within the chest, coupled with a high index of suspicion and careful clinical correlation in each situation, is certainly useful and will aid in obtaining the correct diagnosis in most individuals. In addition, awareness that amyloidosis may mimic the radiographic and clinical appearances of pulmonary tuberculosis, sarcoidosis, metastatic disease,4,5 and bronchogenic carcinoma, as well as various forms of cardiac disease and congestive heart failure, and mediastinal lymphadenopathy15,16 will further aid in arriving at the diagnosis. In the literature, many cases have been described in which coexistent malignant neoplasms occurred in patients whose chest x-ray films demonstrated nodular deposits in the lungs resembling metastases.4,8 Proper aggressive treatment of the localized (and potentially curable)4,8 neoplastic lesions could be pursued only after the specific nature of the pulmonary abnormalities were confirmed to be amyloidosis, rather than disseminated tumor.

References