Localized mediastinal amyloidosis: A misnomer?

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Amyloidosis is a disease related to abnormal protein folding and deposition of that abnormal protein between cells of the body in various tissues and organs, resulting in multiple clinical manifestations. We report a case of amyloidosis with atypical features, isolated to the mediastinum, in a 75-year-old male who presented with fatigue and shortness of breath. Amyloidosis that is isolated to the mediastinum without pulmonary parenchymal involvement is exceptionally rare. It has been hypothesized that localized mediastinal amyloidosis manifesting as amyloidomas is a distinct clinical subtype with a better prognosis than classic systemic amyloidosis. This paper describes the radiologic features of localized mediastinal amyloidosis (along with its pathologic correlation) and compares systemic and isolated disease.

Case report

A 75-year-old male with a prior history of stage II colon cancer, coronary heart disease, hypertension, and gout presented to our hospital's emergency department with a complaint of fatigue and shortness of breath. The subsequent frontal chest radiograph demonstrated a wide mediastinum with clear lung fields (Fig. 1). The differential diagnosis at that time was vast, including acute aortic disease, lymphadenopathy (possibly metastatic), and mediastinal mass. Basic laboratory analysis, including a set of cardiac enzyme markers, showed normal values. A contrast-enhanced CT of the chest showed a normal-sized heart without effusion and no evidence of acute aortic syndrome (Fig. 2). The lungs were clear, without diffuse or focal parenchymal abnormality. However, several large and bulky hypoattenuating mediastinal masses with internal punctate calcifications were seen. The largest was in the subcarinal region.

On further review of prior CT scans at our institution, dating back approximately 10 years, the mediastinal masses were seen to be present but slowly enlarging and growing in number (Fig. 3). Also noted was the fact that some of the masses developed several clusters of punctate or speckled calcification as they stopped enlarging. The diagnoses of sarcoidosis, histoplasmosis, and other granulomatous diseases with calcified adenopathy were entertained. Lymphoma was also considered but was felt to be less likely due to the calcifications. The patient had a history of stage II colon cancer, was status post-hemicolectomy 9 years before presentation, and was thought to be cured. At this time, a
mediastinal biopsy was performed of the subcarinal mass to exclude metastatic disease (Fig. 4).

Histological examination showed deposits of eosinophilic, hyalinized, homogeneous waxy material with surrounding histiocytic and giant-cell reaction. The deposits were positive for crystal violet and Congo red stain. The histological features and special stain results were consistent with amyloid. Subsequent subtyping detected a peptide profile consistent with AL (lambda)-type amyloid deposition.

The patient's care now included a hematologist, who suggested bone-marrow biopsy to confirm systemic amyloidosis. The patient was reluctant to undergo biopsy. He continued routine followup with his primary physician and hematologist. The patient returned approximately 5 months later to the emergency department with a similar presentation of fatigue and shortness of breath. He denied fever, chills, night sweats, or bone pain. A CT scan of the thorax without contrast again showed the extensive mediastinal amyloidomas, with slightly progressive internal punctuate calcifications (Fig. 5). No acute findings were identified. The tracheal bronchial tree was void of calcifications, and the lung parenchyma remained clear. The patient had no other signs or symptoms of amyloidosis elsewhere in his body.

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The patient then agreed to undergo bone-marrow biopsy as an outpatient, which was positive. The hematoxylin and eosin-stained sections revealed a hypercellular marrow infiltrated with scattered plasma cells, which accounted for approximately 10-15% of the total cellularity (Fig. 6A). This was confirmed by CD 138 immunostain for plasma cells (Fig. 6B). The in-situ hybridization for kappa and lambda demonstrated that the plasma cells were lambda-restricted (Figs. 6C, D). Flow cytometry also detected an abnormal plasma-cell population with lambda light-chain
clonality. Congo red stain of the marrow was negative for amyloid. The patient was diagnosed with IgG lambda-restricted plasma-cell myeloma.

**Discussion**

Amyloidosis is a disorder resulting from extracellular deposition of misfolded amyloid proteins, which are insoluble linear fibrils in a β-pleated sheet configuration. The deposition can be localized to one organ or can involve multiple organs or systems, as seen in systemic amyloidosis. So far, 27 amyloid proteins have been associated with human disease (1), and amyloidosis is classified according to the precursor protein. Microscopically, amyloid appears as an eosinophilic material on H&E stain, usually within or surrounding blood-vessel walls. It shows classic apple-green birefringence under polarized light after Congo red staining. Amyloid can also be detected by crystal violet or thioflavin T fluorescent staining, as well as electron microscopy.

Amyloidosis can also be classified as either primary or secondary. The primary form (AL) of amyloidosis is the most common form, with an estimated age-adjusted incidence of 5.1 to 12.8 per million patients (2). In AL amyloidosis, the amyloid is composed of both intact light chain and fragments of the variable NH2-terminus region, which are synthesized by a monoclonal plasma cell population (3). Therefore, AL amyloidosis can occur as a primary disorder or in association with plasma-cell dyscrasia, such as plasma-cell myeloma or monoclonal gammopathy of undetermined significance (MGUS), both of which share similar genetic abnormalities with primary amyloidosis (3). The secondary or reactive forms (AA) are related to chronic inflammatory conditions or tissue-destructive processes such as rheumatoid arthritis or inflammatory bowel disease. The precipitating protein in secondary amyloidosis is always the amino-acid terminus of the acute-phase protein serum amyloid A and is identical in all patients.

Another form of categorization is systemic versus localized disease. In localized disease, it is believed that the amyloid fibril protein is deposited at the site of production, whereas in systemic disease, the protein is synthesized at distant sites and transported in the bloodstream to be deposited at multiple sites (4). Localized amyloidosis is less
common than systemic amyloidosis. Systemic disease is confirmed by bone-marrow biopsy and/or electrophoresis.

Variable manifestations are seen in patients. Features of amyloidosis can be classically seen in the joints, kidney, heart, lungs, and (most commonly) gastrointestinal system (5). Within the thorax, the heart is the most commonly involved organ, especially in primary amyloid, with wall thickening and systolic dysfunction. Pulmonary involvement in primary disease is common. CT findings can be similar to those of pneumonia, and patients typically take antibiotics only to have recurrent symptoms and imaging findings.

Pulmonary amyloidosis has three forms: tracheobronchial, nodular parenchymal, and alveolar septal. Alveolar septal is the least common of the three but can have the worst prognosis; it often leads to respiratory failure. Imaging can demonstrate diffuse inter- and intralobular septal thickening, with micronodules often in a subpleural or bronchovascular distribution (5, 6). Focal nodular or mass-like lesions called amyloidomas are seen in the nodular type, ranging from 0.5 to 15 cm (7). Diffuse but sometimes interrupted calcifications of the large airways can be seen in the tracheobronchial type, which is the most common. CT can demonstrate intraluminal nodules or less common) diffuse thickening of the trachea and bronchi.

In our patient, the CT imaging findings were classic for localized thoracic amyloidosis. Typically, mediastinal and hilar lymphadenopathy are seen without pulmonary parenchymal involvement (8). The adenopathy is homogeneously low in attenuation, with a smooth contour, and slowly enlarges in size and number over a period of several years, becoming very bulky (9). It is not uncommon to see stippled, speckled, or faint calcifications within the enlarged amyloidomas. Pickford et al reported that 33% of lymph nodes affected by amyloidosis have these characteristic calcifications (8). The significance of the calcifications is uncertain. It is unknown whether they develop after the lymph node has stopped enlarging or whether they develop due to the slow and indolent nature of the disease (10).

Mediastinal lymphadenopathy is a rare manifestation of amyloidosis. Up to 37% of cases of generalized primary and secondary amyloidosis have lymph-node involvement, and 75% of patients with thoracic disease have mediastinal adenopathy (11, 12). Pickford et al reviewed 300 cases of amyloidosis. They found only nine cases of intrathoracic lymphadenopathy, and systemic amyloidosis was diagnosed in all cases (8). Mediastinal lymphadenopathy as a localized form of amyloidosis without pulmonary findings is extremely rare. To our knowledge, only eight cases have been described before in the English literature (10, 13-19). The type of fibril obtained by biopsy has only been reported in three of those cases (all AL type, as in our patient). Unfortunately, bone-marrow biopsy was not reported in all the cases. We believe that our case is the first of localized mediastinal amyloidosis to also have positive bone-marrow biopsy results that confirm AL systemic disease.

As with our patient, it is believed that localized mediastinal amyloidosis has a better survival rate, on average 3 years from diagnosis, than classic systemic amyloidosis (6-
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18 months) (10, 20). One could hypothesize that since the characteristic AL fibrillar protein is a fragment of the variable immunoglobulin light and/or rarely heavy chain, and thus different from patient to patient, this variability in the AL fibril could cause the difference in clinical manifestation and thus prognosis, even though both are technically systemic diseases. The terms "localized" or "isolated" may be a misnomer. One could argue that localized mediastinal amyloidosis is a subtype of systemic disease. Obviously, more cases with localized mediastinal manifestations and bone-marrow pathologic correlation are needed to make this distinction.

The differential diagnosis of mediastinal lymphadenopathy with stippled or punctate calcifications includes: metastatic disease, sarcoidosis and other granulomatous processes, (rarely) malignant lymphoma, and amyloidosis. Low-attenuation lymph nodes can be seen in tuberculosis and fungal infections. It is difficult to include amyloidosis in the diagnosis of isolated mediastinal adenopathy with internal punctate calcifications since it is such a rare entity; however, radiologists should be ready to consider it as part of the differential diagnosis, given the proper clinical scenario.

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