A case report of pulmonary amyloidosis recognized by detection of AA amyloid exclusively in alveolar macrophages

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**ABSTRACT**

Amyloidosis is a rare condition in which tissue deposits of inert fibrillar protein result in organ damage and dysfunction. There are several types of amyloid fibrils. Some of the most common forms are AL (amyloid light chain) protein and AA (amyloid-associated) type of amyloid fibril protein. Pulmonary amyloidosis is relatively common but is usually asymptomatic. Thus, the diagnosis may be easily overlooked. A 78-year-old male with a history of multiple myeloma followed by systemic amyloidosis presented with abnormal chest CT showing diffuse interlobular thickening in the whole lung field with bilateral pleural effusion. Bronchoalveolar lavage and transbronchial biopsy were performed. Due to the patient’s poor condition and hemorrhage, only one fragment was available from forceps biopsy. Histologically, there was no amyloid deposition in the lung parenchyma; however, some histiocytes showed eosinophilic granular contents which prompted us to perform additional staining. The cytoplasmic material turned to be positive with direct fast scarlet (DFS) staining and AA amyloid immunostaining. Similar macrophages with AA amyloid were also found in the bronchoalveolar fluid. We experienced a case with AA amyloidosis affecting the lung diagnosed by the presence of intracytoplasmic amyloid in alveolar macrophages. The microscopic changes were so subtle that they may be overlooked. Recognition of amyloid deposition in alveolar macrophages may be an important clue to diagnose pulmonary amyloidosis. Such finding is of particular significance in the small-sized specimens, such as biopsies and cytologic smears.

1. Introduction

Amyloidosis is a disease associated with several inherited, inflammatory and neoplastic disorders in which extracellular deposits of fibrillar proteins result in tissue damage and organ failure. These fibrils are composed of the aggregation of insoluble, misfolded proteins. According to biochemical-clinical classification, amyloid can be broadly classified into two categories: systemic (generalized), involving several organ systems; and localized, in which deposits are limited to a single organ [1]. There are several types of amyloid fibrils. Some of the most common forms are AL (amyloid light chain) protein and AA (amyloid-associated) type of amyloid fibril protein. Typically, they are associated with multiple myeloma and chronic inflammatory conditions, respectively [2].

We presented a case of a 78-year-old male with systemic AA amyloidosis complicating multiple myeloma, in which the observation of alveolar macrophages gave the only diagnostic clue of pulmonary amyloidosis.

2. Case presentation

A 78-year-old male had a medical history of multiple myeloma
diagnosed by bone marrow biopsy. A few months later, upper gastrointestinal endoscopy was performed with a concern of systemic amyloidosis, in which duodenal biopsy revealed patchy aggregation of amorphous eosinophilic material highlighted by direct fast scarlet (DFS) stain; and apple-green birefringence was also noted when observing under polarized light. The positive staining was not observed on potassium permanganate (KMnO4)-DFS stain, which was consistent with the diagnosis of systemic AA amyloidosis.

Two months later, the patient developed left lower lung accentuated consolidation with a widening of interlobular septa and pleural effusion. The imaging suggested interstitial edema (Fig. 1).

Owing to clinical suspicion of systemic amyloidosis with pulmonary involvement, bronchoalveolar lavage, and tranbronchial lung biopsy were performed. Due to hemorrhagic complications of the biopsy, only one tissue fragment was sampled and submitted to histopathological examination. Although no obvious findings of amyloid deposition found in the lung parenchyma, alveolar macrophages showed enlarged cytoplasm containing granular intracytoplasmic material (Fig. 2A). This finding prompted us to perform additional staining. The material was positive with DFS stain (Fig. 2B) and anti-amyloid A immunostaining (Fig. 2D), but negative with KMnO4-DFS stain (Fig. 2C). Similar macrophages were also found in the bronchoalveolar lavage fluid (Fig. 3A–C). A diagnosis of pulmonary amyloidosis has been rendered.

3. Discussion

Systemic amyloidosis is a group of rare diseases caused by tissue deposition of abnormal protein fibrils. Among these diseases, systemic light chain (AL) amyloidosis is the most common. It can involve several organs, including heart, kidneys, liver, peripheral and autonomic nervous system, and gastrointestinal tract [3]. The symptoms are variable and non-specific, depending on the organs affected.

Amyloidosis with the involvement of the lungs is relatively common but rarely symptomatic [4,5]. According to the etiology and distribution, there are three subtypes of pulmonary amyloidosis: diffuse alveolar-septal amyloidosis, nodular pulmonary amyloidosis, and tracheobronchial amyloidosis, in which typical scenarios are systemic AL, localized AL or AL/AH and localized AL, respectively [4].

In a single large series of pulmonary amyloidosis, 181 out of 205 cases (88.3%) were that of AL amyloid. AA amyloid was present in 3 patients (1.5%). The clinical information regarding the clinical form of amyloidosis (local or systemic) was available from 118 patients. Among cases (88.3%) were that of AL amyloid. AA amyloid was present in 3 patients (1.5%). Isobe et al. described systemic amyloidosis in Japanese patients with underlying plasma cell dyscrasias [7]. Among 105 cases, the majority developed systemic AA amyloidosis (43%) and the other subtypes were systemic AL amyloidosis and familial amyloid polyneuropathy [7]. The case presented herein is also an example of AA amyloidosis affecting the lung in a patient with underlying multiple myeloma. Of note, pulmonary amyloidosis could be an incidental finding in lung resection for mass lesions. In a series of 115 cases with incidental, nonneoplastic lung parenchymal findings in resection specimens, 2 patients (0.5%) had amyloidosis [8].

Congo red and DFS stains are useful to confirm amyloidosis, in which apple-green birefringence is highly specific for amyloid fibril. Unfortunately, some factors such as inadequate tissue quantity, small amounts of amyloid and the staining technique can result in false-negative result. Noteworthy, lack of apple-green birefringence on these stains does not exclude the presence of amyloid fibrils. Reactivity with Congo red and/or DFS stains, in combination with immunostaining for subtyping amyloid fibril, is warranted for diagnosis of amyloidosis in spite of lack of apple-green birefringence on these stains [9]. Typing of amyloid fibrils is essential for appropriate treatment. The potassium permanganate method is one of the reliable techniques for differentiating amyloid AA from other forms of amyloid in routine laboratory practice [10]. At present, the most commonly used approach for the fibril typing is immunohistochemistry. Other techniques, including microdissection and mass spectrometry from fixed histological tissue sections, may also be performed; however high costs preclude their introduction in the routine laboratory practice [2].

Typically, amyloidosis is characterized by the deposition of amorphous eosinophilic material in the perivascular stroma. However, this abnormal fibrillar protein can be present within the cytoplasm of macrophages, which are known players in amyloid metabolism. Due to coexisting and predominant extracellular deposition, such cases (especially those of diagnostic significance) have been rarely reported [11–13]. In our case, tranbronchial biopsy showed the uncommon diagnostic feature of AA amyloid deposition, i.e. abnormal fibrils were identified only in alveolar macrophages. They were highlighted by DFS and AA amyloid immunostain. However, no apple-green birefringence was detected under polarized light. This change in alveolar macrophages was so subtle that it could be easily overlooked. In the case of the appropriate clinical context, care should be taken to seek amyloid deposits in alveolar macrophages.

The bronchoalveolar lavage fluid also displayed similar macrophages, in which there was granular cytoplasmic material in macrophages. No extracellular material was observed. Cytologically, it is rather difficult to diagnose amyloidosis based on this feature alone. According to the previously reported cases, a large amount of extracellular amorphous, irregularly shaped material is needed for the diagnosis of amyloidosis [11,12].

One of the most important differential diagnoses in terms of morphological appearance is pulmonary crystal storing histiocytosis. Our patient had a pulmonary histiocytic infiltrate along with a clinical history of multiple myeloma and histologically-proven duodenal amyloidosis. However, DFS staining highlighted abnormal deposits within the cytoplasm of these histiocytes. The chest CT also showed diffuse interlobular thickening in the whole lung field with bilateral pleural effusion. The latter finding was against the possibility of crystal storing histiocytosis, which typically appears as a mass or nodule on chest CT. We performed an extensive literature review on pleuro-pulmonary histiocytosis. To the best of our knowledge, only 18 cases of pleuropulmonary CSH have been described to date [14–18]. All patients had single or multiple lung masses detected by imaging. Most of the 14 cases (78%) had associated plasma cell dyscrasias and non-Hodgkin lymphomas.

Other differential diagnoses include several diagnostic entities containing a large number of macrophage-rich pulmonary infiltrates; for example, inhaled crystalline materials, infections, storage diseases and other histiocytic disorders, e. g. Erdheim-Chester disease and Rosai-Dorfman disease. According to our presented case, no crystalline material, intracellular organism, granuloma or emperipolosis were found. Therefore, these diagnostic entities were ruled out. Clinical correlation

Fig. 1. Chest CT showed left lower lung accentuated consolidation with a widening of interlobular septa and pleural effusion.
also plays a role in distinguishing these diseases. Since amyloidosis has variable and often nonspecific features on imaging, it is a challenging diagnosis for the radiologist. For instance, pulmonary amyloidosis may present as a diffuse reticulonodular interstitial thickening, consolidations, or parenchymal nodules [19]. Therefore, clinical correlation and ancillary studies play an important role in diagnosing pulmonary amyloidosis.

The goal of treatment for patients with coexisting pulmonary amyloidosis and multiple myeloma is to decrease the production of amyloid protein composed of immunoglobulin light chain, in which monoclonal antibodies may benefit patients with such diseases [20]. Chemotherapy and autologous stem cell transplantation are also useful in a subset of patients. Typically, patients with diffuse pulmonary amyloidosis develop progressive deterioration of pulmonary function and symptoms. The prognosis is dismal, in which a median survival for untreated patients is 13 months [20].

4. Conclusion

We described a case of a 78-year-old male with a known history of multiple myeloma presenting with systemic AA amyloidosis manifested as a diffuse interlobular thickening in the whole lung field and bilateral pleural effusion. Our case showed unusual cytohistologic features of amyloid deposition in histiocytes which can have broad differential diagnoses including crystal storing histiocytosis and other histiocyte-rich lesions. This finding is of particular significance in the small-sized specimens, such as biopsies and cytologic smears.

Informed consent

Appropriate written informed consent was obtained for publication of this case report and accompanying images.
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Declaration of competing interest
The authors declare that there is no conflict of interest.

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