Pulmonary amyloidosis in a patient with lymphocytic interstitial pneumonia

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Amyloidosis is a rare heterogeneous disorder characterized by extracellular deposition of insoluble protein fibrils in virtually any organ or tissue. The amyloid deposits progressively disrupt the tissue architecture and impair organ function. Immunologically related amyloidosis is a monoclonal plasma cell disorder in which the amyloid is commonly derived from kappa or lambda immunoglobulin light (L) chains, or L chain protein fragments and is termed AL amyloidosis. It most frequently involves the lung in both systemic and localized forms. We report a case of localized primary pulmonary AL kappa amyloidosis presenting with multiple calcific nodules, consolidations, numerous cysts, cavitation and serum paraproteinemia in a patient with lymphocytic interstitial pneumonia (LIP).

CASE

A 60-year-old Saudi woman was admitted through the emergency room for progressively worsening dyspnea, dry cough and mild fever of two weeks duration. The patient had been well until two years earlier, when she presented to another hospital with slowly increasing dyspnea and dry cough. A diagnosis of LIP was established on bronchoscopic biopsy. Since that time she had been on the oral steroids *Imuran* (azathioprine) and *Ventolin* (albuterol) inhaler. She denied any history of tuberculosis, exposure to chemicals, organic dust, toxic gas, molds, bird feed or smoking. She was not known to have diabetes, hypertension or heart disease. On physical examination she was mildly febrile and dyspneic, but not hypoxic. There was no finger clubbing or pitting edema. Chest auscultation found inspiratory crackles bilaterally. Cardiac, CNS, abdomen, pelvic, breast and neck examinations were unremarkable.

Initial laboratory work up showed elevated ESR (56 mm/h) and a normal CBC, liver and renal function tests. Rheumatoid factor, anti-DNA, antineutrophil and HIV serology were negative. Admission chest radiographs

revealed multiple dense and ill-defined nodules of variable size in both lungs for which the patient was evaluated with CT. A high-resolution and conventional CT (Figure 1) of the chest revealed multiple calcific nodules of 0.3 cm to 5 cm size predominantly distributed in the mid-lower lungs subpleurally and peripherally. The calcification was dense and homogenous in the smaller nodules, while irregular and amorphous or punctate in the larger nodules. Consolidations with a variable degree of amorphous and punctate calcifications were noted at the right upper lobe posterior segment, middle lobe and at lung bases. A cavity with a small fluid level and smooth inner wall was present in the right lower lobe consolidation (Figure 1E). Randomly distributed multiple thin-walled air cysts of varying size (0.3 cm to 6 cm) were present in both lungs. There were a few small and discrete reactive lymph nodes in the superior mediastinum. There was no evidence for calcific lesions in the heart musculature. Pleural, pericardial effusions or thickening were absent.

Given these radiologic findings, the differential diagnoses were limited. We considered metastatic disease, tuberculosis, amyloidosis and Wegener's granulomatosis. A technicium MDP bone scan was requested, revealing no abnormal uptake in the skeleton, but most of the large calcific nodules in the lung did show increased tracer activity mimicking rib metastasis (Figure 2). There was no tracer uptake in the heart and extrathoracic soft tissues. The patient was further evaluated clinically and radiologically for a primary malignancy.

An ultrasound examination of the neck for thyroid and CT scans of the abdomen and pelvis were non-rewarding. We arrived at a diagnosis of metastatic lung disease from an unknown primary tumor or amyloidosis, and a CT-guided transthoracic core biopsy was performed with an 18-gauge needle. A lung core biopsy was fixed in neutral formalin and processed for paraffin embedding. Histologic tissue sections were stained with

Figure 1. CT scans of the chest at different levels on lung window (A-D) and mediastinal window (E, F), showing multiple calcific nodules and thin-walled air cysts of variable sizes in all lung zones bilaterally. Consolidations with variable calcifications are present in the right upper lobe posterior segment (arrows in A and B) and in the middle lobe (m in C). A cavity in the right lung base (arrow in E) is noted. Septal thickening was not present on high-resolution chest scans (not shown).

Figure 2. Whole body technetium MDP bone scans showing multiple nodular areas of increased tracer activity in the lungs bilaterally (arrows).

Figure 3. The lesion in this microphotograph is predominantly composed of mature plasma cells (arrows). The amorphous material among the plasma cell aggregates corresponds to amyloid (Am) (H&E, 20X).

Figure 4. Immunohistochemistry showing positive restricted reactivity for kappa light chain, which is indicated by the dark cytoplasmic staining of the plasma cells (arrows) (immunoperoxidase, 40X).

hematoxylin and eosin stain. After the initial observations, Congo red staining was performed and studied by light and polarized microscopy. Automatized immunohistochemistry was carried out using antigen unmasking and streptavidin peroxidase methods. Commercial antibodies included kappa and lambda. The H&E sections (Figure 3) revealed a variable density of plasma cell infiltration and amorphous interstitial substance with focal microcalcifications. No preserved lung tissue was discernible. Plasma cells showed no atypical features. The amorphous substance showed variable eosinophilic intensity, and stained positive for Congo red, which under polarized light displayed a characteristic "apple-green" color. The vast majority of plasma cells were positive for a kappa light chain (Figure 4). A pathologic diagnosis of amyloidosis with kappa-light-chain restriction was established.

DISCUSSION

The classification of systemic amyloidosis is based on different sub-unit proteins, which defines the organ involvement and disease manifestations. Major types of systemic amyloidosis recognized in humans are (1) a primary or immunoglobulin light chain/light chain fragment (AL) disease, (2) immunoglobulin heavy chain (AH) amyloidosis, (3) secondary or amyloid protein A (AA) disease (4) hereditary and mutant transthyretin (ATTR) disease, and (5) dialysis-related or 2-microglobulin (2M) disease. Lung involvement is more common with primary AL amyloidosis, which may be localized or systemic and rarely reported with other types of amyloidosis. Systemic AL amyloidosis can develop in any organ system, but is most frequently seen in the kidneys, heart, gastrointestinal tract, peripheral nerves, liver and spleen. The respiratory system is involved in up to 50% of patients with amyloidosis and for unknown reasons, a localized form is more common than the diffuse systemic form.¹ Local amyloid deposition to an organ may itself be a focal or a diffuse process.

AL amyloidosis is related to both multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS), depending on the number or total body burden of monoclonal plasma cells. When the cell burden is more than 25% a diagnosis of MM is considered and others as having MGUS, in which the clonal immunoglobulin product is amyloidogenic. Also, primary amyloidosis typically lacks lytic bone lesions and hypercalcemia.² Transformation of AL amyloidosis into MM is extremely rare, while about 10% to 15% of myeloma patients may have co-existing amyloidosis. About 20% of patients with MGUS may progress to MM over a period of 10 years.

Systemic AL lung disease may manifest in different forms. The diffuse interstitial or alveolar septal type is the least common, but is more serious with a poor prognosis and a median survival of 16 months once diagnosed.¹ This is almost an exclusive manifestation of systemic AL disease. On cross-sectional imaging and HRCT of the chest, the patient with diffuse lung disease may show evidence of widespread inter-alveolar septal thickening, well defined small nodules of 2 to 4 mm in size with or without calcifications, focal reticulations, areas of ground glass density, and honeycombing. The nodules may be few in number, multiple or assume a miliary pattern, and are rarely of large size, up to 2.5 cm.² The abnormalities may be distributed randomly, but peripherally, subpleurally and a mid-lower lung predominance is most common. Large nodular pulmonary amyloidomas in systemic AL disease are controversial and rarely reported. A review of the published data from the Mayo Clinic, Boston University, and the Johns Hopkins Hospital failed to identify any nodular pulmonary amyloidomas in 70 patients with systemic AL disease.^{1,3} Hui et al, however, reported 3 cases of nodular lung disease in patients with monoclonality in serum and urine.⁴

Mediastinal and hilar lymphadenopathy, although less common than extra-thoracic adenopathy, may be present in less than 10% of patients with systemic AL amyloidosis. Adenopathy can be widespread, resembling lymphoma on imaging and may show dense foci of amorphous calcifications. Pickford et al reported adenopathy to be the single most common finding in a series of 12 patients with systemic amyloidosis. No patients with localized amyloidosis had adenopathy in their series.² Consolidations with or without amorphous and irregular calcifications and cavitations are seen in less than 15% of patients. There are case reports of pleural effusion, pleural thickening, and amyloid infiltration of diaphragm.^{2,5}

Localized AL pulmonary amyloidosis manifests in three forms: a laryngeal and tracheobronchial type, a nodular type and a multi-nodular type. In the laryngeal and tracheobronchial type there is unifocal or diffuse submucosal deposition of the amyloid substance. The patients usually present with symptomatology of asthma, hemoptysis, atelectasis and chronic infection.¹ A CT scan may show mural nodules, plaques or circumferential thickening of the trachea, and bronchi with luminal narrowing. There may be focal nodular and diffuse calcifications visible within the tracheobronchial wall. Post-obstructive lung parenchymal abnormalities are best depicted on CT studies than on bronchoscopy. The differential diagnosis includes neoplasm, tubercu-

losis, tracheobronchopathia osteoplastica and relapsing polychondritis.

In the nodular type, patients are usually asymptomatic with a benign course and a good prognosis.¹ These patients rarely present with cough, shortness of breath, hemoptysis, and are often recognized incidentally. On CT scan, nodular disease is characterized by multiple or single well-defined nodules with smooth or lobulated margins, ranging in size from 0.4 cm to 15 cm (mean, 4 cm), distributed in subpleural and peripheral locations of one or both lungs. They are more frequent in the mid and lower lung fields. Nodules are commonly multiple in up to 65% of patients with a small, focal or diffuse and dense calcifications in half.^{6,7} Amyloid nodules grow very slowly if at all and almost never regress spontaneously. The nodules that are not densely calcified should grow at a similar rate. Any dysynchronous growth of a single lesion warrants further investigation to exclude carcinoma. Amyloid nodules, reported in about 10% of patients, rarely cavitate. Consolidations, adenopathy, pleural effusion or thickening and alveolar septal thickening are not recognized features of localized AL disease.

Multi-nodular lung amyloidosis with multiple thin-walled cysts in patients with Sjogren's syndrome and LIP have been recently described. The mechanism of cyst formation is probably due to extensive inflammatory cell infiltration of the bronchiolar wall, causing a check valve mechanism.^{8,9} More recently a diffuse cystic and interstitial radiologic pattern in a patient with localized pulmonary amyloidosis was reported.¹⁰ Cystic degeneration of the amyloidomas is another possibility.

Except for the lung lesions, the clinical and radiological work-up on this patient found no other organ amyloidosis. Multiple myeloma was ruled out by lack of bone lesions and a lack of significant plasmacytosis in the bone marrow. Therefore, the origin of the serum kappa monoclonal component can be exclusively attributed to the lung lesion and thus, it can be concluded that this patient had a primary pulmonary AL kappa amyloidosis. This case also demonstrated that localized pulmonary amyloidosis can present with consolidations, cavitation, and diffuse cystic disease in addition to a classic nodular radiologic pattern as well as paraproteinemia. The multiple cysts in our patient may be a manifestation of the amyloidosis or the underlying LIP, which was not confirmed at this admission. Multiple nodular areas of increased tracer activity in the chest on bone scan mimicking rib metastasis is an interesting finding, not reported before to the best of our knowledge.

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