A Rare Lung Nodule Consisting of Adenocarcinoma and Amyloid Deposition in a Patient with Primary Systemic AL Amyloidosis

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Abstract

A 60-year-old woman was found to have proteinuria and a lung nodule. The surgically resected left upper lobe contained a nodule, in which the adenocarcinoma was surrounded by a heavy deposition of amyloid. Subsequent renal and gastric biopsies demonstrated amyloid deposition with Aλ immunoreactivity. She was treated with 2 courses of VAD (vincristine, doxorubicin and dexamethasone), resulting in the disappearance of Bence Jones proteinuria. Her nephrotic syndrome has been improving during the subsequent 3 years. The rare lung nodule consisting of adenocarcinoma and amyloid deposition was a diagnostic clue in this primary systemic AL amyloidosis patient.

Key words: AL-amyloidosis, lung nodule, adenocarcinoma, nephrotic syndrome

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Introduction

A nodular pattern of amyloid deposits in the lung is occasionally seen in either the systemic or localized form of AL amyloidosis, where deposits are derived from immunoglobulin light chain fragments (1, 2). This lesion is differentiated from various pulmonary diseases including malignancy. Here, we report an unusual patient with primary systemic AL amyloidosis who showed a single lung nodule composed of amyloid deposition surrounding adenocarcinoma.

Case Report

A 60-year-old woman with no habit of smoking was found to have proteinuria and an abnormal shadow on the left lung apex at a health screening examination. The lung lesion showed a round-shaped nodule with marginal spicular formation on computed tomography, which was compatible with a radiological finding of adenocarcinoma (Fig. 1a). Tumor markers, including carcinoembryonic antigen, were within the normal range. Based on the systemic survey her disease stage was considered to be stage IA (T1, N0, M0). At age 61 surgical resection of the left upper lobe was performed: the lung lesion was 1.5 cm in diameter and revealed amyloid deposition around adenocarcinoma (Fig. 1b, c, d, and Fig. 2a and b). Additionally, vascular walls in the non-carcinomatous area were also involved by amyloid deposition (Fig. 2a insert), indicating that this amyloidosis was a systemic disorder. Immunohistochemistry revealed positive staining of receptors for advanced glycation end-products (RAGE) mainly on tumor cells (Fig. 1e). She then underwent renal biopsy, which showed amyloid deposition on glomeruli. The patient was referred to us for further examination when she was 62 years old.

On physical examination she was 153 cm tall and weighted 47 kg, and showed moderate leg edema but there were no overt signs of organomegaly, lymphadenopathy, macroglossia, or neuropathy. Routine laboratory tests, including hematology (WBC 4,620/μL; red blood cells 490x...
population. Systemic bone survey demonstrated no apparent cells (232/20,000 cells), which indicated a monoclonal subpopulation. These findings suggested that the patient had plasma cell dyscrasia.

Urinary excretion of protein was 4.0 g/day, with creatinine (10 mg/dL) and albumin (2.8 g/dL) and a decreased serum level of IgG (330 mg/dL, normal 6.8-8.3 g/dL; albumin 2.8 g/dL, normal 4.2-5.1 g/dL). IgM (85 mg/dL) and IgA (171 mg/dL) were normal except for hypoproteinemia (total protein 4.8 g/dL, normal 6.8-8.3 g/dL; albumin 2.8 g/dL, normal 4.2-5.1 g/dL) and was treated with 2 courses of VAD (vincristine 0.4 mg/day and doxorubicin 9 mg/m²/day by infusion on days 1-4, 9-12 and 17-20; all were repeated four weeks later) (5). One year after the chemotherapy Bence Jones protein in her urine disappeared, and both serum levels of FLCs and the κ/λ ratio were within normal ranges (κ-FLC 9.52 mg/L; λ-FLC 27.10 mg/L; κ/λ ratio: 0.35). At age 65 she looked healthy and her serum levels of total protein (6.0 g/dL) and albumin (3.6 g/dL) had significantly increased in comparison to those before treatment. Chest CT showed no pulmonary lesions.

Chem X-ray and CT were unremarkable, and there was no recurrence of lung cancer. The electrocardiogram was normal and the echocardiogram revealed normal cardiac function (fractional shortening in the left ventricle 49.3%, normal >30%). Gastric mucosal biopsy showed amyloid deposition (Fig. 2c). Immunohistochemical analysis of biopsied lung, kidney and stomach tissues revealed that all amyloid deposits were specifically immunolabeled by an anti-Aλ antibody (4) (Fig. 2b insert). She was diagnosed as having primary systemic AL amyloidosis with nephrotic syndrome, and was treated with 2 courses of VAD (vincristine 0.4 mg/day and doxorubicin 9 mg/m²/day by continuous infusion on days 1-4, and dexamethasone 40 mg/day by infusion on days 1-4, 9-12 and 17-20; all were repeated four weeks later) (5). One year after the chemotherapy Bence Jones protein in her urine disappeared, and both serum levels of FLCs and the κ/λ ratio were within normal ranges (κ-FLC 9.52 mg/L; λ-FLC 27.10 mg/L; κ/λ ratio: 0.35). At age 65 she looked healthy and her serum levels of total protein (6.0 g/dL) and albumin (3.6 g/dL) had significantly increased in comparison to those before treatment. Chest CT showed no pulmonary lesions.
A nodular lesion is seen in various pulmonary diseases, including cancer, tuberculosis and fungus infection, but amyloidosis is infrequently considered as a candidate in the differential diagnosis of such a lesion. Amyloidosis affecting lung parenchyma shows two different patterns of lesions: solitary/multiple nodules and diffuse alveolar septal involvement (1, 2, 6). The former is usually caused by the localized AL type and is infrequently associated with the systemic form of AL amyloidosis (2, 6). In both types amyloid nodules are commonly located in the subpleural spaces, frequently showing bilateral distribution (1). The latter is a manifestation of systemic amyloidosis, the major underlying disorder of which is AL amyloidosis (6, 7), while ATTR- or AA-type systemic amyloidosis only very occasionally involves pulmonary tissues (8, 9). In the localized form of AL amyloidosis the amyloidogenic light chains are produced by a local, tissue-based lymphoplasmaacytic dyscrasia (10), while in systemic AL amyloidosis a circulating monoclonal protein is an amyloid precursor and amyloid deposition on vascular walls in the affected organ is a characteristic finding (11). This vascular involvement by amyloid deposition was seen in the biopsied lung, kidney and gastric mucosa in the present patient.

In the present patient the detection of a small nodule on chest radiology, which was later shown to be composed of adenocarcinoma and amyloid deposition, was a chance finding leading to the final diagnosis of primary systemic AL amyloidosis. The coexistence of carcinomatous tissue and amyloid deposition is well known in thyroid medullary carcinoma, and amyloid deposition may also accompany benign endocrine tumors and odontogenic tumors (12). All such tumor-associated amyloid deposition is classified into a local form of amyloidosis (12), but a similar finding has rarely been described in systemic amyloidosis. The transition processes of soluble precursors to insoluble amyloid fibrils are incompletely understood: various cofactors such as serum amyloid P-component, proteoglycans and apolipoprotein E-4 may influence the crystallization of precursor proteins (11). Additionally, the role of a seed or nucleus has been noted (13). Some of these components may contain a β-sheeted sheet structure and are surmised to serve as a nidus or template in accelerating amyloid deposition. In the present patient some carcinoma-associated antigens might have played an important role in inducing locally accelerated deposition of circulating amyloidogenic immunoglobulins.
lin light chain (14), finally producing the unique nodular lesion. Positive staining of RAGE on cancer cells supports this hypothesis. Considering that the lung cancer in our patient was at an early stage, this disease probably developed almost coincidentally with primary systemic AL amyloidosis.

The present patient was also suffering from nephrotic syndrome due to primary systemic AL amyloidosis. Recently, intensive chemotherapies targeting pathogenetic plasma cells, including high-dose melphalan followed by autologous stem cell transplantation (HDM-SCT) (15, 16), have been reported to improve the function of the affected organs in the patients with this disease (17). Our patient refused HDM-SCT (18), and was alternatively treated with 2 courses of VAD (5). She showed complete hematological remission, resulting in subsequent improvement of nephrotic syndrome. Rapid remission of nephrotic syndrome after intensive chemotherapies was reported in a few patients with primary systemic AL amyloidosis (19), while regression of AL amyloid deposits in involved kidneys remains controversial (20) and further studies are required.

The authors state that they have no Conflict of Interest (COI).

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References