Nodular Pulmonary Amyloidosis Preceding Gastric Mucosa-associated Lymphoid Tissue Lymphoma, Initially Suspected to Be Lung Cancer

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Nodular pulmonary amyloidosis, a subtype of pulmonary amyloidosis, is a unique disease that can mimic lung cancer on radiographic imaging and is related to lymphoproliferative disorders. In this report, we describe a case of a 76-year-old male who presented with a solitary nodule in his left lower lung lobe on computed tomography that increased from 6 mm to 13 mm in diameter over 40 months. Lung cancer was suspected; however, transbronchial lung biopsy revealed deposition of an eosinophilic and homogeneous amorphous substance, which showed apple-green birefringence under polarized light after Congo red staining, and immunohistochemistry analysis returned positive results for immunoglobulin lambda light-chain. Upper gastrointestinal endoscopy revealed a gastric mucosa-associated lymphoid tissue (MALT) lymphoma. These findings indicated that this was a case of nodular pulmonary amyloidosis that preceded a diagnosis of MALT lymphoma.

Key words: Nodular pulmonary amyloidosis, Immunoglobulin light-chain, Mucosa-associated lymphoid tissue lymphoma

INTRODUCTION

Amyloidosis is a disease characterized by deposition of insoluble amyloid, an abnormal nylon-like fibrillar protein, in various organs throughout the body, which leads to functional impairment [1, 2]. At least 38 amyloidogenic proteins have been identified to date [3]. The pathogenicity of amyloidosis largely depends on the affected organ (localized or systemic) and the type of amyloid deposited. For instance, Alzheimer's disease is an amyloidosis characterized by localized deposition of amyloid-beta in the central nervous system, which leads to the development of the progressive neurological disorder [4]. Systemic amyloidoses involving multiple organs include amyloid A (AA) amyloidosis secondary to chronic inflammatory conditions, amyloid transthyretin amyloidosis, and immunoglobulin light-chain (AL) amyloidosis [5].

AL amyloidosis is the most common form of localized amyloidosis and is related to deposition of monoclonal light chains produced by a focal plasma cell clone or an underlying lymphoproliferative disorder [6–8]. Herein, we report a unique case of localized nodular pulmonary amyloidosis followed by a diagnosis of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

CASE REPORT

A 76-year-old man, an ex-smoker with a smoking history of 55 pack-years, was referred to our hospital for evaluation of an abnormal shadow in his left lower lung on chest radiography. Chest computed tomography (CT) revealed a nodule with an irregular outline in the superior segment of the left lower lobe. The diameter of the nodule 13 mm at the time of presentation; however, the patient's history indicated that the nodule was 6 mm 40 months earlier (Fig. 1). On physical examination, his lung sounds were normal and lymphadenopathy was not observed. His laboratory workup did not reveal any significant abnormalities, including tumor markers, C-reactive protein level, monoclonal gammopathy, kappa-lambda ratios in serum, and Bence-Jones protein level in urine. An antigen test for Cryptococcus returned negative results. Transbronchial lung biopsies were performed and pathological examination performed using hematoxylin and eosin staining revealed an eosinophilic homogeneous amorphous material in the specimens (Fig. 2A). The material was subjected to Congo red staining (Fig. 2B) and it showed green birefringence under polarized light microscopy (Fig. 2C). Immunohistochemistry analysis returned negative results for transthyretin, AA and AL-kappa (Fig. 2D, 2E

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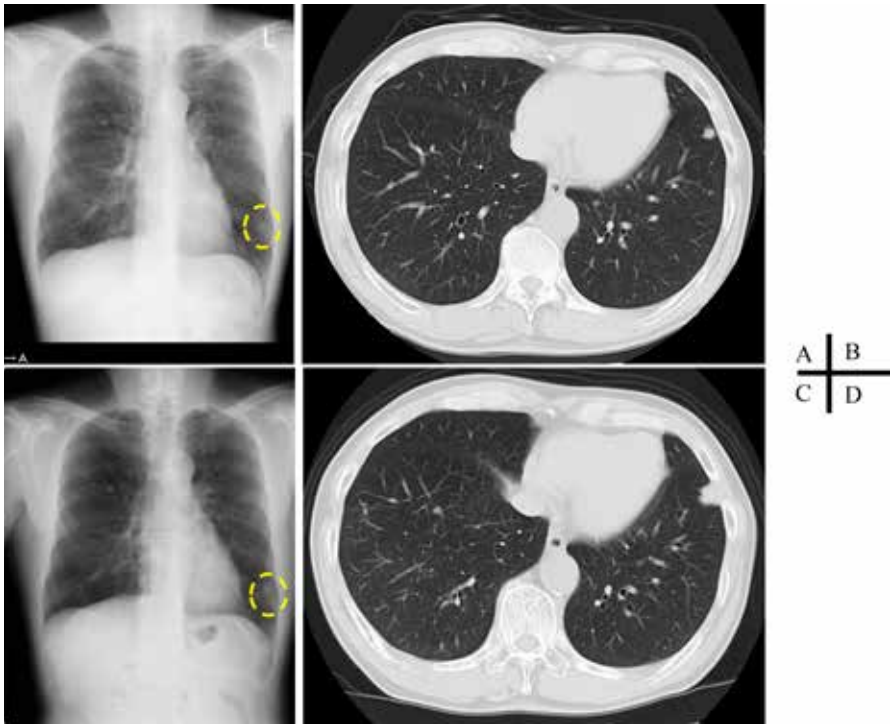

Fig. 1 Chest radiography and computed tomography performed at 40 months before referral (A, B) and at the time of referral (C, D).

and 2F) and positive results for AL-lambda (Fig. 2G). These findings were confirmed by mass spectrometry that showed the greatest number of peptides in the amyloid deposition sites were derived from AL-lambda (approximately 15%).

Given that AL may affect multiple organs, further examinations were performed. The patient's electrocardiography results were normal. Although transthoracic echocardiography revealed mild thickening (11 mm) of the ventricular septum, contractility was well maintained and the left ventricular ejection fraction was 59%, suggesting the absence of cardiac amyloidosis. Neurological examination revealed no abnormal findings, such as numbness. Gastrointestinal endoscopy was performed to examine the patient's gastrointestinal tract. Redness of the mucosa in the greater curvature of the stomach was observed; thus, a biopsy was performed. The results were indicative of MALT lymphoma without evidence of amyloid deposits. Based on these results, the patient was diagnosed with lambda-type localized pulmonary AL amyloidosis.

DISCUSSION

This report describes a case of solitary nodular AL amyloidosis in the lung that preceded a diagnosis of gastric MALT lymphoma. Pulmonary amyloidosis is classified into diffuse alveolar septal, tracheobronchial, and nodular types. Nodular pulmonary amyloidosis is predominantly attributed to AL or AL/AH amyloids and is detected incidentally on CT as single or multiple nodules in the subpleural or peripheral areas of the lower lobes of the lungs [9–11], as in the present case. In a case series of 25 patients with pulmonary nodular amyloidosis reported by Baugmart *et al.* [12], 23 of the patients had multiple nodules, whereas only two patients presented with a single nodule. These nodules appear in various forms, such as sharp/smooth, lobulated, cavitary, or even spiculated that is suggestive of malignancy. Since the differential diagnoses for emerging pulmonary nodules include benign disease entities, including tuberculoma, cryptococcosis, and lung malignancies [13], thorough examinations, such as serological and histological tests, should be considered. Interestingly, we observed that the solitary nodule in the present case doubled in size over three years, making it even more challenging to determine whether it was a benign nodule or lung cancer. Few case reports have described the growth of solitary nodules in pulmonary amyloidosis [14]. The present case is unique because the growing solitary nodule mimicked the clinical presentation of lung cancer.

The coexistence of MALT lymphoma and pulmonary nodular amyloidosis has been reported in some studies [9, 15]. Grogg *et al.* reported that of 14 patients with pulmonary nodular AL amyloidosis in their study, two developed cutaneous MALT lymphoma with or without local amyloid deposits [9]. Yamada *et al.* reported that of 16 patients they analyzed, one had MALT lymphoma concomitant with amyloidosis, whereas two developed MALT lymphoma during follow-up [13]. Interestingly, monoclonal plasma cell accumulation surrounding amyloid nodules in the lung has been reported [16], suggesting that pulmonary amyloidosis of the AL type is related to an underlying lymphoproliferative disorder. Therefore, clinicians should be aware of the potential presence of MALT lymphoma following the diagnosis of AL amyloidosis. In addition, gastrointestinal screening is necessary to exclude incidental gastrointestinal MALT lymphoma.

It has been reported that localized AL amyloidosis has a favorable long-term prognosis despite the involvement of underlying lymphoproliferative disorders. Baumgart *et al.* reported that the 10-year survival rate for AL-localized amyloidosis was 96%, which is much

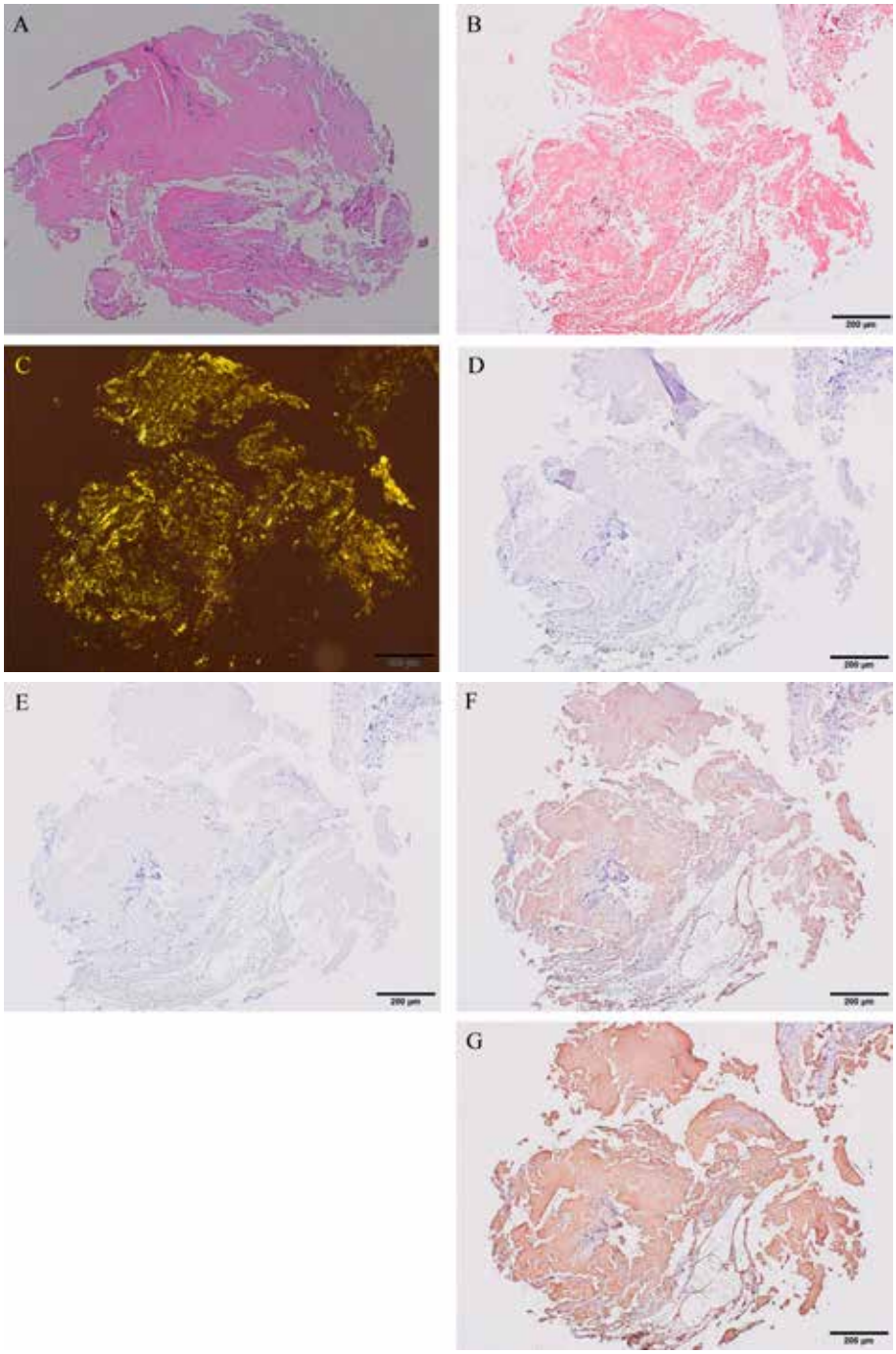

Fig. 2 Pathological findings of the transbronchial lung biopsy sample. (A) Hematoxylin and Eosin staining (x4), (B) Congo red staining (x40), (C) polarizing microscopy (x40), and immunohistochemistry for (D) transthyretin (x40), (E) AA (x40), (F) AL-kappa (x40), and (G) AL-lambda (x40).

higher than the 52% for systemic AL amyloidosis [12]. In an observational study of 501 patients with localized amyloidosis, including 490 patients with AL amyloidosis, which was conducted at the UK National Amyloidosis Centre [6] over a median follow-up period of 74.4 months, the prognosis of the patients with localized AL amyloidosis was similar to that of healthy subjects, with only 1% of the cases of localized AL amyloidosis progressing to systemic amyloidosis. Although little is known about the etiological differences between systemic and localized amyloidoses, the present case is expected to have a good prognosis.

In conclusion, nodular pulmonary amyloidosis is a unique disease that clinically mimics lung cancer. Given that nodular pulmonary amyloidosis, mostly the AL type, could be a localized organ manifestation of an underlying lymphoproliferative disorder, further systemic examination of patients with nodular pulmonary AL amyloidosis is warranted to exclude the possibility of concomitant MALT lymphoma following the diagnosis of the disease.

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