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Case report

Pulmonary amyloidosis complicated with pulmonary hemosiderosis, diagnosed with bronchoscopy

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ABSTRACT

We describe a case of an 82-year-old Japanese woman with pulmonary amyloidosis and hemosiderosis associated with multiple myeloma. She had a background of end-stage renal failure of unknown etiology and had been on maintenance dialysis for 2 years. She complained of exertional dyspnea for four months. High-resolution CT of the chest revealed diffuse ground-glass opacities with mosaic attenuation, consolidation in the left lingular lobe, and wedge-shaped, subpleural nodules in the bilateral lower lobes. A transbronchial lung biopsy of the left lingular lobe showed deposition of amorphous, eosinophilic amyloid at the smooth muscle layer of bronchial tissue, with a positive Congo red staining signal in polarized light. Bronchoalveolar lavage fluid was brownish-yellow, and numerous hemosiderin-laden macrophages were detected with Berlin blue staining. From these findings, a diagnosis of pulmonary amyloidosis complicated with pulmonary hemosiderosis was made. Further work-up led to a diagnosis of multiple myeloma. Pulmonary amyloidosis complicated with pulmonary hemosiderosis is a rare disorder and may be underdiagnosed. Physical examination, such as the appearance of the tongue, can assist the diagnosis of systemic amyloidosis. Use of bronchoscopy allows physicians make an early diagnosis of pulmonary amyloidosis that is minimally invasive.

1. Introduction

Amyloidosis is characterized by deposition of insoluble amyloid fibrils, resulting in dysfunction of vital organs [1]. Pulmonary amyloidosis may be localized or may be only one symptom of systemic amyloidosis. Five different forms are known: diffuse alveolar-septal amyloidosis, nodular pulmonary amyloidosis, tracheobronchial amyloidosis, mediastinal lymph node amyloidosis, and pleural amyloidosis [2–5].

Pulmonary hemosiderosis is characterized by repeated episodes of intra-alveolar bleeding leading to abnormal accumulation of iron as hemosiderin in alveolar macrophages [6]. Pulmonary hemosiderosis may occur with diverse conditions such as systemic vasculitis and connective-tissue diseases [7], while some cases, called idiopathic pulmonary hemosiderosis, have no apparent etiology [7,8].

To improve understanding of these diseases, in this article, we describe a patient with pulmonary amyloidosis and hemosiderosis associated with multiple myeloma diagnosed by bronchoscopy.

2. Case presentation

An 82-year-old woman was admitted to the Department of Cardiovascular Medicine at Hamanomachi Hospital for treatment of atrial fibrillation. She complained of exertional dyspnea spanning four months. Her medical history included end-stage renal failure of unknown etiology and maintenance dialysis for two years. Her medication included 2.5 mg of bisoprolol.

She had a temperature of 36.5 °C, blood pressure of 95/59 mmHg, a heart rate of 68 beats per minute, oxygen saturation of 98% under room air. Physical examination revealed slight late inspiratory crackles in both sides of her chest with no peripheral edema. Multiple nodules and tooth indentation were noted on the tongue (Fig. 1).

An echocardiogram showed a decreased left ventricular ejection fraction of 41%. Myocardial biopsy was performed, but there were no specific features. The patient underwent electrical cardioversion, and the atrial fibrillation returned to sinus rhythm.

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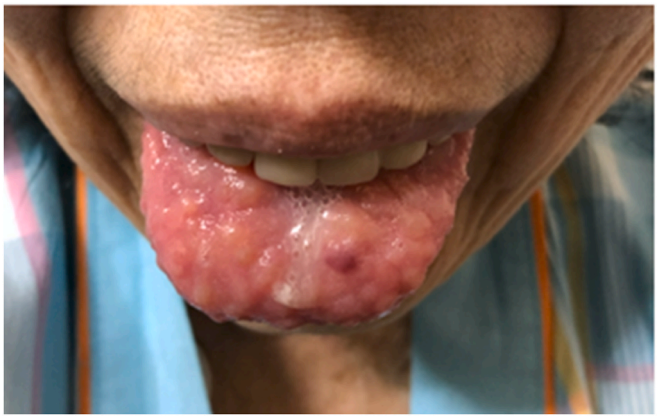

Fig. 1. Oral finding of the patient. Multiple nodules and indentation of the tongue, suggesting tongue amyloidosis.

The patient was then referred to the Department of Respiratory Medicine for abnormal chest imaging. High-resolution CT of the chest revealed diffuse ground-glass opacities (GGO) with mosaic attenuation, consolidation in the left lingular lobe, and subpleural, wedge-shaped nodules in the bilateral lower lobes (Fig. 2). To facilitate diagnosis, bronchoscopy was performed. Bronchoscopy revealed enlarged tortuous submucosal vessels at the main carina and left main bronchus (Fig. 3), suggesting tracheal amyloidosis [9,10]. A transbronchial lung biopsy (TBLB) of the left lingular lobe was performed. Microscopic examination of the TBLB showed deposition of amorphous eosinophilic amyloid at the smooth muscle layer of the bronchial tissue (Fig. 4A). Congo red staining displayed a positive signal in polarized light (Fig. 4B and C). Immunohistochemical staining for amyloid P was positive (Fig. 4D). No pathogen or malignancy was detected. From these findings, she was diagnosed with pulmonary amyloidosis. Bronchoalveolar lavage fluid from left B3 was brownish-yellow and numerous hemosiderin-laden macrophages were detected with Berlin blue staining (Fig. 5), indicating chronic alveolar hemorrhage, resulting in pulmonary hemosiderosis. Cytology of the lavage showed alveolar macrophage predominance (99% macrophages and 1% neutrophils).

Additional serological examinations to evaluate the etiology of pulmonary hemorrhage causing hemosiderosis, anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), and rheumatoid factor (RF), were negative. Therefore, pulmonary hemosiderosis was considered related to pulmonary amyloidosis.

An upper gastrointestinal endoscopy was also performed, and a duodenal biopsy confirmed amyloidosis. In addition, A CT of the body showed soft tissue masses around the hip joints, which were thought to be amyloidosis lesions. These findings suggested systemic amyloidosis.

To investigate the etiology of amyloidosis, further serological examinations were performed. Serum IgG, IgA, and IgM levels were low (380 mg/dL, 19 mg/dL, and 4 mg/dL, respectively). Serum free light-chain analysis showed greatly increased lambda light chain of 28,900 mg/L with kappa light chain of 36.8 mg/L. Serum immunoelectrophoresis showed a monoclonal lambda light-chain peak, and urinary Bence-Jones protein was positive.

Suspecting multiple myeloma, bone marrow examination was performed. Bone marrow examination showed plasma cell neoplasms with lambda light-chain restriction. Flow cytometry analysis of bone marrow

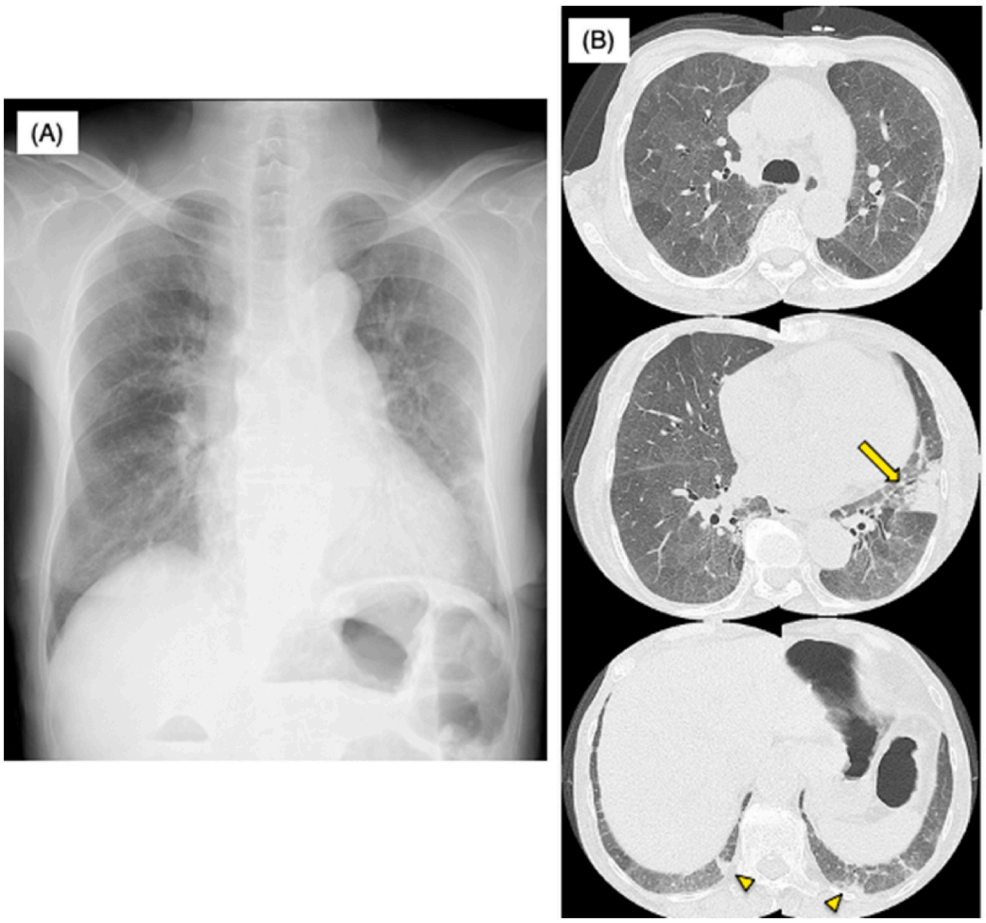

Fig. 2. Radiological findings of the patient. (A) A chest X-ray image on admission. (B) Chest CT images on admission showing diffuse ground-glass opacities (GGO) with mosaic attenuation, consolidation in the left lingular lobe (arrow), and subpleural, wedge-shaped nodules in the bilateral lower lobes (arrowhead).

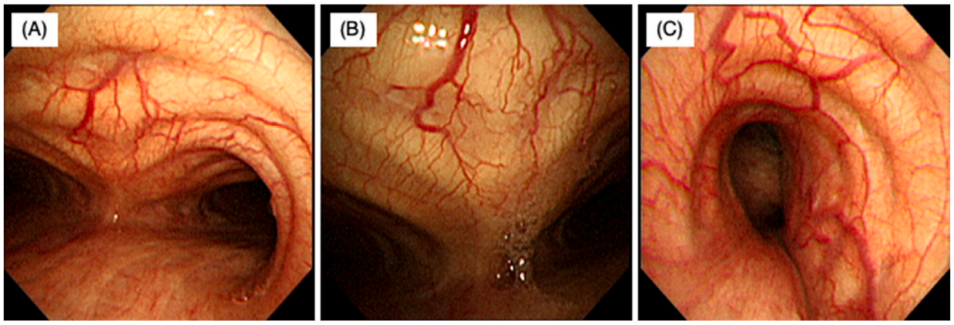

Fig. 3. Bronchoscopic images of the patient. Enlarged, tortuous submucosal vessels were observed at the main carina (A, B) and the left main bronchus (C). No nodules nor masses were found in the patient.

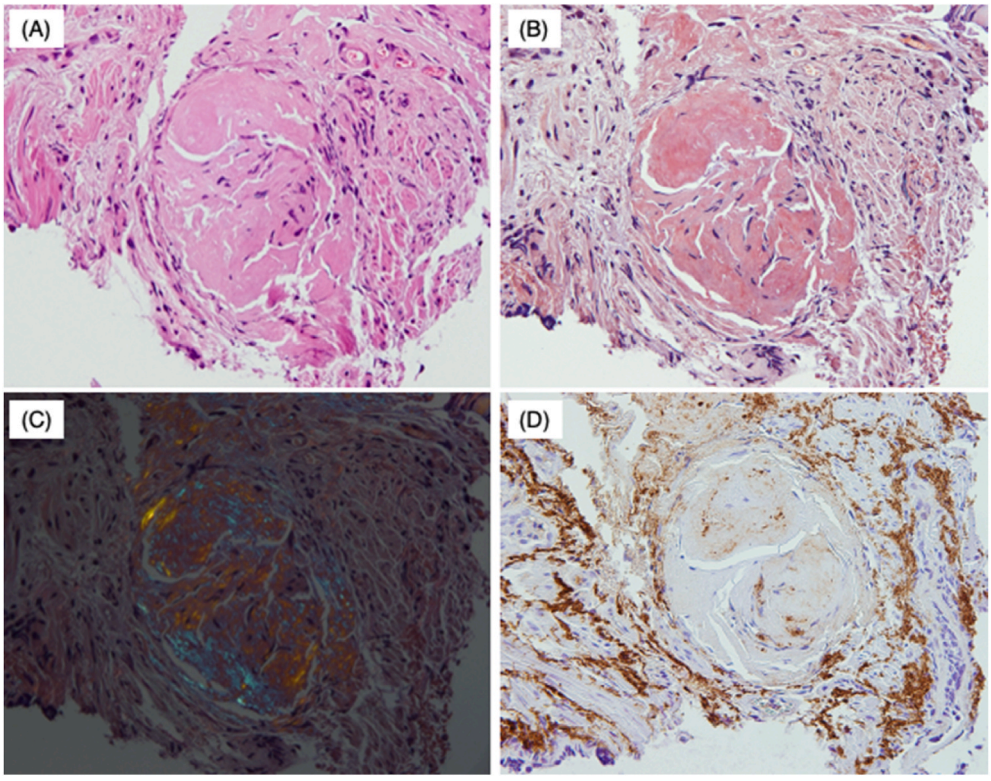

Fig. 4. Pulmonary amyloidosis confirmed by trans-bronchial lung biopsy. (A) Haematoxylin and eosin staining. (B) Congo-red staining with bright field microscopy. (C) Congo-red staining showing positive signals under polarized light. (D) Immunohistochemistry of amyloid P. Magnification×400. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cells revealed a $CD19^{-}CD38^{high}CD45^{-}CD56^{+}CD138^{+}cyLambda^{+}$ cell population, which is a typical immunophenotype of myeloma cells. This confirmed the diagnosis of multiple myeloma, λ light chain type, international staging system Stage 3. Chemotherapy of bortezomib, lenalidomide and dexamethasone was initiated, followed by oral ixazomib, lenalidomide, and dexamethasone. Six months after diagnosis, she is still receiving chemotherapy on an outpatient basis.

3. Discussion

We report a case of pulmonary amyloidosis and hemosiderosis associated with multiple myeloma, that was successfully diagnosed with bronchoscopy. As reported, *ante mortem* diagnosis of pulmonary amyloidosis is challenging. Because pulmonary amyloidosis is mostly asymptomatic, many patients with pulmonary amyloidosis are diagnosed only at autopsy [11]. In fact, among 741 patients with systemic AL amyloidosis reported in a nationwide survey in Japan, only 1.6% were diagnosed by lung biopsy [12]. Further, CT findings of pulmonary amyloidosis are nonspecific; therefore, physicians might not seriously consider amyloidosis in a differential diagnosis. Without a special order from respirologists, it is difficult for pathologists to diagnose pulmonary amyloidosis, especially from small TBLB samples.

In this case, the patient had been aware of gradual shortness of breath for four months, and high-resolution CT of the chest revealed diffuse ground-glass opacities (GGO) with mosaic attenuation, consolidation in the left lingular lobe, and subpleural, wedge-shaped nodules in the bilateral lower lobes four months earlier. Even after the patient underwent electrical cardioversion, and the atrial fibrillation returned to sinus rhythm, her exertional dyspnea remained. The chronic course of the disease was consistent with amyloidosis. Therefore, we considered there was an association between exertional dyspnea and pulmonary amyloidosis. The appearance of the patient's tongue led us to consider systemic amyloidosis as a differential diagnosis. There are many case reports of tongue amyloidosis with multiple myeloma [13–15], and

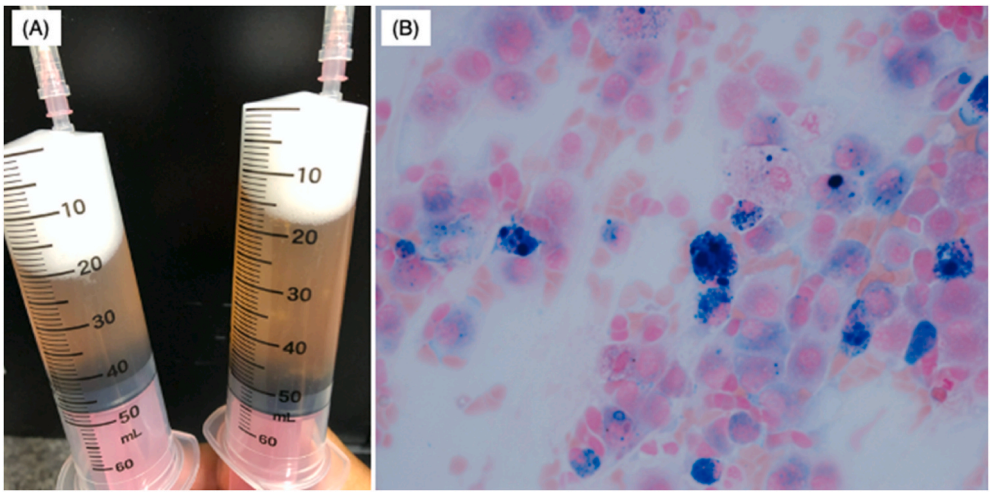

Fig. 5. Hemosiderin-laden macrophages present in bronchoalveolar lavage fluid. (A) Brownish-yellow bronchoalveolar lavage fluid. (B) Numerous hemosiderin-laden macrophages were detected by Berlin blue staining. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tongue amyloidosis indeed leads the final diagnosis of multiple myeloma in the literature [13]. Although pathological diagnosis of tongue amyloidosis was not made in this case, it is highly plausible that the patient had tongue amyloidosis. Thus, physical examination can offer an important clue for diagnosis of amyloidosis.

Multiple myeloma is sometimes complicated with amyloidosis: the affected organs are mostly the heart, kidney, liver, spleen, and lymph nodes [16]. On the other hand, pulmonary amyloidosis, especially the diffuse-septal type, is very rare in multiple myeloma, with few cases reported [4,5,17–19]. Although a definitive diagnosis of diffuse-septal amyloidosis cannot be made without lung biopsy from GGO lesions, it is reasonable to consider the GGO lesion as diffuse-septal amyloidosis in an integrated manner. Pulmonary amyloidosis can present mosaic attenuation [20] as in this case, possibly because of small airways obstructed by amyloid or amyloid deposition in alveolar interstitium [21].

In this case, pulmonary hemosiderosis was confirmed by BALF findings. From a literature search, there are no publications reporting pulmonary hemosiderosis associated with pulmonary amyloidosis. However, it is reported that focal or systemic hemorrhage is commonly encountered in patients with amyloidosis [22]. The authors concluded that hemorrhage in amyloidosis is most often due to amyloid infiltration of blood vessels [22]. Indeed, pulmonary amyloidosis can cause pulmonary hemorrhage [5,23], and it is not surprising that repeated minute amounts of alveolar hemorrhage might result in pulmonary hemosiderosis, perhaps simply underdiagnosed.

The therapeutic principle for patients with pulmonary amyloidosis associated with multiple myeloma is suppression of the production of amyloid protein generated by myeloma cells [24]. The standard treatment for multiple myeloma is a combination of drugs having different mechanisms (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies) along with corticosteroids. In this case, the patient was already in a frail state with end-stage renal failure. We thus concluded that the patient was not able to tolerate intense treatment, and we chose ixazomib, lenalidomide, and dexamethazone in consideration of the patient's condition and compliance.

The effect of ixazomib, a first oral proteasome inhibitor, on multiple myeloma was shown in a double-blind, placebo-controlled, phase 3 trial, which assigned 722 patients who had relapsed and/or who had refractory multiple myeloma, to receive ixazomib plus lenalidomide–dexamethasone (ixazomib group) or a placebo plus lenalidomide–dexamethasone (placebo group) [25]. The addition of ixazomib to a regimen of lenalidomide and dexamethasone was associated with significantly longer progression-free survival [25]. From this result, ixazomib was approved for multiple myeloma. Further, this ixazomib, lenalidomide, and dexamethasone regimen showed efficacy with deep responses in 47% of patients with relapsed AL amyloidosis [26]. Thus, ixazomib, lenalidomide, and dexamethasone therapy is a good option to treat AL amyloidosis accompanied with multiple myeloma.

In conclusion, pulmonary amyloidosis complicated with pulmonary hemosiderosis is a rare disorder that may be underdiagnosed. Physical examination, such as appearance of the tongue, can assist diagnosis of systemic amyloidosis. Use of bronchoscopy allows an early diagnosis of pulmonary amyloidosis with minimal invasiveness.

Patient consent for publication

Written, informed consent was obtained from the patient.

Declaration of competing interest

All authors of the manuscript declare that they have no conflicts of interest.

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