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A descriptive analysis of 21 patients with pulmonary amyloidosis

An observational study

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Abstract

Pulmonary amyloidosis is an extremely rare disease, often detected incidentally because of its asymptomatic nature and potential to result in fatal outcomes. In this study, we aimed to present the clinical and radiological features of patients diagnosed with pulmonary amyloidosis by biopsy. This descriptive study included 21 patients with pathologically diagnosed pulmonary amyloidosis. Pulmonary amyloidosis was classified as diffuse alveolar-septal amyloidosis (DASA), cystic amyloidosis (CPA), tracheobronchial amyloidosis (TBA), nodular amyloidosis (NPA), and extraparenchymal pulmonary amyloidosis (pleural and mediastinal lymph node). Clinical, bronchoscopic, and radiological specific characteristics were presented in detail to be used for differential diagnosis. The median age of the patients was 63 (40–83) years, and 14 (66.7%) were male. Twenty patients (95.2%) presented with at least 1 comorbidity. All patients diagnosed with tracheobronchial amyloidosis were symptomatic at presentation, whereas those diagnosed with NPA/extraparenchymal amyloidosis were often asymptomatic. The patients included 1 case of DASA, 1 case of CPA, 10 cases of NPA, 6 cases of TBA, and 3 cases of extraparenchymal amyloidosis involving the mediastinal lymph node and pleura. Sixteen patients (76.2%) were classified as localized amyloidosis, while 5 patients (23.8%) were classified as systemic amyloidosis following the diagnosis of multiple myeloma, monoclonal gammopathy of undetermined significance, systemic lupus erythematosus, Sjogren's syndrome, and B-cell lymphoma. Bronchoscopic biopsies were sufficient for diagnosis, and notably, even transbronchial needle aspiration could be a useful diagnostic method. During the follow-up, we observed that the disease remained stable without progression. However, it is important to note that patients with concurrent malignancies experience fatal outcomes. In conclusion, it is crucial to distinguish pulmonary amyloidosis from other pulmonary diseases such as malignancies, infectious diseases, and interstitial lung diseases, which may have similar clinical and radiological findings. Bronchoscopic diagnostic methods are usually sufficient for the diagnosis. Although patients with pulmonary involvement mostly remain stable during long-term follow-up without progression, it is important to consider the risk of malignancy.

Abbreviations: APC = argon plasma coagulation, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CPA = cystic pulmonary amyloidosis, CT = computed tomography, CyBorD = cyclophosphamide-bortezomib-dexamethasone, DASA = diffuse alveolar-septal amyloidosis, DM = diabetes mellitus, FDG PET = fluorodeoxyglucose-18 positron emission tomography, HT = hypertension, MALTmucosa-associated lymphoid tissueMGUS = monoclonal gammopathy of undetermined significance, MLNA = mediastinal lymph node amyloidosis, NPA = nodular pulmonary amyloidosis, SLE = systemic lupus erythematosus, SUVmaxmaximum standardized uptake valueTBA = tracheobronchial amyloidosis, TBLC = transbronchial lung cryobiopsy, TBNA = transbronchial needle aspiration.

Keywords: clinical features, demographic characteristics, pulmonary amyloidosis

1. Introduction

Amyloidosis is a disorder caused by the misfolding of autologous proteins. Insoluble and toxic protein aggregates are deposited in the extracellular spaces of organs and tissues as bundles of β-sheet fibrillar proteins, resulting in vital organ dysfunction and eventually death.[1,2] The estimated incidence is 10 cases per million person-years.[3] While seemingly rare, pulmonary involvement is seen in approximately 50% of cases,[2] and

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The datasets generated during and/or analyzed during the current study are publicly available.

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accurate diagnosis of this disorder is paramount because of its potential to result in fatal outcomes.

Commonly affected organs are the kidneys, liver, peripheral and autonomic nervous systems, and soft tissues. Lung involvement is relatively common, but usually asymptomatic; therefore, it is detected incidentally in the majority of patients.[4,5] A comprehensive study of pulmonary amyloidosis conducted at the Mayo Clinic revealed a median survival of 16 months after diagnosis.[2] Lung involvement of amyloid can appear in different forms, including parenchymal, tracheobronchial, and extraparenchymal (pleural and mediastinal lymph nodes).[6] Pulmonary amyloidosis may manifest as either a localized condition or part of systemic amyloidosis, often attributed to hematologic disorders or chronic inflammatory processes.[5,7]

We believe that it is necessary to highlight the diagnostic challenges posed by pulmonary amyloidosis, as it can mimic other lung diseases due to nonspecific clinical symptoms and radiological findings, such as infectious diseases, interstitial lung diseases, and malignancy.[8,9] Thus, we deemed it important to present the clinical and radiological features of 21 patients diagnosed with pulmonary amyloidosis via biopsy at our center.

2. Methods

2.1. Study design and setting

This single-center, descriptive study was conducted at the Department of Pulmonology in a Chest Diseases and Thoracic Surgery Training and Research Hospital, which is one of the prominent referral centers in our country for the diagnosis and management of pulmonary parenchymal and airway diseases. Ethical approval was obtained from the local ethics committee (4/30).

2.2. Study population

A total of 23 patients with pulmonary amyloidosis were identified by searching the hospital's automation system between 2015 and 2023. Patients with missing data and those lost to follow-up were excluded. Finally, 21 patients pathologically diagnosed with pulmonary amyloidosis who met the study criteria were included in the study.

2.3. Data collection

Demographic characteristics, comorbidities, presenting symptoms, laboratory findings, smoking history, radiological features, diagnostic procedures, pathological findings, treatments, follow-up data, and survival times were recorded.

2.4. Definitions

2.4.1. Classification. Based on radiologic and pathologic findings, pulmonary patterns of amyloidosis were classified as diffuse alveolar-septal amyloidosis (DASA), cystic pulmonary amyloidosis (CPA), tracheobronchial amyloidosis (TBA), nodular pulmonary amyloidosis (NPA), and extraparenchymal pulmonary amyloidosis (involvement of pleural and mediastinal lymph node).[6] DASA and CPA were defined as amyloidosis confirmed by histopathological examination of parenchymal tissue. TBA was defined as amyloidosis confirmed by histopathological examination of tracheal and/or bronchial tissue. NPA was defined as amyloidosis confirmed by histopathological examination of the parenchymal nodule. Mediastinal lymph node amyloidosis (MLNA) was defined as amyloidosis confirmed by histopathological examination of the lymph nodes. Pleural amyloidosis was defined as amyloidosis confirmed by histopathological examination of the pleural tissue.

2.4.2. Diagnostic procedures. The diagnosis was made using transbronchial lung cryobiopsy (TBLC) or surgical lung biopsy in patients presenting with interstitial involvement. Suspected endobronchial lesions in the tracheobronchial system, observed on thoracic imaging, were further evaluated using bronchoscopy. In cases with central airway stenosis, rigid bronchoscopy was performed for both diagnostic and therapeutic interventions. Biopsies of the endobronchial lesions in the distal bronchi were obtained using fiberoptic bronchoscopy. Patients presenting with lung parenchymal nodular structures underwent either diagnostic wedge resection or lobectomy depending on the lesion location and size. Endobronchial ultrasonography (EBUS) was used for diagnostic purposes in patients with MLN involvement, while those with pleural thickening underwent a tru-cut biopsy.

2.4.3. Pathological evaluation and diagnosis. In cases of interstitial involvement, amyloidosis accumulation causing thickening of the alveolar septa was observed (Fig. 1A). TBA revealed the presence of acellular eosinophilic substance accumulation originating from the respiratory subepithelial basal layer and extending deep into the mucosa. Surrounding this matrix, inflammation, composed of plasma cells, histiocytes, and multinucleated giant cells, was evident (Fig. 1B). NPA manifests as a well-defined mass lesion with definite boundaries, characterized by extensive globular acellular eosinophilic substance accumulation and an inflammatory infiltrate rich in plasma cells. Within the lymph nodes, amyloidosis was identified as large eosinophilic islands resembling hyalinized nodules (Fig. 1C). Pleural amyloidosis was in the form of acellular amorphous eosinophilic islands between fibrotic tissue layers.

2.4.4. Internal medicine assessment. Serum protein electrophoresis, serum and/or urine immunofixation electrophoresis, and serum-free light chain assay serve as primary screening tests. However, confirmation of the diagnosis typically requires a tissue biopsy. When systemic involvement is

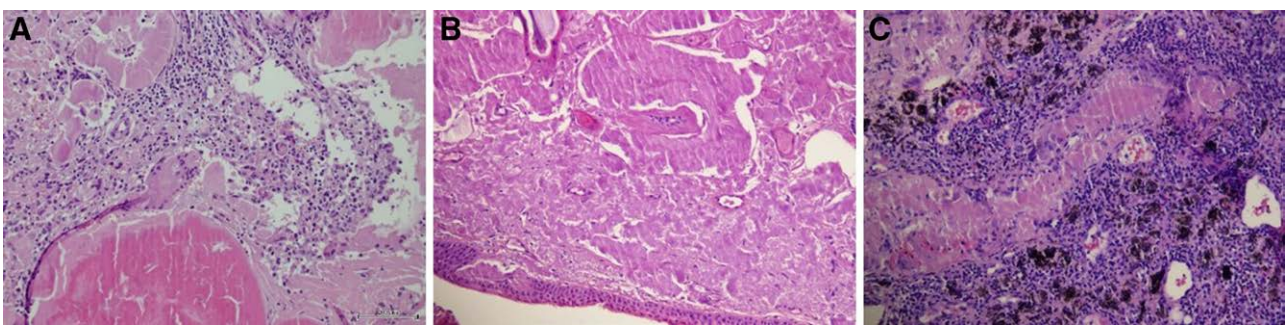

Figure 1. Pathology images of pulmonary amyloidosis cases. (A) Plasma cells, histiocytes, and multinucleated giant cells surrounding the accumulation of dense eosinophilic proteinaceous material. (B) Widespread subepithelial amyloid deposition in the trachea. (C) Nodules amyloid deposition in the lymph node.

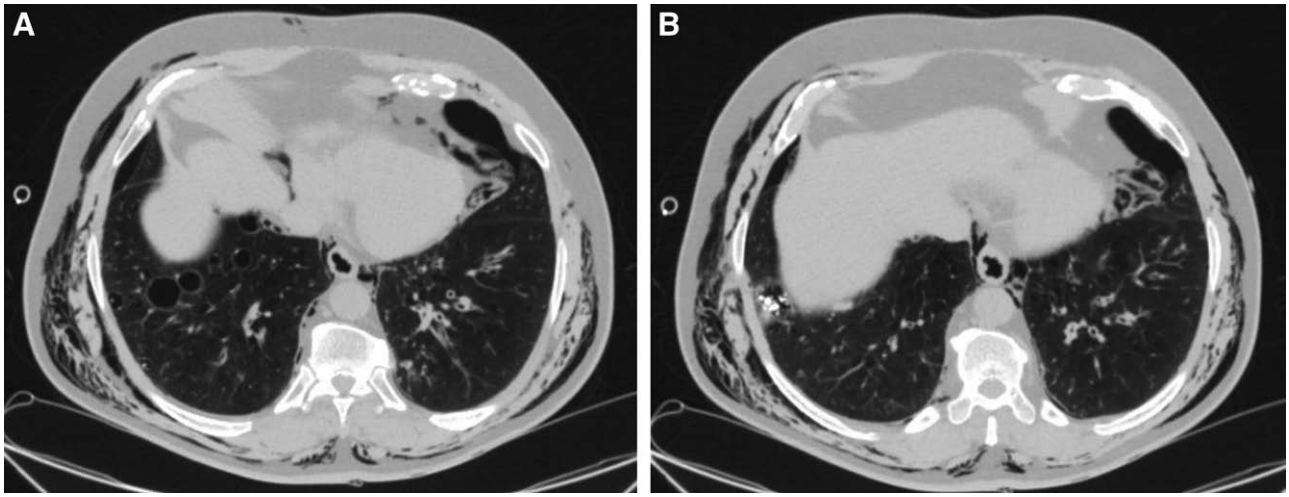

Figure 2. Case of diffuse alveolar-septal amyloidosis. (A) Thoracic computed tomography showing diffuse interlobular septal thickening, centrilobular nodules, and scattered areas of consolidation observed dominant in the right upper and middle lobes, along with bilateral predominantly lower lobes ground-glass opacities prior to treatment. (B) Thoracic computed tomography showing significant regression in interlobular septal thickening, ground-glass opacities, and areas of consolidation after treatment. Additionally, most of the centrilobular nodules were regressed and calcified.

suspected, abdominal subcutaneous fat aspiration using a fine needle is commonly used as a diagnostic tool. It is suggested to commence with the least invasive procedures initially owing to the risk of hemorrhagic complications. In cases of high suspicion or abnormalities detected in protein studies, bone marrow aspiration and biopsy are warranted. Additionally, cardiac biomarkers, such as serum N-terminal prohormone of brain natriuretic peptide and troponin, can aid in raising clinical suspicion for cardiac amyloidosis, prompting further investigation with electrocardiogram and echocardiography, or, if necessary, cardiovascular magnetic resonance imaging.

2.4.5. Treatment. The treatment approach for pulmonary amyloidosis varies based on factors such as the type of precursor protein, extent of organ involvement, and disease distribution. Asymptomatic patients typically require close monitoring. In cases of DASA, the treatment aligns with that of underlying systemic amyloidosis. TBA, on the other hand, often requires bronchoscopic interventions, such as debulking, argon plasma coagulation (APC), cryotherapy, or stenting. There is currently no standardized treatment for NPA or extraparenchymal amyloidosis. Management primarily includes close monitoring and treatment tailored to the underlying disease.

2.5. Statistical analysis

Data were analyzed using SPSS 28.0.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk). Data distribution was evaluated using a histogram, stem-leaf plot, coefficient of variation, skewness/kurtosis, and Shapiro–Wilk test. Descriptive statistics were presented as numbers and percentages for categorical data. For continuous data, mean ± standard deviation was used if the parameter was normally distributed; otherwise, median and interquartile ranges were noted.

3. Results

A total of 21 patients diagnosed with pulmonary amyloidosis, with a median age of 63 years (min–max: 40–83) were included in the study. Among them, 14 (66.7%) were male and 13 (61.9%) had a history of smoking. Twenty patients (95.2%) presented with at least 1 comorbidity. The most prevalent comorbidities were hypertension (HT), chronic obstructive lung disease (COPD), diabetes mellitus (DM), and chronic kidney disease (CKD). The predominant symptoms were dyspnea (42.8%), cough (28.6%), and chest pain (23.8%), while 9 patients were asymptomatic. The study included 1 case of DASA, 1 case of CPA, 10 cases of NPA, 6 cases of TBA, and 3 cases of extraparenchymal amyloidosis involving the MLN and pleura. Sixteen patients were classified as having localized amyloidosis, while 5 patients were classified as having systemic amyloidosis following the diagnosis of multiple myeloma: monoclonal gammopathy of undetermined significance (MGUS), systemic lupus erythematosus (SLE), Sjogren's syndrome, and B-cell lymphoma.

3.1. Diffuse alveolar-septal amyloidosis

One patient (Patient 1) was diagnosed with DASA. A 58-year-old female patient presented with chest pain and weight loss. The patient had a medical history of DM, HT, ischemic heart disease, hypothyroidism, and smoking. Thoracic computed tomography (CT) revealed diffuse interlobular septal thickening observed in all regions, which was dominant in the upper and middle lobes, centrilobular nodules, bilateral predominantly lower lobes ground-glass opacities, and scattered areas of consolidation (Fig. 2A). The diagnosis of amyloidosis was confirmed through TBLC, and the patient was diagnosed with multiple myeloma based on bone marrow biopsy during evaluation by the internal medicine team. Elevated pro-BNP and troponin T levels and echocardiography showed findings suggestive of cardiac amyloidosis, including concentric left ventricular hypertrophy and thickened interventricular septum (14 mm). Daratumumab plus cyclophosphamide-bortezomib-dexamethasone (CyBorD) and tetracycline therapy was initiated. Over a 2-year follow-up period, significant regression was observed in the interlobular septal thickening, ground-glass opacities, and areas of consolidation on thoracic CT scans. Additionally, nearly all centrilobular nodules regressed and calcified, and there was an increased density containing punctate calcifications in the paravertebral region of the right lower lobe (Fig. 2B). The patient was continuously monitored during the current treatment (Table 1).

3.2. Cystic pulmonary amyloidosis

One patient (Patient 2) was diagnosed with CPA. A 66-year-old male patient with COPD and CKD previously asymptomatic, presented with sudden-onset of dyspnea and chest pain. He had

Table 1

Demographic, clinical, and radiological features of patients with pulmonary amyloidosis.

Nosex, age	Classification	Symptoms	Comorbidities	CT findings (maximum diameter)	Diagnostic procedures	Treatment	Follow-up/survival
1 (F, 58)	Diffuse alveolar-septal	Chest pain, weight loss	DM, HT, IHD, hypothyroid	Interlobular septal thickening, centrilobular nodules, ground-glass opacities, consolidation	TBLC	Daratumumab plus CyBorD and tetracycline	Multipl myeloma. Cardiac amyloidosis (at diagnosis). Survival: 2 yr
2 (M, 66)	Cystic	Dyspnea, chest pain	CKD, COPD	Multipl cysts, calcified nodules	Wedge resection	None	No complication. Survival: 3 yr
3 (M, 62)	Tracheobronchial	Dyspnea, stridor	HT	Endotracheal lesion, tracheal thickening	Rigid bronchoscopy	Tracheal resection	MGUS (at diagnosis). No complication. Survival: 3 yr
4 (M, 63)	Tracheobronchial	Dyspnea, cough, sputum	Lung adenocarcinoma, IHD	Endobronchial lesion, mucosal infiltration	Fiberoptic bronchoscopy	None	Died at 2nd year due to lung cancer
5 (F, 68)	Tracheobronchial	Dyspnea, cough	HT	Endobronchial lesion, bronchial thickening	Rigid bronchoscopy	Multiple biopsy, APC	No complication. Survival: 2 yr
6 (F, 60)	Tracheobronchial	Dyspnea, cough, sputum, chest pain	HT, asthma, Hypothyroid	Endotracheobronchial lesions, mucosal infiltration, tracheobronchial thickening	Rigid bronchoscopy	Mechanic resection, APC, cryotherapy, colchicine	No complication. Survival: 3 yr
7 (M, 69)	Tracheobronchial	Dyspnea	HT, DM, liver cancer	Endotracheobronchial lesions, mucosal infiltration	Rigid bronchoscopy	Mechanic resection, APC, cryotherapy	No complication. Died at 2nd year due to liver cancer
8 (M, 83)	Tracheobronchial	Dyspnea, cough, sputum	CKD, HT	Endotracheal lesion	Rigid bronchoscopy	Mechanic resection, APC, cryotherapy	No complication. Survival: 6 yr
9 (M, 66)	Nodular	Asymptomatic	None	Multiple nodules (13 mm)	Wedge resection	None	No complication. Survival: 4 yr
10 (M, 40)	Nodular	Dyspnea, cough	COPD	Multiple nodules (32 mm)	Wedge resection	None	No complication. Survival: 1 yr
11 (M, 75)	Nodular	Dyspnea	IPF, HT, IHD	Single nodule (31 mm)	Wedge resection	None	No complication. Survival: 5 yr
12 (M, 66)	Nodular	Chest pain	DM, HT, COPD	Single nodule (58 mm)	Lobectomy	None	No complication. Survival: 6 yr
13 (M, 46)	Nodular	Asymptomatic	Post-tuberculosis sequelae	Multiple nodules (38 mm)	Wedge resection	None	No complication. Survival: 4 yr
14 (M, 70)	Nodular	Asymptomatic	COPD, CKD	Multiple nodules (23 mm)	Wedge resection	None	Asymptomatic progression of nodules and minimal pleural effusion (4 yr later). Survival: 5 yr
15 (F, 58)	Nodular	Asymptomatic	IHD	Multiple nodules (11 mm)	Wedge resection	Hydroxychloroquine	SLE (at diagnosis). No complication. Survival: 5 yr
16 (F, 56)	Nodular	Cough, sputum, chest pain	DM, Asthma, IHD, GERD	Multiple nodules (25 mm)	Wedge resection	None	Asymptomatic increase and progression of nodules (7 yr later). Survival: 8 yr
17 (M, 60)	Nodular	Asymptomatic	DM, HT, IHD	Single nodule (62 mm)	Wedge resection	None	Progression of nodule and pleural effusion (2 yr later). B cell lymphoma (3 yr later). Survival: 8 yr
18 (F, 45)	Nodular	Asymptomatic	Post-tuberculosis sequelae	Single nodule (14 mm)	Wedge resection	Hydroxychloroquine, pilocarpine	Sjogren syndrome (2 yr later). No complication. Survival: 6 yr
19 (M, 70)	Pleural	Asymptomatic	COPD, CKD	Pleural thickening	Transthoracic FNA biopsy	None	Died at 3rd year (unknown reason)
20 (F, 58)	Mediastinal lymph node	Asymptomatic	CKD, HT, lung adenocarcinoma, carcinoid tumor	Interlobular septal thickening, mediastinal lymphadenopathy, centrilobular nodules, focal opacite	EBUS-TBNA	None	Died at 1st year due to lung cancer
21 (M, 65)	Mediastinal lymph node	Asymptomatic	Waldenstrom macroglobulinemia, COPD, hypothyroid	Mediastinal lymphadenopathy, multiple nodules (50 mm)	Conventional TBNA	Daratumumab plus CyBorD	No complication. Died at 6th year due to COPD exacerbation

APC = argon plasma coagulation, COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease, CyBorD = cyclophosphamide-bortezomib-dexamethasone, DM = diabetes mellitus, EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration, F = female, FNA = fine needle aspiration, GERD = gastroesophageal reflux disease, HT = hypertension, IHD = ischemic heart disease, IPF = idiopathic pulmonary fibrosis, M = male, MGUS = monoclonal gammopathy of undetermined significance, SLE = systemic lupus erythematosus, TBLC = transbronchial lung cryobiopsy.

a history of smoking and presented with pneumothorax on a chest radiograph. Thoracic CT revealed widespread cysts, which were more prominent in the bilateral lower lobes (Fig. 3A), and calcified nodules within and adjacent to cysts in the lower lobe of the right lung with additional subcutaneous emphysema (Fig. 3B). Surgical wedge biopsy of the right lung confirmed the diagnosis of amyloidosis. The patient was followed up without additional comorbidities or medications, and was monitored for stable cysts for 3 years (Table 1).

3.3. Tracheobronchial amyloidosis

Six patients (Patients 3–8) were diagnosed with TBA. All patients were symptomatic, with dyspnea and cough being the most commonly reported symptoms. None of these 6 patients had a history of smoking. Two patients had tracheobronchial involvement, 2 patients had isolated bronchial involvement, and 2 had isolated tracheal involvement (Fig. 4A–C). Furthermore, tracheal thickening was observed in patient 3, bronchial thickening in patient 5, and tracheobronchial thickening in patient 6 (Fig. 4D). Airway obstruction of > 60% was detected in all patients during bronchoscopy. Bronchoscopic findings included polypoid lesions in 2 patients and mucosal infiltration in 3 patients (Fig. 4E). One of the patients was diagnosed with flexible bronchoscopy, while the remaining 2 were diagnosed with rigid bronchoscopy. Severe hemorrhage was observed during bronchoscopic biopsy in only 1 patient. No recurrence or progression was observed during the 3rd, 6th, and 12th months follow-up visits. Patient 3 underwent tracheal resection because of severe stenosis. This patient was diagnosed with MGUS, was followed up without medication for 3 years and died 2 years later due to lung adenocarcinoma. In patient 5, a severe hemorrhage was seen during the biopsy of an endobronchial lesion in the intermediate bronchus, leading to cessation of the procedure following coagulation with APC in rigid bronchoscopy. The patient was still under follow-up without medication for 2 years. The remaining 3 patients underwent mechanical resection, APC, and cryotherapy under rigid bronchoscopy. Patient 6 received additional colchicine therapy and was followed-up for 3 years. Patient 7 died 2 years later because of liver cancer. Patient 8 was followed up without medication for 6 years (Table 1).

3.4. Nodular pulmonary amyloidosis

In this study, 10 patients (Patients 9–18) were diagnosed with NPA. Six of these patients were asymptomatic and 9 had a history of smoking. Four patients presented nodules in the right lung, 3 in the left lung, and 3 bilaterally. Among these nodules, 6 were localized in the upper lobe, 2 in the lower lobe, and 2 demonstrated a diffuse distribution throughout the lung parenchyma. Furthermore, solitary nodules were identified in 5 patients, while the remaining 5 patients exhibited multiple nodules. Peripheral localization of nodules was predominant, observed in 8 patients, whereas central nodules were identified in 1 patient and nodules with dispersed placement were noted in another. The median nodule diameter, considering the largest diameter among patients with multiple nodules, was 28 mm (min–max: 11–62 mm). The margins of the nodules were smooth in 4 patients and spiculated in 6 patients. Calcification was detected in some nodules in 6 patients, 4 of which were eccentric and 2 were described as punctate. Fluorodeoxyglucose-18 positron emission tomography (FDG PET) CT scans were performed for 8 patients, with a median maximum standardized uptake value (SUVmax) of 5.8 (min–max: 2.2–21.2) determined for the lesions. Nine patients underwent surgical wedge resection, and 1 patient underwent lobectomy for diagnosis.

Patients 9–13 were followed up without medication or complications. In patient 14, mild nodule progression and minimal pleural effusion were detected during the 5 years of follow-up period without medication. Patient 15 was concurrently diagnosed with SLE and amyloidosis. The patient underwent hydroxychloroquine treatment and the nodules were monitored for 5 years. In patient 16, an increase in the number of nodules and progression in size were observed without any symptoms after 7 years of follow-up. No comorbidities were detected, and the patient was followed up without any medication for 8 years. In patient 17, nodule progression and minimal pleural effusion were observed 2 years later. Following further evaluation, the patient was diagnosed with B-cell lymphoma and rituximab, cyclophosphamide, vincristine, and prednisolone were initiated. Significant improvement was observed in the radiological findings. The patient was also followed-up without any progression for 8 years. Patient 18, presenting with complaints of dry eyes and mouth, was diagnosed with Sjogren's syndrome. Hydroxychloroquine-pilocarpine was initiated, and no new nodule development was observed over the past 6 years (Fig. 5A–D; Table 1).

3.5. Extraparenchymal pulmonary amyloidosis

3.5.1. Pleural disease. One of the study patients (Patient 19) was diagnosed with pleural amyloidosis (Table 1). A 70-year-old male with COPD and CKD was referred to us because of incidentally detected pleural thickening. The patient was asymptomatic, had a smoking history of 50 pack-years, and had ceased smoking within the past year. Thoracic CT revealed pleural thickening, particularly in the right upper lobe (Fig. 6A). The diagnosis was achieved with pleural amyloidosis via transthoracic fine-needle aspiration biopsy of the pleural area with the highest uptake (SUVmax 6.86) on FDG PET. Following further evaluation, the patient was followed up without medication at another center and died 3 years later.

3.5.2. Mediastinal lymph node amyloidosis. Two patients were diagnosed with MLNA (Patients 20 and 21). Patient 20, a 58-year-old asymptomatic female with no history of smoking, was diagnosed with HT, CKD, and lung adenocarcinoma and was previously operated on for carcinoid tumor. During oncological treatment, she was diagnosed with amyloidosis in an MLN using EBUS-guided transbronchial needle aspiration (EBUS-TBNA) following the development of a newly enlarged MLN. The patient was died 1 year later because of lung adenocarcinoma. Patient 21, a 65-year-old asymptomatic male with a 30 pack-year smoking history, was diagnosed with Waldenstrom macroglobulinemia and was followed up without medication. Thoracic CT revealed lymph nodes in the prevascular, right lower paratracheal, subcarinal, and bilateral hilar regions, with a largest diameter of 2 × 1 cm, as well as 2 subpleural lesions in the right lower lobe and mass lesions in the paracardiac region of the left upper lobe (Fig. 6B). Conventional TBNA was performed on the right lower paratracheal lymphadenopathy, and the pathology was reported as amyloidosis. Daratumumab plus CyBorD was initiated. Significant improvements were observed in existing lesions after treatment. The patient died in the 6th year of follow-up due to COPD exacerbation (Table 1).

4. Discussion

In our study, pulmonary amyloidosis was mostly localized, with nodular and tracheobronchial amyloidosis being the most frequent. We found that the majority of patients were elderly and male; notably, those diagnosed with NPA/extraparenchymal amyloidosis were often asymptomatic at presentation.

We observed that bronchoscopic biopsies were sufficient for diagnosis, and notably, TBNA could be a useful diagnostic method. During the follow-up, we typically noted that the disease remained stable without progression. However, it is

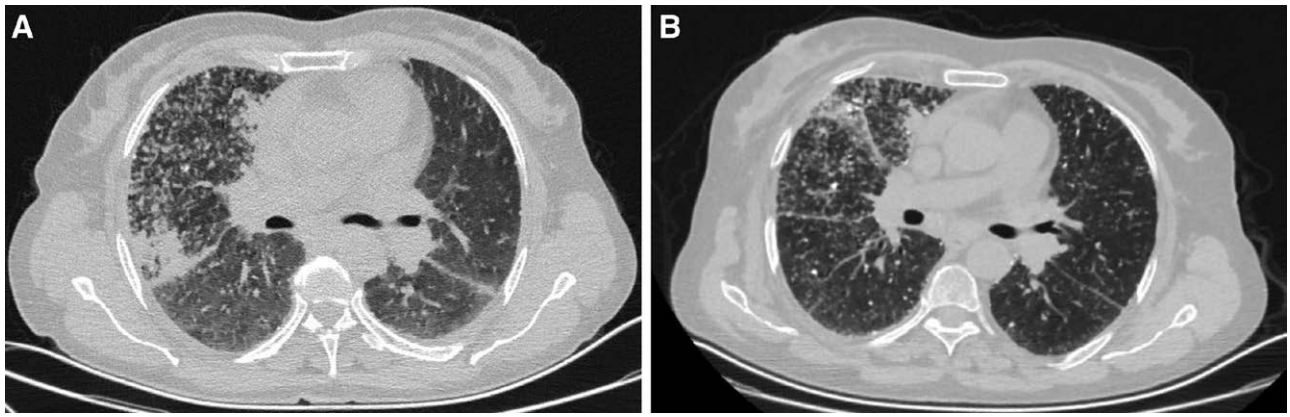

Figure 3. Case of cystic pulmonary amyloidosis. (A) Thoracic computed tomography showing widespread cysts in the right lower lobe with an additional subcutaneous emphysema. (B) Calcified nodules are seen within and adjacent to cysts in the right lower lobe.

important to note that patients with concurrent malignancies experience fatal outcomes.

Diffuse alveolar-septal amyloidosis, also known as diffuse parenchymal amyloidosis, is typically associated with systemic amyloidosis.[2,10] Diagnosis is often based on pathological evaluation through autopsies, as this group of patients rarely manifests with respiratory symptoms.[11,12] Dyspnea may manifest in patients with progressive interstitial lung involvement. However, despite the bilateral interstitial involvement in our patient, no significant dyspnea was observed. In line with the literature, our patient demonstrated thoracic imaging findings including reticular opacities, interlobular septal thickening, and micronodules.[13–15] Transbronchial lung biopsy is a useful and safe method for diagnosing amyloid lung involvement.[16] Our patient was diagnosed with amyloidosis through TBLC, which is highlighted in the current guidelines for the diagnosis of interstitial lung diseases.[17] Further investigations showed that her amyloidosis was due to multiple myeloma. Specifically, pulmonary parenchymal involvement has been reported in 73% of the patients with myeloma-associated amyloidosis.[18] Treatment of DASA is planned according to underlying systemic amyloidosis. Additionally, the primary cause of mortality in pulmonary amyloidosis is often linked to cardiac involvement, and a correlation between cardiac and pulmonary involvement has been reported.[18,19] In our patient, despite the cardiac involvement observed, the patient remains alive after 2 years of follow-up.

Cystic pulmonary amyloidosis represents the least common type of pulmonary amyloidosis.[6] Localized pulmonary amyloidosis in cystic lung disease appears to be significantly more prevalent than systemic amyloidosis, as in our case.[20] Pulmonary cysts, as seen in our case, typically present as numerous, round, thin-walled, and small cysts, with a tendency to be evenly distributed or predominant in the lower lobes, often accompanied by calcified pulmonary nodules.[21] The presence of calcified pulmonary nodules has been reported to be a distinguishing feature for differentiating CPA.[22,23] There are currently limited data regarding CPA treatment, with management primarily focused on treating any underlying disease processes. This disease may exhibit a progressive course. In a study conducted by Zamora et al, 13 out of 21 patients with cystic amyloidosis experienced radiological progression, and 4 patients died during the 5-year follow-up.[20,24] Our patient has been under observation for 3 years, with no progression observed in the existing cysts during follow-up.

Tracheobronchial amyloidosis is a rare disorder characterized by localized, multifocal, or diffuse submucosal plaques of amyloid deposits in various segments of the tracheobronchial tree.[12,25] Pulmonary parenchyma is usually not involved, as seen in our all 6 cases.[26,27] Most cases of localized amyloidosis are rarely associated with systemic amyloidosis.[28,29] In accordance with this, only one of the 6 patients had a diagnosis of MGUS. Patients, as in our cases, are usually symptomatic, and symptoms are typically caused by airway obstruction, depending on the site of amyloid deposition. Typical findings on thoracic CT include irregular calcifications surrounding the tracheobronchial wall, focal nodularity, or narrowing of the airway lumen.[30] The involvement of the posterior tracheal wall, which we observed in 3 patients, has been reported to be a distinguishing characteristic of amyloid deposition.[31] Bronchoscopically, direct visualization typically reveals widespread irregular whitish submucosal lesions, nodules, or polyps, often accompanied by varying degrees of airway narrowing.[32] In the differential diagnosis of tracheobronchial amyloidosis, Tracheobronchopathia osteoplastica should be considered. Tracheobronchopathia osteoplastica is a rare disorder characterized by submucosal bone and cartilage deposits, which can similarly lead to airway obstruction and mimic amyloid deposition in imaging and bronchoscopy.[33] During biopsy or follow-up, caution must be exercised regarding the risk of bleeding. Daniels et al[34] reported that most patients with involvement of the proximal or severe middle airways died due to respiratory failure, pulmonary infections, and massive hemorrhage. In one of our patients, the procedure was terminated because of severe bleeding during biopsy. There is very limited data regarding the treatment of TBA. Close follow-up, without intervention, is commonly performed in asymptomatic patients. For symptomatic patients, as in our patients, debulking via rigid bronchoscopy in the central airways, as well as laser ablation or APC and cryotherapy, is utilized.[29] Since it has been reported that colchicine could be utilized in treatment by impeding the deposition of amyloid fibrils in organs, it was initiated in a patient exhibiting widespread tracheobronchial involvement.[35] The patient was subsequently followed-up for 3 years without progression. In addition, a tracheal resection procedure was performed in 1 patient because of severe airway obstruction and disruption of the tracheal wall structure. Among these patients, 2 of them died due to associated malignancy, while the remaining patients were still under follow-up without complications.

Nodular pulmonary amyloidosis is a rare type of pulmonary amyloid characterized by nodular amyloid deposition, often mimicking malignancy. In the differential diagnosis of NPA, pulmonary hyalinizing granuloma should be considered, as it can contain amyloid deposits and may similarly mimic malignancy.[36] In most cases, NPA is associated with an underlying lymphoproliferative disorder or connective tissue disease, such as mucosa-associated lymphoid tissue lymphoma and Sjogren's syndrome.[6] Similarly, in the study by Grogg et al on nodular amyloidosis, 18 patients were evaluated, and monotypic plasma

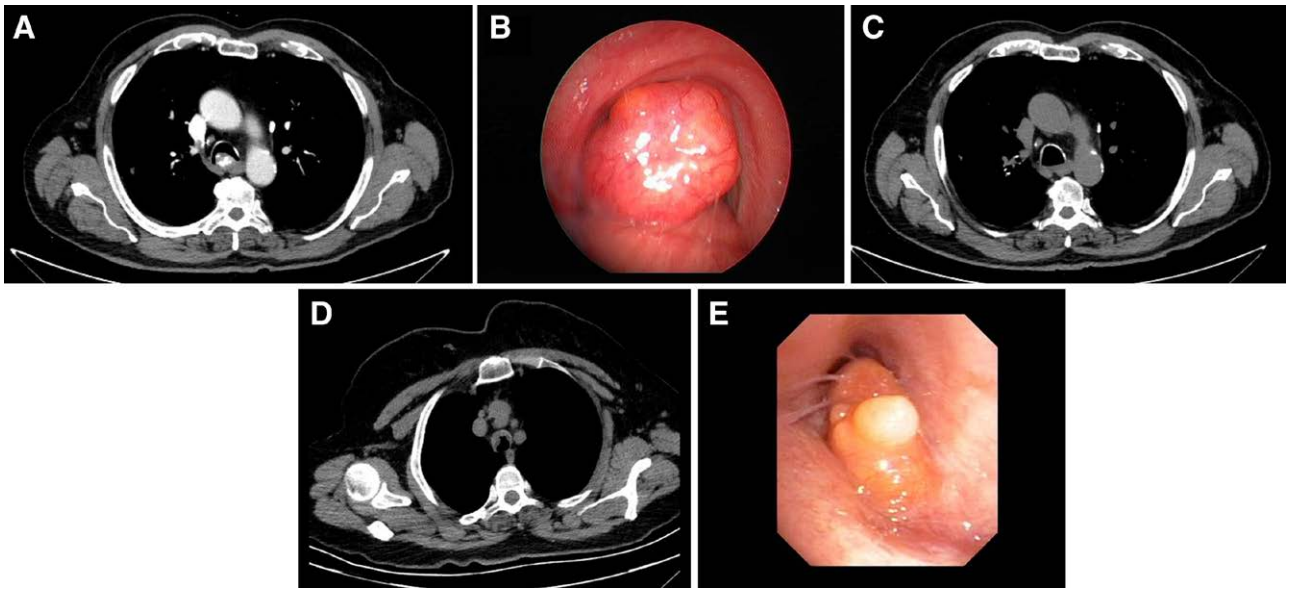

Figure 4. Cases of tracheobronchial amyloidosis. (A) Thoracic computed tomography showing endotracheal lesion containing multiple macrocalcifications on the posterior wall of the trachea. (B) Bronchoscopic view of a polypoid lesion originating from the posterior wall of the trachea, nearly completely occluding the lumen. (C) Thoracic computed tomography showing complete patency of the airway after the treatment. (D) Thickening of the mucosa in the anterior and lateral walls of the trachea. (E) Bronchoscopic view of a whitish, broad-based polypoid lesion originating from the posteriomedial wall of the left main bronchus.

cells were detected in 14 of them. These findings have been reported to support the association of most NPA cases with an underlying lymphoplasmacytic neoplasm within the mucosa-associated lymphoid tissue lymphoma spectrum.[37] However, systemic diseases were detected in only 3 of our patients. Among them, 2 were diagnosed with Sjogren's syndrome and SLE at the time of diagnosis, whereas one was diagnosed with B-cell lymphoma during follow-up. The remaining 7 patients did not have an underlying systemic disease, but 5 of these patients had pulmonary parenchymal damage-causing diseases such as COPD, post-tuberculosis sequelae, and idiopathic pulmonary fibrosis, with the development of NPA primarily attributed to these diseases.[38,39] Nodules typically present as asymptomatic and solitary, and are frequently detected incidentally on chest imaging. Six patients were incidentally diagnosed without any symptoms. Nodules are usually located peripherally and subpleurally, and predominantly in the lower lobes.[40] In 8 of our patients, the nodules were peripheral and subpleural. However, contrary to this lobar distribution, pulmonary nodules were frequently observed in the upper lobes of our patients, which could be attributed to underlying post-tuberculosis sequelae and COPD. They tend to grow slowly and develop cavitation or calcifications. Nodules typically measure <1 cm in diameter, although there have been reported cases in which the nodules reached mass dimensions (>3 cm).[40,41] In our patients, the maximum diameter of the nodules was 62 mm. Additionally, it was observed that nodules progressed slowly without causing symptoms in 3 patients, and some nodules were found to be calcified during follow-up. FDG PET scans may not be reliable for distinguishing NPA from malignancies. A review reported a sensitivity of 63% and a specificity of 70% for pulmonary amyloidosis.[42] The high FDG PET uptake of amyloid nodules is thought to originate from the underlying inflammation or the presence of plasma cells in lymphoma.[43] Consistent with this, PET-CT scans were performed for 8 of our patients, and an uptake with a median SUVmax value of 5.8 (min–max: 2.2–21.2) was observed. NPA lacks a specifically defined treatment, and if an underlying disease is identified, treatment is planned according to the underlying disease.[44] Three of our patients with underlying systemic diseases received specific treatment, and the nodules were monitored. While the nodules in patients with rheumatologic diseases showed stability, a significant improvement in nodules was noted in a patient with lymphoma.

Extraparenchymal pulmonary amyloidosis involves regions such as the pulmonary artery, pleura, and MLN. Pleural amyloidosis is a rare manifestation of amyloid deposition and is reported to occur in only 1% to 2% of patients with systemic amyloidosis.[45,46] Among these patients, pleural effusion is frequently reported, whereas pleural thickening, particularly with a mass-forming appearance, has been documented in only a few case reports.[47,48] Our patient with a pleural mass diagnosed using fine-needle aspiration is an extremely rare case. Our patient had only severe emphysematous COPD, suggesting a potential relationship with the development of amyloidosis.

MLNA is another rare manifestation of amyloidosis, reported to be detected in 1.6% of cases in a study involving 3008 patients diagnosed with amyloidosis.[49] Amyloid lymphadenopathy is most commonly associated with systemic amyloidosis, with cases of isolated transthyretin and secondary amyloidosis.[4,50] One of our 2 patients was diagnosed with recurrent Waldenstrom macroglobulinemia during investigation, while the other was diagnosed with lung adenocarcinoma. MLNA due to amyloid deposition often calcifies[2] but calcification was not observed in the lymph nodes of our patient. The absence of calcification might be related to active disease in our patients. Our findings are consistent with the adequacy of TBNA methods for MLNA diagnosis.[51]

The limitations of our study include its retrospective nature and single-center design. We believe that despite the limited number of patients in our study, it is important to determine which clinical and radiological findings should raise suspicion of amyloidosis. We believe that our study, although not small compared to existing studies, will enrich the literature and provide guidance for clinical practice.

In conclusion, it is crucial to distinguish pulmonary amyloidosis from other pulmonary diseases such as malignancies, infectious diseases, and interstitial lung diseases, which may have similar clinical and radiological findings. Bronchoscopic diagnostic methods are usually sufficient for the diagnosis. Although patients with pulmonary involvement mostly remain stable during long-term follow-up without progression, it is important to consider the risk of malignancy.

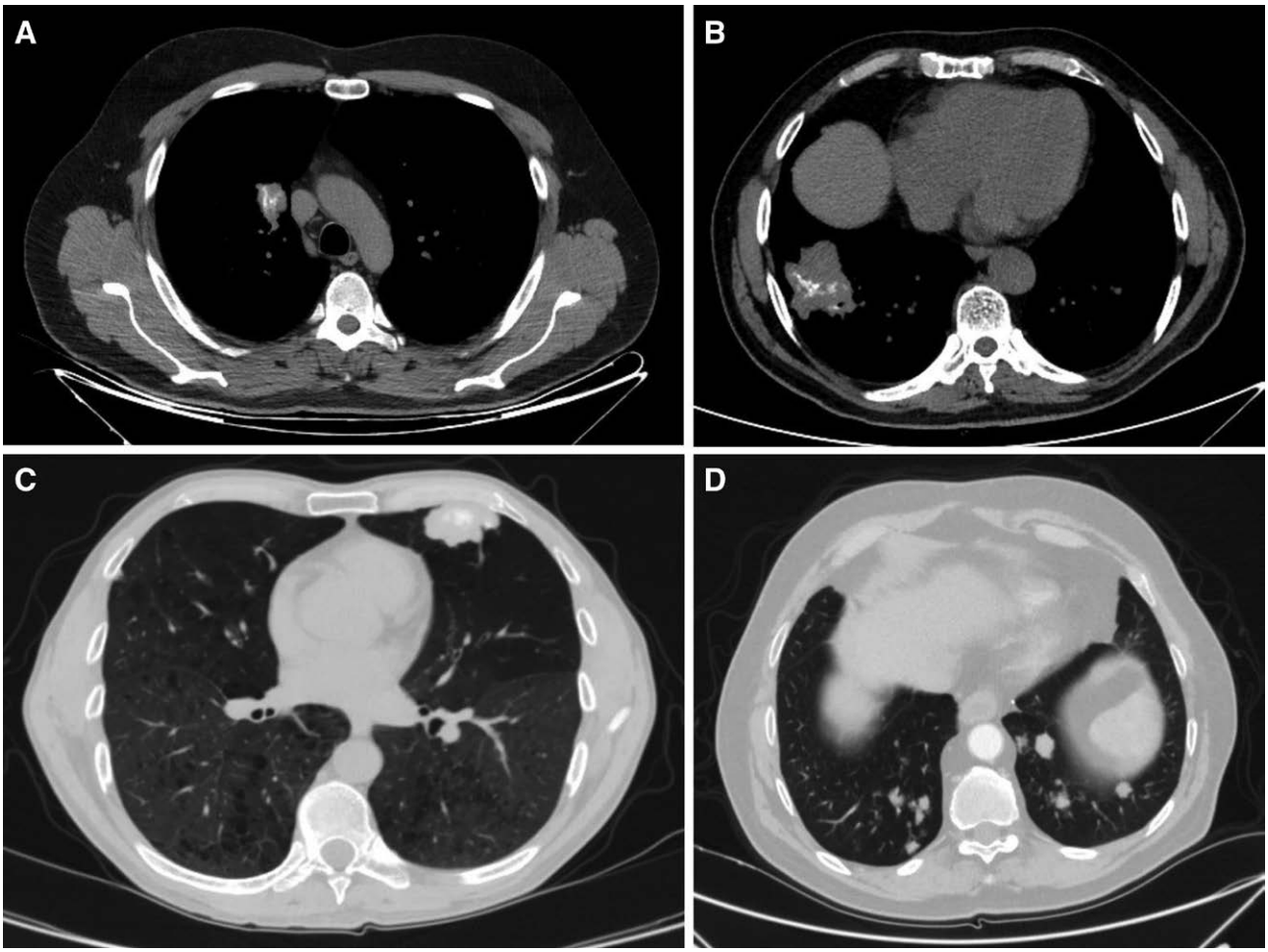

Figure 5. Cases of nodular pulmonary amyloidosis. (A) Thoracic computed tomography showing a 2.2 × 1.2 cm-sized nodular lesion with irregular borders and containing amorphous calcification. (B) The thoracic computed tomography showing a lobulated lesion measuring 4.2 × 3.6 cm with areas of amorphous calcification, located in the laterobasal segment of the right lower lobe. (C) Thoracic computed tomography showing a lobulated lesion measuring 2.6 × 1.8 cm in size, containing areas of calcification, adjacent to the pleura, within an area of severe emphysema. (D) Thoracic computed tomography showing multiple pulmonary nodules in bilateral lower lobes.

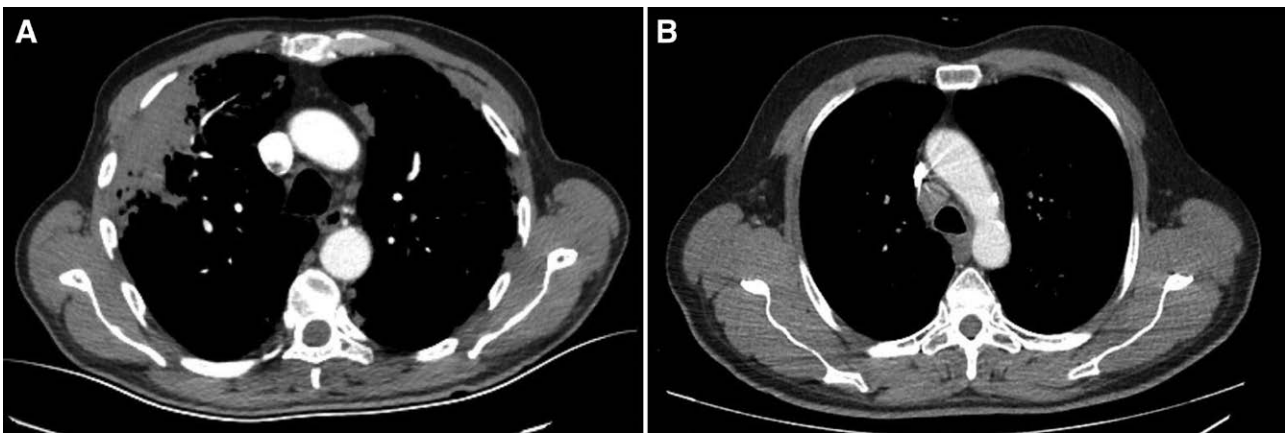

Figure 6. Cases of pleural amyloidosis and mediastinal lymph node amyloidosis. (A) Thoracic computed tomography showing pleural thickening with a mass-forming appearance in the right upper lobe. (B) Thoracic computed tomography showing a lymph node 2 × 1 cm in size in the right lower paratracheal region.

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