Bilateral Hilar and Mediastinal Lymphadenopathy as an Initial Manifestation of Amyloidosis

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A 75-year-old male visited our hospital with bilateral hilar lymph node swelling detected on chest radiography during an annual medical checkup. Chest computed tomography revealed swelling of multiple hilar mediastinal lymph nodes. Histopathological and immunohistochemical examinations of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) specimens from the hilar lymph nodes revealed amyloid deposition. Bilateral hilar and mediastinal lymphadenopathies can be the first manifestations of amyloidosis diagnosed using EBUS-TBNA.

Key Words: Amyloidosis, Hilar and mediastinal lymphadenopathy

INTRODUCTION

Diseases that cause enlarged hilar and mediastinal lymph nodes include malignant tumors (e.g., malignant lymphoma and lung cancer), infections (e.g., acid-fast infections), autoimmune diseases, sarcoidosis, IgG4-related diseases, and amyloidosis. With recent advances in diagnostic techniques using bronchoscopy, these diseases are increasingly diagnosed using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

Amyloidosis is a group of diseases in which soluble proteins with abundant β-sheet structures are converted into amyloid fibers, a unique protein with a fiber structure, and are deposited extracellularly, causing organ dysfunction. More than 30 proteins have been shown to possess amyloidogenic properties. Immunoglobulin light chain (AL) amyloidosis is the most common type of amyloidosis [1] but is still rare, with an incidence of approximately 1 case per 100,000 person-years in the US [2].

The involvement of hilar and mediastinal lymphadenopathy is common in amyloidosis. However, this initial presentation is rare in patients with amyloidosis [3]. Herein, we report a case of AL amyloidosis found in bilateral hilar lymph node swelling on chest radiography, which was diagnosed using EBUS-TBNA.

CASE

A 75-year-old male visited our hospital with bilateral hilar swelling detected on chest radiography during an annual medical checkup (Fig. 1A). There were no subjective symptoms such as fever, weight loss, night sweats, or respiratory symptoms. The patient's medical history was unremarkable. Physical examination revealed a temperature of 35.8°C, no palpable cervical or supraclavicular lymph nodes, clear respiratory sounds, pure heart sounds, and no other findings. Chest computed tomography (CT) revealed a fibrotic lesion, predominantly in the upper lung field (Fig. 1B), and enlarged lower paratracheal, subaortic, and bilateral hilar lymph nodes, demonstrating a diffuse low-density pattern with dotted calcification (Fig. 1C). Blood test results did not show abnormal tumor marker findings, suggesting the presence of lung cancer and lymphoma, except for a mild increase in carcinoembryonic antigen levels (8.8 ng/mL) (Table 1). There were also no findings suggestive of infection (white blood cells, 6200/μL; C-reactive protein, < 0.09 mg/dL; interferon-gamma release assay (-)), sarcoidosis (angiotensin-converting enzyme, 22.1 IU/L), and IgG4-related disease (IgG4, 32 mg/dL) in blood tests. EBUS-TBNA was performed on the right hilar lymph node for a definitive diagnosis, which showed acidophilic unstructured material with positive Congo red staining and positive apple-green birefringence under polarized light microscopy (Fig. 2A, B), leading to the diagnosis of amyloidosis. Immunohistochemical examination was positive for AL-κ (Fig. 2C) and negative for AL-λ, AA, and transthyretin (Fig. 2D–F), resulting in a diagnosis of AL-κ amyloidosis. Gastric mucosal biopsy revealed amyloid deposits. However, no amyloid deposition was observed in the tissue from the transbronchial lung biopsy of the upper lung field, where interstitial changes were seen, from lip biopsy and abdominal wall fat biopsy. Furthermore, there were no findings suggestive

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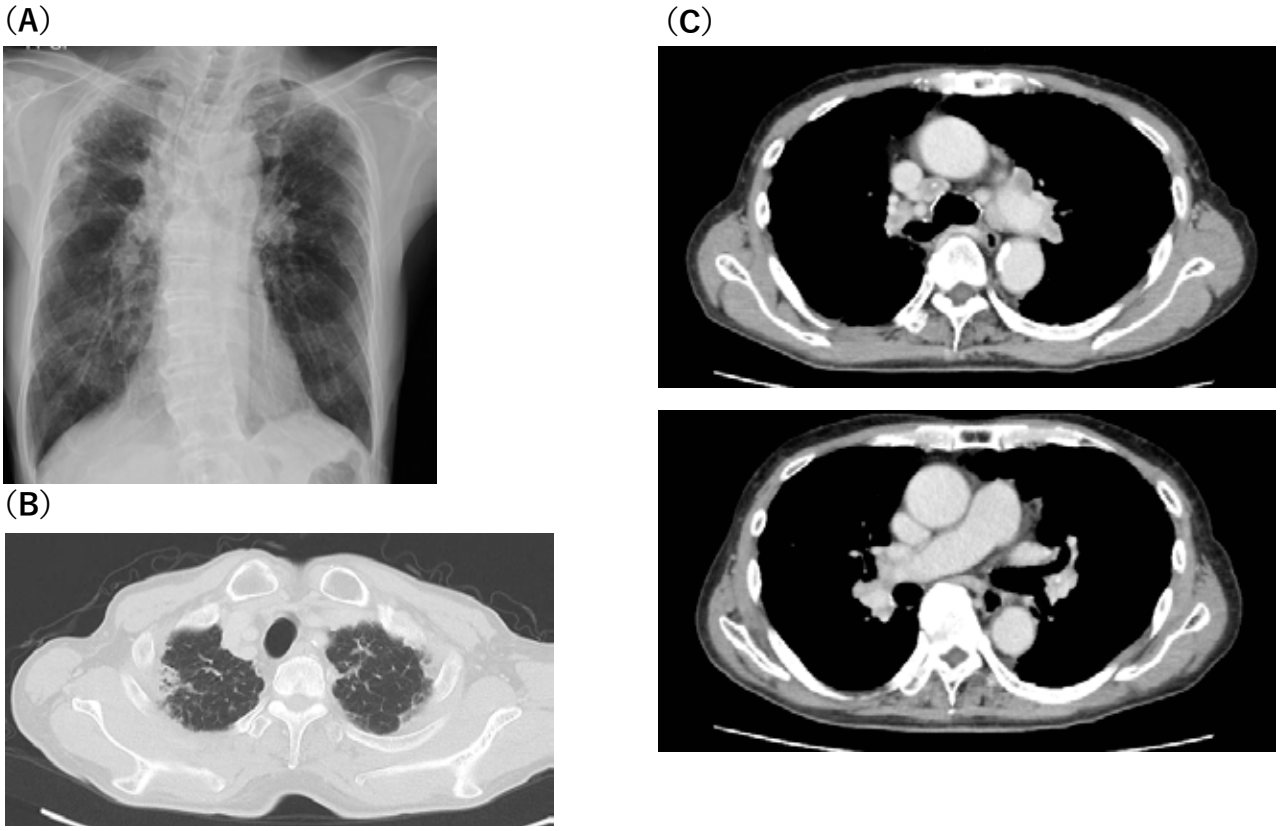

Fig. 1 Chest imaging
The chest radiograph (A) shows an interstitial shadow predominantly in the upper lung field and bilateral hilar swelling. Chest CT shows consolidation of the subpleural lung parenchyma (B) and swelling of the hilar and mediastinal lymph nodes (C).

Table 1 Blood test findings

WBC	6200 /μL	TP	8.2 g/dL	IgG	1226 mg/dL
Neutrophil	52.2 %	AST	27 U/L	IgA	384 mg/dL
Lymphocyte	37.6 %	ALT	21 U/L	IgM	67 mg/dL
Monocyte	6.6 %	LDH	202 U/L	κ free light chain	28.9 mg/L
Eosinophil	3.1 %	BUN	19 mg/dL	λ free light chain	18.5 mg/L
Basophil	0.5 %	Cre	0.99 mg/dL	κ/λ ratio	1.56
		Na	141 mEq/L	Urine Bence-Jones Protein	-
RBC	$4.05*10^6$/μL	K	4.0 mEq/L		
Hb	13.2 g/dL	Cl	103 mEq/L		
Plt	$24.4*10^4$/μL	Ca	9.3 mg/dL	ANA 80	
		CRP	<0.09 mg/dL	RF <5 IU/ml	
		Glucose	119 mg/dL	IgG4 32.0 mg/dL	
				IFNγ -	
		sIL-2R	441 U/mL	BNP 26 pg/mL	
		ACE	22.1 IU/L		
		CEA	8.8 ng/mL		
		CYFRA	≦1.0 ng/mL		
		ProGRP	57.2 pg/mL		

White blood cells: WBC, Red blood cell: RBC, Hemoglobin: Hb, Platelet: Plt, Total protein: TP, Aspartate aminotransferase: AST, Alanine aminotransferase: ALT, lactate dehydrogenase: LDH, Blood urea nitrogen: BUN, Creatinine: Cr, C-reactive protein: CRP, soluble Interleukin-2 receptor: sIL-2R, angiotensin-converting enzyme: ACE, carcinoembryonic antigen levels: CEA, cytokeratin fragment: CYFRA, pro-gastrin releasing peptide: proGRP, antinuclear antibody: ANA, interferon-gamma release assay: IFNγ, brain natriuretic peptides: BNP, Rheumatoid factor: RF

of multiple myeloma or monoclonal gammopathy of undetermined significance, such as urinary Bence-Jones protein, serum M-protein, serum-free light chain abnormality (k/λ ratio 1.56), or bone marrow biopsy findings suggestive of multiple myeloma (plasma cell 0.3%). Electrocardiography revealed a sinus rhythm and no arrhythmias. Serum plasma levels of brain natriuretic peptides were normal (26 pg/mL) and echocardiography revealed normal cardiac function and no wall thickening. Technetium-99m-pyrophosphate

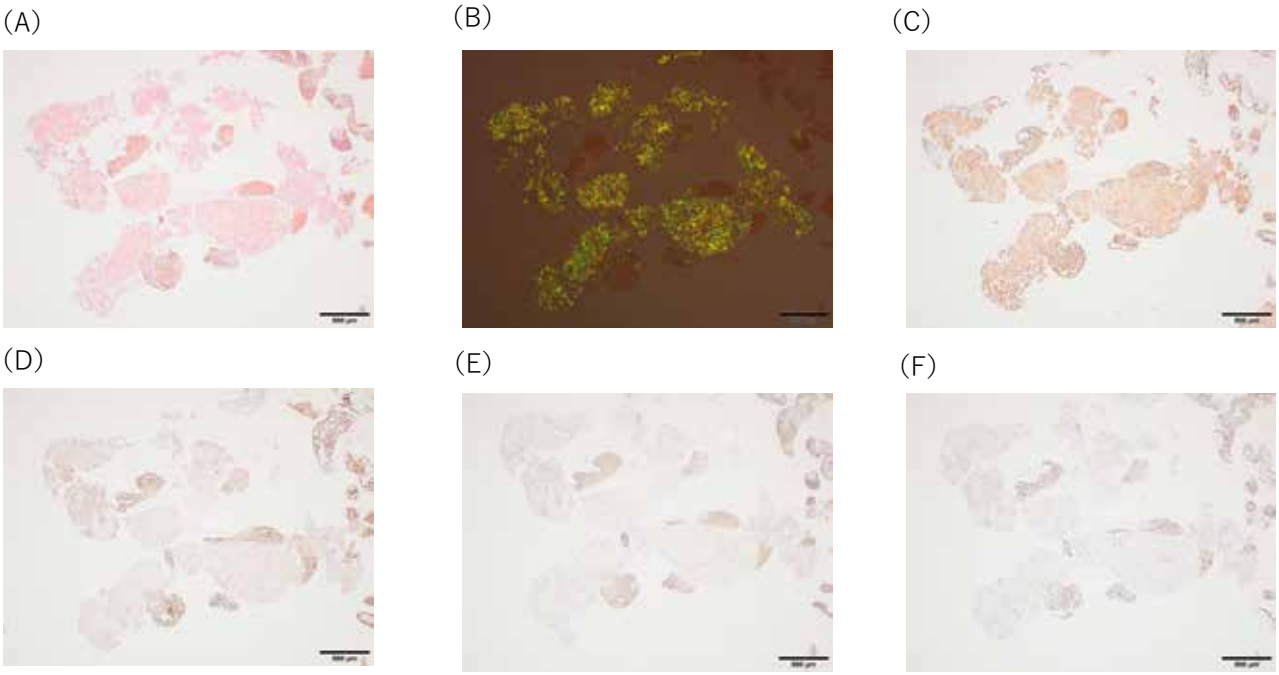

Fig. 2 Hilar lymph node biopsy specimen obtained by EBUS-TBNA (100 ×)
Congo red staining (A) and apple green birefringence were positive under a polarized light microscope (B). Immunohistochemical examination was positive for AL-κ (C) and negative for AL-λ (D), AA (E), and transthyretin (F).

scintigraphy revealed no abnormal accumulation in the myocardium, suggesting the absence of coexisting cardiac amyloidosis. Additionally, there were no findings suggestive of renal dysfunction (negative urinary protein levels) or peripheral neuropathy (no numbness or pain). Therefore, the patient has been under observation without treatment for more than 3 years after being diagnosed with amyloidosis.

DISCUSSION

Respiratory amyloidosis is relatively common and occurs either in a localized or systemic form [4]. The respiratory amyloidosis patterns are divided into five patterns: 1) nodular pulmonary amyloidosis, 2) diffuse alveolar-septal amyloidosis, 3) hilar and mediastinal lymph node amyloidosis, 4) tracheobronchial amyloidosis, and 5) pleural amyloidosis [4, 5]. Hilar and mediastinal adenopathy shows various patterns of calcification, including speckled, diffuse, and eggshell, and are the third most common patterns of respiratory amyloidosis after tracheobronchial and nodular lesions [4, 6].

Amyloidosis with hilar and mediastinal lymphadenopathy was first reported in 1983 [7], and it was first reported in Japan in 1985 [8]. Recently, EBUS-TBNA has become a standard and less invasive technique for the assessment of mediastinal lymphadenopathy, replacing surgical biopsy. Thus, there has been 24 cases of amyloidosis diagnosed from hilar or mediastinal adenopathy using EBUS-TBNA (Table 2) [5, 9–22]. Consistent with previous reports that hilar or mediastinal adenopathy is usually detected in patients with systemic amyloidosis and mostly AL type [3, 4], 16 (67%) cases were systemic or suspected of systemic amyloidosis and 20 (83%) were AL-type or suspected of AL-type, among 24 cases that were diagnosed with amyloidosis using EBUS-TBNA of hilar or mediastinal adenopathy. Although mediastinal lymph node involvement in the absence of pulmonary lesions is extremely rare [23], 11 (46%) cases did not show any lung lesions, including pleural effusion. Additionally, cases of respiratory amyloidosis are reportedly diagnosed mostly after death because many cases are asymptomatic [5]. Therefore, with the widespread use of EBUS-TBNA, amyloidosis is increasingly diagnosed from hilar and mediastinal adenopathy, and the characteristics of amyloidosis with hilar and mediastinal adenopathy may change from previous reports, for example no pulmonary involvement or diagnosis during survival.

CONCLUSION

We encountered a case of hilar and mediastinal lymphadenopathies as initial manifestations of systemic AL-κ amyloidosis, which was diagnosed using EBUS-TBNA. Therefore, amyloidosis should be included in the differential diagnosis of hilar and mediastinal lymphadenopathies.

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REFERENCES

1) Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016; 387(10038): 2641–54.
2) Shimazaki C, Hata H, Iida S, Ueda M, Katoh N, Sekijima Y, *et al.* Nationwide Survey of 741 Patients with Systemic Amyloid Light-chain Amyloidosis in Japan. Internal medicine (Tokyo, Japan). 2018; 57(2): 181–7.
3) Fu J, Seldin DC, Berk JL, Sun F, O'Hara C, Cui H, *et al.* Lymphadenopathy as a manifestation of amyloidosis: a case series. Amyloid : the international journal of experimental and clinical investigation : the official journal of the International

Table 2 Clinical and radiologic findings of patients with amyloidosis diagnosed by EBUS-TBNA

Case	Age	Gender	Type	Local/ Systemic	Secondary/ Primary	First manifestation	Lymph node calcification	Pulmonary lesion	Ref
1	80	male	unknown	local	primary	dyspnea	speckled	none	9
2	77	female	AL	local	primary	cough hoarseness	none	none	10
3	69	male	unknown	unknown	unknown	cough chest pain	none	none	11
4	75	male	AL	systemic: heart, lung, pleura	Waldenstrom's macroglobuline mia	dyspnea	none	multiple lung nodules, bilateral pleural effusion	12
5	75	female	s/o AL/AH	systemic	Extramedullary IgM plasmacytoma	dyspnea, lower leg edema	none	bilateral pleural effusion	13
6	77	male	s/o AL/AH	systemic: heart, pleura?	Monoclonal gammopathy of undetermined significance	dyspnea	speckled	right pleural effusion	14
7	92	male	AL	systemic: bone marrow, pleura?	Lymphoplasmac ytic lymphoma	dyspnea	none	right pleural effusion	15
8	80	male	s/o AL	local	unknown	none (dyspnea and cough due to bacterial pneumonia)	none	none	16
9	64	male	unknown	local	primary	none	speckled	none	17
10	71	male	AL	systemic: heart	primary	dyspnea, lower leg edema	speckled, diffuse	none	18
11	81	male	TTR	systemic: heart	Senile systemic amyloidosis	vomiting, impaired consciousness	diffuse	none (right upper lobe atelectasis due to enlarged mediastinal lymph node)	19
12	63	female	AL	local	Monoclonal gammopathy of undetermined significance	none	speckled	none	5
13	75	male	AL	systemic: kidney, heart, rectum	Waldenstrom's macroglobuline mia	dyspnea	none	none	5
14	78	female	AL	systemic: periorbital ecchymosis	primary	none	speckled	Consolidation (not known due to amyloidosis or not)	20
15	77	female	AL	unknown	unknown	none	speckled	none	21
16	67	female	AL	unknown	unknown	unknown	+ not known in detail	single mass	22
17	71	male	AL	s/o systemic: heart?	s/o Lymphoprolifera tive disease	unknown	none	interstitial lung disease, but not confirmed by biopsy	22
18	70	male	AL	s/o systemic: lung?	Lymphoplasmac ytic lymphoma	unknown	+ not known in detail	single mass (not confirmed by biopsy)	22
19	69	female	AH/AL	s/o systemic: lung?	Rheumatoid arthritis treated with methotrexate	unknown	none	multiple lung nodules (not confirmed by biopsy)	22
20	79	male	AL	s/o systemic: lung?	unknown	unknown	+ not known in detail	multiple lung nodules (not confirmed by biopsy)	22
21	37	male	s/o AL	s/o systemic: lung?	s/o Lymphoprolifera tive disease	unknown	none	multiple lung nodules (stable)	22
22	71	female	s/o AL	s/o systemic: lung?	Follicular lymphoma	unknown	+ not known in detail	single mass (not confirmed by biopsy)	22
23	62	female	AL	s/o systemic: retroperitoneal lymphadenopathy	s/o Lymphoprolifera tive disease	unknown	none	none	22
24	75	male	AL	systemic: gastric mucosa	primary	none	speckled	none	22

AL: light-chain associated amyloidosis, AH: heavy-chain associated amyloidosis, TTR: transthyretin, s/o: suspect of

Society of Amyloidosis. 2014; 21(4): 256–60.
4) de Almeida RR, Zanetti G, Pereira ESJL, Neto CA, Gomes AC, Meirelles GS, *et al*. Respiratory Tract Amyloidosis. State-of-the-Art Review with a Focus on Pulmonary Involvement. Lung. 2015; 193(6): 875–83.
5) Yamada M, Takayanagi N, Yamakawa H, Ishiguro T, Baba T, Shimizu Y, *et al*. Amyloidosis of the respiratory system: 16 patients with amyloidosis initially diagnosed ante mortem by pulmonologists. ERJ Open Res. 2020; 6(3).
6) Czeyda-Pommersheim F, Hwang M, Chen SS, Strollo D, Fuhrman C, Bhalla S. Amyloidosis: Modern Cross-sectional Imaging. Radiographics. 2015; 35(5): 1381–92.
7) Thompson PJ, Jewkes J, Corrin B, Citron KM. Primary bronchopulmonary amyloid tumour with massive hilar lymphadenopathy. Thorax. 1983; 38(2): 153–4.
8) Kikuchi K, Yamamoto A, Hiraga Y, Sasaki M. [A case of amyloidosis with BHL (bilateral hilar lymphadenopathy), suspected to be sarcoidosis]. Nihon Kyobu Shikkan Gakkai Zasshi. 1985; 23(2): 245–8.
9) Leiro V, Fernández-Villar A, Bandrés R, González A, Represas C, Barros JC, *et al*. Primary amyloidosis involving mediastinal lymph nodes: diagnosis by transbronchial needle aspiration. Respiration; international review of thoracic diseases. 2008; 76(2): 218–20.
10) Taiki F, Kazuhiro Y, Takahiro N, Masako C, Akira I, Shigetoshi Y, *et al*. Primary amyloidosis involving mediastinal lymph nodes diagnosed by EBUS-TBNA. Respiratory Medicine CME. 2009; 2(1): 51–3.
11) Khor YH, Steinfort DP, Buchanan MR, Gunawardana D, Antippa P, Irving LB. A 69-year-old smoker with mediastinal and hilar lymphadenopathy. Thorax. 2010; 65(2): 132–8, 87.
12) Ishiguro T, Takayanagi N, Katoh N, Shimizu Y, Hoshi T, Yanagisawa T, *et al*. Waldenström's macroglobulinemia accompanying systemic amyloidosis: the usefulness of endobronchial ultrasound-guided transbronchial needle aspiration for detecting amyloid deposits. Internal medicine (Tokyo, Japan). 2014; 53(24): 2789–93.
13) Morikawa S, Hoshino T, Yamaguchi T, Okamura T, Nakanishi T, Imaizumi K. A case of extramedullary IgM plasmacytoma presenting with an extensive mediastinal diffusely infiltrative lesion diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The Journal of Japanese Society for Respiratory Endoscopy. 2014; 36(3): 282–7.
14) Adachi T, Nakahata M, Moritani S, Iida H, Ogawa K. Enlarging mediastinal/hilar lymphadenopathy with calcification. Clinical case reports. 2016; 4(2): 212–3.
15) Chen HH, Kilic AI, Picken M, Pambuccian SE, Wojcik EM. Amyloid in endobronchial ultrasound-guided transbronchial needle aspiration cytology. Diagnostic cytopathology. 2017; 45(5): 436–40.
16) Tahara M, Yamasaki K, Anso H, Nakagaki N, Imanaga T, Yatera K. A case of suspected localized amyloidosis by endobronchial ultrasound-guided transbronchial needle aspiration. The Journal of Japanese Society for Respiratory Endoscopy. 2018; 40(6): 601–7.
17) Kumar A, Sivasailam B, Marciniak E, Deepak J. EBUS-TBNA diagnosis of localised amyloidosis presenting as mediastinal lymphadenopathy. BMJ case reports. 2018; 11(1).
18) Katayama K, Tachibana K, Arai T, Takeda M, Kasai T, Akira M, *et al*. Primary systemic amyloidosis with calcified hilar and mediastinal lymphadenopathies diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration specimens. The Journal of Japanese Society for Respiratory Endoscopy. 2019; 41(5): 491–6.
19) Sakai Y, Nakao M, Arakawa S, Suzuki Y, Fujita K, Sato H, *et al*. A case of senaile systemic amyloidosis that presented as progressive massive mediastinal lymph node swelling. The Journal of Japanese Society for Respiratory Endoscopy. 2019; 41(3): 262–7.
20) Tani E, Sakurai Y, Iwai A, Hirai K, Sato I, Kinoshita Y, *et al*. Amyloidosis with periorbital ecchymosis triggered by bronchoscopy: a case report. The Journal of Japanese Society for Respiratory Endoscopy. 2020; 42(2): 164–9.
21) Ito T, Yoshida M, Miki H, Goto H, Kodama S, Terashima T, *et al*. The usefulness of endobronchial ultrasound-guided transbronchial needle aspiration or AL amyloidosis presentig as mediastinal lymphadenopathy: a case report The Journal of Japanese Society for Respiratory Endoscopy. 2023; 45(3): 205–9.
22) Naqvi A, Bonert M, Finley C, Czarnecka-Kujawa K, Yasufuku K, Schwock J, *et al*. Role of EBUS-TBNA/EUS-FNA and mass spectrometry for diagnosis and typing of lymph node amyloidosis: 10-year experience in two tertiary care academic centers. Cancer cytopathology. 2023.
23) Gómez AT, Alonso RM, García MM, Fabbricatore AA, García-Tejedor JL. Thoracic amyloidosis: high-resolution computed tomographic findings in 3 cases. J Comput Assist Tomogr. 2008; 32(6): 926–8.