Mediastinal Lymphadenopathy in Patients with Systemic Sclerosis

Panaya Tumsatan MD*, Jitraporn Wongwiwatchai MD*,
Chalida Apinives MD*, Vallop Laopaiboon MD*

** Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background: *There are few studies regarding the characteristics of mediastinal lymphadenopathy (MLN) in patients with systemic sclerosis (SSc). Understanding its features could help radiologists interpret lung imaging more confidently.*
Objective: *To determine the prevalence and characteristics of MLN in patients with SSc and factors associated with MLN.*
Material and Method: *A retrospective review of medical records and high resolution computed tomography (HRCT) of the lungs of all patients with SSc at Srinagarind Hospital, Khon Kaen University, Thailand between 2009 and 2011 was done. Univariate and multivariate logistic regressions were used to analyze the outcomes.*
Results: *Sixty patients were eligible for the present study; the majority of them was women (71.7%) and had diffuse SSc (71.7%). The prevalence of MLN was 56.7% (36 in 60 cases). The distribution of MLN was mainly found in two or more locations (47.1%) and had isodensity on imaging (61.3%). The median size of nodes was 1.2 cm (inter-quartile range 1, 1.4 cm). Only the pulmonary fibrosis score was significantly associated with MLN with the adjusted odds ratio of 1.2 (95% confidence interval 1.1, 1.4, p = 0.03). There was no association between MLN with other factors.*
Conclusion: *MLN was prevalent in patients with SSc. The pulmonary fibrosis score was an independent factor associated with MLN.*

Keywords: *Mediastinal lymphadenopathy, high resolution computed tomography (HRCT), interstitial lung disease (ILD), systemic sclerosis (SSc), ground glass opacity (GGO), pulmonary fibrosis*

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Mediastinal lymphadenopathy (MLN) can occur from a wide-ranging of pathologies and the common causes of MLN are infectious, inflammatory or neoplastic conditions[1]. Several studies showed that MLN was also seen in many interstitial lung diseases (ILDs) including systemic sclerosis (SSc)[2-10]. Although correlations between ILDs and MLN have been broadly reported, little is known about the characteristics of MLN in SSc. Existing studies show that the prevalence of MLN in patients with SSc is 32 to 60%[2,6,10]. In addition, a few studies showed association between pulmonary fibrosis and MLN. One study reported that the occurrence of enlarged mediastinal lymph nodes in SSc was correlated with the extent of pulmonary disease as judged by high resolution computerized tomography (HRCT)[6]. The present study, however, used an old HRCT protocol with 3 mm thick collimation and used a 30 mm interval that might cause an underestimation of the lymph node enlargement.

Correspondence to:
Tumsatan P, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand.
Phone: +66-43-363614
E-mail: tupanaya@yahoo.com

Pulmonary involvement is one of the leading causes of death in SSc patients and MLN was prevalent in these patients. Understanding the characteristics of MLN in SSc would help the radiologist to narrow differential diagnoses. Therefore, the primary objective of the present study was to estimate the prevalence of MLN in SSc patients, and the secondary objective was to describe the characteristics of MLN in SSc patients and factors associated with MLN among these patients.

Material and Method

Patient population

The present study was a cross-sectional study with retrospective data collection that was approved by the Ethics Committee for Human Research at Khon Kaen University. Inclusion criteria were SSc patients who underwent HRCT of the lung in Srinagarind Hospital between 2009 and 2011. The patients had been followed up for at least two years after HRCT of the lungs and the results showed no other diseases such as infection or malignancy. The patients were excluded if the HRCT of the lung showed pulmonary masses/nodules, upper or mid-lung predominance of ground glass opacity (GGO) or fibrosis, profuse micronodules or discrete cysts.

HRCT

The HRCT scans were performed without IV contrast material but with suspended deep inspiration in the supine position throughout the whole lungs. There were two CT scanners in the present study, the Siemens Somatom plus 4 and The Phillips Brillance CT 128-channel scanner. For the Siemens Somatom Plus 4 CT scanner, 1.25 mm collimation, with-1-mm intervals for the lung window and 5-mm interval for mediastinal window were used. For the Phillips Brillance CT 128-channel scanner, 1-mm collimation with a 1 mm interval for the lung window and a 2.5 mm interval for mediastinal window were used.

Image interpretation

The HRCT scans were retrospectively reviewed by two radiologists and the decisions were made by consensus. For severity of ILD, the radiologists evaluated the presence of GGO and pulmonary fibrosis, including septal thickening, traction bronchiectasis and honey combing, and scored them using the CT scoring system of Franquet[11]. After that, a summation of GGO and pulmonary fibrosis were made for the total severity score. The total severity score was used to determine the grades of 0-3 (Table 1).

The presence of MLN was recorded when the short axis diameter was equal to or greater than 10 mm[12,13]. The numbers and characteristics of hyper-/iso-/hypodensity and calcification of the enlarged mediastinal lymph nodes were recorded.

Table 1. CT scoring system to evaluate severity of interstitial lung disease

Score	Feature
GGO	
0	None
1	GGO involving <25% of lobe
2	GGO involving 25-50% of lobe
3	GGO involving >50% of lobe
Pulmonary fibrosis	
0	No fibrosis
1	Fibrosis (septal thickening, HC) <25% of lobe
2	Fibrosis (septal thickening, HC) 25-50% of lobe
3	Fibrosis (septal thickening, HC) >50% of lobe
CT perfusion score	
Grade 0	Normal lobe (total severity score 0)
Grade 1	Mild extent (total severity score 1-7)
Grade 2	Moderate extent (total severity score 8-15)
Grade 3	Severe extent (total severity score >15)

CT = computed tomography; GGO = ground glass opacity; HC = honeycombing
Total severity score is GGO plus pulmonary fibrosis score

The densities of the enlarged lymph nodes were identified as hypo-, iso-, and hyperattenuation as compared with muscle.

Data collection

Data of ages, gender, numbers of organ involvement by SSc, steroid usage and subtypes of SSc were recorded from the patient's medical records. GGO was scored from 0-3 for each lobe of the lungs using the CT scoring system of Franquet[11] and the scores of all five lobes were add together for the GGO score. A similar method was used for the pulmonary fibrosis score. Summation of the GGO and pulmonary fibrosis score of each patient were completed for the total fibrosis score and used to grade the severity of the ILD disease, CT profusion scores, from grades 0-3 (Table 1).

Statistical analysis

Demographic data were analyzed using descriptive statistics, presented in percentages, means and standard deviations. If the distribution of these data was not a normal distribution, then medians, and inter-quartile ranges were used instead. The effects of factors associated with MLN were evaluated using univariate and multiple logistic regressions. For univariate analysis, factors with a $p<0.20$ were then entered into a multiple logistic regression model. A $p<0.05$ was considered to indicate statistically significant differences, and adjusted odds ratios (OR) and their 95% confidence intervals (CI) were reported to consider the strength of association. All the data analyses were carried out using STATA version 10.0 (StataCorp, College Station, Texas).

Results

Sixty patients were eligible for the present study. Baseline characteristics of the studied populations were summarized in Table 2. The majority of the patients was women (71.7%) and had diffuse SSc (71.7%). The prevalence of MLN was 56.7% (36 of 60 cases). The distribution of MLN was mainly found in two or more locations (47.1%) and had an isodensity on imaging of 61.3%. The most common location was right lower paratracheal lymph node. The median size of nodes was 1.2 cm (inter-quartile range 1, 1.4 cm). Three of 60 patients had lymph nodes that were larger than 1.5 cm in short diameter.

Factors associated with MLN using univariate analyses were demonstrated in Table 3. Factors with a p-value <0.2 were age and the pulmonary fibrosis score,

and then entered in multivariate analyses (Table 4). Only pulmonary fibrosis score was significantly associated with MLN with an adjusted odds ratio of 1.2 (95% confidence interval 1.1, 1.4, $p = 0.03$). There were no association between MLN with age, gender, steroid use, subtype of SSc, number of organs involvement, presence of ILD and GGO.

The images of pulmonary fibrosis and GGO were shown in Fig. 1. The examples of hypo-, iso-, and hyperdense mediastinal lymph nodes that existed at 1 cm in diameter were shown in Fig. 2.

Table 2. Baseline characteristics of studied populations

Variables	n = 60
Demographic data	
Age (years), mean (SD)	48.9 (11.5)
Female (%)	43 (71.7)
Subtype of SSc	
- Limited (%)	17 (28.3)
- Diffuse (%)	43 (71.7)
Steroid use (%)	24 (40.0)
No. of organ involvement, mean (SD)	3.3 (1.3)
Abnormal HRCT finding	
ILD	56 (93.3)
GGO score, mean (SD)	6.9 (5.0)
Pulmonary fibrosis score, mean (SD)	4.3 (3.4)
Total severity score, mean (SD)	11.3 (6.7)
CT perfusion score (%)	
- Grade 0	4 (6.7)
- Grade 1	16 (26.7)
- Grade 2	30 (50.0)
- Grade 3	10 (16.6)
Location and characteristics of lymph nodes	
Presence of mediastinal node (%)	34 (56.7)
Location of lymph node in positive cases (n = 34)	
- Right upper paratracheal alone	0 (0)
- Right lower paratracheal alone	8 (23.5)
- Left lower paratracheal alone	3 (8.9)
- AP window alone	2 (5.9)
- Subcarinal alone	5 (14.8)
- Paraaortic alone	0 (0)
- Right upper and lower paratracheal nodes	3 (8.9)
- Right and left lower paratracheal nodes	1 (2.9)
- Right upper, right and left lower paratracheal nodes	1 (2.9)
- Right lower paratracheal and AP window nodes	2 (5.9)
- Right lower paratracheal and paraaortic nodes	2 (5.9)
- Left lower paratracheal node and AP window	2 (5.9)
- AP window and subcarinal nodes	1 (2.9)
- Right lower paratracheal node and subcarinal nodes	1 (2.9)
- Right upper paratracheal, AP window and subcarinal nodes	1 (2.9)
- Right and left lower paratracheal, and subcarinal nodes	1 (2.9)
- Right and left lower paratracheal, subcarinal nodes AP window	1 (2.9)
Size of node involvement, median (IQR 1, 3)	1.2 (1, 1.4)
Characteristics of lymph node (%)	
- Isodensity	19 (61.3)
- Hypodensity	0 (0)
- Hyperdensity	6 (19.4)
- Isodensity + hyperdensity	5 (16.1)
- Isodensity + hypodensity	1 (3.2)

SSc = systemic sclerosis; HRCT = high resolution computed tomography; ILD = interstitial lung disease; AP = aortopulmonary

Discussion

The prevalence of MLN in the present study was 56.7% (36 in 60 cases). It was similar to prior studies which varied from 32 to 60%[2-10]. The prevalence in one study was 32%[6]. The lower prevalence in the present series was probably due to using a different CT technique using a thicker collimation of 3 mm with 10 mm intervals and used larger cut point for MLN, 1.2 cm in diameter.

Only the pulmonary fibrosis score was identified as the independent factor associated with the presence of MLN. This result is different from the previous study that reported the severity of pulmonary involvement and that MLN was not significantly different between the predominant fibrosis and the GGO groups. This was probably because the study scored GGO and fibrosis and looked for correlations with MLN separately. The previous study scored both GGO and fibrosis together and just classified them into predominant fibrosis and predominance GGO groups[6].

The possible explanation regarding the absence of associations between MLN, GGO, and total ILD severity scores was that GGO probably represented acute alveolitis or early fibrosis while MLN might be mainly associated with the severity of lung fibrosis probably due to chronic inflammation[14]. Furthermore, since patients showing traction bronchiectasis were prone to be susceptible to infections such as pneumonia occurring with chronic lung disease such as lung fibrosis, MLN might then be found prevalent in patients with lung fibrosis[6].

The most common MLN location of the present study was the right lower paratracheal location, which was likely to be the same location as described in Garber et al[6] study. At that time, the position of the lymph node was recorded using the lymph node locations as described by Ingram et al[15]. It is likely to be the right lower paratracheal lymph node location in the present AJCC 7th lymph node classification for lung cancer.

Steroid use was not associated with the presence of MLN in the present study. This is in contrast to one report that found the lower prevalence of MLN in cryptogenic fibrosing alveolitis (CFA)

Table 3. Factors associated with positive node using univariate logistic regression analyses

Variables	Positive node	Negative node	OR	95% CI	*p*-value
Age (years), mean (SD)	51.1 (12.3)	46.1 (9.6)	1.1	0.9, 1.1	0.09
Male (%)	12 (35.3)	5 (19.2)	2.3	0.7, 7.6	0.2
Types of SSc (%)					
Limited	10 (29.4)	7 (26.9)	1.0	-	-
Diffuse	24 (70.6)	19 (73.1)	0.9	0.3, 2.8	0.8
Steroid use (%)	13 (38.2)	11 (42.3)	0.8	0.3, 2.4	0.8
No. of organ involvement, mean (SD)	3.5 (1.3)	3.1 (1.2)	1.3	0.9, 2.0	0.2
Presence of ILD (%)	32 (94.1)	24 (92.3)	1.3	0.2, 10.1	0.8
GGO	7 (4.8)	6.7 (5.3)	1.0	0.9, 1.1	0.9
Pulmonary fibrosis score, mean (SD)	5.2 (3.3)	3.1 (3.2)	1.2	1.1, 1.4	0.02*
Total severity score	12.5 (6.6)	9.8 (6.6)	1.1	0.9, 1.2	0.1
CT perfusion score					
Grade 0	2 (5.9)	2 (7.7)	1.0	-	-
Grade 1	6 (17.7)	10 (38.4)	0.6	0.1, 5.4	0.7
Grade 2	18 (52.9)	12 (46.2)	1.5	0.2, 12.1	0.7
Grade 3	8 (23.5)	2 (7.7)	4.0	0.3, 48.7	0.3

Table 4. Factors associated with positive nodes using multiple logistic regression analyses

Variables	Adjusted OR	95% CI	*p*-value
Age	1.0	0.9, 1.1	0.1
Pulmonary fibrosis score	1.2	1.1, 1.4	0.03*

patients who took steroid[11]. The probable reasons are the differences in the studied populations since in that report, patients received high doses of steroids (1.5 g/kg/day) with the maximum dose of 110 mg/day whereas most of the patients in the present study received 30 mg/day of prednisolone or less. The effects of steroids were then not shown to be of statistical significance.

There were some limitations of the present study. Firstly, the sample size was small. There were; however, greater numbers than many studies. Pooling patients from different regions together might be worthwhile. Secondly, selection bias could occur as the patients in the present study were those suspected of pulmonary involvement, the prevalence of MLN might have then been underestimated since asymptomatic patients who had MLN did not undergo HRCT of the lung.

Conclusion

MLN was prevalent in patients with SSc. MLN in SSc patients is not indication that the patients have active intrathoracic infections or a malignancy. If the characteristics of MLN are different from our study such as an excessive number of MLN, atypical locations or isolated hypodense MLN, other causes of intrathoracic diseases should be investigated.

What is already known on this topic?

Many studies had shown association between ILD with MLN but most of them included all causes of ILD. Only a few studies focus on ILD in SSCs patients and MLN. One study reported that the occurrence of enlarged mediastinal lymph nodes in SSc was correlated with the extent of pulmonary disease as judged by HRCT[6]. However, this study used an old HRCT protocol, which is different from present time protocol. In the old HRCT protocol, the collimation was thicker and the interval gap was larger. These differences might cause an underestimation of the lymph node enlargement and may affect the results.

Several studies had shown that MLN was prevalent in patients with SSc. But the characteristic of lymphadneopathy in SSCs has not been described. Understanding the characteristics of MLN in SSc would help the radiologist to narrow differential diagnoses.

What this study adds?

The objective was to look for prevalence of MLN factors that correlate with MLN in SSc patients. The present study showed that pulmonary fibrosis was the only independent factor that was associated with MLN in SSc. This result was different from the previous study. We also described characteristics of

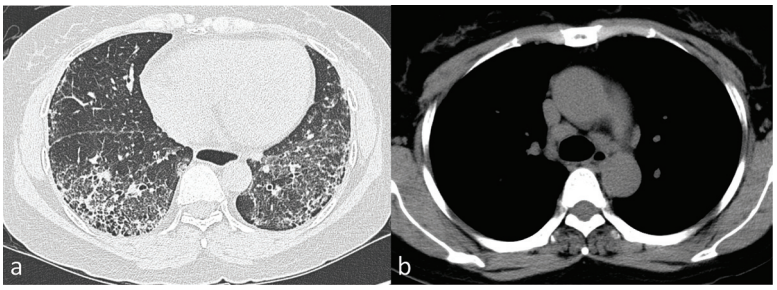

Fig. 1 A 42-year-old woman with SSc. (a) Axial view of HRCT scan shows evidence of septal thickening, traction bronchiectasis and GGO in both basal lungs. (b) Axial view of mediastinal window CT scan demonstrating isodense lymph node enlargement in right and left lower paratracheal areas.

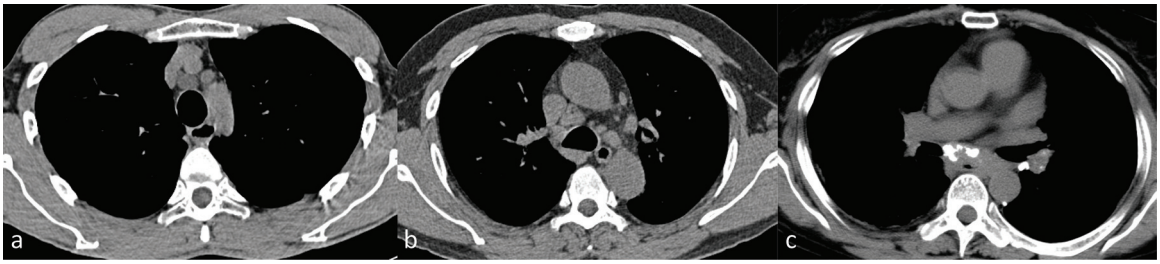

Fig. 2 Axial view of CT scans demonstrating the mediastinal lymphadenopathy. (a) Hypodense lymphadenopathy at right lower paratracheal in 41-year-old male SSc patient. (b) Isodense lymphadenopathy at right and left paratracheal in 46-year-old male SSc patient. (c) Calcified lymph nodes at subcarinal area in a 49-year-old female SSc patient.

MLN including size of the MLN, location, density of lymph nodes, and number of lymph nodes enlargement. If the characteristics of MLN in SSCs are different from our study, other causes of intrathoracic diseases should be investigated.

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Potential conflicts of Interest

None.

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ภาวะต่อมน้ำเหลืองเมดิแอสตินัมโตในผู้ป่วยโรคผิวหนังแข็ง

ปาณยา ทุมสท้าน, จิตราภรณ์ วงศ์วิวัฒน์ไชย, ชลิดา อภินิเวศ, วัลลภ เหล่าไพบูลย์

ภูมิหลัง: *ปัจจุบันมีการศึกษาที่เกี่ยวกับลักษณะต่อมน้ำเหลืองเมดิแอสตินัมโตในผู้ป่วยโรคผิวหนังแข็ง (SSc) มีไม่มาก การทราบลักษณะของต่อมน้ำเหลืองที่โตในผู้ป่วยกลุ่มนี้จะทำให้รังสีแพทย์ให้การวินิจฉัยภาพการตรวจ high resolution CT (HRCT) ของปอดได้อย่างมั่นใจมากขึ้น*

วัตถุประสงค์: *เพื่อหาความชุกของการเกิดต่อมน้ำเหลืองเมดิแอสตินัมโตในผู้ป่วย SSc อธิบายลักษณะของต่อมน้ำเหลืองที่โต และศึกษาหาปัจจัยที่สัมพันธ์กับการเกิดต่อมน้ำเหลืองโต*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังจากเวชระเบียนและภาพ HRCT ผู้ป่วย SSc ทุกรายที่ได้รับการตรวจ HRCT ณ โรงพยาบาลศรีนครินทร์ ในระหว่าง พ.ศ. 2552 ถึง พ.ศ. 2554 และหาความสัมพันธ์ระหว่างการเกิดต่อมน้ำเหลืองโตกับปัจจัยต่าง ๆ โดยใช้สถิติ univariate และ multivariate logistic regressions*

ผลการศึกษา: *จากผู้ป่วยทั้งหมด 60 ราย เป็นเพศหญิง 71.7% และเป็น diffuse SSc subtype 71.7% ความชุกในการเกิดต่อมน้ำเหลืองเมดิแอสตินัม โตในผู้ป่วย SSc เท่ากับ 56.7% (36 จาก 60 ราย) ตำแหน่งที่พบต่อมน้ำเหลืองที่โตมักจะพบอย่างน้อยสองตำแหน่งขึ้นไป ต่อมน้ำเหลืองส่วนมากมีลักษณะ isodensity (61.3%) ขนาด 1.2 ซม. (inter-quartile range 1, 1.4 ซม.) และพบว่ามีเพียงปัจจัยเดียวที่มีผลต่อการเกิดต่อมน้ำเหลืองโต ได้แก่ pulmonary fibrosis score ค่า adjusted odds ratio of 1.2 (95% confidence interval 1.1, 1.4, p = 0.03)*

สรุป: *ผู้ป่วย SSc สามารถตรวจพบต่อมน้ำเหลืองเมดิแอสตินัมโตได้ โดยปัจจัยที่สัมพันธ์กับการเกิดต่อมน้ำเหลืองโตในผู้ป่วยกลุ่มนี้ได้แก่ค่า pulmonary fibrosis score*
