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Tracheal Wall Thickening Is Associated with the Granulation Tissue Formation Around Silicone Stents in Patients with Post-Tuberculosis Tracheal Stenosis

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Purpose: Tracheal restenosis due to excessive granulation tissue around a silicone stent requires repeated bronchoscopic interventions in patients with post-tuberculosis tracheal stenosis (PTTS). The current study was conducted to identify the risk factors for granulation tissue formation after silicone stenting in PTTS patients. **Materials and Methods:** A retrospective study was conducted between January 1998 and December 2010. Forty-two PTTS patients with silicone stenting were selected. Clinical and radiological variables were retrospectively collected and analyzed. **Results:** Tracheal restenosis due to granulation tissue formation were found in 20 patients (47.6%), and repeated bronchoscopic interventions were conducted. In multivariate analysis, tracheal wall thickness, measured on axial computed tomography scan, was independently associated with granulation tissue formation after silicone stenting. Furthermore, the degree of tracheal wall thickness was well correlated with the degree of granulation tissue formation. **Conclusion:** Tracheal wall thickening was associated with granulation tissue formation around silicone stents in patients with post-tuberculosis tracheal stenosis.

Key Words: Trachea, tuberculosis, stenosis, bronchoscopy, intervention, stents

INTRODUCTION

Tracheal tuberculosis is a relatively uncommon form of *Mycobacterium tuberculosis* (*M. tuberculosis*) infection, which may result in symptomatic airway stenosis or respiratory failure.[1] Once fibrotic stenosis of the central airway occurs, they all are known to remain in a fibrostenotic state despite a full course anti-tuberculosis therapy.[2] Furthermore, there is no effective medical treatment, including steroids or other anti-inflammatory agents, to facilitate airway patency.[3]

For patients with post-tuberculosis tracheal stenosis (PTTS), bronchoscopic interventions have been used to resolve airway stenosis, including bougienation, ballooning, laser therapy and silicone stenting.[4] Among these modalities, silicone stenting following mechanical dilatation of the airway is the corner stone in the

treatment of benign tracheobronchial stenosis.[5,6]

Although silicone stent placement is an effective and important therapeutic modality, some patients undergo repeated bronchoscopic interventions for the removal of excessive granulation tissues around the silicone stent which may lead to life-threatening hypoxia in the acute phase.[7] Airway restenosis caused by granulation tissue formation occurs in nearly 40-71% of patients who receive silicone stent placement.[7,8] Thus, it is necessary to ascertain associated factors for granulation tissue formation in PTTS patients.

Some investigators suggested that certain radiologic features in benign central airway stenosis are associated with the clinical outcomes of bronchoscopic intervention.[9] However, there was no established risk factor or associated finding of granulation tissue formation after airway stenting in PTTS patients. In addition, there is no previous study of the tracheal morphology in the fibrotic stage of tracheobronchal tuberculosis. The aim of this study was to identify the risk factors associated with tracheal restenosis due to excessive granulation tissues around a silicone stent in PTTS patients, by the use of clinical variables and tracheal computed tomography (CT) scans.

MATERIALS AND METHODS

Study subjects

A retrospective study was conducted at the Samsung Medical Center (a 1966-bed referral hospital in Seoul, Korea) between January 1998 and December 2010. The Institutional Review Board of the Samsung Medical Center approved the analyses of clinical and radiologic data.

During the study period, 60 PTTS patients underwent bronchoscopic interventions for symptomatic tracheal stenosis. The exclusion criteria were as follows: 1) less than 18 years of age; 2) history of previous bronchoscopic intervention in other hospitals; and 3) no available chest CT scan within two weeks before the bronchoscopic intervention.

Protocol for airway intervention

Tracheal stenosis was identified by using plain chest film, CT images or fiberoptic bronchoscopy. Therapeutic bronchoscopy for PTTS patients was indicated when symptoms, related to airway obstruction, were aggravated or newly developed. Prior to the first therapeutic bronchoscopy, a pulmonary function test (PFT) was performed in most patients except who needed an urgent intervention for life-threatening airway obstruction. A therapeutic bronchoscopy was performed in the standard manner described in previous publications.[5,10] A representative case of PTTS is presented in Fig. 1. Briefly, endotracheal intubation was done using a rigid Hopkins bronchoscope tube (Karl-Storz, Tuttlingen, Germany) under general anesthesia induced by intravenous propofol. Then, the initial exploration of the tracheobronchial tree was followed by fiberoptic bronchoscope (EVIS BF 1T240, Olympus, Tokyo, Japan) through a rigid bronchoscope tube. After identification of tracheal stenosis, all patients underwent mechanical airway dilatation with rigid tube, ballooning (Boston Scientific, Natick, MA, USA), or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Laser-Sonics, Milpitas, CA, USA) cauterization.

Tracheal silicone stent

A Dumon stent (Novatech, Aubagne, France) or N-stent (E1S, Seoul, Korea) was inserted during the rigid bronchoscopy as per the following indications: 1) the length of the stenotic segment at >2 cm; 2) recurrent airway stenosis; or 3) trecheobronchial malacia of the dilated lumen at > 180°. An adequate size of stent was selected as determined by the interventional pulmonologist. Generally, stent removal was considered after 6-12 months of a stable clinical course by a physician's decision.

Definitions

Active tuberculosis was defined by either: 1) a smear or culture positive tuberculosis from sputum or bronchial washings or 2) radiographic, current clinical, or laboratory evidence sufficient to support a medical diagnosis of tuberculosis for which treatment is indicated. Previous tuberculosis was defined as a definite history of active tuberculosis.

Tracheal restenosis due to granulation tissue formation was defined as a mass of fibrous connective tissue at the proximal or distal end of the stent or through the stent interstices that were profuse enough to develop airway symptoms and require re-intervention. The degree of granulation tissues formation was determined to be the number of interventions due to tracheal restenosis caused by granulation tissue formation.

For statistical analysis, we divided the patients into two groups contingent on granulation tissue formation around the silicone stent: the restenosis group was defined as patients who had restenosis due to granulation tissue overgrowth, which was enough to perform additional interventions, and no restenosis group was defined as patients who

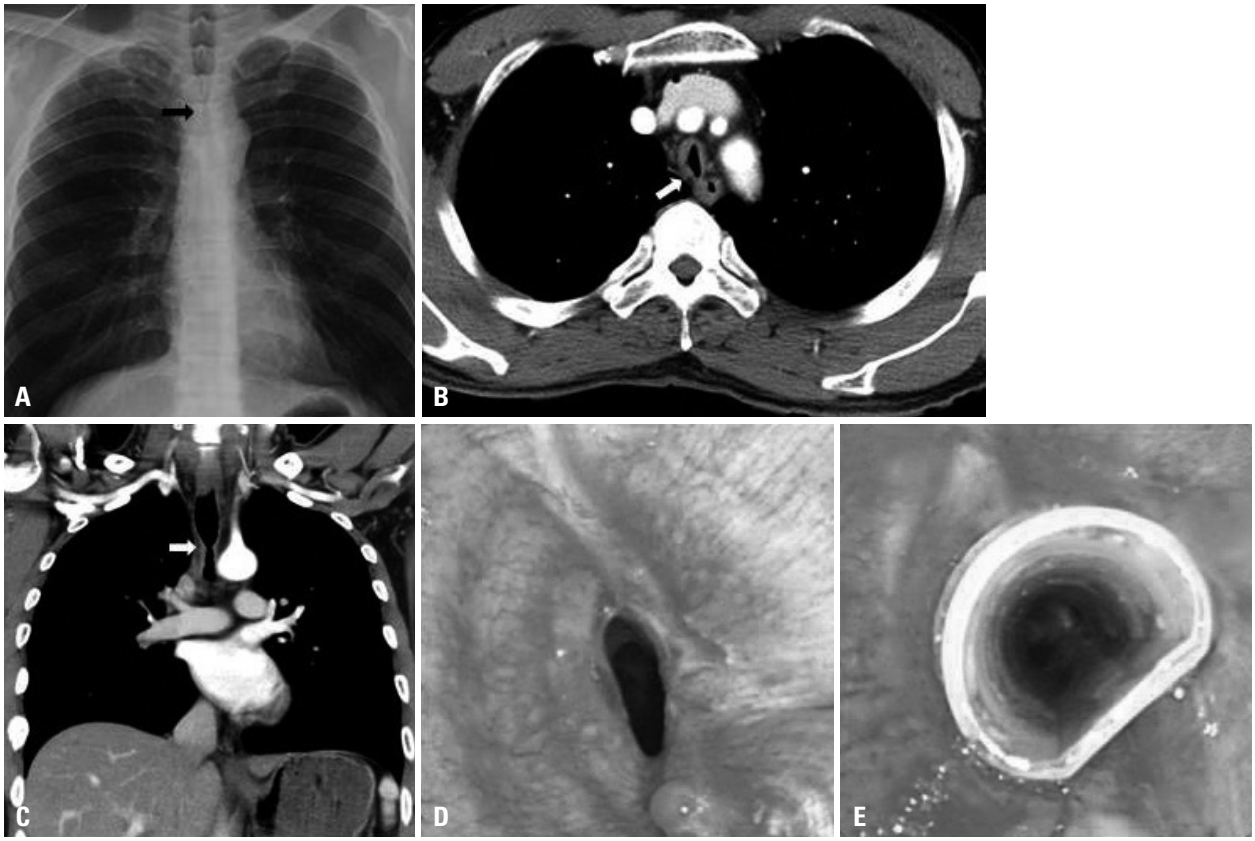

Fig. 1. A representative case of post-tuberculosis tracheal stenosis. (A) The chest radiograph shows narrowing of the lower third of the trachea (black arrow). (B and C) Computed tomography revealed tracheal stenosis (white arrow) at the level of the T3 vertebra. Tracheal wall thickening (5.1 mm) was found at the stenotic lesion. (D and E) A rigid bronchoscopy was performed to reverse airway patency. The lower trachea was 5×10 mm narrowed by a fibrous stricture. After bougienation, a silicone stent was inserted (outer diameter, 14 mm; inner diameter, 12 mm; length, 40 mm).

had no restenosis due to granulation tissue overgrowth.

CT analyses

Two radiologists with a 5 year experience in radiology, who were blinded to the clinical outcomes, analyzed chest CT scans. All CT indices were measured on inspiration CT image.

The following CT characteristics were evaluated: 1) the anteroposterior and transverse diameter at the level of fibrotic stenosis; 2) anteroposterior and transverse diameter at the normal extrathoracic upper trachea level; 3) the length of tracheal stenosis; 4) total tracheal length 5) tracheal wall thickness at the level of fibrotic stenosis; 6) the distance from the tracheal stenosis to the carina; 7) the ratio of the stenosis to the normal upper tracheal diameter (anteroposterior and transverse diameter, respectively); and 8) the ratio of the stenotic length to total tracheal length.

Statistical analysis

The Mann-Whitney U test was used for continuous variables because data were not normally distributed. Comparisons between proportions were performed using the Pearson chi-square test or Fisher's exact test. Thereafter, a multivariate logistic regression analysis was used to re-examine the factors with significance shown by univariate analysis. The Spearman's correlation coefficients, rho (ρ), were used to assess whether there was a relationship between the number of interventions due to granulation tissue formation and various variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Among all the PTTS patients, 18 patients were excluded: 1) 9 received only mechanical dilatation without stent placement; 2) 6 had no available chest CT; and 3) 3 had a previous bronchoscopic intervention in other medical center. Fig. 2 shows the treatment outcomes of 51 PTTS patients who underwent therapeutic bronchoscopy with or without

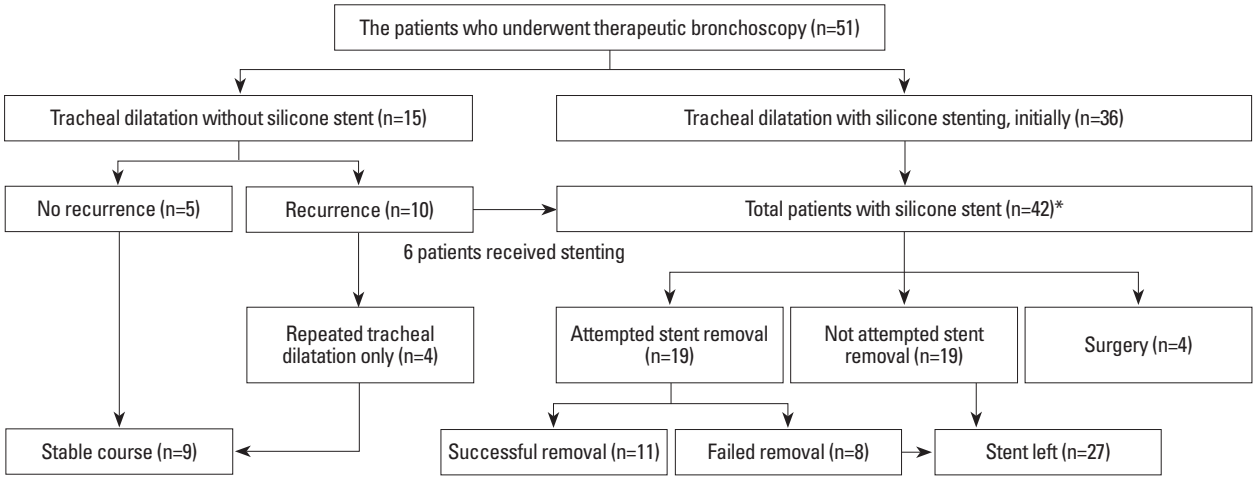

Fig. 2. The therapeutic diagram of patients with post-tuberculosis tracheal stenosis. *Repeated bronchoscopic interventions were performed in an as-needed base according to the physician's decision.

silicone stenting. Silicone stents were inserted in 42 patients: 36 received at first intervention and 6 at second or third intervention.

In 42 study population with silicone stenting, stent removal was attempted on 19 patients (45.2%): 11 had stable clinical course after stent removal, however, 8 had received re-intervention for recurrent stenosis. In addition, there were 4 patients (9.5%) who received surgery for refractory tracheal stenosis.

Clinical characteristics

Table 1 shows the demographics and baseline characteristics of the 42 PTTS patients with silicone stent insertion. The median age was 39 years [interquartile rage (IQR), 31-50)]. Thirty-seven of the 42 patients (88.1%) were female and there was 1 patient with a smoking history.

Pulmonary function tests were performed in 26 patients (61.9%) before the therapeutic bronchoscopy. Sixteen patients, who presented with severe dyspnea or underwent urgent intervention, could not perform spirometry. The mean forced expiratory volume in one second (FEV1) % predicted was 43 (IQR, 31-67) and 23 patients (88.5%) had obstructive PFT patterns described as FEV1 <80% predicted and FEV1/forced vital capacity ≤70%. Only 3 patients (11.5%) had normal PFTs. After the interventions, significantly great increase of the median FEV1 % predicted (74%; IQR, 63-84) was observed.

Bougienation was the most frequently used airway dilatation method combined with a silicone stent (35 patients, 83.3%). Ballooning and Nd:YAG laser were used in 14 patients (33.3%) and 7 patients (16.7%), respectively. Thirty-three patients had N-stent placement (78.6%) and 9 patients had Dumon stents placed (21.4%). Tracheal restenosis due to granulation tissue formation around the silicone stent were found in 20 patients (47.6%), and those were removed by repeated bronchoscopic intervention: twelve patients received only one repeated intervention and 8 received two or more.

CT findings and indices

All patients underwent CT scan within 2 weeks before initial intervention. Thirty-five (83%) of total patients received CT scanning within 1 week before initial intervention.

Most patients had tracheal stenosis at the middle to lower trachea: twenty-four patients (57.1%) had tracheal stenosis at the lower third level of the trachea; 16 (38.1%) had at middle third; and only 2 (4.8%) had at the upper third. Table 2 shows the results of the 11 CT indices of the total study population.

Analysis for factors associated with granulation tissue

Univariate analysis revealed that multiple factors were associated with granulation tissue formation (Table 1 and 2). The median luminal diameter change after the intervention was significantly larger in the no restenosis group as compared to the restenosis group (6.0 mm vs. 4.0 mm, p=0.040). The median length of stenosis in the no restenosis group was 35.0 mm which was significantly shorter than the restenosis group (p=0.045). The median tracheal wall thickness of the stenotic region in the no restenosis group was significantly thinner than the restenosis group (3.9 mm vs. 6.6 mm, p=0.005).

Various CT ratios were calculated from measured data. The ratio of the stenotic length to the total tracheal length was statistically different between the two groups (p=0.044).

Table 1. Baseline Characteristics of Patients with Silicone Stenting

Characteristics	Total patients (n=42)	No restenosis group (n=22)	Restenosis group (n=20)	*p* value*
Age, yrs	39 (31-50)	46 (32-60)	36 (30-45)	0.064
Female gender	37 (88.1)	17 (77.3)	18 (90.0)	0.247
Active TB on first IT	1 (2.4)	1 (4.5)	0 (0)	0.524
Anti-TB medication on first IT	20 (47.6)	9 (40.9)	11 (55.0)	0.361
Interval from TB medication to first IT, months	6.8 (3.4-36.4)	7.3 (3.7-38.3)	6.1 (3.3-18.7)	0.481
Interval from symptom onset to first IT, months	2.7 (0.7-7.6)	2.5 (0.8-5.6)	2.7 (0.7-12.0)	0.910
Baseline PFTs†				
FEV1, percentage predicted	43 (31-67)	45 (34-70)	41 (28-66)	0.646
FVC, percentage predicted	88 (75-94)	89 (77-97)	88 (61-94)	0.540
FEV1/FVC ratio	48 (29-57)	36 (29-54)	50 (29-58)	0.540
PFTs after intervention				
FEV1, percentage predicted	74 (63-84)	79 (75-84)	70 (56-77)	0.077
FVC, percentage predicted	94 (85-108)	92 (86-109)	95 (83-108)	0.799
FEV1/FVC ratio	66 (52-73)	65 (62-73)	67 (48-75)	0.646
PFT change after intervention				
FEV1, percentage predicted	21 (11-40)	30 (16-46)	18 (6-32)	0.148
FVC, percentage predicted	8 (0-16)	3 (-2-15)	8 (0-20)	0.443
FEV1/FVC ratio	18 (5-28)	25 (8-37)	12 (2-28)	0.237
Results of initial airway dilatation				
Ballooning	14 (33.3)	7 (31.8)	7 (35.0)	0.827
Laser therapy	7 (16.7)	3 (13.6)	4 (20.0)	0.444
Bougienation	35 (83.3)	19 (86.4)	16 (80.0)	0.444
Length of silicone stent, mm	50 (40-50)	50 (40-50)	50 (40-50)	0.749
Dumon stent insertion	9 (21.4)	4 (18.2)	5 (25.0)	0.435
N-stent insertion	33 (78.6)	18 (81.2)	15 (75.0)	0.435
Tracheal diameter change after IT, mm	5.5 (4.0-6.0)	6.0 (5.0-6.0)	4.0 (4.0-6.0)	0.040
The number of ITs per patient	2 (1-5)	1 (1-1)	4 (2-9)	<0.001

TB, tuberculosis; IT, intervention; PFT, pulmonary function test; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.
*Univariate analysis was performed to compare no restenosis group and restenosis group.
†Spirometry was performed in 26 of 42 patients before therapeutic bronchoscopy.

Other calculated CT ratios were not different between the two groups.

A multivariate logistic regression model was used to determine the independent factors for granulation tissue formation (Table 3). Among the variables assessed, the tracheal wall thickness was independently associated with granulation tissue formation after silicone stenting [odd ratio, 1.937; 95% confidence interval (CI), 1.131-3.320; p=0.016]. Linear correlation analysis shows the positive correlation between the number of interventions due to granulation tissue formations and tracheal wall thickness (ρ=0.662). Receiver operating characteristic curve analysis revealed fair predictive value of tracheal wall thickness for the occurrence of granulation tissue formation (p=0.005, area under the curve= 0.756) (Fig. 3). In addition, the tracheal diameter change after intervention was independently associated with granulation tissue formation (odd ratio, 0.437; 95% CI, 0.212-0.904; p=0.026), however, the correlation with the number of interventions due to granulation tissue formations was weak (ρ=-0.197).

DISCUSSION

Previous studies reported that granulation tissues in the tracheobronchial tree are associated with airway infection, stimuli from a foreign body (including an airway stent) or excessive radial force to trachea induced by an airway stent.[7,8,11,12] However, little information is available on the risk factors of granulation tissue formation after airway stenting.

The present study was designed to evaluate the risk factors for granulation tissue formation after silicone stent placement

Table 2. The CT Indices in Patients with Silicone Stenting

CT index*	Total patients (n=42)	No restenosis group (n=22)	Restenosis group (n=20)	*p* value†
Normal tracheal diameter‡				
Anteroposterior diameter	18.2 (16.9-19.2)	17.8 (17.2-18.6)	18.4 (15.6-20.0)	0.588
Transverse diameter	15.2 (13.7-16.3)	15.2 (13.4-16.2)	15.0 (13.7-16.9)	0.554
Stenosis size				
Anteroposterior diameter	9.2 (7.2-11.7)	9.4 (7.2-12.7)	8.9 (7.2-11.5)	0.358
Transverse diameter	6.8 (5.9-8.1)	7.0 (6.4-8.2)	6.8 (5.2-7.3)	0.279
TTL	100.0 (95.0-110.0)	105.0 (95.0-110.6)	98.8 (91.9-109.4)	0.311
Length of tracheal stenosis	40.0 (30.0-50.0)	35.0 (25.0-40.0)	42.5 (35.9-51.9)	0.045
Tracheal wall thickness of stenosis	5.0 (3.7-6.93)	3.9 (3.3 –5.3)	6.6 (4.1-8.1)	0.005
Distance from stenosis to carina	36.5 (20.0-51.3)	35.0 (15.0-51.3)	39.0 (23.5-53.8)	0.659
Ratio of stenosis to normal diameter‡				
Anteroposterior diameter ratio	0.51 (0.43-0.64)	0.57 (0.43-0.68)	0.50 (0.42-0.59)	0.154
Transverse diameter ratio	0.44 (0.39-0.53)	0.47 (0.40-0.55)	0.43 (0.37-0.49)	0.144
Ratio of the stenotic length to TTL	0.36 (0.28-0.49)	0.33 (0.24-0.40)	0.41 (0.34-0.61)	0.044

TTL, total tracheal length.
*All presented diameters were described as millimeters.
†Univariate analysis was performed to compare no restenosis group and restenosis group.
‡The normal tracheal diameters were measured at the middle level of extrathoracic trachea in the axial CT image, which were preserved from fibrotic stenosis.

Table 3. Multivariate Analysis of the Factors Associated with Excessive Granulation Tissue Formation*

	Odds ratio	95% CI	*p* value	ρ†
Age	0.965	0.908-1.025	0.245	-
Gender	0.561	0.206-18.411	0.561	-
Diameter change after intervention	0.437	0.212-0.904	0.026	-0.197
Length of tracheal stenosis	0.951	0.742-1.219	0.693	-
Ratio of the stenotic length to total tracheal length	24.779	0.000-44.663	0.519	-
Tracheal wall thickness	1.937	1.131-3.320	0.016	0.662

CI, confidence interval.
*Presented indices were analyzed as continuous variables except for gender.
†Spearman's rho (ρ) was calculated with the number of interventions due to granulation tissue formation and significant variables in multivariate analysis.

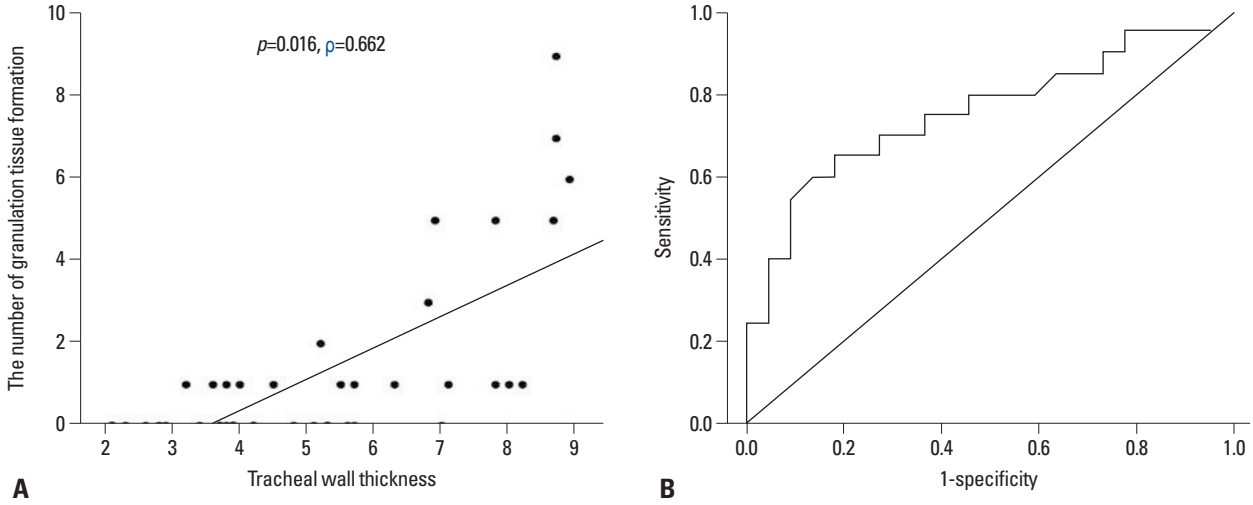

Fig. 3. Relationship between the number of granulation tissue formations and tracheal wall thickness. (A) Scatter diagram shows positive correlation between the number of granulation tissue formation and tracheal wall thickness (p=0.016, ρ=0.662). (B) Receiver operating characteristic curve for predicting the occurrence of granulation tissue formation (p=0.005, area under the curve=0.756).

in PTTS patients. Our results showed that tracheal wall thickness was independently associated with granulation tissue formation around the silicone stent. Furthermore, the degree of tracheal wall thickness fairly predicted the development of granulation tissue in receiver operating characteristic curve analysis and well correlated with the number of intervention due to granulation tissue formation. Although the statistical power was weak, the degree of difference in the tracheal luminal diameter before and after the stenting might also be associated with granulation tissue formation.

For the tracheal wall thickness of PTTS patients, we could apply two hypotheses. First, the thickened tracheal wall was not terminated inflammatory or in a healing process from *M. tuberculosis* infection or its sequela, although the bronchoscopic findings indicated fibrotic disease. This ongoing or inflammatory reaction is accelerated through airway stent insertion that produces pressure to the tracheal wall or stimulates the tracheal wall as a foreign body. Therefore, excessive granulation tissue developes. In addition, mechanical dilatation itself is affected as a physical injury that promots a healing response in not fully recovered tissue.

The normal tracheal wall is usually measured at 1-3 mm in a CT image.[13] The wall thickness is increased under active tuberculosis of the tracheobronchial tree and decreases in the fibrotic or recovered state.[14] In the current study, patients within normal range of tracheal wall thickness (≤h3 mm) had no granulation tissue after stenting. However, some patients with a tracheal wall thickness above 3 mm, which might not have fully recovered from *M. tuberculosis* induced inflammation, had granulation tissue overgrowth. These patients received a repeated rigid bronchoscopy to remove granulation tissue and there was indeed a trend of an increase in the number of interventions as the wall thickness increased.

A second hypothesis was that an overgrowth of granulation tissue was associated with personal susceptibility to an excessive healing response in the respiratory tract from infection, physical injury or foreign body stimuli. Certain patients might possess the nature of excessive or abnormal healing, and initial *M. tuberculosis* infection thickened the tracheal wall more than normal patients, therefore, these were maintained in a fibrotic stage due to dense fibrosis and profound connective tissue deposition. Thereafter, granulation tissue overgrowth occurred after silicone stenting that was additional trigger of the healing process induced by physical injury, foreign body stimulation or both.

Some investigators suggested a genetic susceptibility with aberrations in the healing process.[15] However, there was no previous study to identify personal susceptibility of the abnormal healing process in the respiratory tract. Further research into molecular or genetic rationale is required.

There are several limitations in the current study. The first limitation is that the study was designed in a retrospective manner. Authors discovered the correlation of tracheal wall thickness and granulation tissue formation, however, the causal relationship is uncertain. Further well-designed prospective studies are required to ensure our results. Second, although PTTS is a rare condition, the study sample was small. To the best of our knowledge, however, previous studies were designed with a diverse group of patients, a majority of patients with bronchial stenosis and small number of tracheal stenosis, as a fibrotic sequel of tuberculosis. The number of patients in the present study was larger than previous studies on PTTS patients.

In summary, the results of current study indicate that tracheal wall thickness is associated with the granulation tissue formation after silicone stenting in patients with PTTS. These findings might be useful for pulmonary interventionists, however, further prospective research is needed to establish the risk factors of granulation tissue overgrowth around silicone stent.

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