Thoracic endometriosis-related pneumothorax distinguished from primary spontaneous pneumothorax in females

（女性の原発性自然気胸と胸腔内子宮内膜症関連気胸の鑑別）

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ABSTRACT

Purpose: Thoracic endometriosis-related pneumothorax (TERP) is a secondary condition specific for females, but in a clinical setting, TERP is often difficult to distinguish from primary spontaneous pneumothorax (PSP) based on a relationship between the dates of pneumothorax and menstruation. The aim of this study is to clarify the clinical features of TERP as compared with PSP.

Methods: We retrospectively reviewed the clinical and histopathological files of female patients with pneumothorax who underwent video-assisted thoracoscopic surgery in the Pneumothorax Research Center during the six-year period from January 2005 to December 2010. We analyzed the clinical differences between TERP and PSP.

Results: The study included a total of 393 female patients with spontaneous pneumothorax, of whom 92 (23.4%) were diagnosed as having TERP and 33.6% (132/393) as having PSP. We identified four factors (right-sided pneumothorax, history of pelvic endometriosis, age ≥ 31 years old and no smoking history) that were statistically significant for predicting TERP and assigned 6, 5, 4, and 3 points, respectively, to establish a scoring system with a calculated score from 0 to 18. The cut-off values of a calculated score ≥ 12 yielded the highest positive predictive value (86.0% with a 95% confidence interval (CI) of 81.5% - 90.5%) for TERP and negative predictive value (95.2% with 95% CI of 92.3% - 98.0%) for PSP.

Conclusions: TERP has several distinct clinical features from PSP. Our scoring system consists of only four clinical variables that are easily obtainable and enables us to suspect TERP in female patients with pneumothorax.

Key words: primary spontaneous pneumothorax, thoracic endometriosis-related pneumothorax, thoracic endometriosis, pneumothorax

INTRODUCTION

Spontaneous pneumothorax is classified into primary (PSP) and secondary categories. PSP refers to a spontaneously occurring air leakage into the pleural space in patients with no clinically apparent underlying lung disease [1]. The diagnosis of PSP is confirmed histopathologically with subpleural blebs and bullae and no obvious abnormality in pulmonary parenchyma [2]. Catamenial pneumothorax is a condition limited to females and reported to account for about 20 to 30% of women with pneumothorax [3, 4]. It is defined simply by the onset of pneumothorax during a menstrual cycle: the pneumothorax that occurs between 24 hours before and 72 hours after the initiation of menses [5]. Because catamenial pneumothorax is usually caused by thoracic endometriosis [6, 7], a large part of catamenial pneumothorax is diagnosed as thoracic endometriosis-related pneumothorax (TERP) after thoracic surgery. However, catamenial pneumothorax may include female patients with PSP that happens to occur in the peri-menstrual period.

TERP is defined as pneumothorax due to thoracic endometriosis, and the diagnosis of TERP requires histopathological confirmation [5]. Generally, ectopic endometrial tissues are found in the diaphragm in TERP, whereas no abnormality in pulmonary parenchyma is apparent. The mechanism of TERP has been speculated as follows: 1) Air enters into the thoracic cavity from the peritoneum through a

diaphragmatic defect caused by the implantation of endometrial tissues. This air in the peritoneum may be from outside the body and pass through ovarian tubes [8]. 2) Alternatively, air enters into the thoracic cavity from the airway through a defect of visceral pleura caused by the implantation of endometrial tissues [9, 10].

Until recently, TERP had been thought to develop only as catamenial pneumothorax. However, Alifano et al. recently reported that 37.9% of TERP cases developed as non-catamenial pneumothorax [11]. Accordingly, TERP is difficult to distinguish from PSP based on the relationship between the calendar dates of pneumothorax and menstruation; theoretically, catamenial TERP, non-catamenial TERP, catamenial PSP, and non-catamenial PSP exist. Furthermore, TERP is virtually indistinguishable from PSP based on the findings of imaging tests such as chest X-ray and computed tomography (CT), because the amount of ectopic endometrial tissue implanted within the respiratory system is too small for detection by such examinations [5]. A preferable scenario is that TERP is suspected before surgery, because the approaches for therapy as well as the recurrence rate [12, 13] are quite different between TERP and PSP.

As previously described, the clinical features of TERP are right-sided pneumothorax and a history of pelvic endometriosis [5]. In contrast, patients with PSP tend to be tall [14] and usually have a smoking history [15, 16]. However, few reports

directly compare the clinical features of TERP and PSP nor do they clarify the significance of each clinical variable. The aim of this study is to clarify the clinical features of TERP as compared with PSP.

METHODS

Study population

The clinical and histopathological files of all female patients who underwent video-assisted thoracoscopic surgery (VATS) in the Pneumothorax Research Center during the six-year period from January 2005 to December 2010 were retrospectively reviewed. The patients who were histopathologically diagnosed as having TERP or PSP were included in this study. According to Alifano et al., we made a diagnosis of TERP when the existence of endometrial stroma or the endometrial glands in the resected diaphragm and/or lung tissue was confirmed immunohistochemically by the presence of strong nuclear staining for either estrogen or progesterone receptors [11]. The diagnosis of PSP was made when 1) pneumothorax occurred in otherwise healthy individuals with normal or essentially normal underlying lungs on CT images of the chest, and 2) blebs and/or bullae were histologically confirmed in the resected lung specimen. In patients with PSP, we were unable to collect information from medical records on the relationship between the occurrence of pneumothorax and menstrual cycle.

For patients with TERP and PSP, we compared the ages, pneumothorax side, height, body weight, smoking habits, history of pelvic endometriosis, number of pneumothorax episodes before surgery, duration of follow-up after surgery and postoperative recurrence rate. We assigned the scores to each clinical variables found to be an independent predictor for the diagnosis of TERP, weighted according to the beta-coefficients from the multivariate logistic model [17]. We calculated a total score for each patient and analyzed the performance characteristics of the score for the diagnosis of TERP. The study was approved by the institutional review board of Nissan Tamagawa Hospital (approval number 12-012).

Statistical analysis

The quantitative data are presented as means ± SD. The differences between the patients with TERP and PSP were analyzed using the Chi-square test for categorical variables and student's *t*-test for quantitative variables. A multiple logistic regression analysis was used to assess the role of several variables as predictive factors for TERP. The contribution of each potential predictive factor was denoted by an odds ratio and the associated 95% confidence interval (CI). A receiver operating characteristic (ROC) curve was used to analyze the probability of TERP diagnosis in dependence on the calculated score. A value of $p < 0.05$ was considered to be significant. A statistical

software package (JMP, version 10.0.2; SAS Institute; Cary, NC, USA) was used for the statistical analysis.

RESULTS

A total of 562 female patients with spontaneous pneumothorax was admitted for treatment during the six-year study period. Of these, 393 patients underwent VATS for pneumothorax. Ninety-two (23.4%) of the 393 patients were diagnosed as having TERP and 33.6% (132/393) as having PSP. Thirty (32.6%) of the 92 patients with TERP had catamenial pneumothorax with the remainder (62/92, 67.4%) classified as non-catamenial.

Characteristics of the study population are summarized in Table 1. The patients with TERP showed significantly distinct features differing from those in the patients with PSP. The TERP group were older, shorter and usually had right-sided pneumothorax plus pelvic endometriosis but little or no history of smoking. Many preoperative pneumothorax episodes were noted. One exception was a patient with TERP whose pneumothorax was left-sided. The postoperative recurrence of pneumothorax was more frequently noted in patients with TERP.

To find the predictive factors for TERP, we performed multivariable analysis (Table 2). The right-sided pneumothorax showed the greatest odds ratio among the other

predictive factors, followed by history of pelvic endometriosis, age ≥ 31 years old, no smoking history, the number of preoperative pneumothorax episodes ≥ 4, and height ≤ 159 cm in that order.

Next, we assigned a score to each predictive factor to establish discriminant analysis between TERP and PSP. We excluded two factors, height and the number of preoperative pneumothorax episodes, from the discriminant analysis, since these are likely to be greatly influenced by race and the medical treatment available for pneumothorax; additionally, these two factors interfered with generalizing the outcome. Accordingly, we adopted the four factors to which scores of 3 to 6 were assigned then established a system with calculated scores from 0 to 18 (Table 2). These scores were tested at different cut-off values. The cut-off values of a calculated score ≧12 yielded the highest positive predictive value (86.0% with 95% CI of 81.5% - 90.5%) for TERP and negative predictive value (95.2% with 95% CI of 92.3% - 98.0%) for PSP (Table 3). The ROC curve reflects the accuracy of the diagnostic test: area under the curve was 0.9665 (Figure 1).

DISCUSSION

We found that TERP had distinct clinical features as compared with those of PSP, enabling us to establish a simple scoring system to distinguish TERP from PSP. We

demonstrated that this system had a satisfactorily high positive predictive value for TERP as well as a negative one for PSP. The scoring system utilizes four clinical variables identified here that are easily obtainable by history taking and physical examination: the side of pneumothorax, history of pelvic endometriosis, patient age, and smoking history. These clinical variables have been reported in the literature to be associated with TERP or PSP [5, 14 – 16]. Although a concrete diagnosis of TERP is required for histologic examination of the diaphragm or the lung tissue, the scoring system developed here seems to be suitable for suspecting TERP, thereby reducing the oversight of TERP in female patients with pneumothorax.

Catamenial pneumothorax has been reported to occur on the right side in almost all such cases [5], and only two case reports of left catamenial pneumothorax [9, 18] and two case reports of bilateral catamenial pneumothorax [19, 20] exist. However, those reports lacked information about the histopathological diagnosis of thoracic endometriosis. This study thus provides the first description of a left-sided TERP based on a histopathological diagnosis. PSP has no documented laterality so far [2]. Therefore, the presence of left pneumothorax in females has a high diagnostic value for PSP.

Evaluating the past history of pelvic endometriosis is valuable for diagnosing TERP in female patients with pneumothorax. In this study, 58.7% (54/92) of the patients with TERP had a history of pelvic endometriosis. The percentage of patients with pelvic

endometriosis among those with catamenial pneumothorax varies broadly and is reported to be 18 to 84% [4, 21]. In the majority of patients with thoracic endometriosis, the condition is believed to have spread from pelvic endometriosis [5]. Therefore, the variations in published results are likely due to the different methods used to diagnose pelvic endometriosis. A definitive diagnosis of pelvic endometriosis requires diagnostic laparoscopy, and results from that procedure indicate that the prevalence of pelvic endometriosis among patients of reproductive age is 5 to 10% [22]. In the present study, 2.3% (3/132) of the patients with PSP had a history of pelvic endometriosis.

Previous analyses of catamenial pneumothorax calculated a mean age within the 30s with a range in such patients from 15 to 54 years [5]. However, patients with PSP are often in their early 20s but rarely beyond the age of 40 years [2]. The mean age of patients with TERP examined here was about 10 years older than that of patients with PSP. Therefore, it is important to consider the patient's age when diagnosing TERP in female patients with pneumothorax.

Habitual smoking has been associated with a risk of developing PSP [15, 16]; additionally, patients with PSP tended to be taller than control patients in a previous study [14]. Elsewhere, TERP did not correlate with either the patients' height or habitual smoking [5]. The results of our study are consistent with these findings.

This study has several limitations. First, our subjects were located at the

Pneumothorax Research Center, which is specialized for the treatment of pneumothorax and where many patients with intractable pneumothorax are referred. Accordingly, clinical features for TERP and PSP may be biased. Second, we included only the patients with PSP whose diagnoses were confirmed histologically. Since we usually resect lung tissue only when large and/or multiple bullae are apparent during surgery, the patients with PSP in our study may represent a biased population that is not representative for PSP. Third, we could not have evaluated the significance of the onset of pneumothorax during a menstrual cycle as a factor in differentiating TERP from PSP, because no information about the relationship of pneumothorax onset and menstrual period was obtainable for the patient with PSP. Finally, because this was a retrospective cohort study, a prospective study to validate our scoring system is needed.

In conclusion, we have established a scoring system for the diagnosis of TERP that is based on the assignment of weighted values to easily include four clinical variables. This system has a highly positive predictive value for TERP as well as a negative predictive value for PSP. This logical scheme provides a useful tool for predicting TERP in the care of female patients with pneumothorax.

Conflicts of interest

None of the authors has any conflicts of interest with regard to this study.

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Figure legends

Figure 1. ROC-curve for the prediction of TERP using the calculated score.

Note that the score of 12 gives 93.5% of sensitivity and 89.4% of specificity. The method for calculating the score appears in the footnote of Table 2.

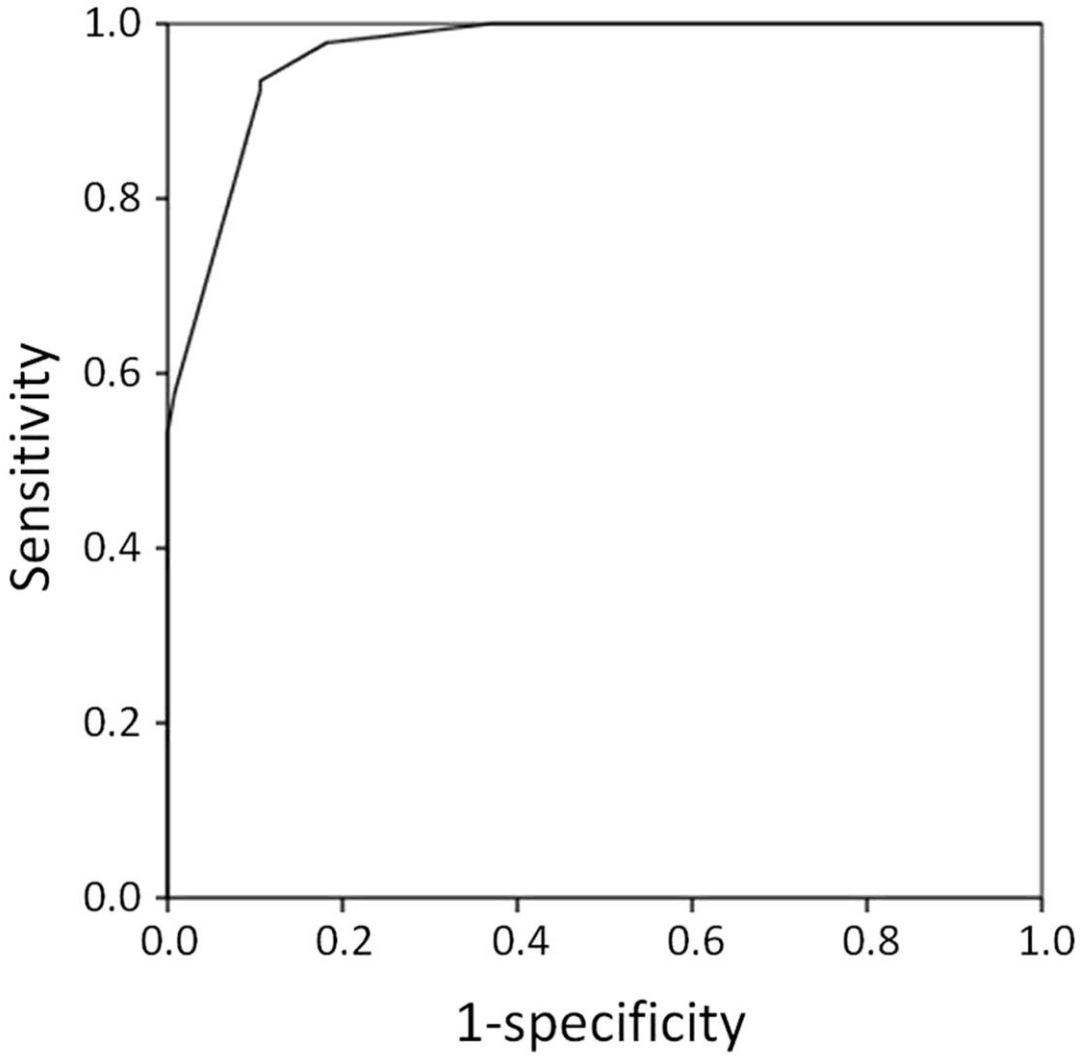

Table 1. Characteristics of study population.

	Patients with TERP (n = 92)	Patients with PSP (n = 132)	p value
Age (years old) (range)	38.6 ± 5.7 (24 - 50)	27.7 ± 9.8 (14 - 67)	< 0.01
Side of pneumothorax			
Right	91 (98.9%)	56 (42.4%)	< 0.01
Left	1 (1.1%)	76 (57.6%)	
Height (cm)	159.0 ± 4.9	160.9 ± 5.9	< 0.05
Weight (kg)	49.1 ± 5.7	47.6 ± 6.1	0.074
Smoking habit			
Current/former smoker	6 (6.5%)	41 (31.1%)	< 0.01
Non-smoker	86 (93.5%)	91 (68.9%)	
History of pelvic endometriosis	54 (58.7%)	3 (2.3%)	< 0.01
The number of preoperative pneumothorax episodes	8.1 ± 3.2	2.8 ± 1.6	< 0.01
Postoperative follow-up period (months)	36.2 ± 22.3	12.0 ± 11.8	< 0.01
The number of patient with postoperative recurrence	36 (39.1%)	23 (17.4%)	< 0.01

Table 2. Factors predicting TERP.

Risk factors	Odds ratio	95% CI	p value	Score Assigned*
Right pneumothorax	440.3	15.0 - 12943.4	< 0.01	6
History of pelvic endometriosis	115.1	10.2 - 1306.2	< 0.01	5
Age ≥ 31 year	78.0	12.1 - 502.1	< 0.01	4
No history of smoking	13.4	3.0 - 61.0	< 0.01	3
The number of preoperative pneumothorax episodes ≥ 4	5.8	1.4 - 23.6	< 0.05	NA
Height ≤ 159 cm	4.1	1.2 - 14.2	< 0.05	NA

* If each risk factor does not exist, the score "0" is given in the following equation:

Calculated score = Right pneumothorax (score 6 or 0) + History of pelvic endometriosis (score 5 or 0) + Age ≥ 31 years old (score 4 or 0) + No history of smoking (score 3 or 0).

NA, not adopted

Table 3. Diagnostic significance of calculated score to differentiate between TERP and PSP.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Calculated score ≥ 12	0.935 (0.902 - 0.967)	0.894 (0.854 - 0.934)	0.860 (0.815 - 0.905)	0.952 (0.923 - 0.980)

Numbers in parentheses indicate 95% CI.

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