Clinical characteristics of catamenial and non-catamenial thoracic endometriosis-related pneumothorax

（月経随伴性気胸およびその他の時期に発症する胸腔内子宮内膜症関連気胸の臨床的特徴）

千葉大学大学院医学薬学府
先端医学薬学専攻
（主任：巽浩一郎教授）

福岡みずき
ABSTRACT

Background and Objectives

A major pathogenic factor for catamenial pneumothorax is thoracic endometriosis. On the other hand, thoracic endometriosis-related pneumothorax (TERP) can develop as either catamenial or non-catamenial pneumothorax. Therefore, the aim of this study was to elucidate the clinical differences between catamenial and non-catamenial TERP.

Methods

The clinical and pathological data in female patients who underwent video-assisted thoracoscopic surgery at the Pneumothorax Research Center during an eight-year period were retrospectively reviewed. This study included 150 females with surgico-pathologically confirmed TERP. The subjects were divided into two groups, those having all of the pneumothorax episodes in the catamenial period (CP group) and those who did not (non-CP group). We compared the clinical characteristics and surgico-pathological findings between these two groups.

Results

Of the 150 TERP patients, 55 (36.7%) were classified in the CP group, and 95 (63.3%) in the non-CP group. In regard to the locations of endometriosis, all TERP patients had diaphragmatic endometriosis, while pleural implantation was recognized in 34 of the 55
(61.8%) patients in the CP group and 42 of the 95 (44.2%) patients in the non-CP group (p<0.05).

Conclusions

A significant difference in the proportion of patients with pleural endometriosis was observed between catamenial and non-catamenial TERP. The ectopic sites of the endometriosis may be responsible for the timing of the pneumothorax episodes.

Key words:

Catamenial pneumothorax, endometriosis, pneumothorax, spontaneous pneumothorax, Video Assisted Thoracoscopic Surgery

Short title:

Endometriosis-related pneumothorax

Abbreviations:

thoracic endometriosis-related pneumothorax (TERP)
catamenial pneumothorax (CP)
video-assisted thoracoscopic surgery (VATS)
INTRODUCTION

Catamenial pneumothorax (CP) had been considered to be an unusual condition, but with increasing interest in the disease, it has been reported more frequently, and is now considered to account for 20-30% of the cases with primary spontaneous pneumothorax in females of reproductive age [1-2]. CP is generally defined simply as a recurrent pneumothorax occurring between the day before and three days after the onset of menstruation [3-4]. A major part of the pathogenesis of CP is thoracic endometriosis [5-6]. Thoracic endometriosis-related pneumothorax (TERP) is the term used to refer to a pneumothorax accompanied with thoracic endometriosis.

Until recently, TERP had been considered to develop only as catamenial pneumothorax. However, Alifano et al. reported that one-third of TERP cases presented in the intermenstrual period [7]. Thus, TERP can develop as a catamenial pneumothorax as well as a non-catamenial pneumothorax. There have been only a few reports of non-catamenial TERP (the report by Alifano’s group and our group), thus the clinical characteristics of non-catamenial TERP have not been clarified [7-9]. The purpose of this study was to clarify the characteristics of this condition and to speculate on the pathogenic mechanism underlying non-catamenial TERP by comparing it with catamenial TERP.
MATERIALS AND METHODS

Study population

The clinical and pathological files of all female patients who underwent video-assisted thoracoscopic surgery (VATS) in the Pneumothorax Research Center for the surgical treatment of a spontaneous pneumothorax during the eight-year period from January 2005 to December 2012 were reviewed retrospectively. The surgery was performed as a VATS procedure under general anesthesia. No patients underwent thoracotomy. We included 150 females who had surgico-pathologically confirmed TERP. During surgery, we searched the thoracic cavity systematically with a thoracoscope to find bullae and blebs, diaphragmatic abnormalities (holes and nodular lesions) and nodular lesions in the thoracic wall (Figure 1). We resected the abnormalities of the diaphragm, lung, and thoracic wall where possible. In addition, a cellulosic mesh (Surgicel Johnson and Johnson, Inc., New Brunswick, NJ, USA) was inserted to cover the diaphragm. The resected lesions were histopathologically diagnosed as thoracic endometriosis when the endometrial glands or stroma were positively stained for estrogen/progesterone receptors or CD10.

We asked all of the patients with TERP about the temporal relationship between the pneumothorax episodes and menses in order to divide them into a CP group
and a non-CP group. We defined the date of pneumothorax as the date of the onset of chest symptoms (chest pain, difficulty of breathing, or some respiratory discomfort). We were sure to ask patients about the date of pneumothorax on each clinic visit. The data of the patients with recurrence after surgery were not included in the analysis. We defined the CP group as those having all of the pneumothorax episodes during the catamenial period (i.e. from the day before to within three days after the onset of menstruation [7-9]), with the remaining patients classified as the non-CP group.

For the patients with catamenial and non-catamenial TERP, we compared the age, pneumothorax side, height, body weight, smoking habits, history of pelvic endometriosis, value of serum CA125, number of pneumothorax episodes before surgery, duration of follow-up after surgery and the postoperative recurrence rate. Furthermore, we compared the locations of endometrial implants in the thoracic cavity between the catamenial and non-catamenial TERP. The study was approved by the institutional review board of Nissan Tamagawa Hospital (approval number 14-015).

Statistical analysis

The quantitative data are presented as the means ± SD. The differences between the patients with catamenial and non-catamenial TERP were analyzed using the
Chi-square test for categorical variables and Student’s $t$-test for quantitative variables. 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

During the eight-year period, a total of 714 females with a spontaneous pneumothorax underwent VATS in our center. One hundred and fifty (21.0%) of the 714 patients were diagnosed as having TERP.

A total of 570 pneumothorax episodes had occurred in the patients with TERP before the surgery, giving a mean of 3.8 ± 2.3 episodes per patient. Figure 2 shows the distribution of the pneumothorax episodes according to the menstrual cycle. The relationship between the day of episodes and menstruation was available for 288 episodes (50.5%). A total of 180 (59.4%) of the 288 episodes developed during the catamenial period.

Of the 150 patients with TERP, 55 (36.7%) were classified as being in the CP group, and the remainder (95/150, 63.3%) were classified as the non-CP group. Table 1 shows the clinical characteristics of each group. It should be noted that all but one of the patients developed a right-sided pneumothorax. The patients with catamenial and non-catamenial TERP showed similar clinical features.

Table 2 shows the ectopic sites of thoracic endometriosis in each group. All of the TERP patients had endometrial implants in the diaphragm. Thirty-four of the 55 (61.8%) patients in the CP group and 42 of the 95 (44.2%) patients in the non-CP group
had implants not only in diaphragm, but also in the pleura. This difference was statistically significant (p < 0.05). Endometriosis in the visceral pleura was observed in 22 of the 55 (40%) patients in the CP group and 30 of the 95 (31.5%) patients in the non-CP group (p=0.30).
DISCUSSION

We found that diaphragmatic endometriosis was detected in all of the patients with TERP, and that pleural endometriosis was also detected in some of them. It is important that the proportion of patients with endometriosis in both the diaphragm and pleura was significantly higher in the CP group than in the non-CP group, because the ectopic sites of endometriosis may be related to the timing of pneumothorax episodes.

The pathogenesis of thoracic endometriosis has been explained by the following three theories. 1) Migration: the migration of pelvic endometriosis through the peritoneum to the diaphragm [9]. 2) Embolization: transplantation of pelvic endometriosis through lymphatic or vascular embolization [10]. 3) Metaplasia: coelomic metaplasia of epithelium in the thorax [11]. The fact that most of the cases of TERP develop in the right-side lung supports the migration theory [12-14]. The presence of intrapulmonary endometriosis supports the embolization theory [10]. Metaplasia to endometrial tissue has been reported in patients with ectopic endometriosis other than in the thorax [11]. Therefore, this phenomenon is also considered to occur in the thoracic cavity. In the present study, a laterality of the right lung and the specialized distribution of endometriosis were recognized in the location of thoracic endometriosis. Recently, Legras et al. reported 229 female patients with
pneumothorax, including 54 TERP patients. This study showed a similar distribution of thoracic endometriosis to our own study, i.e. 53 (98.1%) had a right-sided pneumothorax, 52 (96.3%) had endometrial implants in the diaphragm, and 11 (12.2%) had endometrial implants in the pleura [8]. Thus, TERP was speculated to develop largely due to the migration of pelvic endometriosis through defects in the right diaphragm. Furthermore, endometrial cells do not stay still on the diaphragm, but progress to disseminate to the dorsal thoracic wall or pleura.

Our study showed that catamenial TERP tended to be detected with pleural endometriosis more frequently than non-catamenial TERP. We thought that the timing of pneumothorax episodes with TERP probably varied because air from outside entered through two different passages; the transdiaphragmatic passage and transpleural passage. Endometriosis in the visceral pleura may cause a pneumothorax to occur during the early menstrual period, because the lung surface with sloughing endometriosis is directly broken [15-16]. To cause transdiaphragmatic passage, air from outside needs to overcome three different blockades; the cervix of the uterus, ovarian tubes and diaphragm [17]. All three of these are ordinarily closed, but when these blockades fail for sort reason at the same time or one after another, TERP can develop in the intermenstrual period. Another possible explanation for the development of
non-catamenial TERP is as follows. 1) Non-catamenial TERP may be a milder disease, hence the onset of chest symptoms may be delayed. 2) For the patients with pneumothorax due to the transdiaphragmatic passage of air, it seems likely that the pneumothorax developed more gradually than in patients in whom pneumothorax developed due to the transpleural passage of air, hence the date of presentation may be less precise.

Alifano et al. speculated that when air from outside enters into the peritoneum through the genital tract due to uterine contractions, physical activity or sexual intercourse, this air can enter into the thorax in the intermenstrual period [10]. We doubted this hypothesis, because we have not experienced any cases of pneumothorax caused by physical activity or sexual intercourse based on our patient interviews. Most of the patients were at their office jobs at the time of onset.

We discovered that the only significant difference between the CP and non-CP groups was the proportion of the patients with pleural endometriosis. We could not find any significant difference in the rates of visceral pleural endometriosis. This result is probably due to the difficulty of inspecting for thoracic endometriosis, because these endometriotic implants are very small, as we reported previously [18]. When ectopic endometrial sites are found in the parietal or visceral pleura, the endometrial tissues
may extend to both the parietal and visceral pleural surfaces. Thus, TERP patients with pleural endometriosis are likely to develop pneumothorax due to transpleural air passage.

This study is associated with several limitations. First, our subjects were located at the Pneumothorax Research Center, which specializes in the treatment of pneumothorax. Many patients with intractable pneumothorax are referred to this facility. Accordingly, the clinical features for TERP may be biased. Second, this was a retrospective cohort study, as such we may have failed to detect the temporal relationship between the pneumothorax episodes and menses in some cases. A prospective study to confirm our results is needed. Finally, because it was difficult to inspect all of the sites of thoracic cavity, especially in the fissures, small endometrial implants may have been missed. This could have led to bias.

There have rarely been reviews or large series of case reports of TERP because it is a relatively unusual disorder. However, we have extensive experience with the treatment of TERP, including surgery for TERP. As a result, we were able to perform detailed interviews and evaluations of TERP in our cases.
CONCLUSION:

We have clarified the precise distribution of thoracic endometriosis in TERP patients. Furthermore, the ectopic sites of endometriosis differed between the CP group and non-CP group. This study provides a good basis for considering the pathogenesis of TERP.

ACKNOWLEDGEMENTS:

We thank Brian Quinn (Japan Medical Communication) for excellent assistance in the review of English.
REFERENCES


5) Channabasavaiah AD, Joseph JV. Thoracic endometriosis: revisiting the association between clinical presentation and thoracic pathology based on thoracoscopic findings in 110 patients. Medicine (Baltimore) 2010; 89: 183-188.


Table 1. The characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Patients with TERP n=150</th>
<th>Patients with catamenial TERP n=55</th>
<th>Patients with non-catamenial TERP n=95</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old) (range)</td>
<td>38.3 ± 5.2 (24-50)</td>
<td>38.4 ± 4.8 (29-47)</td>
<td>38.3 ± 5.6 (24-50)</td>
<td>0.91</td>
</tr>
<tr>
<td>Side of pneumothorax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>149 (99.3%)</td>
<td>55 (100%)</td>
<td>94 (98.9%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Left</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.3 ± 5.3</td>
<td>159.3 ± 5.4</td>
<td>159.3 ± 5.2</td>
<td>0.96</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>49.5 ± 5.8</td>
<td>50.6 ± 5.3</td>
<td>49.0 ± 6.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former smoker</td>
<td>13 (8.7%)</td>
<td>7 (12.7%)</td>
<td>6 (6.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>137 (91.3%)</td>
<td>48 (87.3%)</td>
<td>89 (93.7%)</td>
<td></td>
</tr>
<tr>
<td>The number of patient with a history of pelvic endometriosis</td>
<td>83 (55.3%)</td>
<td>31 (56.4%)</td>
<td>52 (54.7%)</td>
<td>0.85</td>
</tr>
<tr>
<td>The value of serum CA125 (U/mL)</td>
<td>31.1 ± 34.8</td>
<td>29.0 ± 30.6</td>
<td>33.1 ± 37.8</td>
<td>0.51</td>
</tr>
<tr>
<td>The number of preoperative pneumothorax episodes</td>
<td>3.7 ± 2.4</td>
<td>3.4 ± 2.3</td>
<td>4.0 ± 2.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Postoperative follow-up period (months)</td>
<td>28.4 ± 20.0</td>
<td>26.0 ± 18.1</td>
<td>29.4 ± 22.0</td>
<td>0.33</td>
</tr>
<tr>
<td>The number of patients with recurrence after surgery</td>
<td>51 (34.0%)</td>
<td>20 (36.4%)</td>
<td>31 (32.6%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

There were no missing data for any of these variables. The data are presented as no (%) or the mean ± SD. The P values were calculated by comparing the patients with catamenial and non-catamenial TERP.
Table 2. The ectopic sites of thoracic endometriosis in patients with catamenial and non-catamenial TERP

<table>
<thead>
<tr>
<th>Thoracic endometriosis in the diaphragm and pleura</th>
<th>Patients with catamenial TERP n=55</th>
<th>Patients with non-catamenial TERP n=95</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic endometriosis in the diaphragm</td>
<td>21 (38.2%)</td>
<td>53 (55.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thoracic endometriosis in the diaphragm and visceral pleura</td>
<td>34 (61.8%)</td>
<td>42 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>Thoracic endometriosis in the diaphragm and parietal pleura</td>
<td>16 (29.1%)</td>
<td>18 (18.9%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Thoracic endometriosis in the diaphragm, visceral and parietal pleura</td>
<td>12 (21.8%)</td>
<td>12 (12.6%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Thoracic endometriosis in the diaphragm, visceral and parietal pleura</td>
<td>6 (10.9%)</td>
<td>12 (12.6%)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

All of the patients had thoracic endometriosis in the diaphragm, while some of them also had endometriosis in the pleura (visceral, parietal or both). The P values were calculated by comparing the patients with catamenial and non-catamenial TERP.
**Figure Legends**

**Figure 1.**

The thoracoscopic views of endometrial implants on the tendinous part of the right diaphragm [A], on the visceral pleura [D], and on the parietal pleura [G]. Blue-brown implants [A], small bulla [D], and tiny lucent nodules [G] were detected. Endometrial glands and/or stroma were detected in the resected specimens (hematoxylin-eosin) [B, E, H]. These glands and/or stroma exhibited nuclear staining for estrogen receptors [C, F, I].
Figure 2.

The distribution of pneumothorax episodes in the TERP patients. The red bars indicate catamenial pneumothorax; the pneumothorax that occurs between 24 hours before and 72 hours after the initiation of menses. Day 1 means the day of onset of menstruation. Day -1 means the day before the onset of menstruation.
Respirology vol. 20 No. 8

平成 27 年 11 月 20 日 公表済