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Thoracic endometriosis syndrome: Comparison between catamenial pneumothorax or endometriosis-related pneumothorax and catamenial hemoptysis



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ABSTRACT

Objectives: To evaluate the clinical features of thoracic endometriosis syndrome (TES) represented by catamenial pneumothorax (CP), endometriosis-related pneumothorax (ERP), and catamenial hemoptysis (CH). **Study design:** In this retrospective study, we enrolled 25 patients with TES, 18 of whom had CP/ERP and 7 had CH, to investigate the clinical presentation, effectiveness of treatment, and recurrence rates in these disorders.

Results: The age at onset was significantly lower in patients with CH than in patients with CP/ERP ($P < 0.05$). In 94.4% of patients with CP/ERP, pneumothorax was observed on either the right side or bilaterally, however there was no tendency toward laterality of CH among our cases. In our study, patients with CP/ERP predominantly underwent surgical management and the recurrence rate during treatment was higher in patients with CP/ERP than in those with CH. We found that the recurrence frequency of CP/ERP was lowest under the combination therapy with thoracic surgery and postoperative hormonal therapy.

Conclusion: Our findings suggest that CP/ERP and CH are different pathological conditions and CP/ERP is more difficult to manage than CH.

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Introduction

Thoracic endometriosis syndrome (TES) is one of extra-genital endometriosis, which is characterized by the presence of endometrium-like tissues in the thoracic cavity. Manifestations of TES include: catamenial pneumothorax (CP), catamenial hemothorax, catamenial hemoptysis (CH), and lung nodules [1]. According to a meta-analysis of published cases between 2001 and 2007, the clinical presentation of TES includes pneumothorax (72%), hemoptysis (14%), hemothorax (12%) and lung mass (2%) [2]. Recently, endometriosis-related pneumothorax has been reported to develop as either catamenial pneumothorax or non-catamenial pneumothorax [3–5]. Non-catamenial endometriosis-related pneumothorax is also included in TES. TES has been recognized as a rare condition, and the etiology and pathology are still not well known. The three hypotheses that may explain the pathogenesis of thoracic endometriosis include coelomic metaplasia, lymphatic or

hematogenous embolization, and retrograde menstruation through a defect in the diaphragm [1,6]. None of these can explain all of the clinical presentations of TES. The management of this condition is highly variable because of the lack of recommendations. Although combined surgical and hormonal treatment have been proposed, there is no consensus [7]. A recent study reported that patients with CP had more hospitalizations and more frequent surgeries than those with non-catamenial pneumothoraces according to a large nationwide database of hospitalized patients [8]. Furthermore, the recurrence rates of CP/ERP, even after surgery or hormonal therapy were high at 32% and 27%, respectively [3]. Therefore, we sought to perform a retrospective analysis of cases of TES in our facility to investigate the clinical presentations, effectiveness of treatment, and recurrence rates.

Materials and methods

Cases

We identified 25 patients treated for thoracic endometriosis between January 2000 and December 2016 at Tokyo University

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Hospital. We retrospectively analyzed the clinical features and management (including age, BMI, parity, symptomatology, laterality, method of diagnosis, complications, surgical management, hormonal therapy, and recurrence) by reviewing the medical records. These factors were compared between patients with catamenial pneumothorax, or endometriosis-related pneumothorax (CP/ERP), and patients with catamenial hemoptysis (CH). For recurrent cases of CP/ERP, the cumulative recurrence frequency was calculated by dividing the number of recurrences by the observational period, and this was analyzed based on the method of treatment. The observational period was defined as the time from the diagnosis of TES to either loss to follow-up or December 2016. This study was approved by the Institutional Review Board of Tokyo University Hospital and informed consent was waived owing to the retrospective nature of this study.

Definition of thoracic endometriosis syndrome

In this study, the inclusion criteria for TES were: (1) pathological diagnosis (presence of endometrial glands and stroma, or isolated endometrial stroma staining positively with estrogen/progesterone receptors and/or CD10), (2) intraoperative findings (presence of endometriotic lesions on visceral and parietal pleura or on diaphragm), (3) chest computed tomography (CT) imaging (the presence of pleuro-diaphragmatic nodules, ground glass opacity, and air filled cavities), (4) Clinical symptoms and chest X-ray examination (recurrent episodes of pneumothorax, hemoptysis, hemothorax or chest pain related to menstruation).

Statistical analysis

The statistical analyses were performed using JMP pro version 13 (SAS Institute Inc, Cary, NC, USA). The continuous data are presented as means and standard deviations (SD) and were analyzed using *t*-tests. The categorical data were analyzed using chi-square test and Fisher's exact tests and are presented as numbers and percentages. A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of patients

As shown in Table 1, the characteristics of patients with TES were compared between patients with CP/ERP and those with CH. Of the 25 patients with TES, 18 presented with CP/ERP (72.0%), and 7 with CH (28.0%). The mean age at diagnosis of TES was 34.8 ± 7.3 years, and the mean age of diagnosis was significantly lower in the CH group (29.6 ± 4.6 years) than in the CP/ERP group (36.8 ± 7.3 years). The mean body mass index (BMI) of patients with TES was 19.5 ± 1.9 kg/m², and there was no significant

difference between the two groups. We found that only 13 of our 25 patients had medical histories that provided smoking status, of which 8 patients were in the CP/ERP group, and 5 patients were in the CH group. Of these, there was one cigarette smoker in the CP/ERP group and one cigarette smoker in the CH group. Seven of 25 (28.0%) cases involved coexisting pelvic endometriosis, and we found no significant difference between the cases of CP/ERP and CH.

Symptom and diagnosis

As shown in Table 2, all of the CP/ERP cases involved dyspnea, and all the CH cases involved bloody sputum. As for laterality, 16 cases (89%) in the CP/ERP group were right-sided, one case was left-sided (5.6%), and one case was bilateral (5.6%). In the CH group, three cases were right-sided, three cases left-sided, and one case with unknown laterality. There was a significant difference in the frequency of right-sided versus left-sided disease between CP/ERP and CH (*P* < 0.05). The symptoms occurred during menstruation in all the 7 CH patients, but only in 14 of 16 CP/ERP patients. Additionally, in two of the cases, the symptoms occurred during the non-menstrual period (in these two cases, endometriosis was confirmed in the thoracic cavity by operative pathology). All of the patients in the CH group were diagnosed based on their symptoms, and in the CP/ERP group, 7 of 18 were diagnosed by symptoms and chest X-ray examination, 6 by pathology of surgical specimens, 3 by operative findings, and 2 by CT imaging.

Treatment and recurrence

The details of recurrence and treatment of the two groups is shown in Table 3. During or after treatment, ten of 18 cases in CP/ERP group recurred, and no cases in the CH group recurred (*P* < 0.05). In 15 of the 18 patients with CP/ERP, thoracic surgery was performed, as shown in Table 3, while there were no cases of CH in which thoracic surgery was performed (*P* < 0.05). Of the 15 cases of CP/ERP, after thoracic surgery recurrence occurred in seven cases (46.7%), and a second surgery was performed in three cases due to recurrence. The details of thoracic surgery are listed in Table 4. Postoperative recurrence occurred even during postoperative hormonal therapy in the CP/ERP group only. No recurrence was observed during hormonal therapy (HT) in the CH group.

We analyzed the recurrence frequency of CP/ERP according to the treatment provided. The observational periods, after the diagnosis of TES, were divided into four periods defined as: "No surgery/Before surgery," "After Surgery," with HT, and without HT. Next, we determined the cumulative treatment period and the total recurrence count. The recurrence frequency was calculated as the total recurrence count divided by each cumulative treatment period. As shown in Table 5, in the "No Surgery/Before Surgery" period, one recurrence occurred during the period without HT, and

Table 1
Demographic and clinical characteristics of patients with thoracic endometriosis.

(Number of Cases)	In total (25)	CP/ERP (18)	CH (7)	P-value	
Age at diagnosis (y.o.)	34.8 ± 7.3 (18–47)	36.8 ± 7.3 (18–47)	29.6 ± 4.6 (22–35)	<i>P</i> < 0.05	
BMI (kg/m ²)	19.5 ± 1.9 (15.4–22.9)	19.7 ± 1.9 (15.4–22.9)	19.2 ± 1.9 (16.5–21.5)	n.s.	
Smoking history	2/13 (15%)	1/8 (13%)	1/5 (20%)	n.s.	
Parity	0	14/25 (56%)	9/18 (50%)	5/7 (71%)	n.s.
	> = 1	11/25 (44%)	9/18 (50%)	2/7 (29%)	–
Infertility	6/25 (24%)	6/25 (24%)	5/18 (28%)	1/7 (14%)	n.s.
Pelvic endometriosis (duplicate included)	7/25 (28%)	7/25 (28%)	6/18 (33%)	1/7 (14%)	n.s.
	Ovarian Endometrioma	4/25 (16%)	3/18 (17%)	1/7 (14%)	n.s.
	Adenomyosis	5/25 (20%)	4/18 (22%)	1/7 (14%)	n.s.
	Intestinal Endometriosis	1/25 (4%)	0/18 (0%)	1/7 (14%)	n.s.
History of gynecologic surgery	8/25 (32%)	8/25 (32%)	6/18 (33%)	2/7 (29%)	n.s.

Table 2
Symptom and Diagnosis of thoracic endometriosis.

		CP/ERP	CH	P-value	
Symptom	Dyspnea	18/18 (100%)	0/7 (0%)	P < 0.05	
	Chest pain	18/18 (100%)	3/7 (43%)	P < 0.05	
Laterality	Bloody sputum	0/18 (0%)	7/7 (100%)	P < 0.05	
	Right	16/18 (89%)	3/6 (50%)	P < 0.05	
	Left	1/18 (5.6%)	3/6 (50%)	P < 0.05	
	Both	1/18 (5.6%)	0/6 (0%)	n.s.	
	Menstruation	14/16 (88%)	6/6 (100%)	n.s.	
Relation between symptom and menstrual cycle	non-menstrual period	2/16 (13%)	0/6 (0%)	n.s.	
	Diagnosis				
Duration from First Onset to Diagnosis (month)		8.7 ± 9.7 (1–36)	8.4 ± 17.5 (1–48)	n.s.	
	Method of Diagnosis	Symptoms and Chest X-ray	7/18 (44%)	7/7 (100%)	
		Pathology	6/18 (39%)	0/7 (0%)	
		Thoracoscope	3/18 (17%)	0/7 (0%)	
		Imagings (CT)	2/18 (11%)	0/7 (0%)	

Table 3
Recurrence and thoracic endometriosis syndrome with/without surgery and hormonal therapy.

	CP/ERP		CH		P-value
	cases	recurrence cases	cases	recurrence cases	
Recurrence after diagnosis	18	10 (55.6%)	7	1 (14.3%)	P = .062
Recurrence after treatment	18	10 (55.6%)	7	0 (0%)	P < 0.05
with surgery	15 (83.3%)		0 (0%)		P < 0.05
postoperative recurrence	15	7 (46.7%)	0	0	
	during hormonal therapy	1	0	0	
	during no hormonal therapy	5	0	0	
	Both	1	0	0	
recurrence before surgery	15	1 (6.7%)	0	0	
	during hormone therapy	1	0	0	
	during no hormonal therapy	0	0	0	
wihtout surgery	3 (16.7%)		7 (100%)		
during hormonal therapy	3	2 (66.7%)	7	1 (14.3%)	
during no hormonal therapy	0	1	0	0	
Both	1	0	0	0	

Table 4
Surgery for CP/ERP.

	cases	recurrence cases
First surgery	15	7 (46.7%)
Thoracoscopic diaphragmatic resection	4	2 (50%)
Thoracoscopic partial pneumonectomy	2	2 (100%)
Thoracoscopic partial pneumonectomy + pleurodesis	1	0 (0%)
Thoracoscopic diaphragmatic resection + partial pneumonectomy	4	1 (25%)
Thracic surgery (details unknown)	4	2 (50%)
Second surgery	3	
(pyothorax after spontaneous pneumothorax) Drainage + partial pneumonectomy + pleurodesis	1	0 (0%)
Pleurodesis	1	0 (0%)
Thoracoscopic partial pneumonectomy + pleurodesis	1	0 (0%)

Table 5
Cumulative recurrence frequency of CP/ERP.

	No surgery/Before surgery		After Surgery	
	No hormonal therapy	Horomonal therapy	No hormonal therapy	Horomonal therapy
Total observation period (year and month)	3y 0m	12y 7m	43y 5m	42y 1m
number of recurrence	1	3	6	2
Frequency of recurrence (time/year)	0.33	0.24	0.14	0.05

2 recurrences were seen during HT, and therefore, the overall cumulative recurrence frequencies were 0.33 times per year and 0.24 times per year, respectively. In the “After Surgery” period, 6 recurrences were detected during the period without HT and two recurrences occurred during HT, thus the overall cumulative recurrence frequencies were 0.14 times per year and 0.05 times per year, respectively.

Hormonal treatment

As shown in Table 6, hormonal therapy was initiated using either a GnRH agonist, low dose oral contraceptives (OC), dienogest or danazol. In this case series, various hormone therapy medications were used to control CP/ERP or CH. Among these, continuous OC and dienogest were predominant as the optimal treatment in terms of effects, adverse effects, and feasibility of long-term use. Regarding the patients with CH, no recurrences were observed after any of the hormonal treatment regimens. Table 7 shows that the recurrence rates were 18.0%, 33.3%, 16.7% or 0% with continuous OCs, cyclic OCs, dienogest or GnRH agonists, respectively.

Comments

In this study, we elucidated the difference between the clinical features of CP/ERP and CH. First, the age at onset was significantly lower in CH compared to CP/ERP. Second, 94.4% of CP/ERP occurred on either the right side or bilaterally, while there was no tendency toward laterality of CH in our cases. Third, most of the patients with CP/ERP underwent surgical management. Last, the recurrence rate during treatment was higher in patients with CP/ERP than in those with CH. These differences suggested that CP/ERP and CH are different pathological conditions. We also observed that CP/ERP

Table 7
Recurrence rate during each hormonal therapy.

	CP/ERP		CH	
	cases	cases with rec.	cases	cases with rec.
Hormonal Therapy				
Continuous OC	11	2 (18.0%)	5	0 (0%)
Cyclic OC	6	2 (33.3%)	2	0 (0%)
Dienogest	6	1 (16.7%)	2	0 (0%)
GnRH agonist	5	0 (0%)	4	0 (0%)
danazol	0		1	0 (0%)

seemed to be more difficult to manage compared to CH. A combination of thoracic surgery and postoperative hormonal therapy were required to reduce the recurrence frequency of CP/ERP.

Of the 25 patients in our study, 18 patients had CP (72.0%) and 7 patients had CH (28.0%), which is in line with previous literature showing that CP was the most frequent manifestation of TES [1]. When comparing CP/ERP and CH, the mean age of patients diagnosed with CH was approximately 9 years lower than that of the patients with CP/ERP. This result is in line with previous reports [2,9], indicating that CH is early-onset TES.

The right hemithorax is affected in more than approximately 90% of TES cases [1,2]. In our study, 16 cases (88.9%) of CP/ERP were right-sided, but there was no significant tendency toward laterality among the CH cases. Previous reports showed that the frequency of left-sided CH was 25 to 40%, which was less than that obtained in our results [2,10]. However, left-sided CH was still more frequent than left-sided CP/ERP. The three hypotheses that may explain the pathogenesis of thoracic endometriosis include coelomic metaplasia, lymphatic or hematogenous embolization, and retrograde menstruation through a defect in the diaphragm

Table 6
Details of hormonal therapy.

CP/ERP							
	Case No.	operation	Recurrence during no HT	third to last	second to last	previous	last treatment
Recurrence	1	+	+		GnRH _a	cyclic OC ^a	conti OC
	2	+	+			GnRH _a	conti OC
	3	+	–				conti OC ^a
	4	+	–				conti OC ^a
	5	+	+				conti OC
	6	–	–				dienogest ^a
	7	+	+			cyclic OC ^a	dienogest
	8	+	+			conti OC	cyclic OC
	9	–	+				cyclic OC
	10	+	+				–
No recurrence	11	+	–	GnRH _a	cyclic OC	conti OC	dienogest
	12	+	–			conti OC	dienogest
	13	+	–			conti OC	dienogest
	14	+	–				dienogest
	15	+	–				conti OC
	16	+	–			cyclic OC	conti OC
	17	–	–			GnRH _a	conti OC
	18	+	–				GnRH _a
							–
CH							
Case No.	operation	Recurrence during no HT	third to last	second to last	previous	last treatment	
1	–	+	GnRH _a	danazol	conti OC	dienogest	
2	–	–		GnRH _a	cyclic OC	conti OC	
3	–	–			GnRH _a	conti OC	
4	–	–				conti OC	
5	–	–				conti OC	
6	–	–			GnRH _a	dienogest	
7	–	–				cyclic OC	

^a Denotes recurrence.

[1,6]. According to the retrograde menstruation theory, right-sided dominance of CP/ERP occurs because the clockwise flow of ascites containing endometrial cells reaches the right sub-diaphragmatic area through the right paracolic gutters [11]. However, the pathogenesis of CH might differ from this theory because of the lack of laterality in CH. Other authors reviewed the cases of 74 patients with CH and proposed that the underlying cause was likely to be lymphatic or hematogenous embolization [10]. Accordingly, CP/ERP and CH are suggested to be distinct entities, although both of them are types of TES.

In our cases, the recurrence rate during treatment was higher in patients with CP/ERP compared to those with CH ($P < 0.05$). Fifteen of 18 patients with CP underwent thoracic surgery, while none of the patients with CH underwent thoracic surgery. With CH, surgical resection methods including lobectomy, segmentectomy, and video-assisted thoracoscopic surgery (VATS) are still controversial [12], although VATS as a treatment for CH has been reported recently [13,14]. Additionally, patients with CH did not experience recurrence during hormonal therapy. These results suggested that CH, unlike CP/ERP, is more likely to be treated with hormonal therapy without surgery. Thoracic surgery for patients with non-massive hemoptysis seemed to be over-treatment, because proper control could be achieved by hormonal or conservative therapy [15]. In our study, OCs, dienogest, and GnRH agonists were all effective treatments for patients with CH. However, OCs and dienogest are optimal for patients with mild symptoms as shown in this study because unlike GnRH agonists, they do not induce hypo-estrogenic effects even after long-term treatment [16,17].

The high recurrence rate in CP/ERP was in line with other previous reports [3]. The recurrence rate after hormonal therapy alone was reported to be more than 50%, which was inferior to surgery in preventing recurrence [1]. Furthermore, it has been suggested that the CP and ERP are best treated using a combined approach that includes thoracic surgery and subsequent hormonal therapy [1,6,9,18,19]. In this study, the cumulative recurrence frequency was lowest after surgery and postoperative hormonal therapy.

Continuous OCs and dienogest have been reported to be as effective as GnRH agonists for pelvic endometriosis [20–22], and also effective for extra-genital endometriosis [23,24]. Furthermore, continuous OC regimens were reported to be more effective for preventing the recurrence of dysmenorrhea after endometrioma surgery than cyclic OC regimens [25]. Compared with cyclic regimens, the avoidance or delay of cyclic bleeding by continuous regimens significantly reduced the frequency and severity of endometriosis-related pain [26]. Likewise, continuous regimens may reduce the frequency of symptoms associated with CP/ERP.

The limitations of this study include its retrospective nature and the limited number of patients due to the rarity of the disease. Furthermore, the recurrence rate of CP/ERP is still high under the current methods of management. Therefore, further study is required to verify our results and develop the optimal treatment regimen for CP/ERP.

Conclusion

In conclusion, the results of our study suggested that CP/ERP and CH were different pathological conditions, considering the difference in age at onset, laterality and recurrence rates. Furthermore, the current management of CP and ERP is not satisfactory, because the recurrence rates are still high, despite surgery and hormonal therapies. Determination of the optimal management for TES is still required to reduce its high recurrence rate.

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Conflict of interest statement

The authors declare that they have no conflicts of interest to disclose.

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