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## **Review Article**

## Thoracic endometriosis: a brief review

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#### **ABSTRACT**

Endometriosis is characterized by the presence of functional endometrial like glands and stroma outside the uterus. The most common extra pelvic site is thoracic cavity, which produces a range of clinical and radiological manifestations which include catamenial pneumothorax, hemothorax, hemotysis, and pulmonary nodules resulting in thoracic endometriosis syndrome. This article reviews the condition of thoracic endometriosis syndrome, with details about symptoms, clinical examination, radiological features and management options are reviewed. The theories explaining such uncommon locations of endometriosis are discussed briefly. The role of local therapy and hormonal therapy, and description of our experience with two cases are presented.

**Keywords:** Endometriosis, Thoracic disease, Catamenial pneumothorax, Haemothorax, Pulmonary nodule, Hormone therapy

## INTRODUCTION

Endometriosis is the most common benign disorder defined as the presence of functional endometrial like glands and stroma outside the uterus. It affects about 6-10% of the reproductive aged women however the incidence is much higher.<sup>1</sup> Among this population, 12% are estimated to experience endometriosis of nonreproductive organs called as the extragenital endometriosis. The most common extra pelvic form is thoracic endometriosis. <sup>1-4</sup> It affects the airway, pleura, lung parenchyma and diaphragm producing a range of clinical and radiological features collectively known as thoracic endometriosis syndrome (TES).<sup>2-4</sup> The clinical features include catamenial pneumothorax (73%) is the most common presenting feature followed by catamenial hemothorax (14%), and hemoptysis (7%).4 However, Bobbio et al has stated to consider including endometriosis related diaphragmatic hernia, catamenial chest pain and endometriosis related pleural effusion in thoracic endometriosis syndrome.4 Mean age at presentation of pelvic endometriosis is between 25-30 years. Whereas the mean age of TES presentation is 34.1,3,4,8 Channabasavaiah

et al has quoted that the mean duration of symptoms before the diagnosis of TE was 14±2.4 months.<sup>4</sup> There is a significant association between the presence of pelvic endometriosis and TES, with the latter occurring approximately 5 years later.<sup>8</sup> It should be remembered that pelvis endometriosis is not the prerequisite for developing TES, it is only a risk factor.<sup>6</sup>

The purpose of this review article is to focus on different age at presentation, association with pelvic endometriosis and management options.

# PATHOPHYSIOLOGY OF THORACIC ENDOMETRIOSIS

In 1938, Schwarz was the first to describe the endometriosis in lung parenchyma. The etiology of TES is multifactorial. There is no single theory to explain all the signs and symptoms of TE. Hence there are several theories explaining them yet the complete pathophysiology of Thoracic endometriosis has not been completely understood.

#### Retrograde menstrual flow theory

Popularly known as Sampson's theory, he along with other investigators centuries back formulated this theory which is based on the retrograde migration of the endometrial cells through the fallopian tube into the peritoneal surfaces. The right sided predominance of thoracic endometriosis can be explained by the fact that peritoneal fluid flows in a clockwise pattern in the peritoneal cavity, from pelvic floor to the right paracolic gutter to the right hemidiaphragm. The endometrial tissue in the peritoneal cavity also follows the same pattern. On reaching the right hemidiaphragm, falciform ligament of the liver and phrenicocolic ligaments will prevent them from further travel to left side. The change in the intraperitoneal pressure during breathing, will allow the endometrial tissues to migrate via the diaphragmatic defects to the thoracic cavity, explaining the right sided predominance in the thoracic endometriosis. 1,3,4,6 Also, this theory alone can explain the right sided predominance as well. Hence, Sampson's is considered the simplest theory which requires less assumption.

### Coelomic metaplasia theory

This theory involves the metaplasia of coelomic epithelial cells, that is the mesothelial cells in the pleura and the peritoneal surface into endometrial glands and stroma. This transformation requires the stimuli by estrogen. But there is no data to explain how a single cell transforms into two different type of cells that is endometrial epithelial cell and stromal cell. The only support for this theory is occurrence of endometriosis in Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome with non-functional endometrium and very rare cases of endometriosis in male urinary system who are receiving high doses of estrogen for prostate cancer. But this theory cannot explain the right sided predominance of thoracic endometriosis.

#### Lymphatic and hematogenous dissemination theory

Almost 80 years back, it was demonstrated that administration of endometrial tissue into vessels in the face of animals eventually led to development of pulmonary endometriosis. Also, circulating endometrial cells have been found in the blood of patients with spontaneous pneumothorax. There are animal studies showing that intravenously injected endometrial tissue remain viable and invades the lung parenchyma and Joseph et al reported a case of recurrence of symptoms after hysterectomy with bilateral salpingo-oophorectomy suggesting microembolization as the mechanism of TE. This is the only convincing theory to explain the occurrence of endometriosis in distant sites of body such as brain and hone

## Prostaglandin theory

Several investigators could not find any diaphragmatic defects or pleural endometriosis in patients presenting with

spontaneous recurrent pneumothorax.<sup>16</sup> Later, a hormonal theory was postulated which proposed that the prostaglandin F2 alpha, a potent constrictor of the bronchioles and vasculature that is detected to be high in the plasma of the women during menstruation.<sup>1,3,16-19</sup> This can lead to rupture of the subpleural blebs and bullae, resulting in the catamenial pneumothorax. This is the only explanation for the patients in whom the only finding noted is blebs and bullae.<sup>20</sup>

This theory does not explain the right sided predominance or the other clinical and radiological presentation.

## CLINICAL PRESENTATION AND DIAGNOSIS OF TES

Irrespective of the pathogenesis, the first presenting symptom in thoracic endometriosis depends on the site of the lesion. If a critical mass of proliferating endometrial tissue is located in communication with the patent bronchus, the patient will present with hemoptysis. <sup>8</sup> Channabasavaiah et al has stated that hemoptysis occurring in younger subjects may be the earliest manifestation of parenchymal lung involvement in thoracic endometriosis. <sup>8</sup>

If the primary focus of proliferating endometrial tissue is not seen near the communicating patent bronchus, with the progression of the disease, these will seed into the visceral pleural due to the constant negative intrapleural pressure.<sup>26</sup> Hence, with the constant proliferation and shedding during the menstrual cycle along with local inflammation becomes responsible for the cyclic chest pain experienced by the patients.<sup>4</sup> As this parenchymal disease advances, the visceral endometrial implant will break the pleural membrane during the cyclic proliferation and shedding process causing pneumothorax. When clinically correlated with menstrual cycle, it is termed as catamenial pneumothorax. 4 When this becomes significant, the patient will seek medical attention. Pneumothorax is seen in 74% of cases, making it the most frequent presenting feature of TE.<sup>4,21,25</sup> Catamenial pneumothorax is defined by at least 2 episodes of pneumothorax occurring spontaneously 24 hours before onset of menses and within 72 hours after onset of menses. 1,3,16,25 A recent case report has highlighted that recurrent episodes of spontaneous pneumothorax can also occur during the intermenstrual period and ovulatory period as well.<sup>27</sup> Chest pain associated with dyspnea is the most common presenting symptoms. Cough is not generally seen in patients with pneumothorax.<sup>4</sup> Hence it is generally difficult to differentiate between spontaneous pneumothorax (SP) and thoracic endometriosis related pneumothorax (TERP), Haga et al conducted a study, in which they compared four clinical variables which included right-sided pneumothorax, history of pelvic endometriosis, age  $\geq$ 31 years, 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. A score of 12 was able to accurately predict 86% of the cases

of TERP. The negative predictive value was even better (95%). Hence, the authors strongly suggested the usage of this score for clinicians who suspect TERP in female patients with pneumothorax. But this scoring system has not been evaluated in actual clinical practice, probably due to lack of adequate cases in any one single institution. Catamenial pneumothorax is unilateral and right-sided in almost all cases, although there are exceptional reports of left-sided pneumothorax. 1,2,5,6,8,28,44 Since pneumothorax is the most common presenting features of TE, hence any women with pelvic endometriosis complaining of chest pain during menstrual cycle should be systematically investigated for an earlier diagnosis of TE. 29

Sometimes the pneumothorax might not occur, or it may be small to escape medical attention, in that case the visceral pleural implants will continue to proliferate and shed during cycles into the pleural spaces. These endometrial implants will further seed into parietal and diaphragmatic pleural surfaces, leading to chest pain. ensue.4 Catamenial Eventually hemothorax will hemothorax is an infrequent manifestation of TES, occurring in 14% of the cases of this syndrome. 1,3,4,21,30 Catamenial hemothorax may present in association with CP, but this occurrence is uncommon.8 The right side is involved in almost all the cases, although one case of associated right pneumothorax and left hemothorax has been reported.<sup>9,30,31</sup> The most common presenting symptoms are chest pain associated with dyspnea and cough.4 In some instances, signs can mimic those of pulmonary embolism.<sup>9,32</sup> Severe anemia is possible.<sup>9,32</sup> Computed tomography scans may show additional features such as nodular lesions of pleura, multiloculated effusions or bulky pleural masses.

The cyclic hemoptysis occurring during menses is very rare. Hemoptysis is seen only in 7% of the cases. 4,21,25 TES presents as mild to moderate hemoptysis or very rarely as a lung nodule. Never as life-threatening hemoptysis. 1,16 Cough is the predominant feature when compared to chest pain.4 Hemoptysis is usually seen in the younger population. Due to the availability of invasive techniques, diagnosis can be made earlier but studies have shown that a minimum of more than 4 episodes of hemoptysis is generally seen before the definitive diagnosis of TE is made.4 Computed tomography signs of pulmonary endometriosis include ill-defined or well-defined nodules. thin-walled cavities, opacities. formations, and ground glass opacities. 16 All of these lesions, which are expressions of the endometrial implants or secondary hemorrhage, may change in size during the menstrual cycle. Unfortunately, computed tomography seems to have a low diagnostic yield in tracheobronchial endometriosis without parenchymal involvement. 16,25

Virtual bronchoscopy has been suggested to have some additional value in this setting. Bronchial angiography has been employed, but normal angiograms are found in as many cases as pathologic ones. <sup>16</sup>

As the clinical symptoms are variable in TES, and requires temporal association with menstrual cycle, the initially history taking especially in reproductive age group women presenting with nonspecific symptoms such as chest pain, cough, dyspnoea and if she is a known case of pelvic endometriosis, one should always have high level suspicion and consider thoracic endometriosis as a differential diagnosis and evaluate the women further.

#### **DIAGNOSIS**

Diagnosis of TES is challenging, because the symptoms and the radiological features are non-specific.<sup>25</sup> The main feature is the temporal association of these features with the menstrual cycle. Hence, the diagnosis can be improved if the imaging studies are done within 72 hours of onset of the menses and also repeating the same during the midcycle as well. This will help us to see the disappearance of the lesions in the mid cycle, further increasing the suspicion over the diagnosis of TES. 1,16,25 Also the radiologist should also be aware of this syndrome which will help to initiate a pelvic exploration for endometriosis in the same sitting which can further improve the diagnosis and also benefit the patient. The imaging modalities included are - chest radiographs (CXR), computed tomography (CT), magnetic resonance imaging (MRI), bronchoscopy and video assisted thoracoscopic surgery (VATS).

### CT features

A multidetector row CT of the whole thorax and upper abdomen is required. Although the specificity is low, CT is the first line of imaging method because it helps in ruling out other lung pathologies. Features of pneumothorax or pneumoperitoneum or both and presence of bullae or blebs with right sided predominance with cyclical changes, point towards the diagnosis of catamenial pneumothorax. For diaphragmatic lesions, one has to be cautious to look specifically for the abdominal side of diaphragm and mostly in the posterosuperior side for lesions. Fresence of solitary or multiple nodules, or thin walled cavities or ground glass opacities, usually in the peripheral part, along with variation in their size with different phases of the menstrual cycle, is a key feature pointing towards catamenial hemoptysis. 16,25

### **MRI** features

The high contrast resolution used in MRI, helps in better characterization of hemorrhagic lesions.<sup>25</sup> The pleural based lesions appearance as homogeneously high intensity signals in T1 and T2 weighted images.<sup>32</sup> It has been said that MRI is a better diagnostic tool for identifying the diaphragmatic endometriosis lesions.<sup>25</sup>

## **Bronchoscopy**

Usually done in cases presenting with hemoptysis. Descriptions of bronchoscopy findings are, therefore,

extremely rare with fewer than 10 cases having been reported. 34,35 Multiple, bilateral purplish-red submucosal lesions, which ooze easily if touched, seem to be the commonest feature, but the spectrum of tracheobronchial abnormalities ranges from a striking diffuse hyperemia with pronounced mucosal oozing to a single, tiny red mucosal spot. 4 Curiously, bronchial biopsy almost constantly fails to provide a tissue diagnosis regardless of the bronchoscopic findings, whereas brush cytology frequently shows distinctive features of endometrial cells. 33

Even when all the sampling bronchoscopic procedures have failed to yield a diagnosis of endometriosis, follow-up bronchoscopic examination in the middle of the menstrual cycle typically documents the disappearance of the previously reported findings, thus strengthening the clinical suspicion.

#### Video assisted thoracoscopic surgery

VATS is both diagnostic and therapeutic. Tissue diagnosis is the gold standard for diagnosis of thoracic endometriosis. In the largest review of patients with catamenial pneumothorax, 52.1% were diagnosed with thoracic endometriosis based on VATS findings. The most commonly reported intraoperative findings included diaphragmatic lesions (38.8%): endometriosis of the visceral pleura (29.6%); discrete lesions such as bullae. blebs, or scarring (23.1%); and no findings (8.5%).<sup>36</sup> Improved endoscopic evaluation for suspected thoracic endometriosis can be achieved by utilizing the combined thoracoscopic and laparoscopic approach as described by Nezhat et al in 2009.<sup>37</sup> Additionally, techniques for optimal diaphragmatic evaluation have been described such as placing the patient in steep reverse Trendelenburg position and using an atraumatic liver retractor or grasping forceps to push the liver caudally. Using a 30-degree endoscope or an adjustable viewing-angle endoscope can further help in better visualization. Rarely, cutting the falciform ligament is necessary for complete evaluation of the right hemidiaphragm.3

## Histopathological and immunological diagnosis

Kawaguchi et al has stated that classic histopathologic features of endometriosis are represented by a "triad" composed of endometrial glands, stroma. hemosiderin-laden macrophages.<sup>7,38</sup> However, in contrast to pelvic endometriosis, endometrial glands are not always present in thoracic endometriosis it is only the stroma that is present called as stromal endometriosis. The typical endometrial glands and stroma can be diagnosed by HE staining but it is difficult to distinguish endometrial stroma and inflammatory cells by HE staining alone. Given these challenges. diagnostic criteria based immunohistochemistry, that is by using ER, PR and CD10 markers are required for thoracic endometriosis diagnosis. The ER, PR and CD10 are present in endometrial stromal cells whereas only ER and PR are present in endometrial glands.<sup>7,39</sup> Further, the staining pattern was classified as scattered and aggravated patterns. The scattered pattern was positive for only ER and PR. Whereas the aggravated pattern was positive for ER, PR and CD10. As a control Kawaguchi et al used specimens resected from males with history spontaneous pneumothorax and these samples were stained positive for only ER and PR.<sup>7</sup> Hence, it was concluded that to diagnose a case of thoracic endometriosis using a tissue sample, if the HE staining is negative, immunohistochemistry should be performed and an aggravated pattern which stains positive for ER, PR and CD10 should be present for accurate diagnosis.<sup>7</sup>

#### **MANAGEMENT**

Management of thoracic endometriosis is individualized. The main aim in management is to prevent the recurrence after addressing the current symptoms once the diagnosis of thoracic endometriosis is made. There can be combined (medical and surgical) and sequential approach. The first line of management is based on the presenting signs and our analysis of its pathogenesis. Due to the advances in minimally invasive procedures, VATS can be used for diagnostic and therapeutic purposes. When combined with laparoscopy, then the management seems comprehensive as it will involve both the thoracic and pelvic cavity. But the choice of using VATS alone or VATS and VL again depends on the presenting complaints and radiological images.

#### MEDICAL MANAGEMENT

It has been understood for some time that endometriotic tissue is hormonally sensitive, and that symptoms of endometriosis usually improve during pregnancy or after menopause. Currently available medical therapies for endometriosis act by attempting to create a hypoestrogenic environment by mimicking: menopause (GnRH analogues), amenorrhoea (chronic anovulation danazol) or pregnancy [oral contraceptives (Ocs) or progestins]. Unlike surgery, these methods of treatment are non-invasive and are not operator dependent. 1,16,40 However, a disadvantage for women desiring pregnancy in the near term is that conception is generally not possible during medical therapy—indeed, many of these agents are also used as effective contraceptives. Therefore, before choosing therapy, health care providers should consider an individual woman's family plans and fertility status. Other drugs that can be considered are aromatase inhibitors and, tumor necrosis factor alpha (TNF alpha) inhibitors, matrix angiogenesis inhibitors, metalloproteinase inhibitors and certain immunomodulators. These drugs show decreased spreading of lesions and reduced disease related symptoms. 40

The difference in the efficacy, outcome, recurrence rate on stopping the drug has not been studied completely till date. Hence the factors like drug cost, patient preference, side effects should dictate which medications to be used. 1,3,16,40

#### SURGICAL MANAGEMENT

Patients presenting with catamenial pneumothorax, if diaphragmatic defects along with lesions are noted, then the surgical management is the first line of approach. This involves, optimal visualization of the diaphragm is obtained by positioning the patient in steep reverse Trendelenburg while gently pushing the liver caudally. Endometriotic implants on the diaphragm are most commonly black, blue, or reddish-purple in appearance. Hydrodissection followed by excision or CO<sub>2</sub> laser vaporization is a recommended endoscopic treatment for diaphragmatic endometriosis. Alternative modalities when a CO<sub>2</sub> laser is not available are plasma jet energy and ultrasonic energy. These are preferred to the use of cold scissors due to the potential for bleeding requiring bipolar hemostasis. The use of monopolar electrocautery on the diaphragm should be minimized because of its potential side effects like greater depth of tissue penetration, thus increasing the risks of necrosis or fenestration formation. Furthermore, monopolar energy can potentially induce heart arrhythmias or errant diaphragmatic muscular contractions. 1,16 After treatment of diaphragmatic lesions if the resected surface is small use of endoscopic stapler device is the most appropriate approach but if there are large perforations use of synthetic mesh is recommended .In cases in which the lesions affect the full thickness of the diaphragm, the combined VL/VATS approach is useful in achieving complete resection of the diseased tissue. Depending on the size of the diaphragmatic defect, this can be repaired using either the endoscopic stapler or synthetic **Patients** with catamenial pneumothorax experiencing mild symptoms, thoracocentesis has been used for symptomatic relief. Tube thoracostomy has been used in the treatment of some patients with CP. 1,3,16

Patients presenting with catamenial hemothorax, needs initial treatment with thoracocentesis followed by VATS, if the superficial endometriotic implants are noted, one should fulgurate lesions using bipolar diathermy/CO<sub>2</sub> laser/Nd-YAG laser/argon laser or plasma energy, while deeper endometriotic implants should be excised using sharp dissection, other modalities used are parenchymalsparing procedures such as wedge resection with a stapling device, subsegmentectomy, or in some cases, lobectomy. An alternative intervention for TES is pleurodesis. 1,3,16 This can be accomplished chemically with talc or tetracycline, or mechanically with pleural ablasion and pleurectomy. Use of pleurodesis demonstrated to allow a median recurrence-free interval of 61 months in 28 patients. It was also reported to decrease the recurrence rate of pneumothorax after VATS by 20-25% compared in those who did not have pleurodesis performed at the time of surgery. 42,43

Patients with catamenial hemoptysis, bronchoscopy is first tried. But this will not help in making the diagnosis, but at times will help us in identifying the bleeding lobe or the segment. Hence in these patients after radiological imaging, medical management should be opted first. If the

patient does not respond, a combined surgical-medical management should be executed. 1,3,16 Thus, VATS is the ultimate step in the diagnosis and management of TES. The outcome of surgeries is operator dependent. But inorder to improve the outcome, the timing of performing the procedure is also important. It has been proposed that VATS should be performed within 72 hours of onset of the menstrual cycle for a successful outcome.

In our experience, we encountered 2 cases of TES over a period of 3 years, of which one case was a 30 years old, P1L1A1, with catamenial breathlessness for 5 years (MMRC grade 2) associated with dry cough and loss of appetite and loss of weight since one and half years. Menstrual cycles were regular with severe dysmenorrhea evaluation, right sided gross pleural effusion with mediastinal shift with mild pleural effusion on left side were noted. In view of her cyclical symptoms and raised CA125 levels decision for thoracoscopy was made which coincided with the 3rd day of the menstrual cycle. Multiple hyperemic nodules over the diaphragmatic pleura were noted, which was sent for HPE. HPE confirmed the diagnosis of thoracic endometriosis. Pleurodesis was done with injection doxycycline 100 mg. Patient was started on injection leuprolide 3.75 mg every month for 6 months. Patient improved symptomatically.

The other case was a 27-year-old female, unmarried, with multiple hospital visits in the past 1 year came to us with complaints of catamenial breathlessness, loss of weight and reduced appetite, symptoms seen predominantly during menstrual cycle. Due to multiple episodes of pleural effusion, the patient was subjected bronchoscopy + BAL -reported as chronic inflammation. Patient later was clinically diagnosed with TB and received ATT for 6 months. Despite which symptoms did not reduce. So, she was referred to our institute for further evaluation and management. Initial assessment showed right pleural effusion which was confirmed by CECT. USG abdomen and pelvis showed bilateral endometriotic cysts of approximately 5×5 cm. CA125 value was 49 u/ml. So she was subjected to thoracoscopy with pleural biopsy on day 3 of the cycle, which showed multiple hyperemic nodules all over the parietal and visceral pleura, biopsy from nodules were taken and sent for HPE which confirmed endometriosis. Pleurodesis was done with injection doxycycline 100 mg was performed and patient was started on tablet dienogest 2 mg for 6 months. Patient improved symptomatically. At 6 months chest X ray was within normal limits and endometriotic cysts had decreased significantly.

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