REVIEW ARTICLE

Thoracic endometriosis syndrome: current concept in pathophysiology and management

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ABSTRACT

Background: Thoracic endometriosis is a rare pathology. The diagnosis is often delayed or missed, however recently, there has been significant advances in the knowledge of this condition and hence, an improvement in the diagnosis and treatment.

Objective: To review the current concepts in the pathophysiology and management of thoracic endometriosis syndrome.

Methodology: The main source of information included manual library search and journal publications on PubMed/Medline, Google Scholar, and EMBASE.

Results: Many theories have been proposed to explain thoracic endometriosis syndrome, but none of them can fully explain the different manifestations of thoracic endometriosis syndrome (TES) which include catamenial pneumothorax, catamenial haemothorax, catamenial haemoptysis, pulmonary nodule, catamenial pneumomediastinum and isolated chest pain. Radiologic and endoscopic modalities are necessary for making a diagnosis, in addition to a high index of suspicion. Medical treatment traditionally involves the use of oral contraceptive pills, progestational agents, danazol and gonadotrophin releasing hormone analogues. Surgical treatment involves the use of video-assisted thoracoscopy (VAT) or thoracotomy.

Conclusion: A multidisciplinary approach is recommended for the optimal management of TES.

***Keywords**: Catamenial pneumothorax, catamenial haemoptysis, catamenial haemothorax, pulmonary nodule*

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. It affects about 10% of women in reproductive age group; the incidence of extrapelvic endometriosis in these women being approximately 12%.[1,2]

Thoracic endometriosis syndrome (TES) is a rare manifestation of extragenital endometriosis. It is defined as the presence of

endometrial tissue in the thoracic cavity, proven histologically by identification of the presence of endometrial stroma and glands in the lesions found in the chest.[3] The diagnosis is, however, considered suggestive in the presence of only stroma and pulmonary parenchymal haemorrhages / or haemosiderin-laden macrophages.[4] The most common sites of TES include the pleura (parietal and visceral), lung parenchyma, diaphragm and airway.

The spectrum of presentation of TES includes catamenial pneumothorax (73%), catamenial haemothorax (14%), catamenial haemoptysis (7%), pulmonary nodules (6%), catamenial pneumomediastinum and isolated chest pain.[5,6]

Thoracic endometriosis has been shown to be associated with pelvic endometriosis in 60-80% of cases, however, a recent study shows a concurrent rate of 100%.[6-8] Thoracic endometriosis syndrome is also associated with infertility.[9]

The management of TES involves a multi-disciplinary approach.[8] Medical treatment is achieved by the use of hormonal drugs; however, recurrence is high with using this form of management alone. Surgical treatment is achieved via the use of video-assisted thoracoscopy, and less commonly, a thoracotomy.

We reviewed this topic to provide surgeons, pulmonologists and gynaecologists with up-to- date information in managing this rare disease entity.

METHODS

A literature search on the subject was done from 1950 to date using manual library search and journal publications on PubMed / Medline, Google Scholar, and EMBASE. We found about 189 articles. Full texts of about 100 publications were collected and studied. We chose these articles based on their content of up-to-date information relating to the epidemiology, pathogenesis, pathology, clinical features, investigations and treatment. The relevant articles included original articles, case series, case reports and literature reviews.

RESULTS

a. Epidemiology

Endometriosis afflicts women in their reproductive years. It is more common among nulliparous women and those with short and heavy menstrual cycle.[1] It has been rarely reported in men, postmenopausal patients and adolescents with uterine abnormalities.[10,11]

The most commonly described lesions in thoracic manifestation are those on the diaphragm (38.8%) and visceral pleura (29.6%).[12]

In a retrospective study which recruited 110 patients with TES, the mean age at presentation of patients presenting with thoracic endometriosis was 35years ± 0.6years with a range of 15-54years.[6] The peak incidence of TES was 30-34years, compared with the peak incidence of pelvic endometriosis, which was from 24-29years; approximately 5years later.[13]

Thoracic endometriosis syndrome is more commonly located on the right side, occurring in approximately 85-90% of cases.[14] Left sided and bilateral lesions have also been described.[15,16]

b. Pathogenesis

Many theories have been postulated to explain thoracic endometriosis; however, none of them can wholly explain the phenomenon.

One of the most popular is the Sampson Theory of Retrograde Menstruation.[16,17] The theory states that eutopic endometrium is sloughed into the peritoneal cavity via the patent fallopian tubes during menstruation. This is supported by the fact that retrograde menstruation has been observed in 90% of healthy menstruating women during laparoscopy.[18]

Other findings that support the theory of retrograde menstruation are the findings that endometriosis is more common in women with Müllerian anomalies and those with

unusually longer length and shorter cycles of menstruation.[19,20] These Müllerian anomalies cause increased retrograde menstrual flow and result in outflow obstruction. The fact that endometriosis does not occur in most women despite this high prevalence of retrograde menstruation suggests that there are a lot of other implicating factors and additional steps necessary for the development of endometrial implants from retrograde menstruation.

They may include the role for escape from immune clearance, attachment to peritoneal epithelium, invasion of the epithelium, establishment of local neovascularity and continued growth and survival.[21] This theory has also failed in explaining endometriosis in patients who have had tubal ligation.

The Concept of Peritoneal Circulation does not only augment the theory of retrograde menstruation but, also, explains the reason why thoracic endometriotic lesions occur predominantly right-sided. Peritoneal circulation occurs in a natural clockwise direction; commences in the pelvis and reaches the right sub-phrenic space via the right paracolic gutter.[22] The endometrial cell and debris, subsequently, enter the thoracic cavity.

Another important theory is that of Coelomic Metaplasia.[23] This is based on the fact that both endometrial and mesothelial cells are derived from coelomic epithelium. The mesothelial cells can undergo metaplastic change under appropriate pathogenic stimuli, brought about by the refluxed menstrual blood.[24] This theory actually explains the occurrence of endometriosis in females that are not menstruating and in males with endometriosis, but failed to explain the predominantly right-sidedness of lesions of TES.

The Theory of Lymphovascular Microembolization of endometrial tissue explains the pathogenesis of pulmonary parenchymal endometriosis and bronchopulmonary endometriosis.[24] Microembolization of the endometrial tissue may result from trauma following or during gynaecological intervention. The Theory of Lymphovascular Microembolization explains catamenial haemothorax, catamenial haemoptysis and pulmonary nodules; however, the pathogenesis of catamenial pneumothorax and non-catamenial endometriosis related pneumothorax cannot be explained by this mechanism.

Diaphragmatic pores or fenestrations may be congenital or acquired. Diaphragmatic fenestrations may be located in the areas of endometriotic implants. These pores vary in sizes, usually small; however, a defect of up to 4inches and a defect large enough to permit hepatic protrusion have been reported.[25,26] Morgagni's hernia has also been reported in association with catamenial pneumothorax.[27] Based on the presence of these pores, Kirschner introduced the Concept of the Porous Diaphragm Syndrome, which hypothesizes that the presence of pre-existing diaphragmatic defects allows gas and fluids to traverse this boundary.[28] However, porous diaphragm cannot explain all cases because diaphragmatic defects have been previously documented in only 19-33% of them, and cases of recurrent pneumothoraces are still being reported after hysterectomies.[29]

The theories below mainly explain the pathogenesis of catamenial pneumothorax:

Theory of Transperitoneal-Transdiaphragmatic Migration of Endometrial Tissue

It is believed that, there exists, a trans-fallopian movement of the air from the vagina to the peritoneal cavity aided by absent cervical mucus plug during menses. Peritoneal circulation augments movement towards the right sub-diaphragmatic space. Air, subsequently, enters the pleural space through the diaphragmatic defect on account of negative intra-thoracic pressure and the "piston-like" action of the solid liver bulk.[22,24]

Another mechanism that can explain catamenial pneumothorax is **Increase in the Local and Circulating Prostaglandin $F_2\alpha$** during menses.[30] This may induce alveolar

rupture via vasoconstriction and bronchiolar constriction, ultimately leading to pneumothorax. Visceral endometrial tissue can slough off causing alveolar leak and pneumothorax.[14,31] This hypothesis explains the sole finding of only bullae and blebs in 23.1% of all explored cases.[32]

Another mechanism has been implicated by Lillington GA, *et al*. It is believed that swelling of the endometrial tissue located in the terminal bronchioles can cause localized hyperinflation by check-valve mechanism leading to pneumothorax.[33] Hereditary factors may also play a role.

c. Pathology

Diagnosis is based on the presence of endometrial glands and stroma. The surrounding stromal cells resemble those of the proliferative phase. Of important significance is the presence of haemosiderin-laden macrophages, if present. Oestrogen and progesterone receptors are demonstrable on the glands using immunohistochemistry. The glands also stain positively for cytokeratin-7, BER-EP4, while the stroma may stain for actin, desmin, vimentin, oestrogen and progesterone.[34] Thyroid transcription factor-1(TTF-1) is a pulmonary marker, and alveolar epithelium stain positively for it.[35] Cluster of differentiation (CD) 10 is a sensitive immunohistochemical marker for endometrial-type stromal cells and is of value in establishing a definitive diagnosis of endometriosis.[36]

d. Major Types and Clinical Features

i. Catamenial Pneumothorax and Non-catamenial Endometriosis related Pneumothorax

Catamenial pneumothorax was first described by Maurer, *et al*, in 1958.[37] It is the most frequent presentation of thoracic endometriosis syndrome and is defined as spontaneous recurrent pneumothorax occurring within 72hours of onset of menstruation.[38] However, cases of pneumothorax occurring in the inter-menstrual period associated with thoracic endometriosis have also been reported; the so called non-catamenial endometriosis related pneumothorax.[39]

Catamenial pneumothorax is mainly right-sided, however, left-sided and bilateral cases have been reported.[16,40,41]

Previous studies revealed catamenial pneumothorax as the most common cause of TES, however, when the catamenial chest pain/pleurisy is distinguished from documented pneumothorax, pneumothorax was responsible for only 40% of symptoms, while chest pain was seen in 80% of cases.[8] In another study, pneumothorax was noted to be the third most common symptom occurring at a rate of 24%.[13]

Diagnosis is usually made after many episodes of spontaneous pneumothorax.[2] Most patients will likely complain of symptoms in synchrony with menstruation or just around the period; although, occurrence in the inter-menstrual period does not simply exclude this pathology. The main symptoms include dyspnoea, recurrent cough, recurrent pleuritic chest pain and scapular pain; the first episodes occurring at an older age than those presenting with idiopathic pneumothorax. Symptoms are usually mild, though complicated cases have been reported.

Recurrence rate of catamenial pneumothorax is high. This may be related to endometrial glands in the diaphragm. When compared with non-recurrent cases, recurrent cases appear to have a higher ratio of endometrial glands in the diaphragm (66.7% vs 37.8%).[42]

ii. Catamenial haemoptysis

Rodman and Jones were the first to propose the term 'catamenial haemoptysis'.[43] This is a rare manifestation of thoracic endometriosis, accounting for just 7% of TES.[5] It is usually mild and the volume of haemoptysis is usually between 5-50ml /day of blood and episodes last for 3-

5days. No report of massive or fatal haemoptysis secondary to thoracic endometriosis has been reported.[24]

Catamenial haemoptysis usually denotes pulmonary parenchymal endometriosis with or without endobronchial involvement. Yu JH, *et al,* reported a case of endobronchial endometriosis simulating central type lung cancer and presenting with dyspnoea and cough of four days duration without haemoptysis.[35] Some reported cases have been shown to resolve spontaneously and did not re-occur within the period of observation.[44] It is absolutely necessary to rule out very important causes of haemoptysis like tuberculosis, pulmonary infection, bronchiectasis and bronchogenic carcinoma. A coincidence of haemoptysis occurring concurrently with menses will help to differentiate these conditions from catamenial haemoptysis.

iii. Catamenial Haemothorax

Most of the reported cases are unilateral and right-sided.[45] Cases of bilateral haemothorax or left-sided haemothorax have been reported.[46,47] Ravindra, *et al,* reported a case of concurrent haemothorax and contralateral haemopneumothorax.[48] Massive blood-stained pleural effusion has been reported in association with intra-abdominal endometriosis without evidence of thoracic endometriosis.[49] Catamenial haemothorax may be asymptomatic or may be associated with shortness of breath and pleuritic chest pain. Effluent may range in colour from haemorrhagic to chocolate fluid, and up to 2.3L of fluid have been reportedly drained from the chest.[50] Catamenial haemothorax has been associated with pleural and diaphragmatic endometriosis.

iv. Pulmonary Nodules

This is the most uncommon manifestation of TES accounting for 6% of cases. They may be asymptomatic or they may present with catamenial haemoptysis.[6] This manifestation appears to be more commonly seen in comparatively older women. Jukna, *et al*, reported a case of thoracic endometriosis masquerading as a peripheral nodule of the left lung in a 50-year old woman with a history that is not characteristically catamenial.[15] Lung cancer is, therefore, an important differential diagnosis, more especially when a nodule presents with eccentric cavitations.

INVESTIGATIONS

Chest radiograph is cheap and available; however, its use is limited. Rarely, small diaphragmatic defects showing as bubbles at the level of the diaphragm, opacities corresponding to partial liver herniation through right diaphragmatic defects have been described.[51]

Chest CT scan is the first line of investigative modality of choice in thoracic endometriosis. It is, however, poorly specific but has an advantage of helping to rule out other pulmonary lesions. Computerized tomographic findings may reveal ill-defined opacities, areas of focal consolidation, areas of bullous disease and ground glass appearance. These features are not pathognomonic of the disease, but strongly suggest pulmonary endometriosis. Diaphragmatic endometrial implants may present as hypo-attenuating areas. The features seen in CT scan may change during the menstrual phase and disappear after menses; hence comparing CT findings during and after menstruation may help to support diagnosis.[52]

Magnetic resonance imaging (MRI) is, equally, very valuable in the diagnosis of pulmonary endometriosis because of the presence of blood products in the endometrial deposits.[53] It is, also, useful in ruling out other diseases. Magnetic resonance imaging is superior to CT scan in making a diagnosis of thoracic endometriosis because there is less exposure to irradiation and it is more sensitive in differentiating pleural from parenchymal endometrial implants. Bronchoscopic evaluation of the airway requires proper timing. It may yield normal findings because pulmonary endometriosis

involves the distal parenchyma. Wang, *et al,* demonstrated multiple purplish-red submucosal patches that bleed easily when touched.[54] In patients with catamenial haemoptysis, it may be useful in localization of the involved lobe or segment.[24] The procedure is better performed during menses, especially the first 2 days of menses. Repeat bronchoscopic evaluation performed in the middle of menstrual cycle may show disappearance of previous tracheo-bronchial lesions.[54]

The tissue biopsy obtained, aspirate or fluid from broncho-alveolar lavage should be sent for histocytological analysis and the diagnosis of pulmonary endometriosis is supported by the presence of endometrial tissue.[55] Cytologic evaluation of the brushing specimens may be useful in diagnosis.[54] It may demonstrate clusters of small cuboid cells which is consistent with an endometrial origin unlike cytological examination of pleural fluid which is rarely useful.[54]

Serum CA-125 is a biomarker that has shown some promise in diagnosis of endometriosis. An elevated serum CA-125 is associated with any process that irritates the mesothelial cells e.g. endometrium, peritoneum and pleura.[2] Concentration of CA-125 may be elevated both in the serum and peritoneal fluid of patients with endometriosis. Serum CA-125 may be more useful in the detecting severe forms of endometriosis as the level is significantly increased in severe and deep cases.[56]

Video-assisted thoracoscopy is useful in direct visualization of endometriosis implants on the visceral, parietal, diaphragmatic pleura and pulmonary nodule. Biopsy can be obtained during thoracoscopy; however, it is important to note that negative biopsy does not rule out endometriosis.

There is a role of pelvic ultrasound scan in patients being investigated for thoracic endometriosis. Pelvic ultrasound scan and laparoscopy are more sensitive in detecting associated pelvic endometriosis, as thoracic endometriosis coexists with pelvic endometriosis.[6,7,8] Laparoscopic evaluation will also serve the opportunity to routinely identify diaphragmatic lesions.[8]

TREATMENT

Conservative Treatment

Conservative treatment of thoracic endometriosis involves the use of pharmacological agents; however, the use of bronchial artery embolization and laser treatment has been rarely described.

Pharmacological Treatment: Pharmacological treatment is usually used as an adjunct to surgical treatment of the thoracic endometriosis. The combined approach of hormonal therapy and surgery may be the best approach, because recurrence rate after hormonal manipulation alone can be as high as 50%.[57] There are principal forms of hormonal suppressive therapy and they include the use of oral contraceptive pills, progestational agents, danazol and gonadotropin releasing hormone analogues.

Oral contraceptives function by inducing atrophy of the endometriotic tissue, down-regulating the proliferation of endometrial cells increasing apoptosis in endometriotic tissue reducing retrograde menstruation and menstrual flow hence preventing reseeding of refluxing endometrial tissue.[58,59,60] It, also, reduces production of prostaglandins and inhibit ovulation.[61] It is safe, well tolerated and reduction in the anatomical relapse have been observed when oral contraceptives was administered for one year after surgery. Side effects include fluid retention, headaches, nausea, bloating mood changes, hirsutism, etc.

Progestational agents suppress LH, FSH, and prevent ovulation. They are cheap and safe. Danazol is a derivative of 17-alpha ethinyl testosterone and inhibits LH and FSH with resultant hypoestrogenic state. It is notorious for causing hyperandrogenic side effects such as acne, voice deepening hirsutism and decrease in breast size.

Gonadotrophin-releasing hormone agonists (e.g. Goserelin, Lenprolide) induce pseudomenopausal state. They are effective, though costly, and may cause undesirable side effects like hot flashes, mood swings, decreased libido, genital atrophy and depletion of bone minerals.

Bronchial artery embolization may be a suitable first line treatment for catamenial haemoptysis. Reported cases of patients treated with bronchial artery embolization revealed that patients did not experience recurrence of symptoms subsequently.[62,63]

Lasers have been found to be useful in treating thoracic endometriosis. Various forms of laser treatment have been used in the treatment of endobronchial endometriosis.[64,65]

Surgical Treatment

Tube thoracostomy is useful in the initial management of catamential pneumothorax, haemothorax and haemopneumothorax.

Surgical approaches can either be via a thoracotomy or video-assisted thoracoscopic (VAT) approach. Lateral or postero-lateral thoracostomy is performed where VAT is not available. Video-assisted thoracoscopy is the gold standard for diagnosis and treatment of thoracic endometriosis. It affords the surgeon the opportunity to take biopsies of parenchymal or parietal nodules, excise parenchymal and endometriotic lesions, resect blebs, perform parietal pleurectomy and mechanical pleural abrasion and talc pleurodesis.

Small parenchymal and superficial diaphragmatic lesions can be conservatively treated with monopolar energy, bipolar energy, CO_2 laser and plasma energy. Pulmonary resection surgeries such as segmentectomy, wedge resection and lobectomy are indicated in lesions involving the deep pulmonary parenchyma or huge pulmonary implants.

Sutures, mechanical staplers and diaphragmatic patches have been used to close large diaphragmatic fenestrations.[66,67] Polyglactin mesh has been used to suture the defects in the diaphragmatic surface using an endoscopic tacker device via VATS or less commonly using muscle sparing thoracotomies.[68] Non-absorbable PTFE mesh has been used to cover multiple diaphragmatic pores in a patient with catamenial pneumothorax.[69]

It may be ideal to operate on these patients in the inter-menstrual period. Under general anaesthesia, lung protective ventilatory modes are ideal, as the presence of parenchymal injury and damage may predispose the patients to ventilator induced lung injury.[70]

Nezhat, *et al*, have developed a protocol which employs a multi-disciplinary approach of VAT and video-assisted laparoscopy for direct visualization and treatment of the thoracic endometriosis, sub-diaphragmatic disease and pelvic endometriosis, since both thoracic endometriosis and pelvic endometriosis have been found to coexist.[8]

The role of pleurodesis is important to prevent significant pleural re-accumulation. This may be in the form of chemical pleurodesis (using tetracycline, doxycycline, etc.) or mechanical pleurodesis (employing parietal pleurectomy or pleural abrasion). Standard pleurodesis alone may not be sufficient especially when surgery is associated with diaphragmatic procedure, hence it may be useful to also perform apical resection and apical pleurectomy, if indicated.[71]

Although complete surgical excision may prevent recurrence, rates of about 30% recurrence have been documented after surgery for catamenial pneumothorax.[72] No recurrence was noted for 45 months in three patients when gonadotrophin-releasing hormone analogue was introduced following surgical treatment of thoracic endometriosis; however, post-operative recurrence was observed in a patient in whom the hormonal drug was delayed for six weeks.[73]

Following recurrence of catamenial pneumothorax, repeat operation can be safely performed despite having had previous surgeries. Missed diaphragmatic lesions are frequently seen during repeat surgery.[74]

CONCLUSION

Thoracic endometriosis is rare and the management involves a multi-disciplinary approach. An effective work-up and a combination of both medical and surgical treatments are required to reduce the risk of recurrence.

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