Extragenital Endometriosis

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Abstract: In recent years, there have been significant changes in many aspects of extragenital endometriosis ranging from the epidemiology to the management of the disease. Advances in minimally invasive surgery and expansion of the field have lead to further research in management of extragenital endometriosis. As a result, treatment has shifted from medical management toward a surgical, multidisciplinary approach. Surgery for extragenital endometriosis clearly improves outcome through relief of symptoms, improved quality-of-life, increased fertility rates, and reduced recurrences. Endoscopy has a pivotal role as both a diagnostic and therapeutic tool.

Key words: endometriosis, extragenital, intestinal endometriosis, urinary tract endometriosis, thoracic endometriosis, laparoscopy

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity, affecting as many as 15% of fertile women and up to 50% of infertile women.1 It occurs commonly in the pelvic organs, especially in the ovary. Occurrence outside the pelvis is termed extragenital or extrapelvic endometriosis. Although a relatively common condition, endometriosis remains difficult to recognize, diagnose, and treat because of its extremely variable presentation, which is particularly true for extragenital endometriosis.

The clinicopathologic characteristics of 34 cases of extragenital endometriosis over a 9-year period at Glasgow Royal infirmary were reviewed. A total of 379 cases of endometriosis were diagnosed by histology during the period, giving an 8.9% prevalence of extragenital manifestations. Eleven (32.3%) cases were found in the intestinal tract, 2 (5.9%) in the urinary tract, and 21 (61.8%) were in other sites, including Pfannenstiel scar, inguinal canal, umbilicus, and perineum. Of all the cases, 52.9% presented to gynecologists and the mean time to diagnosis was 24.54 months (range 13.2 to 35.8). Pain was the most common presentation.

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(76.5%), with cyclic pain reported in only 41.2%. A palpable mass was found in 41.2%, especially in Pfannenstiel scar tissue (26.5%), which suggested an iatrogenic cause.²

There are currently no accepted classification systems for extrapelvic endometriosis. In 1989, Markham et al proposed a classification system that divided extragenital endometriosis into 4 different classes:

class I involving the intestinal tract;
class II involving the urinary system;
class III involving the lung and thoracic cavity; and

class IV involving "all other sites" including skin and nervous tissue.

They further recommended subdividing the degree of involvement into extrinsic and intrinsic, with further characterization of the lesion by size. Interestingly, one of the only sites where extragenital endometriosis has not been reported is the spleen. Patients presenting with symptomatic, verified extragenital endometriosis, represent 10% to 15% of all cases of endometriosis requiring laparotomy.⁴

The endometrial tissue grows invasively into the surrounding structures; mainly into muscle and connective tissues, rarely into the mucosa. In fascia or ligaments, the lesions are hard and fibrous. In subeutaneous—tissues—and muscles, they are softer and with diffuse limits. In smooth or striated muscle, endometriosis causes a pronounced cell hyperplasia with very little fibrosis; it is here that the endometriotic centers seem to flourish. Endometriosis often gives rise to pronounced fibrotic adhesions and can exhibit an infiltrative tendency that may be misinterpreted as a neoplastic tumor.

**Pathophysiology**

Following the original clinical description of endometriosis, much has been accomplished in further understanding this debilitating and burdensome disease. Generally classified by the proposed origin of implants, several theories have developed to explain the pathogenesis of this disease.

Though no single theory explains all the manifestations of endometriosis, the retrograde menstruation theory has gained widespread acceptance as an explanation for the dissemination of endometrial cells.⁵ Initially proposed by Sampson in the 1920s, the retrograde menstruation theory is both intuitively attractive and supported by multiple lines of scientific evidence. According to this theory, eutopic endometrium is sloughed through patent fallopian tubes into the peritoneal cavity during menstruation. This hypothesis has the greatest scientific validity because viable endometrial cells have been seen in menstrual flow and these cells have been successfully transplanted into the peritoneal cavity.

Although retrograde menstruation explains the physical displacement of endometrial fragments into the peritoneal cavity, additional steps are necessary for the development of endometriotic implants. These additional steps include attachment of endometrial fragments to the peritoneum, invasion of the epithelium, establishment of a vascular supply, and circumvention of the immune response. The factors that influence the survival and subsequent implantation of these cells remain unknown. Innate or acquired properties of the endometrium, peritoneum, and immune system represent plausible mechanisms to support the establishment of endometriotic implants.

Another theory suggests that metaplasia of coelomic epithelium represents a distinct pathogenic mechanism for the establishment of endometriotic implants.⁶ According to this hypothesis, normal peritoneal tissue transforms by metaplasia into ectopic endometrial tissue.

The closely related induction theory suggests that an endogenous inductive stimulus, such as a hormonal or immunologic factor, promotes the maturation of un-
differentiated cells into endometrial cells in the peritoneal lining. It has also been proposed that residual cells from embryologic mullerian duct migration maintain the capacity to develop into endometriotic lesions under the influence of estrogen.

Originally described in the 1920s, the theory of benign metastasis proposes that ectopic endometrial implants are the result of lymphatic or hematogenous dissemination of endometrial cells. Evidence for this mechanism is substantial. Microvascular studies show the presence of lymph flow into the ovary from the uterus, suggesting a role for the lymphatic system in the etiology of ovarian endometriosis. One study involved histologic examination of surgical specimens from 276 patients. The combined incidence of ovarian endometriosis and adenomyosis was 56%. Endometriosis within lymph nodes has been documented in 6.5% of women at lymphadenectomy and 6.7% of women at autopsy. The strongest evidence for the theory of benign metastasis is derived from reports of histologically proven endometriotic lesions occurring in sites distant from the uterus or pelvis, including bone, brain, and lung tissue.

Normally, refluxed endometrial tissue is rapidly cleared from the peritoneal cavity by the immune system. Dysregulation of this clearance mechanism has been implicated in predisposing individuals to implantation and growth of endometrial cells. Interestingly, larger tissue fragments, as opposed to individual cells, show an increased capacity to implant, presumably because of protection from immune clearance afforded to cells residing on the inner aspect of such fragments. Additionally, eutopic endometrium was more resistant to lysis by natural killer (NK) cells from women with endometriosis than from those without disease. Subsequent studies identified that constitutive shedding of ICAM-1 by endometrial stromal cells (ESCs) from patients with endometriosis may be the mechanism by which these cells escape NK cell-mediated clearance. Impaired NK cell function may confer a unique survival advantage to the regurgitated endometrial cells, thereby predisposing to endometriosis.

The classic histologic appearance of extragenital endometriosis is characterized by endometrial glands and stroma, responding in synchrony with the uterine endometrium. Repeated hemorrhage produces surrounding fibrosis and edema in the involved ectopic sites. These actions may modify the appearance of the lesions, leaving only glands without active stroma, dilated glands with flattened epithelium, or cysts without epithelium. In some cases, the only clue to the presence of endometriosis may be the existence of hemosiderin-laden macrophages, without glands or stroma.

With increasing anatomic distance from the uterus, endometriotic lesions have an increased tendency to lose hormonal receptors, to exhibit no hormonal response and to appear asynchronous when compared to the endometrium. This variation explains why symptoms produced by ectopic endometrium are cyclic and hormonally related in only approximately 50% of patients. It also explains why many distant endometriotic lesions do not respond to hormonal manipulation.

Hormone-dependent lesions, similar to those seen in the uterine endometrium, can also be seen in ectopic endometrium. Hyperplasia, especially in ovarian endometriosis, has been described as coexisting with uterine endometrial hyperplasia. Rare cases of cytologic atypia, without structural changes characteristic of carcinoma, have been described as atypical endometriosis. Occasionally, it may be difficult to differentiate atypical endometriosis from carcinoma. Pathologic confirmation of malignant transformation of benign endometriosis requires the contiguous presence of benign and malig-
nant disease. There have been 38 reported cases of malignant change in endometrial implants outside the uterus and ovary, not associated with other foci of endometrial cancer (28 adenocarcinomas, 7 adenoacanthomas, 2 clear cell carcinomas, and 1 squamous cell carcinoma). All cases were in the pelvis, with the majority arising in the rectovaginal septum and vagina. Survival has been poor, with a reported 5-year survival rate of approximately 20%.

The spectrum of symptoms found in patients with extragenital endometriosis, depends on symptoms that derive from the presence of extragenital disease and those related to the simultaneous existence of pelvic disease. Typically, symptoms present cyclically, correlated with menstruation—so-called catamenial symptoms—which are considered pathognomonic. Later in disease progression, symptoms become more continuous with much individual variation. The clinical diagnosis and histologic picture can be difficult to interpret. The glandular tissue is most often sparse. Sometimes hemosiderin inclusions can be found, or possibly epithelial cell remnants, suggestive of a spontaneous healing process.

The leading principles of treatment include tailoring therapy to individual patients, and maintaining ovarian function in women of child-bearing age. Knowledge of the natural history of the endometriotic tissue is limited. However, because symptoms usually progress over time, extragenital endometriosis should be treated. Drugs induce temporary quiescence of active deep lesions and may be useful in selected circumstances. However, in most cases of severely infiltrating disease, surgery is the final solution.

**Intestinal Endometriosis**

The reported frequency of intestinal endometriosis varies from 3% to 34% of women affected with the disease. Endometriomas on the bowel typically involve the serosa and muscularis propria, rarely involving the mucosa or submucosa. Endometriotic involved bowel reacts with significant fibrosis and overgrowth of the muscularis propria, often leading to narrowing and strictures of the bowel lumen. There is a strong association between ovarian and bowel endometriosis, with 80% of affected individuals having coexistent pelvic disease. Up to 50% of patients with severe endometriosis have gastrointestinal endometriosis. The most common sites of bowel involvement are: the rectosigmoid (51%), the appendix (15%), the small bowel (14%), the rectum (14%), and the cecum and colon (5%).

The pathogenesis of endometriosis, particularly bowel endometriosis, is a matter of great debate. A more clear understanding of the pathogenesis will eventually lead to more rational, evidence-based treatment. For many years, peritoneal lesions have been thought to be caused by retrograde menstruation and peritoneal implantation. The metastatic theory is historically associated with Sampson and, more recently, Nisolle and Donnez. The latter investigators have compared eutopic endometrium with peritoneal and rectovaginal endometriotic tissue. They concluded that rectovaginal endometriosis is probably derived from embryologically determined rests of mullerian tissue within the rectovaginal septum. There is also variation in the estrogen and progesterone receptor content, so that the regulatory mechanisms of rectovaginal endometriosis differ from those of eutopic endometrium.

Endometrial implants are typically located in the antimesenteric edge of the bowel. Macroscopically, they look as small, pigmented nodules on the peritoneum or as larger lesions, which infiltrate the muscular layer and narrow the bowel lumen. On microscopic sections, endometrial glands and stroma invade the bowel wall from the serosa inward.
In the muscularis, endometriotic nodules may be surrounded by smooth muscle hyperplasia and fibrosis, which may produce mural thickening and associated luminal stenosis. However, not all deep endometriotic bowel nodules are surrounded by extensive fibrosis. Endometriosis also may cause functional damage when it invades Auerbach’s plexus, the submucosal Meissner plexus and the interstitial cells of Cajal. The submucosa may be involved by endometriosis, but infiltration of the lesion into the mucosa is quite rare. Multiple endometriotic lesions of the bowel can be divided into 2 different categories: small satellite lesions located around a main one, and isolated nodules located at some distance from each other (ie, the sigmoid and cecum). Although the former pattern is very common, true “multiple” locations have been observed in 15% to 35% of cases.

Symptoms of diarrhea, constipation, perimenstrual changes in bowel habits, rectal bleeding, pain with defecation, tenesmus, abdominal distension, small caliber stools or colicky abdominal pain should make one suspect large bowel or rectosigmoid endometriosis. In more advanced cases, the presenting symptom may be those of a bowel obstruction. Obstructive symptoms can result from direct occlusion by transmural endometriosis or from circumferential constriction from intramural edema, fibrosis, or hemorrhage. Intussusception can result from localized edema or hemorrhage. Perforation can also occur. In postmenopausal patients, symptoms occur because of active residual disease, or from post-endometriotic scarring.

Any female patient with a history of chronic laxative use or futile attempts at management of constipation with dietary changes, should lead one to suspect intestinal endometriosis. Because these patients may have other complaints related to endometriosis, it is necessary to ask specifically about bowel symptoms.

In our experience, the truly asymptomatic patient with marked intestinal involvement is rare.

A careful bimanual and rectal exam may detect uterosacral nodularity, immobility, cul-de-sac fixation or nodularity. Immobility of the rectum or a pelvic mass that cannot be separated from the bowel may also be detected. Stool should be tested for occult blood. Patients with symptoms or physical findings suggestive of rectosigmoid endometriosis, severe stage endometriosis, or obliteration of the posterior cul-de-sac should have a preoperative colonoscopy, with or without a barium enema. Suspicious mucosal lesions should be biopsied to exclude malignancy.

Magnetic Resonance Imaging (MRI) scan, barium enema, colonoscopy or endorectal ultrasound rarely contribute to the diagnosis or alter the operative plan in cases of superficial endometriosis involving the gastrointestinal tract. However, they can be useful in cases of deeply infiltrating endometriosis, or to rule out alternative causes of a patient’s symptoms. Many patients with the above symptoms will be advised to undergo a diagnostic laparoscopy that is often inadequate. Frequently, patients are not placed in a sufficiently steep, Trendelenburg position to allow proper inspection of the pouch of Douglas. The patient should also be appropriately placed on the operating room table with the buttocks well over the edge, to allow for adequate vaginal and uterine manipulation. Even with “classical” visual findings consistent with endometriosis, all lesions should be biopsied to document endometriosis and exclude malignancy. Palpation with laparoscopic instruments, a rectal finger or probe should be done to outline the extent of endometriotic involvement.

Endometriosis of the appendix has been described in 17% of patients with bowel involvement. Appendiceal involvement may present as an incidental finding with or without pelvic disease.
Acute symptoms are similar to those of appendicitis, but may not include leukocytosis. The appendix should be inspected in all patients undergoing surgery for endometriosis and appendectomy is recommended if it seems abnormal. Endometriosis has also been Meckel's diverticulum.

Surgical treatment of bowel endometriosis remains controversial. Obviously, when obstructive symptoms are present, surgery is mandatory. However, in the absence of obstruction, it remains unclear whether surgery should be carried out, and if so, to what extent. At the present time, surgical removal of bowel endometriosis seems to be the most effective treatment in severely symptomatic patients. Several studies have shown that surgical removal of all endometriotic lesions, including those within the bowel, is associated with a significant improvement in gastrointestinal symptoms and quality-of-life.24,25 Historically, surgical treatment of intestinal endometriosis has been carried out with a coeliotomy. The first series of laparoscopic techniques successfully used to treat colonic endometriosis was reported by Nezhat et al26 in 1992. This followed the report of a successful laparoscopic resection of stage IV endometriosis in 1986. Since then, minimally invasive techniques to treat intestinal endometriosis have been increasingly used and reported in the literature.27-31

Commonly, gynecologic surgery is required at the time of surgical excision of intestinal endometriosis, therefore, a multidisciplinary approach is essential between the general or colorectal surgeon and gynecologist. Although the ability to treat intestinal endometriosis laparoscopically is feasible, this fact should not change the indications for the mode of surgical treatment.32-34

Endometriotic implants involving the distal ileum frequently require mobilization of that region and the right colon. This helps facilitate a laparoscopically assisted ileocolic resection with an ileo-ascending colostomy (carried out rarely), or laparoscopically assisted ileal resection with an ileoileostomy.

The sigmoid colon is the most commonly affected bowel segment requiring resection, which may be carried out with a sigmoid colectomy with transanal anastomosis. Care should be taken to follow sound surgical principles, including creation of a well vascularized, tension free anastomosis to minimize the risk of an anastomotic leak.

A variety of surgical techniques are available for treatment of rectal endometriosis. The choice of technique depends on the size, location, degree and depth of involvement of the endometriotic implant. As a general rule, less is better when it comes to removal of rectal endometriosis as long as the implant can be completely excised. There is no need to carry out a difficult low anterior resection when a shave or disc excision of the anterior rectal wall is all that is necessary. This is done to minimize potential complications and preserve normal rectal function.

Laparoscopic treatment of intestinal endometriosis is a relatively new technique, and only recently have surgical outcome and quality-of-life studies published in the literature.35 Fortunately, even in an emergency, like a bowel obstruction with an unprepared bowel, colostomy is rarely necessary. With complete removal of all visible disease and restoration of normal bowel anatomy, the rate of recurrence is low, even in patients preserving ovarian function.36 Robotic assistance may allow more bowel resections to be carried out by laparoscopy. In recent years, we have carried out 4 segmental colon resections and 2 disc excisions of the bowel for endometriosis with robotic assistance. We have noticed that robotics may enable the surgeon to see better and to suture more easily.
Urinary Tract Endometriosis

Involvement of the urinary tract by endometriosis is a rare condition, occurring in 1% to 5% of all cases, with the bladder, ureter, and kidney making up a 40:5:1 ratio, respectively. Endometriosis of the bladder can be considered a type of deeply infiltrating endometriosis. It is thought that ureteral involvement most commonly develops with severe ovarian endometriosis. As in gastrointestinal endometriosis, malignant transformation can occur in urinary tract lesions.

VESICAL ENDOMETRIOSIS

The subperitoneal, mullerian remnant, metaplasia theory, and the uterus-vesical adenomyosis extension theory are not compatible with most imaging, surgical, and pathologic findings. Vesical endometriosis seems to originate from the implantation of regurgitated endometrial cells in the anterior cul-de-sac, and not from uterine adenomyosis. Within the bladder, endometriotic lesions are generally found in the trigone, dorsal wall, or at the ureterovesical junction. Transmural involvement is common.

The most frequent presenting complaints were urgency (78%), frequency (71%), suprapubic pain (43%), urge incontinence (21%) and dyspareunia (21%). Of these patients, 86% did not have a history of recurrent urinary tract infections. Hematuria is reported in 33% of cases, but is cyclic in only half of these cases. Occasional patients will also have a pelvic mass that should be evaluated preoperatively.

Patients suspected of having bladder endometriosis should be evaluated by cystoscopy and intravenous pyelogram (IVP). Cystoscopy may reveal mucosal involvement, an extrinsic mass effect, or may be normal. A visible lesion detected on cystoscopy should be biopsied. A majority of bladder lesions are superficial peritoneal implants and do not have involvement of the muscularis or mucosa.

The treatment of urinary tract endometriosis is controversial because the rarity of this condition makes randomized studies difficult. Encouraging results following medical management have been described, but close follow-up is recommended (especially with ureteral involvement). Long-term side effects are significant and symptomatic disease often recurs when therapy is discontinued. We do not agree with surgical castration (hysterectomy and bilateral salpingooophorectomy), which has been reported to prevent relapses. Superficial disease can be vaporized or fulgurated, whereas invasive endometriosis should be excised. This can be carried out by laparotomy or laparoscopy depending on the lesion, skill, and experience of the surgeon. When endometriosis invades the mucosa of the bladder, segmental resection of the lesion is the treatment of choice. Laparoscopic segmental resection of bladder endometriosis was first reported by Nezhat in 1992. Since then, other series have been reported.

URETERAL ENDOMETRIOSIS

Ureteral endometriosis is rare, accounting for less than 0.3% of all endometriotic lesions. Ureteral lesions usually occur in the distal third of the ureter, below the pelvic brim. Disease is predominantly unilateral, with the left ureter affected more commonly than the right, although bilateral disease does occur. Extrinsic lesions, which generally occur in the context of extensive pelvic disease, compress involved ureters and are 4 times more common than internal or primary lesions of the ureter. Presenting symptoms include hematuria, flank pain, backache, abdominal pain, or dysuria. Symptoms are not consistently related to menstrual cycles. Occasionally, asymptomatic ureteral involvement may be found during surgery or on IVP. An IVP should be done in all patients suspected of having ureteral
endometriosis or who have peritoneal disease overlying the ureter. If the ureter is completely obstructed, retrograde pyelography establishes the location of obstruction, and may allow placement of a ureteral catheter for temporary renal drainage. In cases of hydronephrosis or hydronephrosis, ultrasound or CT scan may be useful in excluding the presence of another mass lesion. Patients with renal compromise may benefit from percutaneous nephrostomy for urinary diversion before definitive surgery.

Conservative laparoscopic surgery to relieve ureteral obstruction and remove pathologic tissue is the management of choice. Laparoscopic resection and reanastomosis of the ureter, including ureteroneocystotomy with and without psoas hitch, for ureteral endometriosis was first reported by Nezhat et al in 1992.39 For external ureteral endometriosis the aim of surgery is to relieve compression or entrapment of the ureter. Ureterolysis should be conducted in all patients before endometriotic nodule resection, to identify and prevent ureteral damage. Systematic ureteral stenting before surgical dissection of the pelvic wall has been recommended, but in our experience it is rarely required in patients with posterior nodules. Stenting is recommended in the case of partial cystectomy for anterior nodules when the ureteral meati are adjacent to the lesion. Ureteroneocystotomy with a psoas bladder hitch must be carried out when the deep infiltrating lesions are extensive or invade the ureteric wall. The frequency of associated endometriotic lesions (urinary, gynecologic, gastrointestinal) justifies a multidisciplinary surgical approach.

Internal ureteral endometriosis mandates segmental resection of the ureter. Depending on the site of involvement, the procedure of choice is either ureteroureterostomy or ureteroneocystotomy. Although these are usually conducted at laparotomy, laparoscopic approach has been reported.39 There does not seem to be specific advantage to hysterectomy and bilateral salpingo-oophorectomy in preventing recurrence.

**RENAL ENDOMETRIOSIS**

Involvement of the kidney has been infrequently reported. Presenting symptoms include flank or back pain, hematuria, hydronephrosis, or a renal mass. Diagnosis has been made with IVP, computerized tomography (CT) scan or MRI. Unfortunately, in the absence of a biopsy there is no accurate preoperative method to exclude malignancy, so a majority of patients are treated with nephrectomy. There has been no report of regression of renal endometriosis with GnRH agonist therapy, but follow-up was limited.

**Diaphragmatic and Thoracic Endometriosis**

Thoracic endometriosis syndrome (TES) is a rare disorder characterized by the presence of functional endometrial tissue in the pleura, the lung parenchyma, and the airways. Thoracic endometriosis syndrome (TES) encompasses 4 main clinical entities: catamenial pneumothorax (CP), catamenial hemothorax (CH), catamenial hemoptysis (CH), and lung nodules.43 In a recent published series, up to one-third (30%) of women hospitalized with a diagnosis of spontaneous pneumothorax had CP. Since the first description by Maurer et al in 1958, more than 250 cases of this unique entity have been described causing spontaneous recurring pneumothorax in women.44 Thus, it is plausible that thoracic endometriosis is an under reported cause of secondary spontaneous pneumothorax, in an age group of women when most cases of pneumothorax are thought to be primary.45

Like other sites of extragenital endometriosis, thoracic endometriosis seems to affect a slightly older population than
does pelvic disease. The mean age at presentation for thoracic endometriosis is 34.2 ± 6.9 years, with a range from 15 to 47 years. Interestingly, pelvic endometriosis precedes thoracic endometriosis symptoms by approximately 5 to 7 years. Fifty to 84% of women diagnosed with thoracic endometriosis have associated pelvic endometriotic lesions. The percentage of women with pelvic disease who develop thoracic endometriosis is largely unknown.

Most thoracic endometriosis lesions are solitary, with the right hemithorax (mainly pleura and less commonly the lung parenchyma), being involved in up to 92% of cases and the left hemithorax in 5% of cases; the remaining 3% have bilateral involvement.

Catamenial pneumothorax is the most frequent presentation of thoracic endometriosis syndrome, occurring in approximately 80% of the cases; catamenial hemothorax occurs in 14%, and catamenial hemoptyasis in 5%. The least common are endometriotic lung nodules.

**CATAMENIAL PNEUMOTHORAX**

A number of hypotheses have been suggested to explain the etiology of catamenial pneumothorax. According to one hypothesis, open communication between the atmosphere and peritoneal cavity during menstruation allows air to migrate into the thoracic cavity through diaphragmatic fenestrations and porosities, which is supported by the almost 9:1 right-sided predominance of endometriotic pleural implants. Another hypothesis suggests that diaphragmatic defects are caused by endometriosis. A third hypothesis involves metastatic spread of endometriosis through the uterine veins into the venous system. Last, prostaglandin F2, a potent constrictor of bronchioles and vascular structures, which can be found in the plasma of some women during menstruation, may destroy alveolar tissue owing to vasospasm, thus leading to pneumothorax.

Rossi and Goplerud have suggested that a synchronous increase in prostaglandin F2 with menstruation could induce catamenial pneumothorax. At peak levels, the potent bronchial and vascular constrictor, prostaglandin F2, may cause rupture of preformed subpleural blebs in otherwise normal lungs. This hypothesis could explain why 23.1% of all explored cases have only bullae or blebs, and in 8.5% no pathologic findings have been shown.

Lymphatic or hematogenous embolization from the uterus or pelvis may explain parenchymal or bronchopulmonary endometriotic nodules and other extrapelvic locations. In fact, a review of autopsy data showed that cadavers with bronchopulmonary endometriosis usually had bilateral lesions, whereas pleural and diaphragmatic lesions were almost always right sided.

Lillington et al coined the term catamenial pneumothorax. They proposed a model in which the expansion of intraparenchymal, subpleural endometriotic tissue during menses would cause a check-valve airway obstruction, eventually leading to alveolar rupture. Women with bronchopulmonary endometriosis tend to have a history of uterine manipulation or trauma (eg, hysteroscopy, dilation and curettage). This supports the lymphovascular embolization theory. Those with pleural disease most often have a history of pelvic endometriosis.

Catamenial pneumothorax is defined as recurrent pneumothorax occurring within 72 hours after onset of menstruation. Although catamenial pneumothorax is typically cyclic, noncyclic recurrences can occur in the immediate premenstrual period or ovulatory phase.

Patients with catamenial pneumothorax present with symptoms that are usually nonspecific such as pleurisy, cough, and shortness of breath. They may also have referred periscapular or neck pain owing to diaphragmatic irritation. In most cases, symptoms are mild-to-moderate; severe presentations are rare.

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CATAMENIAL HEMOTHORAX
Catamenial hemothorax is an uncommon manifestation of TES accounting for approximately 14% of cases. Symptoms are nonspecific and the presence of a bloody pleural effusion is variable. Computed tomography (CT) of the chest may show multiloculated effusions, nodular lesions of the pleura, or bulky pleural masses.

CATAMENIAL HEMOPTYSIS
Catamenial hemoptysis has a rather variable manifestation, with neither massive hemoptysis nor deaths being described thus far. An association with menses may not always be appreciated. Diagnostic delays of up to 4 years after the onset of symptoms have been reported, which is often seen in patients with catamenial hemoptysis and lung nodules.52

DIAGNOSIS: THORACIC ENDOMETRIOSIS
The most valuable tool in the diagnosis of thoracic endometriosis is a high level of clinical suspicion.53 A catamenial constellation of symptoms should be considered pathognomonic for the disease. Chest radiograph, CT, magnetic resonance imaging, thoracentesis, and bronchoscopy are useful in evaluating patients presenting with pneumothorax, hemothorax, hemoptysis, or lung nodules. These diagnostic tests help rule out malignancy, infection, and other pathologies. However, they all have limited diagnostic yield for thoracic endometriosis syndrome, with variable and inconsistent findings.52 Interestingly, in the case of bronchopulmonary endometriosis, bronchoscopy-directed biopsies of suspected lesions usually fails to provide a tissue diagnosis, whereas brush cytology frequently shows distinctive features of endometrial cells.

Video-assisted thoroscopic surgery (VATS) is at present the gold standard for both the definitive diagnosis and surgical treatment of catamenial pneumothorax.54,55 In the largest review of CP cases assessed with VATS, more than 50% of the patients were diagnosed as having thoracic endometriosis. Diaphragmatic abnormalities (fenestrations or endometriosis, alone or combined) are now the most commonly described lesions (38.8%), followed by endometriosis of the visceral pleura (29.6%). In the remainder of cases, discrete lesions, such as bullae, blebs, and scarring (23.1%), or no findings (8.5%) are noted.

Combining VATS with laparoscopy in a single session is another diagnostic approach, which has recently been reported that allows assessment of the thoracic cavity, pelvis, and subdiaphragmatic region.45-50,56,57 This combined approach may be particularly helpful in cases of inconclusive VATS, which may be the result of endometriosis involving only the abdominal diaphragm, causing catamenial phrenic nerve irritation and pain.57

TREATMENT: THORACIC ENDOMETRIOSIS
Medical treatment has long been considered the first step in the management of thoracic endometriosis. Danazol, progestational agents, oral contraceptive pills, and GnRH analogues have all been used widely.55 Among the agents studied, GnRH agonists are more effective in controlling recurrences of CP, especially when used for prolonged periods of as long as 1 year.58

Medical treatment often serves as a diagnostic tool. In women with suspected thoracic endometriosis a response to medical treatment may be considered diagnostic, and surgical treatment may then be sought. Thoracentesis and chest tube placement are obviously first-step therapeutic interventions in the emergency room. Although exploratory thoracotomy was carried out extensively in the past, Nezhat et al.56 report that it is rarely necessary. VATS is currently the gold standard for surgical treatment of TES, especially catamenial pneumothorax. VATS provides
magnification and exposure of possible defects that are sometimes better visualized than at thoracotomy. However, misdiagnosis may occur, especially if the patient is positioned for an axillary thoracotomy, as complete visualization of the diaphragm is difficult in this position. A better approach for performance of VATS is with the patient positioned for a posterolateral thoracotomy. Signs of thoracic endometriosis are sought by inspection of the lung, pleura and diaphragm. The diaphragm is also carefully inspected for the presence of defects. Simultaneous laparoscopy aids in the surgical treatment of implants on the abdominal aspect of the diaphragm.\textsuperscript{57}

When endometriotic implants are the sole findings during VATS and are in the size range of a few millimeters, regardless of their location (ie, parietal, visceral, or diaphragmatic pleura), they can be carefully fulgurated using bipolar diathermy or CO\textsubscript{2} laser. Larger endometriotic implants of the visceral pleura may be excised using sharp dissection.\textsuperscript{52}

Large lesions or deep parenchymal endometriotic nodules are best treated with parenchymal-sparing procedures, such as wedge resection or subsegmentectomy, but occasionally lobectomy may be required.\textsuperscript{51}

Another important therapeutic intervention is pleurodesis (mechanical, chemical, pleurectomy, or talcum). It can be conducted alone or in conjunction with excision of an endometriotic implant or perforation. Of 79 VATS-treated patients, 28 underwent pleurodesis alone, with a median recurrence-free interval of 61 months (10 d to 164 mo).\textsuperscript{47} Pleurodesis, especially in younger patients, should always be carried out concomitantly with VATS exploration. This way an accurate diagnosis and treatment can be instituted and recurrences avoided. Hormonal treatment with GnRH agonist seems to improve the outcome.

Finally, hysterectomy and BSO is the treatment of last resort when other options have been exhausted. Nonetheless, TES may recur if intrathoracic disease has not been properly addressed and hormone replacement treatment is initiated.\textsuperscript{43}

**DIAPHRAGMATIC ENDOMETRIOSIS**

Transportation of viable endometrial cells in peritoneal fluid follows a characteristic clockwise circulation pattern. The peritoneal fluid moves from the pelvis up the right paracolic gutter to the diaphragm, across the upper abdomen, and back down the left paracolic gutter. Direct spread of endometriosis to the diaphragm, especially on the right hemidiaphragm, has been increasingly reported. Diaphragmatic endometriosis may be asymptomatic, produce pain in the right upper quadrant, or may present with referred pain to the right shoulder. These symptoms are more likely if there has been penetration of the diaphragm by endometriosis with extension into the pleural space, pneumothorax, hemothorax, or hemoptysis. In one case, a pregnant patient developed hemoperitoneum because of bleeding from an ectopic pregnancy that had implanted on diaphragmatic endometriosis.

Initially, GnRH agonist therapy may be used for patients with symptomatic diaphragmatic endometriosis, reserving surgery for women who have acute symptoms or who do not respond to hormonal suppression. Resection of the involved area with repair of any associated diaphragmatic defects is the surgical treatment of choice. Before surgery, the possibility of pleural or pulmonary involvement should be investigated. Primary laparoscopic treatment of diaphragmatic endometriosis has also been described by Nezhat et al.\textsuperscript{53}

If the abdominal aspect of the diaphragm is involved by endometriotic implants, an experienced team of gynecologic and thoracic surgeons can carry out hydrodissection, laser fulguration, or excision successfully for small lesions.\textsuperscript{57} However, if larger implants or defects...
are present, they should be approached through VATS, as the liver bulk and limited subdiaphragmatic space may not allow complete resection.59

Diaphragmatic lesions (endometriotic implants or perforations) are probably best treated by resection using endoscopic stapler devices, provided that the resected surface is relatively small. Larger diaphragmatic perforations can be sutured, although significant recurrences have been reported with this method.60 Nezhat et al56 reported the first laparoscopic and thoracoscopic management of diaphragmatic and lung endometriosis.

In large diaphragmatic excisions, the use of mesh to repair the resulting defect has been described in 3 women who at 45 months’ follow-up suffered no recurrences,5 although other investigators have not confirmed these results.54,55

Other Sites of Extra Genital Endometriosis

LIVER ENDOMETRIOSIS
Hepatic endometriosis was first described in 1986. It is rarely seen, with only 19 cases reported in the literature. Seventeen cases were treated by laparotomy and 2 cases by laparoscopy.61

Malignant transformation of endometriosis has been reported, occurring mainly in the ovary. Malignancy must be excluded when endometriosis is discovered in unusual sites like the liver. The presence of more endometrial implants on the right lobe than the left lobe of the liver is supportive of the retrograde menstruation theory with peritoneal fluid circulation. The lymphovascular theory can explain intraparenchymal endometriomas and those located in proximity to the falciform ligament.62

A wide variety of symptoms ranging from an incidental finding to acute abdomen have been described in hepatic endometriosis. The most common presenting symptom is epigastric or right upper quadrant abdominal pain. Other possible presentations are malaise, nausea, vomiting, obstructive jaundice, portal vein thrombosis, and hepatomegaly. Catamenial epigastric pain is characteristic, although rarely seen.61

The diagnostic method of choice is CT scan of the abdomen. Other modalities include ultrasound and MRI. A large heterogeneous mass containing septated, thick-walled cystic lesions is a common radiographic presentation.

Final diagnosis can only be made by pathologic evaluation.61 On account of the risk of malignant transformation, the first-line treatment is surgical resection with adequate margins.63

Cutaneous Endometriosis
Cutaneous endometriosis should be suspected in any female presenting with cyclic or noncyclic pain, emanating from a mass in the vicinity of a previous surgical scar, the umbilicus or in the inguinal region. Surgical excision of the cutaneous endometriotic implants can be carried out and is curative.

Abdominal wall endometriosis (AWE) is defined as endometrial tissue within the abdominal wall, superficial to the peritoneum. This definition includes lesions that were not a result of a previous surgical procedure, but many cases of AWE are associated with cesarean section scars. AWE is often misdiagnosed as a hernia, hematoma, or lipoma resulting in surgical consultation.

Sampson first described the theory of implantation in 1927 to explain AWE. According to this theory, during cesarean section, endometrial cells escape through the incision in the uterus and implant within the abdominal wound. Halban developed the theory of vascular dissemination. In this theory individual endometrial cells escape from the uterus through
lymphovascular channels, gain access to the peripheral circulation and are carried to ectopic sites. A third theory involves metaplasia of cells in the abdominal wall into endometrial tissue. This metaplasia may be induced by imitative metaplasia or hormonal manipulation. Some investigators advocate a combination of these theories to explain AWEs.

At cesarean section lifting the uterus outside of the pelvis before making the uterine incision was shown to significantly reduce the likelihood of developing AWE.\textsuperscript{64,65} Other ideas for reducing AWE development after cesarean section and hysterectomy include using separate needles for the uterine and abdominal closure, avoiding use of a sponge to clean the endometrial cavity, removing a functional corpus luteum at the time of hysterectomy, prophylactic hormonal therapy after hysterectomy and the use of high-pressure irrigation.\textsuperscript{66} The above techniques may seem intuitive, but none have been tested rigorously.

The classic symptoms of an abdominal wall endometrioma are catamenial pain associated with an abdominal wall mass. However, cyclic pain is not a universal characteristic of cutaneous endometriosis.\textsuperscript{64,67} It has been shown that more often patients with cutaneous endometriosis present with a mass (96%) or noncyclic pain (87%), whereas only 57% present with cyclic symptoms, Other common signs and symptoms are bleeding from superficial lesions and lower abdominal pain.\textsuperscript{68} As a rule there is a significant time delay between a patient's index surgery and the onset of symptoms, usually an average of 3.6 years (95% CI 2.5-4.8).

Physical examination should focus on determining the presence of a fascial defect or if the mass is attached to the anterior fascia. No further studies are necessary in patients with a classic presentation. Additional studies such as ultrasound, fine-needle aspiration (FNA), CT scan, or MRI may be obtained if the lesion is very large, there is concern for fascial involvement, or if the diagnosis is in doubt. This information may assist with surgical planning especially when an abdominal wall reconstruction is anticipated.

Surgical management offers the best chance for both definitive diagnosis and treatment. The treatment of choice for AWE is wide local excision of the lesion with negative margins.\textsuperscript{66,69} If the AWE is incorporated into the musculature of the abdominal wall it requires en bloc resection of the underlying myofascial elements. Surgeons should be prepared for a coexisting hernia, and that a mesh repair may be necessary.

**OTHER EXTRAPELVIC SITES**

Endometriosis has also been described in virtually every location that can be reached by hematogenous, lymphatic, or direct dissemination. Musculoskeletal endometriosis has been described in the shoulder, thigh, knee, pubis, thumb, forearm, and bone. All patients with pain in these locations owing to endometriosis were treated by local excision.

The most common site of endometriosis involving the nervous system has been within nerves in or near the pelvis. Sciatic nerve endometriosis presents as sciatic pain, occasionally associated with muscle weakness, sensory deficits, and pelvic pain.\textsuperscript{70} Cyclic sciatica, which refers to sciatic pain related to menses, should be considered suggestive of endometriosis. Similarly, endometriosis involving the obturator nerve, producing pain and proximal muscle weakness, has also been described. This case, like those of sciatic nerve endometriosis, was treated by exploration and excision of endometriosis and associated fibrosis surrounding the nerve. Although the direct spread of pelvic endometriosis to and along nerves coursing through the pelvis seems logical, not all patients have been found to have pelvic disease.
Although extrapelvic endometriosis is a rare condition, it occasionally presents to general surgeons. Endometriosis has been diagnosed incidentally during inguinal hernia repair, and treated with simple excision of the lesions with the involved portion of the round ligament. Direct intraperitoneal spread of endometriosis to the adjacent omentum is common. Isolated areas of omental involvement occur by transmission through peritoneal fluid or lymphatics. One patient with isolated omental endometriosis had abdominal pain, abdominal distension and ascites. Treatment was by excision of the endometriosis and ovarian suppression with medroxy progesterone acetate.

Pancreatic endometriosis has been reported in 2 patients. One had upper abdominal pain and mass; the other had left flank pain and a mass suggestive of renal origin. In each case, a partial pancreatectomy and splenectomy was carried out, and the second patient also had a left nephrectomy.

Direct extension of endometriosis from the cul-de-sac or down the rectovaginal septum into the vagina is probably more common than has been reported. Vaginal endometriosis highlights the ability of pelvic endometriosis to invade contiguous structures. Symptoms include pain, dyspareunia, pressure, postcoital bleeding, and the presence of a palpable mass.

Cervical endometriosis has been seen as an isolated entity and in association with pelvic or rectovaginal disease. These lesions are generally superficial and seem bluish or hemorrhagic. Usually asymptomatic, they are found incidentally at examination, but they may cause pain, dyspareunia, intermenstrual bleeding, or postcoital bleeding.

Vulvar, perineal and perianal endometriosis is generally reported to occur in episiotomy and other vulvar surgical scars. Characteristically, these genital lesions produce pain and dyspareunia. Examination reveals a painful mass that may have a bluish or hemorrhagic discoloration depending on the depth of the lesion. The majority of these patients do not have coexistent peritoneal disease. The most likely explanation for endometriosis in episiotomy scars, without concurrent peritoneal disease, is direct implantation of endometrial tissue at the time of vaginal delivery.

Vulvar, perineal, and perianal endometriotic lesions should be biopsied to exclude other pathologic processes and malignancy. Treatment is by local excision. Vaginal or cervical disease that results from cul-de-sac or rectovaginal disease should be removed en bloc with the peritoneal endometriosis.

**Endometriosis in Men**
Lesions characteristic of endometriosis have been reported in men undergoing treatment for prostate cancer with orchietomy and high-dose estrogen therapy. In 3 cases, lesions in the bladder caused hematuria. A fourth patient had endometriosis in the abdominal wall that presented as a painful mass in his surgical scar. All 4 cases were treated by local excision and repair. The patient with abdominal wall endometriosis required a second excision, and eventually had to discontinue estrogen therapy for relief of pain.

Coelomic metaplasia, induced by the reduction of testosterone production following orchietomy, and augmented by estrogen therapy, could account for these cases. Similarly, stimulation of endometrial cell rests by this same hormonal milieu within the prostatic utricle could cause growth of endometrial tissue, which could then spread, as it does in females. Support for this latter theory is given by the report of 10 cases of prostate cancer with a histologic pattern identical to endometrial cancer, which was presumed to originate from endometrial cell rests in the prostatic utricle.
Summary

Endometriosis is an enigmatic disease that can spread throughout the body. It may be explained by retrograde menstruation, activation or differentiation of local stem cells, lymphatic dissemination, direct extension from foci of endometriosis, or by hematogenous spread of endometrial cells. Extraginalendometriosis may present with painful bleeding, infertility, or organ dysfunction. Although cyclic symptoms and organ dysfunction are characteristic of endometriosis, more than 50% of patients with extragenital endometriosis do not have catamenial symptoms.

The primary treatment for extragenital endometriosis is removal of the lesion. Any woman of reproductive age with cyclic pain, bleeding, infertility, or organ dysfunction should raise clinical suspicion for endometriosis. If endometriosis can be confirmed, GnRH agonist therapy may be the first treatment. If medical therapy is not successful, surgical excision of the lesion may be an alternative. The use of operative laparoscopy for excision of endometriosis continues to gain momentum, essentially replacing laparotomy. Hysterectomy and bilateral salpingo-oophorectomy in women of reproductive age should rarely be considered optimal therapy. Unfortunately, there are many patients who present with extragenital endometriosis several years after hysterectomy and bilateral salpingo-oophorectomy. These patients have fallen victim to the misbelief that hysterectomy and bilateral salpingo-oophorectomy is curative for extragenital endometriosis. With proper forethought and diligence, extragenital endometriosis can be diagnosed and treated properly in women of reproductive age without hysterectomy and bilateral salpingo-oophorectomy.

References


Erratum

Surgical Approaches to Postobstetrical Perineal Body Defects (Rectovaginal Fistula and Chronic Third and Fourth-degree Laceration): Erratum.

In the article that appeared on page 134 of the March 2010 issue of Clinical Obstetrics and Gynecology, Normal F. Miller was mentioned incorrectly as one of the authors. The authors of this article should read: John O. L. DeLancey, MD and Mitchell B. Berger, MD, PhD.1

This error has been noted in the online version of the article, which is available at www.clinicalobgyn.com.

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