Endometriosis and Endometriosis-Associated Tumors

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Abstract

Endometriosis is a chronic gynecologic disorder that affects ~10% of adolescent girls and premenopausal women. The condition, classically defined as the presence of endometrial glands and stroma outside of the uterine cavity, is multifactorial and highly recurrent, and causes considerable morbidities that can significantly diminish the quality of life of affected women. The disease is linked to immune dysfunctions, infertility, and increased risk for ovarian and other cancers. The histological diagnosis of endometriosis, while typically uncomplicated, may be compromised by the heterogeneity of the endometriotic foci which can manifest a spectrum of lesions with distinct and atypical features of stromal and glandular components. Moreover, signs and symptoms of endometriosis remain nonspecific and there is a current lack of predictive noninvasive markers. This chapter aims to provide current understanding of the etiology, pathogenesis, and clinicopathologic features of endometriosis and to highlight the remaining challenges clinicians and pathologists face in the diagnosis, management of symptoms, and provision of care in women with this condition.

Keywords

Endometriosis · Pathological features · Endometriosis-associated tumors

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12.1 General Characteristics

Endometriosis is a benign, but chronic, gynecologic condition of adolescent girls and reproductive-age women. The disease is defined as the presence of viable endometrial glands and stroma in extrauterine sites and its development is widely recognized as an estrogen-dependent, pro-inflammatory process [1, 2]. Clinical sequelae of endometriosis include painful menstrual periods, pelvic pain, ovarian cysts, and/or infertility [1]. While the prevalence of endometriosis is difficult to quantify, it is estimated that 25–50% of infertile women, and 30–80% of women with pelvic pain, have a diagnosis of endometriosis [3]. Endometriosis may be a disabling condition for many women (estimated at >200 million worldwide) during the prime years of their lives, and endometriosis-related healthcare expenditures are significant [4, 5] . Treatment of endometriosis may include medical management and/or surgery [6, 7]. However, as a chronic condition without a known cure, endometriosis remains a challenge for affected women and their healthcare providers.

Endometriosis affects women of all races and ethnicities, with a strong familial association [8]. Susceptibility to endometriosis also depends on a variety of environmental, immunologic, and endocrine factors [9]. Risk factors for the development of endometriosis include early onset of menarche, longer menstrual bleeding, and short menstrual cycles, while parity and paradoxically obesity and smoking are considered protective [6]. Women with endometriosis also exhibit higher rates of concurrent pain, mood, or autoimmune conditions [10, 11].

Women with endometriosis may be asymptomatic, or may report a wide range of symptoms including dysmenorrhea, dyspareunia, chronic pelvic pain, infertility, abnormal bleeding, or ovarian cysts [2]. There are currently no well-validated screening tests for endometriosis, and definitive diagnosis can only be made by surgical biopsy and histopathologic confirmation of ectopic endometrium in extrauterine locations [12]. In clinical practice, many women with

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suspected endometriosis receive empiric medical therapy, with hormonal suppression and/or pain control, to avoid the inherent risks of diagnostic surgery. To assist with conception in infertile women, assisted reproductive technologies such as *in vitro* fertilization may be employed [13]. As a chronic condition, endometriosis-related symptoms may progress, regress, or remain stable until menopause, when endometriosis generally becomes quiescent. There is increasing evidence, however, that endometriosis may persist even in the postmenopausal state [14]. Women with endometriosis have a two- to threefold increased risk for ovarian cancers and other malignancies such as endometrial and breast cancers [15].

The definitive diagnosis of endometriosis can only be made surgically, with histopathologic visualization of both endometrial glands and stroma within a surgical biopsy. Endometriosis lesions may vary in appearance at the time of laparoscopy; the classic description is that of a blue or black "powder burn lesion," but implants may also be hemorrhagic or nonpigmented [16, 17]. However, even with experienced laparoscopic surgeons, there may be inconsistencies between suspected endometriosis (by visual appearance) and confirmed endometriosis by histopathology [16, 18, 19], highlighting the importance of histologic evaluation.

12.2 Clinical Relevance

The American Society for Reproductive Medicine (ASRM) has developed the most commonly accepted classification system for endometriosis [20]. This guideline accounts for lesion size, appearance, anatomic location, and depth of invasion of endometriotic lesions visualized during diagnostic surgery (Table 12.1). Based on these parameters, patients are stratified into four stages: stage 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe). Stage 1 endometriosis is characterized by small, isolated, superficial endometriosis implants on the peritoneum or within the ovaries. On the other hand, stage 4 endometriosis is characterized by numerous endometriosis lesions, which may be superficial or deeply infiltrating, in addition to dense peritoneal or pelvic adhesions, and possibly a large ovarian endometriosis cyst. The majority of women with endometriosis are assigned to stages 1–2; however, there is little correlation between stage of endometriosis and severity of pain symptoms [21]. A recent consensus statement by the World Endometriosis Society has incorporated additional endpoints that are highly relevant to women with endometriosis [22].

Table 12.1 American Society for Reproductive Medicine Classification for Endometriosis[a]

Stage	Location (size)	Depth of endometrial explants
I. Minimal	Peritoneum (1–3 cm) Ovary (<1 cm)	Superficial Superficial
II. Mild	Peritoneum (>3 cm) Ovary (<1 cm) Ovary-filmy adhesions	Deep endometriosis Superficial Superficial
III. Moderate	Peritoneum (>3 cm) Ovary (1–3 cm) Ovary Ovary-filmy adhesions Fallopian tubes(<1 cm)	Deep endometriosis Deep endometriosis Dense adhesions Superficial Dense adhesions
IV. Severe	Peritoneum (>3 cm) Ovary (1–3 cm) Ovary Fallopian tube (>2 cm) Cul de sac	Deep endometriosis Deep endometriosis Dense adhesions Dense adhesions Complete obliteration

[a]Reference [20]

At present, there are no good serum markers with sufficient accuracy currently to assess the severity of endometriosis. Serum Cancer Antigen-125 (CA-125) levels have been reported to significantly differ in patients with pelvic versus extra-pelvic (i.e., pelvic > extra-pelvic) lesions [23]. Another study failed to confirm this finding and instead observed that extra-pelvic endometriosis was associated with higher patient serum CA-125 levels and lesions displaying increased expression of the epithelial-mesenchymal transcription factor ZEB1 than pelvic endometriosis [24]. The use of magnetic resonance imaging (MRI) to distinguish endometriotic tissue from adhesions and fibrosis has been recently reported and may be suitable for the diagnosis of endometriosis at unusual anatomic sites in symptomatic patients [25].

Given the nonspecific nature of endometriosis symptoms, the diagnosis of the condition is often delayed. Indeed, while the mean age at diagnosis is ~25–29 years, most patients manifest symptoms of pelvic pain and dysmenorrhea at the start of menarche. Symptoms of endometriosis do not differ between women surgically diagnosed during adolescence compared with those diagnosed as adults [26]. A summary of the differential diagnosis of endometriosis depending on the symptom was provided in Mounsy et al. [27]. Dysmenorrhea in endometriosis may be primary or secondary. Generalized pelvic pain, while characteristic of endometriosis, may also arise from malignant or benign neoplasms, pelvic adhesions, pelvic inflammatory disease, obstructive genital anomalies, or non-gynecologic causes. Women with dyspareunia may have endometriosis but the differential diagnosis also includes pelvic infection and bowel or urinary pathology. The diagnosis becomes more challenging if the lesions are located in distal sites. Thus, direct visualization (via laparoscopy) and histological confirmation of biopsied lesions must be strongly considered for cases of suspected endometriosis to facilitate timely initiation of appropriate therapy.

Clinically useful serum biomarkers for diagnosis and staging of endometriosis and/or to differentiate endometriosis subtypes are currently lacking. Cancer Antigen (CA) 125, CA 19-9, and the cytokine interleukin-6 have been suggested

as possible noninvasive markers; however, an extensive meta-analysis raised questions on their diagnostic specificity and accuracy [28]. One study reported that a four-marker panel of CA-125, macrophage chemotactic protein-1, leptin, and macrophage migration inhibitory factor could diagnose 48% of subjects with 93% accuracy [29], but this procedure has yet to be incorporated clinically. Tumor necrosis factor levels in the peritoneal fluids were found to be higher in women with than in those without endometriosis [30]; however, the test may have limited application since it relies upon an invasive procedure.

Recent studies using mouse models of endometriosis [31] and women with the condition [32] have tested the feasibility of using circulating microRNAs (miRNAs) as biomarkers for endometriosis. While the results appear promising, the accuracy and specificity of these identified miRNAs have yet to be rigorously vetted in clinical settings.

12.3 Pathogenesis of Endometriosis

Several theories have been proposed to explain the pathogenesis of endometriosis. Below, we discuss four theories which may account for the development and persistence of endometriosis in affected women. It is important to recognize that no individual theory has been accepted to fully explain this complex, multifactorial disorder [33, 34].

12.3.1 Histogenesis

12.3.1.1 Retrograde Menstruation

The concept of retrograde menstruation is the most cited explanation for the pathogenesis of endometriosis. This theory involves the retrograde flow of endometrial glands and stromal cells, sloughed during menses, through the fallopian tubes and into the peritoneal cavity [2, 35]. Implantation and proliferation of these endometrial cells then occur within ectopic sites, where they are resistant to apoptosis [9].

Support for the theory of retrograde menstruation has been demonstrated in animal models [36, 37]. In addition, the prevalence of endometriosis is increased in women with obstructive outflow tract anomalies, such as cervical stenosis, where the likelihood of retrograde menstruation is higher [1, 38]. The risk of endometriosis also increases with shorter menstrual cycles, increased menstrual frequency, and heavier menstrual flow, lending support to the role of menstruation in the pathogenesis of endometriosis [2]. Though not explained by retrograde menstruation, endometriosis lesions which develop in perineal scars following an obstetric laceration, or in abdominal incisions after cesarean delivery, are likewise best explained by the migration or transplantation of endometrial cells into ectopic, extrauterine locations.

Nevertheless, retrograde menstruation occurs frequently in women with patent fallopian tubes who do not develop endometriosis [39, 40]. In addition, endometriosis has been noted in previously hysterectomized women, and even in men undergoing treatment for prostate cancer [41]. Such findings suggest that menstruation is not definitively required for the development of endometriosis and highlight the multifactorial nature of the condition.

12.3.1.2 Metaplasia

An alternative theory is that of coelomic metaplasia. Coelomic epithelial cells are found within the peritoneal cavity, such as on the surface of the ovary, in addition to the pleural space. It is proposed that coelomic epithelial cells may undergo metaplastic transformation into endometrial cells, leading to ectopic endometrial lesions which ultimately develop into endometriosis [2, 42]. Metaplasia may be induced by exposure to chemical insults (such as menstrual fluid) or high levels of estrogen [43].

Support for this theory includes observations that endometriosis may be found in distant sites such as the pleural cavity, where coelomic epithelium exists, and that endometriosis can occur in prepubertal girls prior to the onset of menarche [33, 44]. Furthermore, case reports have demonstrated surgical evidence of endometriosis in women with *Mayer-Rokitansky-Kuster-Hauser syndrome* (defined as congenital agenesis of the uterus, cervix, and vagina due to failure of the Mullerian duct to develop), indicating that a functional uterus is expendable for the development of endometriosis [44–46].

12.3.1.3 Stem Cell Theory

In normal menstrual cycles, the human endometrium is continually regenerated by both local adult progenitor cells and bone marrow-derived multipotent stem cells [41]. Stem cells are undifferentiated cells which are characterized by their ability to self-renew and to later develop into a variety of mature cell types [39]. Support for the role of endometrial stem cells in the pathogenesis of endometriosis and their potential involvement in ectopic endometrial proliferation and differentiation have largely come from experimental mouse and nonhuman primate models [41].

In women with endometriosis, refluxed stem cells (via retrograde menstruation) deposited into the peritoneal cavity can subsequently undergo differentiation into endometrial glands and stroma [35, 41]. The migration of extrauterine stem cells through lymphatic or vascular channels may contribute to the development of distant endometriosis lesions [39]. Understanding the phenomenon of "stem cell trafficking" is a growing field of endometriosis research [47].

12.3.1.4 Tubal Origin of Ovarian Endometriosis

The fallopian tube has been recently proposed as a cellular contributor to the development of endometriosis [48]. About a decade ago, it was noticed that there are very early morphologic changes in cases of ovarian endometriosis, defined as "initial endometriosis" [49]. Subsequently, a study of the cellular origin of ovarian low-grade serous carcinoma found that ovarian epithelial inclusions (also called as endosalpingiosis) are most commonly derived from the fallopian tube [50]. Considering that initial endometriosis (Fig. 12.1) morphologically overlaps with ovarian epithelial inclusions, it was proposed that ovarian endometriosis, which develops from ovarian "initial endometriosis," may also arise from the fallopian tube. In a study to evaluate this hypothesis, microarray analysis was used to compare gene expression between the fallopian tube and the endometrium of patients with ovarian endometriosis and corresponding lesions. There were significant gene expression similarities between the fallopian tube and ovarian endometriosis, compared to expression profiles between the endometria and ovarian endometriosis. It was concluded that a substantial portion of ovarian endometriosis may originate from the fallopian tube [51].

The above findings are relevant in light of growing evidence that ovarian epithelial cancers, and possibly endometrioid cancers, may originate in the fallopian tubes [52–54]. Additionally, epidemiologic evidence suggests that *bilateral salpingectomy* (defined as the surgical removal of the bilateral fallopian tubes) may decrease lifetime risk of ovarian cancer in high-risk (e.g., women with *BRCA1/2* gene mutations) as well as in low-risk populations [55–57]. If future investigations confirm the contribution of the fallopian tubes to the pathogenesis of endometriosis, the findings may have significant therapeutic and preventative implications for reproductive-age women who have completed childbearing.

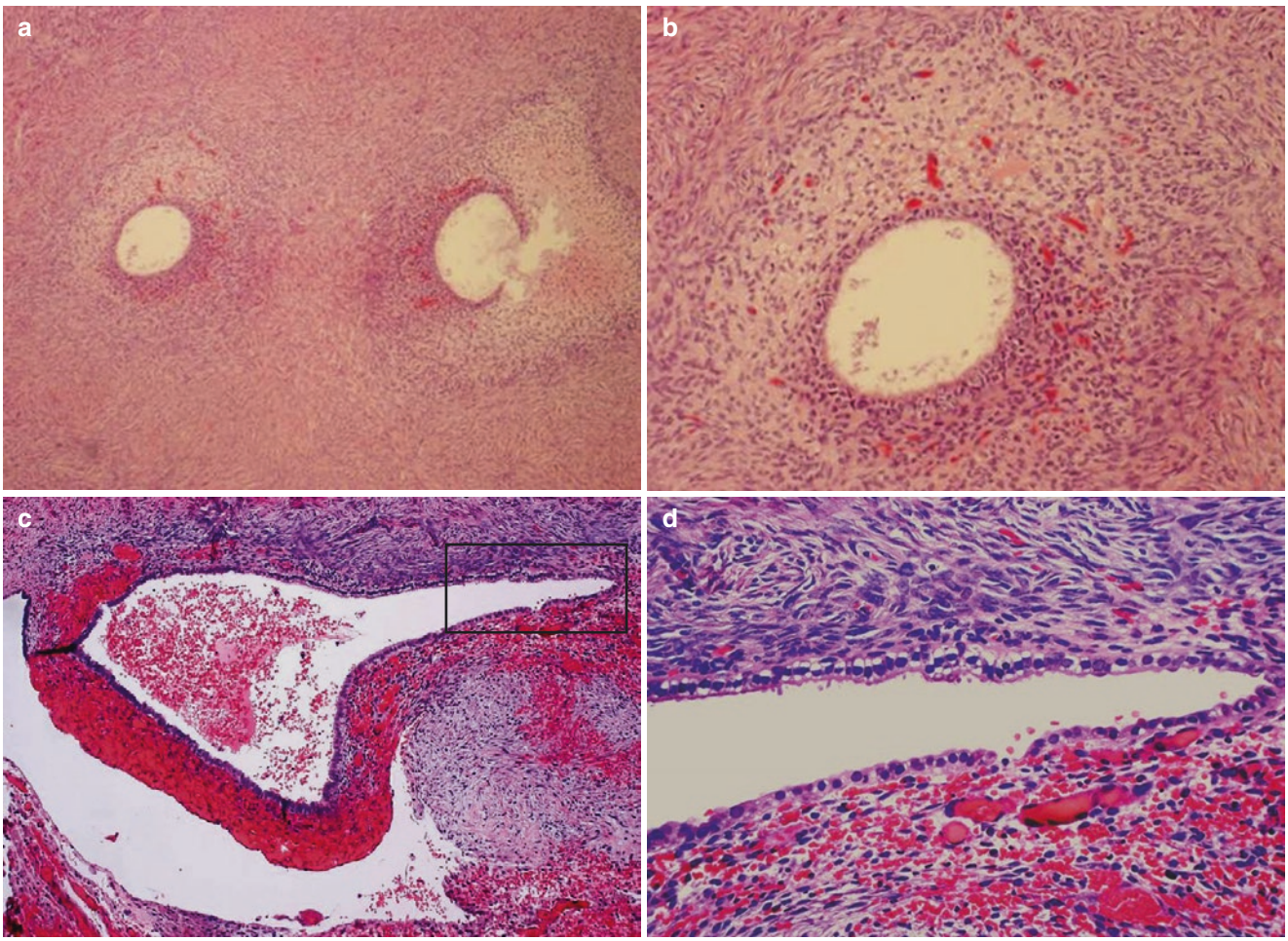

Fig. 12.1 Initial endometriosis. Shown here are ovarian epithelial-like inclusions in the ovarian cortex. Stromal changes including microcapillary vessels are present surrounding the epithelial inclusions (**a**). Stromal and vascular changes are evident in a magnified view (**b**). Another inclusion-like structure shows fresh bleeding adjacent to the glandular structure (**c**, left and mid-right), while typical ovarian stroma is present on the top right (**c**). The dramatic differences noted in the stroma surrounding the ovarian epithelial inclusions are presented at a higher magnification (**d**). The non-spindle stroma enriched with microcapillary vessels represents the earliest morphologic change of endometriosis

12.3.2 Etiology

12.3.2.1 Genetics

Genomic (and proteomic) studies comparing ectopic lesions and eutopic endometria from women with endometriosis with endometria from women without the disease have demonstrated altered expression of a large number of molecules, but their individual contribution as a mechanistic cause of lesion incidence and establishment remains largely undefined [58–61]. Table 12.2 provides a partial list of novel, recently identified genes that have been strongly implicated in disease establishment, based on clinical (afflicted women) and experimental (mouse models of endometriosis) observations [62–72]. The list does not include steroid hormone receptors and pro-inflammatory molecules, which are discussed in more detail in subsequent sections (below). The broad functional spectrum of the listed genes underscores the multifactorial and heterogeneous nature of the disease. Different mechanisms such as aberrant (hyper- or hypo-) methylation, somatic mutations, or posttranslational modifications involving microRNAs may explain the loss or gain of functions of these genes, leading to abnormal regulation of endometrial proliferation and apoptosis that characterize endometriosis [73–75].

Genome-wide association studies (GWAS) have been increasingly utilized to evaluate genetic contributions to endometriosis [76]. Genetic variants in loci, predominantly located in intergenic or intronic regions and in different chromosomes, have identified *WNT4* (wingless-type MMTV integration site family member 4), *GREB1* (growth regulation by estrogen in breast cancer 1), *FN1* (fibronectin1), *ID4* (inhibitor of DNA binding 4), *VEZT* (verzatin), and *MAP3K4* (mitogen-activated protein kinase kinase kinase 4) as candidate genes. Nevertheless, a major challenge in the understanding of disease pathogenesis and causes of disease heterogeneity is the identification of which of these genes represent "drivers" as opposed to "passengers."

Table 12.2 Genes potentially involved in endometriosis

Gene name	Model	Expression	References
HOXA10	Women	Decrease, stromal EC	[47]
P450 Arom	Mice	Increase, stromal EC	[48]
	Women	Increase, pain	
SRC1 (variant)	Mice	Increase, stromal EC	[50]
	Women	Increase, stromal EC	
COUP-TFII	Mice	Decrease, stromal EC	[51]
	Women	Decrease, stromal EC	
Cx43	Women	Decrease, stromal EU	[52]
KLF9	Mice	Decrease, stromal EC	[53]
	Women	Decrease, stromal EC	
REA	Mice	Decrease, stromal EC	[54]
	Women	Decrease, stromal EC	
PTEN	Mice	Decrease, stromal EC	[55]
	Women	Decrease, stromal EC	[56]
KRAS	Mice	Increase, EU	[57]
	Women	Increase, EU	

[a]HOXA10, HomeoboxA10; P450 Arom, P450 aromatase;SRC1 (variant), steroid receptor co-activator 1 (70 kDa variant); COUP-TFII, chicken ovalbumin upstream promoter-transcription factor II; Cx43, connexin 43; KLF9, Krüppel-like factor-9; REA, repressor of estrogen receptor activity; PTEN, phosphatase and tensin homolog deleted in chromosome 10; KRAS, Kirsten-ras sarcoma virus oncogene

[b]Expression change is relative to endometrium of women without endometriosis; *EU* eutopic endometrium of women with endometriosis, *EC* ectopic lesions

12.3.2.2 Sex Steroid Hormones and Receptors

Dysregulation of steroid hormone signaling is a major feature of endometriosis, given the estrogen dependence of the disease. Estrogen-modulated events including cell proliferation, angiogenesis, and cyst formation are exacerbated in endometriosis due in part to alterations in the ratio of estrogen receptor (ER) isoforms ER-α and ER-β; increased local estrogen biosynthesis (due to higher aromatase enzyme activity in ectopic lesions); and decreased progesterone receptor expression leading to unopposed estrogen action [77]. The pathological overexpression of ER-β (100 times higher in endometriosis than in normal endometrial tissue) relative to ER-α is caused by deficient methylation of the ER-β promoter and has been experimentally demonstrated using a mouse model of endometriosis, to result in enhanced inflammation and reduced apoptosis in lesions leading to disease progression [78, 79]. Progesterone resistance is also a characteristic feature of endometriosis. The loss of progesterone sensitivity is due to reductions in progesterone receptor expression and transcriptional activity, promoted in part by the increased inflammatory status of endometriotic lesions [59, 80, 81]. Current drugs for the management of endometriosis are aimed at decreasing systemic and local estrogen synthesis, reducing estrogen activity, and increasing progesterone sensitivity [82]. Due to side effects from long-term use of these medications, ongoing studies continue to explore new therapies to increase efficacy with minimal discomfort [83, 84].

12.3.2.3 Immune Response and Inflammatory Factors

Recent studies have provided support to the link between endometriosis and many immune diseases. Immune dysfunctions associated with endometriosis include systemic lupus erythematosus, rheumatoid arthritis, allergies, and asthma [11, 85, 86]. Endometriosis patients (and corresponding ectopic lesions) demonstrate elevated levels of pro-inflammatory cytokines, including interleukins (IL)-1, 6, 17A, and 33 as well as macrophage-stimulating factors (e.g., granulocyte-monocyte colony-stimulating factor) than women without the disease [87]. While it is not clear whether endometriosis is a cause or a consequence of immune dysfunctions, removal of ectopic lesions was shown to

significantly reduce the systemic inflammatory profiles in these women, suggesting lesions as major drivers of systemic inflammation [88]. The enhanced inflammatory status of women with endometriosis is likely caused by the highly estrogenic dependence of the disease, given the demonstrated cross talk between pro-inflammatory molecules (e.g., IL-6) and estradiol during early disease progression [89] and the role of estrogens in the recruitment of pro-inflammatory molecules within ectopic lesions [90]. Thus, recently identified estrogen receptor antagonists that can concurrently suppress estrogenic and inflammatory activities [91] may show promise as preventative and treatment strategies for endometriosis.

As mentioned earlier, the role of progesterone resistance in the progression of endometriosis may be linked to the enhanced inflammatory status of women with the disease. Gene expression analyses have shown that loss of progesterone receptor expression in lesions is associated with their higher expression of inflammatory cytokines [58, 59]. Mechanistically, it has been demonstrated that inflammatory molecules such as IL-1 and tumor necrosis factor (TNF)-α can significantly reduce progesterone receptor expression [81]. Conversely, progestin treatment of endometriotic stromal cells can suppress TNF-α-induced inflammation [92].

The significant contribution of pro-inflammatory molecules to endometriosis raises the interesting potential for nonsteroidal anti-inflammatory drugs such as prostaglandin synthesis inhibitors (e.g., cyclooxygenase-2 inhibitors) and diets rich in anti-inflammatory components (e.g., resveratrol in grapes) in the management of endometriosis. While there is sufficient support to these possibilities in animal models [93, 94] and in studies using endometriotic stromal cells [95], their potential has yet to be achieved in a clinical setting [96].

12.4 Pathologic Features of Endometriosis

Endometriosis, pathologically, is defined by the presence of ectopic functional endometrial tissue, which may be accompanied by cyclic bleeding induced by hormonal changes and associated with adjacent tissue response and accompanying adhesion or scar formation.

12.4.1 Clinicopathologic Types

Endometriosis lesions are most commonly located in the pelvic surface of peritoneum and ovary (*peritoneal endometriosis*), in the ovary as cysts lined by endometrioid mucosa (*ovarian endometriomas*), and in pelvic structures between the rectum and vagina as a solid mass comprised of endometriotic tissue with local adipose and fibromuscular tissue (*deep-infiltrating endometriosis*). Rectovaginal endometriosis accounts for 5–10% of women with disease. Endometriosis may also be established at distant locations such as the pleural space, diaphragm, or breast [16]. The implantation and proliferation of endometrial cells in ectopic sites result in inflammation, fibrosis, and distortion of normal anatomy.

The ovary and peritoneum are the most frequent locations of pelvic endometriosis. Other pelvic sites include the bowel [97] or bladder. Extra-pelvic lesions are less common, likely deeply infiltrating, and found in such anatomic locations as hepatobiliary and urinary systems, upper abdomen (lung, thorax), abdominal wall, and adrenal glands.

Diagnosis of pelvic and extra-pelvic lesions can be challenging. Endometriosis of the uterine cervix is generally asymptomatic and can be mistaken for cervical neoplasia due to the presence of a cervical mass [98, 99]. Intestinal endometriosis may present with abdominal pain or gastrointestinal bleeding [100], and the differential diagnoses may include diverticulitis, appendicitis, Crohn disease, irritable bowel syndrome, carcinoma, and lymphoma. Patients subsequently diagnosed with thoracic endometriosis may initially present with shoulder pain, catamenial pneumothorax, and/or hemoptysis [101]. In patients with bowel endometriosis, lesions display a characteristic "comet" appearance and have been associated with obliteration of the cul-de-sac and pelvic pain [102]. Abdominal wall endometriosis occurs when endometrial cells attach to the fascia or dermis at the time of obstetrical or gynecological surgery. Approximately 1% of women who have had a caesarean delivery subsequently presented with focal pain and/or palpable mass near the surgical scar which was diagnosed as endometriosis [103].

12.4.1.1 Peritoneal Endometriosis

Peritoneal endometriosis, also termed superficial endometriosis, is typically present on the surface of the peritoneum or the serosa of the peritoneal organs. Lesions of endometriosis can be single or in clusters. Grossly, they may present as raised, cystic, polypoid, or nodular.

Peritoneal endometriosis may show different colors under gross or laparoscopic examination, based on the "*age*" of the disease. Early lesions are typically colorless and 2–3 mm in size (Fig. 12.2).The lesions then may become red (fresh or recent bleeding) (Fig. 12.3), blue or black (old or remote bleeding) (Figs. 12.4 and 12.5), and white (inflammation and fibrosis) (Fig. 12.2), representing different stages of growth. It takes years for an early cystic colorless lesion to develop into a whitish scar-like lesion. Peritoneal lesions may be multifocal (i.e., other lesions are located within a 2 cm area) or multicentric (i.e., lesions are located beyond 2 cm from the main lesion); as many as 50 lesions may involve the peritoneum.

Presence of endometroid epithelia as well as endometrial stromal cells varies depending on the disease status. Typically, both can be found in more than 95% of red lesions,

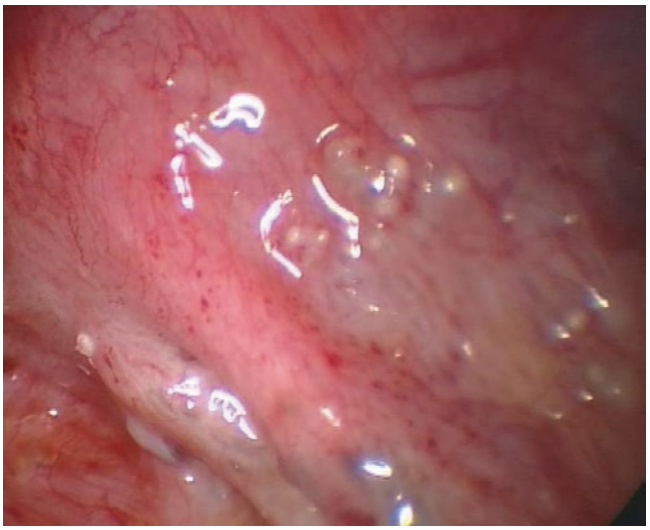

Fig. 12.2 Peritoneal endometriosis. A laparoscopic view of the peritoneal cavity reveals several transparent cystic structures, ranging from 2 to 4 mm in size, which represent foci of endometriosis prior to bleeding. Also shown are several white raised nodules (2–3 mm in size) probably representing endometriosis with fibrotic changes

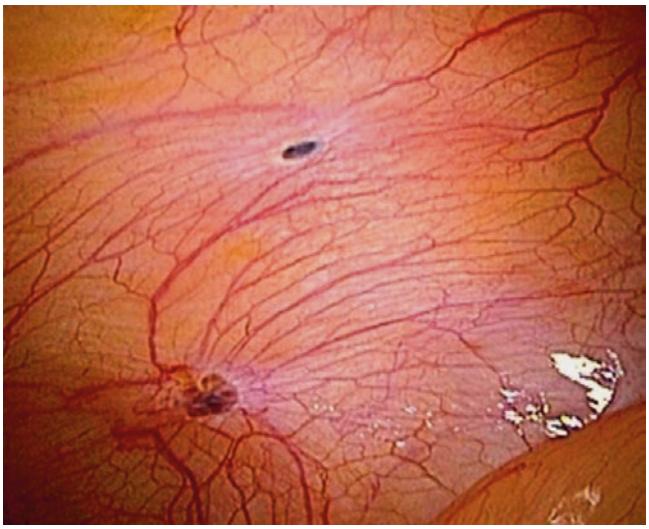

Fig. 12.4 Peritoneal endometriosis. Shown here are one black, "powder-burn" spot in the center and another purple spot in the lower area. Both represent relatively old hemorrhage in endometriotic lesions. Based on the color, the purple lesion is more likely less established than the black lesion

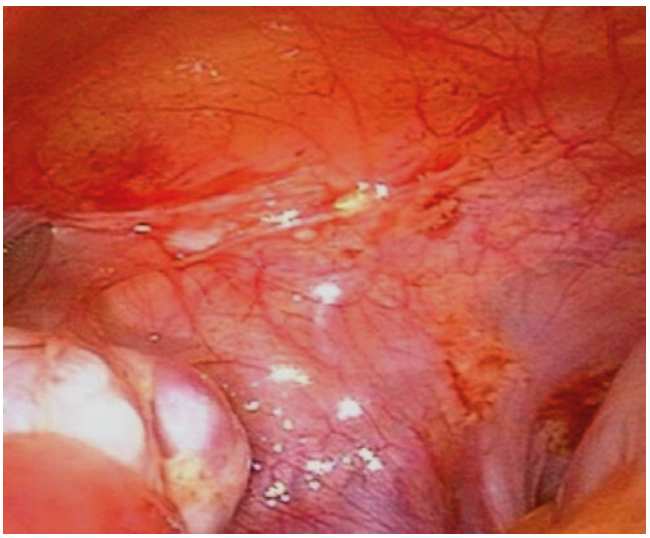

Fig. 12.3 Peritoneal endometriosis. This laparoscopic view of the peritoneum shows several red-tan, irregular-shaped, slightly raised lesions, which represent foci of endometriosis with fresh bleeding

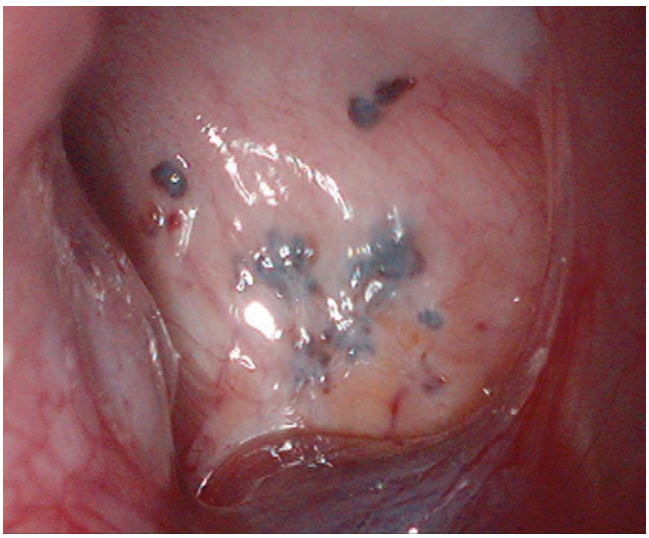

Fig. 12.5 Peritoneal endometriosis. Multiple blue and black lesions representing old hemorrhage within foci of endometriosis are shown

and in only 50–60% of bluish or black lesions. The clinicopathologic appearance of peritoneal endometriosis is summarized in Table 12.3.

12.4.1.2 Ovarian Endometriosis

Endometriosis in the ovary typically presents as a cystic lesion with either a single cyst or multilocular cysts. Ovarian endometriotic cysts are termed endometriomas. The cystic wall is typically thickened because of fibrotic reaction. Blood clot or condensed blood containing chocolate-like material (aptly named "chocolate cyst") is a common gross finding (Figs. 12.6, 12.7, 12.8, and 12.9). Large cysts can form around the ovary and may acutely rupture, causing release and adherence of their contents to the abdominal cavity.

12.4.1.3 Deep-Infiltrating Endometriosis

Deep-infiltrating endometriosis (also called *adenomyosis externa*) is the most severe clinical form of endometriosis and in >95% of cases is associated with severe pain. It typically presents as solid, multifocal nodules larger than 0.5 cm in diameter which can grow up to 5–6 cm in size [104, 105].

Table 12.3 Clinicopathologic appearance of peritoneal endometriosis

Gross color	Disease status	Appearance	Microscopic finding of endometrial tissue (%)
Colorless	Prior to bleeding	Grey small cysts	
		Focally raised	Close to 100
Red	Early bleeding	Granular and polypoid	
		Red or yellowish	Up to 95
Blue or black	Active growth	Burned appearance	
		Irregular folding	50–60
White	Healing stage	Focal adhesion	
		Scar	<30–50

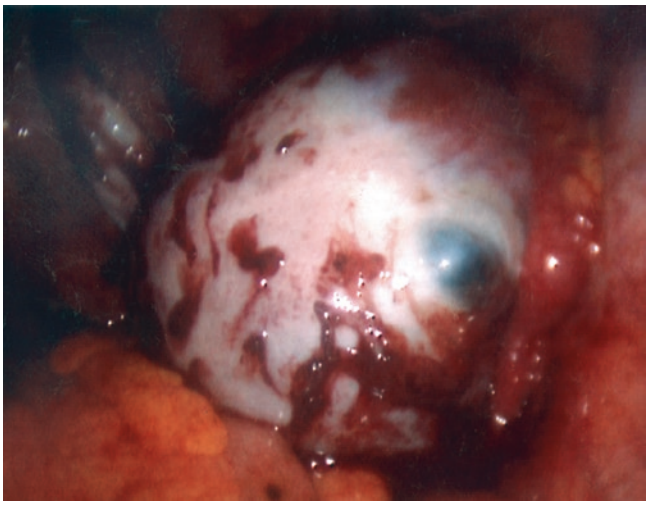

Fig. 12.6 Ovarian endometrioma. The ovary shows the presence of a blue cystic lesion on the surface. A brown viscous material seen oozing onto the surface of the ovarian mass represents an unopened ovarian endometrioma

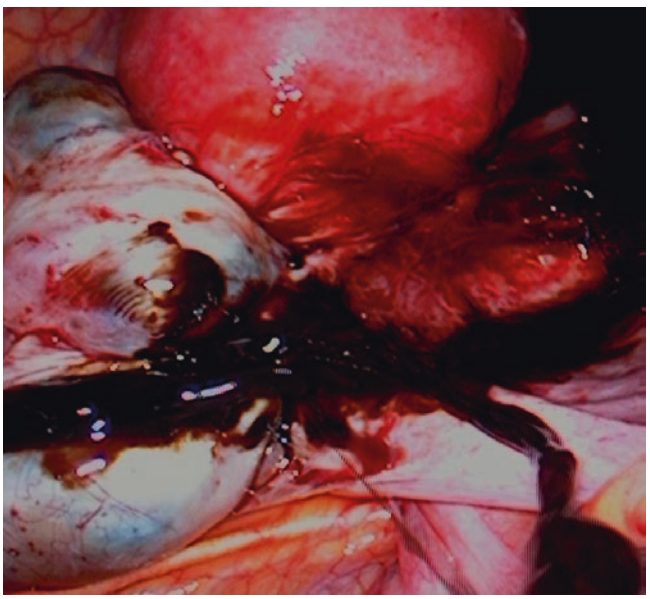

Fig. 12.7 Ovarian endometrioma. Contents of an endometrioma ooze onto the surface of this ovary

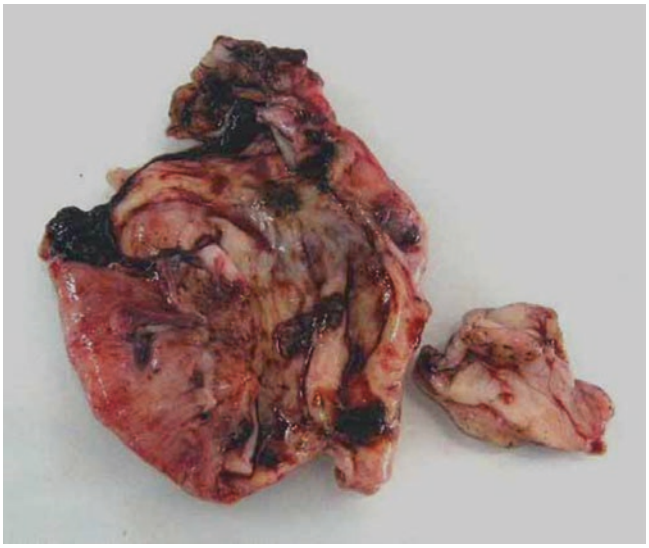

Fig. 12.8 Ovarian endometrioma. Upon sectioning, this ovarian endometrioma contains multiple small cystic areas containing old blood. The cyst wall is thickened. Foci of endometriosis are also present on the serosal surface (lower left)

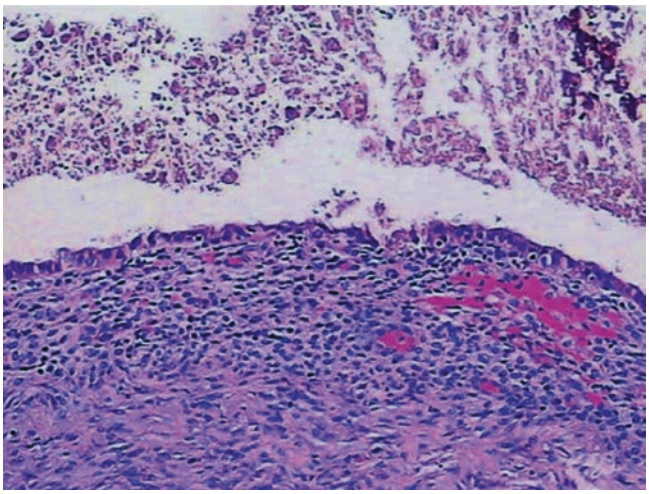

Fig. 12.9 Ovarian endometrioma. Microscopically, the cyst wall is lined by a single layer of epithelium. Located underneath are the typical stromal and vascular changes of endometriosis. Degraded cellular debris are present within the lumen

In contrast to peritoneal endometriosis and ovarian endometriomas, the lesions are found deep within connective tissue and can cause massive fibrosis and muscular hyperplasia. Typically, they are present in uterine ligaments or the walls of pelvic organs such as the bladder, rectum, and pouch of Douglas (Figs. 12.10, 12.11, and 12.12). Deep-infiltrating lesions are classically diagnosed by laparoscopy and pathological evaluation to rule out occult malignancy and managed by either laparoscopy or laparotomy [106, 107]. However, these lesions may recur even after surgical management.

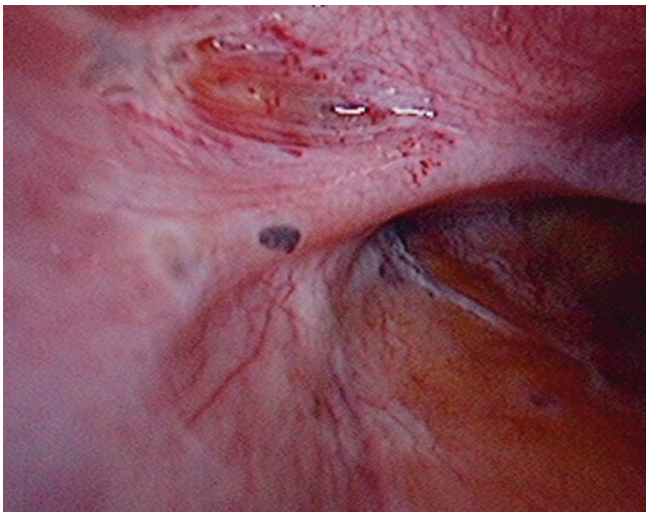

Fig. 12.10 Endometriosis involving round ligament. Endometriosis, seen as black and grey-white lesions, is present on the broad ligament. The ligament is thickened, possibly due to fibrosis induced by endometriosis

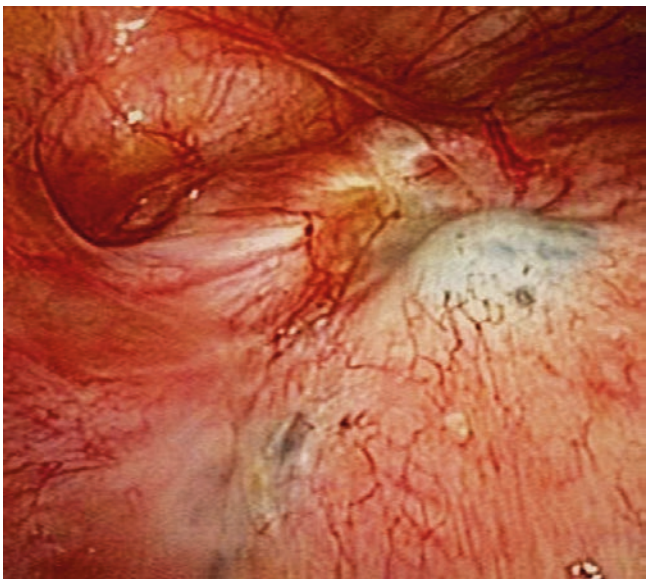

Fig. 12.11 Deep-infiltrating endometriosis involving Douglas' pouch. Shown is a deeply embedded nodule with a blue raised surface (middle right), typical of a deep-infiltrating endometriosis. Additional areas of small peritoneal surface involvement are also seen (lower middle)

12.4.2 Microscopic Features of Endometriosis

Microscopically, endometriosis is composed of endometrioid glandular epithelia surrounded by endometrial-like stroma, which is enriched with capillary vessels. The cellular composition may vary between lesion types. Foci of endometriosis are commonly associated with bleeding, fibrosis, and smooth muscle proliferation. Typical microscopic findings are summarized in Table 12.4.

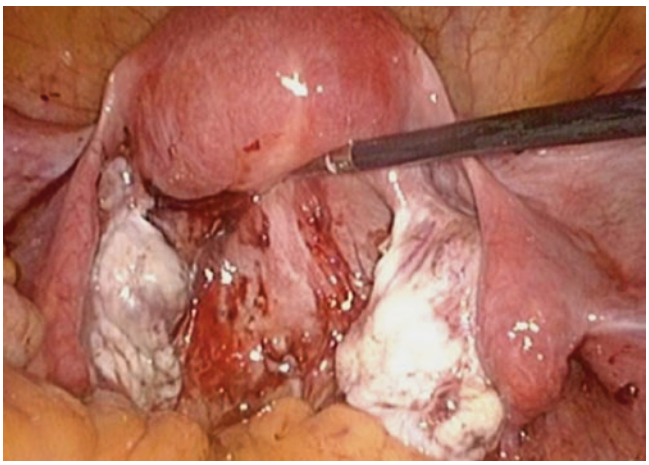

Fig. 12.12 Deep-infiltrating endometriosis involving Douglas' pouch. Another example of deep-infiltrating endometriosis involving the pouch of Douglas. A raised nodule is displayed underneath the posterior wall of the uterus (laparoscopic forceps)

Table 12.4 Histologic features of endometriosis

	Components
Epithelial associated cells	Endometrioid or tubal like cells
	Glandular or tubular structures
	Surface epithelia
Stromal fibrosis, pseudoxanthoma cells, macrophages	Endometrioid stromal cells
	Capillary vessels
	Spiral arteries
Secondary tissue changes	Surface adhesions
	Smooth muscle proliferation
	Fibrosis and scar formation

Microscopic findings of endometriosis are usually influenced by circulating levels of hormones, and lesions may show proliferative or secretory appearance (Fig. 12.13). Recognition of the stromal compartment can help in subtle cases. These cells typically surround the glands or lie just underneath the epithelial surface. The endometrial stroma is enriched with capillary vessels and occasionally contains well-developed spiral arteries. Typically, the stromal cells are immunopositive for CD10 (also known as common acute lymphocytic leukemia antigen, CALLA) [99], which aids in diagnosis (Fig. 12.14).

Presence of histiocytes is another microscopic feature of endometriosis. There are two kinds of histiocytes—pseudoxanthomatous cells and hemosiderin-laden macrophages; the former is more common than the latter in endometriosis (Fig. 12.15). Pseudoxanthomatous cells result from the degradation of both epithelial cells and red blood cells within the foci of endometriosis. Hemosiderin-laden macrophages are formed when red blood cells become the dominant products of endocytosis. From this perspective, the presence of pseudoxanthomatous cells is more specific for endometriosis,

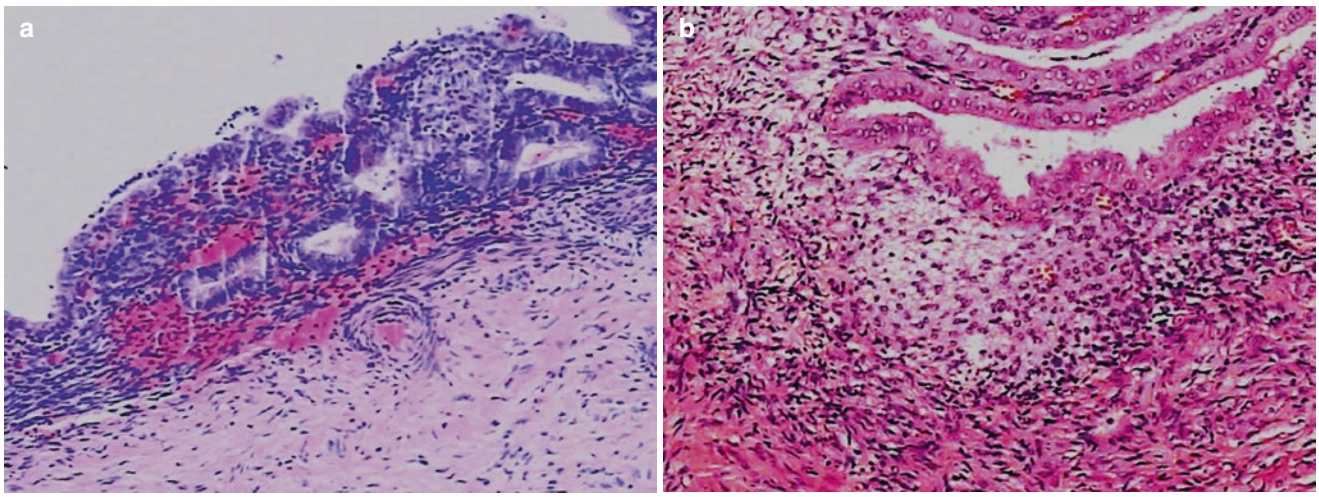

Fig. 12.13 (**a**) Endometriosis showing proliferative-type endometrial glands. Proliferative endometrium is present in this focus of endometriosis. (**b**) Endometriosis showing secretory-type endometrial glands. Secretory endometrium is seen in this focus of endometriosis

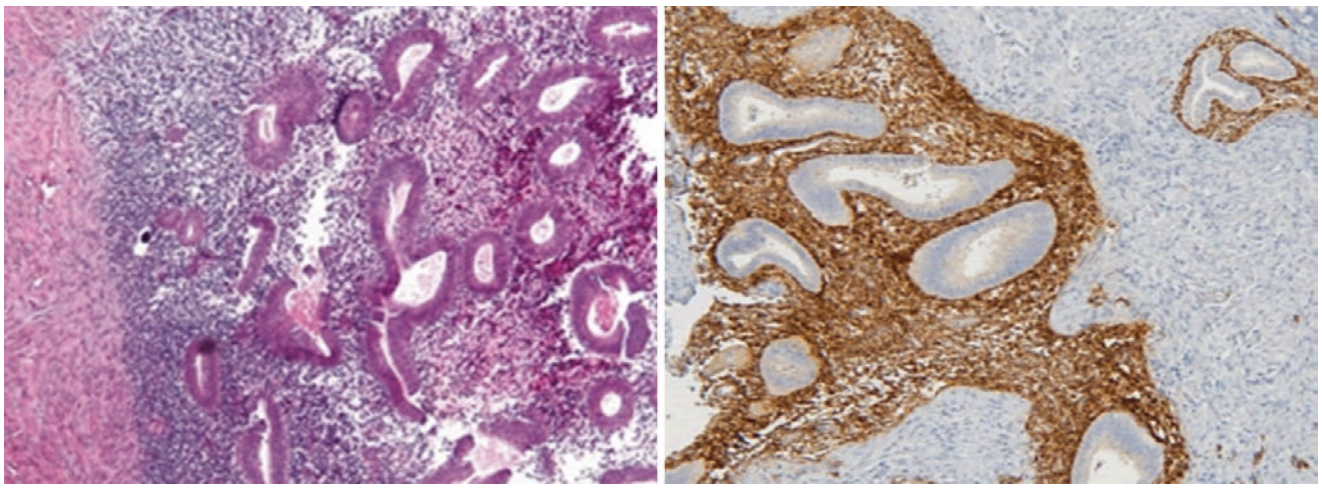

Fig. 12.14 CD10 is positive for the stromal cells of endometriosis. Stromal cells of endometriosis stained with H&E (left panel) and immunostained with anti-CD10 antibody (right panel)

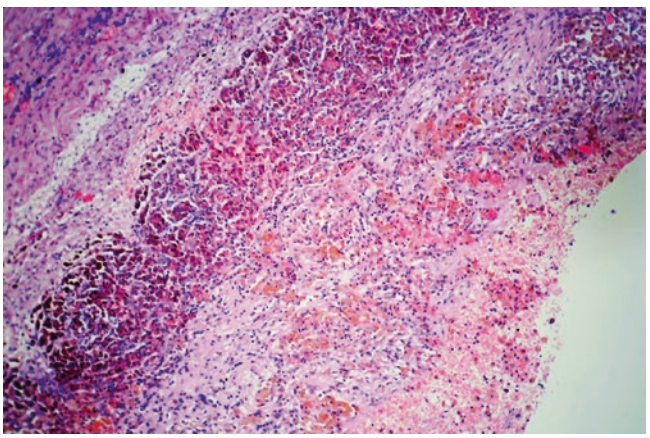

Fig. 12.15 Pseudoxanthomatous cells and hemosiderin-laden macrophages in endometriosis. A representative section of an ovarian cyst wall associated with an endometrioma. Pseudoxanthomatous cells are present within the lower right corner, while hemosiderin-laden macrophages are present in the center layer

since any bleeding-associated lesion can present with hemosiderin-laden macrophages.

Different locations of endometriosis may have different gross and microscopic appearances, as demonstrated in representative pictures of endometriosis in the ovary (Fig. 12.9), tubal serosa (Figs. 12.16 and 12.17), uterine serosa (Figs. 12.18 and 12.19), uterine ligament (Fig. 12.10), endocervical mucosa (Figs. 12.20 and 12.21), colon (Fig. 12.22), abdominal wall after C-section (Fig. 12.23), omentum (Fig. 12.24), and lymph nodes (Fig. 12.25).

12.4.3 Differential Diagnosis

Many conditions can mimic endometriosis. These include corpus luteum cyst, endosalpingiosis, stromal hyperplasia, ectopic decidua, and rete ovarii (Table 12.5; Figs. 12.26, 12.27, 12.28, 12.29, and 12.30). The key diagnostic clue for

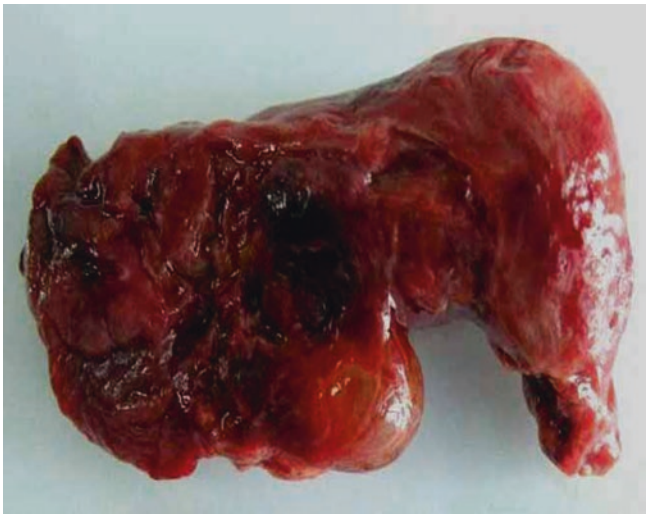

Fig. 12.16 Endometriosis involving the fallopian tube. Grossly, the fallopian tube is thickened. Multiple foci of endometriosis are present within the tubal wall

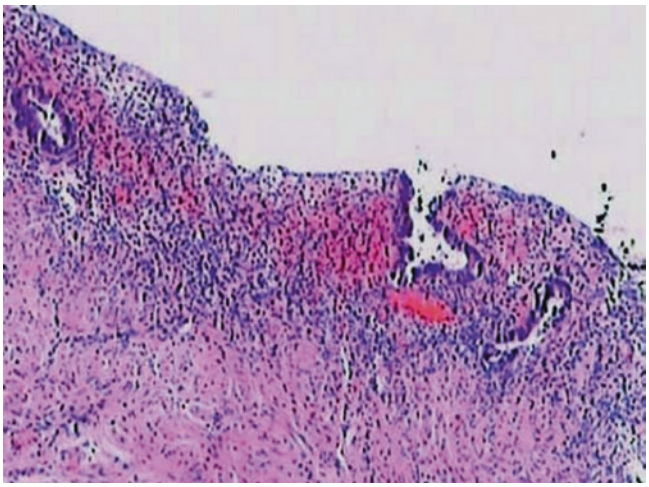

Fig. 12.17 Endometriosis involving the fallopian tube. Microscopically, endometriosis lines the surface of the cyst wall. The muscular layer of the fallopian tube is present underneath

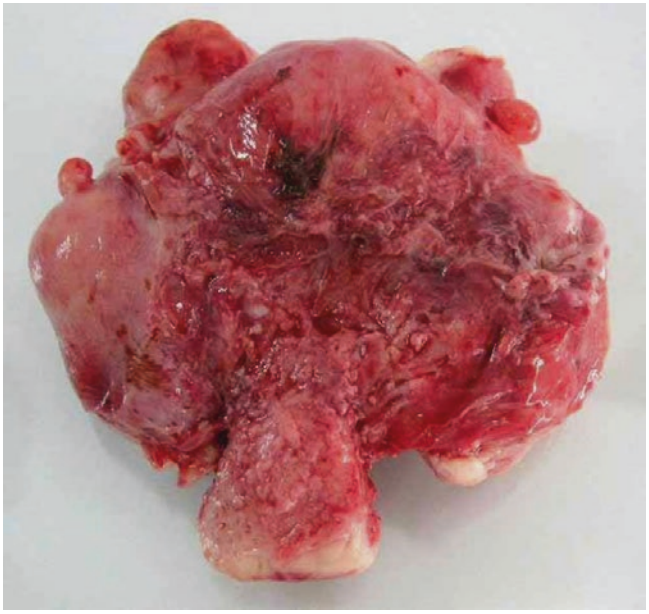

Fig. 12.18 Endometriosis involving the uterine serosa. A hysterectomy specimen showing shaggy uterine serosal surface due to severe adhesions caused by endometriosis

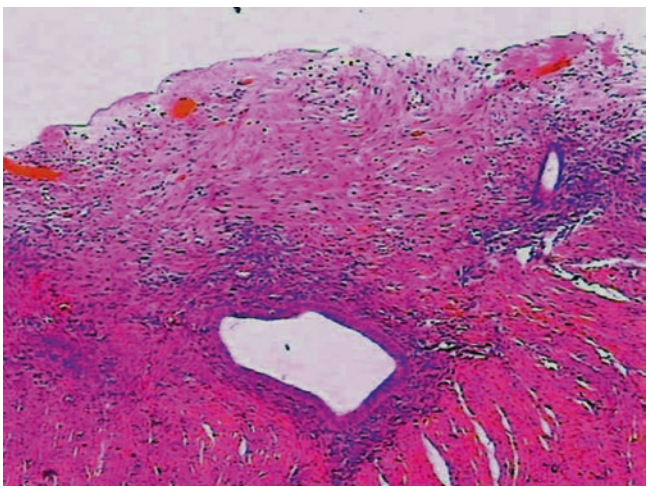

Fig. 12.19 Endometriosis involving the uterine serosa. Microscopically, the serosa shows endometriotic glands and fibrosis

the diagnosis of endometriosis is to find both epithelial and stromal components, although this is not always easy. While CD10 is a sensitive immunohistochemical marker of endometrial stroma in ectopic sites, especially in women with minimal disease, its use is limited in situations where the amount of stroma is sparse.

There are many other differential diagnoses pathologists should consider. For instance, deeply infiltrating endometriosis involving the colon can be confused with either metastatic cancer or cancer of the colon. When endometriosis is treated by progestin, the stromal cells become decidualized, which can raise the histologic differential diagnosis of gastrointestinal stromal tumor. The correct diagnosis is usually not difficult if the basic concepts of endometriosis as well as the possibility of its widespread distribution are kept in mind.

12.4.4 Special Types of Endometriosis

12.4.4.1 Polypoid Endometriosis

Polypoid endometriosis is a rare type of endometriosis that presents as large lesions which may simulate polyps and are generally mistaken for malignant tumors [108]. This type of endometriosis usually accompanies typical endometriosis at other sites and/or may manifest later in women with a history of endometriosis. Lesions occur predominantly at mucosal or serosal surfaces of the colon, uterus, cervix, and vagina or within cyst cavities of the ovary but are also found, albeit less frequently, in the omentum, bladder, and retroperitoneum.

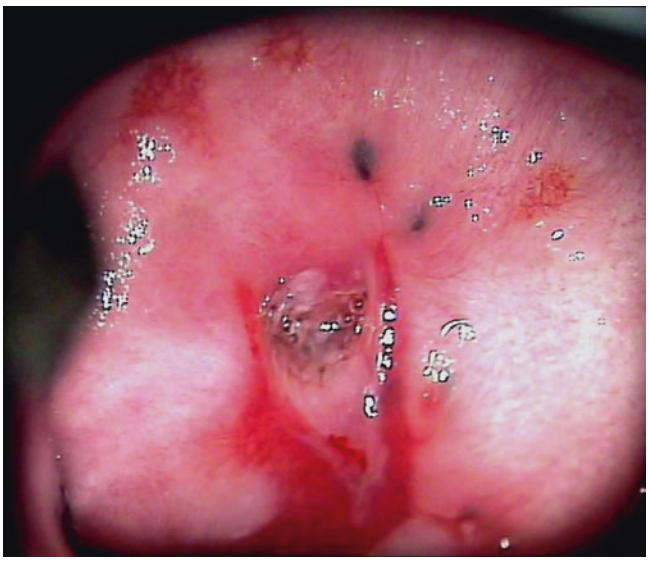

Fig. 12.20 Endometriosis involving the endocervical mucosa. A colposcopic view of the cervix shows blue or black spots on the cervical mucosa

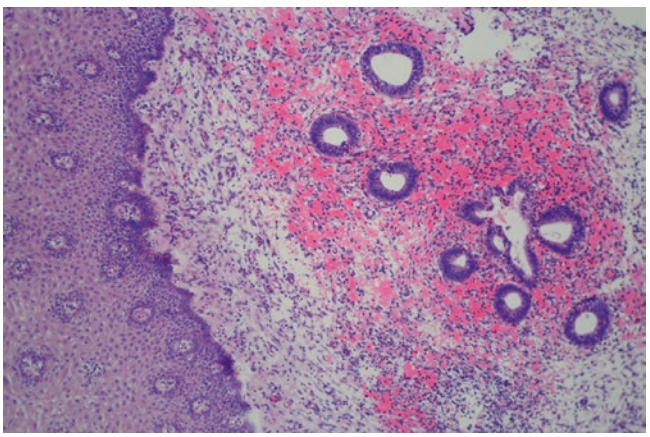

Fig. 12.21 Endometriosis involving the endocervical mucosa. Microscopically, the superficial endometriosis is located directly beneath the squamous mucosa

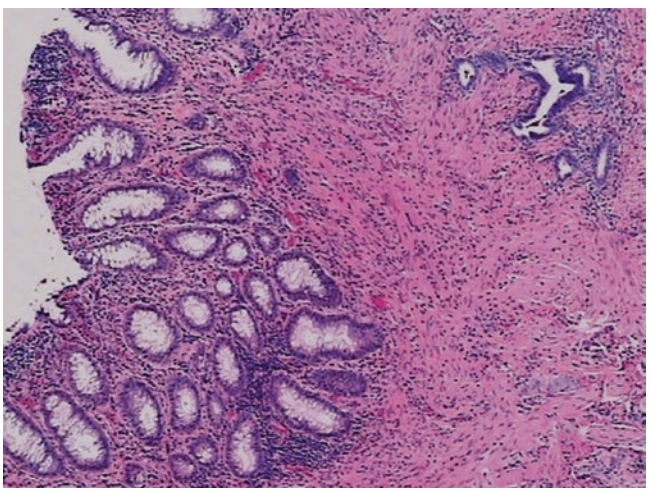

Fig. 12.22 Endometriosis involving the colon. Colonic mucosa shown on the left, with a focus of endometriosis shown on the upper right

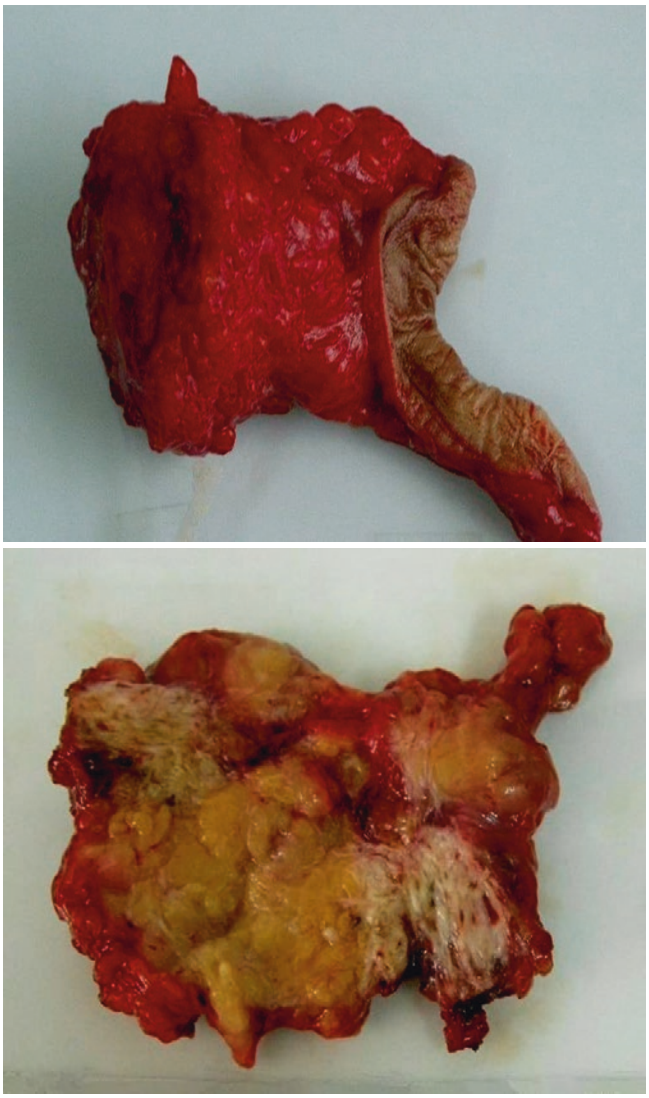

Fig. 12.23 Endometriosis involving a dermal scar. Resected skin and dermal scar are shown on the top panel. Cross section of the specimen shows several foci of endometriosis (black spots) and fibrosis (bottom panel)

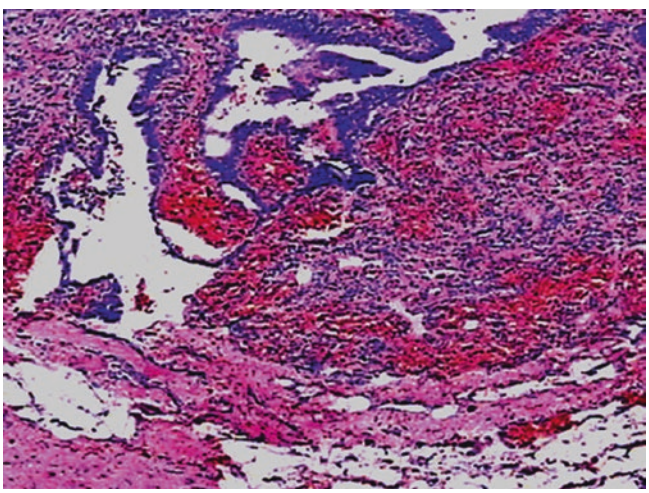

Fig. 12.24 Endometriosis involving the omentum. Foci of endometriosis (upper left) and fatty tissue (bottom) are shown. Extensive chronic inflammation is present

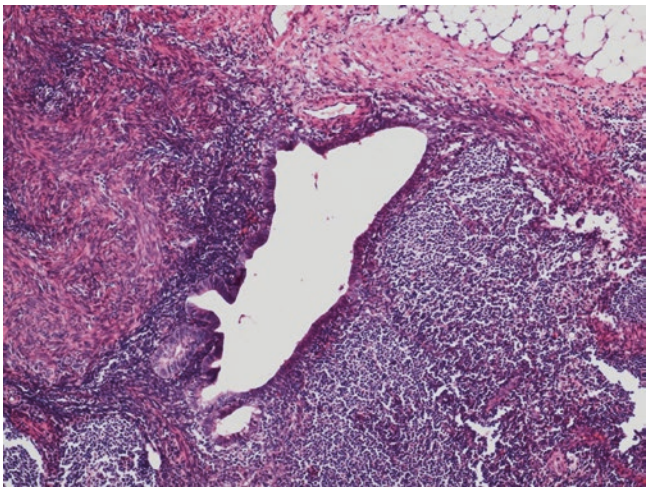

Fig. 12.25 Endometriosis involving the lymph node. A few endometriotic glands are localized underneath the nodal capsule

Table 12.5 Differential diagnosis of endometriosis

Disease	Similarities	Differences
Corpus luteum	Fibrosis and hemorrhagic appearance of the cystic wall	A single-time bleed instead of repeated episodes of bleeding Classic yellowish color Presence of theca interna cells without fibrosis Without epithelial and stromal cells
Endosalpingiosis or ovarian epithelial inclusions	Locations are similar to endometriosis Presence of glandular structures	Absence of endometrioid stromal cells No evidence of bleeding and fibrosis
Stromal hyperplasia	May appear as glandular or cystic structures with adjacent adhesions	May be lined by mesothelial cells Absence of bleeding or epithelial or stromal cells
Ectopic decidua	Sheets of decidual cells	Absence of glandular cells Absence of bleeding and fibrosis
Rete ovarii	Glandular structures	Located in hilar region Epithelial cells are cuboidal or low columnar No evidence of bleeding

Gross features: Macroscopically, polyps are solid with a round and smooth shape [109]. Polyp size may be as large as 20 cm. It can be single or multiple, and is typically associated with bleeding and/or formation of a cystic space.

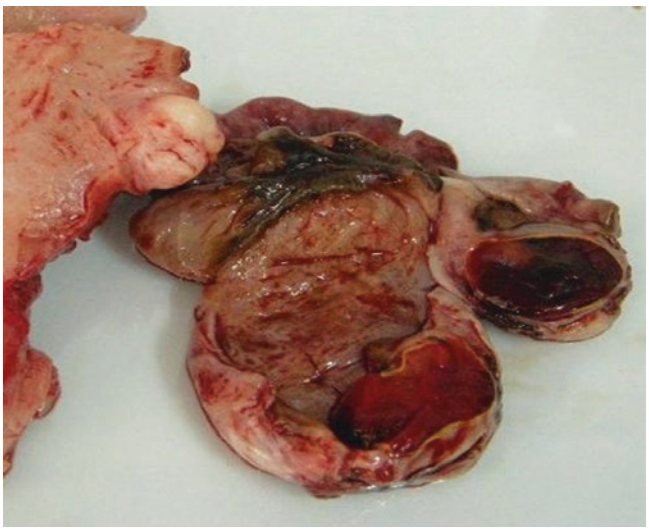

Fig. 12.26 Corpus luteum of the ovary. A corpus luteum may also contain old blood; however, the cyst wall is thin and without fibrosis. A characteristic yellow cyst wall is typically present (lower middle)

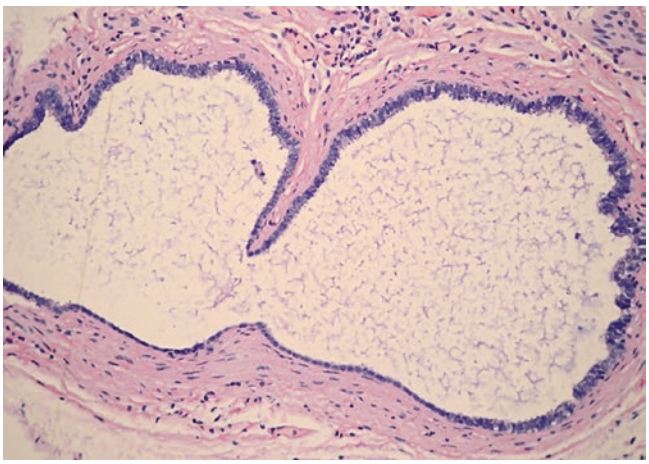

Fig. 12.27 Endosalpingiosis involving the fallopian tube. The cystic gland represents endosalpingiosis. The epithelial lining can be similar to the epithelial cells of the endometriosis; however, there is no endometrial stroma. Instead, the cyst is surrounded by smooth muscle, indicating a tubal location

Microscopic features: Microscopically, the polypoid masses are composed of an admixture of endometrial glands and stroma; the glands are typically hyperplastic, with or without atypia, while the underlying stroma is dense (Fig. 12.31) [108]. Epithelial metaplastic changes are common. However, typical foci of endometriosis are usually present in adjacent areas.

Differential diagnosis: The most common differential diagnosis is low-grade adenosarcoma. The lack of stromal atypia and overgrowth differentiates these lesions from ade-

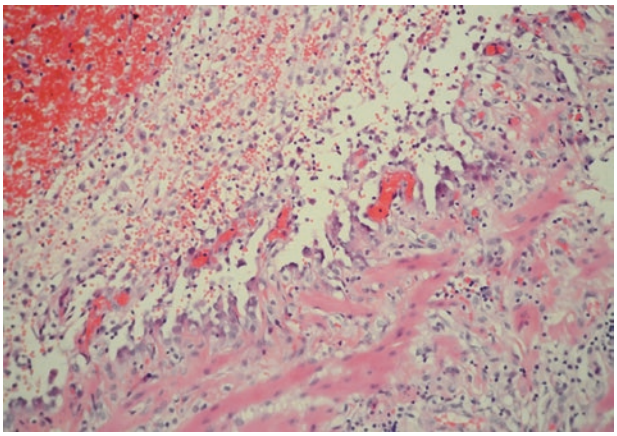

Fig. 12.28 Mesothelial hyperplasia within the peritoneum. Mesothelial hyperplasia is common in the peritoneum. This image shows mesothelial proliferation in the center, which may occasionally simulate glands. No endometrioid stroma is seen

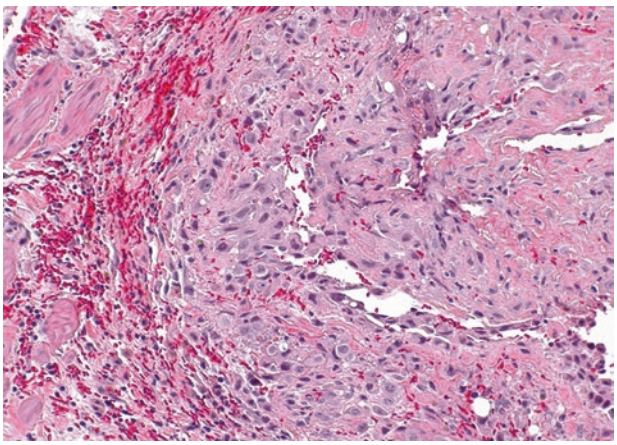

Fig. 12.29 Ectopic decidua. Ectopic decidual cells may simulate endometrial stromal cells; however, they contain large amounts of eosinophilic cytoplasm and lack associated epithelium. These lesions are common in pregnant patients

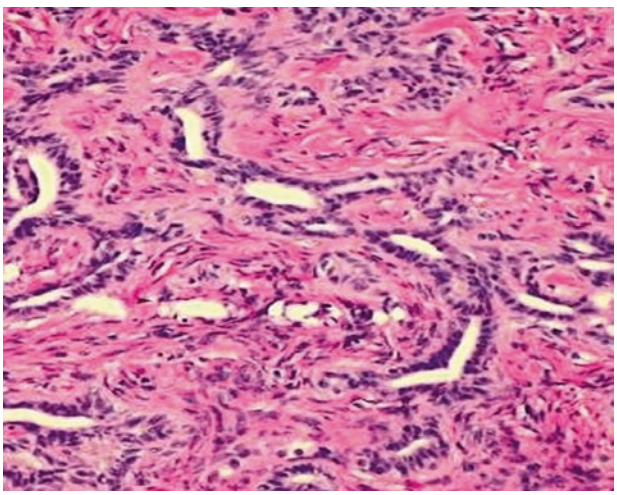

Fig. 12.30 Rete ovarii. Rete ovarii are typically present within the ovarian hilar region. They are composed of many irregular or slit-like spaces without endometrioid stroma and are commonly surrounded by smooth muscle

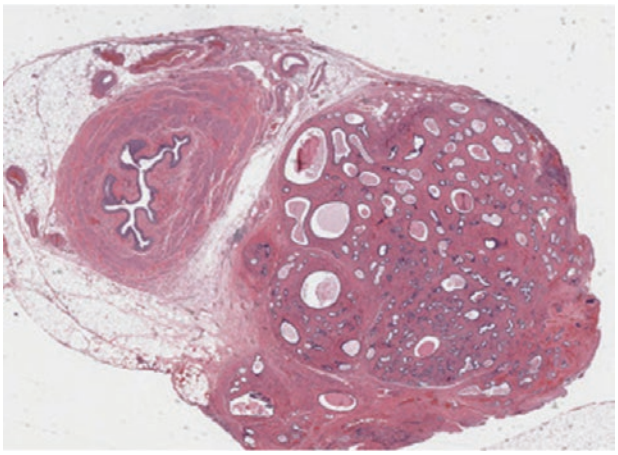

Fig. 12.31 Polypoid endometriosis involving the fallopian tube. A polypoid lesion measuring approximately 5 mm is present in the tubal serosa. Many endometrial glands with cystic dilations are noted. The stroma may be fibrotic in areas. These lesions may mimic malignancy (courtesy of Dr. Li Dong)

nosarcoma. Other entities that may be considered in this setting include fibroepithelial polyp, polypoid adenomyoma, and Mullerian papilloma.

Prognosis: Polypoid endometriosis behaves in a similar manner to otherwise typical endometriosis. Gene expression analyses showing that vaginal polypoid endometriotic lesions exhibit highly similar profiles with those of peritoneal endometriosis [110] provide additional support to their endometriotic nature.

12.4.4.2 Stromal Endometriosis

Stromal endometriosis is another rare type of endometriosis, aptly named for the predominance of stroma and relative lack of endometrial type glands. Histologically, the lesions present as small microscopic nodules or plaques of endometrioid-type stroma superficially located just beneath the mesothelial surface, suggesting their potential origin from mesothelial or submesothelial cells via a metaplastic process [111]. Associated histological features include mesothelial proliferation, inflammation, and giant cell or granuloma formation. It can be mistaken for both malignant and benign neoplasms. Stromal endometriosis is typically seen in association with classic endometriosis and the clinical and pathological features of these lesions are similar.

12.5 Other Histological Features of Endometriosis

The histologic analyses of endometriotic lesions may be confounded by alterations in the appearance of both the glandular and stromal components in biopsies. Hormonal (Fig. 12.32) and/or metaplastic changes (Fig. 12.33) may

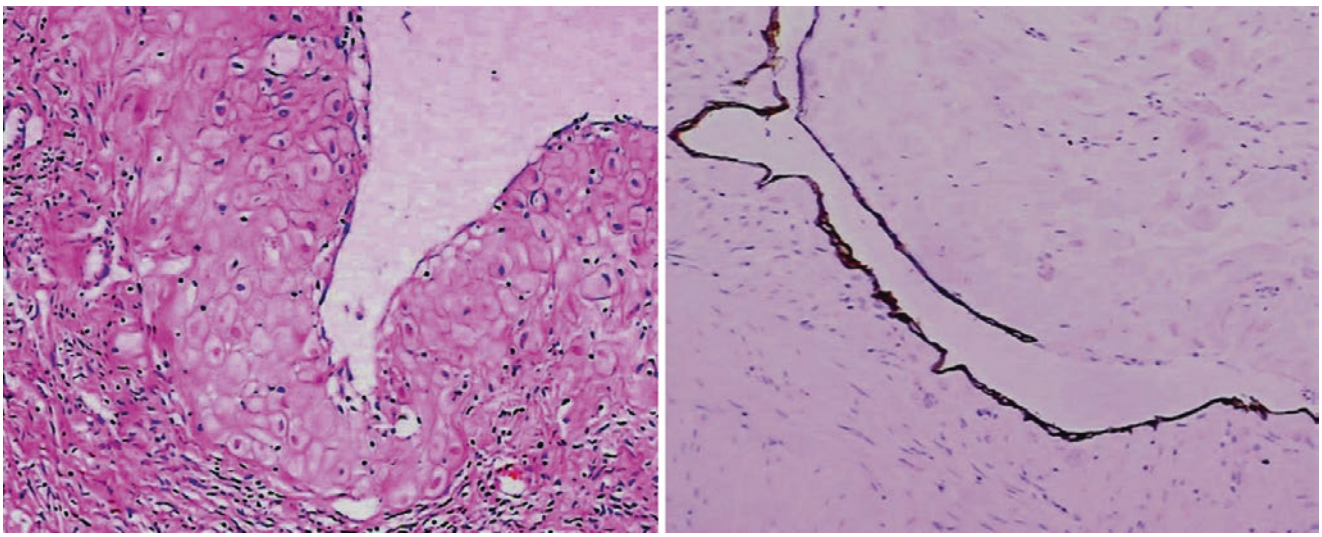

Fig. 12.32 Endometriotic cyst found in a term pregnancy. High levels of progesterone during pregnancy commonly cause decidual changes in endometriosis. The ovarian cyst shown here displays extensive decidualization (left), and the epithelial lining is not obvious until stained for cytokeratin 7 (CK7) (right)

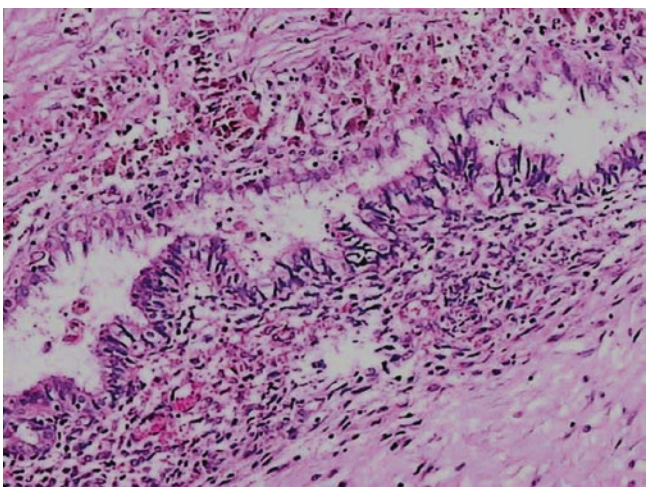

Fig. 12.33 Endometriosis with metaplasia. Metaplasia including squamous, mucinous, eosinophilic, and ciliated metaplasia may occur in endometriosis. Mucinous metaplasia can be seen in this image

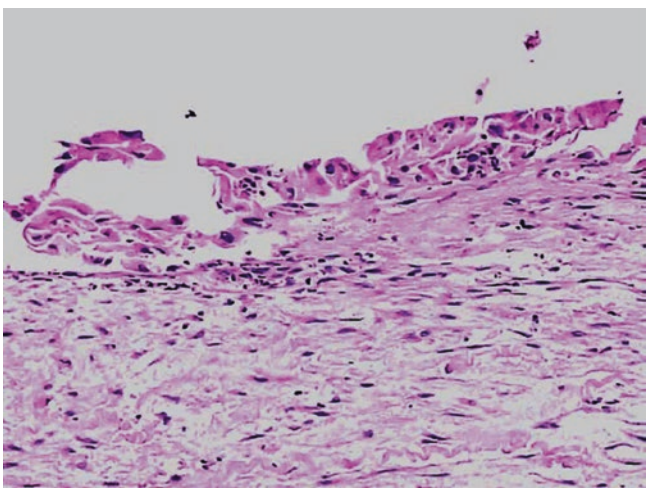

Fig. 12.34 Endometriosis with reactive epithelial changes. Nuclear atypia is apparent in this focus of endometriosis; however, epithelial proliferation and mitotic areas are not visible. The atypical nuclei represent reactive and/or degenerative changes secondary to the hostile environment created within endometriosis

alter the presence and/or appearance of endometriotic glands. Endometriosis, particularly cystic lesions with absent or scant glands, may be a result of the hostile surrounding environment. Those lesions with glands displaying hyperplasia or atypical hyperplasia are collectively referred to as atypical endometriosis (see below).

Reactive "nuclear atypia" in endometriotic glands presents as enlargement of the nucleus, hyperchromasia, and multiple, tiny nucleoli, with variable degrees of nucleocytomegaly (Figs. 12.34 and 12.35). These atypical nuclei are not uncommon and represent degenerative changes in the toxic environment. They could be confused with the hyperplastic process seen in true atypical endometriosis.

The stromal component of lesions may also be obscured or effaced by conditions such as fibrosis, smooth muscle metaplasia, and presence of infiltrates of foamy and pigmented histiocytes [112]. The inflammatory status affects the histologic diagnosis of endometriosis since these changes can cause associated morbidities such as infection within endometriotic cysts, florid mesothelial hyperplasia, peritoneal inclusion cysts, and pseudoxanthomatous salpingitis [112]. Complication of the diagnosis also arises when other conditions, such as peritoneal leiomyomatosis or gliomatosis, are admixed with the endometriotic foci.

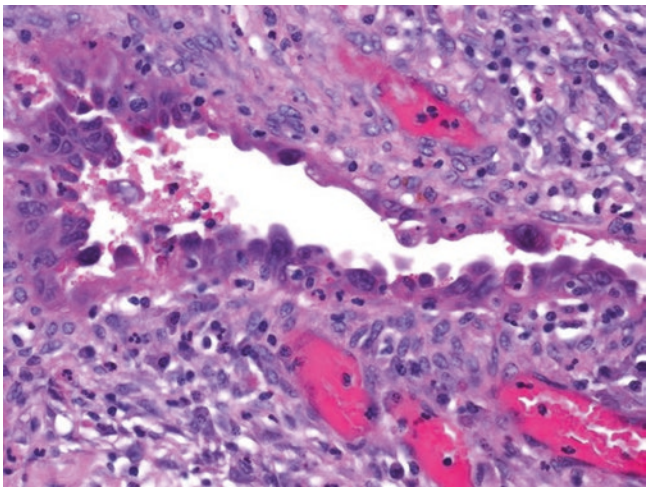

Fig. 12.35 Endometriosis with reactive epithelial changes. Similar scenario as illustrated in Fig. 12.34

12.6 Endometriosis-Associated Tumors and Its Malignant Transformation

12.6.1 Endometriosis and Ovarian Carcinoma

Endometriosis is considered to be a benign disease with pathological features resembling cancer [113]. In particular, endometriotic lesions have the ability to invade surrounding tissues, metastasize to extra-pelvic locations, evade apoptosis, and manifest enhanced angiogenesis. In a study of deep-infiltrating endometriotic lesions with no associated tumors, a significant fraction (10 of 39 cases; 26%) displayed mutations in genes (*ARID1A, PIK3CA*, *KRAS, PPP2R1A*) known to drive cancer development [75]. Such findings provide strong support to the cancer-like features of endometriosis.

The malignant transformation of endometriosis is rare, only reported in about 1% of all documented cases of endometriosis [114]. The premise that endometrioid ovarian cancer may originate from endometriosis was first described by Sampson in 1925 [113]. The three original criteria for establishing the association remain in use to date: (1) evidence of coexistence of endometriosis and tumor in the ovary; (2) exclusion of metastasis originating from other sources; and (3) presence of endometrial stroma and epithelial glands in tumors. Inclusion of histological proof demonstrating the transition of benign endometriotic lesions to neoplastic lesions was later incorporated as a fourth criterion [115].

The ovary is the most common site for the development of malignancy from endometriosis, accounting for ~80% of endometriosis-associated tumors. The rest of the endometriosis-associated malignancies are attributed to malignant transformation of extra-ovarian endometriosis such as the intestines, bladder, abdominal wall, thorax, and cervix [116]. Based on the histopathology and molecular features, ovarian cancers are categorized into five subtypes, namely high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous. High-grade serous carcinoma comprises the majority of ovarian cancers (70%), followed by endometrioid (10%) and clear cell (10%) cancer subtypes. The 5-year survival for high-grade serous carcinoma (62%) is lower than that for endometrioid (100%), clear cell (75%), and mucinous (80%) carcinomas [117].

Ovarian clear cell carcinoma (OCCC) is highly associated with endometriosis, followed by endometrioid ovarian carcinoma (EOC), serous carcinoma, and mucinous carcinoma [118]. Patients with OCCC and endometriosis have been found to be significantly younger, to be more likely nulliparous, and to have poorer overall survival than those with OCCC alone [119]. Ovarian endometriosis may constitute an independent prognostic factor in OCCC since patients with OCCC and endometriosis also displayed a higher incidence of early-stage disease compared to those with non-endometriosis-associated OCCC [120]. The pathogenesis of OCCC arising from endometriosis remains unclear. Endometriosis-associated OCCC and non-endometriosis-associated OCCC exhibited similar alterations in gene sets related to the PI3K/Akt, p53, and ERBB2 pathways, with no differences in frequency [121].

12.6.2 Malignant Transformation of Endometriosis

Figure 12.36 summarizes the postulated multistep progression of benign endometriotic lesions to ovarian tumors. Atypical endometriosis is considered to represent an early intermediate step in the neoplastic progression. First described by Czernobilsky and Morris [122], atypical endometriotic lesions are characterized by the presence of epithelial cells with eosinophilic cytoplasm, large pleomorphic hyperchromatic or pale nuclei, increased nuclear-to- cytoplasmic ratios, cellular crowding, tufting, and stratification (Fig. 12.37). Atypical endometriosis is found in 8% of cases of typical endometriosis and is commonly associated with OCCC and EOC. In an earlier report of OCCC (50 total) and EOC (31 total) cases, 27 and 13, respectively, were associated with endometriosis and of these 18 of 27 and 7 of 13 exhibited atypical endometriosis [123]. In another study involving 15 EOC cases, 6 tumors were determined to have endometriosis, all of which were characterized as atypical [124]. Atypical endometriosis in these cases was found to be mixed with, or contiguous to, the tumors [123, 124]. The chronological association between atypical ovarian endometriosis and OCCC has been previously reported, with a 3-year time lapse [125]. In a case report, a 33-year-old woman who had previously undergone three laparoscopic surgeries over a period of 10 years for treatment of endometriosis was

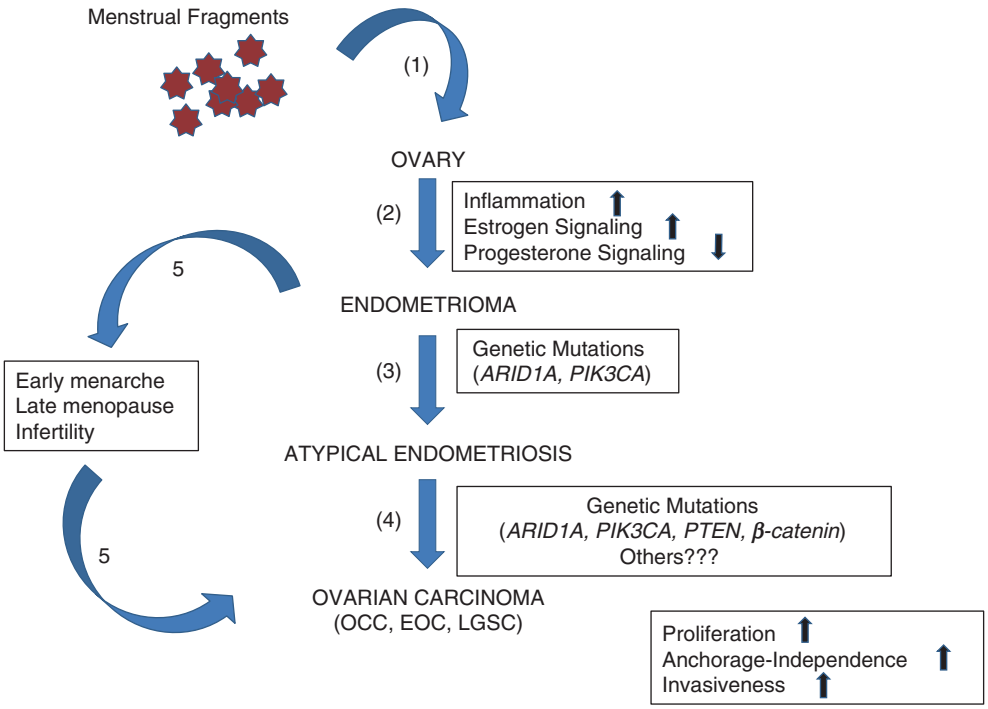

Fig. 12.36 Model for multistep progression of benign endometriotic lesions to ovarian tumors. Menstrual fragments (from retrograde menstruation) attach to the ovary (**1**), a process promoted by pro-inflammatory, pro-estrogenic, and anti-progestogenic events (**2**). Mutations in key genes (e.g., *ARID1A, PIK3CA*) are considered to promote the progression of an endometrioma to atypical endometriosis (**3**) and subsequently to full-blown carcinoma (**4**). Not currently known is whether and how additional genetic dysregulations result in specific ovarian cancer types (OCC, EOC, LGSC). Early menarche, late menopause, and infertility are considered risk factors for the development of endometrioma to ovarian cancers (**5**). OCC, ovarian clear cell carcinoma; EOC, endometrioid ovarian carcinoma; LGSC, low-grade serous carcinoma

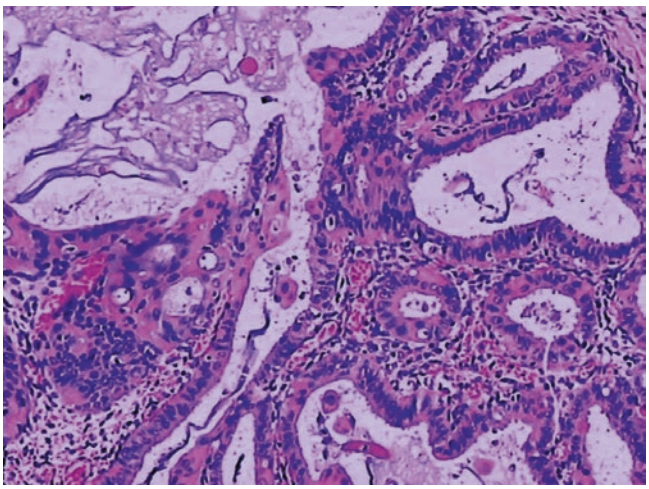

Fig. 12.37 Atypical endometriosis. In contrast to Figs. 12.34 and 12.35, this lesion shows glandular proliferation in addition to nuclear atypia, which are characteristic of atypical endometriosis

diagnosed with grade 1 EOC after her third surgery. A histological review of her lesions after the second surgery confirmed the diagnosis of atypical endometriosis [126] . These, and other related findings, suggest that atypical endometriosis is likely to be a precancerous lesion and patients with atypical endometriosis should be followed closely for extended periods to eliminate the possibility of developing ovarian cancer.

An important question remains—how may ovarian carcinoma develop from endometriotic lesions? Huntsman and his group [127] initially identified tumor suppressor *ARID1A* as a mutated gene in OCCC by comprehensive whole-genome sequencing of 18 samples; 6 of these samples displayed somatic *ARID1A* mutations. Further analyses of distinct ovarian cancer subtypes demonstrated that *ARID1A* mutations were highly associated with OCCC relative to EOC (55 of 119 OCCC; 10 of 33 EOC) but were not associated with high-grade serous carcinomas (0 of 76) [127]. Loss of *ARID1A* expression was subsequently shown in benign endometriosis, atypical endometriosis, and endometriosis-associated OCCC [128, 129]. In these samples, *ARID1A* loss frequently (but not exclusively) coexisted with *PIK3CA* mutations. The coincident mutations of *ARID1A* and *PIK3CA* in endometriotic lesions and primary OCCC have been confirmed in other studies [43]. Moreover, knockdown of *ARID1A* in an immortalized endometriosis cell line caused phenotypic changes (e.g., anchorage-independent growth, increased invasive ability) characteristic of neoplastic transformation [130]. The loss of *ARID1A* coincident with increased levels of phosphorylated gamma histone H2AX

(γH2AX), and enhanced activation of the apoptotic pathway, was also demonstrated in EOC and contiguous endometriosis at greater frequencies than in benign endometriotic lesions [131]. Thus, benign endometriotic lesions carrying cancer-associated mutations in ARID1A and PIK3CA likely serve as precursors for ovarian malignancies.

In a review of databases pathologically screened for suspected cases of atypical endometriosis, Stamp et al. [132] reported that loss of ARID1A in atypical endometriosis was consistently associated with the development of ARID1A-negative endometriosis-associated ovarian cancer. In another comparison of atypical endometriosis and neoplastic lesions by targeted next-generation sequencing, ARID1A and PIK3CA genes were confirmed as frequently mutated; mutations in genes associated with Notch and Wnt/β-catenin signaling pathways [131] were also noted. Nevertheless, it remains unclear if endometriosis-associated EOC and OCCC evolve similarly, since the expression of other genes such as hepatocyte nuclear factor 1β, hypoxia-inducible factor 1α, and NFκ-B p65 was not identical between EOC and OCCC and their respective coexisting endometriotic lesions [133]. Related to the latter, it was recently proposed that OCCC and EOC may originate from distinct cells within endometriotic tissue [134] .

Another potential contributory mechanism to ovarian tumorigenesis implicates the stromal compartment [135]. When compared with more distant ovarian stroma, endometriosis-associated ovarian tumors display increased expression of steroidogenic genes and enzymes involved in steroid hormone synthesis. Early changes in endometriotic stroma involving the activation of steroid hormone production may thus lead to abnormal proliferation of adjacent ovarian epithelia to promote neoplastic growth.

12.6.3 Seromucinous Carcinoma and Other Endometriosis-Associated Tumors

Seromucinous tumors and borderline tumors are less common neoplasms of the ovary. Seromucinous tumors typically display papillary architecture, an admixture of cell types, including endocervical-like mucinous, eosinophilic, squamous, clear, and signet-ring cells, and morphological overlap with low-grade serous, mucinous, and endometrioid carcinomas [136] . These tumors are associated with endometriosis at a relatively high frequency (23 of 92 cases) [117]. Similar to EOC and OCCC, they show loss of *ARID1A* expression due to somatic inactivation occurring with significant frequency (8 of 24 cases; 33%) [137]. Borderline tumors, first described as "semi-malignant" ovarian tumors, display biological characteristics intermediate between malignant and benign tumors and are classified to be of serous or non-serous subtypes. The serous subtype is closely related to low-grade serous carcinomas and exhibits higher potential for malignancy and recurrence [138]. By contrast, the non-serous subtype presents mostly at FIGO stage 1 and has higher overall survival. One study reported that 30% of borderline serous tumors exhibit endometriosis [139]. In a large cohort of women with subfertility [140], an increased risk for borderline tumors was associated with both ovarian and extra-ovarian endometriosis. However, in studies conducted as part of the Ovarian Cancer Association Consortium, an association between borderline tumors and self-reported endometriosis was not observed [141]. Further studies are needed to clarify these associations.

Numerous analyses have shown that extra-pelvic endometriosis can also develop into malignant tumors. Abdominal endometriosis-associated clear cell carcinoma [142, 143] has been reported and additionally metastasis in the bladder and the lymph nodes was also detected [140]. Malignant transformation of deep-infiltrating endometriosis has also been reported in the pancreas [144] as well as in the appendix leading to intestinal neoplasia [145]; colon/rectum leading to endometrial stromal sarcoma [146]; vagina [147]; small intestine [114]; cervix [148]; and bladder [149]. Because these conditions are relatively rare, the mechanisms underlying their progression to neoplasia have yet to be extensively assessed.

12.7 Conclusions

The possibility that endometriosis can progress from a benign to a neoplastic condition, in addition to its comorbidities, provides a strong impetus for the early detection and effective management of the disease. To address this challenge, it is imperative in the long term to focus resources on (1) the identification of new targets to monitor early disease onset, eliminate disease recurrence, and allow targeted therapy; (2) the development of new hormonal treatments with minimal side effects and contraindications while preserving fertility and ovarian function; and (3) the fine-tuning of current technologies and development of new procedures to improve accuracy of lesion diagnosis. In the short term, continuous vigilance to reduce recurrence should be part of the standard of care for diagnosed patients.

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