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Histopathological characteristics of adenomyosis: structure and microstructure

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Summary. Adenomyosis is a benign uterine disease that pathologically shows endometrial glands and stroma in the myometrium. There are multiple lines of evidence that adenomyosis is associated with abnormal bleeding, painful menstruation, chronic pelvic pain, infertility, and spontaneous pregnancy loss. Pathologists have researched adenomyosis by studying tissue specimens from its first report more than 150 years ago, and differing viewpoints on its pathological alterations have been advanced. However, the gold standard histopathological definition of adenomyosis remains controversial to date. The diagnostic accuracy of adenomyosis has steadily increased due to the continual identification of unique molecular markers. This article provides a brief description of the pathological aspects of adenomyosis and discusses adenomyosis categorization based on histology. The clinical findings of uncommon adenomyosis are also presented to offer a thorough and detailed pathological profile. Furthermore, we describe the histological alterations in adenomyosis after medicinal therapy.

Key words: Adenomyosis, Histopathology, Structure, Microstructure, Classification

Introduction

Adenomyosis is the presence of ectopic, nonneoplastic endometrial glands and stroma in the myometrium, and the ectopic endometrium is typically surrounded by hypertrophy and hyperplastic myometrium (Chapron et al., 2020). The term 'cystosarcoma adenoides uterinum' was first used by Rokitansky in 1860 to describe the presence of endometrial glands in the myometrium (Rokitansky, 1860). Following that, researchers have used words such as 'adenomyomata', 'cystoadenomyomata', 'adenomyoma', 'diffuse adenomyoma', and 'adenomyosis uteri', to characterize this phenomenon. In 1925, Frankl coined the word 'adenomyosis' to describe mucosal invasion of the myometrium and made the first clear distinction between adenomyosis and adenomyoma (Frankl, 1925). In 1972, Bird et al. formally proposed the definition of adenomyosis as "the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, nonneoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium", which has been used to this day (Bird et al., 1972).

Adenomyosis is a benign uterine disorder in which women affected may present with abnormal uterine bleeding (AUB), dysmenorrhea, dyspareunia, or infertility (Upson and Missmer, 2020; Buggio et al., 2021; Moawad et al., 2022). Nevertheless, one-third of these women are asymptomatic (Peric and Fraser, 2006). Adenomyosis has remained a histopathological diagnosis made after hysterectomies in perimenopausal women with heavy menstrual bleeding or pelvic pain (Taran et al., 2012; Orazov et al., 2016). Over the last decade, adenomyosis has also become a condition identified in young fertile-age women due to recent advancements in imaging techniques (Van den Bosch and Van Schoubroeck, 2018; Celli et al., 2022), but a consensus for the definition and classification of adenomyosis is still lacking. Adenomyosis greatly affects the quality of life of these women. However, management has not been standardized, and there are no Food and Drug Administration (FDA) approved medical therapies specifically indicated for the treatment of adenomyosis. As a result, adenomyosis is currently managed using modalities developed for contraception and symptoms (Kho et al., 2021).

Here, we provide a succinct summary of our current understanding of adenomyosis from a pathology

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perspective. This review aimed to elucidate the structure and microarchitecture of adenomyosis and to discuss its molecular features to further the understanding of adenomyosis.

Methods

This review was based on a search of the literature for studies on histopathology and molecular aspects in women with adenomyosis to understand the microarchitecture features of adenomyosis. From inception to October 2022, an extensive literature search was conducted using multiple databases, including PubMed, Web of Science, and Medline, to select studies using keywords applied to histopathologic features of adenomyosis, and the references included in selected publications were also screened.

Results

Gross pathological features of adenomyosis

Adenomyosis can manifest as a diffusely thickened mass affecting one side of the uterine wall or as a localized involvement of variable degrees, forming an intramyocardial mass (Ringrose, 1962). Macroscopically, the uterus is enlarged and bulbous when the whole myometrium or one of the myometrial walls is diffusely involved; in general, the involved uterus retains its overall shape and seldom surpasses 280 grams or the weight of a uterus corresponding to 12 weeks of gestation (Ferenczy, 1998). Adenomyosis is generally a diffuse lesion, mainly within one uterine wall, usually the posterior wall, which accounts for more than half of adenomyosis (McElin and Bird, 1974) (Fig. 1A). This enlargement is mostly caused by myometrial smooth muscle hyperplasia and hypertrophy that occurs with adenomyosis foci. Unlike uterine fibroids, adenomyosis has no clear boundary. In cross-section views, adenomyotic lesions show areas of hyperfasciculation of the myometrium with swirling trabecular structures (Uduwela et al., 2000; Antero et al., 2020). Grossly, ectopic lesions are grayish white with brown stained areas visible when secondary to hemolyzed blood and hemosiderin deposits (Fig. 1B). Aside from diffuse lesions, adenomyosis may also present as a confined nodule called adenomyoma (Haines, 1947). Adenomyotic nodules are recognized as fibrotic, elastic hard nodules in the uterine myometrium (Tahlan et al., 2006). These nodules consist of smooth muscle surrounding endometrial glands and stroma. Typically, an adenomyoma is fused to the surrounding normal uterine muscle and, therefore, has no distinct boundary.

Microscopic pathological features of adenomyosis

Microscopically, endometrial glands and stroma within adenomyosis foci are similar to the basal layer in the eutopic endometrium where a complex horizontally connected glandular structure is normally formed and distinct from the isolated, unbranched, longitudinally arranged glands of the functional endometrium (Emmanuel et al., 2019; Tempest et al., 2020) (Fig. 2A,B). Similar to the basal glands of the eutopic endometrium, endometrioid glands are usually inactive. However, most of the glands in endometriosis are functional, which is one of the important differentiation points between adenomyosis and endometriosis (Maruyama et al., 2020). As a result, the clinical signs of adenomyosis are induced by the enlargement of the uterus and the increase in vascular components without the reaction of endometrial periodic shedding. However, secretion changes, including stromal decidualization, may occur during pregnancy and exogenous progestin therapy (Ferenczy, 1998). In addition, the endometrium in adenomyosis has proliferative potential and is the site of endometrial growth. Approximately 10% of patients with adenomyosis typically have extensive fibrotic changes rather than endometrioid stroma with or without surrounding smooth muscle hyperplasia (Pistofidis et al., 2014).

Pathological diagnostic criteria of adenomyosis

Since Frankl first proposed the term ‘adenomyosis’ in 1925 (Frankl, 1925), there have been many attempts to reach a consensus on how to define adenomyosis

Table 1. Pathological diagnostic criteria of adenomyosis.

Diagnosis	Reference
Microscopic field of view	
>8 mm (two low-power fields)	Sandberg and Cohn, 1962
>4 mm (one low-power field)	Vercellini et al., 1993
>2.5 mm (one-half low-power field)	Norris and Zaloudek, 1987
Uterine wall thickness	
>1/3 of the total thickness	Hendrickson, 1987
>25% of the total thickness	Ferenczy, 1998
Other histopathological features	
Normal boundary between the endometrium and the myometrium is disrupted	Uduwela et al., 2000
The ectopic endometrium is basal type non-secretory tissue with a direct connection to the eutopic basalis	Bazot et al., 2001

(Table 1). The classic diagnosis of adenomyosis relied on the identification of heterotopic endometrial glands and stroma within the myometrium. There has been controversy over the years about the distinction between adenomyosis and normal myometrium. Researchers have called for stricter diagnostic criteria and warned against overdiagnosis. However, a general consensus is lacking for defining robust histological criteria for the microscopic diagnosis of adenomyosis with differences as high as ninefold between reporting histopathologists (Seidman and Kjerulff, 1996).

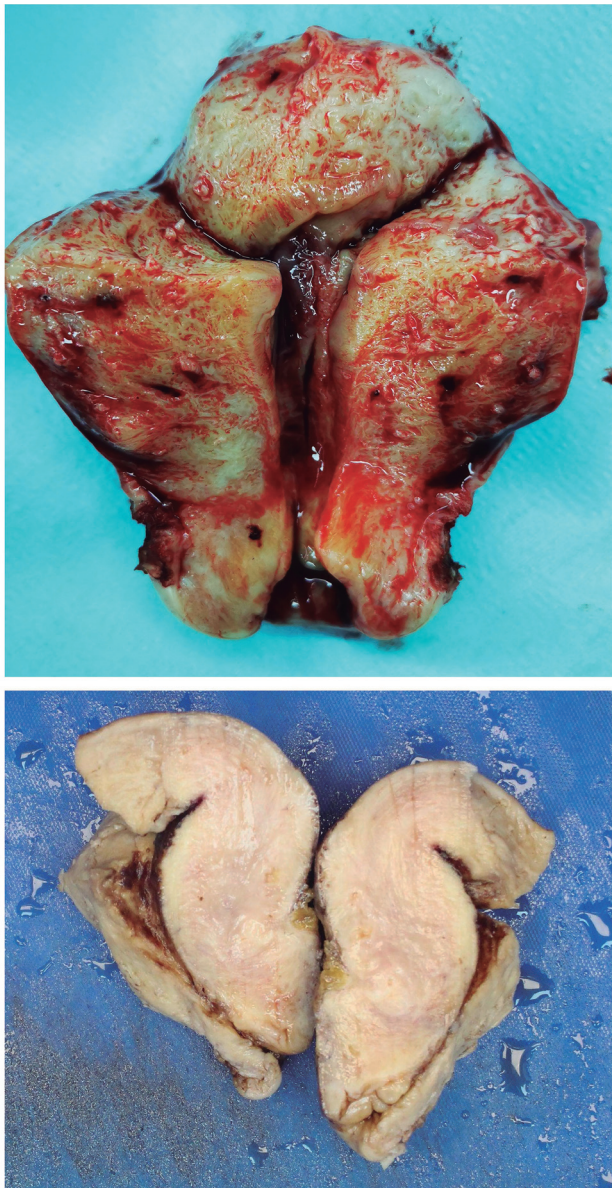

Fig. 1. Gross features of adenomyosis. **A.** Diffuse enlargement of the uterine corpus with smooth muscle hyperplasia and hypertrophy appearing as hyperfasciculation of the myometrium with a swirl trabeculated pattern and indistinct limits. **B.** A bivalved surface from a hysterectomy specimen shows multiple foci of adenomyosis with petechia-like areas in the myometrium. The smooth muscle appears hypertrophied and disarrayed.

Traditionally, histological diagnosis is made when the endometrial glands and stroma have at least one low-power field (>4 mm) below the endometrial junction (Vercellini et al., 1993). Nevertheless, even two low-power (>8 mm) field distances have been proposed (Sandberg and Cohn, 1962). According to Zaloudek et al., adenomyosis should be diagnosed when the distance between the inferior endometrial border and the affected myometrial region exceeds one-half of the low-power field (>2.5 mm) (Norris and Zaloudek, 1987).

Other investigators have used the proportion of lesions involving the myometrium as a diagnostic criterion. In Hendrickson's view, adenomyosis should only be diagnosed when more than one-third of the total thickness of the uterine wall is involved (Hendrickson, 1987). Ferenczy considered that the distance between the endomyometrial junction and the nearest adenomyosis should be >25% of the total thickness of the myometrium (Ferenczy, 1998).

In addition, pathologists have proposed diagnostic criteria based on other histopathological features. Uduwela et al. (2000) considered disruption of the normal border between the endometrium and the myometrium as a diagnostic criterion for adenomyosis. In contrast, Bazot et al. (2001) concluded that the ectopic endometrium in adenomyosis is basal-type nonsecretory tissue with a direct connection to the eutopic basalis.

In general, normal endometrial tissue extends into the superficial myometrium and may be mistakenly diagnosed as superficial adenomyosis, which complicates clinicopathological studies of adenomyosis. Therefore, biomarkers that help differentiate true adenomyosis from an irregularly bordered endometrium are particularly important. Ohara et al. (2014) used the immunohistochemistry score to estimate that the expression of moesin is higher in adenomyosis than in normal endometrium. In particular, moesin is significantly overexpressed in adenomyotic stromal cells compared to normal endometrial stromal cells. Recently, Qu et al. (2020) provided new evidence to support the upregulation of the stimulator of interferon gene (STING), the upstream regulator of NF-κB, in epithelial cells of adenomyosis compared to the eutopic endometrium. These results suggest that moesin and STING help differentiate adenomyosis from normal endometrium. Furthermore, for some endometrial adenocarcinomas secondary to adenomyosis, this condition is indistinguishable from true endometrial adenocarcinoma invading the myometrium, particularly if there is extensive involvement of adenomyosis by adenocarcinoma. Nascimento et al. (Nascimento et al., 2003) demonstrated that CD10 may be a useful biomarker in the distinction of adenomyosis associated with endometrial adenocarcinoma from myoinvasive endometrial adenocarcinoma.

Histopathological classification of adenomyosis

Over the years, pathologists have made a number of recommendations for classifying adenomyosis (Table 2). Early histological classification criteria focused on portraying the extent of endometrial infiltration within the myometrium to determine the severity of the disease. According to the depth of myometrial penetration of adenomyotic foci, Bird et al. (1972) graded lesions invading the subendometrial basalis, mid-myometrium, and outer myometrium as mild, moderate, and severe, respectively. Levgur et al. (2000) classified adenomyosis as superficial (<40%), intermediate (40%-80%), and deep (>80%) according to the penetration ratio of the lesion. Siegler and Camilien (1994) graded the severity according to adenomyotic involvement of the inner third (superficial adenomyosis), two-thirds, and entire myometrium (deep adenomyosis). In addition, other researchers have used different criteria to classify adenomyosis. According to the difference in origin, Sampson (1921) classified adenomyosis into three types, namely, invasion from within, invasion from without,

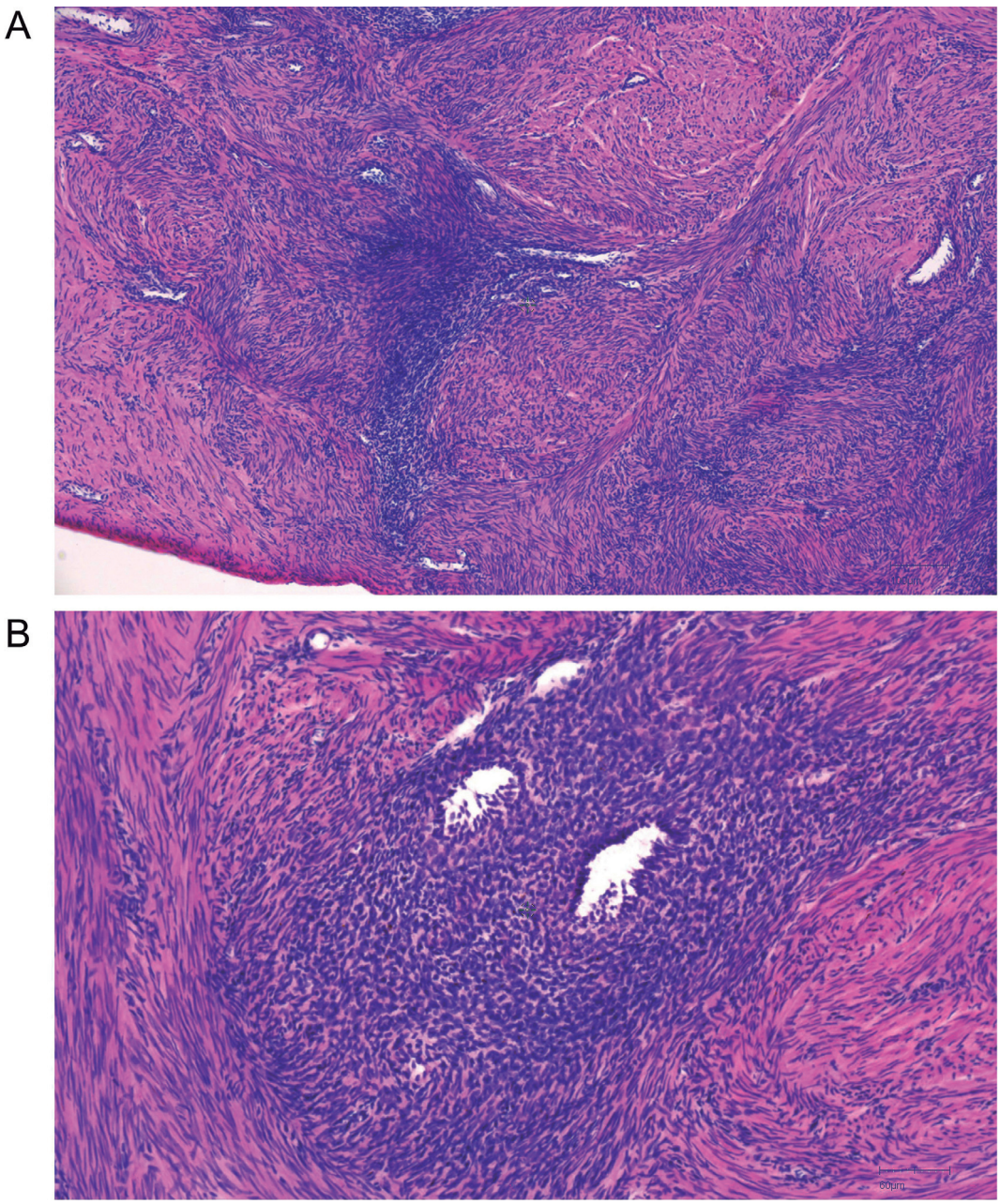

Fig. 2. Microscopic features of adenomyosis. **A.** Microscopic features showing presence of glandular epithelium and stroma surrounded by hypertrophic smooth muscle cells (H&E stain). **B.** Higher magnification view showing the details of the epithelial and stromal components of adenomyosis (H&E stain). A, x 20; B, x 40.

and intramyometrial. Nishida, (1991) divided adenomyosis into two categories, namely, continuous from the endometrium and continuous from serosa, according to the difference in the continuous parts of adenomyosis. Unfortunately, there are currently no widely accepted criteria for the pathological classification of adenomyosis, which may be due to a lack of reproducible results from studies that link pathological features to clinical presentation.

In recent years, researchers have employed multiple parameters to evaluate the severity of adenomyosis for a more accurate definition. Vercellini et al. (2006) recommended assessing the depth of myometrial penetration of glands and stroma by strict diagnostic criteria as well as describing the extent of intramuscular lesion expansion with a grading system. The potentially important parameters are as follows: the affected area (inner or outer myometrium); the localization (anterior, posterior, or fundus); the pattern and size (diffuse or focal specified as muscular or cystic); and the degree of spread of the condition in terms of the number of foci per low-power field (1-3 islets, grade 1 disease; 4-10 islets, grade 2 disease; >10 islets, grade 3 disease).

Several histopathology systems have assessed the relevance of pathological findings to the symptoms of patients with adenomyosis by various techniques. In some studies, the two most common symptoms of pain and abnormal uterine bleeding (AUB) were assessed. Levgur et al. (2000) evaluated clinical data from 111 adenomyosis patients and their uteri specimens; they found that menorrhagia and dysmenorrhea were present in 36.8% and 77.8% of patients with deep foci, respectively, whereas menorrhagia and dysmenorrhea were present in 13.3% (P<0.001) and 12.5% (P<0.001) of patients with intermediate depths, respectively. In contrast, Bird et al. (1972) reported no relationship between the depth of involvement and bleeding symptoms; however, they reported that the number of 'islets' of adenomyotic glandular tissue per low-power field is proportional to the amount of uterine bleeding. Similarly, Sammour et al. (2002) found that there was no identified relationship between the depth of involvement and the symptoms of AUB, but they reported there is a strong correlation with the reported bleeding volume according to the number of adenomyotic foci per slide.

The relationship between pain (dysmenorrhea, chronic pelvic pain, or dyspareunia) and histopathologically defined adenomyosis has been evaluated. Dysmenorrhea has been reported to correlate with the number and depth of involvement of glandular tissue lesions within the myometrium (Bird et al., 1972; Nishida, 1991; Levgur et al., 2000). Sammour et al. (Sammour et al., 2002) evaluated the relationship of dyspareunia and 'other pain' to the number and depth of adenomyotic lesions; they found a positive correlation between pain and the number of adenomyotic lesions but no correlation with the depth of lesion involvement.

Coexisting and unusual pathology of adenomyosis

According to statistics, adenomyosis often coexists with other gynecological diseases, such as endometriosis (Di Donato et al., 2014), leiomyomas (Brucker et al., 2014), and endometrial polyps (Munro, 2019). In a retrospective analysis of 296 patients diagnosed with adenomyosis, Pervez and Javed (2013) found that the most frequent combination of diagnoses was leiomyoma and adenomyosis; they also reported that the

Table 2. The main features used in the proposed histopathological classification systems for adenomyosis.

	Classification systems	Basis of classification
Group 1	Invasion from within	The origination
Group 2	Invasion from without	
Group 3	Intramyometrial	
Mild	Subendometrial basalis	Depth of invasion
Moderate	Mid-myometrium	
Severe	Outer myometrium	
Type 1	Continuous from endometrium	Localization of adenomyosis
Type 2	Continuous from serosa	
Group 1	Inner 1/3	Depth of penetration
Group 2	2/3	
Group 3	Entire myometrium	
Superficial	<40%	Depth of invasion
Intermediate	40-80%	
Deep	>80%	
Mild	Inner 1/3 (or microscopic foci)	Degree of involvement
Focal	Adenomyoma	
Severe/Diffuse	Outer 2/3 (include entire myometrium)	
Mild	Up to 1/3; 1-3 islets	Configuration: Diffuse, discrete
Moderate	1/3 to 2/3; 4-10 islets	
Severe	> 2/3; >10 islets	

pathological conditions associated with adenomyosis included leiomyomas in 150 patients (50.6%), endometrial polyps in 16 patients (5.4%), genital prolapse in 12 patients (4.05%), chronic endometritis in 10 patients (3.3%), endometrial hyperplasia in 5 patients (1.6%), and endocervical polyps in 2 patients (0.6%).

Less common forms of adenomyosis, such as cystic adenomyoma and polypoid adenomyoma, have also been described. Submucous adenomyomas with cyst formation were first described by Cullen in 1908 in five hysterectomy specimens from women (Cullen and Thomas, 1908), and it was reported that cystic adenomyosis was more common in younger women (Brosens et al., 2015) and that the cysts measured approximately 10 mm. Cullen reported that the cavities were lined by normal endometrial mucosa and were filled with brown-colored contents. Cullen demonstrated that in advanced cases, submucous adenomyoma with cyst formation can be part of a more complex structure with subperitoneal and submucous extension (Cullen and Thomas, 1908). Polypoid adenomyoma is a rare lesion associated with adenomyoma, usually originating in the lower uterine segment and forming a single polypoid lesion or multiple polyps (Lee et al., 2004; Sajjad et al., 2019). The epithelial component of polypoid adenomyoma infrequently shows endocervical mucous columnar cells instead of endometrial glandular cells (Gilks et al., 1996). Histologically, the polypoid lesion is lined by compressed endocervical mucosa, and it is composed of smooth muscle bundles and scattered benign-looking endocervical glands. Some glands are dilated, and endocervical mucous cells contain a varied volume of mucin in the cytoplasm (Takeda et al., 2014).

Endometrioid carcinoma is the most common malignant histological type of adenomyosis, but it is still a rare entity. Koshiyama et al. (2002) reported only four cases in 564 patients (0.74%) operated on between 1981 and 2001. Most cases with adenocarcinoma arising in adenomyosis are associated with adjacent endometrial adenocarcinomas (Hernandez and Woodruff, 1980). Izumi et al. (2020) reported a patient with endometrial cancer arising from adenomyosis (EC-AIA). This patient's surgical specimen showed a thickening of the posterior wall of the uterus, and diffuse endometrioid adenocarcinoma and adenomyotic glands were identified in the myometrium of the uterine corpus. Moreover, transitions from adenomyotic glandular epithelium to adenocarcinoma were observed in this patient (Izumi et al., 2020). A histopathological study of another reported patient with EC-AIA showed grade 1 endometrioid adenocarcinoma. In this patient, the lesion was located only in the muscle layer of the body, and the endometrium was intact; in addition, cancer nests adjacent to the adenomyotic foci were also observed in this patient (Taga et al., 2014). Based on the previously proposed criteria, the pathological criteria for diagnosis of EC-AIA were proposed: 1) evidence of preexisting adenomyosis at the site of the malignant lesion; 2) presence of glandular cells and/or endometrial stromal cells; 3) evidence for transition between benign and malignant glandular structures; 4) carcinoma must have no invasion or metastasis from other sources; and 5) the eutopic endometrium must be free of carcinoma (Taga et al., 2014).

Previously reported EC-AIA has been reported to originate from noncystic adenomyosis, and malignant neoplasms originating from cystic adenomyosis are rarely reported. Mori et al. (2015) reported a rare case of endometrioid adenocarcinoma arising from cystic adenomyosis. On the cut surface, the entire tumor was located within the myometrium and was markedly distant from the endometrial cavity. Histological examination revealed moderately differentiated endometrioid adenocarcinoma, and endometrial glands and stroma were present within the myometrium. These intramural endometrial lesions were distributed between the tumor and the serosal surface of the uterus. The ciliated cell variant of endometrioid adenocarcinoma (CCVEA) is an extremely rare tumor, and in almost all these cases, the carcinoma arises in the endometrium. However, Rashid and Akhtar (2021) encountered a case of CCVEA with a possible origin in an adenomyoma. This patient underwent a hysterectomy and bilateral salpingo-oophorectomy, which grossly showed that the endometrial cavity expanded by thick friable material interspersed with areas of necrosis. Histologically, the endometrium was necrotic with complex atypical hyperplasia and a focal ciliated variant of endometroid carcinoma.

Pathological changes in adenomyosis after medical treatment

Medications for adenomyosis include suppressive hormonal treatments, such as continuous use of oral contraceptive pills, high-dose progestins, selective ER modulators, selective PR modulators, the levonorgestrel-releasing intrauterine device (LNG-IUS), aromatase inhibitors, danazol, and gonadotrophin-releasing hormone agonists (GnRHa) (Pontis et al., 2016). Several studies have focused on the pathological changes of adenomyosis after medical treatment.

Khan et al. (2010a,b) investigated the *in vivo* pattern of changes in cell proliferation in the endometria and pathological lesions derived from GnRHa-treated and untreated patients with adenomyosis, and they reported that exogenous treatment with a variable concentration of GnRHa significantly suppresses the proliferation of cells derived from the endometria and pathological lesions of women not only with endometriosis but also with adenomyosis and uterine myoma. These direct anti-proliferative effects of GnRHa *in vitro* correspond to *in vivo* results with Ki-67, a cell proliferation marker, in intact tissues. The Ki-67 index is significantly lower in both endometrial and pathological lesions derived from GnRHa-treated women than in samples from GnRHa-nontreated women. Subsequently, Khan et al. (2010a,b) also reported that GnRHa reduces angiogenesis.

Although GnRHa therapy has no effect on microvessels in adenomyotic lesions, there is a substantial decrease in microvessel density in endometria and autologous myometria produced from adenomyosis patients. These data suggest that the reduction in adenomyosis size following GnRHa therapy may be due to a decrease in blood flow in the pathologic lesions or adjacent myometrial tissues.

The LNG-IUS facilitates the local delivery of progestin derivatives to the endometrium, and numerous studies have shown its effect on relieving adenomyosis-related dysmenorrhea and heavy menstrual bleeding (Cho et al., 2008). Cho et al. (2015) focused on the effect of LNG-IUS treatment on lymphangiogenesis and lymphovascular density (LVD) in patients with adenomyosis. By immunohistochemical analysis of the D2-40 and LYVE-1 lymphatic endothelial cell markers in endometrial and myometrial tissue, Cho et al. found that LVDs in the endometrium and myometrium are significantly higher in patients with adenomyosis than in controls, and they also reported that the LVDs are normalized in endometrial and myometrial tissues after treatment with the LNG-IUS.

Conclusion

Adenomyosis is a heterogeneous group of diseases, including different subtypes, with different pathological manifestations. The profile and the symptomatology of patients with adenomyosis are linked to the adenomyosis phenotype, particularly with the diffuse nature of lesions in the internal myometrium or focal lesions within the external myometrium. Adenomyosis can be diagnosed by anatomopathological examination of the uterine myometrium, and it has been diagnosed by imaging (transvaginal pelvic ultrasound and/or MRI) in recent years. However, the criteria for diagnosing adenomyosis widely vary, resulting in possible overdiagnosis. Thus, there is an urgent need for stringent and widely accepted diagnostic criteria to define the presence of adenomyosis, the depth of penetration, and the degree of foci spread. More importantly, exploring biomarkers that accurately distinguish adenomyosis from normal endometrium is of great interest. Therefore, future pathological studies are required to consider patients' symptoms and imaging findings to identify adenomyosis at an early stage as well as to develop a unified, shared diagnostic criteria profile and classification to provide more accurate diagnostic criteria and individualized treatment options for adenomyosis.

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