

# Atypical Endometriosis: a Clinicopathologic Study of 163 Cases

Donghui Guo  
Shujie Pang  
Yan Shen

Department of Pathology, Tianjin Central  
Obstetrics & Gynecology Hospital, Tianjin  
300052, China.

Correspondence to: Donghui Guo  
Tel: 86-22-23043189  
E-mail: Dhuiguo@sina.com

**OBJECTIVE** To investigate the clinicopathologic features of atypical endometriosis (AEM), and to discuss the relations between AEMs and tumors.

**METHODS** A retrospective analysis was performed on 163 cases of AEMs. The changes in the glandular epithelium, stroma, and their background and the relationship with coexisting tumors were observed.

**RESULTS** The AEMs account of for 4.4% (163/3,724) of the endometriosis (EM) cases. Of 172 AEM foci of 163 patients, 168 were in the ovary, and the other 4 were in the fallopian tube, cervix and uterine serosa. Of the cases of ovarian EM, 6.8% were AEM. All of the 27 cases (15.7%) of the AEMs associated with a tumor were found in the ovaries, of which 15 were malignant, 9 borderline, and 3 benign. Of the ovary AEMs, 14.9% were associated with a borderline or malignant tumor. The AEM epithelia were mainly arranged in the form of surface epithelia, with only a few glands. Present were characteristic features of moderate to marked pleomorphism, epithelial tufting, bud or firework-like structures on microscopy. Epithelial metaplastic changes were observed in 86 cases (50%) of the 172 AEM foci. Epithelium, endometrioid stroma, and fibrotic-collagen formed a three-layer structure in the wall of the AEM cysts. The endometrioid stroma were usually thin compared to the fibro-collagen tissue. The transformation from an AEM to a tumor was found in most of the malignant tumors.

**CONCLUSION** AEM lesions have some features which are similar and also differ from both of the tumor and EM. AEMs have a relative higher potential for tumorigenesis and canceration, especially for ovarian cancer. The process of damage, repair, and scarring in EM foci over a long period may play a role in the development of EM into AEM and eventually into tumor formation.

**KEYWORDS:** atypical endometriosis, ovarian tumor, clinicopathology.

## INTRODUCTION

Endometriosis (EM) was found in up to 29% of women undergoing laparotomies<sup>[1]</sup>. The risk of malignant transformation in ovarian EM may be from 0.7% to 2.5%<sup>[2-4]</sup>, but this might be an underestimate. In recent years, two important terms have been used in regard to EM and related lesions. One term which has been accepted is EM-associated ovarian cancer. The other is atypical endometriosis (AEM), coined by LaGrenade and Silverberg in 1988<sup>[3]</sup>. This may be an intermediate-step between EMs and EM-associated ovarian cancer, and may confer an increased risk for subsequent tumor development. At present, the studies on AEMs have been few; and further intensive studies on the clinicopathologic and molecular-genetic changes have been insufficient. Here, we report 163 cases of AEM and focus on its incidence, pathological features, and some diagnostic problems. The aim of this study was to characterize the clinicopathological features of AEMs, and

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attempt to clarify the relationship between AEMs and tumors.

**MATERIAL AND METHODS**

A series of consecutive cases coded as EMs, AEMs and EMs or AEMs with a tumor during the period 2004 to 2006 was retrieved from the Departments of Pathology at Tianjin Central Obstetrics and Gynecology Hospital. In this study, we reviewed the slides and then re-evaluated the samples obtained from 3,724 patients with a total of 6,820 EM foci, and related lesions including cases of EM or AEM associated with a tumor previously diagnosed histopathologically. The AEM were verified in 163 cases, including 26 cases associated with a tumor. The diagnosis of AEM was based on the following features proposed by LaGrenade and Silverberg<sup>[3]</sup>, Czernobilsky and Morris<sup>[5]</sup>. These features included: EM lesion (s) on both endometrioid epithelium and stroma; large hyperchromatic, or pale nuclei with moderate to marked pleomorphism; increased nuclear-to-cytoplasmic ratio, cellular crowding, stratification, or tufting; and without stromal invasion. The gross and microscopic features were observed for all cases, including the epithelium, stroma and the AEM background and the coexistence with a tumor.

**Statistical analysis**

Statistical analyses were performed using the SPSS for Windows version 11.5 software package. A *P*<0.05 was considered to show a significant difference.

**RESULTS**

**Clinical features of AEM**

Of the EM cases, 163 were AEM, or 4.4% (163/3,724). The frequency of AEMs in the ovaries was 6.8% (161/2,363); 7 were bilateral, 154 were unilateral, being on either side and in 2 cases the side was not apparent. The frequency of AEMs in other areas were as follows: fallopian tube and mesosalpinx 1.3% (1/78case), cervix 1.3% (1/79case) and uterine serosa 0.2% (2/828 case). The total number of AEMs were 172 foci in 163 patients. One patient had three sites of AEM, which were in the left ovary, mesosalpinx, and uterine serosa respectively. None of another 2,619 EM foci had AEM lesions, including a total of 158 EM foci from the pelvic peritoneum, sacrouterine ligament, and other periuterine ligaments; 848 foci from the intestines, ureters and bladder;113 foci from the vagina, abdominal wall, hilum and perineum. A total of 74 patients had one ovarian AEM with EM le-

sions in the contralateral ovary.

The patients ranged in age from 18 to 68 years (average 39.1, median 40). There were 81 patients (49.7%) who were 39 years old, or younger, and only 10 (6.1%) who were 51, or older. A total of 95 cases (58.3%) were found with a pelvic cavity mass, 29 cases (17.8%) had dysmenorrhea, and 24 cases (14.7%) had abdominal pain or distension. In 19 other cases incidental dysuria, menometrorrhagia, sterility, uterine myomas, and uterine prolapse was found.

AEMs associated with a tumor in the same ovary were found in 27 ovaries (15.7%) of 26 patients (16.0%). Of all of the epithelial types of ovarian tumors, there were 15 cases that were malignant, 9 cases that were borderline, and 3 cases of cystoadenoma (Table 1). One case of bilateral ovarian AEM was found in combination with a borderline and individual benign seromucous cystoadenoma. One case of left ovarian AEM coexisted with endometrioid adenocarcinoma in both ovaries. One case exhibited AEM with seromucinous borderline cystoadenoma in the right ovary and EM with a mucinous cystoadenoma in the left ovary. There were 4 cases of ovarian AEM found with tumors in the contralateral ovary, which were mucinous borderline cystoadenoma, mucinous cystoadenoma, serous cystoadenoma and fibroma respectively.

**Table 1. The conditions of AEMs with tumors in the same ovary.**

Tumor types	Left No.	Right No.
Endometrioid adenocarcinoma	2	5
Clear cell carcinoma	4	3
Cystadenofibroma transformation malignance		1
Seromucinous borderline cystoadenoma	2	3
Serous borderline cystoadenoma	3	
Mucinous borderline cystoadenoma		1
Benign cystoadenoma*	1	2
<b>Total</b>	<b>12</b>	<b>15</b>

\*Each of serous, mucinous and seromucous type had 1 case.

**Pathologic features of AEM**

The gross appearance of the AEMs were similar to those of EMs. A total of 141 of ovarian AEMs without a coexisting tumor were predominately cystic, either unilocular, or with a few irregular loculi (138, 98.0%), with solid areas noted in a few lesions. The ovarian sizes were from 1 to 18 cm with a median diameter of 5 cm (Table 2). Ridge protuberance within

the cyst wall was frequently present. The cysts were filled with a chocolate-brown fluid with cyst walls of various thickness that often displayed a thick, fibrous and slightly rigid consistency. In 61 cases there was no pronounced difference in the sizes of the ovarian AEMs without a tumor with EM in the contralateral ovary ( $\chi^2=2.846, P=0.241>0.05$ , Table 3). One AEM located in the deep position of the cervix wall, formed a haemorrhagic cyst of 5.5 cm. None of the AEM cysts showed gross papillary excrescences. The AEM foci of the uterus or fallopian tube had serosal incrustation, roughness, or surface adhesions and desquamated surfaces. In 27 ovarian AEM associated with a tumor, the carcinomas were often cystic, or cystic and solid (9/15, 6/15), and papillary protuberances were frequently found (10/15). The borderline and benign tumors were cystic. In addition to being filled with brown, haemorrhagic fluid, the tumors sometimes contained mucus, and gelatinous necrotic material (9/27).

**Tablet 2. Size of the ovarian AEM.**

Size of ovary (cm)	No. (%)
≤3	26 (18.4)
3.1~5	48 (34.1)
≥5.1	64 (45.4)
Unclear	3 (2.1)
Total	141 (100)

**Table 3. Comparison of the size of ovarian AEM with EM.**

Size (cm)	AEM No. (%)	EM No. (%)
≤3	19 (31.1)	20 (32.8)
3.1~5	20 (32.8)	27 (44.3)
≥5.1	22 (36.1)	14 (22.9)
Total	61 (100)	61 (100)

The epithelium of 172 AEM foci were mainly arranged in the form of surface epithelium lining the cysts. Only a few glands were found under the surface epithelium in some foci. In 109 foci (63.4%), only the surface epithelium was found, 45 foci (26.2%) exhibited surface epithelium mixed with glands, and 18 foci (10.5%) had only glands. The margins of the glands sometimes were irregular, or without integrity because of splitting, or cleaving after being pressed by the stroma. The epithelial cells showed moderate to marked pleomorphism, and the nuclei were larger and hyperchromatic with an increased nuclear to cytoplasmic ratio, focally with prominent stratification. Epithelial tufting was present in most of sites, typically having a bud, or firework-like appearance, a

few papilliform structures were identified in 76 cases (44.2%). On microscopy (Fig.1) the papillae were moderate in size in 60 cases (78.9%), large size in 7 cases and with fibroedematous stalks. Filiform papillae were found in 4 cases without complex branching. The epithelial changes in AEM are usually present in local or partial areas, still with typical EM changes. Epithelial metaplastic changes were observed in 86 (50%) of 172 AEM foci, 6 cases were bilateral. Ten foci had 2 types of metaplasia and 1 case had 3 types of metaplasia (Table 4, Fig.2).

**Table 4. Metaplasias in AEM.**

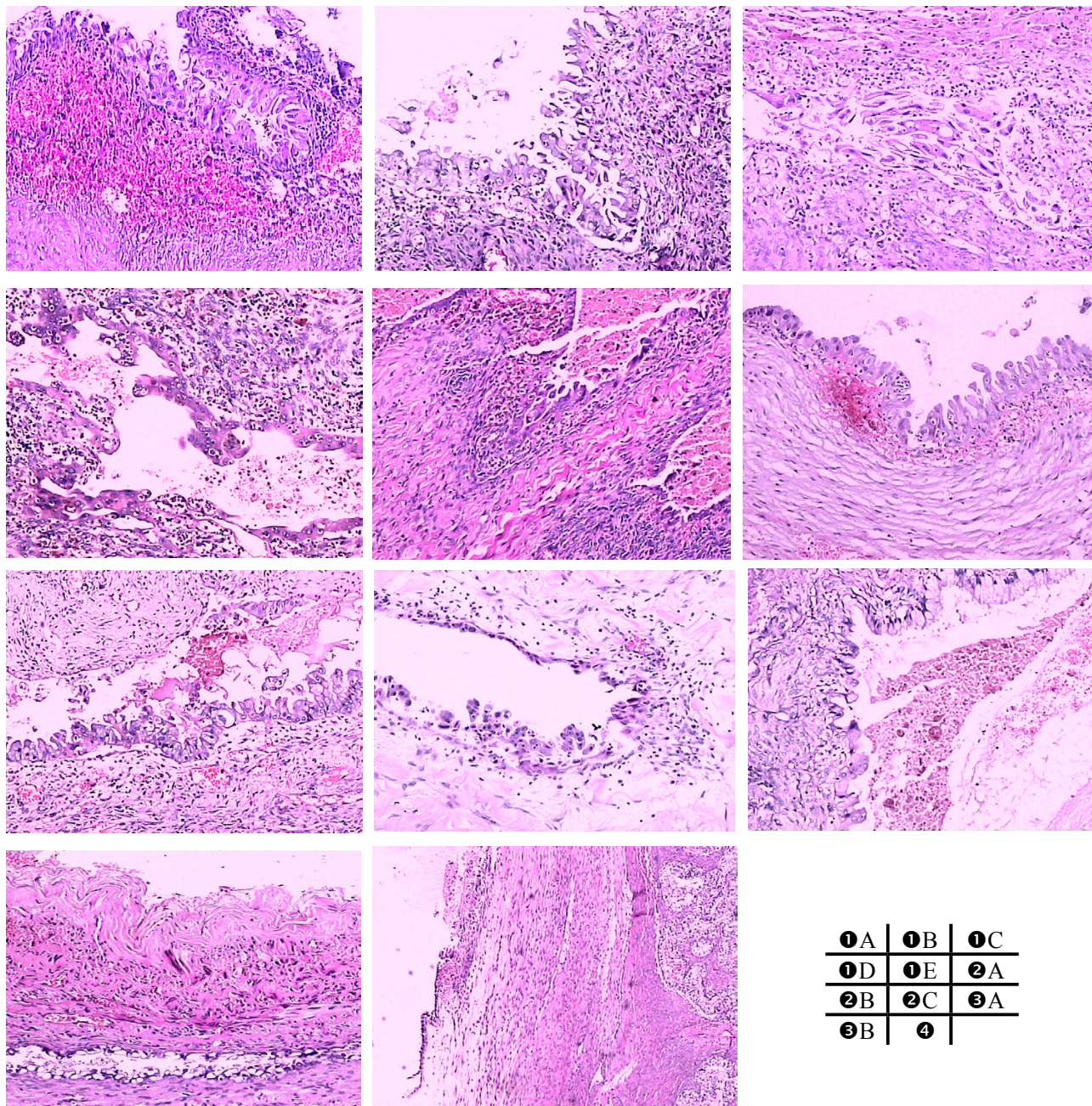
Type	No.	%
Eosinophilic	52	50.0
Ciliated cell	32	30.7
Mucinous	16	15.4
Clear	3	2.9
Squamous	1	1.0
Total	104	100

The center of the AEM cysts were filled with old haemorrhage. The cyst walls consisted of the epithelium and stroma, which were divided into endometrioid stroma and proliferative fibrotic-collagen tissue under or around the epithelium. This becomes a three-layer configuration consisting of epithelium, endometrioid stroma and fibrotic-collagen (Fig.3). The endometrioid stroma within the AEM foci were usually thin, 92.4% of them less or equal to 0.5 mm. Instead, the fibro-collagen tissue was often thick and 72.7% were more than, or equal to 0.5 mm ( $\chi^2=151.792, P=0.000$ , Table 5). Many hemosiderin components were often mixed with fibro-collagen tissues. Patches of scar-like tissue were easily found. The inflammatory backdrop was not prominent in the AEM. Though nearly all cases had some leucocytes, moderate, or abundant leucocyte infiltration was found in only 12 cases and 2 cases respectively.

**Table 5. The thickness of AEM.**

Thickness (mm)	Endometrioid stroma No. (%)	Fibro-collagen No. (%)
≤0.09	62 (36.0)	5 (2.9)
~≤0.5	97 (56.4)	42 (24.4)
~≤0.9	13 (7.6)	31 (18.0)
~≤1.9	0	52 (30.2)
~≤2.9	0	30 (17.5)
≥3	0	12 (7.0)

Twenty-seven cases of AEM were associated with a tumor. The foci of the AEM were usually in the



**Fig.1.** Epithelium cells of AEM. A, prominent pleomorphism and stratification; B&C, epithelial tufting, as buds or firework-like; D, irregular gland; E, papilliform structures.  
**Fig.2.** Epithelium and stroma. A, forming epithelium, endometrioid stroma and fibrocollagen three layer configuration; B, AEMs overlay thin endometrioid stroma and thick fibrocollagen tissue; C, scar-like tissue is under AEMs.  
**Fig.3.** Metaplastic changes. A, mucinous metaplasia; B, clear cell metaplasia, an AEM focus of uterine serosa.  
**Fig.4.** AEM associated with a tumor, the clear cell carcinoma is on the right.

side of the tumor or in the margin of a cyst. In some cases, the AEM were mixed with a tumor component. In other cases, AEM and the tumor component were adjacent to each other, or on both sides of the cyst wall (Fig.4). The transformation from AEM to the neoplasm was found in most of the malignant neoplasms (14/15), and in some of the borderline tumors (4/9), and benign tumors (1/3) ( $P=0.008<0.05$ ). The

epithelial metaplastic changes were found in 16 of 27 cases of AEM having a tumor. Of the 16 cases showing epithelial metaplastic changes, 5 had a carcinoma, 9 had a borderline tumor and 2 a benign tumor. Most types of metaplasia were ciliated and mucinous. In half of the AEMs with a tumor, EM foci were found on the contralateral ovary (14/27, 51.8%), a percentage slightly more than in the cases of AEM without

a neoplasm (49/136, 36.0%). However the difference was not pronounced ( $\chi^2=2.378$ ,  $P=0.123>0.05$ ).

## DISCUSSION

The incidence of AEM is not well known. The percentage of ovarian AEM of EM reported in the literature has varied between 1.2% to 12.2% or even more<sup>[1,3,6]</sup>. Most of the AEMs reported previously were based on a relatively small sample size (less than 300 cases). In this series, the AEM cases were from EM lesions at 6,820 sites of 3,724 patients. This may be the largest group both in the number of AEMs and the EM foci up to now. In this study, using strict criteria to re-evaluate the samples of all of the 6,820 EM lesions, the statistical data showed that the rate of AEM was 6.8% (161/2,363 cases) in the ovarian EM, including 7 cases in bilateral ovaries. There have been only a few reports of extraovarian AEMs in the literature<sup>[7]</sup>. We found 4 cases of extraovarian AEM occurring in the fallopian tube, cervix and uterine serosa respectively. This supplemented the data for the location of AEMs outside of the ovary. However, we did not find any AEM lesions in 2,506 EM foci, including the pelvic peritoneum, periuterine ligament, intestines, and the urinary tract, even though they are also the common EM sites. Our data indicate that AEMs occur mainly in the ovary, and occasionally in other locations. The distribution of AEMs was not uniformly found in various sites of the pelvic cavity, and the quantity of AEM was disproportionate to the number of EM foci.

AEMs derived from common EM lesions, kept the characteristic features of EM with endometrioid epithelium, stroma, and hemosiderin, or hemofuscin, and present with significant pleomorphism of epithelial cells, having identical features of tumor cells. The AEMs had some features of both EM and tumors, but also differed from them. The endometrioid tissue of the AEMs in most cases of this group became thin, usually showing atrophy, or a configuration without hormonal influence. The AEMs with "ectopic endometrial hyperplasia" were not evident in our series. The component of epithelium and stroma of AEMs was commonly disproportional. In this study, 63% of the AEM lesions had only endometrioid surface epithelial lining of the endometriotic cysts, with a few gland components found underneath it. The endometrioid stroma was not abundant and seemed less developed than in common EMs. In addition, AEMs have significant cellular atypia, with epithelial buds or pullulation in 78% of the lesions and a papillary structure in 44% of the lesions on microscopy. However, the severe inflammatory background was

unconspicuous in most AEMs, and was ill defined as an inflammatory reaction. Fibrotic-collagen might be present in both common EMs and AEMs. In this group, more than 90% of the AEM foci have fibrotic-collagen, which was often thick, and this thickness extended over the endometrioid stroma. Atypical epithelia cells may be situated on the surface and overlay fibrotic and scar-like tissue, or even be within it. This means that the EM lesions might have been present for a long time. The phenomena of hormonal inactivity, significant cellular atypia, and scarring present in AEMs seemed different from physiological changes of the eutopic endometrium. The EM lesions that have experienced damage, repair and scarring changes over a long period of time, may have been exposed to some harmful, or carcinogenic factor released during this process. This might cause the development of EMs into AEMs and the final onset of tumorigenesis. The hormonal action may not be the major factor in the developmental of EMs to AEMs and of EMs, or AEMs into tumors.

The frequency of AEMs associated with tumors is not clear. Most of AEMs associated with a tumor occurred in the ovary, rarely in the pelvic, or gastrointestinal tract and or other places<sup>[7-9]</sup>. In our study, 15.7% of ovarian AEMs coexisted with a tumor, and if benign tumors are excluded, it was 14.9% of ovarian AEMs having a borderline and malignant tumor. These data indicated that the ovarian AEMs have a relative higher potential for tumorigenesis and cancer formation. It has been reported in the literature that 0.7 to 2.5% of EMs have a risk of developing into malignant tumors. We support the theory that AEMs may be a precancerous lesion<sup>[9-12]</sup>. The tumors of the ovary accompanying AEMs, were mainly epithelial types. They may be benign, borderline or malignant, with the ratio increasing from benign to malignancy i.e. 11%, 33% and 55%.

Endometrioid and clear cell histology account for 93% of malignant tumors. The borderline and benign tumors in our series were serous, mucinous, and seromucous types originating from the mullerian. The phenomena of AEMs and EMs occurring with tumors not confined in malignant types were described in the literature and confirmed in our cases<sup>[4,11]</sup>. The category of EMs associated cancer might extend to the EM-associated tumors, and the investigation of this hypothesis should be conducted with extensive testing. The relationship between AEMs and tumors may be direct, or indirect<sup>[13-15]</sup>.

In our study, most cases of AEMs associated with a tumor showed a direct transition from the AEMs epithelium to a tumor, especially for malignant tumors, but also were found nearby, or on both sides

of the cyst wall. The epithelium of the tumor might have a consistent or different type compared to AEM. Epithelial metaplastic changes were found in 63% of ovarian EM reported by Fukunaga and Ushigome<sup>[16]</sup>. In our series, we observed metaplastic changes in half of the AEMs, and eosinophilic and ciliated cell metaplasia was the most common type, identified by Fukunaga et al. and other authors. But both of these changes perhaps were not the true metaplasia<sup>[17]</sup>, as ciliated cells normally are found along the surface epithelium of the endometrium. We observed that AEMs were also often formed in the surface-type epithelium. Eosinophilic cell changes may be present in several types of cytoplasmic transformations. It is also a frequent feature of atypical cells. How to interpret these changes and whether or not the metaplastic changes of AEMs played an important role in the tumor genesis is not known.

In our group, most AEM patients were at a reproductive age, with a median age of 40 years. The symptoms and gross appearance of AEMs resembled common EMs. Varying degrees of cellular atypia are common in EM lesions. It is important for the pathologist to recognize, or identify the characteristic features of AEMs, especially the significant cellular atypia, with cellular buds and papillary structure, which are different from an inflammatory reaction. Abundant inflammatory cells, slight atypia, and regular epithelium indicate a reaction change. Residual EM lesions must be recognized in EM-related ovarian cancer, which display a three-layer structure including endometrioid epithelium and stroma, as well as fibrotic-collagen often mixed with hemosiderin. The characteristic features of the three-layer structure both in EMs and AEMs was not found in the non-EM-derived epithelial tumor.

Since AEM lesions may be limited to local areas, they can be found in the white colored "aging" part or scar-like tissue in EM cysts, and should not be overlooked in sampling. In the examinations of these tumors, special attention should be paid to whether or not there is a trace of scar tissue in EMs and AEMs, and should be included in the diagnosis and identification of the AEM into routine practice.

In summary, we observed 163 cases of AEM lesions, which have some features of both EM and tumors, but differed from them. AEMs have a relatively high risk of becoming malignant. Except for malignant tumors, borderline and benign tumors can also coexist with AEM. AEMs may play an important role in the case of EM-associated tumors.

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