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Atypical polypoid adenomyoma of the uterus: A reappraisal of the clinicopathological and immunohistochemical features

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ABSTRACT

Atypical polypoid adenomyoma (APAM) is an uncommon uterine mixed epithelial and mesenchymal tumor. The discrimination from endometrial carcinoma remains to be clarified. In this study, we compared the clinicopathological and immunohistochemical features between 36 APAMs and 48 endometrial carcinomas. APAM with a highly complex structure (n = 13) coexisted with atypical hyperplasia (n = 5) and endometrial carcinoma (n = 1). Two patients had endometrial carcinomas at 1 and 102 months. Four patients recurred at 1–57 months but none died of disease. The fibromuscular stroma demonstrated 3 uncharacterized features: a broad bundle (10/36), a lobular structure separated by the stromal branches (26/36), and the extension of fibromuscular stroma underneath the surface epithelium (31/36). However, these features were not seen in endometrial carcinomas except the vaguely lobular pattern. Both APAM and endometrial carcinoma showed a similar immunostaining pattern except high Ki67 index in endometrial carcinomas ($p < 0.05$). Our study suggests that the distinct features of the fibromuscular stroma can aid in the differential diagnosis between APAM and endometrial carcinoma.

1. Background

Atypical polypoid adenomyoma (APAM), an uncommon uterine tumor in young women, was first described by Mazur et al. in 1981 [1]. The polypoid tumor is composed of endometrial glands with squamous metaplasia, structural complexity, and variable cytological atypia in the setting of myofibroblastic stroma. The International Classification of Diseases for Oncology (ICD-O) 8932/0, in which "0" infers a benign behavior, has been designated for APAM in the recent WHO classification [2]. In fact, its clinical results remain conflicting to date. Longacre et al. [3] introduced the term "APAM of low malignant potential (APAM-LMP)" for some cases with sufficiently complex structure that met the criteria for a well-differentiated endometrial carcinoma. Persistent or recurrent APAMs after conservative management have not been infrequently encountered. Complex atypical hyperplasia and endometrial carcinoma can occur synchronously or metachronously within APAM and/or the surrounding endometrium. APAM may be best regarded as "analogous to a localized form of atypical endometrial hyperplasia" [4].

The distinction of APAM with complex architecture from endometrial carcinoma with myometrial invasion is of great clinical significance, but is problematic at times even for an expert gynecological pathologist. APAM is commonly associated with the presence of a vague lobular architecture, short interlacing fascicles of the myofibroblastic stroma, and an absence of marked cytological atypia [2–5]. However, even these features do not always confidently discriminate APAM from endometrial carcinomas; as such, the differential diagnosis remains a critical issue. Moreover, the immunohistochemical pattern has only been investigated in a limited number of APAMs [6–9]. No studies have been focused on the differential expression pattern between the glandular and squamous morular elements, which will essentially facilitate our understanding towards the pathogenesis of APAM. Our comprehensive study was undertaken to define the delicate morphological and imunohistochemical features that can aid in the histological diagnosis and pathogenesis of APAM.

2. Materials and methods

This study was conducted with the approval of the hospital's Institutional Review Board (IRB: 20170135). Thirty-six APAMs were

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found from the institutional database, Women's Hospital, School of Medicine, Zhejiang University, China, between 2003 and June 2017. Forty-eight well-differentiated endometrioid carcinomas were randomly selected for comparison. The archival hematoxylin-and-eosin (H &E) slides were independently reviewed by at least two of the authors (LB, SH & CQ) according to the criteria from recent WHO classifications [2]. We defined APAM with a highly complex structure as modified from the criteria for APA-LMP [3].

Immunohistochemistry was carried out using diluted antibodies as follows: CD10 (56C6; Leica Biosystems, Buffalo Grove, USA; dilution 1:100), caldesmon (h-CALD; Santa Cruz Biotechnology, Dallas, USA; 1:200), smooth muscle actin (SMA) (1A4, Abcam, Cambridge, UK; 1:200), estrogen receptor (ER) (SP1; Thermo Fisher Scientific, Waltham, USA; 1:300), progesterone receptor (PR) (SP2; Thermo Fisher Scientific, Waltham, USA; 1:500), Ki67 (MIB1; Thermo Fisher Scientific, Waltham, USA; 1:400), SOX9 (CH-90; Santa Cruz Biotechnology, Dallas, USA; 1:50), β-catenin (E247; Thermo Fisher Scientific, Waltham, USA; 1:100), cyclin D1 (SP4; Thermo Fisher Scientific, Waltham, USA; 1:50), p40 (Polyclonal; Santa Cruz Biotechnology, Dallas, USA; 1:100), and CDX2 (EP25; Abcam, Cambridge, UK; 1:100). A two-step En Vision immunostaining procedure (DAKO, Carpentaria, USA) was performed according to the manufacturer's protocols. The immunostaining of glandular component and squamous metaplasia was individually interpreted by the researchers (LB, YM & SH) with the assessment of both the percentage of positive cells (0, < 5%; 1+, 5%–24%; 2+, 25%–49%; 3+, 50%–74%; 4+, ≥75%) and staining intensity (0, no staining; 1, weak; 2, moderate; 3, strong). A composite immunoscore (range: 0–7) was calculated by adding the scores of positive cells and the staining intensity. The composite score < 4 was defined as weak positive and ≥4 as strongly positive. Ki67 index was calculated by counting in 10 high power fields (HPFs) from the hotspots.

The SPSS 13.0 (SPSS, Inc., Chicago, IL, USA) software package was applied for the statistical analyses. The Paired–Wilcoxon test, one-way ANOVA, or χ^2 test was used to detect the significance of difference in variables between the glandular and morular elements in APAM or between APAM and endometrial carcinomas. The statistical threshold was set at 0.05 (two-sided).

3. Results

3.1. Clinical features

The clinical features of these cases were given in Table 1. The age of the patients ranged from 20 to 59 (mean 33; median 30) years. The clinical manifestations included abnormal uterine bleeding (n = 20), uterine endometrial polyps on sonography (n = 69) and infertility (n = 3). Four patients were incidentally detected for other diseases (uterine leiomyoma 2, adenomyoma 1 and ovarian cyst 1). The location of APAMs included the uterine corpus (n = 23), the fundus (n = 4), and the lower uterine segment (n = 9). Six patients had multiple polyps. The largest dimension of the polyps ranged from 0.5 to 6.0 cm (mean 2.2 cm; median 2.0 cm).

Thirty-three APAM patients underwent polypectomy (31 under a hysteroscopy). Sixteen patients with polypectomy received large-dose progesterone therapy. The pregnancy outcomes of 10 patients with polypectomy under hysteroscopy and progesterone therapy were published previously [10]. Hysterectomy was initially performed in 3 patients with the concurrent endometrial carcinoma (n = 1, FIGO stage Ia), atypical hyperplasia (n = 1) or multiple uterine leiomyomas (n = 1), and subsequently (1–105 months) in 4 patients with endometrial carcinoma (n = 2, both at FIGO stage Ib), persistent endometrial hyperplasia without atypia (n = 1), and diffuse adenomyosis (n = 1) (Table 1). Four patients recurred at 3–57 months after their first treatment. The recurrent diseases included APAM (n = 1), endometrial atypical hyperplasia (n = 2), and hyperplasia without atypia (complex hyperplasia) (n = 1). No patients were died of disease at present.

The patients with well-differentiated endometrioid carcinoma ranged in age from 27 to 79 (mean 54.6, median, 53) years. Thirty-two patients were postmenopausal, and 16 were premenopausal. Most patients (46/48) were presented with abnormal uterine bleeding. Forty-seven patients had tumors in the corpus and 1 in the lower uterine segment. The patients underwent staging surgery including a total abdominal hysterectomy with bilateral salpingo-orphorectomy and dissection of pelvic lymph nodes. Ten, thirty-three and five patients had no, superficial and deep myoinvasion, respectively. There were 40 patients at FIGO stage Ia, 5 at Ib, and 3 at II.

3.2. Histopathology

APAM showed a characteristic morphology consisting of irregular or simply branched endometrial glands, frequently with a complex architecture, mild-to-moderate cytological atypia, and squamous metaplasia in the septa of the myofibroblastic stroma [Fig. 1A, B]. Thirteen APAMs with a highly complex architecture resembled atypical hyperplasia/endometrial intraepithelial neoplasm or well-differentiated endometrioid carcinoma [Fig. 1C]. APAM harbored rare mitotic figures (no more than 2/10HPFs) and no abnormal forms in the glands. Squamous metaplasia was extensive (> 10%) in 32 cases. It was intimately admixed with the branching complex glands, at times resulting in a *pseudo-* "*solid*" or "*cribriform*" pattern [Fig. 1D]. Squamous morule was seen in 34 cases, whereas typical squamous metaplasia (with keratin formation) was focally present in 4 tumors. Three APAMs with typical squamous metaplasia harbored a highly complex architecture and 2 were associated with endometrial carcinoma.

The fibromuscular stroma in APAM showed 3 distinct features [Fig. 1E–G]: a broad bundle (10/36 cases), the fibromuscular branches separating the glands into vague lobules (26/36 cases), and the presence of fibromuscular bundle underneath the surface epithelium (31/36 cases). The fibromuscular stroma showed no cytological atypia and rare mitotic figures (< 2/10 HPFs). Lymphocyte infiltration was rich in one APAM.

Twenty-nine APAMs had endometrial curetting or contained small admixed but separate fragments of endometrium (suggestive of the surrounding endometrium). The histology changes included normal endometrium (n = 19) and abnormal changes (n = 10: hyperplasia without atypia 4, atypical hyperplasia 5, and well-differentiated endometrial carcinoma 1). The abnormal surrounding endometrium harbored an overlapping morphology with APAM, but they lacked a significant myofibroblastic component. The highly complex APAMs were more frequently associated with abnormal histology in the surrounding endometrium than the common APAMs (8/12, 66.7% versus 2/16, 12.5%; $p < 0.05$). Moreover, atypical hyperplasia and endometrial carcinoma were all found in APAM with a highly complex architecture.

Compared with APAM, the endometrial carcinomas showed a more complex glandular structure, characteristically of a true confluent glandular pattern with the loss of intervening stroma. Three myoinvasive carcinomas showed a lobular pattern [Fig. 1H], but they had more pronounced cytological atypia. Moreover, the peri-lobular stroma was essentially smooth muscle instead of myofibroblasts [Fig. 1I]. The smooth muscle neither formed a broad bundle, nor directly extended underneath the surface epithelium. The morular squamous metaplasia was focal in 22 cases, and extensive in 5. Typical squamous metaplasia was seen in 13 endometrial carcinomas.

3.3. Immunohistochemical findings

Significantly staining differences were found between the glandular components and squamous morules ($p < 0.05$) [Table 2], but were not between APAM with and without a highly complex structure or between APAM with and without the surrounding abnormal endometrium ($p > 0.05$, data not shown). The representative staining patterns are

Table 1
Clinical features of 36 APAM.[a]

Case#	Age	G & P	Clinical Presentation, Time	Location	Size (cm)	Endometrial Pathology	Treatment	Follow-up
1	39	G0P0	Uterine leiomyoma, 2mo	Fundus	1.3*0.6	NE	PUH;PT	LFU
2	36	G0P0	Uterine polyp, 6mo	Fundus	5*2.3*2	EAH	PUH;PT	EAH, 50mo, with PT; ANED 112mo
3	27	G1P0	Infertility,2yr	Corpus	2.2*1.7*0.4	EAH	PUH;PT	Recurrence 57mo; Persistent EAH, 79mo; TAH, 105mo; ANED, 134mo.
4	30	G0P0	AUB, 6d	Fundus	4*3*3	EAH	PUH;PT	ANED, 96mo.
5	23	G0P0	AUB, 5yr	Corpus	3*2*2	EH	PUH;PT	ANED, 81mo.
6	24	G0P0	AUB, 2yr+	Corpus	2.1*1.8*1.2	EAH	PUH;PT	ANED, 48mo.
7	30	G0P0	AUB, 2mo	Corpus	2*1.5*1	NA	PUH;PT	Myomectomy, 6mo; ANED, 39 months.
8	26	G0P0	AUB, 6mo	LUS	1.5*1*1	NE	PUH;PT	ANED, 35mo.
9	20	G0P0	AUB, 2mo+	LUS	4*2*2	NE	PUH;PT	ANED, 37mo.
10	30	G0P0	Uterine polyp, 4 mo	Corpus	1.5*1.0*1.0	NE	PUH	LFU
11	43	G2P1	AUB, 2yr+	Corpus	1.4*1.1*0.6	EAH	TAH	ANED, 23mo.
12	29	G0P0	AUB, 2mo	LUS	3.3*2.9*2.3	EH	PUH;PT	TAHBS for EC, 1mo; ANED, 21mo.
13	37	G2P1	AUB, 13yr+	Corpus	1.5*1.2*1	EC	TAHBSO	ANED, 107mo.
14	35	G0P0	AUB, 20d	Corpus	1*1*0.8	NE	polypectomy	LFU
15	53	G1P1	AUB, 4mo	Corpus	3.1*2.2*2	NA	PUH	LFU
16	37	G0P0	AUB, 3mo	LUS	1.8*1.2*0.7	NA	polypectomy; PT	TAHBSO for EC, 102mo; ANED, 147 mo.
17	29	G0P0	Infertility, 3yr	Corpus	2*2*1	NE	PUH	LFU
18	59	G2P2	Uterine polyp, 6mo	Corpus	1*0.6*0.6	NE	PUH	LFU
19	40	G1P0	AUB, 12mo	Corpus	1.4*1*0.8	NE	PUH;PT	ANED, 85mo.
20	32	G0P0	AUB, 3mo	LUS	2.4*2.2*2.2	NA	PUH	Recurrent APAM, 1mo; ANED, 60mo.
21	35	G1P0	Uterine polyp, 1yr+	Corpus	0.5*0.4*0.3	NE	PUH	ANED, 49mo.
22	33	G2P0	Uterine polyp, 1yr+	Corpus	1.7*1.5*1.1	NE	PUH	LFU
23	28	G1P0	Right ovarian cyst, 2mo	LUS	1.7*0.8*0.7	NE	PUH;PT	EH, 18mo; ANED, 42mo.
24	47	G2P1	Uterine leiomyoma, 1mo	Fundus	2.5*2*2	NA	TAH	ANED, 24mo.
25	28	G0P0	AUB,1yr	Corpus	2*1.6*1	EH	PUH	ANED, 39mo.
26	44	G2P1	Uterine adenomyosis, 3mo	Corpus	1.5*15.*1.5	NE	PUH;PT	TAHBSO, 4mo; ANED, 49mo
27	30	G0P0	AUB, 3mo	Corpus	1.5*1*1	NE	PUH	ANED, 12mo.
28	28	G0P0	AUB, 6mo	Corpus	3*2*2	NE	PUH	ANED, 47mo.
29	25	G0P0	Uterine polyp, 1mo+	Corpus	1.7*2*1.3	NA	PUH	ANED, 34mo.
30	42	G1P0	AUB, 6mo	LUS	0.8	EH	PUH;PT	ANED, 37mo.
31	24	G0P0	Infertility, 3yr	LUS	0.8*0.8*0.5	NE	PUH	ANED, 35mo.
32	34	G1P0	Uterine polyp, 4mo+	Corpus	0.5*0.3*0.3	NE	PUH	ANED, 22mo.
33	26	G0P0	Uterine polyp, 1d	Corpus	6.0*2.0*2.0	NA	PUH;PT	ANED, 26mo.
34	26	G1P0	Uterine polyp, 2yr+	Corpus	1.5*0.8*0.8	NE	PUH	ANED, 34mo.
35	43	G1P0	AUB, 1mo+	LUS	2.4*1.7*2.2	NE	PUH	ANED, 22mo.
36	29	G1P1	AUB, 2mo	Corpus	2.0*2.0*1.0	NA	PUH	ANED, 17mo.

Abbreviations: ANED, alive with no evidence of disease; APAM, Atypical polypoid adenomyoma; AUB, abnormal uterine bleeding; d, day; EAH, endometrial atypical hyperplasia; EC, endometrial carcinoma; EH, endometrial hyperplasia; G&P, gestation & parity; LFU, lost to follow-up; LUS, lower uterine segment; mo, month; NA, not available; NE, normal endometrium; PT, progesterone therapy; PUH, polypectomy under hysteroscopy; TAH, total abdominal hysterectomy; TAHBSO, total abdominal hysterectomy with bilateral salpingo-orphorectomy; yr, year.

[a] Cases 1–13 were APAMs with a highly complex structure. Cases 1–9 & 12 were reported, previously [10].

shown in Fig. 2A–I.

Squamous morule in APAM was invariably associated with nuclear β-catenin, higher CDX2 and CD10 expression, compared with their glandular components [Fig. 2A–C]. ER and PR were diffusely expressed in the glandular elements, but almost null in squamous morule (< 1% in most cases) [Fig. 2D]. The Ki67 index was extremely low (< 1%) in squamous morule, but it was much higher in the glandular epithelium (Table 2) [Fig. 2E]. Cyclin D1 and SOX9 were downregulated in squamous morule compared with that in the glandular epithelium [Fig. 2F]. The stromal cells in APAMs were strongly positive for SMA [Fig. 2G], focally positive for CD10, and negative for caldesmon [Fig. 2H, I].

Ki67 index was significantly higher in the glandular elements of endometrial carcinomas (mean ± SD 32.43% ± 20.49%) than in APAM (mean ± SD 20.86% ± 16.51%) ($p < 0.05$). The staining pattern of other antibodies was identical between endometrial carcinoma and APAM, such as consistent nuclear β-catenin, CDX2 and CD10 expression in squamous morules, and stronger ER and PR expression, SOX9 and cyclin D1 upregulation and higher Ki67 index in the glandular components relevant to the squamous metaplasia. In myoinvasive endometrial carcinomas, the peri-lobular smooth muscle was typically SMA and caldesmon positive [Fig. 2J, K].

4. Discussion

APAM is an uncommon benign polypoid mixed epithelial-mesenchymal tumor in the uterus [1,3,4,11–14]. Some issues remain to be resolved, such as the clinical behavior, differential diagnosis from myoinvasive endometrial carcinoma, and no consensus on the immunohistochemical features [4,7]. Most studies contained limited cases. In the current large and comprehensive clinicopathological survey, we not only confirmed the myofibromatous stroma (SMA+, h-caldesmon-, CD10 focal+) in APAM [6,9,15], but also provide several novel clues to aid in the differential diagnosis.

A difficult problem arises in distinguishing APAM with a highly complex architecture from myoinvasive endometrial carcinoma [3,15]. APAM might occasionally be misdiagnosed as endometrial carcinoma in the curettage materials [3,9,14]. Vague lobular architecture and a lack of marked cytological atypia are helpful clues for the diagnosis of APAM. However, insignificant atypia is not uncommon in well differentiated endometrial carcinomas. Vague lobular pattern can also be found in myoinvasive endometrial carcinoma. Evidence of stromal invasion, such as the true glandular confluence and a haphazard infiltration of irregular glands in the desmoplastic stroma, is the key to the differential diagnosis, but, unfortunately, it is not always appreciable in endometrial curetting as we will discussed later. A higher Ki67

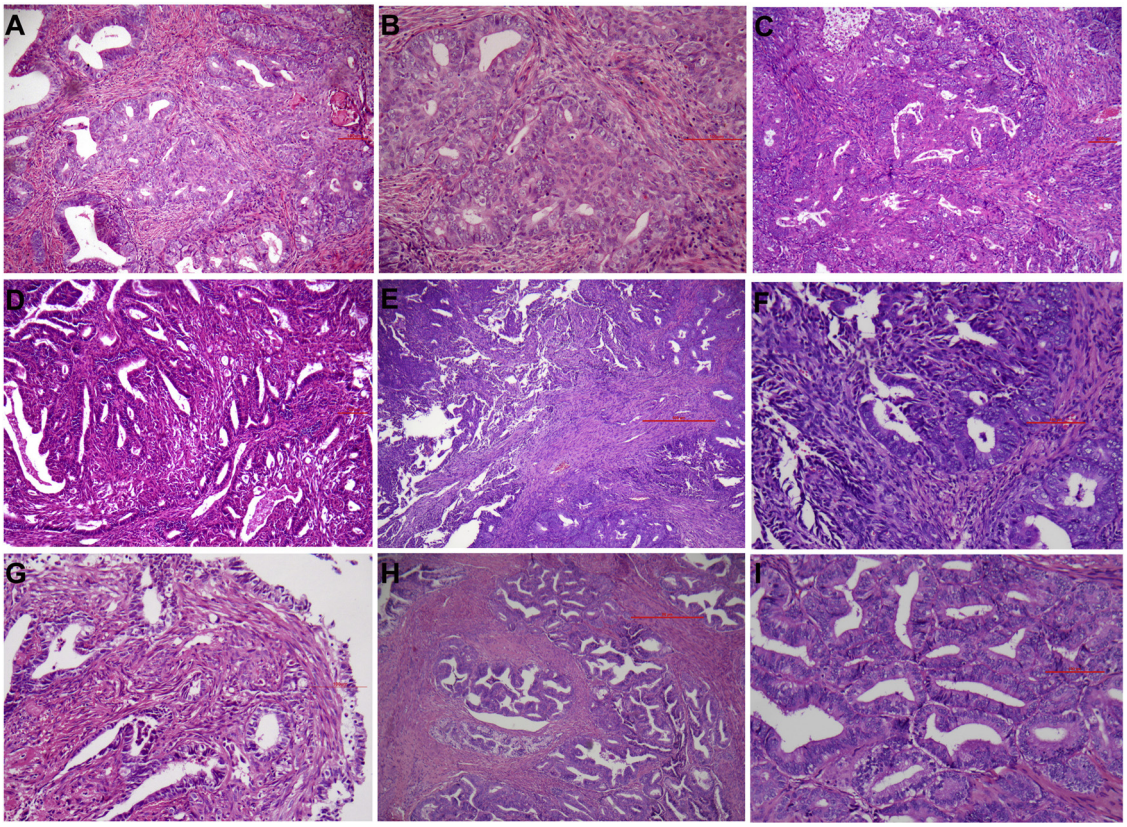

Fig. 1. Histopathological features of APAM.
APAM consists of irregular endometrial glands, frequently with a complex architecture and extensive squamous metaplasia in the septa of myofibroblastic stroma (A). The cytological atypia is generally low-to-moderate (B). Some cases with a highly complex architecture are difficult to be differentiated from endometrial carcinoma (C). The extensive squamous morule is intimately admixed with complex glands (D). The fibromuscular stroma is characteristic of a broad bundle of fibromuscular stroma with branches separating the glands into vague lobules (E, F), and the extension of small bundles directly underneath the intact surface epithelium (G). Myoinvasive endometrial carcinoma also shows a lobular pattern with more pronounced nuclear atypia, and surrounded by smooth muscles (H, I). (Original magnifications: 50× E, H, I; 100× A, C, D; 200× B, F, G).

Table 2
Comparison of immunostaining results between the glandular components and squamous morules in APAM.

Antibodies	Gla (Mean ± SD)	Mor (Mean ± SD)	*p* value
β-catenin (M)	6.58 ± 0.81	0.08 ± 0.50	< 0.0001
β-catenin (N)	0.21 ± 0.88	5.88 ± 1.39	< 0.0001
SOX9	4.64 ± 1.62	3.67 ± 1.96	< 0.05
Cyclin D1	4.69 ± 1.47	3.69 ± 2.49	0.05
ER	7	0.06 ± 0.24	< 0.0001
PR	6.56 ± 1.41	0	< 0.0001
Ki67 index	20.86% ± 16.51%	1.52% ± 0.83%	< 0.0001
CD10	0.14 ± 0.49	2.86 ± 0.55	< 0.0001
CDX2	0.08 ± 0.28	6.29 ± 0.74	< 0.0001
p40	0.09 ± 0.29	0.45 ± 1.58	> 0.05

*Abbreviations: Gla, glands; Mor, morules; M, membrane staining; N, nuclear staining.
** The additive immunoscore of positive cells and staining intensity was given for all antibodies except Ki67 index.
***Paired-Wilcoxon test was applied.

index was found in endometrial carcinomas than in APAM. However, from the practical viewpoint, Ki67 staining did not aid in the differential diagnosis due to the overlapping expression pattern between these two entities. The most useful diagnostic clues came from the distinct distribution of myofibroblastic stroma in APAM. These undocumented features included a broad bundle, a streaming fibromuscular stroma separating the glands into vague lobules, and the extension of fibromuscular stroma underneath the surface epithelium. Particularly, the last feature was only found in APAMs (31/36). Lobular pattern was observed in 3 myoinvasive endometrial carcinomas. However, the glands were separated by non-streaming caldesmon + smooth muscle fibers while APAM harbored a stroma with branching caldesmon- myofribroblasts. Hence, we feel like that the unusual features of the fibromuscular stroma in APAM are distinct from that in endometrial carcinoma. These stromal features warrant further investigation as potential morphological hallmarks to differentiate APAM from myoinvasive carcinoma.

Two forms of squamous metaplasia, morule and typical, have been found in a variety of endometrial entities including APAM [3,14]. However, the distribution of both forms has not been specifically discussed in APAM yet. We here demonstrated that typical squamous metaplasia was focally present in APAM (n = 4), but relatively more common in endometrial carcinoma (n = 13). Three of four APAM with typical squamous metaplasia harbored a complex architecture, and 2 were associated with endometrial carcinoma. Accumulative data are encouraged to reveal the underlying association between typical squamous metaplasia in APAM and a high risk for significant findings in the surrounding endometrium.

Squamous morule in APAM and endometrial carcinoma showed a characteristic immunostaining pattern (nuclear β-catenin+, CDX2+, and CD10+) as reported previously [16–18]. ER and PR expression was lost in squamous morule while both were diffuse strong in the glandular component. In endometrial curetting, true glandular confluence, such as cribriform and solid pattern, is the key to support the diagnosis of endometrial carcinoma rather than APAM. However, the intimate admixture of extensive squamous metaplasia and the extremely crowding

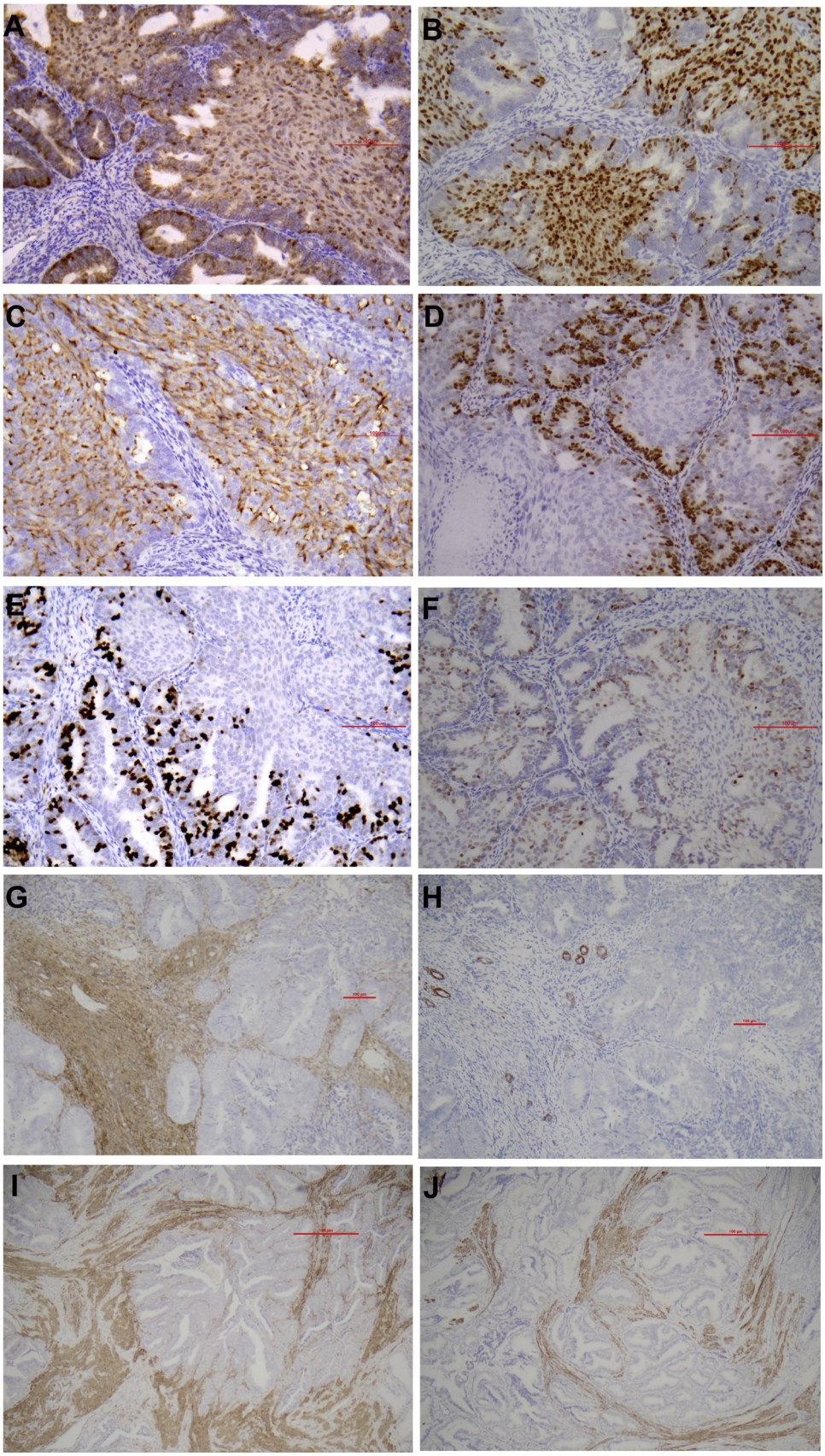

Fig. 2. Representative immunostaining figures of APAM.
In APAM, squamous morule shows nuclear β-catenin (A), strong CDX2 (B) and CD10 (C) expression, loss of ER expression (D), and lower Ki67 index (E) and cyclin D1 downregulation (F) compared with the glandular elements. The combination of A–D demonstrated no confluent/solid glands in APAM. The fibromuscular cells in APAM are strongly positive for SMA (G) and negative for caldesmon (H) while the smooth muscle bundle in myoinvasive endometrial carcinomas was both SMA (I) and caldesmon (J) positive (Original magnifications: 50× I, J; 100× G, H; 200× A–F).

glands in APAM can generate complex architectures, such as a pseudosolid and cribriform appearance, particularly when the fibromuscular stroma surrounding the glands is attenuated; as such, the recognition of glandular confluence remains problematic. Our observation suggests that the reverse staining pattern of these markers can clearly demonstrate the central morule and the peripheral glandular element, and highlight the morule-associated *glandular complexity* in APAM *rather than the true confluence in endometrial carcinoma*. Therefore, such specific immunostaining patterns can contribute to the differential diagnosis between APAM and endometrial carcinoma.

Downregulation of cyclin D1 and SOX9, and extremely low Ki67 index was observed in squamous morule relevant to the glandular element. Nuclear β-catenin, a feature of squamous morules [16–18], can activate Cyclin D1 and SOX9 [19,20]. The activation of β-catenin and downregulation of cyclin D1 and SOX9 may correlate with the low proliferative activities in morule. Takahashi et al. [7] suggested that the activation of β-catenin signaling seems to be essential for the morular phenotype. Loss of ER and PR expression in morule, which might be associated with hypermethylation in the gene promotor region [21], may also play a role in suppressing the proliferating activities.

In our study, we found that 8 of 13 patients with a highly complex structure had coexistent endometrial hyperplasia without atypia, atypical hyperplasia (including one with endometrial carcinoma one month later), and endometrial carcinoma in the surrounding endometrium. One patient had endometrial carcinoma in one month following her polypectomy. Moreover, two patients relapsed as consistent atypical hyperplasia and treated by a long-term large-dose progesterone therapy. These clinicopathological findings suggest a possible link between a complex structure of APAM, and local relapse or coexistent endometrial carcinoma. Our observations supported the term, APAM-LMP, which has been proposed by Longacre et al. [3] for a subset of APAM with a highly complex structure and potential local recurrence. The recurrent/persistent rate of APAM is approximately 30% [12]. The coexistence of, or progression to, endometrial carcinoma in APAM has occasionally been reported [11,22,23]. Several common risk factors, such as obesity and prolonged estrogen stimulus, may provide the potential link between APAM and endometrial carcinomas [24]. Němejcová et al. [4] found that some APAMs had the shared immunohistochemical and molecular features of endometrial carcinoma, such as loss of PTEN expression and K-RAS mutations. They have suggested that APAM may be best regarded as “analogous to a localized form of atypical endometrial hyperplasia”.

In conclusions, we suggest that the distribution of fibromuscular stroma may serve as morphological hallmarks to distinguish between APAM and endometrial carcinoma although further studies are required. A consistent immunophenotype of nuclear β-catenin, extremely low Ki67 index, and loss of ER and PR expression in squamous morule indicates the essential role of activated β-catenin signaling for the morular phenotype. A subset of APAM with a highly complex structure had tumor recurrence, and the coexistent complex atypical hyperplasia/endometrial carcinoma, implicating a low malignant potential and cancer risk.

Declaration of interest

None.

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