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Patterns of SATB2 and p16 Reactivity Aid Distinction of Atypical Polypoid Adenomyoma from Myoinvasive Endometrioid Carcinoma and Benign Adenomyomatous Polyp on Endometrial Sampling

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Running Title: SATB2 and p16 in APAM vs Myoinvasive Carcinoma

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ABSTRACT

Aims:

Atypical polypoid adenomyoma (APAM) is an uncommon uterine lesion composed of complex endometrioid glands with frequent squamous morular metaplasia and fibromuscular stroma. On endometrial curettage, biopsy, or polypectomy specimens, the admixture of endometrioid glands and smooth muscle raises the differential diagnosis of myoinvasive endometrioid carcinoma. Reproductive age patients with APAM may opt for fertility preservation, whereas myoinvasive carcinoma is treated surgically. One previous study reported an incidental finding that the stroma of APAM, in contrast to other polypoid lesions, was positive for SATB2. APAM has also been

reported to show increased stromal p16 staining. We aimed to assess whether SATB2 and p16 are useful stains for distinction of APAM from myoinvasive carcinoma and benign adenomyomatous polyps.

Methods and results:

Cases of "atypical polypoid adenomyoma" (n=32), "adenomyomatous polyp" (n=39), and "myoinvasive endometrioid carcinoma" (n=30) were identified. Morphologic features were assessed, along with the intensity and extent of SATB2 and p16 expression in the stromal component of each lesion. SATB2 expression was seen in the stromal component of 30/32 (94%) APAM, compared to 0/39 (0%) benign adenomyomatous polyps and 5/30 (17%) myoinvasive endometrioid carcinomas. Stromal p16 expression was seen in 31/31 (100%) APAM, versus 20/39 (51%) benign adenomyomatous polyps and 12/30 (40%) myoinvasive endometrioid carcinomas.

Conclusions:

Patchy to diffuse SATB2 reactivity and block-type p16 staining of fibromuscular stroma separating atypical endometrioid glands is more consistent with APAM than myoinvasive endometrioid carcinoma. These stains are potentially useful adjuncts to careful morphologic evaluation of endometrial biopsies/curettings.

Key words: atypical polypoid adenomyoma; SATB2; p16; myoinvasive endometrioid carcinoma

INTRODUCTION

Atypical polypoid adenomyoma (APAM) is an uncommon uterine lesion composed of complex endometrioid glands with frequent squamous morular metaplasia in a background of smooth muscle stroma with short interlacing fascicles. [1] On endometrial curettage, biopsy, or polypectomy specimens, the presence of endometrioid glands and smooth muscle stroma raises the differential diagnosis of myoinvasive endometrioid carcinoma. [2, 3]

Accurate distinction between APAM and myoinvasive endometrioid carcinoma on endometrial biopsies or curettings can facilitate management decisions. APAM may be treated conservatively to allow for preservation of fertility; approximately two-thirds of patients opt for local excision (polypectomy or curettage). [4-5] In contrast, myoinvasive endometrioid carcinoma is most commonly treated by hysterectomy. The vast majority of APAMs are considered to be benign, although recurrence is not uncommon. Endometrial carcinoma is detected in 8.8% of patients after treatment with curettage or polypectomy. [6] APAM is typically regarded as a localized form of endometrial intraepithelial neoplasia / complex atypical hyperplasia. [1]

In most cases, curettings of myoinvasive endometrioid carcinoma will show detached fragments of tumor in addition to fragments with myoinvasion. [1] While many cases of APAM and carcinoma show only mild to moderate cytologic atypia, marked cytologic atypia favors a diagnosis of myoinvasive endometrioid carcinoma. [1] Short interlacing fascicles of muscle separating endometrial glands may favor a diagnosis of APAM, since normal myometrium shows more elongated fibers. [1] Still, there is significant morphologic overlap between these entities.

Various immunohistochemical stains have been studied in this context due to the subtle morphologic distinctions between APAM and myoinvasive cancer. Ohishi and colleagues previously investigated the utility of CD10 immunohistochemistry for diagnosis of APAM versus myoinvasive carcinoma. [3] In their cohort, 1/7 APAM showed focal weak staining of the stroma between glands, whereas all 19 myoinvasive carcinomas showed fringe-like positivity in the stroma immediately adjacent to a subset of myoinvasive neoplastic glands. Nonetheless, it is known that smooth muscle neoplasms and benign endometrial stroma (surface or adenomyosis) may both show areas of CD10 reactivity. [7] Horita and colleagues have reported that h-caldesmon is either negative or focally positive in APAM stroma but diffusely positive in infiltrated myometrium (with the caveat that stromal reaction may be negative or focally positive). [8] Travaglino and colleagues reported a case of APAM with fringe-like CD10 reactivity and stromal h-caldesmon reactivity which progressed to carcinoma. [9] McCluggage and Van de Vijver have reported an incidental finding that the stroma of APAM is positive for the nuclear marker SATB2, whereas the stroma of other polypoid lesions is not. [10] Kihara and colleagues demonstrated increased stromal p16 in APAM compared to myoinvasive endometrioid carcinoma. [11] The immunohistochemical features of each component of APAM have recently been documented in a review article by Travaglino and colleagues. [12]

Benign adenomyomatous polyps may also enter the differential diagnosis for APAM. Adenomyomatous polyps, while often not considered separately from other endometrial polyps, are endometrial polyps with myomatous stroma. [13] Among 84 such cases reported by Strickland and colleagues, 55% were sessile polyps with vaguely fascicular myomatous stroma admixed with glands and 40% were pedunculated polyps with a stalk of disorganized smooth

muscle extending toward the surface and entrapping benign glands. Distinction from APAM is based on the complexity of the glandular proliferation and degree of cytologic atypia. The stroma of benign adenomyomatous polyps is typically positive for CD10; caldesmon is typically negative in the sessile polyps but positive in the pedunculated polyps. [13] While SATB2 expression in benign adenomyomatous polyps has not been extensively studied, McCluggage and van de Vijver reported that SATB2 was negative in the stroma of 5 adenomyomatous polyps and 11 of 12 endometrial polyps (with focal staining in one case). [10] Moritani and colleagues reported that 89% of endometrial polyps show stromal p16 expression, with a mean of 47% cells positive. [14]

Here, we aim to assess whether SATB2 and p16 are useful stains for distinction of APAM from myoinvasive endometrioid carcinoma and benign adenomyomatous polyps on endometrial biopsies or curettings. To our knowledge, this is the first study comprehensively evaluating SATB2 expression patterns in APAM, myoinvasive endometrioid carcinoma, and benign adenomyomatous polyp.

MATERIALS AND METHODS

With Institutional Review Board approval, the University of Michigan pathology and consultative archives were searched for cases of "atypical polypoid adenomyoma" (n=32), "adenomyomatous polyp" (n=40, including 39 benign adenomyomatous polyps and one adenomyomatous polyp cannot rule out atypical polypoid adenomyoma), and "myoinvasive endometrioid carcinoma" (n=30) sampled between 1989 and 2020. Four of the myoinvasive endometrioid carcinoma specimens were from biopsy or curettage; the remainder were from hysterectomy specimens. Study pathologists (HIW and SLS) reviewed all cases to confirm the diagnosis, assess morphologic features, and record available clinical follow-up information regarding recurrence and development of carcinoma.

The morphologic features assessed include gland to stroma ratio, presence of irregular endometrial gland contours, intraluminal complexity, presence of cytologic atypia, presence of

squamous metaplasia/differentiation, keratinization, mitotic rate, and characteristics of the fibromuscular stroma.

Immunohistochemical stains for SATB2 (clone EP281, dilution 1:200, Cell Marque, Rocklin, CA) were performed manually (Histoserv, Germantown, MD). The intensity (weak, moderate, or strong) and extent (focal/patchy versus diffuse) of nuclear SATB2 expression in the epithelial and stromal components of each lesion was recorded. Immunohistochemical stains for p16 (clone E6H4, pre-dilute, Ventana; Roche, Basel, Switzerland) were performed with an automated immunostainer (Ventana Bench-Mark XT; Roche, Basel, Switzerland) according to the manufacturer's protocol. The intensity (weak, moderate, or strong), extent (focal/patchy versus diffuse), and localization (nuclear and/or cytoplasmic) of p16 staining in the stromal components of each lesion was recorded. Staining was considered diffuse when present in a majority (>50%) of cells. Block-type p16 positivity was defined as clusters of continuous cells with strong nuclear or nuclear and cytoplasmic staining. [15]

RESULTS

In this cohort, the mean age of patients with APAM was 41 years, compared to 47 years for patients with benign adenomyomatous polyps and 60 years for patients with myoinvasive endometrioid carcinoma. Ten patients with APAM (31%) had concurrent cancer, but none developed new cancer after APAM diagnosis. Two patients with benign adenomyomatous polyps (5%) were subsequently diagnosed with hyperplasia (one with focal endometrial intraepithelial neoplasia and one with benign hyperplasia), but none developed cancer. The 47-year-old patient with an adenomyomatous polyp (cannot exclude APAM) was subsequently diagnosed with focal endometrial intraepithelial neoplasia / complex atypical hyperplasia. Demographics and clinical information are presented in **Table 1**.

The average gland to stroma ratio was higher for the myoinvasive component of endometrioid carcinoma (3:1) than APAM (1.5:1). In contrast, benign adenomyomatous polyps were stroma-predominant (1:2.5). Clear-cut lobular architecture was more often seen in APAM (34%) than in the myoinvasive component of endometrioid carcinoma (13%) or benign adenomyomatous

polyps (3%). All cases of APAM showed at least focal areas with irregular outer contours of endometrial glands, as did 93% of myoinvasive endometrioid carcinomas and 92% of benign adenomyomatous polyps. Intraluminal complexity (cribriforming, epithelial bridging) was seen in all myoinvasive endometrioid carcinomas, a subset of APAM (38%), and one benign adenomyomatous polyp (3%). At least mild cytologic atypia was seen in most cases of APAM (97%) and myoinvasive endometrioid carcinoma (93%), but was only rarely seen in benign adenomyomatous polyps (5%, focal). Squamous morular metaplasia was seen in almost all cases of APAM (94%), while 57% of myoinvasive endometrioid carcinomas showed areas of squamous differentiation. Squamous metaplasia was not seen in any benign adenomyomatous polyp. Keratinization was seen in 71% of myoinvasive endometrioid carcinomas with squamous differentiation, in contrast to 34% of APAM with squamous metaplasia. The average mitotic rate was higher in myoinvasive endometrioid carcinoma (11 per 10 high-power fields) than APAM (6 per 10 high-power fields), although the range overlapped between the two entities. The mitotic rate of benign adenomyomatous polyps was typically lower (1 per 10 high-power fields; range 0-14). Desmoplasia was more commonly seen in myoinvasive endometrioid carcinoma than APAM (60% versus 13%, **Figure 1A-B**). All APAM and 97% of myoinvasive endometrioid carcinomas showed small muscle bundles separating endometrial glands (**Figure 1C-D**). In contrast, benign adenomyomatous polyps demonstrated large muscle bundles and clusters of thick-walled blood vessels. Muscular stroma was seen beneath the surface endometrium in 19% of APAM cases (**Figure 1G-H**) and 10% of benign adenomyomatous polyps; the only myoinvasive carcinoma with this finding arose in a background of APAM. Morphologic features are presented in **Table 2**.

SATB2 Expression is More Commonly Seen in APAM Compared to Myoinvasive Endometrioid Carcinoma

Stromal expression of SATB2 was seen in 94% (30/32) cases of APAM (**Figure 2A-D**) versus 17% (5/30) myoinvasive endometrioid carcinomas (**Figure 2E-F**). SATB2 reactivity was diffuse in 28% (9/32) APAM, focal/patchy in 66% (21/32), and negative in 6% (2/32). Diffuse stromal SATB2 staining was not seen in any case of myoinvasive carcinoma. Three cases showed focal weak staining, one showed focal weak to moderate staining, and one showed patchy weak to moderate staining. Detailed SATB2 staining results are displayed in **Table 3**.

Of note, three cases of myoinvasive endometrioid carcinoma showed focal weak to moderate SATB2 staining in normal endometrial stromal cells (in surface endometrium or adenomyosis). Two cases of myoinvasive endometrioid carcinoma showed weak to moderate nuclear or cytoplasmic SATB2 staining in deep myometrial bundles, although no reactivity was seen in the fibromuscular stroma immediately surrounding invasive glands. Weak to moderate nuclear staining for SATB2 was occasionally seen in vessel walls (focal), lipoleiomyomas, and rare glandular cells with tubal metaplasia. Squamous morules show frequent SATB2 reactivity regardless of the entity they are seen in (26/30 APAM with squamous morules and 9/14 myoinvasive endometrioid carcinomas with squamous morules); therefore, care should be taken to distinguish staining of squamous morules from staining of stroma.

SATB2 Expression is Markedly Enriched in APAM Compared to Benign Adenomyomatous Polyps

Stromal expression of SATB2 was seen in 94% (30/32) cases of APAM compared to 0% (0/39) benign adenomyomatous polyps. Focal moderate SATB2 staining was seen in the one adenomyomatous polyp for which a diagnosis of APAM could not be ruled out. Importantly, SATB2 reactivity was not seen in the stroma of definitively benign adenomyomatous polyps (**Figure 2G-H**).

Stromal p16 Expression is Not Uncommon in APAM, Benign Adenomyomatous Polyps, or Myoinvasive Endometrioid Carcinoma

For one APAM case, further material was not available for p16 staining. Increased nuclear and cytoplasmic staining for p16 protein was seen in the fibromuscular stroma for 100% (31/31) APAM, 51% (20/39) benign adenomyomatous polyps, and 40% (12/30) myoinvasive endometrioid carcinomas, as well as the adenomyomatous polyp for which a diagnosis of APAM could not be ruled out. Importantly, inflammatory cells often showed moderate nuclear and cytoplasmic staining for p16, which often made interpretation challenging in cases of myoinvasive endometrioid carcinoma (particularly those with the "MELF" pattern of invasion). Rounded cells in the surface endometrial stroma or areas of adenomyosis can show staining for p16. Detailed

staining results for p16 are displayed in **Table 4**, and representative photomicrographs of stained slides are presented in **Figure 3A-H**.

Stromal Block-Type p16 Expression is More Specific, but Less Sensitive, for APAM

Block-type p16 expression was seen in 45% (14/31) APAM, 10% (4/39) benign adenomyomatous polyps, and 0% (0/30) myoinvasive endometrioid carcinomas, and was not seen in the adenomyomatous polyp for which a diagnosis of APAM could not be ruled out. Although stromal block-type p16 expression can be seen in benign adenomyomatous polyps as well, it is more highly associated with APAM (p=0.0019).

Of the 10 APAM cases with concurrent endometrioid carcinoma, stromal SATB2 reactivity was focal/patchy in 9 (90%) cases. Stromal p16 reactivity was seen in all 9 stained APAM with concurrent non-myoinvasive endometrioid carcinoma (focal/patchy in 8 cases and diffuse in 1, with 3 showing areas of block positivity).

DISCUSSION

Despite the significant morphologic overlap that can be seen in biopsies and curettings of APAM and myoinvasive endometrioid carcinoma, there are nuanced morphologic and immunohistochemical features that can facilitate distinction of these two entities. The stromal staining patterns of SATB2 and, to a lesser extent, p16, may facilitate accurate classification.

In our cohort, the fibromuscular stroma surrounding myoinvasive endometrioid carcinoma was often a close mimic of the fibromuscular stroma of APAM. The gland to stroma ratio was often higher in the myoinvasive component of endometrioid carcinoma than in APAM; however, some cases of myoinvasive endometrioid carcinoma show atypical glands with smooth outer contours and a lower gland to stroma ratio. Lu et al reported that 72% (26/36) of their APAM cases showed fibromuscular branches separating glands into vague lobules, with fibromuscular bundles present beneath surface epithelium in 86% (31/36). [16] This feature was seen less frequently in our cohort, but was only identified in APAM cases. Squamous morules were common in APAM cases, as has been previously reported; keratinizing squamous differentiation

is more common in endometrioid carcinoma. [2, 16] Though desmoplasia has been described as a feature supportive of myoinvasion [16], two APAMs in our cohort showed desmoplastic stroma despite the absence of carcinoma. Lu et al report seeing no more than 2 mitotic figures per 10 high-power fields in their APAM cases [16]; however, the mean mitotic rate in our cohort was 6/10 HPF. Based on these features, it is not surprising that fragmented samples of APAM may be misdiagnosed as myoinvasive carcinoma. On the other hand, some cases of myoinvasive endometrioid carcinoma show vague lobular architecture and insignificant cytologic atypia, leading to misinterpretation as APAM. [16]

Overall, stromal expression of SATB2 and p16 appear to be supportive of diagnosis of APAM. Stromal reactivity for SATB2 was seen in 94% of APAMs, compared to 17% of myoinvasive endometrioid carcinomas and 0% of benign adenomyomatous polyps. In three cases of myoinvasive endometrioid carcinoma, stromal SATB2 reactivity was seen in fibromuscular stroma of the endometrial mass and myometrium/reactive stroma surrounding myoinvasive glands. Focal weak to moderate expression of SATB2 is non-specific; however, patchy or diffuse moderate stromal reactivity was seen much more commonly in APAM (50%) than myoinvasive carcinoma (3%). As previously reported by McCluggage and van de Vijver, squamous morules were frequently positive for SATB2 in our cohort. [10]

Although increased stromal p16 staining was more often seen in APAM than myoinvasive endometrioid carcinoma or benign adenomyomatous polyps, it was seen fairly commonly in all three entities. Block-type stromal p16 positivity was not seen in myoinvasive carcinoma, but this finding has limited sensitivity as it was present in only 45% of APAM cases. Some benign adenomyomatous polyps in our cohort showed block-type p16 staining; this finding is consistent with previous reports of stromal p16 reactivity in endometrial polyps. [14] Occasional block-type p16 staining in the stroma of benign adenomyomatous polyps may also be expected, since Strickland and colleagues reported that a subset of benign adenomyomatous polyps show an immunoprofile similar to APAM. [13] A major benefit of using p16 is that many laboratories already have access to this antibody, whereas they may not have an in-house SATB2 stain. No myoinvasive carcinomas showed diffuse stromal reactivity for SATB2 or p16.

Strengths of this study include the comprehensive evaluation of 32 APAMs, given the rarity of the neoplasm. The spectrum of immunohistochemical findings for each diagnostic entity was recorded, and potential pitfalls were described. One significant limitation of this study is the inclusion of only 4 myoinvasive endometrioid carcinoma samples from endometrial biopsies or curettings, given the suggestion that these stains may be useful in that setting. However, use of sections from hysterectomy specimens increases confidence in the diagnosis of APAM rather than myoinvasive endometrioid carcinoma.

In summary, APAMs and myoinvasive endometrioid carcinomas in our cohort showed significant morphologic overlap, and the entities we studied more reliably showed distinct SATB2 expression patterns than p16 expression patterns. Based on our data, patchy to diffuse SATB2 reactivity and block-type p16 staining in fibromuscular stroma separating atypical endometrioid glands are more commonly seen in APAM than myoinvasive endometrioid carcinoma. Evaluation for specific SATB2 and p16 immunohistochemical staining patterns, in addition to careful morphologic examination, can increase our confidence in accurate classification of APAM and myoinvasive carcinoma in endometrial biopsies or curettings.

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FIGURE LEGENDS

Figure 1. Atypical polypoid adenomyoma (APAM) and myoinvasive endometrioid carcinoma show significant morphologic overlap. Although desmoplasia is considered essentially pathognomonic for invasive carcinoma (A, H&E, 200x), similar changes may be seen in the stroma of APAM (B, H&E, 200x). Small to medium muscle bundles may be seen separating endometrial-type glands in both invasive endometrioid carcinoma (C, H&E, 200x) and APAM (D, H&E, 200x). Some cases of myoinvasive endometrioid carcinoma show a

lobulated, deceptively bland pattern of invasion (E, H&E, 100x), and sampled fragments may resemble the lobulated growth of glands in APAM (F, H&E, 100x). One feature that seems to be unique to APAM is the presence of muscle bundles beneath surface endometrium (G and H, H&E, 200x).

Figure 2. SATB2 expression is most frequently seen in atypical polypoid adenomyoma (APAM), as compared to benign adenomyomatous polyp and myoinvasive endometrioid carcinoma. SATB2 expression was most frequently observed in APAM (A and C, H&E, 100x and 200x) with nuclear expression in squamous morules (B, SATB2 IHC, 100x) and stroma (D, SATB2 IHC, 200x). In contrast, the fibromuscular stroma of myoinvasive carcinoma (E, H&E, 200x and F, SATB2 IHC, 200x) and benign adenomyomatous polyp (G, H&E, 200x and H, SATB2 IHC, 200x) was negative for SATB2.

Figure 3. p16 expression can be seen in stroma associated with atypical polypoid adenomyoma (APAM), benign adenomyomatous polyp, or myoinvasive endometrioid carcinoma, but is enriched in APAM. A large subset of APAMs showed diffuse stromal p16 reactivity (A, H&E, 200x and B, p16 IHC, 200x), but 10% showed only focal stromal p16 staining (C, H&E, 200x and D, p16 IHC, 200x). While p16 was negative in the stroma of 36% of benign adenomyomatous polyps in our cohort, many benign adenomyomatous polyps (E, H&E, 200x) showed at least patchy p16 positivity (F, p16 IHC, 200x). p16 staining, if present at all, was typically focal in the stroma of myoinvasive endometrioid carcinomas; however, inflammatory cells often show moderate reactivity (G, H&E, 200x and H, p16 IHC, 200x).

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Table 1. Demographics and Clinical Information

Diagnosis	Age	Concurrent Cancer	Subsequent Cancer
Atypical polypoid adenomyoma	41 (17 – 71)	10 (31%)	0 (0%)
Myoinvasive endometrioid carcinoma	60 (37 – 77)	---	---
Benign adenomyomatous polyp	47 (18 – 76)	0 (0%)	0 (0%)
Adenomyomatous polyp, cannot rule out atypical polypoid adenomyoma	47	0 (0%)	0 (0%)

Table 2. Morphologic Features

Diagnosis	Average gland to	Clear-cut lobular	Irregular gland	Intraluminal complexity	Cytologic atypia	Squamous metaplasia/dif	Keratinizing squamous	Mitotic rate (per 10 HPF),	Characteristics of fibrom	Muscular stroma beneat	Desmoplastic stroma

	stroma ratio	architecture	contours			ferentiation	metaplasia/differentiation	mean (range)	uscular stroma	h surface endometrium	
Atypical polypoid adenomyoma	1.5:1	11 (34%)	32 (100%)*	12 (38%)[#]	31 (97%)	30 (94%)[#]	11 (34%)[^]	6 (1 – 11)	Small muscle bundles separating glands	6 (19%)	4 (13%)
Myoinvasive endometrioid carcinoma	3:1	4 (13%)	28 (93%)	30 (100%)	28 (93%)	17 (57%)	12 (71%)[^]	11 (1 – 41)	29 (97%) with at least few small to medium muscle bundles betwee	1 (3%)[@]	18 (60%)[%]

									n glands 7 (23%) with pink fibrotic stroma between glands		
Benign adenomyomatous polyp	1:2.5	1 (3%)	36 (92%)[!]	1 (3%)[$]	2 (5%)[&]	0 (0%)	0 (0%)	1 (0 – 14)	Large muscle bundles and thick-walled vessels	4 (10%)	0 (0%)
Adenomyomatous polyp, cannot rule	1:1	1 (100%)	1 (100%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	5	Small muscle bundles	0 (0%)	0 (0%)

out atypical polypoid adenomyoma									separating glands		

*Three cases with few irregular glands; #Focal in one case; ^Percentage represents percentage of cases with squamous metaplasia/differentiation showing keratinization; @Carcinoma arising from atypical polypoid adenomyoma; %Focal in four cases; !Nine cases with few irregular glands; $Few papillae; &Mild, focal

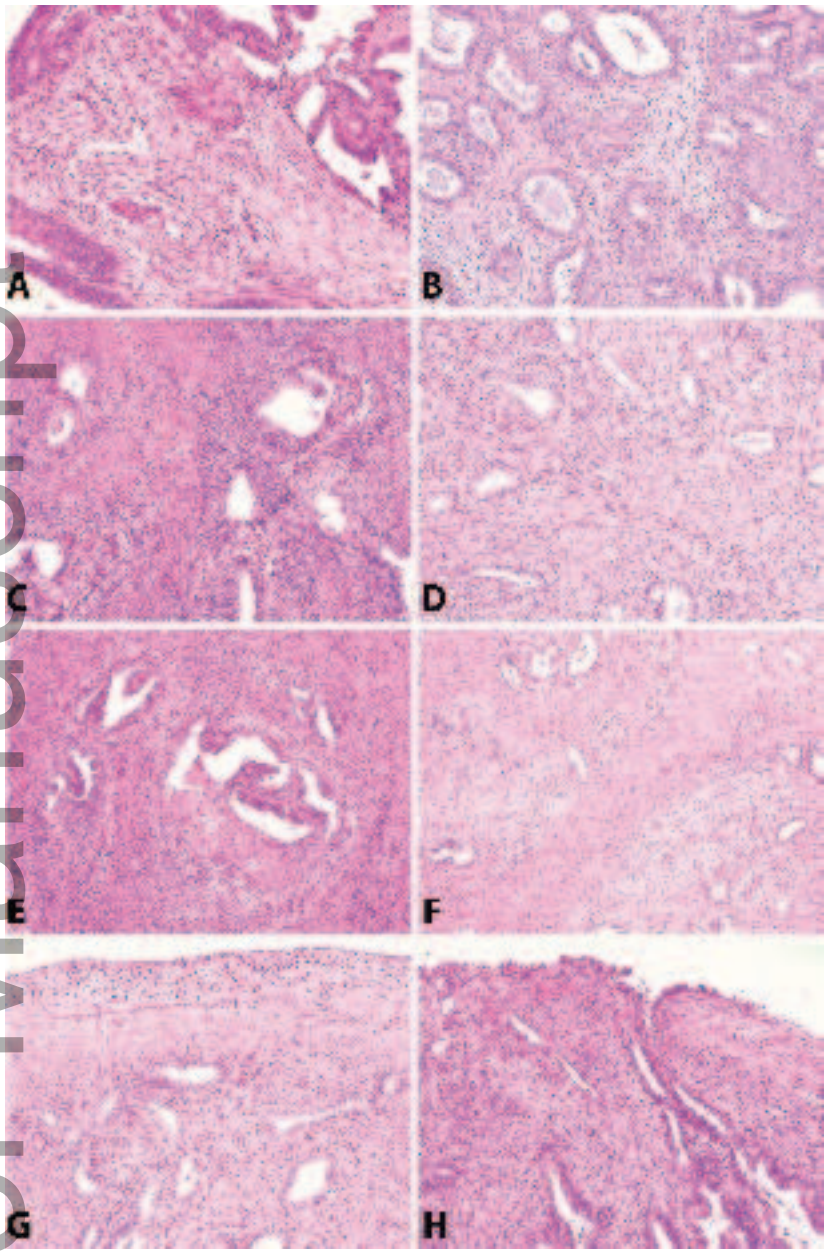
Table 3. SATB2 Staining

	Atypical polypoid adenomyoma	**Myoinvasive endometrioid carcinoma**	**Benign adenomyomatous polyp**	**Adenomyomatous polyp, cannot rule out atypical polypoid adenomyoma**
Diffuse	9 (28%)	0 (0%)	0 (0%)	0 (0%)
Focal/Patchy	21 (66%)	5 (17%)	0 (0%)	1 (100%)
Negative	2 (6%)	25 (83%)	39 (100%)	0 (0%)

Table 4. p16 Staining

	Atypical polypoid adenomyoma	**Myoinvasive endometrioid carcinoma**	**Benign adenomyomatous polyp**	**Adenomyomatous polyp, cannot rule out atypical**

				polypoid adenomyoma
Block-type	14 (45%)	0 (0%)	4 (10%)	0 (0%)
Diffuse	13 (42%)	0 (0%)	0 (0%)	0 (0%)
Focal/Patchy	18 (58%)	12 (40%)	25 (64%)	1 (100%)
Negative	0 (0%)	18 (60%)	14 (36%)	0 (0%)



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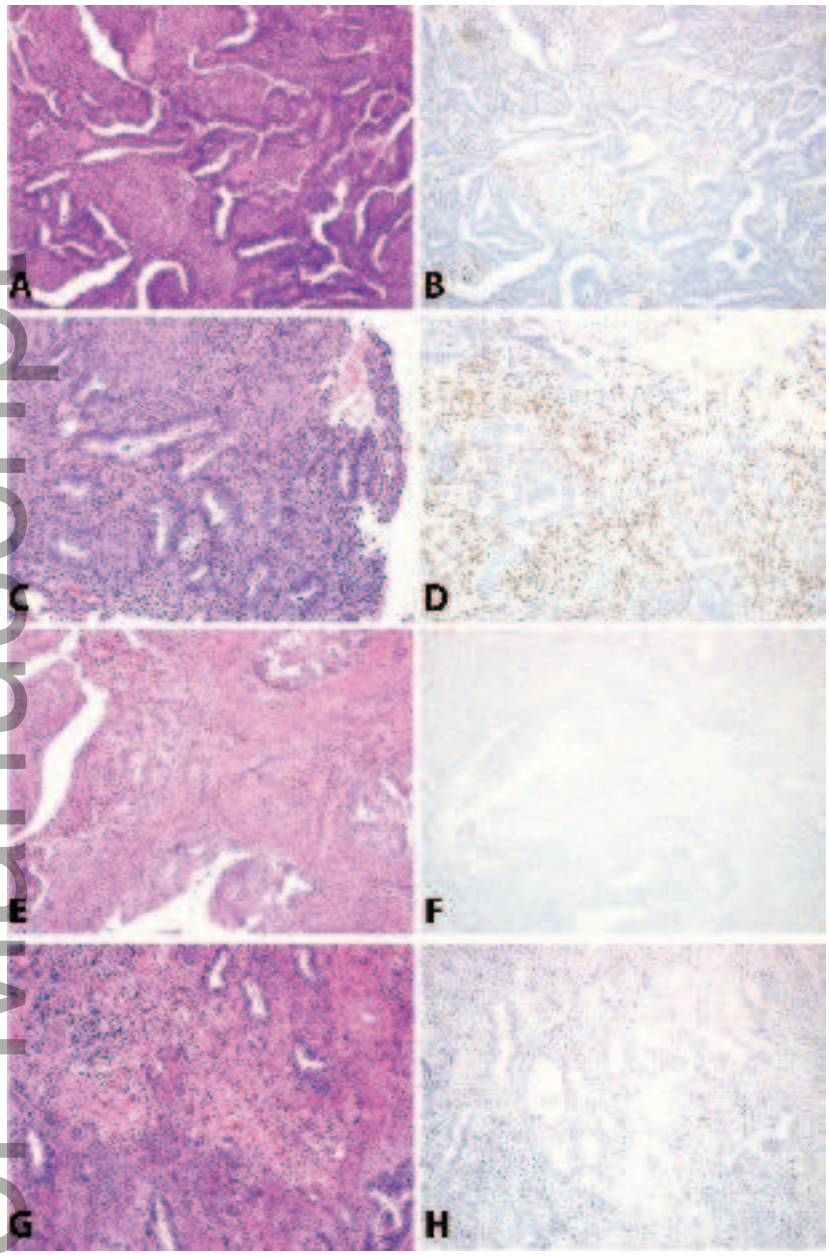

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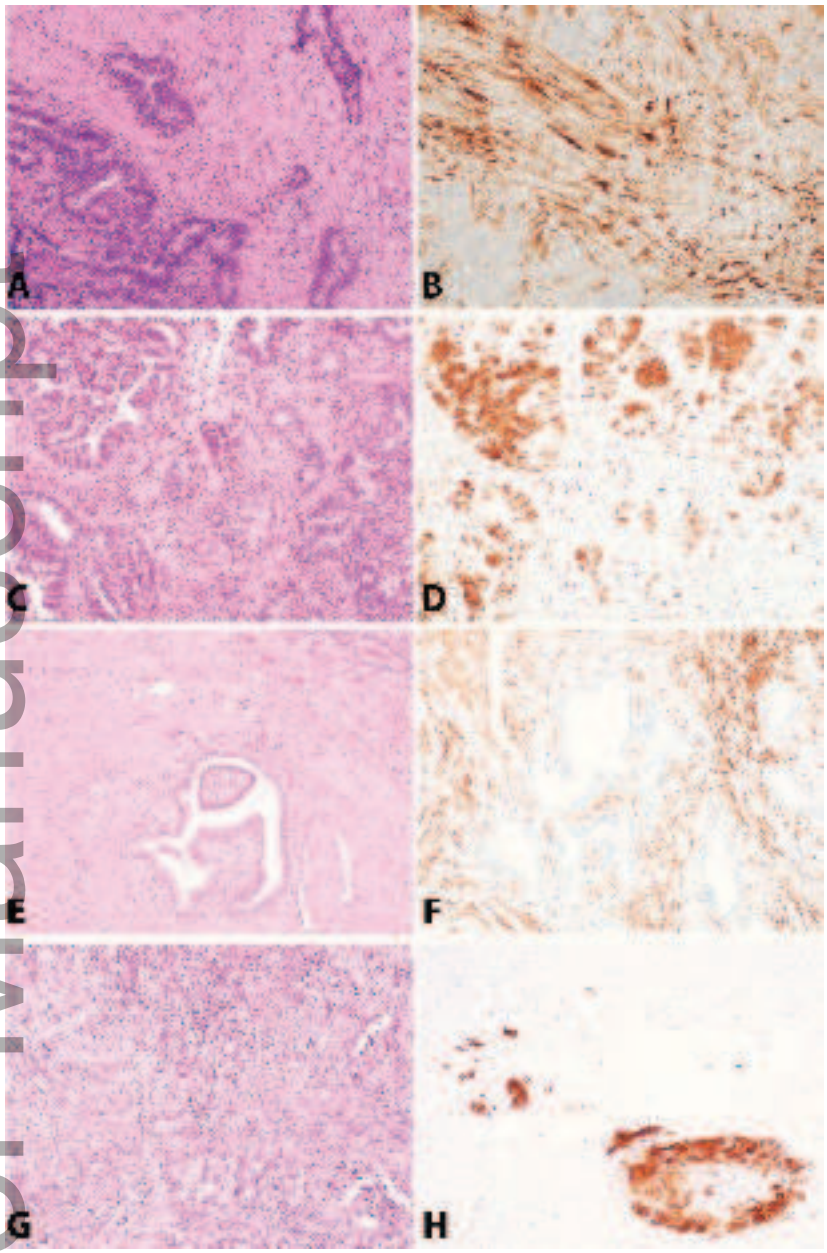

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