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Original contribution

# Clinicopathological and immunohistochemical features of uterine adenomyomatous polyps☆

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**Summary** Adenomyomatous polyps (APs) of the uterus (also termed polypoid adenomyomas and pedunculated adenomyomas) are exophytic proliferations composed of myomatous stroma admixed with endometrial glands. APs can be diagnostically challenging, mimicking polypoid neoplasms such as atypical polypoid adenomyoma and adenosarcoma. The purpose of this study was to describe the clinicopathological, morphologic, and molecular features of APs, as well as to raise awareness of this entity as a potential source of diagnostic confusion. We identified APs diagnosed at Brigham and Women's Hospital from 2000 to 2015. We reviewed histologic slides and obtained archival tissue for immunohistochemical and molecular studies. APs seen in consultation were associated with a broad differential, including adenosarcoma, atypical polypoid adenomyoma, and endometrial neoplasia. We performed a histologic review of 84 APs diagnosed at our institution and identified 2 distinct morphologic types of APs, which we have termed type 1 (with vaguely fascicular myomatous stroma intimately admixed with glands) and type 2 (containing a well-defined stalk of smooth muscle entrapping glands). Most APs exhibited CD10-positive (100%; 72/72) and desmin-positive (97%; 70/72) stroma. Diffuse caldesmon positivity was present in 97% (28/29) of type 2 polyps compared with 8% (3/39) of type 1 APs. APs did not harbor mutations in exon 2 of *MED12*. APs are not uncommon in routine practice and may be misinterpreted as more worrisome lesions. We identified 2 types of APs with distinct morphology and immunophenotype. The absence of *MED12* exon 2 mutations suggests that the pathogenesis of APs is separate from uterine leiomyomas.


## 1. Introduction

Benign polypoid lesions of the uterus are common pathologic specimens, generally encountered after clinical findings of abnormal uterine bleeding, infertility, or an incidentally discovered uterine mass [1]. Adenomyomatous polyps (APs) of the uterus are a relatively common entity encountered in this

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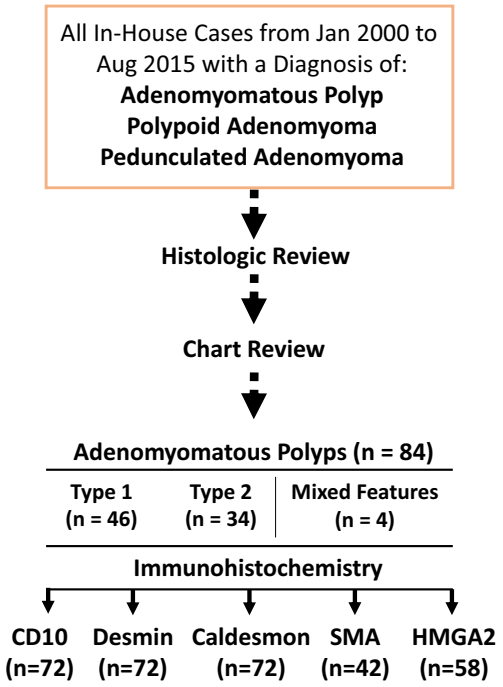


**Fig. 1** Study design and methods. Our pathology database was queried for the above diagnoses to identify patients with APs. A total of 84 APs were histologically confirmed, and we performed IHC on a subset of these polyps.

setting. Herein, we use the term AP (also known as polypoid adenomyomas and pedunculated adenomyomas) to refer to proliferations of myomatous stroma admixed with endometrial glands with exophytic growth into the uterine cavity. Previously considered in conjunction with conventional endometrial polyps and uterine adenomyomas [2,3], few studies have considered APs as a distinct entity. In their seminal study on endometrial polyps, Peterson and Novak [2] reported that APs were much less common than conventional polyps, comprising 1.3% of all endometrial polyps in their study.

Despite their incidence, there are still a number of unanswered questions regarding the histogenesis of APs. It is currently unclear whether APs represent neoplastic proliferations, hamartomatous growths, a metaplastic process, or a variant of adenomyosis. The relationship between APs and infertility and hormonal therapy is also a subject of debate [4,5]. APs have a diverse histology, according to case reports [6-8], and can appear similar to more worrisome entities, including atypical polypoid adenomyoma and adenosarcoma [3,9]. If APs represent superficial smooth muscle neoplasms, it is possible that they harbor mutations in the *MED12* (mediator complex subunit 12) gene, which is reportedly altered in up to 70% of uterine leiomyomas [10], or gene rearrangements involving *HMGA2* (high mobility group AT-hook 2) [11]. The aim of the current study was to describe the clinical, histologic, immunophenotypic, and molecular characteristics of APs diagnosed at our institution.

## 2. Materials and methods

### 2.1. Case selection and histomorphologic review

We identified all cases of AP, polypoid adenomyoma, pedunculated adenomyoma, or polyp with adenomyomatous features diagnosed at Brigham and Women's Hospital (BWH) and received from September 2000 to April 2015 (Fig. 1). Slides and archival formalin-fixed and paraffin-embedded (FFPE) tissue blocks were requested from the repository. For each case, we reviewed the surgical pathology report and recorded the final diagnosis, the specimen type, and gross size of the polyp, if possible. We reviewed the electronic medical record to evaluate radiologic and hysteroscopic reports and recorded the preoperative clinical diagnosis/impression and the anatomic location of the lesion. We also reviewed the medical record to evaluate for patient history of polyps, fibroids, adenomyosis, abnormal uterine bleeding, pelvic pain, infertility, hormonal therapy, endometriosis, polypectomy/curettage, cesarean delivery, or any prior endometrial sampling.

We queried the institutional pathology database to identify all pathologic consultation cases with a diagnosis of AP,

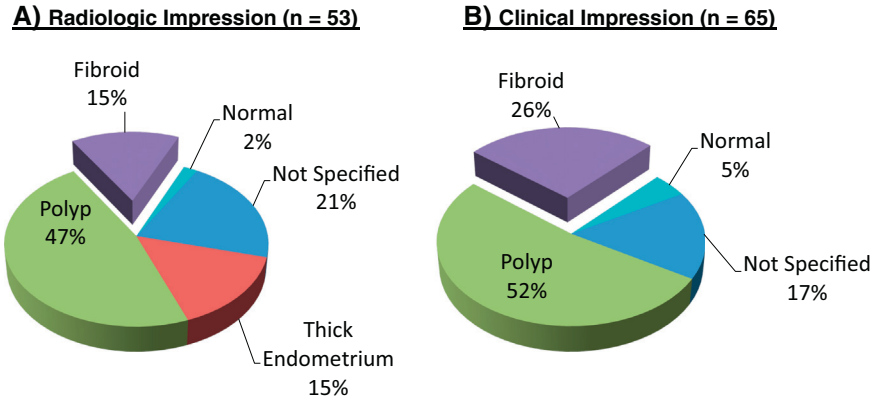


**Fig. 2** Radiologic (A) and clinical (B) impressions of APs. Radiologic information was not available for 31 cases. Physical examination or hysteroscopic information was not available for 19 cases.

**Table 1** Clinicopathological characteristics of APs

| Sample size | All APs (n = 84) | Type 1 (n = 46) | Type 2 (n = 34) | *P* * | Mixed (n = 4) |
|---|---|---|---|---|---|
| Pathological characteristics | | | | | |
| Average size (cm) | 2.5 | 2.2 | 2.7 | .26 | 2.3 |
| Gross hemorrhagic foci present (%) | 23.8 | 17.4 | 35.3 | .12 | 0 |
| History of endometrial/endocervical polyps (%) | 32.1 | 30.4 | 32.4 | 1.00 | 50.0 |
| History of fibroids (%) | 32.1 | 30.4 | 35.3 | .81 | 25.0 |
| History of infertility (%) | 9.5 | 4.3 | 17.6 | .07 | 0 |
| Clinical characteristics | | | | | |
| Average age (y) | 51 | 51 | 52 | .71 | 48 |
| Abnormal uterine bleeding (%) | 61.9 | 65.2 | 58.8 | .64 | 50.0 |
| Postcoital bleeding (%) | 1.2 | 0.0 | 2.9 | .43 | 0 |
| History of pelvic pain (%) | 6.0 | 6.5 | 5.9 | 1.00 | 0 |
| Endometriosis (%) | 3.6 | 4.4 | 0 | .51 | 25.0 |
| History of D&C, cesarean delivery, or EmBX (%) | 39.3 | 39.1 | 38.2 | .82 | 50.0 |
| History of exogenous hormonal therapy [a] (%) | 28.6 | 21.7 | 47 | .03 * | 25.0 |
| Hormone replacement therapy (%) | 13.1 | 4.3 | 23.5 | .02 * | 25.0 |
| Oral contraceptive pills (%) | 9.5 | 8.7 | 11.8 | 1.00 | 0 |
| Clomiphine (%) | 3.6 | 2.2 | 5.9 | .57 | 0 |
| Tamoxifen (%) | 6.0 | 6.5 | 5.9 | 1.00 | 0 |
| History of IUD placement (%) | 4.8 | 8.7 | 0 | .13 | 0 |
| Favored as fibroid by imaging (%) | 9.5 | 10.9 | 8.8 | 1.00 | 0 |
| Favored as fibroid by clinician (%) | 14.3 | 15.2 | 8.8 | .50 | 50.0 |

Abbreviations: D&C, dilation and curettage; EmBX, endometrial biopsy; IUD, intrauterine device.

[a] Including history of oral contraceptive pills, tamoxifen, clomiphene, or other hormone replacement therapy.

* *P* values correspond to the comparison of type 1 *vs* type 2 APs. Polyps with mixed features were excluded from the analysis ($P < .05$).

polypoid adenomyoma, pedunculated adenomyoma, or polyp with adenomyomatous features received from October 2007 to May 2015. The corresponding consultation letters were reviewed, and the differential diagnosis was recorded, including the referring pathologist's most worrisome consideration. For in-house cases, histomorphologic review was performed by 2 pathologists with expertise in gynecologic pathology (M. R. N. and B. E. H.), who reviewed slides to confirm the presence of an endometrial polyp, assess tissue quantity for immunohistochemistry (IHC), and document morphologic features.

## 2.2. Immunohistochemistry

IHC was performed in a manner previously described [12]. Antigen retrieval was performed by incubation with 10 mM citrate buffer (pH 6.0) in a pressure cooker. IHC studies were performed using antibodies directed against the following antigens: CD10 (clone 56C6; Cell Marque, Rocklin, CA), desmin (clone DE-U-10; Sigma-Aldrich, St Louis, MO), h-caldesmon (clone h-CD; Dako/Agilent, Santa Clara, CA), SMA (clone 1A4; Sigma-Aldrich), and HMGA2 (59170AP; Biocheck, Foster City, CA). All primary antibodies were incubated with slides for 1 hour at room temperature. The Dako EnVision System (Dako Envision horseradish peroxidase–labeled polymer antimouse) was used to visualize all staining. Immunoreactivity was qualitatively assessed as positive or negative, and of note, only strong, diffuse staining of desmin and caldesmon was considered positive, because desmin may demonstrate a weak dot-like staining pattern in normal endometrial-type stroma and caldesmon highlights vessel walls. For comparison, we also performed IHC on a cohort of recently diagnosed endometrial polyps, retrospectively identified from the pathology database.

## 2.3. *MED12* sequencing

Genomic DNA was extracted from FFPE tissue sections using the QIAamp FFPE tissue kit (catalog no./ID: 56404). The extracted DNA was quantified using NanoDrop spectrophotometer (Thermo Scientific). Polymerase chain reaction using primers for exon 2 of *MED12* (forward: 5′-CCCTA CTCTCCCACCCCTTC-3′; reverse: 5′-CTTCAGCCTGGC AGAGTTGT-3′) was performed on the extracted genomic DNA followed by Sanger sequencing, in a manner similar to that previously described [13].

## 2.4. Statistical analysis

Fisher exact test was used to evaluate the statistical significance of categorical variables, and an unpaired Student *t* test was used to compare continuous variables. All *P* values are 2-sided, and significance was evaluated at the .05 level. GraphPad Prism version 5 (GraphPad Software, San Diego, CA) was used for statistical analyses.

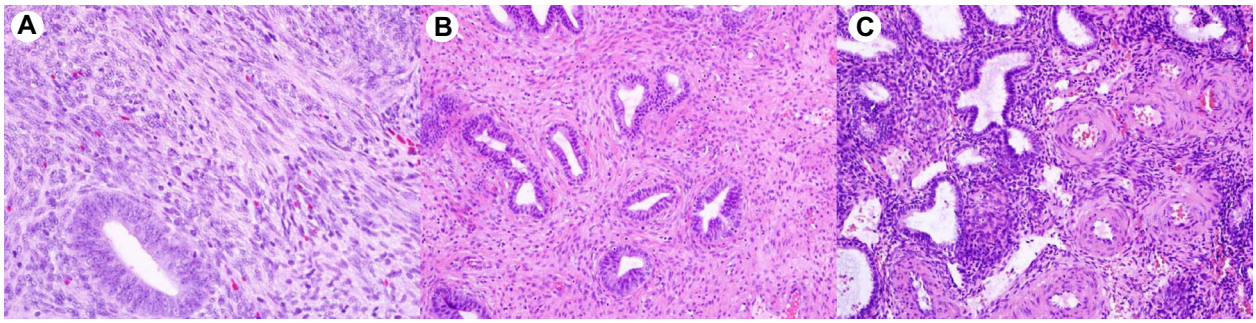


**Fig. 3** Histologic appearance of APs. A, The stroma of type 1 APs appeared somewhat fascicular and intimately associated with endometrial glands (hematoxylin and eosin [H&E], original magnification ×40). B, Type 2 APs demonstrated an eosinophilic stroma radiating from a myomatous stalk and entrapping normal glands (H&E, ×20). C, As a comparison, the stroma of conventional endometrial polyps appeared storiform, lacking the fascicular growth pattern of the APs (H&E, ×20).

## 3. Results

### 3.1. Clinical characteristics and morphologic features of APs

We identified 84 patients with a pathologic diagnosis of AP sampled at our institution, obtained from the following procedures: polypectomy (47), endometrial biopsy (15), hysterectomy (13), and myomectomy (9). The average age of patients (n = 84) was 51 years (range, 27-89 years). The most common symptom was abnormal uterine bleeding, which was reported in 52 (62%) cases; only 12 APs (14%) were incidental. A significant percentage (15%) were identified as fibroids by radiologists, and 26% were identified as fibroids by clinicians (Fig. 2). The anatomic location of the polyp was recorded in 42 cases, including the corpus (18), fundus (12), endocervix (6), lower uterine segment (4), and cornu (2). Clinicopathological data are listed in Table 1.

Two patterns of APs were documented at morphologic slide review (Fig. 3). The first, which we termed "type 1," were predominantly sessile and exhibited vaguely fascicular myomatous stroma intimately admixed with glands. The second, termed "type 2," were characterized by a well-defined stalk of disorganized smooth muscle radiating to the surface and entrapping glands. Overall, this latter group (type 2 APs) appear to be a benign overgrowth of different cell populations native to the surrounding tissue (myometrium, endometrial glands, and endometrial stroma), with an architecture resembling that of hamartomatous polyps seen in some hereditary disorders [14]. Type 1 APs were observed in 46 polyps (55%), and type 2 APs were observed in 34 cases (40%). Features of both type 1 and type 2 polyps were observed in 4 cases (5%). One AP with mixed histology was diagnosed as an "atypical adenomyomatous polyps," which demonstrated a significant amount of stromal atypia and features that border on, but not diagnostic of, adenosarcoma.

Of polyps evaluated after hysterectomy, coexisting intramural adenomyomas/adenomyosis was identified in 25% (1/4) of type 1 APs and 12.5% (1/8) of type 2 APs. A gross border was present in 75% (3/4) of type 1 and 100% (8/8) type 2 polyps evaluated at the time of hysterectomy (n = 7). The clinical and radiologic impression of type 1 and type 2 APs was extremely similar; however, none of the type 2 APs were considered "normal" by either radiologic or clinical impression.

### 3.2. Immunohistochemical profile of type 1 and type 2 APs

The results of IHC for CD10, desmin, caldesmon, SMA, and HMGA2 are summarized in Table 2. CD10 was generally positive in the stroma of all polyps. All of the APs stained positive for at least one smooth muscle marker. Desmin was found to be a fair marker of myomatous stroma, staining 97% of APs and 50% of conventional polyps. SMA was a more reliable marker of myomatous stroma, staining 95% of APs and 25% of conventional polyps. Caldesmon staining of well-defined myomatous fascicles was a common finding for type 2 APs; positive caldesmon staining was observed in 97% of type 2 APs but only 8% of type 1 APs (Fig. 4). HMGA2 was positive in the fascicular stalk and myomatous stroma of type 2 APs (56%) and a subset of type 1 APs (10%). Cellular (n = 5) and conventional (n = 16) endometrial polyps were similarly stained and showed variable positivity for desmin, caldesmon, and SMA. In summary, APs had characteristic staining patterns by IHC, with type 1 APs positive for CD10, desmin, and SMA and negative for caldesmon; in contrast, type 2 APs demonstrated strong caldesmon positivity within the central stalk.

### 3.3. *MED12* exon 2 sequencing of APs

Sanger sequencing of exon 2 of the *MED12* gene was attempted on tissue from 55 APs, and 53 (96%) were successfully sequenced, which included 34 type 1 APs, 18 type 2 APs, and 1 AP with mixed type 1 and 2 features. All of the APs (100%; 53/53) demonstrated a wild-type sequence of *MED12* exon 2.

**Table 2** IHC for CD10, desmin, caldesmon, SMA, and HMGA2

| | CD10 | Desmin [a] | Caldesmon [a] | SMA [a] | HMGA2 |
|---|---|---|---|---|---|
| All APs | 100% (72/72) | 97% (70/72) | 47% (34/72) | 95% (40/42) | 31% (18/58) |
| Type 1 | 100% (39/39) | 95% (37/39) | 8% (3/39) | 91% (21/23) | 10% (3/29) |
| Type 2 | 100% (29/29) | 100% (29/29) | 97% (28/29) | 100% (17/17) | 56% (14/25) |
| Mixed | 100% (4/4) | 100% (4/4) | 75% (3/4) | 100% (2/2) | 25% (1/4) |
| Cellular EMPs | 80% (4/5) | 0% (0/5) | 0% (0/5) | 50% (2/4) | 0% (0/1) |
| Conventional EMPs | 100% (16/16) | 50% (8/16) | 6% (1/16) | 25% (4/16) | N/A |

Abbreviation: EMPs, endometrial polyps.

[a] Only strongly diffuse staining of desmin, caldesmon, and SMA was considered a positive result.

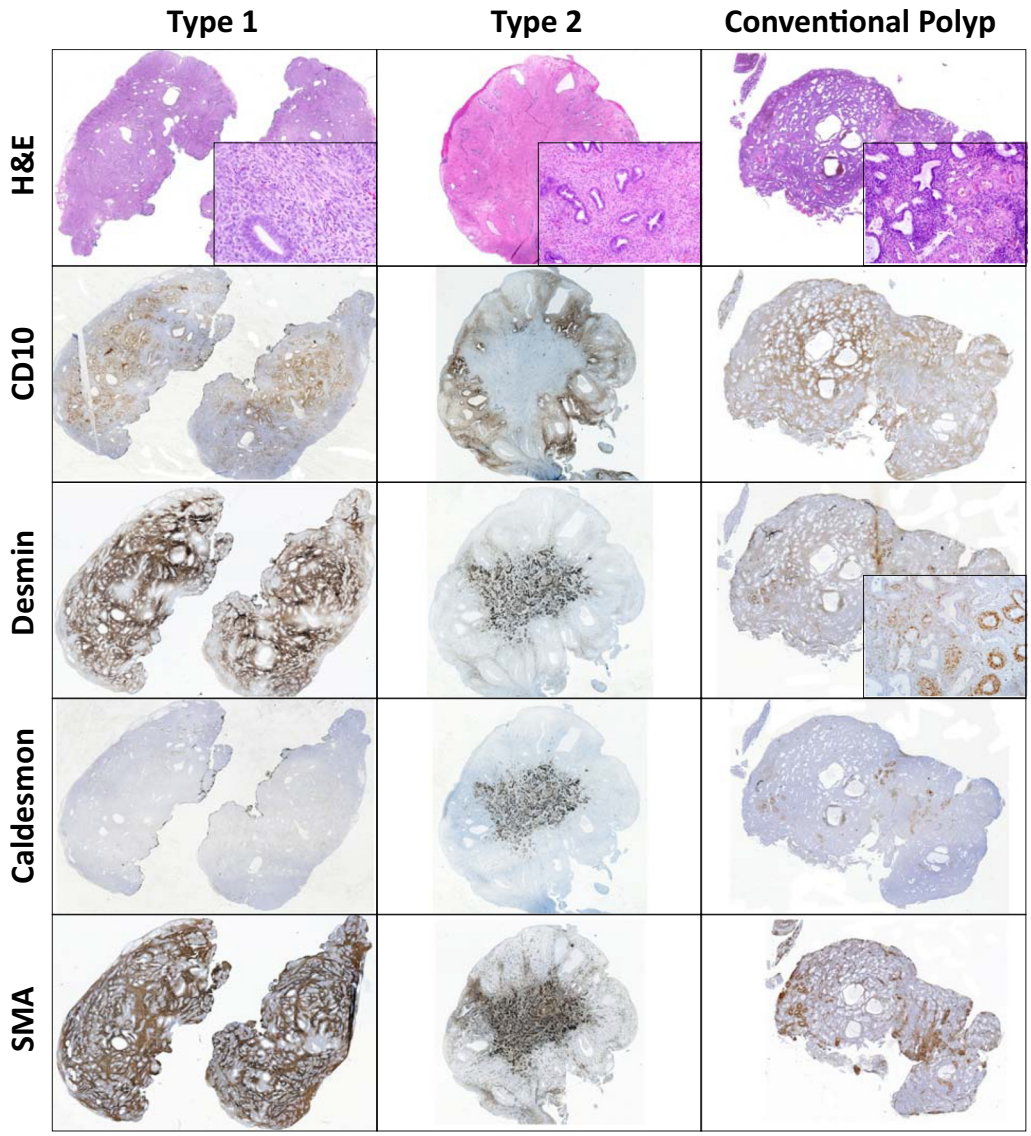


**Fig. 4** IHC of APs. Type 1 APs had cellular, vaguely myomatous stroma that was strongly positive for desmin and negative for caldesmon. Type 2 APs tended to have a hamartomatous appearance, with well-defined caldesmon-positive fascicles and stalks. Conventional polyps showed periglandular staining for desmin in a dot-like cytoplasmic pattern but were negative for caldesmon. Photomicrographs were obtained from ×1 whole-slide scans.

**Table 3** APs seen in consultation

| Differential diagnosis | Percent (no. cases) |
|---|---|
| Adenosarcoma | 21 (13) |
| Atypical polypoid adenomyoma | 15 (9) |
| EMCA/EIN/endometrial hyperplasia | 11 (7) |
| Unusual endometrial polyp | 10 (6) |
| Endometrial stromal tumor | 10 (6) |
| Adenomyoma | 7 (4) |
| Leiomyoma | 5 (3) |
| Adenofibroma | 5 (3) |
| Unusual endocervical polyp | 3 (2) |
| Adenoma malignum | 3 (2) |
| Carcinosarcoma | 3 (2) |
| AP | 2 (1) |
| Adenomyosis | 2 (1) |
| Inflamed decidua | 2 (1) |
| Gestational trophoblastic disease | 2 (1) |
| Total | 61 cases |
| No differential diagnosis provided | 15 cases |
| Incidentally noted at BWH | 9 cases |

NOTE. The listed diagnosis represents the most clinically significant item on the differential provided by the referring pathologist.

### 3.4. Review of APs seen in consultation

There were 85 cases seen in consultation with a diagnosis of AP at BWH. Upon review of consultation request letters, we found that referring pathologists were concerned about a wide range of diagnostic entities (Table 3). A number of cases (15) had no differential diagnosis provided by the referring pathologist, and 9 APs were incidentally noted by BWH pathologists and not the subject of the consultation. Of the 61 cases with a differential diagnosis, a substantial number of letters (21%) indicated that the pathologists considered adenosarcoma.

## 4. Discussion

Historically, APs have been described alongside conventional endometrial polyps and uterine adenomyomas in scientific reports [2,3]. To date, there have not been many studies dedicated to APs as a distinct entity. We identified 2 distinct morphologic types of APs during our histologic review. It is unclear whether prior studies included one or both of these subtypes in their evaluations because this distinction has not been previously described. Type 1 APs appear architecturally similar to conventional endometrial polyps, whereas type 2 APs contain a central leiomyomatous stalk that is strongly caldesmon positive, similar to hamartomatous polyps of the colon. The stalk of type 2 polyps may represent a mesenchymal neoplasm or may simply be a direct extension of the myometrium. In addition to morphologic differences, type 2 APs were associated with a history of hormone replacement therapy compared with type 1 APs ($P = .02$), and there was a trend for type 2 polyps to be larger in size. These differences support a distinct pathogenesis and may have clinical implications.

The differential diagnosis of APs can be quite broad, as evidenced by the consult cases we reviewed. Often, APs can be distinguished from conventional endometrial polyps by histology alone, demonstrating a myomatous endometrial stroma admixed with endometrial glands (with or without the presence of a stalk). In difficult cases or in the research setting, the presence of myomatous stroma can be confirmed by IHC for smooth muscle markers, as shown by our IHC results. APs are distinguished from adenomyomas by the degree of exophytic growth into the uterine cavity. In contrast to APs, adenomyomas are located in the myometrium and are predominantly intramural, although superficial ones may bulge into the space similar to submucosal leiomyomata.

When seen in consultation, concern for adenosarcoma was often in the differential diagnosis with AP. The presence of glandular cuffing and of cytologic atypia with increased mitoses are important clues to distinguishing a subtle adenosarcoma from AP. The precise relationship of type 1 and type 2 APs with atypical polypoid adenomyoma is currently unclear and is not directly addressed by our study, but APs should contain benign-appearing noncrowded glands without worrisome cytologic features. Other entities that were considered included endometrial adenocarcinoma (which were seen to involve APs in a few instances), endometrial stromal sarcoma, carcinosarcoma, leiomyomas, adenoma malignum, adenofibroma, and gestational trophoblastic neoplasm.

Other studies have characterized endometrial polyps that have similar histomorphology to adenosarcomas. A recent study characterized atypical uterine polyps (n = 29) with features suggestive of adenosarcoma (such as phyllodes-like architecture, intraglandular polypoid projections, periglandular stromal alterations, stromal cell atypia, and increased mitoses) [15]. The findings demonstrated that such polyps have a benign clinical course. In another study, endometrial polyps with atypical stromal cells (n = 15) were similarly shown to be indolent [16], and desmin positivity was present in up to 62.5% of polyps stained, suggesting that some APs may have been included in this cohort. Only a single AP in our in-house cohort was diagnosed as an atypical AP, with features bordering on adenosarcoma. In this case, the pathologist recommended follow-up in 6 months with sampling of both cervix and endometrium, with no recurrence documented to date.

The molecular profile of APs has not been addressed by prior studies. We found that APs may have overlap in clinical presentation and immunophenotype with leiomyomas. This is particularly true for type 2 APs, which demonstrated a fascicular myomatous stroma that was strongly positive for SMA, desmin, and caldesmon by IHC. To examine the possibility of whether APs are related to leiomyomas, we performed sequencing of exon 2 of the *MED12* gene. Most uterine leiomyomas (50%-70%) have been found to harbor mutations at this locus, especially at the highly conserved codon 44 [10,13], and mutations of this gene are rarely encountered outside the

gynecologic tract [17]. All of the APs in our study demonstrated wild-type sequences of *MED12* exon 2, suggesting that the pathogenesis of APs is distinct from leiomyomas. Although HMGA2 positivity was more common in type 2 APs, we did not examine APs for *HMGA2* gene rearrangements. At this time, additional molecular studies would be necessary to determine whether APs are true hamartomas or neoplasms. Of note, *MED12* sequencing has been previously performed in cohorts of adenosarcomas (n = 19), finding no alterations within exon 2 [18]. However, the results of this study conflict with another, which identified *MED12* exon 2 mutations in 3 so-called "variant adenosarcomas" [19]. Similar to the APs in our study, *MED12* mutations are not present in adenomyosis or adenomyomas [20], a finding that is compatible with a common pathogenesis for these lesions.

In conclusion, APs are not uncommon in routine diagnostic practice and may represent a diagnostic challenge in some cases. Clinically, most patients present with abnormal uterine bleeding. A large proportion of patients with APs have a history of polyps and/or fibroids, and APs are often mistaken for fibroids on clinical examination. Our study demonstrates that there are 2 distinct types of APs, one of which is similar to conventional endometrial polyps (type 1) and the other has a hamartomatous appearance that is more likely to be associated with hormone replacement therapy (type 2). Awareness of the varied morphologic appearances of APs can help distinguish this entity from clinically worrisome mimics.

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This study has been performed according to the Declaration of Helsinki. Institutional review board approval was obtained. Informed consent was not required for our study.

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