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ARTICLE

Atypical uterine polyps show morphologic and molecular overlap with mullerian adenosarcoma but follow a benign clinical course

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A subset of clinically benign uterine polyps shows atypical morphologic features worrisome for, but not diagnostic of, Mullerian adenosarcoma. We report clinicopathologic data for 63 polyps from 58 women with atypical morphologic features including abnormal architecture, abnormal periglandular stroma, stromal atypia, and mitoses >2 per 10 hpf. Four (11%) of 36 women with follow-up tissue sampling had residual/recurrent atypical polyp. Twelve (27%) of 44 women underwent hysterectomy subsequent to a diagnosis of atypical polyp. No patient developed adenosarcoma over median follow-up of 150 months. Twenty-one primary atypical polyps underwent molecular profiling. Five (24%) harbored chr 12q13-15 gain or amplification, 9/20 (45%) harbored chr 6q25.1 gain, and 7/21 (33%) had no significant copy number alterations. Gains of chr 1q, chr 8p12, and chr 10q11.21-23, amplifications of chr 12q24.12-13, chr 15p24.1-26.1, and chr 18q21.33, and loss of chr 7 and chr 11q21 were each seen in a single polyp. Mean tumor mutational burden was 3.1 (range, 0.76–8.365) mutations/Mb. Pathogenic point mutations were identified in 12/20 (60%) primary atypical polyps. We propose the term "atypical uterine polyps" for these lesions, which show biologic overlap with early Mullerian adenosarcoma but lack molecular alterations characteristic of clinically aggressive adenosarcoma and appear to follow a benign clinical course. Conservative management with close clinical follow-up and repeat sampling can be considered for these lesions, when clinically appropriate.

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INTRODUCTION

Uterine polyps are benign monoclonal mesenchymal neoplasms[1], comprising fibrous stroma admixed with histologically unremarkable non-neoplastic endometrial or endocervical glands. They occur across a wide age range but are most often seen in the perimenopausal period[2–4]. Multiple synchronous or metachronous polyps are not uncommon and may, in some cases, represent a single, clonal, clinically benign neoplasm[5].

Endometrial polyps fall into distinct molecular subgroups[6]. Approximately half harbor recurrent rearrangements of chr 6p21 or chr 12q13-15, resulting in overexpression of mesenchymal growth factors HMGA1 and HMGA2, respectively[1,6–13]. Amplification of chr 12q13-15 has been described in a single endometrial polyp[14] but is considered exceptionally rare. Conversely, approximately half of endometrial polyps show no cytogenetic abnormalities[6] and may be related to altered estrogen signaling or to recurrent pathogenic point mutations in oncogenes, including *KRAS*, *PPP1R2A*, and *ARHGAP35*[15,16]. However, the precise pathogenic role of these point mutations is unclear[15,17]. The pathogenesis of endocervical polyps is less well characterized, but may also be related to excess estrogen[3].

Uterine adenosarcoma is a malignant neoplasm of endometrial or, less often, endocervical stroma[18,19]. Like conventional benign uterine polyps, adenosarcoma presents as a polypoid mass and occurs across a wide age range, most frequently in the perimenopausal or early postmenopausal period[18–22]. However, adenosarcomas are, on average, larger than benign uterine polyps[18,19,23] and show malignant histologic features, including phyllodiform architecture, periglandular cuffing by hypercellular stroma with subepithelial stromal condensation, stromal atypia, and increased stromal mitoses[18,19]. Most uterine adenosarcomas show relatively indolent behavior, with an overall 20–30% risk of recurrence[18,22,24]. However, a subset show features associated with more aggressive clinical behavior, including myometrial invasion, sarcomatous overgrowth, or high-grade stromal atypia[18,19,22,25,26].

Uterine adenosarcomas are molecularly heterogeneous. Recurrent copy number alterations have been reported, including amplification of chr 12q13-15 (including *MDM2, CDK4*, and *HMGA2*), *TERT, MYBL1*, and *BCL2*[23,27–30]. However, each of these alterations is seen in a minority of adenosarcomas. Recurrent point mutations in *BCOR*, *ROS1*, *TP53*, and *ATRX* are also described in minor subsets[23,27,30], and *TP53* and *ATRX* mutations are associated with high-grade morphology and adverse outcome[23,26].

The vast majority of histologically banal endometrial and endocervical polyps follow a benign clinical course. However,

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recurrent endocervical[20,31,32] or endometrial[18] polyps may precede diagnosis of adenosarcoma, suggesting that uterine adenosarcoma may in some cases develop from a histologically unremarkable polyp. A potential relationship between banal polyps and adenosarcoma is further suggested by a subset of uterine polyps with intermediate histologic features, which are worrisome for adenosarcoma, but quantitatively or qualitatively insufficient for an adenosarcoma diagnosis. Such worrisome histologic features can include abnormal architecture, abnormal periglandular stroma, stromal atypia, and/or increased mitotic activity, which may be focal or diffuse within the polyp. These atypical uterine polyps pose a considerable diagnostic problem with significant therapeutic implications, particularly in women of childbearing age. In an earlier study of 27 women with atypical uterine polyps, 2 had a recurrent atypical polyp on follow-up, but none progressed to adenosarcoma or had an adverse disease-related outcome[33]. However, clinicopathologic data on atypical uterine polyps is confined to a single study, and their molecular features have not been described.

We hypothesized that atypical uterine polyps could represent (1) incipient adenosarcomas, (2) unusual morphologic variants of conventional uterine polyps, (3) a distinct molecular entity, or (4) a heterogeneous group comprising a combination of these. To examine these hypotheses, we evaluated 22 atypical uterine polyps by targeted next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or both. To better characterize their behavior, we also provide clinicopathologic data on 58 women with atypical uterine polyps.

MATERIALS AND METHODS

Cohort

This study was approved by the institutional review board at Brigham and Women's Hospital. The cohort comprised 63 (58 primary; 5 residual/recurrent) atypical uterine polyps from 58 women (including additional follow-up information on 29 previously reported atypical uterine polyps from 27 women[33]). Novel cases were identified from the electronic pathology database using combinations of the terms (1) "polyp"; (2) "atypical" or "unusual"; and (3) "endometrial," "endometrium," "endocervical," "endocervix," "uterine," or "uterus." The resulting pathology reports were manually reviewed, identifying 43 additional candidate atypical uterine polyps diagnosed between 2005 and 2020.

Clinical and morphologic parameters

All available hematoxylin and eosin (H&E)-stained slides were reviewed. For study inclusion, a polyp needed to show at least one of the following atypical features, albeit insufficiently qualitatively or quantitatively developed for diagnosis of adenosarcoma: (1) abnormal architecture (early or focal phyllodiform growth, rigid cystic glands, and/or intraluminal papillary projections); (2) abnormal periglandular stroma (mild or focal periglandular stromal cuffing and/or subtle subepithelial condensation); (3) stromal atypia (characterized by enlarged hyperchromatic nuclei with smudged chromatin, as previously described[34]). Stromal mitotic count was also noted, with >2 mitoses per 10 high-power fields (hpf; 40x objective, field diameter 0.55 mm, 10 hpf = 2.4 mm^2) considered increased; however, increased mitotic count in the absence of other atypical features was insufficient for study inclusion. Out of 43 candidate atypical polyps, 34 (20 in-house, 14 consults) met morphologic inclusion criteria.

Clinical parameters, including patient age, relevant medical history, presenting signs/symptoms, site and sampling technique for initial diagnostic specimen, follow-up type and interval, subsequent uterine pathology, and outcome were obtained from the electronic medical record. Two types of follow-up were considered: (1) "pathological follow-up," defined by repeat uterine tissue sampling or hysterectomy with pathological examination; and (2) "clinical follow-up," defined by ongoing medical observation, providing information about the patient's clinical disease status and survival. Polyp size was determined by clinical, radiographic, and/or pathologic examination. Morphologic parameters evaluated in each polyp included individual atypical features (see inclusion criteria, above), the extent of polyp involvement by atypical features, and epithelial differentiation. Morphologic assessment for study inclusion was performed by two gynecological pathologists (B.E.H. and M.R.N. for 29 previously reported polyps; D.B.C. and M.R.N. for 34 novel polyps).

Immunohistochemistry

Immunohistochemical assay conditions are described in SupplementaryTable 1. Twenty-eight polyps were evaluated by HMGA2 immunohistochemistry. Six polyps were excluded due to insufficient tissue. Two polyps with *MDM2* amplification by FISH (see below) were evaluated by MDM2 immunohistochemistry. HMGA2 and MDM2 overexpression were defined by strong diffuse nuclear staining. Twenty-one polyps with NGS data were evaluated by ER and PR immunohistochemistry. The extent of ER and PR expression in periglandular stromal cells was classified as diffuse (≥90%) or patchy (<90%).

Fluorescence in situ hybridization

HMGA2 fluorescence in situ hybridization (FISH) was performed on 8 polyps with positive HMGA2 immunostaining, and *MDM2* FISH was performed in both polyps with *HMGA2* amplification. FISH analysis was performed on 4 µm tissue sections and evaluated using laboratory-developed, clinically validated dual-color break-apart *HMGA2* probes specific for the 5′ and 3′ regions of 12q14.3, and with *MDM2* at 12q15 and D12Z3 (chromosome 12 alpha satellite probe) at 12p11.1-q11.1 (Abbott Molecular; Abbott Park, IL, USA). Labeling and hybridization of the probes were performed according to standard laboratory protocols. FISH results were evaluated in tumor areas marked by a gynecological pathologist (D.B.C.). Copy number gain was defined by 3 or 4 gene copies, and amplification was defined by ≥5 gene copies.

Next-generation sequencing

Twenty-three polyps were analyzed by hybrid capture NGS on the 447-gene OncoPanel platform[35]. Each case was annotated for point mutations, small insertions and deletions, and copy number alterations. Variants were filtered to remove technical artifacts, synonymous variants, and any population variants at >0.1% frequency in the Genome Aggregation Database (https://gnomad.broadinstitute.org/), and the remaining pass-filter variants were assessed for likely pathogenicity by a molecular pathologist (L.M.S.). Copy number alterations were determined with an internally developed pipeline (RobustCNV). Copy number of ≥6 was defined as "amplification," whereas lesser copy number gains were classified as "gains." *HMGA2* was not included in the gene panel, though chr 12q13-15 (including the chr 12q14.3 band containing *HMGA2*) was tiled for copy number calling. Accordingly, *HMGA2* copy number alterations were inferred from alterations in flanking genes. NGS Sequencing data from this study are publicly available through the AACR Genie database.

RESULTS

Clinical findings and outcomes

Clinical data are summarized in Table 1. Detailed clinical and morphologic data on all patients are in Supplementary Table 2. The final cohort included 63 (58 primaries, 5 residual/recurrent) atypical uterine polyps from 58 women, ranging from 23–75 (mean, 50) years old. Twenty-nine women (50%) presented with abnormal uterine bleeding (including 12 with postmenopausal bleeding), 21 (36%) presented with a polyp on clinical examination or ultrasound, and 8 (14%) were discovered incidentally on workup for other indications. Forty-seven (81%) women had endometrial polyps, compared with 11 endocervical. Forty-two (72%) were diagnosed by endometrial biopsy, curettage, and/or polypectomy, 15 (26%) by endocervical curettage and/or polypectomy, 3 (5%) in hysterectomy specimens, and 1 was spontaneously passed.

Follow-up was available for 47 patients (Fig. 1). (All 11 cases without follow-up information came from authors' consultation files.) In 3 women, atypical uterine polyp was diagnosed at hysterectomy, obviating further pathological follow-up. Of the remaining 44 women at risk for residual or recurrent disease, 8 (18%) had no further tissue sampling, whereas 36 (82%) had follow-up pathological examination, including curettage in 28 (78%) and hysterectomy in 8 (22%). The median time from the initial diagnosis to first follow-up pathological examination was 3 months (range, 0.3–104 months; interquartile range, 1.1–6.9 months).

Table 1. Clinical and outcomes data.

Location	
Endometrium	47 (81%)
Endocervix	11 (19%)
Age range (mean), in years	23–75 (50)
Presenting signs/symptoms	
Abnormal uterine bleeding	29 (50%)
Polyp on clinical exam or ultrasound	21 (36%)
Incidental	8 (14%)
Initial uterine sampling	
Endometrial biopsy/curettage/polypectomy	42 (72%)
Endocervical curettage/polypectomy	15 (26%)
Hysterectomy	3 (5%)
Spontaneously passed	1 (2%)
Follow-up uterine sampling	
Not performed	8 (18%)
Endometrial/endocervical curettage	28 (48%)
Hysterectomy	8 (14%)
Not applicable due to hysterectomy at initial diagnosis	3 (5%)
Unknown	11 (19%)
Diagnosis at follow-up sampling ($n = 36$)	
No lesion	16 (44%)
Banal polyp	16 (44%)
Atypical uterine polyp	4 (12%)
Clinical follow-up, in months	
Median	150
Range	2–350
Interquartile range	55–186
Clinical outcome	
Alive, no evidence of disease	46 (79%)
Dead of other cases	1 (2%)
Unknown	11 (19%)

Among 36 women undergoing follow-up pathological examination, 16 (44%) had no lesion identified, 16 (44%) had a morphologically conventional polyp, and 4 (11%) had residual or recurrent atypical uterine polyp (including 1 patient with 2 recurrences). The 4 instances of residual/recurrent atypical uterine polyp were diagnosed at 1, 5, 7, and 11 months after initial diagnosis (see supplementary information 1). Four more women underwent a hysterectomy after initial follow-up curettage (that showed no lesion in 1, banal polyp in 2, and atypical polyp in 1), for a total of 12/44 women (27%) undergoing hysterectomy subsequent to a diagnosis of atypical uterine polyp.

No patient developed uterine adenosarcoma over median pathological follow-up of 7.5 months (range, 0.7–115 months; interquartile range, 3–14 months) and median clinical follow-up of 150 months (range, 2–350 months; interquartile range, 55–186 months). No patient received adjuvant radiation or chemotherapy. At last follow-up, 46 women were alive with no evidence of disease, and 1 woman had died of pancreatic ductal adenocarcinoma 25 months after diagnosis of atypical uterine polyp.

Gross and microscopic findings

Pathological findings in the 58 primary atypical uterine polyps are summarized in Table 2. Representative photomicrographs are shown in Fig. 2. Clinicopathologic features of the 5 residual/recurrent atypical polyps are detailed in Supplementary Information 1. Due to frequent specimen fragmentation, size could be determined in only 21 polyps (median, 2.4 cm, range, 0.5–5.8 cm). Abnormal architecture was present in 46 (79%), including early or focal phyllodiform architecture ($n = 32$) and/or rigid cystic glands ($n = 29$). Mild or focal periglandular stromal cuffing was seen in 44 (76%), including foci of subtle subepithelial stromal condensation in 13. Mitoses ranged from 0–16 (median 1, mean 2) per 10 hpf, with greater than 2 mitoses per 10 hpf in 16 (28%). Mitotic activity was higher in endometrial polyps (median, 1 per 10 hpf; range, 0–16) than in endocervical polyps (median, 0 per 10 hpf, range 0–4), though the difference was not statistically significant ($P = 0.19$, Mann–Whitney U test, two-tailed). (Out of 7 endometrial polyps with ≥6 stromal mitoses per 10 hpf, 6 also harbored epithelial mitoses and proliferative-pattern glands, and 1 patient was on tamoxifen for prior breast cancer). Stromal atypia was seen in 10 (17%), characterized by enlarged, irregular, hyperchromatic nuclei with smudged chromatin, single nucleoli, occasional nuclear pseudo inclusions, and (in one case) multinucleation. No heterologous elements were identified. Fourteen (24%) polyps showed 1 atypical feature (including 7 endometrial polyps with stromal atypia only), 30 (52%) showed 2 atypical features, and 14 (24%) showed 3 atypical features. No polyp showed all 4 atypical features. It is emphasized that the atypical features in these polyps though worrisome, were insufficiently developed to warrant diagnosis of adenosarcoma on consensus morphologic review by subspecialty gynecologic pathologists.

No clinical or morphologic features—including age, number, type, or distribution of atypical features; or interval from the initial diagnosis to pathologic follow-up—were significantly associated with the presence of residual/recurrent atypical polyp on follow-up sampling. In the 4 patients with residual/recurrent polyp on follow-up sampling, the residual/recurrent polyp in each case showed the same atypical morphologic feature(s) noted in the initial atypical polyp. In 2 of 4 cases, the atypical morphologic features more extensively involved the residual/recurrent polyp compared with the initial polyp specimen. However, complete histologic examination of both residual/recurrent polyps (both from hysterectomy specimens) showed that the atypical morphologic features still fell qualitatively short of the threshold for diagnosis of adenosarcoma.

Immunohistochemical and molecular findings

Immunohistochemical and molecular findings are represented in Fig. 3. Point mutations are detailed in Table 3. In total, HMGA2 immunohistochemistry was performed on 28 polyps with available tissue. Successful molecular profiling was performed on 22 (21 primary and 1 residual/recurrent) atypical uterine polyps, including NGS alone in 17, FISH alone in 1, and both assays in 4.

Stromal cells in 8 (29%) of 28 polyps showed immunohistochemical HMGA2 overexpression (Figs. 4, 5). In polyps only partially involved by atypical morphologic features, HMGA2 has overexpressed in the morphologically unremarkable as well as the morphologically atypical foci. The glandular component of all polyps showed negative to patchy weak HMGA2 expression, interpreted as nonspecific[7].

HMGA2 FISH was successfully performed in 5 primary atypical uterine polyps with immunohistochemical HMGA2 overexpression (3 polyps failed hybridization − 1 each from 2010, 2011, and 2017). FISH confirmed *HMGA2* copy number gain ($n = 2$) or amplification ($n = 2$) in 4 of 5 polyps (Figs. 4, 5, Supplementary Table 3), and identified no apparent copy number alteration in the remaining polyp. No *HMGA2* rearrangements were identified. *MDM2* FISH was performed in both polyps with *HMGA2* amplification and confirmed co-amplification of *MDM2* and *HMGA2* in both. MDM2 overexpression was confirmed in both by immunohistochemistry (Figs. 4, 5, Supplementary Table 3).

NGS was successfully performed in 20 primary atypical uterine polyps and 1 residual/recurrent atypical polyp (2 polyps failed quality control − 1 each from 2010 and 2019). NGS identified 0-5

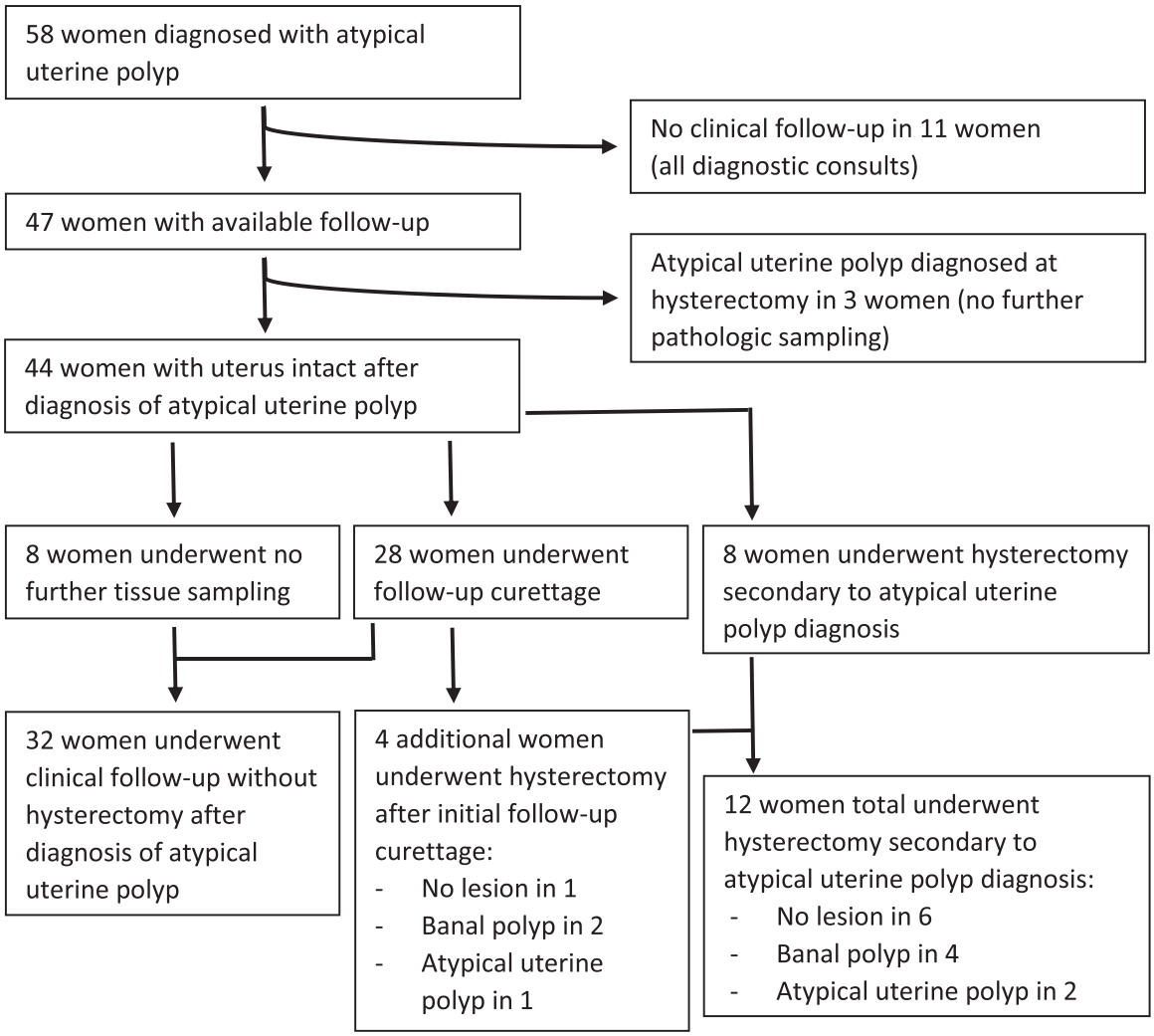

Fig. 1 Patient management diagram. Comprehensive procedural and pathologic outcomes for 58 women with atypical uterine polyp.

(median, 1) copy number alterations per polyp. Three recurrent copy number profiles were identified:

1. Chr 12q13-15 gain or amplification (3-8 copies) was seen in 6 (27%) of 22 polyps (including 1 residual/recurrent atypical polyp) and varied in size from chr 12q13.2-q15 amplification (polyp #1; see Fig. 3) to isolated chr 12q14.3 (*HMGA2*) amplification (#4; confirmed by FISH). FISH and NGS yielded concordant *HMGA2* copy number calls in 3 of 4 polyps evaluated by both techniques (Fig. 5), with 1 discordant call attributed to inadequate NGS coverage of a small chr 12q14.3 amplicon. Of 6 polyps with positive HMGA2 IHC and molecular profiling, *HMGA2* gain or amplification was present in 4 and absent in 2. *MDM2* FISH and NGS showed concordant *MDM2* amplification in 2 of 2 cases evaluated by both techniques. Supplementary Table 3 provides detailed correlation of immunohistochemical, FISH, and NGS results for *HMGA2* and *MDM2*.

   One polyp (#1) with chr 12q13-15 amplification (estimated 8 copies) also showed low-level whole-arm gain of chr 1q (estimated 1-2 copy gain), whole-chromosome loss of chr 7 (estimated 1 copy deletion), amplification of chr 12q24.12-13 (estimated 8 copies), amplification of chr 15p24.1-26.1 (estimated 12-25 copies), and amplification of chr 18q21.33 (*BCL2*; estimated 21 copies). On consensus morphologic re-review, this polyp showed features considered borderline between atypical uterine polyp and adenosarcoma (Supplementary Fig. 1).
2. Low-level copy number gain (estimated 2.5-5 copies) of chr 6q25.1 (*ESR1*) was detected in 9 primary and 1 residual/recurrent atypical uterine polyps across 3 sequencing runs. There was no difference in immunohistochemical expression of ER or PR in the stroma of polyps with versus without *ESR1* gain (Supplementary Fig. 2). One polyp (#6) showed *ESR1* gain as well as chr 14q32.12 (*SERPINA1*) amplification (estimated 6 copies). One pair of primary (#5a) and residual/recurrent (#5b) polyps showed both *ESR1* gain and chr 12q14.1 (*CDK4*; estimated 3 copies) gain.
3. Seven polyps showed no significant copy number alterations. Two of these (#15, 17) showed immunohistochemical HMGA2 overexpression, suggesting that this pathway may be activated by alternative mechanisms in a subset of atypical polyps with apparently silent copy number profiles. All 6 polyps with chr 12q13-15 gain or amplification and both polyps with immunohistochemical HMGA2 overexpression but no apparent copy number gains were endometrial, suggesting that HMGA2 pathway activation may be site-specific. Both endocervical and endometrial polyps were represented in the molecular subgroups with chr 6q25.1 (*ESR1*) copy number gain and with no significant copy number alterations.

Table 2. Morphologic data.

Size range (median), in cm	0.5–5.8 (2.4)
Atypical morphologic features	
Abnormal architecture	46 (79%)
Abnormal periglandular stroma	44 (76%)
Mitoses >2 per 10 hpf	16 (28%)
Stromal atypia	10 (17%)
Number and combiantions of atypical features	
1	**14 (24%)**
Abnormal architecture only	2
Abnormal periglandular stroma only	5
Stromal atypia only	7
2	**30 (52%)**
Abnormal architecture and periglandular stroma	26
Abnormal architecture and stromal atypia	1
Abnormal architecture and increased mitoses	3
3	**14 (24%)**
Abnormal architecture, periglandular stroma, and increased mitoses	12
Abnormal architecture, periglandular stroma, and stromal atypia	1
Abnormal architecture, stromal atypia, and increased mitoses	1
4	**0**
Polyp involvement by atypical features	
Partial	43 (74%)
Diffuse	15 (26%)
Epithelial differentiation	
Tubal	**44 (76%)**
Mixed tubal & mucinous	9
Mixed tubal & secretory	1
Mixed tubal & proliferative	3
Mucinous	**1 (2%)**
Secretory	**1 (2%)**
Banal inactive endometrial glands	**10 (17%)**
Banal endocervical glands	**2 (3%)**

The bold values represent total numbers (e.g., 14 patients had only 1 atypical feature), whereas the non-bolded numbers in the rows below each bolded number represent the breakdown of that sum (e.g., of 14 patients with only 1 atypical feature, 2 had abnormal architecture only, 5 had abnormal periglandular stroma only, and 7 had stromal atypia only).

Two polyps showed unique copy number profiles, not belonging to the above-defined subgroups. One polyp (#13, representing the patient's second recurrence of an atypical endocervical polyp) showed copy number gains at chr 8p12 (*NRG;* estimated 3-4 copies) and chr 10q11.21-23 (*RET*, *ERCC6;* estimated 3 copies). The other (#14) showed copy number loss at chr 11q21 (MRE11A; partial 1 copy deletion, spanning the 5' end of the gene to exon 10), as well as a pathogenic *KRAS* mutation. No polyp had alterations associated with aggressive clinical behavior in adenosarcoma, including *MYBL1* amplification, *CDKN2A* deletion, *BAP1* deletion, *TP53* deletion or mutation, *RB1* deletion, *ATRX* mutation, or *DICER1* mutation.

Among 20 primary atypical uterine polyps sequenced by NGS, median tumor mutational burden was 3.04 (range, 0.76-8.37) mutations/Mb. Pathogenic point mutations in oncogenes and/or tumor suppressor genes were identified in 13 polyps (see Table 3). Of 7 polyps with stromal atypia only, 4 underwent successful molecular profiling: 2 (#11, 12) showed *ESR1* gains only, 1 (#2) showed chr 12q13-15 amplification only, and 1 (#4) showed *ESR1* gain and chr 12q13-15 amplification. The 2 residual/recurrent lesions profiled by NGS (#5b, 13) had unique molecular profiles, precluding identification of molecular features associated with recurrence. One pair of matched primary and residual/recurrent polyps (#5a, 5b) showed identical molecular profiles, supporting a clonal relationship.

DISCUSSION

This study comprises related clinicopathologic and molecular components:

1. A comprehensive clinicopathologic profile of 58 women with uterine polyps showing atypical features non-diagnostic of adenosarcoma, expanding upon a prior cohort of 28 cases reported from our institution[33].
2. A molecular profile of 22 atypical uterine polyps, using a targeted NGS panel, FISH, and immunohistochemistry to explore the biologic relationship of our atypical uterine polyps to reported molecular features of conventional benign endometrial polyps and uterine adenosarcoma.

Comprehensive clinicopathologic profiling of 58 women with atypical uterine polyps confirms the clinical and morphologic characteristics reported previously[33]. Although we found a modest (11%) risk of residual/recurrent atypical polyp at short-term follow-up, none of our cases progressed to uterine adenosarcoma, despite long-term follow-up (median, 12.5 years) and conservative (i.e., non-hysterectomy) management in two-thirds of patients. Architectural abnormalities are the most common atypical morphologic feature, closely followed by abnormalities of periglandular stroma, with these two features often co-occurring. Increased mitoses are seen in a minority, principally in endometrial polyps from women in the proliferative phase of the endometrial cycle, and were never the sole atypical feature. Atypical uterine polyps (median, 2.4 cm; range, 0.5–5.8 cm) were, on average, significantly smaller than adenosarcomas (mean, 6.3 cm; range, 2–12 cm) seen at our institution[23].

Molecular profiling identifies three principal subgroups of atypical uterine polyps: (1) atypical polyps with chr 12q13-15 gain or amplification, (2) atypical polyps with chr 6q25.1 gain, and (3) atypical polyps with no detectable copy number alterations. Our atypical polyps shared multiple recurrent molecular alterations with low-grade uterine adenosarcoma, but they harbored fewer total copy number alterations per polyp (range, 0–5; median, 1) than previously reported in low-grade adenosarcoma (range, 0–12; median, 3)[23]. Together, these findings indicate that at least some atypical uterine polyps may represent incipient uterine adenosarcomas.

HMGA2 overexpression is a shared feature of morphologically conventional endometrial polyps, atypical uterine polyps, and adenosarcomas. Variably sized gains or amplification of chr 12q13-15 (harboring *HMGA2*) were identified in 5 (24%) of 21 primary atypical uterine polyps, falling within the 24-33% prevalence of this alteration in uterine adenosarcoma[23,27,30]. Chr 12q13-15 amplifications occur in the full clinical-morphologic spectrum of adenosarcomas, including tumors with and without sarcomatous overgrowth and tumors with and without local or distant recurrence[23,26,27,29,36]. In contrast, chr 12q13-15 amplification is exceptionally rare in conventional endometrial polyps[14], that instead harbor chr 12q14.1 (*HMGA2*) rearrangement[6,7,10–13]. Furthermore, approximately 30% of banal endometrial polyps[7], 10% of atypical uterine polyps, and 25% of adenosarcomas[29] show immunohistochemical HMGA2 overexpression in the absence of *HMGA2* rearrangement or amplification, which may result from dysregulation of key

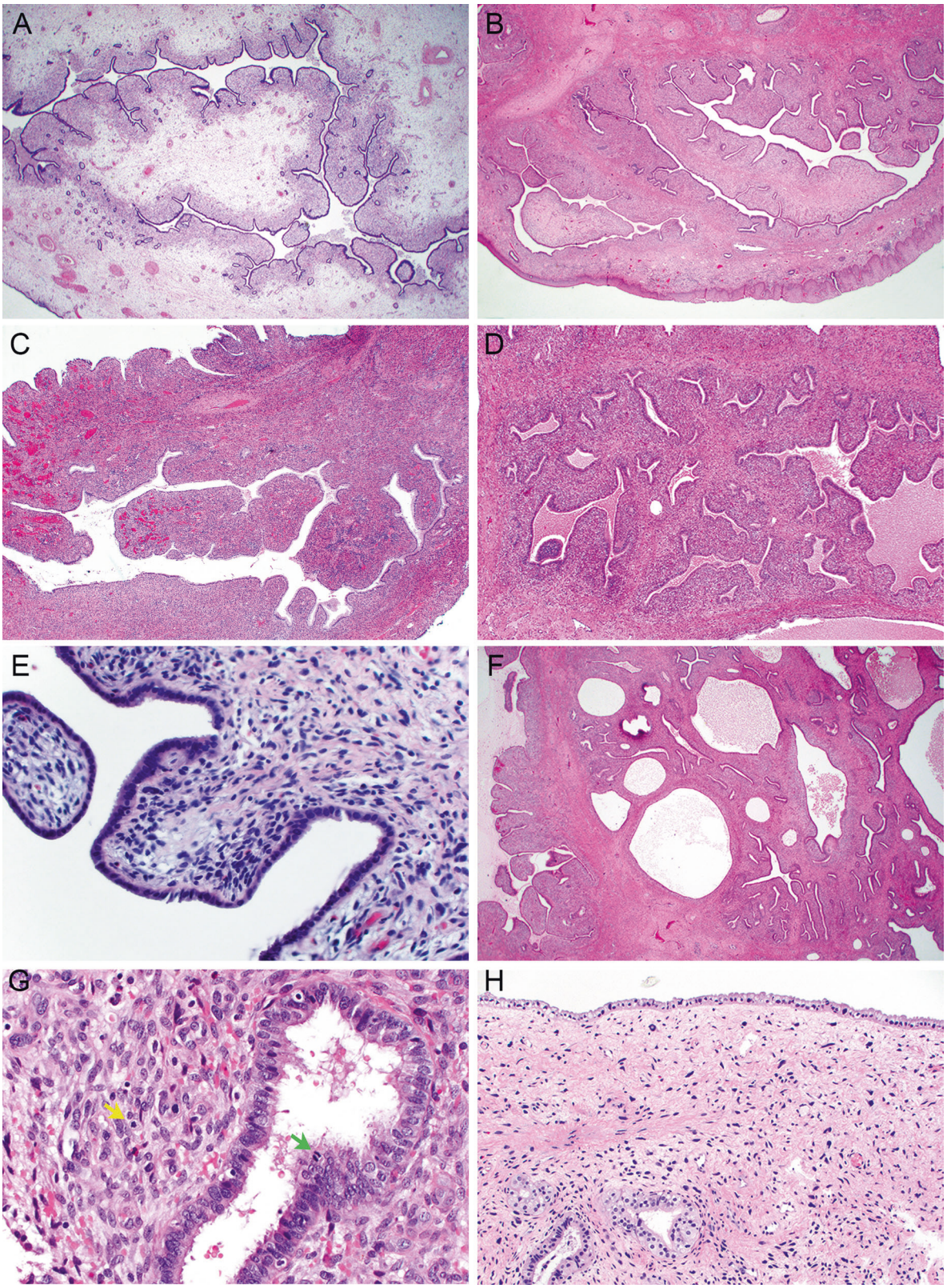

Fig. 2 Morphologic features in atypical uterine polyps. A Focal phyllodiform growth with periglandular stromal cuffing in an edematous stromal background (Case 22, 20x). **B** Focal phyllodiform growth with subtle periglandular stromal cuffing (Case 10, 20x). **C** Focal phyllodiform growth and blunt papillary surface projections, without significant periglandular stromal changes (Case 6, 20x). **D** Periglandular stromal cuffing with blunt intraglandular papillary projections, but without overt phyllodiform architecture (Case 13, 40x). **E** Subtle subepithelial stromal condensation (Case 14, 400x). **F** Rigid dilated cystic glands (center) and blunt surface papillary projections (left), with subtly increased periglandular stromal cellularity (Case 10, 20x). **G** Increased stromal mitoses (yellow arrow) were, in most cases, seen concurrent to increased epithelial mitoses (green arrow) (Case 20, 400x). **H** Moderate stromal cytologic atypia (Case 11, 200x).

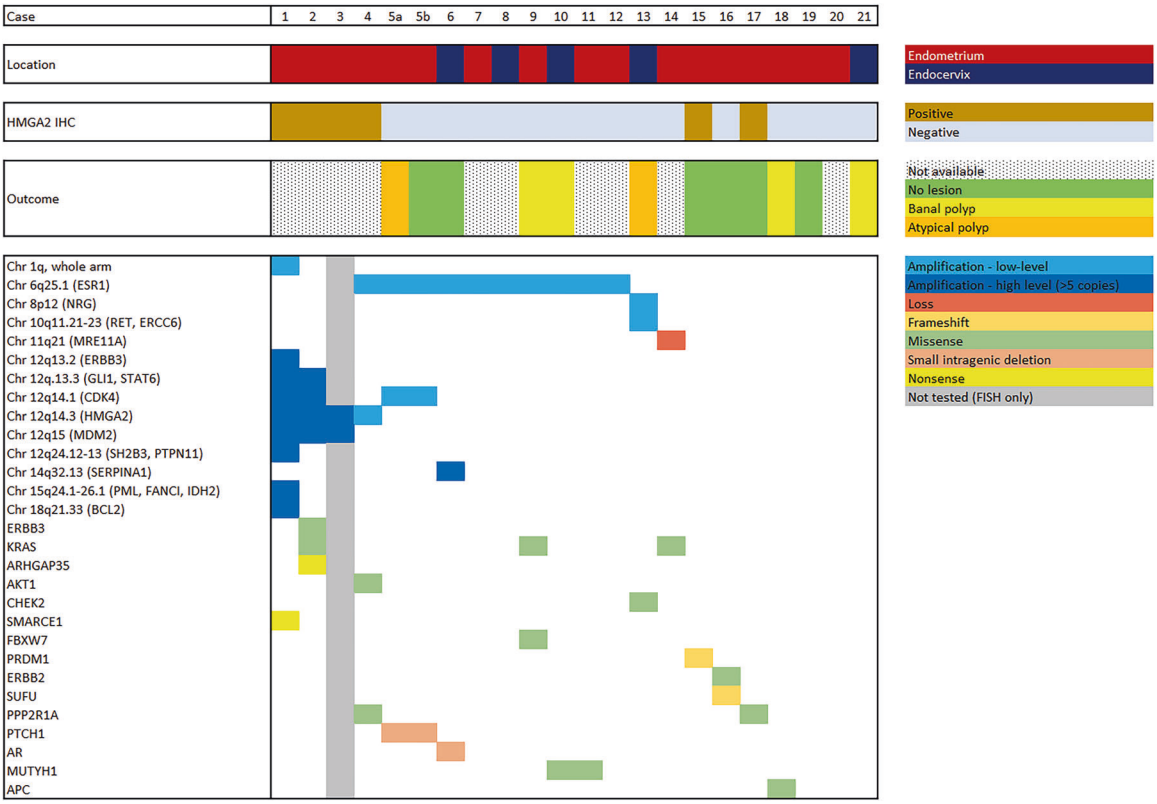

Fig. 3 Molecular, immunohistochemical, and clinical data for 22 polyps profiled by targeted NGS and/or *HMGA2* FISH.

Table 3. Pathogenic point mutations and small insertion-deletion events identified by targeted next-generation sequencing in 21 atypical uterine polyps.

Gene	Polyp	Mutation
AKT1	4	p.E17K
APC	18	p.I1307K
AR	6	p.Q88del
ARHGAP35	2	p.E371*
CHEK2	13	p.I157T
ERBB2	16	p.R475W
ERBB3	2	p.V104M
FBXW7	9	p.R465C
KRAS	2, 9, 14	p.G12D, G12V, G13D
MUTYH1	10, 11	p.G393D, E480del
PPP2R1A	4, 17	p.S256F, R183Q
PRDM1	15	p.L562Ffs*5
PTCH1	5a, 5b	42 bp insertion in exon 3
SMARCE1	1	p.S389*
SUFU	16	p.T196Pfs*39

For genes mutated in multiple polyps, specific mutations are shown in order respective to the polyps listed in the neighboring column.

miRNAs or from *HMGA2* truncation in exon 3, leading to evasion of miRNA-mediated gene silencing[37–39].

One atypical uterine polyp (#1) harbored chr 12q13-15 amplification alongside a whole-arm gain of chr 1q, chr 12q24.12-24.13 amplification, chr 15q24.1-26.1 amplification, and chr 18q21.33 amplification. Three of these copy number alterations have been reported in adenosarcoma: Chr 1q gain has been reported in adenosarcomas with low-grade and high-grade morphology, with and without sarcomatous overgrowth, and with and without local or distant recurrence[23,27,30]. Chr 12q24.12-24.13 amplification has been reported in 10–40% of adenosarcomas, likewise spanning the spectrum of morphologic grade and clinical behavior[23,30]. And high-level amplification of chr 18q21.33 (*BCL2*) was found in ~25% of adenosarcomas in one series[30]. Tellingly, on consensus morphologic re-review, this lesion was difficult to classify, with features worrisome but indeterminant for adenosarcoma. The concordance of particularly worrisome morphologic features and multiple adenosarcoma-like molecular alterations further supports a biological continuum between atypical uterine polyp and adenosarcoma.

Chr 6q25.1 copy number gain (including *ESR1*, encoding the estrogen receptor) was detected in 9 (45%) of 20 primary atypical uterine polyps sequenced by NGS. Chr 6q24.3-q25.3 gains were reported in 2 of 10 adenosarcomas (both morphologically low-grade, without recurrence) studied by whole-genome sequencing in one series[30], suggesting that this subset of atypical uterine polyps may also be molecularly related to adenosarcoma. An adenosarcoma with *ESR1-NCOA3* fusion has also been reported[36]. Chr 6q25.1 copy number alterations have not been described in endometrial polyps[15].

Seven (33%) of 21 primary atypical uterine polyps showed no copy number alterations. Likewise, minor subsets of morphologically banal endometrial polyps[6] and low-grade uterine adenosarcomas[23,28] also show "quiet genomes," without significant copy number alterations. In uterine adenosarcoma, absence of copy number alterations has been associated with indolent behavior. In one study of 18 adenosarcomas, all 4 lesions with no copy number alterations lacked sarcomatous overgrowth and none recurred[23]. Conversely, copy number alterations are significantly greater in adenosarcomas with high-grade stromal atypia and sarcomatous overgrowth[23,29,36]. In our cohort, 2 of 6 atypical uterine polyps with at least 1 copy number alteration had residual/recurrent lesion on follow-up sampling,

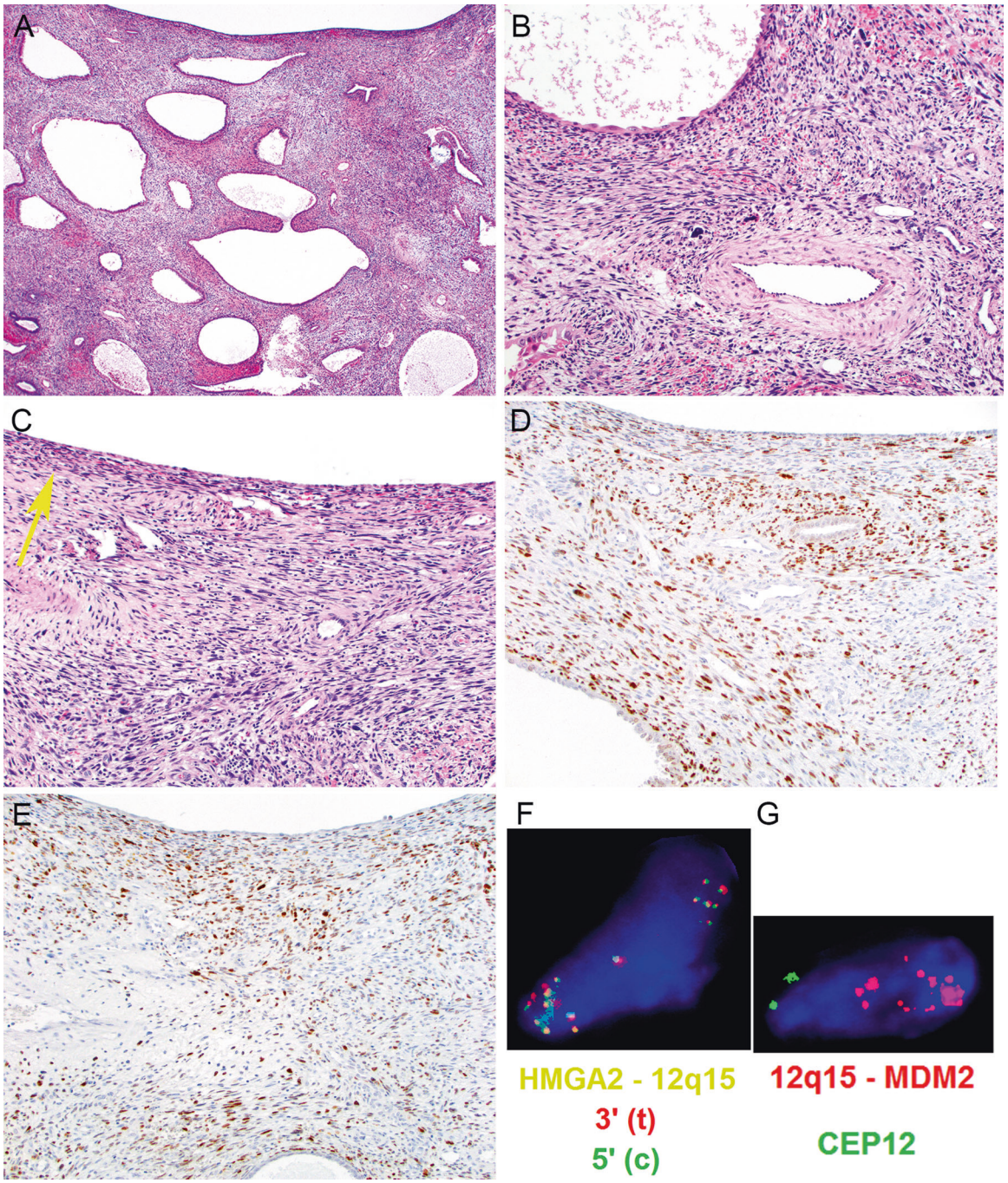

Fig. 4 Morphologic, immunohistochemical, and molecular profiling of an atypical uterine polyp (Case 3). A Subtle periglandular stromal hypercellularity. **B** Scattered atypical nuclei with hyperchromatic smudged chromatin. **C** Subtle subepithelial stromal condensation (**C**, upper left, arrow) (200x). **D** Stromal cell HGMA2 overexpression by immunohistochemistry (200x). **E** Stromal cell MDM2 overexpression by immunohistochemistry (200x). **F** Breakapart *HMGA2* FISH shows *HMGA2* amplification without evidence of *HGMA2* rearrangement. **G** *MDM2* FISH shows *MDM2* amplification, without polysomy of chr 12.

compared with 0 of 6 polyps with no copy number alterations, suggesting that a quiet genome may be associated with more indolent behavior in this setting, as well. Given the rarity of residual/recurrent lesion on follow-up, a very large series of atypical uterine polyps with comprehensive molecular analysis and robust clinical follow-up would be needed to confirm this impression.

Beyond these 3 recurrent molecular subgroups, 2 atypical uterine polyps showed unique copy number profiles. One polyp harbored chr 11q21 (*MRE11A*) loss, which was reported in 2 of 10 adenosarcomas studied by whole-genome sequencing[30]. A second polyp harbored low-level gains in chr 8p12 (*NRG*) and chr 10q11.21-23 (*RET*, *ERCC6*)- although neither of these alterations has been reported in adenosarcoma, one karyotype-based study found frequent chr 8 alterations in uterine adenosarcoma[28].

In this series, 12 (60%) of 20 primary atypical uterine polyps sequenced by NGS harbored pathogenic point mutations (Fig. 3, Table 3), including recurrent point mutations seen in adenosarcoma. *AKT1* p.E17K hotspot mutation was identified in 1 atypical polyp and

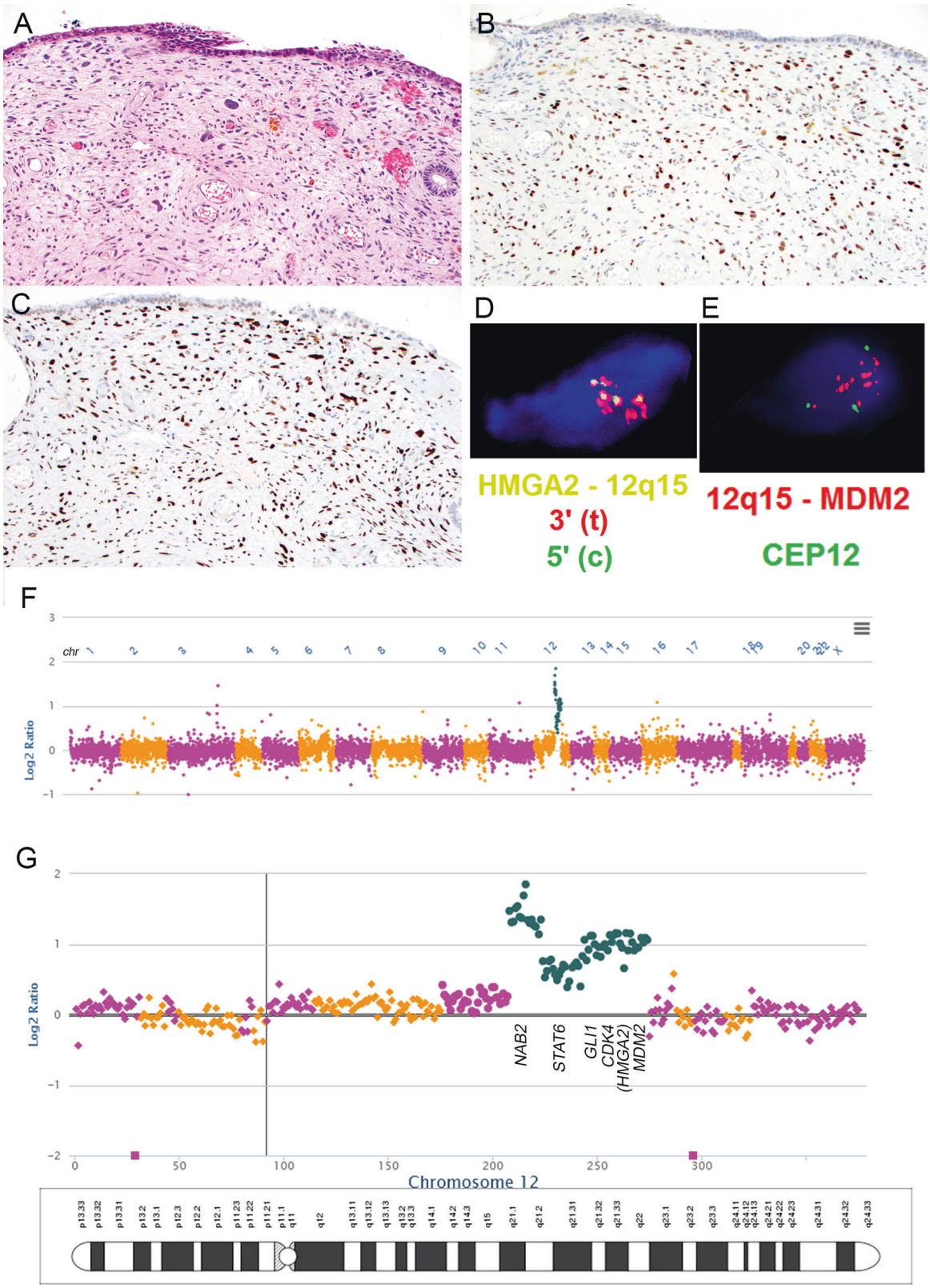

Fig. 5 **Morphologic, immunohistochemical, and molecular profiling of an atypical uterine polyp (Case 2). A** Moderate stromal cytologic atypia (200x). **B** Stromal cell HGMA2 overexpression by immunohistochemistry (200x). **C** Stromal cell MDM2 overexpression by immunohistochemistry (200x). **D** Breakapart *HMGA2* FISH shows *HMGA2* amplification without evidence of *HGMA2* rearrangement. **E** *MDM2* FISH shows *MDM2* amplification. **F**, **G** NGS copy number profiling shows a largely quiet genome with a single amplification on chr 12, encompassing chr 12q13-15 (*NAB2*, *STAT6*, *GLI1*, *CDK4*, *HMGA2*, and *MDM2*). Note that the *HMGA2* locus is indicated in parentheses, as the NGS panel tiles chr 12q14.3 but not *HMGA2*.

has been reported in 2 low-grade adenosarcomas, with PTEN/AKT/PIK3CA pathway mutations in 26–72% of adenosarcomas overall[23,27]. *ERBB2* and *APC* missense mutations were each identified in 1 atypical uterine polyp, and have likewise been reported in adenosarcoma[23]. A *SMARCE1* nonsense mutation was identified in 1 atypical uterine polyp with a complex copy number profile. Although *SMARCE1* mutations have not been reported in adenosarcoma, loss-of-function mutations in other SWI/SNF proteins have, including *SMARCA4* nonsense mutation[23] and *SMARCB1* frameshift mutation with loss of heterozygosity[27]. Despite these shared alterations, atypical uterine polyps have a significantly lower tumor mutational burden (3.1 mutations/Mb) than adenosarcomas (~9.6 mutations/Mb)[23].

Conversely, *KRAS*, *ARHGAP35*, and *PPP2R1A* mutations detected in our samples have also been reported in morphologically banal endometrial polyps. In a study of 4 endometrial polyps by whole-exome sequencing with matched germline DNA, 1 polyp each harbored a mutation in *PPP2R1A* and *ARHGAP35*, and *KRAS* mutations were detected in 2 of 4 polyps and in an additional 14 of 31 polyps studied by validation PCR (16/35 total, 46%)[15]. However, we favor these oncogene mutations in our atypical polyps to represent incidentally captured alterations in the epithelial compartment, as recent evidence indicates that the endometrial epithelium accumulates pathogenic mutations in cancer-related genes (including *ARHGAP35*, *PPP2R1A*, *KRAS*, *ERBB3*, *ERBB2*, and *FBXW7*) from an early age[17], and laser capture microdissection-based mitochondrial DNA profiling in adenosarcoma has shown no clonal relationship between the epithelial and stromal compartments[27].

Although the majority of uterine adenosarcomas show low-grade morphology and relatively indolent behavior[18,22,24], a minority show high-grade morphologic features associated with more aggressive clinical behavior[18,22,25,26] and recurrent molecular alterations. Sarcomatous overgrowth is associated with increased copy number losses[23,29], and aggressive clinical behavior is associated with amplification of *MYBL1* amplification[23] and deletion of *CDKN2A*[23,29,36], *BAP1*[23,26,27,30,36], *TP53*[29], and *RB1*[23,29]. Additionally, high-grade stromal atypia, sarcomatous overgrowth, and heterologous rhabdomyosarcomatous differentiation are linked to point mutations in *ATRX*, *DICER1*, and *TP53*[23,26,27,36]. In keeping with their low-grade morphologic features, no atypical uterine polyp harbored these "high-grade" alterations. It is noteworthy, however, that high-grade and low-grade adenosarcomas share common molecular features, particularly chr 12q13-15 amplification, suggesting that atypical uterine polyps, low-grade adenosarcoma, and high-grade adenosarcoma represent a molecular continuum, rather than discrete biologic entities. This, in turn, raises the possibility that, if morphologic or molecular-based risk stratification for these lesions could be refined, a subset of lesions currently diagnosed as adenosarcoma might be safely managed conservatively – a particular benefit to young women wishing to preserve fertility.

Some pathologists may diagnose a subset of our atypical polyps as uterine adenofibroma – a reportedly rare neoplasm comprising benign glands and stroma[32]. Although we do not use this diagnosis at our institution, proposed definitions of uterine adenofibroma[18,19,32,40] overlap somewhat with the criteria for our atypical uterine polyps. Furthermore, uterine adenofibroma and adenosarcoma without sarcomatous overgrowth have similar immunoprofiles[19], and adenofibromas may rarely invade the myometrium[40] or recur after hysterectomy[19]. These findings suggest that a subset of adenofibromas represent subtle or incipient adenosarcomas, akin to our atypical uterine polyps, and indicate that such lesions may occasionally be clinically aggressive, despite universally benign behavior in our series. This study provides a basis for molecular comparison to lesions diagnosed as adenofibroma, which could further elucidate the relationship of these entities.

This study has certain limitations. First, diagnosis of this sort of atypical uterine polyp is not codified, and there is likely variability in diagnostic criteria, nomenclature, and management. The distinction of subtle atypical polyps from conventional benign endometrial polyps is challenging: on morphologic re-review, we considered nearly one-quarter of polyps initially diagnosed as "atypical uterine polyp" to instead represent banal endometrial polyps. On the other end of the spectrum, distinction from subtle low-grade adenosarcoma is also challenging, and the molecular overlap between atypical polyps and low-grade adenosarcoma suggests that these entities exist on a continuum. Second, molecular testing could only be performed on a subset of atypical polyps, potentially limiting our detection of certain molecular findings. Targeted NGS may also miss some pathogenic alterations, as well as balanced structural variants, which may play a role in adenosarcoma pathogenesis[28,30]. Also, our NGS panel tiles chr 12q14.3, but *HMGA2* is not among the sequenced genes; accordingly, NGS-detected *HMGA2* copy number gains are inferred, albeit with a high degree of confidence. The low-level *ESR1* copy number gains detected in this study also warrant orthogonal validation. Finally, molecular studies of conventional benign endometrial polyps are principally based on karyotyping, and large NGS-based studies of conventional benign endometrial polyps are lacking, which complicates comparison with our molecular findings. We cannot exclude that a subset of morphologically banal endometrial polyps harbors some of the alterations described here.

In summary, uterine polyps with atypical features worrisome for, but not diagnostic of, adenosarcoma share multiple molecular alterations with low-grade adenosarcomas, providing evidence that these two entities exist on a biological spectrum and that atypical uterine polyps, in some cases, likely represent incipient adenosarcoma. However, our clinicopathologic data confirm that these atypical uterine polyps are associated with an extremely low risk of a malignant clinical course.

We considered alternate terminology for these lesions, out of concern that "atypical uterine polyp" could be confused with "atypical polypoid adenoma" or "atypical endometrial hyperplasia," particularly among non-pathologists. However, we ultimately felt that the "atypical" designation was important to ensure proper clinical attention to this diagnosis. In individual instances, the terms "atypical endometrial polyp" and "atypical endocervical polyp" may be used for greater specificity. To avoid clinical misinterpretation, we have omitted the word "adenosarcoma" or "adenosarcoma-like" from the proposed terminology.

In routine practice, we recommend a diagnosis of "atypical uterine polyp" for endocervical or endometrial polyps with abnormal architecture (subtle or focal phyllodiform growth, rigid cystic glands, and intraluminal papillary projections) and/or subtle periglandular stromal cuffing and/or stromal atypia. Stromal mitoses should be considered in the context of the background endometrium, as increased mitoses may be seen in a proliferative background. Increased mitoses alone do not warrant a diagnosis of atypical uterine polyp. Atypical morphologic findings may be focal or diffuse, but they must be mild in degree, falling short of the diagnostic threshold for adenosarcoma. Atypical uterine polyp is, at present, a fundamentally morphologic diagnosis. Available evidence does not identify any immunohistochemical or molecular assays that predict behavior in atypical uterine polyps or that meaningfully distinguish these lesions from subtle adenosarcomas, and no ancillary studies are currently advocated for routine use. Given the rarity of these lesions, it is appropriate to include a diagnostic comment communicating their biological nature and expected clinical behavior. We advocate a low threshold for seeking expert consultation.

Our findings suggest that atypical uterine polyps can be managed conservatively. Nonetheless, clinical follow-up with repeat tissue sampling is advised given their apparent biologic overlap with adenosarcoma. Given that all 4 instances of recurrent atypical uterine polyp in this series were discovered within 1 year, repeat sampling at 6–12 months appears prudent, though earlier sampling is advised if there is clinical suspicion for recurrence. Further studies are warranted to develop more robust morphologic and molecular risk stratification models for uterine stromal neoplasms, to more precisely determine whether a subset of

lesions presently diagnosed as adenosarcoma might also be safely managed without hysterectomy.

DATA AVAILABILITY

NGS Sequencing data from this study are publicly available through the AACR Genie database. Detailed clinicopathologic data for patients undergoing molecular characterization are available in Supplementary Table 2.

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AUTHOR CONTRIBUTIONS

DBC and MRN performed study concept and design, all authors performed development of methodology and writing, review and revision of the paper, all authors provided acquisition, analysis and interpretation of data, and statistical analysis. All authors read and approved the final paper.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

This study was approved by the institutional review board at Brigham and Women's Hospital.

ADDITIONAL INFORMATION

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