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CASE REPORT

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Endometrial polyps with bizarre stromal cells: a Benign or a low-grade lesion?

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Abstract

Background Polyps containing bizarre stromal cells are occasionally observed in the lower gynecologic tract, including the vagina, cervix, and endometrium, predominantly in perimenopausal or postmenopausal patients. These cases have traditionally been considered benign without subsequent recurrence or malignancy.

Case presentation We describe a rare instance of a rapid enlarging endometrial polyp characterized by atypical stromal cells in a 76-year-old postmenopausal woman, who presented with vaginal bleeding. Histologically, the polyp was noted for its abundance of atypical stromal cells interspersed among thick-walled vascular channels. Higher magnification revealed eosinophilic cytoplasm in the stromal cells, which exhibited both mono- and multinucleation, hyperchromasia with coarse chromatin, and an absence of conspicuous nucleoli and mitotic figures. A consensus among two of three consulting expert gynecological pathologists supported a benign endometrial polyp diagnosis; however, one pathologist raised the possibility of adenosarcoma, highlighting the diagnostic dilemma these unique lesions present. Despite a hysterectomy recommendation, the patient chose monitoring over immediate surgery. Persistent vaginal bleeding led to her return six months later, whereupon a 7-cm polypoid lesion in the endometrial cavity was found and removed via hysterectomy. The histopathology mirrored the initial findings, showing no myometrial invasion, prompting a re-evaluation of the presumed benign nature of the polyp given its rapid growth. Remarkably, RNA sequencing analysis of the polyp detected a *JAK2::NFIB* gene fusion, a novel finding for endometrial polyps with atypical stromal cells, the clinical implications of which remain to be elucidated.

Conclusion The rapid recurrence of the polyp within six months raises new questions about the true biological nature of these entities and the relevance of gene fusions like *JAK2::NFIB* in their pathogenesis, meriting further investigation.

Keywords Endometrial polyp, Endometrial polyp with bizarre nuclei, Endometrial adenosarcoma, Endometrial sarcoma not otherwise specified

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Background

Polyps with bizarre stromal cells are an uncommon histological finding, predominantly documented within vulvovaginal areas. Such cellular anomalies are less frequently observed within the endometrium, and to date, the English literature features only a limited number of case reports—roughly less than two dozen—describing endometrial polyps (EMPs) exhibiting these unusual cells [1–5]. The identification and correct interpretation of these atypical stromal cells in EMPs are paramount to avoid the pitfalls of overdiagnosis, which may lead to unnecessary aggressive treatment strategies.

The clinical course of EMPs with bizarre stromal cells, as detailed in reported cases, consistently demonstrates benign behavior. Notably, there has been no documentation of recurrence or metastasis following treatment. This is significant, considering the potential for these unusual cellular features to mimic more aggressive neoplastic processes such as endometrial sarcomas or adenosarcomas.

However, Some of EMPs, particularly those diagnosed from sampling specimens, have been reported to have a recurrence rate of 5.6% within 4.36 months. However, on Cox regression multivariate analyses, no single clinicopathologic feature was associated with a recurrence[6]. Importantly, recurrence does not indicate malignancy.

Historically, the rarity of these occurrences has meant that most have been documented as individual case reports, leaving comprehensive molecular characterization largely unexplored. This gap in knowledge limits our understanding of the pathophysiology and potential genetic underpinnings of these lesions. Our current case contributes a new dimension to the existing literature by detailing an instance of an EMP with bizarre stromal cells that exhibited rapid enlargement within six months after what was believed to be complete or near-complete removal via a dilatation and curettage procedure. This unusual clinical course suggests there is much more to learn about the biological behavior of these polyps and highlights the need for further investigation, including molecular analysis, to elucidate the nature of these intriguing entities.

In this case report, we present the clinical course, pathological findings, and molecular analysis of an EMP with bizarre stromal cells, emphasizing the challenges in diagnosis and management of such cases.

Case presentation

Clinical information

A 76-year-old postmenopausal woman presented to our institution with a four-day history of abnormal vaginal bleeding. Her medical history is significant for longstanding hypertension spanning two decades, type II diabetes managed for seven years, and three instances of cerebral infarction. She has been on a regimen of oral antihypertensive medication and aspirin for several years, with no reported use of tamoxifen or other steroid hormones.

An initial ultrasound examination detected a $3.3 \times 3.0 \times 2.5$ cm mass with heterogeneous echogenicity and distinct margins within the uterine cavity. Magnetic resonance imaging (MRI) further characterized the lesion, showing an endometrial thickness of 1.1 cm, with irregular and slightly hypointense T2-weighted signal intensity adhering to the posterior uterine wall. The endometrial lesion exhibited characteristics resembling cotton fluff, with low or no contrast enhancement, suggestive of an EMP possibly accompanied by a small blood clot in the uterine cavity (Fig. 1a).

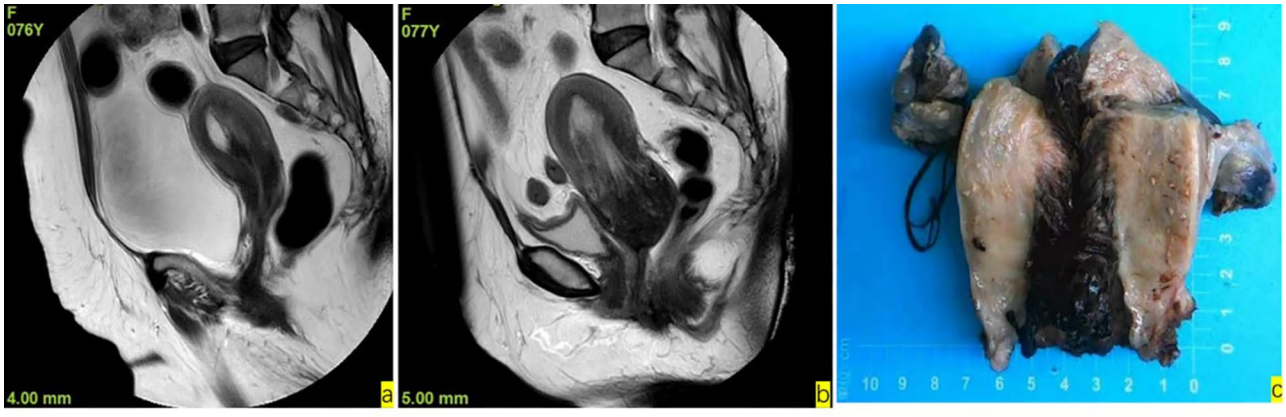

Fig. 1 MRI and Gross Pathological Images of the Uterine Lesion
(**a**) Pre-polypectomy MRI depicting an endometrial thickness of 1.1 cm within the uterine cavity and a polypoid lesion approximately 3.5 cm in diameter adhering to the posterior wall. (**b**) Follow-up MRI, six months post-polypectomy, illustrating a polypoid mass up to 7 cm across within the uterine cavity. The image captures a distinct demarcation between the lesion and the myometrium, suggesting a non-invasive growth pattern. (**c**) Gross specimen from the THBSO procedure, post-fixation, displaying a large polypoid lesion with a dark red appearance. The lesion is well-defined against the adjacent myometrium, corroborating the absence of myometrial invasion

Given the increased risk of endometrial malignancy, especially in postmenopausal women, conventional management for such findings typically involve a total hysterectomy with bilateral salpingo-oophorectomy (THBSO). However, the patient declined the surgery, citing concerns about her overall health and considering the generally benign nature of EMP. Opting for a less invasive approach, she underwent a hysteroscopic polypectomy, complemented by a comprehensive dilatation and curettage (D&C) procedure, followed by routine postoperative surveillance. A follow-up ultrasound two weeks later revealed no residual lesion within the endometrial cavity.

Six months later, upon experiencing a recurrence of vaginal bleeding, the patient sought medical attention again. A subsequent MRI revealed a mass in the pelvic endometrial cavity measuring $7.1 \times 3.4 \times 2.5$ cm, with a distinct pedicle extending from the upper edge to the uterine wall and a clear demarcation from the uterine myometrium (Fig. 1b).

Given the potential for EMP recurrence and the non-excludable risk of malignancy, the gynecologist recommended THBSO once more. After careful consideration, the patient consented to the procedure and a laparoscopic-assisted vaginal THBSO was subsequently performed.

Pathological findings

The patient's pathological evaluation is delineated from two distinct surgical interventions: the initial biopsy with polypectomy and curettage, followed by a THBSO.

Gross Examination: Initially, the endometrial polypectomy yielded fragmented tissue, collectively measuring $4.0 \times 2.5 \times 1.3$ cm, exhibiting a gray to brown coloration. During the THBSO, the uterine cavity was found to contain a $7 \times 2.5 \times 2.5$ cm polypoid mass with a smooth surface and a pliable consistency upon palpation. It originated from a broad pedicle, 2.2 cm at its widest point, anchored at the uterine fundus. The surrounding endometrium displayed a dark-red hue (Fig. 1c). Cross-sectioning of the lesion, its pedicle, and adjacent myometrium revealed no evidence of invasive growth. The bilateral fallopian tubes and ovaries were unremarkable.

Microscopic Examination: The fragments from the initial procedure were characteristic of typical EMPs, with the exception of a denser stromal compartment containing darker, larger cells. These atypical stromal cells, with pronounced nuclear atypia, were distributed throughout the polyp, primarily beneath the surface epithelium. In contrast, the glandular epithelial cells of the endometrium appeared without apparent abnormality. The atypical stromal cells varied from mono- to multinucleated forms, all hyperchromatic with a smudged chromatin pattern and no significant nucleoli. Mitotic figures and necrosis were absent (Fig. 2a-c). The THBSO specimen echoed these histologic features, with the added observation of marked congestion in portions of the polyp and non-polypoid endometrial tissue. An exhaustive examination confirmed the absence of myometrial invasion (Fig. 3a-c).

Immunohistochemical Profile: Immunohistochemical staining of the polypectomy specimen revealed diffuse positivity for CD10, Desmin, and P16 in the atypical stromal cells. There was weak and focal positivity for estrogen and progesterone receptors (ER and PR), along with smooth muscle actin (SMA). Stains for S100 and CD68 were negative, and p53 showed wild-type staining pattern. The proliferation index, indicated by Ki-67, was approximately 10% (Fig. 4a-d). In the THBSO specimen, the atypical cells were negative for ER and PR, but the expression of other markers was consistent with the initial biopsy.

Molecular Analysis: Given the distinctive nature of the EMP and the divergent diagnostic perspectives from expert pathologists, we proceeded with molecular analysis upon receiving patient consent. The initial biopsy was sent for OncoFusion gene RNA sequencing (covering

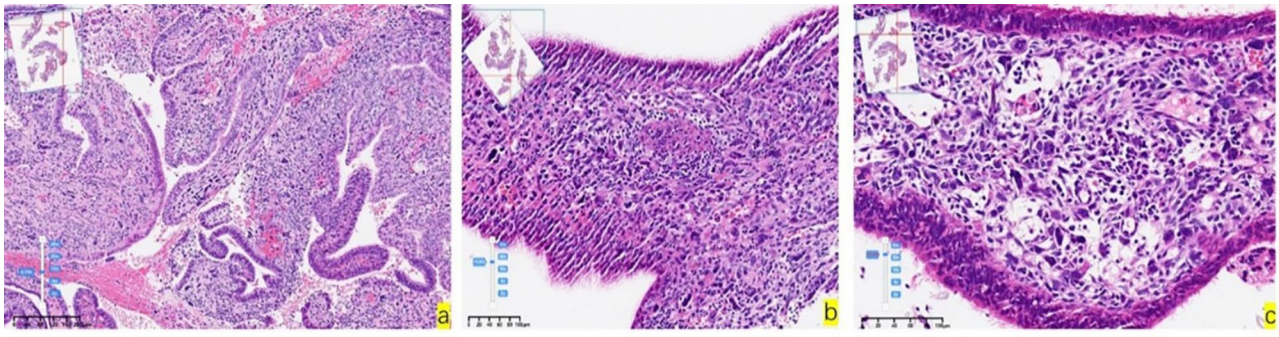

Fig. 2 Histopathological Characteristics of EMP with Bizarre Stromal Cells. (**a**) Low magnification (×40) reveals a polypoid structure composed of regular endometrial glands amidst a dense population of atypical stromal cells. (**b**) Medium magnification (×100) allows for clearer observation of the atypical stromal cells, showcasing their distribution and morphological variance within the lesion. (**c**) High magnification (×400) emphasizes the atypical features of the stromal cells, including hyperchromatic and variably sized nuclei, some with multinucleation, set against a backdrop of benign glandular elements

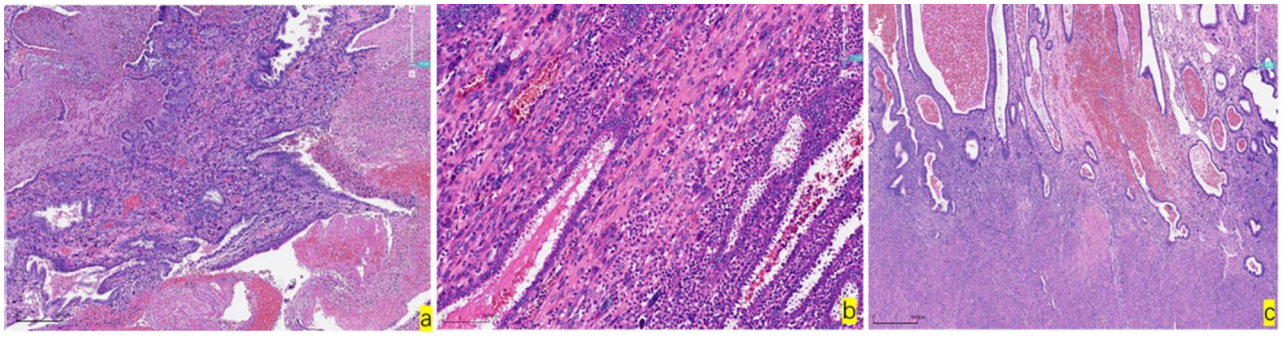

Fig. 3 Histopathological Features of EMP with Bizarre Stromal Cells in the LAVHBSO Specimen. (**a**) Low magnification (×100) captures the widespread distribution of bizarre stromal cells and prominent hemorrhage within the glandular structures. (**b**) Medium magnification (×200) details the bizarre stromal cells amidst diffuse infiltration by neutrophils. (**c**) Low magnification (×40) highlights the marked bizarre stromal cells and delineates the distinct demarcation between the endometrial and myometrial tissues

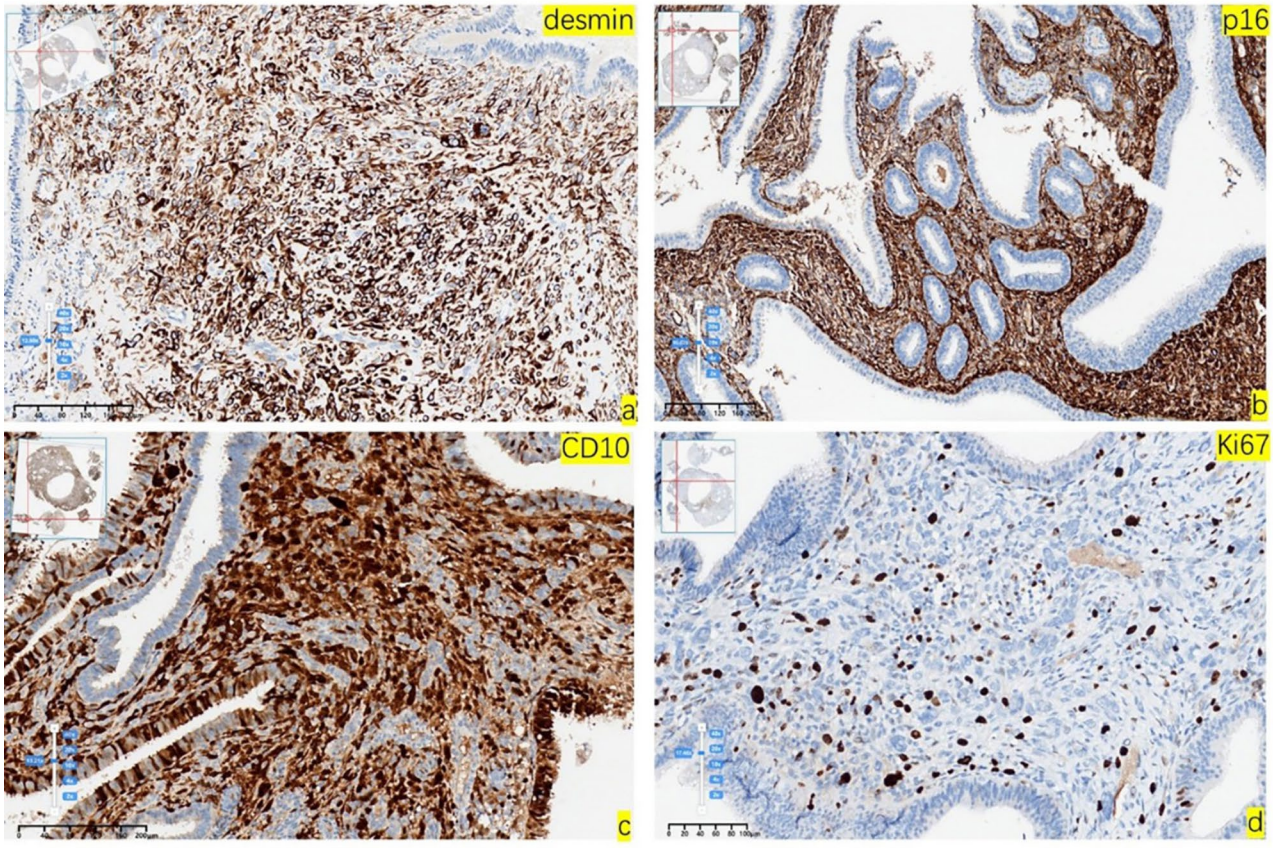

Fig. 4 Immunohistochemical Profiling of Bizarre Stromal Cells. (a) Desmin expression is diffuse across the stromal cells(×100). (b) p16 is diffusely positive in the stromal cells(×100). (c) CD10 is diffusely expressed, highlighting the endometrial mesenchymal origin of the stromal cells (×200).
(d) Ki67 labeling is limited, marking a small subset of the stromal cells, which may reflect a low proliferative index (×200)

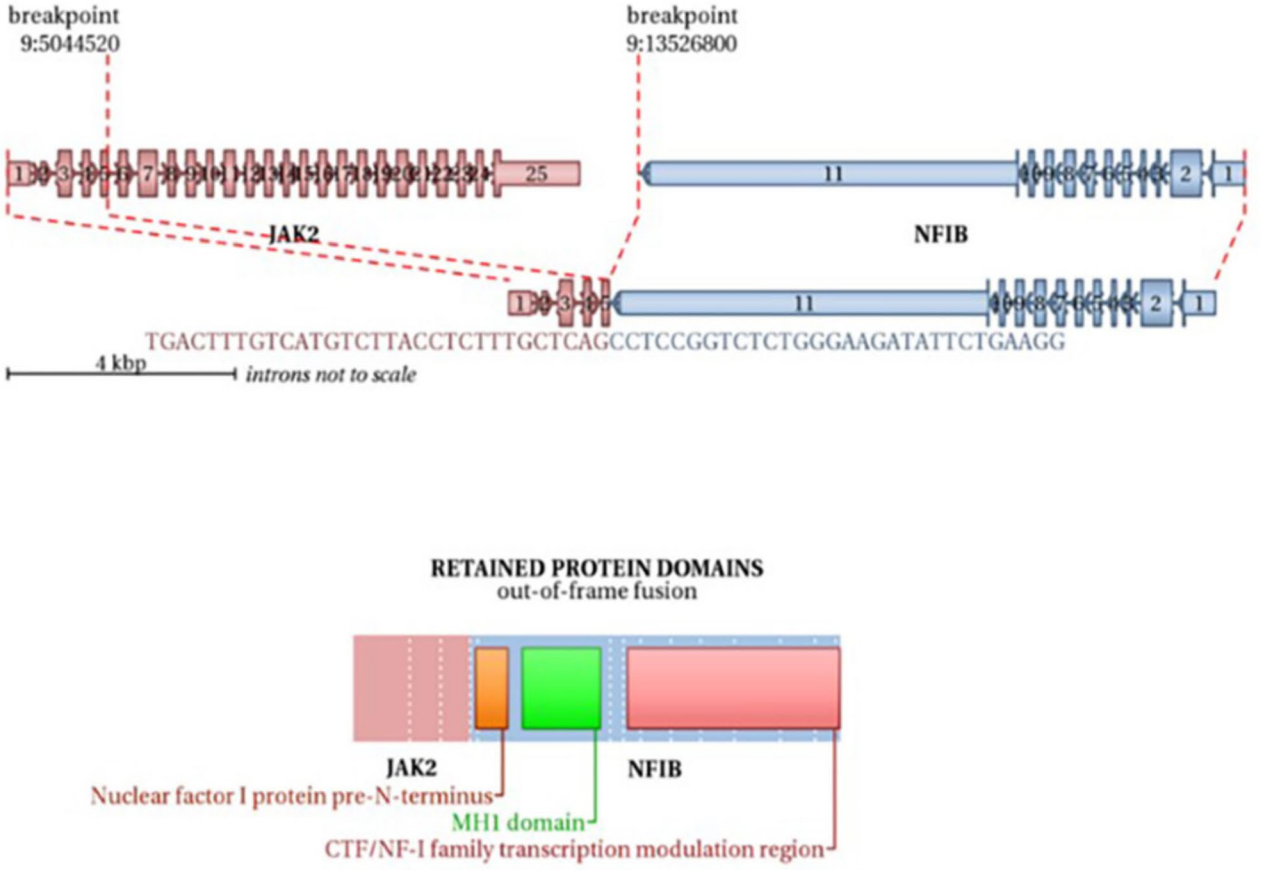

Fig. 5 Intergenic gene rearrangement of *JAK2::NFIB*

555 genes) at Beijing Jiyinjia Medical Laboratory. While no gene rearrangements typically associated with sarcomas were identified, a *JAK2::NFIB* (intergenic) gene rearrangement was detected (Fig. 5). The clinical significance of this finding remains uncertain. Due to the morphological similarity with the biopsy, molecular testing on the THBSO specimen was not conducted.

The patient was followed routinely. After the operation, she did not get further treatments, and she was asymptomatic with no evidence of disease for over 11 months.

Discussion

Endometrial polyps with atypical stromal cells are an infrequent pathological finding, first described in 1995 by Creagh et al. [1]. These cells are characterized by their stellate or enlarged appearance, hyperchromatic nuclei, significant nuclear atypia, occasional multinucleation, and typically, an absence of mitosis [1–5]. Traditionally, the presence of these cells within polyps has been regarded as a degenerative or reactive change without clinical consequence [1]. However, the extent of nuclear atypia often presents a diagnostic conundrum for pathologists, despite a history of benign clinical course, particularly when assessed in curettage specimens [2, 5].

Differential diagnoses for these polyps include adenosarcoma, endometrial stromal sarcoma (ESS), leiomyoma with bizarre nuclei in polypoid shape, leiomyosarcoma, and carcinosarcoma. Biopsy specimens pose particular challenges due to the cytological features that may mimic malignancy [2, 6–11]. In the current case, the consensus among expert gynecological pathologists concluded the diagnosis as a benign endometrial polyp with bizarre stromal cells, although one considered the possibility of adenosarcoma.

Adenosarcomas is featured by its stromal hypercellularity, periglandular stromal cuffing, leaf-like projections into the glandular lumina, and the increased stromal mitotic activity (≥ 2 mitoses/10 high power fields), or homologous/heterologous sarcomatous stroma cell overgrowth. In contrast, EMPs with bizarre stromal cells lack these characteristics [2–11]. In routine practice, some "atypical uterine polyps" with subtle or focal phyllodiform growth, rigid cystic glands, intraluminal papillary projections and/or subtle periglandular stromal cuffing and/or stromal atypia present considerable

diagnostic and therapeutic difficulties [12]. Another differential diagnosis is high-grade endometrial stromal sarcoma (HG-ESS). In our case, although the morphology of stromal cells is bizarre, they do not show any mitosis or necrosis, which is not consistent with the characteristics of high-grade sarcoma [10]. The absence of invasion, active mitosis, tissue necrosis, and other malignancy indicators, coupled with the rapid growth of the lesion, still indicated the need for close follow-up.

Interestingly, the recurrence or significant regrowth of the polyp within a short six-month period post-removal raises questions about its biological behavior. Such rapid recurrence from a completely or nearly completely resected lesion to a 7 cm polyp is atypical and unprecedented in the literature[2,6–9]. Although the hysterectomy specimen did not show myometrial invasion or features of malignancy, this unusual rapid enlargement suggests a unique underlying biology.

Studies by Moritani S et al. and Stewart et al. found that p16 expression in the stromal cells is characteristic of endometrial polyps (13–14). Unfortunately, no specific biomarkers have been identified that can definitively determine the nature of these tumors [1–10].

Molecular test is often useful in differentiating sarcomas in pathology practice. Targeted RNA sequencing is an ancillary test for diagnosing endometrial stromal tumors, can reclassify a quarter (Seven cases) of low-grade ESS (LG-ESS) (negative for JAZF1 and/or YWHAE rearrangements in FISH) as high-grade ESS with BCOR rearrangement (2 cases), malignant epithelioid neoplasm with GLI1 rearrangement (2 cases), NCOA fusion-positive uterine tumors (2 cases), and one uterine leiomyoma (15–16). Loss-of-function mutations in TP53, RB1, and ATRX, homozygous deletions of BRCA2 have been found in uterine leiomyosarcomas. Genomes of low-grade tumors were largely silent [17].

Some studies also investigated cytogenetics in benign endometrial polyps and found 57% of cases would have clonal chromosome rearrangements. These cytogenetically abnormal rearrangements located in the 6p21-p22 region, the12q13-15 region, or the 7q22 region [18]. A study on atypical uterine polyps found that five cases (24%) harbored chr 12q13-15 gain or amplification, nine cases (45%) harbored chr 6q25.1 gain, and other gains of chr 1q, chr 8p12, chr 10q11.21-23, amplifications of chr 12q24.12-13, chr 15p24.1-26.1, chr 18q21.33, and loss of chr 7 and chr 11q21 were seen in single polyps [12]. The *JAK2::NFIB* intergenic gene rearrangement found in this case, not previously reported in EMP with bizarre stromal cells, may provide new insights into the atypical proliferation observed in EMPs, and add a new layer of complexity. Polyp proliferation depends on multiple genetic alterations and factors including enzymes, obesity, age, menopause status, and steroid hormone receptors [19]. JAK2 mutations have been associated with poor outcomes in certain malignancies, while NFIB has been implicated in organ development and cancer, offering potential for targeted therapies [20–22]. However, the exact clinical significance of the specific rearrangement remains to be determined.

It is important to note that rapid growth does not necessarily equate to malignancy or recurrence, but it warrants careful consideration and may suggest a previously unrecognized biological spectrum for EMPs with bizarre stromal cells. Further molecular studies are essential to elucidate the significance of such genetic alterations and their correlation with tumor behavior.

Chapel et al. proposed the term "atypical uterine polyps" for these lesions which showed biologic overlap with Mullerian adenosarcoma, but lack of characteristically molecular alterations and had a benign clinical course [12]. With considerable progress being made, we may see a new way of pathologic analysis centered on molecular and immunohistochemical indicators, similar to those used in endometrial cancer, becoming standard for more accurate tumor risk stratification [23].

This case report has certain limitations and weakness. First, the diagnosis was not uniformly agreed upon; two consulting experts diagnosed it as a benign polyp with bizarre nuclei, while one expert considered it adenosarcoma, highlighting the diagnostic challenge. Second, molecular testing identified a new intergenic gene rearrangement of *JAK2::NFIB*, though its significance remains unclear. Finally, as a case report, it is not representative of a group of lesions but provides a hint towards understanding. More cases and longer follow-up are needed to elucidate the true biological behavior of these entities.

Conclusion

In summary, while EMPs with bizarre stromal cells are generally considered benign, the unusual regrowth observed in this case underscores the need for vigilant surveillance and possibly a re-evaluation of the criteria for benignity. More extensive case studies and molecular research are essential to fully understand the implications of gene rearrangements and the true nature of these lesions. Consequently, conservative management and meticulous follow-up, including repeat sampling at 6–12 months, remain prudent for these patients, acknowledging the potential for exceptional cases that deviate from the established benign course.

Abbreviations

EMPs	endometrial polyps
MRI	Magnetic resonance imaging
THBSO	total hysterectomy with bilateral salpingo-oophorectomy
D&C	dilatation and curettage
ER	estrogen receptors
PR	progesterone receptors

SMA	smooth muscle actin
ESS	endometrial stromal sarcoma
LG-ESS	low grade ESS
HG-ESS	high grade ESS

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Author contributions
M Wang Wrote the initial draft and made the initial diagnosis; F Gao Processed samples and stained the slides; H Zhang Constructed and Revised the draft, consulted the diagnosis; W Zheng Consulted the diagnosis and made the final revision of the draft. All authors reviewed the manuscript.

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Data availability
Original data (nondisclosure of patient's privacy) in the manuscript could be available on request. The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive in National Genomics Data Center, China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA009728) .

Declarations

Ethics approval and consent to participate
The study has been approved by the Research Ethics Committee of Dong E County People's Hospital of Shangdong Province (No. K2024-001-01). All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki. The study was conducted in accordance with the local legislation and institutional requirements. The patient and her parents provided written informed consent to participate in this study. Written informed consent was obtained from all of the participants in the study.

Consent for publication
The patient has signed an informed consent for her personal and clinical details along with images to be published in this study. Her identity has been kept confidential.

Competing interests
The authors declare no competing interests.

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