Case Report

Endometrial carcinoma in a young woman - Tracing the transition from atypical hyperplasia to polymerase epsilon-mutant cancer: A case report

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ABSTRACT

Although historically more common in peri- and postmenopausal women, there is a noticeable rise in cases of endometrial hyperplasia and cancer among younger women of childbearing age due to contemporary lifestyles. A 31-year-old, P0L0A2 woman (body mass index of 15.5 kg/m^2) with a history of infertility treatment presented with complaints of abnormal uterine bleeding for 2 months. Transvaginal sonography (TVS) showed a normal uterus with an 18 mm endometrium, and dilatation and curettage revealed endometrial hyperplasia with focal atypia. She was advised to undergo a magnetic resonance imaging (MRI) pelvis, but was lost to follow-up. She re-presented after 3 months with persistent bleeding; repeat TVS showed a 13 mm endometrium, and MRI confirmed endometrial thickening. Repeat biopsy showed endometrial intraepithelial neoplasia. Although medical management with progesterone was advised, she opted for a hysterectomy with bilateral salpingectomy. Final histopathology showed endometrioid endometrial carcinoma, stage IA2, grade 1. Molecular analysis revealed a polymerase epsilon mutation, indicating a favorable prognosis. Primary treatment for endometrial hyperplasia with atypia typically involves hysterectomy, though fertility-sparing options may be considered for young patients. Furthermore, immunohistochemistry and molecular classification of endometrial carcinoma are crucial, especially in young females, as they significantly influence management and prognosis.

Key words: Endometrial hiperplasia, Endometrial intraepithelial neoplasia, Endometroid endometrial carcinoma, Hysterectomy, Progesterone

Endometrial carcinoma predominantly affects postmenopausal women, comprising approximately 4% of female cancers in India. Although relatively rare in young women, its incidence has been on the rise among those in the reproductive age group in recent years [1]. This increase may be attributed to a variety of factors, including the heightened prevalence of risk factors among adolescents. These risk factors include anovulatory conditions resulting in prolonged estrogen exposure, such as early menarche, polycystic ovarian syndrome, nulliparity, infertility, obesity, and genetic predispositions, such as Lynch syndrome and Cowden syndrome [2]. Among young adults, abnormal uterine bleeding stands out as the most common presenting symptom. Treatment strategies vary based on the clinical stage at the time of diagnosis, ranging from surgical interventions to chemo-radiation as necessary. Fertility-sparing options, including hormonal therapy, are typically reserved for young women diagnosed with early-stage cancers.

Herein, we present a rare case diagnosed with endometrial cancer in a young woman of 31 years old without any typical risk factors. The only symptom to approach the diagnosis of endometrial cancer was abnormal uterine bleeding. This case is reported to highlight the unusual occurrence of endometrial carcinoma in a young, nulliparous woman with infertility and persistent abnormal uterine bleeding. The case underscores the importance of vigilant surveillance, timely repeat biopsies, and individualized management in reproductive-age women. In addition, the presence of a polymerase epsilon (POLE) mutation illustrates the prognostic value of molecular testing in guiding treatment and follow-up.

CASE REPORT

A 31-year-old nulliparous woman (P0L0A2) presented to the gynecological outpatient department in December

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2023 with a chief complaint of continuous vaginal bleeding persisting for the past 2 months. She previously had regular menstrual cycles, characterized by bleeding lasting 4–5 days every 28–30 days. Her family history was unremarkable, with no known hereditary or gynecological disorders. She was married for 5 years and was eager to conceive. She had a history of two spontaneous first-trimester abortions, with the last abortion occurring in 2021.

On general clinical examination, the patient was of a thin build with a body mass index of 15.5 kg/m^2 rest all her vitals were stable. Abdominal examination was unremarkable, while per speculum examination revealed a nulliparous cervix with a foul-smelling, blood-tinged discharge seen coming through the os. Bimanual examination revealed a retroverted, mobile, normal-sized uterus with bilateral free fornices.

Her transvaginal ultrasound (transvaginal sonography [TVS]) revealed a uterus measuring 85 × 41 × 56 mm with a thickened endometrium of 18 mm and bilateral normal fallopian tubes and ovaries. Given the thickened endometrium and continuous bleeding per vaginum, the patient was planned for therapeutic and diagnostic dilatation and curettage.

Her histopathology report of endometrial biopsy revealed endometrial hyperplasia with focal atypia in the setting of disordered proliferative endometrium. Further imaging with pelvic magnetic resonance imaging (MRI) was advised, but the patient was lost to follow-up.

The patient revisited the outpatient department with similar complaints of continuous bleeding per vaginum for one and a half months. Her repeat TVS revealed an endometrial thickness of 13 mm despite ongoing vaginal bleeding. Given her young age, a pelvic MRI was performed, revealing an endometrial thickness of 10 mm. No significant diffusion restriction or evidence of invasive malignancy was observed (Fig. 1a). Histopathology report of her repeat endometrial biopsy revealed features suggestive of Endometrioid intraepithelial neoplasia (EIN) (Fig. 1b). Her Pap smear report was negative for intraepithelial lesion or malignancy.

The patient was counseled regarding her condition, including the risks of malignancy and the importance of follow-up after medical management. Despite being offered medical management options, such as oral progesterone or a levonorgestrel intrauterine system, the patient and her husband opted for surgical management due to concerns about the potential risk of malignancy and the inability to report for regular follow-ups.

Her preoperative investigations, including complete blood counts (hemoglobin 10.9 g/dL, total leukocyte count 6,700/mm^3, platelet count 250,000/mm^3), liver and renal function tests, thyroid function tests, and fasting (80 mg/dL) and postprandial blood sugars (98 mg/dL), were all within normal limits and her tumor markers revealed CA-125 levels of 9.7 U/mL. After thorough documentation and informed consent, a laparotomy was performed, including peritoneal washings, total abdominal hysterectomy, and bilateral salpingectomy.

Intra-operative findings included a grossly normal uterus with bilateral healthy fallopian tubes. Bilateral ovaries were also normal on gross appearance. Hence, only the uterus with bilateral fallopian tubes were removed, leaving the ovaries *in situ*. On gross examination, the uterus measured 8.5 × 5 × 3 cm with an endocervical canal of 3 cm. On cut open, there was no gross lesion present in the endometrial or endocervical canal (Fig. 2a). On microscopic examination, an endometrial tumor was identified whose size could not be determined as it was not visible to the naked eye. The tumor on histopathology was found to be endometroid endometrial carcinoma-not otherwise specified of grade 1, showing a villo-glandular pattern with severe cytologic atypia noted in <50% of tumor cells. The depth of invasion of the tumor was 0.1 cm, which is <50% of myometrial invasion (total myometrial thickness was 1.5 cm) (Fig. 2b). There was no serosal, lower uterine segment, or cervical stroma involvement noted. Her peritoneal fluid washings were also negative for the malignancy. Hence, the final impression of endometroid endometrial carcinoma stage IA2 Grade 1 was made.

The patient tolerated the surgery well and was discharged in satisfactory condition on postoperative day 8, following suture removal. Molecular testing was advised, including POLE mutation, mismatch repair deficiency (MMRd), no specific molecular profile, and

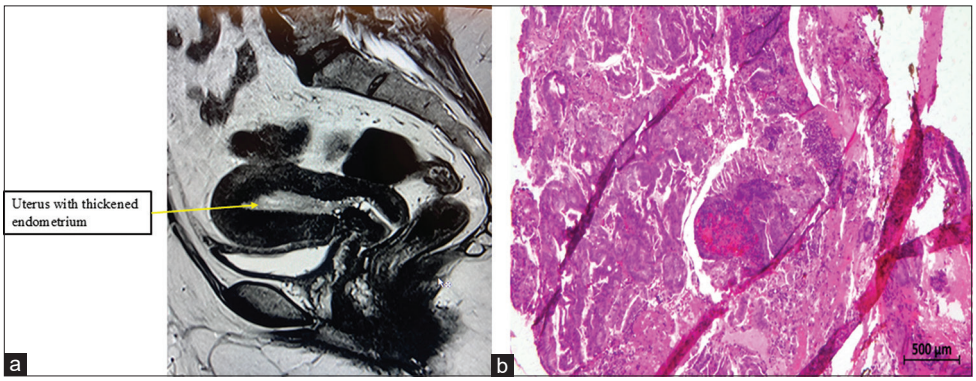

Figure 1: (a) Magnetic resonance imaging showing a normal-appearing uterus with thickened endometrium. (b) Histopathology of endometrial biopsy - increased glands-to-stroma ratio with irregular, variable-in-size endometrial glands lined by enlarged and pleomorphic nuclei having vesicular chromatin and prominent nucleoli in a moderate amount of eosinophilic cytoplasm (Hematoxylin and Eosin ×50)

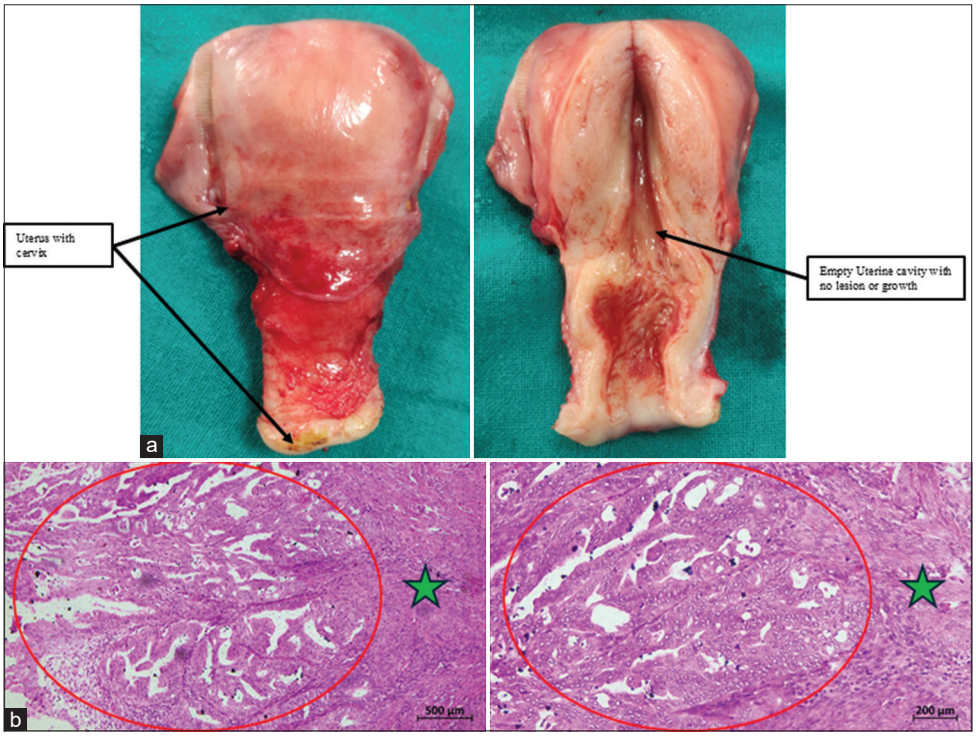

Figure 2: (a) Gross appearance of the specimen after hysterectomy, showing uterus with cervix, with a cut-open specimen showing no obvious lesion or growth in the uterine cavity. (b) Histopathology of hysterectomy specimen - Closely spaced irregular glands with maze-like arrangement lined by round to oval nuclei showing nuclear stratification, vesicular chromatin, and prominent nucleoli (red circle) with minimal myometrial (Green star) invasion (Hematoxylin and Eosin ×50, ×100)

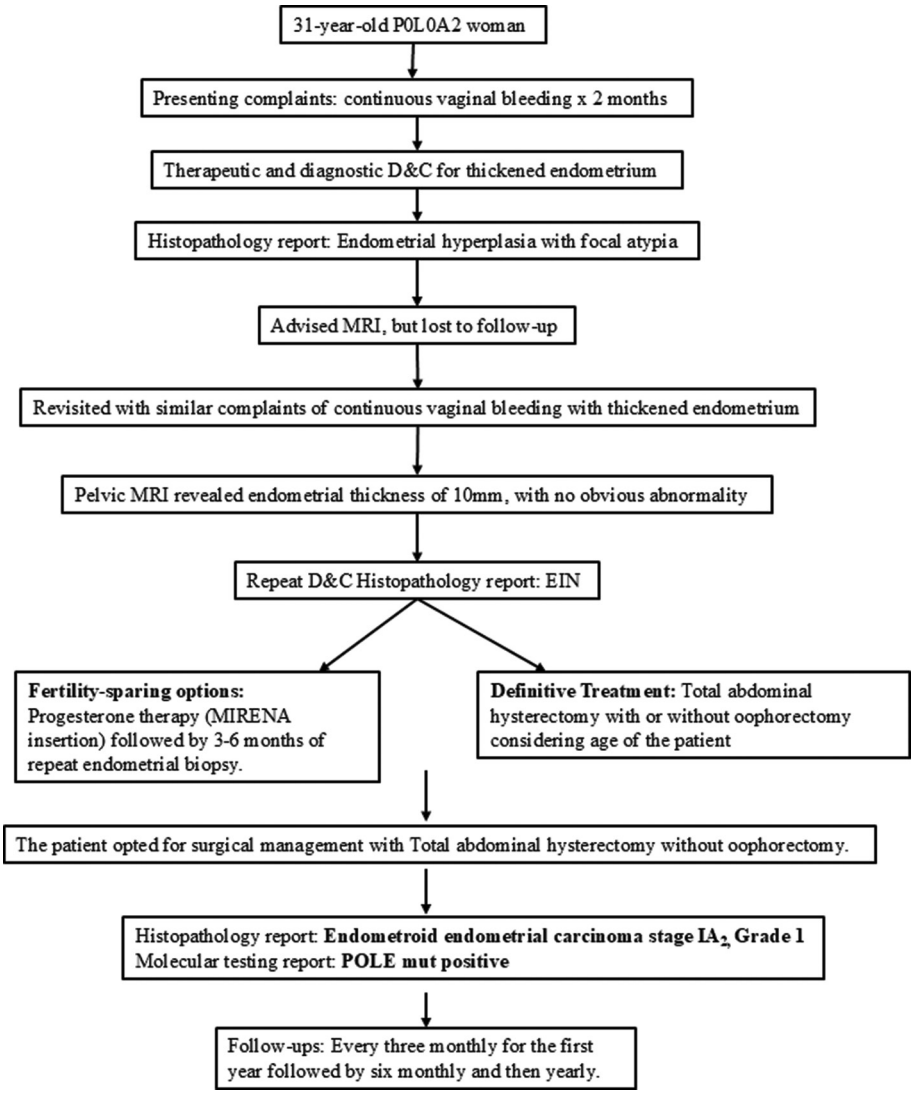

Figure 3: Illustrates the chronological timeline of events and the patient's management plan

p53 status. The results revealed POLE-mutant positivity, indicative of a favorable overall prognosis. The patient was advised to have regular follow-ups every 3 months for the 1st year, followed by every 6 months and yearly thereafter. Fig. 3 illustrates the chronological timeline of events and the patient's management plan.

DISCUSSION

Endometrial hyperplasia, a precursor to endometrioid adenocarcinoma, is classified by the World Health Organization into benign hyperplasia and atypical hyperplasia/EIN, with the latter carrying a significant risk of malignant progression [3]. Abnormal uterine bleeding is the hallmark symptom, necessitating prompt histological evaluation [4]. Consequently, immediate evaluation through tissue sampling for pathology or imaging is warranted for any abnormal bleeding.

Risk factors for hyperplasia progressing to endometrial cancer include obesity, diabetes, hypertension, and conditions leading to prolonged estrogen exposure [5]. The risk of concurrent carcinoma with atypical hyperplasia is substantial (32.1%), with an annual progression rate of 8%, underscoring the need for definitive treatment [5].

For young women with atypical hyperplasia/EIN or well-differentiated, early-stage endometrial cancer, fertility-sparing progestin therapy is an option, achieving a complete response in approximately 50% of patients [6]. However, this requires strict adherence to monitoring via endometrial sampling every 3–6 months due to high recurrence rates (~35%) [7]. Our patient, despite meeting the criteria for conservative management, opted for surgery due to concerns about malignancy and follow-up challenges. Her final diagnosis of Stage IA2 carcinoma on the hysterectomy specimen highlights a critical challenge: The potential for endometrial sampling to underestimate a coexisting carcinoma.

Preservation of the ovaries may be considered safe for specific premenopausal individuals who meet the following criteria: Absence of a familial history of breast or ovarian cancer, no indication of Lynch syndrome, and normal-appearing ovaries [8].

Immunohistochemistry and molecular classification play a critical role in assessing the prognosis of endometrial carcinoma, particularly in young females. Optimal benefits from progesterone management are observed in women with non-ultra-mutated DNA POLE and non-hypermutated MMRd tumors. Conversely, women with p53 abnormal tumors should undergo standard surgical staging and, if required, adjuvant therapy, as conservative management would be inappropriate [9].

CONCLUSION

This case highlights the rare occurrence of early-stage endometrial carcinoma in a young, nulliparous woman with persistent abnormal uterine bleeding, despite initially benign imaging findings. It underscores the importance of timely repeat evaluation, vigilant follow-up, and individualized management, especially in women desiring fertility. The identification of a POLE mutation further emphasizes the value of molecular testing in guiding prognosis and long-term care. Together, these findings reinforce the need for early intervention and comprehensive, personalized treatment strategies in complex gynecological conditions.

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