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Fertility Preserving Management of Grade 2 Endometrial

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Abstract

Background: Endometrial cancer, although typically diagnosed in postmenopausal women, can rarely affect younger individuals, presenting a unique challenge when fertility preservation is desired. Studies have shown that oral progestin and progestin-releasing Intrauterine Devices (IUDs) can induce regression in endometrial hyperplasia and grade 1 endometrioid endometrial carcinoma. However, there is limited information available on the effectiveness of these treatments in women with grade 2 disease.

Case: A 29-year-old woman was diagnosed with grade 2 endometrial carcinoma during investigations for secondary infertility. She expressed a strong desire for future fertility and, after thorough counseling, underwent conservative management with the placement of a Levonorgestrel-Releasing Intrauterine Device (LNG-IUD) combined with oral megestrol acetate for 12 months. The patient underwent multiple endometrial samplings during this period to monitor disease regression. Subsequently, she conceived spontaneously but experienced a first-trimester missed abortion. Remarkably, she conceived spontaneously again and is currently pregnant, with her baby expected in March 2025.

Conclusion: In young patients seeking to preserve fertility with grade 2 endometrial cancer, a progestin-releasing IUD combined with oral progesterone after hysteroscopic tumor resection may offer a viable treatment option.

Introduction

Endometrial cancer is typically treated with hysterectomy as the primary approach. However, in certain cases where fertility preservation is a priority, progestin-based therapy can be considered as a temporary measure. This approach is particularly suitable for carefully selected women who are of childbearing age and have well-differentiated (G1) endometrioid endometrial cancer that is limited to the inner layer of the uterus (intramucous) [1,2].

Data on treating moderately differentiated (G2) endometrial tumors while preserving fertility is scarce. The available information, mostly from case reports and small retrospective studies, does not provide clear conclusions about using conservative methods in these cases, especially regarding long-term outcomes [3-9]. G2 endometrioid endometrial cancers typically show lower response rates to progestin therapy compared to G1 cases. Complete regression rates are also lower, and it usually takes longer to achieve complete regression in G2 tumors [10,11].

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When deciding on fertility-sparing management for endometrial cancer, it is crucial to consider the oncological risks associated with potentially incomplete diagnosis or treatment. The accuracy of preoperative assessments for tumor grade and myometrial invasion can vary, particularly for higher-grade tumors. This variability can lead to higher risks if definitive surgery is delayed for fertility preservation, especially in early-stage G2 endometrial cancer [12,13].

Case Presentation

A 29-year-old woman, previously healthy, presented with concerns regarding secondary infertility. During investigations, she was incidentally found to have an endometrial polyp. Histopathological examination revealed endometrial adenocarcinoma. Her staging work up showed no distance metastasis by CT scan of the chest-abdomen-pelvis and endometrial thickening, as per pelvic MRI, measures approximately 2.5 cm without visible masses, and there are no significant signs of pelvic lymph node enlargement (Figure 1).

The histopathological review, conducted by an experienced pathologist in Gynecologic cancer, confirmed the presence of endometrial endometrioid adenocarcinoma, graded as FIGO grade 2, in the endometrium following curettage. The tumor exhibits solid areas. Additionally, the background endometrium displays features of an endometrial polyp and chronic endometritis. Immunostaining for PAX-8 revealed positive results in tumor cells. Immunohistochemical testing for Mismatch Repair (MMR) Proteins showed intact nuclear expression of MSH6 and PMS2, indicating a low probability of Microsatellite Instability-High (MSI-H), Image 2. Molecular testing for POLE mutations, which is an important component of the molecular classification of endometrial cancer, was not performed due to unavailability at our institution. While this represents a limitation in fully categorizing the tumor's molecular profile, the intact MMR protein expression and clinical context provided a sufficient basis for the therapeutic decisions made.

Genetic testing was done and showed a Variant of Uncertain Significance, c.22G>C (p.Gly8Arg), was identified in NTHL1; regarding the test that was done it is a sequence analysis and deletion/duplication testing of the 84 genes listed in the Genes Analyzed section. Invitae Multi-Cancer Panel

Despite recommendations for total abdominal hysterectomy and bilateral salpingo-oophorectomy with sentinel lymph node of the pelvis in accordance with our guidelines, the patient expressed a strong desire for fertility preservation. So, our multidisciplinary team recommended a less invasive approach consisting of hysteroscopy, with resection of any residual tumor, and hormonal therapy utilizing a levonorgestrel-releasing Intrauterine Device (IUD) along with megestrol. Following this recommendation, the patient underwent hysteroscopy on April 26, 2022, upon examination, the patient's vulva and vagina appeared normal, and the cervix exhibited a healthy appearance. Hysteroscopy revealed postoperative changes at the upper posterior wall of the endometrial cavity, extending towards the fundus, with dusky tissues observed in the same area. Resection of the base of the polyp was done, and retrieved tissues was sent for histopathological examination. Subsequently, cauterization of the posterior wall using ball cautery was conducted, and insertion of a levonorgestrel-releasing Intrauterine Device (IUD) with a total dose of 52 mg and daily released dose of approximately 20 mcg was done. The histopathological examination revealed late proliferative to early secretory endometrium with fibrin thrombi, and no morphologic evidence of malignancy was observed, image 2G. She was started on megestrol therapy at a dose of 200 mg once daily from May 12, 2022, until May 30, 2023.

The patient's progress was closely monitored through a series of follow-up appointments aimed at assessing her response to treatment and overall health. Specifically, three follow-up hysteroscopies with endometrial biopsies were conducted on specific dates: June 9, 2022; December 13, 2022; and September 12, 2023.

During the initial follow-up on June 9, 2022, histopathological analysis revealed a decidualized endometrium, indicating a consistent response to progestin treatment, image 2H. This finding was indicative of the desired effect of progestin therapy on the endometrial tissue.

Subsequent follow-ups on December 13, 2022, and September 12, 2023, showed further positive outcomes. The biopsy results on December 13, 2022, indicated decidualized stroma and atrophic glands, which are consistent with the expected treatment effect. This demonstrates continued progress in the patient's response to the prescribed therapy.

On September 12, 2023, the histopathological findings revealed chronic endometritis with secretory changes and stromal decidualization. While chronic endometritis may indicate ongoing inflammation, the presence of secretory changes and stromal decidualization suggests a favorable response to treatment, with no evidence of hyperplasia or malignancy observed in any of the biopsies.

These sequential findings from the follow-up hysteroscopies and endometrial biopsies highlight the patient's positive response to progestin-based therapy. The absence of hyperplasia or malignancy further confirms the effectiveness of the treatment in managing the patient's condition while preserving fertility.

Throughout the surveillance period, the patient underwent pelvic MRI scans to complement the follow-up hysteroscopies and endometrial biopsies. Specifically, MRI scans were conducted on May 10, 2022, March 12, 2023, and June 12, 2023, providing valuable insights into the patient's condition.

The overall impression from these MRI scans was reassuring, as there were no suspicious masses or interval changes compared to previous scans. This consistency in findings underscores the effectiveness of the treatment protocol and the patient's continued response to therapy.

After her latest hysteroscopy and endometrial biopsy, which included the removal of the Intrauterine System (IUS), her case was thoroughly discussed with the GYN MDC. The final decision was to allow her to attempt conception, with close monitoring by her medical oncologist and gynecologic oncology surgeon. She underwent assessment in December 2023, and a CT scan of the chest, abdomen, and pelvis was performed. The scan revealed no pelvic mass lesions that needed correlation with recent pelvic MRI findings and no evidence of distant visceral metastasis. These results are reassuring, indicating a stable and positive response to treatment. The absence of concerning masses and distant spread supports the effectiveness of her current management plan, emphasizing the importance of ongoing surveillance and therapeutic strategies to ensure her continued well-being.

After her last visit and CT scan, the patient became pregnant the following month. Her last menstrual period was on January 5, 2024, and the viability of her pregnancy was confirmed by ultrasound during her fourth week of gestation. However, during a follow-up examination one month later, she was diagnosed with a missed abortion at eight weeks. Subsequently, on March 27, 2024, she underwent surgical evacuation of the products of conception. Histopathological examination of the evacuated tissues revealed decidua and chorionic villi, confirming the presence of products of conception, with no evidence of malignancy detected, Image 2I. And she is pregnant now in her third trimester, which is uneventful till the moment.

This case underscores the challenges encountered when managing endometrial cancer in young women with fertility preservation concerns. Close monitoring, multidisciplinary collaboration, and patient-centered decision-making are imperative in such cases to optimize outcomes while addressing the patient's individual preferences and concerns. Further evaluation of imaging findings and long-term follow-up will be crucial in guiding ongoing management and assessing treatment response.

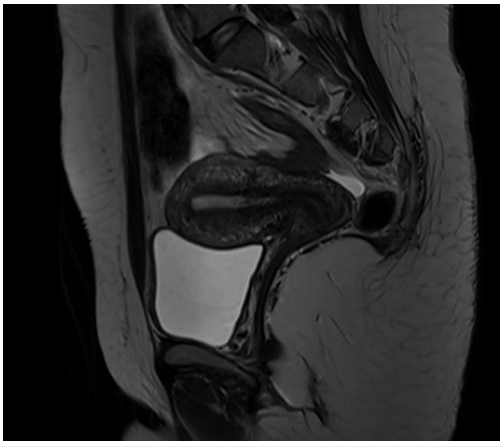

Figure 1: Pretreatment pelvic MRI showing thickened endometrium.

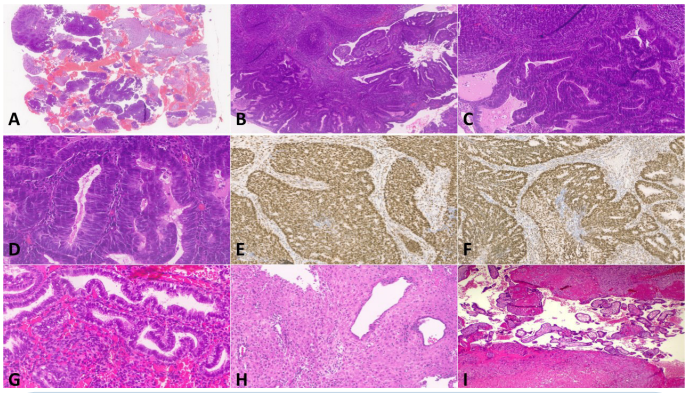

Figure 2: **(A-D)** Histopathologic examination of the curettage revealed endometrial endometrioid adenocarcinoma, FIGO grade 2 with focal solid growth (H&E 1x, 10x, 20x and 40x). **(E-F)** Immunohistochemical testing for Mismatch Repair (MMR) Proteins showed intact nuclear expression of PMS2 and MSH6 respectively. **(G-H)** Histopathologic examination of subsequent biopsies showing changes consistent with hormonal therapy: secretory phase endometrium **(G)** and decidualized stroma with atrophic glands **(H)** (H&E: 10x) **(F)**. I: Histopathological examination of the evacuated tissues after missed abortion showing normal products of conception without malignancy (H&E: 4x).

Conclusion

This case highlights the complexities of managing endometrial cancer in young women desiring fertility preservation. By opting for surveillance and hormonal therapy, the patient avoided surgical intervention while aiming to maintain reproductive capacity. Close monitoring for disease recurrence and adverse effects of megestrol therapy is essential. Further research is warranted to elucidate the long-term efficacy and safety of hormonal therapy in this population.

Author declarations

Ethical clearance

This case report complies with the ethical guidelines of our institution, where such reports are exempted from IRB approval. All patient-related data have been anonymized to protect confidentiality, and no identifiable information is disclosed in the manuscript.

Acknowledgment

We extend our gratitude to the patient and their family for allowing us to share this case for educational purposes. We also acknowledge the support of the staff at King Hussein Cancer Center for their contributions during the patient's management.

Conflict of interest

We confirm that the authors have no conflicts of interest to disclose regarding the publication of this case report.

We appreciate your time and consideration of our work and would be happy to provide any additional information or materials as needed.

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