GYNECOLOGIC ONCOLOGY: CASE STUDY

Endometrial Cancer Following Levonorgestrel-Releasing Intrauterine System Insertion in Young Women with Atypical Hyperplasia: Two Case Reports and Literature Review

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Abstract

Levonorgestrel-releasing intrauterine system (LNG-IUS) insertion is the first-line treatment for atypical hyperplasia (AH) in young women who wish to retain their fertility. However, the procedure is not always effective, and may allow AH to progress to endometrioid endometrial cancer (EEC). Two young women with AH who wished to preserve their fertility developed EEC following 52-mg LNG-IUS in insertion at our institution. One was a 34-year-old woman diagnosed with endometrial cancer 2 years after LNG-IUS insertion. The second was a 30-year-old woman diagnosed 17 months after LNG-IUS insertion. Proactive molecular risk classification for endometrial cancer (ProMisE) classification revealed that the first and second patients had p53-abnormal (p53abn) EEC and mismatch repair deficient (MMR-d) EEC, respectively. MMR-d and p 53abn were frequently observed in both AH and EEC specimens. Studies suggest that MMR-d and p53abn are predictors of the occurrence adverse effects after fertility-preserving treatment for EEC. AH is a precursor of EEC. Therefore, p53 and mismatch repair (MMR) mutation may be used to identify women with AH who will not likely benefit from progestin therapy. Molecular assays in women with AH will likely be useful for identifying novel predictive biomarkers of progestin resistance and to improve the safety of conservative treatment. Combined assessment of progesterone receptor (PR) with these predictive molecular markers may improve the predictive ability.

Keywords Atypical hyperplasia · Endometrioid endometrial cancer · Fertility preservation · Levonorgestrel-releasing intrauterine system (LNG-IUS) · Mismatch repair deficiency (MMR-d) · p53-abnormal (p53-abn)

Introduction

Atypical hyperplasia (AH) may progress to endometrioid endometrial cancer (EEC). Without treatment, 28% of AH cases progress to carcinoma [1], with a concomitant carcinoma rate of up to 43% [2]. Total hysterectomy is advised due to underlying malignancy or cancer progression risk [1–3]. However, conservative fertility-sparing treatments are often preferred in young patients. The levonorgestrel-releasing intrauterine system (LNG-IUS) is a first-line fertility-sparing treatment for young women with AH [3, 4]. However, the system does not always prevent EEC development [4]. We report two young women with AH who underwent LNG-IUS insertion as fertility-sparing treatment. In both cases, AH progressed to EEC. Molecular markers, such as p53 wild type and MRR-d, may be used to identify women with AH and EEC who may benefit from progestin treatment; however, additional work will be needed to identify and validate the usefulness of molecular markers.

Case Report

Case 1

A 34-year-old G1P1 woman with a body mass index of 28.4 and no significant medical or family history presented with a pelvic mass. Two years previously, she underwent hysteroscopy, dilation, and curettage to treat menorrhagia.
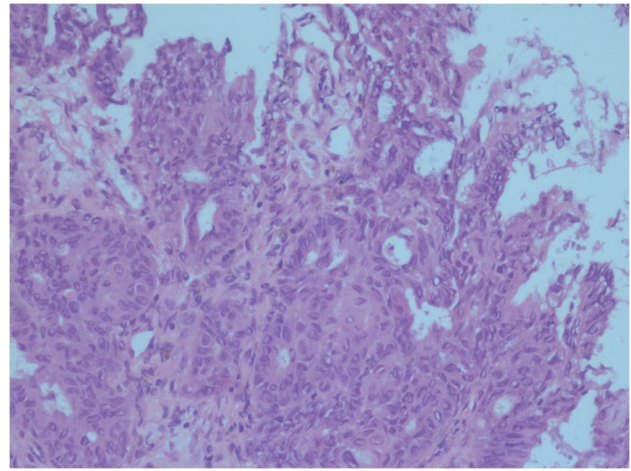
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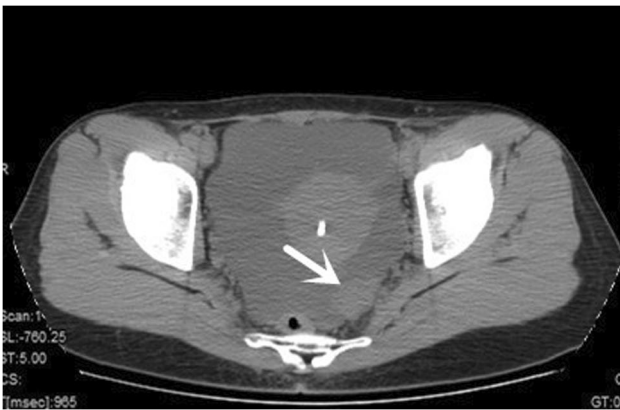
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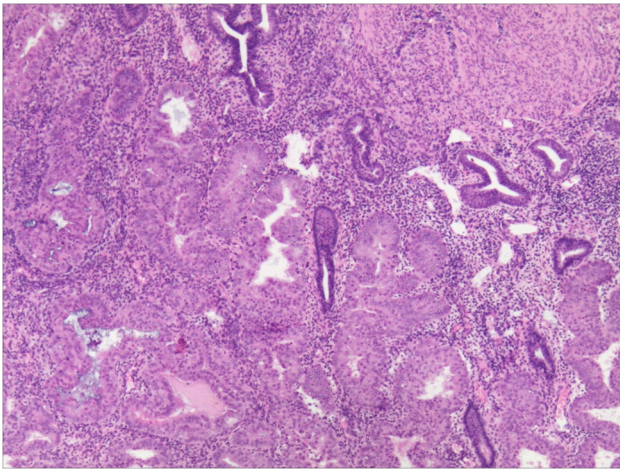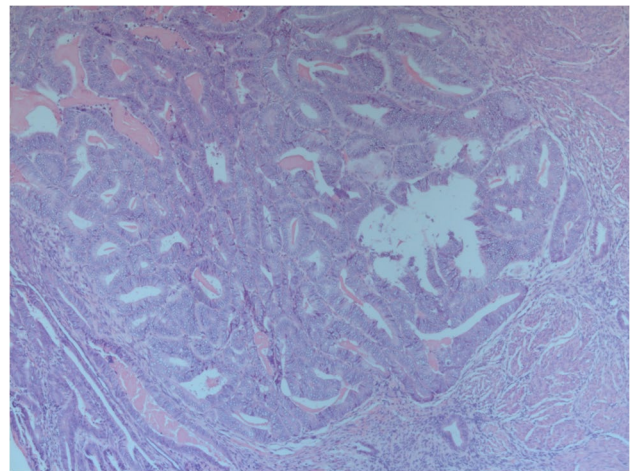
Fig. 1 Histology of the endometrium showed atypical hyperplasia. HE 4×

Fig. 3 Histology of the broad ligament mass which is seen in Fig. 2 revealed endometrioid cancer. HE 20×

Fig. 2 Pelvic cavity computed tomography scan revealed the LNG-IUS in situ and cancer metastases behind the uterus


Fig. 4 Histology of the hysterectomy showed endometrioid cancer in the endometrium. HE 4×

Histopathological examination revealed AH (Fig. 1), according to the 2014 World Health Organization classification system. She wished to preserve her fertility; therefore, she was treated with 40 mg/day medroxyprogesterone acetate for 6 months following her AH diagnosis. Two consecutive negative biopsies were obtained via quarterly endometrial evaluations. Subsequently, a 52-mg LNG-IUS was inserted. Therefore, assisted reproduction was recommended. However, fertility specialist and follow-up appointments were disrupted due to COVID-19 pandemic. Two years after LNG-IUS insertion, the patient presented with a pelvic mass (Fig. 2) and underwent debulking surgery. Histopathological findings suggested EEC (Fig. 3). Immunohistochemical testing revealed that the patient was ER, PR, CK5/CK6, CK, KI-67, and PAX-8 positive; and PTEN, CDX-2, WT-1, CEA, CK20, and p53 negative. Uterine histopathological examination revealed no ovarian or fallopian tube abnormalities,

and the presence of three cancerous lesions located in the endometrium (Fig. 4), intermuscular layer, or serosal surface of the uterine body. Proactive molecular risk classification for endometrial cancer (ProMisE) revealed p53-abnormal (p53abn) EEC.

Case 2

A 30-year-old G2P1 woman with a body mass index of 22.3 and no significant medical or family history presented with a 6-month history of abnormal uterine bleeding. Seventeen months previously, she underwent hysteroscopy and polypectomy for menorrhagia caused by a lower uterine segment polypoid. A histopathological examination revealed atypical endometrial polyps (Fig. 5). She wished to retain
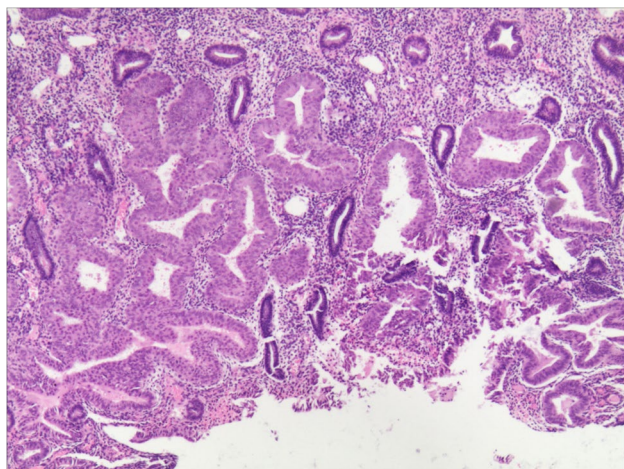
Fig. 5 Histology of the endometrium revealed atypical endometrial polyps. HE 4×

fertility; therefore, for the following 6 months, she was treated with 40 mg/day medroxyprogesterone acetate. Two consecutive negative biopsies were obtained via quarterly endometrial evaluations. Subsequently, a 52-mg LNG-IUS was inserted. Seventeen months later, she presented with a 6-month history of abnormal uterine bleeding and was unable to see her doctor due to the COVID-19 pandemic. Magnetic resonance imaging revealed a lower uterine mass (Fig. 6) with slightly irregular margins. A hysteroscopy with biopsy was performed. Histopathological examination revealed well-differentiated endometrioid adenocarcinoma (Fig. 7). Subsequently, staging was performed. Immuno-histochemical test results revealed CKpan, Ki-67 (approximately 65%), P53, PMS2, ER, PR, vimentin positivity, and MLH1, MSH6, napsin A, PTEN, and NSH2 negativity. ProMisE classification revealed mismatch repair (MMR)-deficient (MMR-d) EEC.

Discussion

Several progestogens have been used for conservative treatment of EH, with LNG-IUS considered the most effective. Despite seemingly responding well to levonorgestrel, AH may progress to EEC after LNG-IUS insertion. Among all case reports included in Medline published in English prior to October 1, 2021, nine are cases of EEC following LNG-IUS insertion [5–12]. Including ours, there are 11 reported cases of EEC following LNG-IUS insertion. Five, two, and three patients underwent LNG-IUS insertion for menorrhagia treatment, contraception, and endometrial protection, respectively. No reason for LNG-IUS insertion was given in three patients. Moreover, four patients had normal pre-insertion hysteroscopic findings. Clinical details of the 11
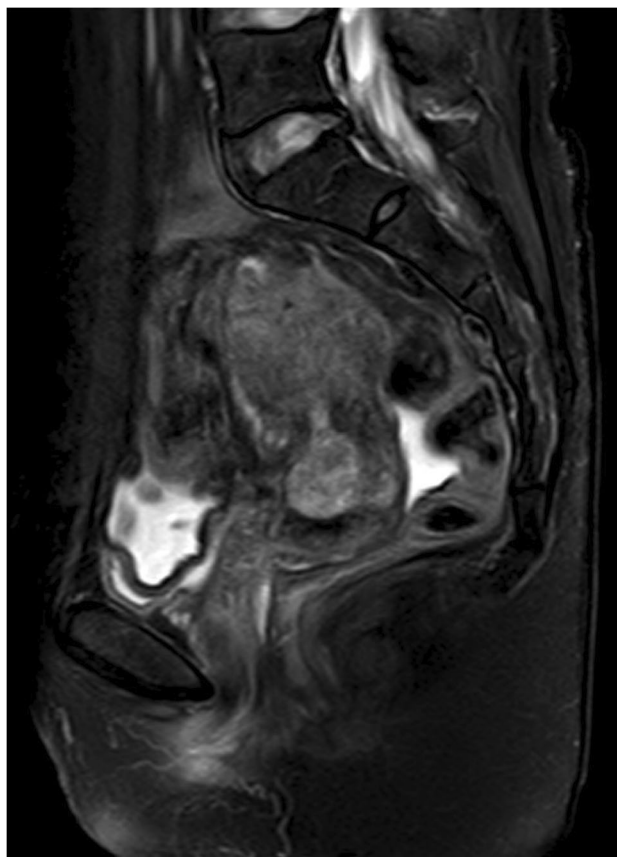
Fig. 6 Pelvic cavity magnetic resonance imaging scan showed a mass with slightly irregular margins occupying the lower uterine segment

patients are summarized in Table 1. These findings suggest the existence of a subtype of AH with intrinsic or emergent progestin resistance, the identification of which is critically needed to improve patient selection for fertility preservation.
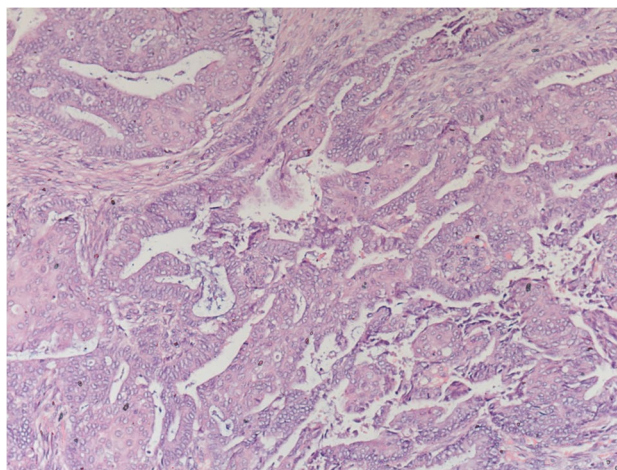
Fig. 7 Uterine histology confirmed well-differentiated endometrioid adenocarcinoma. HE 10×

Table 1 Summary of the literature

No	Age	Purpose	Previous pathology	Time (months)	Finally pathology	FIGO stage	References
1	54	Heavy periods	Proliferative endometrium	18	EC	IA1	Sinha [5]
2	54	HRT	Proliferative endometrium	12	EC-G1	IIB	Jones [6]
3	48	Menorrhagia	Not sampled	36	EC-G2	IIIC	Jones [6]
4	36	Contraceptive	Not sampled	12	EC-G1	IB	Abu J [7]
5	55	Heavy periods	Not sampled	48	EC-G2	IC	Ndumbe [8]
6	39	Heavy periods	Nonsecretory endometrium	48	EC-G2	IB	Flemming [9]
7	56	Heavy periods	Negative find	60	EC	IB	van der [11]
8	50				EC-G1	IA	Thomas [10]
9	52	Contraceptive	Not sampled	46	EC- G1	IA1	Kuzel [12]
10	34	Fertility preservation	Atypical hyperplasia	24	EC-G2	IIIB	Current series
11	30	Fertility preservation	Atypical hyperplasia	17	EC-G1	II	Current series

Purpose, purpose of the LNG-IUS insertion; previous pathology, endometrial pathology before the LNG-IUS insertion; time, the time since the LNG-IUS inserted to endometrial cancer was diagnosed

EC endometrioid adenocarcinoma; *G1* grade 1; *G2* grade 2

Multiple clinicopathological factors have been investigated as potential indicators of the progestin response in EH and EEC; however, most studies have reported non-significant or conflicting results. For example, obesity is a leading risk factor for EH and EEC in premenopausal women. Some studies have shown that obesity is associated with failure to achieve AH and EEC regression and increased recurrence, whereas others have reported no association between obesity and outcome. Other clinical factors, including age, menopause status, diabetes, gravidity, parity, polycystic ovarian syndrome, smoking, and hypertension, have been investigated; however, reported findings vary among studies. In addition, studies investigating the effectiveness of commonly used pathological markers such as progesterone receptor (PR) and estrogen receptor (ER), androgen receptor (AP), heat shock protein family A member 5 (HSPA5), BCL2-associated X (BAX), Ki67, B-cell lymphoma 2 (BCL2), cytochrome c oxidase subunit II (COX2), cleaved caspase, mutL homolog 1 (MLH1), phosphatase, paired box 2 (PAX2), and tensin homolog (PTEN) produced non-significant or conflicting results. To date, PR and ER have been reported as marks of AH and EEC. However, conflicting results have been reported regarding the predictive value of PR and ER [13, 14]. Use of isoforms of PR, particularly PR β, appears to be promising [15]. Therefore, in addition to assessing PR expression alone, the function, subtype, and downstream gene activation of PR should be investigated. Both patients described in this report had elevated levels of PR and ER expression in endometrial tissue with AH. In both cases, AH progressed to EEC despite treatment with levonorgestrel. However, the fact that progesterone inhibits EH to endometrial cancer (EC) and promotes AH and EEC regression is undeniable. To some extent, progesterone has anticancer properties. The presence of AH and EC with

emergent progestin resistance may occur do to the failure of progesterone to confer anticancer effects. A combined assessment of PR and other molecular markers may improve the prediction of progestin resistance in patients with AH and EEC.

EC is increasingly classified according to specifications of the Cancer Genome Atlas (TCGA) or ProMisE system, which categorizes ECs into POLE mutated, MMR-d, p53 wild type, or p53abn. Patients 1 and 2 had p53abn and MMR-d EEC, respectively. An increasing number of studies have suggested that ProMisE can be used to reproducibly categorize, provide prognostic information, and identify predictive biomarkers in patients considering fertility-preserving treatments for EEC [16]. Among the four molecular subtypes included in the ProMisE classification system, patients with p53-abnormal ECs have the worst prognosis [17, 18], while those with ECs overexpressing of p53 are at increased risk of relapse and have poor survival rates [19]. In addition, mutations in p53 are associated with failure to achieve disease regression. Leon et al. suggested that patients with p53-abnormal ECs should be excluded from conservative treatment [20]. However, p53 variants occurring in the context of MMR-d or POLEmut EC should not be excluded [20]. In addition to p53abn, germline MMR-d tumors are associated with a poor prognosis [21]. Germline MMR-d EECs account for approximately 5–10% of MMR-d EECs. Germline mutations in MRR genes including MLH1, MSH2, MSH6, PMS2, and EPCAM resulted in loss of MRR protein deficiency [22, 23]. MRR germline mutations, known as Lynch syndrome (LS), are associated with an increased risk of both endometrial and ovarian cancer. Approximately 25% of young women with LS and EEC have comorbid ovarian cancer [24]. In addition, germline MMR deficiency is associated

with increased risk of recurrence and failure to achieve disease regression. Therefore, women with MMR-deficient EECs, particularly those with LS, require careful evaluation using both molecular and imaging methods. These women also require close monitoring if progestin therapy is offered [17, 21, 25–27]. Given the importance of MMR deficiency, the International Society of Gynecological Pathologists recommends that universal MMR testing be performed in young women who wish to preserve their fertility. Conversely, for patients with POLE-mutated and p53 wild-type tumors, prognosis is good; therefore, these women are ideal candidates for conservative treatment. Studies on the effects of fertility-sparing progestin therapy on some EC molecular subtypes have shown that POLE-mutated tumors, and p53 wild-type tumors with wild-type cyclin D1 and catenin beta 1 that are ER-positive and PR-positive, lack 1q32.1 amplification, have low levels of L1 cell adhesion molecule expression and DNA damage, and are without Lynch syndrome that are potential candidates for conservative therapy [28].

AH is a precursor of endometrioid carcinoma. There is a high level of concordance in genetic mutations observed between paired AH and EEC specimens [29]. Mutations identified in the patients described in this report also had highly concordant genetic mutations. ProMisE classification in patient 1 revealed p53abn EEC. Immunohistochemical examination of the AH specimen of patient 1 did not reveal p53 positivity. The ProMisE classification in patient 2 revealed MMR-d EEC. We evaluated MLH1, MSH6, PMS, and MSH2 via an immunohistochemical examination of the AH specimen from patient 2. Results observed differed from those of advanced endometrial carcinoma specimens only with respect to MSH2. Detailed pathological features of both patients are summarized in Table 2. Mutation of *TP53* and the resultant inactivation of p53 contributes to cancer development, progression, and metastasis. Moreover, the presence of a mutation in p53 is associated with resistance to therapy and poor prognosis. p53abn has also been associated with failure to achieve disease regression in women with AH. Individuals with MMR deficiencies have a significantly increased risk of developing EC. In addition, MMR protein deficiency, commonly associated with LS, is predictive of a

poor response to progestin treatment in AH and EEC [15]. Therefore, p53abn and MMR-d may be predictive biomarkers of progestin resistance [28].

Molecular assays used to identify new predictive biomarkers and improve the safety of conservative treatment in women with AH are needed. An analysis of the TCGA program and other systematic cancer genome sequencing studies showed that cancers are driven by mutations in tumor suppressors and oncogenes, without chromosomal translocations [30–32]. Li et al. showed that AH and healthy samples shared less than 5% similarity regarding mutations identified, indicating clonality with a high degree of divergence [33]. Mutational profiles of paired AH and EC are highly concordant in the majority of cases [34, 35]. Evidence of clonal evolution has been demonstrated in whole-exome sequencing studies of paired AH and concurrent EC [33]. Multiple AH lesions may arise concurrently or metachronously from the endometrium as a result of the "field effect". Some AH lesions may be more likely to transition to EC than others. AH, which is associated with a high risk of EC, may be resistant to progesterone. Therefore, detailed geographical mapping of the endometrium is needed to fully assess the heterogeneity of molecular alterations among individual AH lesions [33]. Whole-exome sequencing of paired AH and EC samples may identify molecular markers of progesterone resistance, and mutations with significant overlap among AH and EC may be genetic markers of progesterone resistance.

Conclusion

In summary, LNG-IUS insertion can effectively treat AH; however, it is sometimes ineffective due to progestin resistance. Cases presented in this report underscore the importance of regular follow-up post-LNG-IUS insertion. Genomic analyses provide an excellent opportunity to stratify risk of EC progression and may be useful for identifying molecular markers of EECs in patients considering fertility-preserving treatments. There was a high degree of concordance among genes mutation identified in AH and EEC specimens. Molecular assays have the potential to be useful for identifying novel predictive biomarkers of

Table 2 Pathological features of our patients

No	Specimens	PR	ER	p53wt	MLH1	MSH6	NSH2	PMS2	ProMisE
Case 1	AH	+	+	−					
	EEC	+	+	−					p53abn
Case 2	AH	+	+		−	−	+	+	
	EEC	+	+		−	−	−	+	MMR-d

PR progesterone receptor; *ER* estrogen receptor; *p53wt* p53 wild type; *ProMisE* proactive molecular risk classification for endometrial cancer; *AH* atypical hyperplasia; *EEC* endometrioid endometrial cancer; *p53abn* p53-abnormal; *MMR-d* mismatch repair deficient

progestin resistance and improving the safety of conservative treatment in women with AH. Combined assessment of PR with identified molecular markers may improve predictive accuracy.

Data Availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval This is an observational study. The Second Hospital of Hebei Medical University Research Ethics Committee has confirmed that no ethical approval is required.

Consent to Participation Written informed consent was obtained from the parents.

Consent for Publication Patients signed informed consent regarding publishing their data and photographs.

Conflict of Interest The authors declare no competing interests.

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