



Fertility-sparing treatment for Lynch syndrome complicated by atypical endometrial hyperplasia—multidisciplinary consultations: a case report

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Abstract: Lynch syndrome (LS) is an autosomal dominant hereditary tumor syndrome characterized by tumors in the uterus and ovaries of female patients. Atypical endometrial hyperplasia (AH) or endometrial carcinoma (EC) in LS patients is caused by germline mutations. Few studies have analyzed the role of estrogen or the role of fertility-sparing therapies for these patients. Here we reported a LS patient who had AH and attempted to preserve her fertility under close monitoring and after multidisciplinary consultations. The lesion was completely reversed after 3 months of treatment with levonorgestrel-releasing intrauterine system (LNG-IUS), and no recurrence was noted during the 9-month follow-up. The possibility of LS should be considered in AH patients with a family history of relevant cancers. Meanwhile, for LS patients with complicated AH and a strong desire to retain infertility, fertility-sparing treatment may be attempted to reverse endometrial lesions under close monitoring and after adequate evaluation.

Keywords: Lynch syndrome (LS); atypical hyperplasia (AH); endometrial cancer; fertility-sparing treatment

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Introduction

Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common type of hereditary colorectal syndrome. As an autosomal dominant cancer syndrome, LS is associated with an increased risk for tumors in the rectum, uterus, ovary, stomach, small intestine and other organs (1).

For young patients with endometrial carcinoma (EC) and/or precancerous endometrial lesions—i.e., atypical hyperplasia (AH)—long-term estrogen exposure without progesterone antagonism is considered the main cause of the disease. Therefore, fertility-sparing progestin therapy after adequate evaluation is feasible in these patients. The

complete remission rate for patients with EC or AH has been reported as 73% to 89% and 90%, respectively (2-4).

The incidence of EC is about 3% in the general population but reaches 40% to 60% in women with LS (5,6). In addition, LS patients with EC are relatively young, with an average age of onset of 49.7±10.5 years, which is 10 to 20 years younger than the average age of EC in the general population (7,8). Young patients with early stage EC who desire a fertility-sparing therapy are often given progestin based treatment. However, in patients with LS, the etiology is not necessarily related to the unopposed estrogen exposure, but rather to the genetic alterations in the tumor (e.g., MLH1, MSH2, MSH6, and PMS2 genes,

as documented in the literature) (1). Since few studies have investigated the role of fertility-sparing progestin therapy in LS patients, its efficacy and safety remain unclear (9).

Here, we report one case of LS complicated by AH. Both the patient and her family strongly requested the preservation of her fertility potential. After multidisciplinary discussions, the levonorgestrel-releasing intrauterine system (LNG-IUS) was applied for the fertility-sparing treatment. Three months later, the lesion was completely reversed, and no recurrence was noted during a 9-month follow-up.

Case presentation

A 39-year-old woman (gravida 1, abortion 1; BMI 21.3 kg/m²) was admitted because of “irregular vaginal bleeding for half a year and atypical endometrial hyperplasia (AH) was detected by diagnostic curettage in our hospital”. Since the patient had a strong desire to preserve her fertility, multidisciplinary consultations were arranged.

Multidisciplinary consultations before treatment

- (I) Department of Medical Imaging: ultrasound revealed that the endometrium measured 0.3 cm in single-layer thickness, with uneven echoes; normal bilateral adnexa; bilateral breast cysts were visible (tendency to develop benign tumors).
- (II) Department of Gynecologic Oncology: (i) laboratory tests: tumor markers (CA125, HE4), liver function, and coagulation function were within the normal ranges. (ii) Comorbidities: she had no cardiovascular or cerebrovascular disease; also, she had no history of thrombosis, smoking, or allergy. (iii) Family history: her father was diagnosed with colon cancer at the age of 63, and her grandmother was diagnosed with breast cancer at the age of 55. Since the patient had a family history of relevant cancer, the possibility of LS was considered. A second hysteroscopy was performed, which revealed that the endometrium was thin, a white floccule sized 0.5×0.3×0.2 cm³ was observed at the posterior wall, and there were no truncated blood vessels or glandular openings on the endometrial surface. A biopsy was obtained from the endometrium
- (III) Department of Pathology: (i) during the first consultation meeting attended by senior gynecologic pathologists, pathological analysis of the specimen

obtained by curettage revealed “atypical endometrial hyperplasia”. (ii) Hysteroscopic biopsy revealed AH along with ER (+), PR (+), P53 (–), MLH1 (+), MSH2 (–), MSH6 (–), and partial loss of PMS2.

- (IV) Department of Reproductive Endocrinology: anti-Müllerian hormone (AMH) level was 0.2 ng/mL, suggesting poor ovarian reserve, Insulin release testing showed a fasting blood glucose of 6.75 mmol/L and a 2-hour 75-g oral glucose tolerance test showed a blood glucose of 14.99 mmol/L. Sex hormone measurement results were within the normal ranges.
- (V) Department of Endocrinology: the patient was diagnosed with type 2 diabetes mellitus (T2DM). She was advised to adjust her diet, test blood sugar level regularly, and take metformin 500 mg twice daily.

Summary of multidisciplinary consultations

- (I) The current diagnoses include AH, LS (suspected diagnosis), T2DM and poor ovarian reserve.
- (II) According to her family history and immunohistochemistry (IHC) results, LS was highly suspected, and therefore, early genetic testing was recommended. However, since LS-related cancer lesions are a consequence of gene mutations, the efficacy of fertility-sparing progestin treatment remains unclear. In addition, given the poor ovarian reserve, the patient’s fertility would be even more compromised by the time a complete reversal of the endometrial hyperplasia would be achieved. Nevertheless, both the patient and her family were still interested in preserving her fertility potential. Since the patient had T2DM, and her breast cysts were still undergoing further examinations, the application of levonorgestrel intrauterine system (LNG-IUS) was considered for preserving her fertility. The endometrium was to be assessed 3 months after drug administration.

Multidisciplinary consultation during the first stage of treatment (by the 3rd month)

- (I) Department of Medical Imaging: ultrasound revealed that the endometrium measured 0.2 cm in single-layer thickness, with slightly uneven echoes; the intrauterine device (IUD) was well located in the uterus.
- (II) Department of Gynecologic Oncology: (i) there

were no adverse reactions during the treatment. The patient's body weight decreased by 4.5 kg. No obvious menstrual cycle or spotting were noted. Her blood sugar level was within the normal range. Tumor markers, liver function, and coagulation function were normal. (ii) Hysteroscopy showed that the endometrium was thin and pinkish; grayish-white polypoid lesions sized about 0.2 to 0.5 cm were seen at the bilateral uterine horns. Endometrial hyperplasia was visible on the surface where specimens were harvested for pathological examination.

- (III) Department of Pathology: atrophic glands and stromal decidualization-like change were found in all the examined endometrial tissues, although no proliferative change was visible.
- (IV) Department of Gastrointestinal Surgery: genetic testing revealed a germline mutation in the MSH2 gene, and thus a diagnosis of LS was confirmed. Colonoscopy showed multiple colorectal polyps, and polypoid hyperplasia was found during pathological examination.
- (V) Department of Breast Surgery: the breast cysts were benign nodules, as suggested by ultrasound.

Summary of multidisciplinary consultations

- (I) The endometrium showed good response to progesterone therapy, and no adverse drug reactions occurred. The use of LNG-IUS can be continued. A re-evaluation of the endometrium after 3 months of consolidation therapy is suggested, and early reproductive genetic counseling is feasible.
- (II) Regular follow-up in the departments of breast surgery and gastrointestinal surgery is required. The first-degree relatives of the patient should receive further examinations to rule out potential LS.

Multi-disciplinary consultations during the second stage of treatment (by the 6th month)

- (I) Department of Medical Imaging: Ultrasound revealed that the endometrium measured 0.15 cm in single-layer thickness, with even echoes; the intrauterine device (IUD) was located at the central part.
- (II) Department of Gynecologic Oncology: (i) there was no adverse reaction during the treatment. Her body weight increased by 4 kg. No obvious menstrual cycle was noted. Her blood sugar level

was within the normal range. Tumor markers, liver function, and coagulation function were normal. (ii) Hysteroscopy showed that the endometrium was extremely thin, evenly distributed, and pinkish in color. A 0.5 cm pinkish polypoid lesion was seen at the junction of the lower uterine segment and endocervix, along with dendritic thickening of vessels on the surface. Specimens harvested by biopsy were sent for pathological examination.

- (III) Department of Pathology: no proliferative changes were observed in the submitted tissues, suggesting a good response to progesterone therapy.
- (IV) Department of Reproductive Endocrinology: the AMH level was <0.06 ng/mL.
- (V) Department of Breast Surgery: ultrasound showed no obvious abnormality.

Summary of multidisciplinary consultations

The progesterone treatment was effective and the endometrial lesions were completely reversed. However, the patient has a history of infertility and her ovarian function has been declining. The chance of a successful pregnancy via assisted reproductive technologies is extremely low. Maintenance LNG-IUS treatment is thus recommended.

Follow-up

The patient was followed up for 9 months (the last outpatient follow-up visit was on April 16, 2019). The IUD was properly placed, and no recurrence was observed.

iMDT discussion

Discussion among physicians from the West China Second University Hospital

LS

LS is an autosomal dominant hereditary tumor syndrome characterized by tumors in the colon or rectum, uterus, and ovaries of female patients (10). The main causes of the disease are the germline mutations of the mismatch repair gene (MMR) family including *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and the large fragment deletion of the 3' portion of the epithelial cell adhesion molecule (*EPCAM*) gene (formerly called *TACSTD1*), which lead to the epigenetic silencing of *MSH2*. The miscoded DNA cannot be corrected, eventually resulting in tumorigenesis (1,11-13).

The clinical diagnosis of LS is usually performed following a family history of LS or LS-related cancers. The specificity of the Amsterdam II criteria and revised Bethesda criteria for a diagnosis of LS are 61% and 49%, respectively (11). Criteria focused on Chinese LS pedigrees have also been made available (1). For patients with a family history of relevant cancers, genetic screening is recommended. Molecular diagnostic techniques include MMR protein IHC, detection of microsatellite instability (MSI), detection of MLH1 demethylation, and next-generation sequencing (NGS) for germline mutation. First, IHC or MSI detection is performed on the lesion specimen. Both screening methods have a similar sensitivity (77% to 100%) and specificity (38% to 81%). However, IHC is used more widely in clinical settings, as it is technically simple and easy to perform (14–16). When IHC or MSI testing of the tumor indicates MLH1 deletion, an analysis of MLH1 promoter methylation should be performed to exclude epigenetic silencing of MLH1. In case that MMR IHC of the tumor tissue shows deficient mismatch repair (dMMR) of MSH2, MSH6, and PMS2, MLH1 methylation is negative or MSI detection reveals high-frequency MSI (MSI-H), NGS should be performed. The diagnosis of LS would be made if there is evidence of germline mutation of MMR (1,11–13).

Association of LS with endometrial cancer

In 2013, The Cancer Genome Atlas (TCGA) categorized EC into polymerase epsilon (POLE), MSI, copy number abnormalities-low (CN-L), and copy number abnormalities-high (CN-H) based on genomic sequences, which accounts for 7%, 28%, 39%, and 26% of cases, respectively (17). Among them, the pathogenic mechanism of MSI is highly heterogeneous, with sporadic MSI caused by the hypermethylation of MLH1 promoter being the most common type, followed by hereditary LS caused by MSH2 inactivation due to MMR germline mutation and exon-level deletions in the 3' end of the *EPCAM* gene. There are also a few “Lynch-like syndromes” that have not been clearly defined: although MMR IHC suggests dMMR or MSI detection reveals MSI-H, genetic germline testing rules out the diagnosis of LS (17).

For women with LS, gynecologic tumors can present as their sentinel cancers; a retrospective review noted that gynecologic cancer was the sentinel cancer in over 50% of cases and preceded the colon cancer diagnosis by a median of 11 years (18). Patients with LS have a 40% to 60% risk of developing EC in their lifetime (10,19). Compared with non-hereditary EC, patients with LS develop EC at a

younger age, diagnosed at an earlier stage (stage I patients account for 66.6%), have a higher incidence of involvement of the lower uterine segment or development of ovarian cancer (OC) (25% and 21.6%, respectively) and have better prognosis (with a post-treatment 5-year survival rate of 88%); however, the distribution of histological types remains controversial (1,7,8,20). Furthermore, there is currently limited evidence concerning the impact of fertility and lifestyle on the risk of developing EC in LS patients.

According to the Prospective LS Database (PLS) and other literature, the risk of developing EC is 20–49%, 21–57%, and 16–71% for the *MLH1*, *MSH2*, and *MSH6* gene mutations respectively, with the corresponding prevalence of EC before 40 years old being 2%, 3%, and 0% (20,21). In order to reduce the risk of EC in LS patients, the Manchester International Consensus Group recommends that women with LS who have completed childbearing undergo prophylactic surgery around the age of 35 to 40 (20). For patients who have not undergone prophylactic surgery, endometrial biopsy, gynecological ultrasound, and serum CA125 testing may be performed every 1 to 2 years to rule out gynecologic tumors (1,13).

Association of LS with AH

AH is a precancerous lesion of the endometrium. EC can be found in specimens obtained from about 30% to 40% of AH patients undergoing hysterectomy immediately after diagnosis or receiving a second biopsy within 1 year (4,22).

Thus far, few articles have described the relationship between LS and AH. One study found that women with LS had a 3.9% (2/51) probability of developing AH (23). The largest study was performed at the University of Texas Medical Center in the United States. Of 118 randomly selected AH patients, 4 (3.4%) demonstrated loss of MMR protein expression; for patients with LS, there was a similar loss of MMR protein expression in AH tissue and EC tissue, whereas abnormal MMR expression was rare in the normal background endometrium (16). Berends *et al.* (24) confirmed the loss of MMR protein expression in early endometrial lesions (including simple hyperplasia, complex hyperplasia, and AH). Similarly, de Leeuw *et al.* (25) detected the loss of MMR protein expression in LS patients' endometrial lesions including simple hyperplasia, complex hyperplasia and AH, along with MLH1 methylation. Nieminen *et al.* (26) performed dynamic detection on the endometrium of 13 LS patients and concluded that the loss of MMR protein expression could be found in the endometrial tissue 12 years before the development of EC. IHC of MMR is

not routinely performed in AH patients. However, since our current patient had a suggestive family history, relevant tests were performed, which confirmed the presence of LS. Subsequently, early screening and clinical intervention of potential tumors will benefit our patient and her relatives.

In summary, MLH1 methylation and MMR germline mutations can also exist in AH patients. Meanwhile, abnormal MMR protein expression can be detected in early endometrial lesions in LS patients. Therefore, IHC screening should be considered in high-risk AH patients with a family history of LS associated cancers, so as to increase the detection rate of LS and facilitate clinical intervention in the early stages of the disease.

Relationship of LS-complicated endometrial lesions with fertility-sparing treatment

Generally, long-term estrogen exposure without progesterone antagonism is considered the main cause of AH and EC, and therefore fertility-sparing progestin therapy after adequate evaluation is feasible in these patients (7,9,27). Fertility preservation may be more relevant for LS patients with EC, because of the earlier age of onset; however, since the endometrial lesions are caused by genetic mutations, the efficacy of fertility-sparing treatment using progesterone remains unclear (1).

Among the guidelines and expert consensuses discussing the fertility-sparing treatment for AH and EC, only the European Society of Gynecological Oncological (ESGO) guidelines describe LS-complicated EC and its fertility-sparing treatment. According to the ESGO guidelines, the effectiveness of fertility-sparing treatment for EC in LS patients remains unclear.

At present, few studies have explored the correlation between endometrial lesions and progesterone treatment in LS patients. Dashti *et al.* (28) investigated 1,128 LS patients and found 133 patients (11.8%) had EC. The etiologies of EC in these patients had no significant correlation with exogenous or endogenous estrogen exposure; however, progesterone alone (administered via oral, intramuscular, and intrauterine topical routes) may have a protective effect on the endometrium.

A phase II clinical trial confirmed that the development of EC and AH in LS patients was similar to that in the general population (i.e., also based on endometrial hyperplasia), and short-term use of the progestin compound Depo-Provera (depo-MPA) or progestin-containing oral contraceptive pills (OCP) can effectively induce a decrease in endometrial proliferation in LS patients (23). Lucas *et al.* (16) reported

one AH patient with the loss of PMS2 protein expression (without receiving genetic testing), in whom EC developed after two years of progestin treatment. Sparac *et al.* (29) reported a LS patient who developed EC and had received fertility-sparing treatment. The patient's family history met the Bethesda criteria (without completing genetic testing) (12). The endometrial lesion was completely reversed after 3 months of treatment with oral medroxyprogesterone (MPA) 400 mg/d, and the patient completed childbearing (29). Marton *et al.* (30) described two LS patients with well differentiated EC within endometrial polyp that were treated by progestin with either MPA 400 mg daily or LGS-IUS for 3 months. In both patients, disease reversal was observed on repeated biopsies and both had subsequently achieved successful pregnancies.

Our current case involved a LS patient with AH. The lesion was completely reversed after 3 months of LNG-IUS treatment; however, the patient has not completed childbearing due to her ovarian insufficiency. Currently she is still receiving progesterone therapy and has not experienced relapse.

To summarize, progesterone may have protective effects on the endometrium of LS women and may even effectively reverse endometrial lesions. However, individual assessment should be performed before fertility-sparing therapy is considered.

Several issues regarding the diagnosis and treatment of the case should be further discussed

Question 1: can fertility-sparing treatment be attempted in LS patients complicated with EC/AH?

Expert opinion 1: Dr. Oded Raban & Dr. Walter H. Gotlieb

In a study performed by Zakhour *et al.*, progestin therapy had a lower resolution rate of grade 1 EC and complex AH in patients with abnormal MMR genes by IHC, compared to those with intact MMR genes (0% *vs.* 41%). However, patients in the dMMR group were significantly older, and had received various progestin regimens over the course of 13 years, none of which included LNG-IUS (31). Comparing progesterone receptor expression, a retrospective report did not demonstrate a difference between EC with a loss of MMR genes and EC with normal MMR expression (32). Given these data, progestin can be considered in LS patients with EC, bearing in mind the

lower response rate.

Expert opinion 2: Dr. Simone Ferrero

Yes, it can be attempted, however the patient should be exhaustively informed about the risk of LS transmission to the newborn (genetic consultation is recommended).

Question 2: can fertility-sparing treatment be performed in PR-negative LS patients complicated with EC/AH?

Expert opinion 1: Dr. Oded Raban & Dr. Walter H. Gotlieb

While most well differentiated EC are positive for progesterone receptors (PR), tumors that are PR negative (<10%) were reported to have a lower response rate compared to PR positive. Nevertheless, current guidelines do not recommend routine testing for PR, since even PR negative tumors can respond to progesterone treatment (9,33).

Expert opinion 2: Dr. Simone Ferrero

PR expression is predictive of response to progestin treatment (either oral or LNG-IUS). Therefore, this information should be clearly explained to the patient and, if she is strongly motivated, a conservative treatment can be attempted. In addition, the woman must be informed that her chances of success are lower than those of women with a PR positive EC/AH.

Question 3: are there any special considerations when choosing a fertility-sparing treatment for LS patients complicated with EC/AH (compared with ordinary EC/AH patients)?

Expert opinion 1: Dr. Oded Raban & Dr. Walter H. Gotlieb

Patients with LS have an increased risk for OC. Synchronous EC and OC can be found in up to 20% of LS patients, and these are characterized by an earlier age of onset, early stage, and endometrioid histology (20,34). Therefore, when considering fertility preservation, there is a place for careful evaluation of the adnexa, mainly in young patients (35). In addition, due to the increased risk of colorectal cancer, patients should undergo colonoscopy prior to fertility preserving conservative treatment.

Expert opinion 2: Dr. Simone Ferrero

The patient should be exhaustively informed about the risk of LS transmission to the newborn (genetic consultation is recommended).

Question 4: are there any special considerations during follow-up visits, efficacy evaluation, and treatment decision-making when performing a fertility-sparing treatment for LS patients complicated with EC/AH (compared with ordinary EC/AH patients)?

Expert opinion 1: Dr. Oded Raban & Dr. Walter H. Gotlieb

Various follow-up strategies post fertility-sparing treatment for EC/AH have been described, with current guidelines recommending reevaluation of the endometrium every 3–6 months (9,36). There are no specific recommendations addressing the subgroup of patients with LS. It is recommended that patients would try to conceive as soon as possible when complete response is achieved (33,37,38). Even though some data suggest that oophorectomy could be avoided in young patients with EC (39,40), for patients with LS and EC, hysterectomy with salpingo-oophorectomy should be considered and discussed with the patient once childbirth is completed.

Expert opinion 2: Dr. Simone Ferrero

There is no evidence about different follow-up visits for LS patients. When the patient satisfies her desire of pregnancy, it should be recommended (like the other patients) to perform surgical intervention explaining the it is likely that her recurrence risk is higher than in general population.

Conclusions

Since EC is the second most frequent tumor in LS, a young patient with EC should always be asked for the family history. Once diagnosed as LS and complicated with EC, conservation treatment in young women may be considered as an opinion, but strict selection criteria for inclusion are essential, including evaluation of her conditions, tumor grade, age, desire for pregnancy and fully informed consent.

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