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Case Report
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Mismatch Repair Status Analysis on Endometrial Biopsy as a Predictor of Endometrial Cancer Behavior in Fertility Sparing Treated Women

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Abstract

Conservative management for patients with mucosal-confined endometrial cancer is a safe approach. Due to the latest evidences, endometrial cancer molecular characterization results crucial for proper risk stratification.

A young woman with G1 endometrioid endometrial cancer diagnosed by hysteroscopy was treated conservatively. After cancer persistence, she underwent radical surgery for advanced disease. Post-hoc immunohistochemical analysis was performed comparing the first-diagnosis biopsy (mismatch repair deficiency) to surgical specimen (mismatch repair proficiency). Interestingly, not only the cancer changed biochemically, but it also shifted from a confined tumor to an advanced disease with bulky lymph nodes and negative endometrial infiltration. Eventually, the patient was diagnosed with Lynch syndrome.

A wiser evaluation of the mismatch repair deficiency should have guided to the proper therapeutic algorithm, also suggesting genetic tests. This case report represents an encouragement to further investigations on molecular assessment as a predictor for endometrial cancer risk stratification in conservative management.

Keywords: Cancer; Endometrium; Fertility; Genital Neoplasms; Immunohistochemistry

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Introduction

Endometrial Cancer (EC) is the fourth most diffuse malignancy in developed countries, also representing the most common gynecological cancer [1]. In about 80% of cases, EC is diagnosed when the disease is still confined to the uterus. Though total hysterectomy with bilateral salpingo-oophorectomy is considered the standard treatment, a conservative management, consisting in oral or intra-uterine progesterone with or without hysteroscopic endometrial resection and follow-up biopsies every 3 to 6 months, is recommended in women desiring off spring [2]. Although considered a safe approach, a subgroup of patients shows no cancer regression, recurrence or progression to more advanced stages [3]. For this reason, the study of new molecular markers able to predict response to conservative treatment is extremely important. Only a few small-population studies investigated the role of Mismatch Repair status (MMR) as a promising predictor marker for conservative treatment outcomes [4-6]. In this case report, we aim to bring to attention the peculiar clinical history of a young woman diagnosed with Mismatch Repair deficiency (MMR-d) EC on hysteroscopic biopsy, treated conservatively, with a atypical disease persistence: Complete local response with spreading of cancer to pelvic and aortic Lymph Nodes (LNs), with concurrent molecular switch into MMR-proficient immunophenotype.

Case Presentation

Medical history

A 37-year-old woman in good clinical conditions is referred to our attention. In her history no comorbidities or previous surgeries were reported. Family history was significant for colon cancer. The patient was nulliparous, with strong desire for offspring. In March 2017 she was diagnosed with endometrial polyposis through ultrasound, for which she underwent operative hysteroscopy in April 2017 in another hospital, with positivity for complex atypical Endometrial Hyperplasia (EAH). Histological samples from polypectomy were revised from our pathologists

Table 1: Results from IHC analysis: Comparison between endometrial biopsy (2017) and surgical specimen (2021).

	Endometrial biopsy (September 2017)		Surgery (February 2021)
Diagnosis	EAH (resected polyp)	G1 eEC (endometrial sampling)	eEC cells in metastatic LNs
MMR status	MSH2-, MSH6+, MLH1+, PMS2+ (MMR deficiency)	MSH2-, MSH6-, MLH1+, PMS2+ (MMR deficiency)	MSH2+, MSH6+, MLH1+, PMS2+ (MMR proficiency)
ER	1+, 60%	1+, 10%	1+; 5%
PR	3+, 85%	3+, 40%	1+; 1%
P53	missing data	missing data	wild type

EAH: Endometrial Atypical Hyperplasia; G1 Well-Differentiated; eEC: endometrioid Endometrial Cancer; LNs: Lymph Nodes

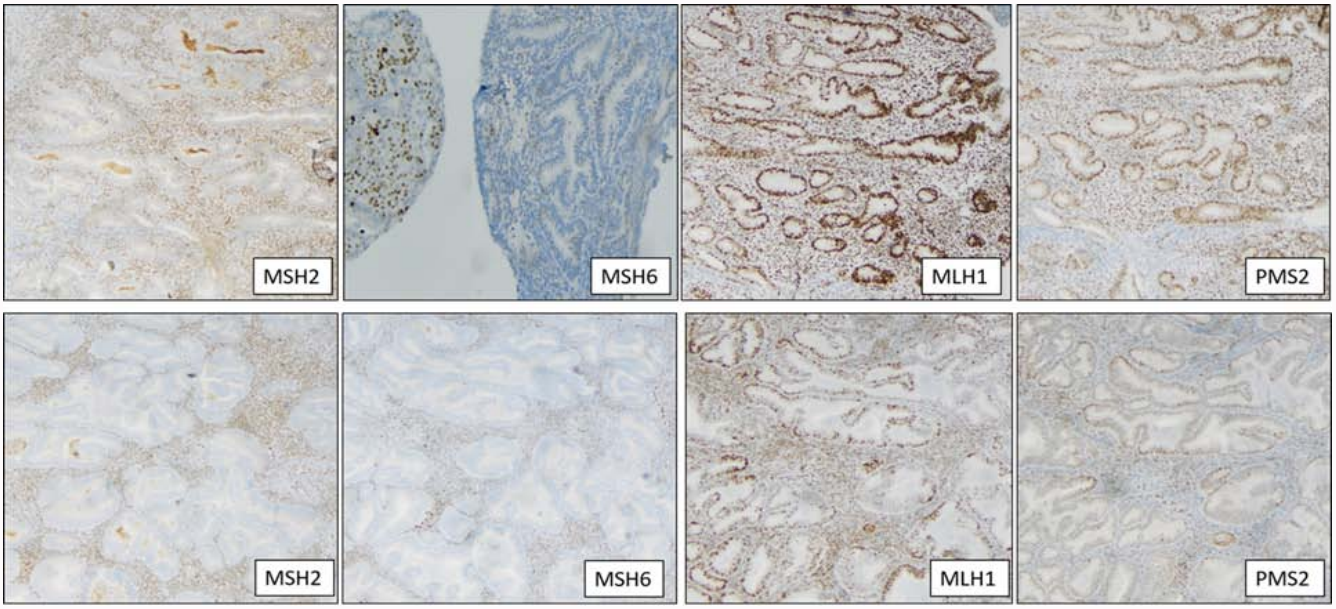

Figure 1: (IHC analysis from the first endometrial biopsy showing MMR-d pattern, September 2017). Upper line: EAH from the resected polyp with missing IHC staining forMSH2 protein (MSH2 negative). Lower line: EC from endometrial sampling with missing IHC staining for both MSH2 and MSH6 proteins (MSH2 and MSH6 negative).

with expertise in gynecology oncology, with diagnosis of EAH, with focal transformation into G1 (well differentiated) endometrioid EC (eEC). On MRI a 6 mm × 15 mm polypoid-like formation without evidence of myometrial infiltration was identified. The patient underwent polypectomy and endometrial biopsy in our hospital in September 2017. The polyp was positive for EAH and the endometrial biopsy was diagnostic for G1 eEC. The patient was prescribed Medroxyprogesterone acetate and a three-monthly follow-up plan with pelvic transvaginal ultrasound and scheduled hysteroscopies was programmed. In September 2018 endometrial biopsy resulted in EAH. This finding was confirmed in the following endometrial sampling in January 2019. The patient was advised to continue Medroxyprogesterone acetate and an intrauterine progesterone-medicated device (IUD) were positioned. In May 2020, the follow-up biopsy was diagnostic for G1 eEC. At ultrasound, an 11 mm × 9 mm × 11 mm hyperechogenic endometrial tissue at the uterine fundus and a minimal irregularity of the endometrial-myometrial margin at the anterior uterine wall were identified. Nevertheless, an additional endometrial biopsy in September 2020 was negative. The following histological examination in December 2020 confirmed a G1 eEC.

Transvaginal ultrasound (December 2020)

Endometrium was 5 mm thick and the medicated-IUD properly positioned. Ovaries appeared normal and no endopelvic effusions or dilatation of the renal pelvis were visible. At the aortic bifurcation, on the right, a hypoechogenic, inhomogeneous, a vascular formation of 12 mm × 7 mm with regular margins was identified. Other formations with the same ultrasonographic features were visible at the left external iliac vessels (16 mm × 13 mm) and at the left external iliac vessels (16 mm × 10 mm and 9 mm × 10 mm). The abovementioned lesions were to be referred in the first hypothesis to lymphadenopathies.

Chest-abdomen-pelvis TC scan with intravenous contrast (January 2021)

A 1.5 cm solid nodule suspected for lymphadenopathy was detected at the right iliac bifurcation. Along the internal iliac vessels, solid and uneven bilateral formations of 2.5 cm, suspected for pathological LNs, were identified. Non-confluent LNs of up to 1 cm was observed in the inguinal-femoral region bilaterally.

Oncofertility counseling

The patient was counseled on the clinical indication of a radical surgery. Once informed, the patient voluntarily chose to keep both ovaries.

Surgery (February 2021)

The patient underwent laparoscopic Querleu-Morrow class a radical hysterectomy, bilateral salpingectomy, ovarian suspension, systematic pelvic lymphadenectomy and removal of intercavoaortic lymphadenomegaly. Before hysterectomy, a cervical injection of indocyanine green 1 cc per side was performed, for which no fluorescent sentinel LN was identified. Lymphadenomegalies of 3 cm were identified in the external iliac and obturator region on the

right, and internal iliac area on the left. Hence, a bilateral pelvic lymphadenectomy was performed. On examination of the para-aorto-caval region, a lymphadenomegaly of 2 cm was found at the interaortocaval level and removed. Ovaries were fixed to the psoas muscle fascia bilaterally. Surgery time was 158 min with minimal blood loss and no intraoperative complications. The postoperative stay was regular, with no complications, and the patient was discharged after three days.

Histological examination

Macroscopic, microscopic and Immunohistochemical Analysis (IHC) were performed.

Macroscopic and microscopic examination: The uterus was removed with both tubes. At the endometrial fundus, a raised, necrotic-hemorrhagic area of 1.5 cm was observed. Thrombized vascular structures and associated chronic inflammation with multinucleated foreign-body giant cells were recognized in its context. No residual tumor or endovascular neoplastic emboli were detected. The adjacent endometrium appeared atrophic with associated stromal pseudo-decidualization. The cervix was affected by chronic cervicitis with foci of superficial squamous and glandular metaplasia, with no evidence of neoplastic infiltration. Salpinges were negative. Out of 7 pelvic LNs removed, 2 were positive for EC metastases (1/5 at the right and 1/2 at the left). The bulky LN removed at the paraaortic region was positive for EC secondary disease.

Immunohistochemistry: We compared IHC of the first endometrial biopsy performed in our center (September 2017) with IHC performed on the surgical specimen (February 2021).

Results from the comparison are shown in Table 1. IHC staining pattern for the first biopsy (September 2017) are shown in Figure 1.

Inguinal LNs examination

Due to the clinical and radiological suspicion on bilateral inguinal LNs, the patient underwent ultrasonographic-guided biopsy of one left inguinal LN localized at the 1st level of Daseler, which was the node with the most worrisome features (confluent with subverted ultrasonographic structure). Biopsy was negative for EC metastases. Nevertheless, in consideration of the highly suspected ultrasound characteristics, the patient was referred for nodal surgical staging in March 2021, during which a bulky left inguinal LN was removed and studied intraoperatively. Intraoperative analysis was negative for secondary EC disease; therefore a systematic aortic lymphadenectomy and a radicalization of the previous pelvic lymphadenectomy were performed for staging purposes. Eventually, at the definitive histological examination, over 6 aortic, 3 pelvic and 1 inguinal LNs removed, none was positive for EC metastases.

Genetic analysis

Considering the woman's family history, personal history and the aforementioned IHC features, the patient underwent germinal genetic test, which turned out to be diagnostic for Lynch syndrome.

Adjuvant treatment

In consideration of FIGO stage IIIC2, the patient was referred for adjuvant chemotherapy and radiotherapy.

Discussion

In this case report we describe the clinical history of a young patient with MMR-d EC conservatively treated, with disease progression during hormonal treatment. We compared the IHC features of the first diagnosis biopsy with the ones on surgical specimen. Interestingly, we identified some relevant differences: on the 2017 endometrial biopsy, tumor cells exhibit MMR-d immunophenotype, whereas the 2021 surgical specimen shows features of MMR-p immunophenotype. It is crucial to underline that not only the cancer has changed from a biochemical perspective, but it has also concurrently shifted from a macroscopically confined tumor (early stage) to an advanced disease with bulky aortic and pelvic LNs. Noteworthy, we observed a complete local response to treatment, with no evidence of tumor on uterine samples, with parallel spreading of EC to pelvic and aortic LNs. A post-hoc germinal genetic examination was performed and the patient was diagnosed with Lynch syndrome.

These data need to be reframed in perspective of the ProMisE classifier, which outlines four molecular groups of EC with different prognosis: 1) POLE-mutated (POLE-mt, good prognosis, very high mutational rate and mutations in the exonuclease domain of Polymerase-ε); 2) Mismatch Repair-deficient (MMR-d, intermediate prognosis, high mutational rate and microsatellite-instability); 3) p53-abnormal (p53-abn, poor prognosis, TP53 mutations, low mutational rate and high somatic copy number alterations rate); 4) p53-wild-type (p53-wt, good-to-intermediate prognosis, low mutational and somatic copy number alterations rates) [7-9]. In their retrospective study, Chung et al. analyzed how mismatch repair status influences response to EC fertility-sparing treatment [4]. Among 57 patients, 9 (15.8%) had MMR-d on endometrial biopsy obtained before progesterone treatment. Results show that patients with MMR-d had a significantly lower complete response rate than those with MMR-p/p53-wt in terms of best overall response (44.4% *vs.* 82.2%) and complete response rate at 6 months (11.1% *vs.* 53.3%), concluding that molecular classification has a prognostic significance in EC fertility sparing management, thereby enabling early risk stratification. An Italian study by Falcone et al. [5] investigated on the molecular features of 25 patients with EC conservatively treated [5], stating that ProMisE classifier application on resectoscopic specimens could be a pragmatic model for stratifying genetic risk of women with EC. Specifically, in the group of MMR-d conservatively-treated patients, for a 50% of women the presence of such mutations correlates with a worse outcome (persistence/progression or metachronous Lynch syndrome associated tumors). A retrospective Italian study of Raffone et al. [6], investigated the association between MMR status and resistance rate to conservative treatment, recurrence rate and MMR-d reliability in predicting the risk of recurrence [6]. Endometrial samples from 69 young women affected from AEH or mucosal-confined EC were collected before conservative approach and IHC features were examined. Results show that 8.7% of women was MMR-d. For this subset of patients, resistance to treatment was more common compared to p53-wt group (33.3% *vs.* 15.9%) with no statistical significance (p=0.2508) and recurrence after a complete regression occurred significantly more commonly than p53-wt women (100% *vs.* 26.4%, p<0.0001). Moreover, MMR-d status was found to be a highly specific predictive marker for recurrence (sensitivity =22.2%, specificity =100%) [10,11]. Moreover, Zakhour et al. [12], observed that in young women with loss of MMR proteins by IHC there was a higher incidence of invasive cancer and a lower incidence of resolution with progestin therapy [12].

According to the few available evidences [8,10-12], MMR-d status seems to be related to lower response rate to treatment, higher risk of recurrence and worst prognosis compared to p53-wt. Considering this, we may deduce that a wiser evaluation of molecular the MMR-d

status should had guided to the proper therapeutic algorithm for the patient of this case report: The study of personal and family history with Lynch Syndrome blood test, a closer and more intensive follow-up program or a different surgical management.

This case-report spontaneously arises questions about the possibility to apply molecular classification in young EC patients' management. The study of the role of MMR status by IHC may represent a potential stand-alone predictor marker for risk stratification in this subset of patients: EC offspring-desirers with MMR-d should be managed more intensively with the inclusion of II-level imaging in their follow-up schedule, contrariwise p53-wt women could be followed-up in accordance with current guidelines.

Further and larger studies are needed for a deeper understanding of these phenomena and for a wiser application of its potential.

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