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Case Report

A Novel *MSH2* Pathogenic Variant in a Synchronous Endometrial and Ovarian Cancer Patient: A Case Report

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Abstract

Synchronous endometrial and ovarian cancer is a rare condition with a prevalence of 1%-2% of all women affected by gynaecological cancers. The coexistence of endometrial and ovarian cancer has been reported in the sporadic setting in about 10% of cases, but in up to 20% occurs in the context of Lynch syndrome. Lynch syndrome is an autosomal dominant syndrome characterized by pathogenic variants in the Mismatch Repair (MMR) genes. MMR system is implicated in genomic stability by correcting mismatches produced during DNA replication. MMR deficiency promotes cancerogenesis due to microsatellite instability. In this report, we present a case of a 37 years old woman affected by synchronous endometrial and ovarian cancer. A targeted NGS-based pipeline highlighted a novel pathogenic variant in the *MSH2* gene. Patient work flow and cancer-specific treatment are also provided. Universal screening at the diagnosis of all endometrial cancers for MMR status leads to identify patients with Lynch Syndrome and offering specific surveillance programs for patients and family members.

Keywords: Lynch syndrome; Endometrial cancer; Ovarian cancer; Mismatch repair system; Microsatellite instability

Introduction

Endometrial Cancer (EC) and Ovarian Cancer (OC) represent the most prevalent gynecological malignancies diagnosed in the Western world [1]. The simultaneous identification of two or more gynecological cancers, or a new one within six months after the initial diagnosis, defined as synchronous cancer, is a rare event. In particular, the coexistence of EC and OC is an uncommon condition with an estimated prevalence of 10% in sporadic cases of OC and in 5% of EC [2]. It has been reported that synchronous EC and OC are mostly endometrioid, grade I, and diagnosed in early stage with a good prognosis. Synchronous EC and OC have also been reported up to 22% in the context of Lynch Syndrome (LS) and in this case, endometrial cancer represents the sentinel cancer [3].

LS is the most frequent inherited cancer predisposition syndrome, with are ported frequency of 1/370 individuals in the general population [4]. LS are an autosomal dominant condition due to inherited pathogenic variants in the genes encoding the proteins of the DNA Mismatch Repair (MMR) system: mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), mutS homolog 6 (*MSH6*), and PMS1 homolog 2 (*MSH6*) [5]. Also deletions of Epithelial Cell Adhesion Molecule (EpCAM) can lead to LS due to the silencing of *MSH2* gene. Less commonly, inherited inactivation of the MMR system can arise from germline hypermethylation of the promoter region of *MLH1* [6]. In LS carriers, where a constitutional MMR variant is existent, a second somatic hit in the *MMR* gene with the result of the second allele inactivation, leads to instability of DNA repeat sequences (microsatellites) and Microsatellite Instability (MSI) phenotype in the tumor. Actually, international guidelines recommend in all EC samples at diagnosis LS universal screening by Immunohistochemistry (IHC) or by PCR to identify a deficiency of MMR system proteins or MSI phenotype. Testing for MMR or MSI status began crucial not only to identify patients at risk for LS but also as a prognostic and predictive factor useful to personalize patient therapy with immune checkpoint inhibitors [7,8]. About 3% and 10% of MMR deficient and MSI of all EC respectively are associated with a germline variant of one of the MMR genes. Moreover, LS carriers have a lifetime cumulative risk of 85% to 90% of colon cancer, 40%-60% lifetime risk of EC, and 8%-10% lifetime risk of OC [9,10].

Here we describe a case of 37 years old woman treated in our Institution affected by synchronous EC and OC with a novel germline pathogenic variant in the *MSH2* gene. Patient cancer history, family pedigree analysis, and molecular characterization of the new *MSH2* variant are here provided.

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Case presentation and Results

Case history

A nulliparous 37 years old woman, who had undergone to hysteroscopic polypectomy for an endometrial endometrioid adenocarcinoma well-differentiated G1in October 2020, was referred to the Department of Gynecologic Oncology of Fondazione IRCCS Policlinico Universitario A. Gemelli (Italy, Rome) in November 2020.

An accurate transvaginal ultrasound examination revealed isoechogenic tissue intensely vascularized on color Doppler which infiltrated the posterior cervical stroma and, at the left ovary, a solid unilocular formation with "ground-glass" content, with the internal presence of an avascular hyperechogenic papilla (Figure 1).

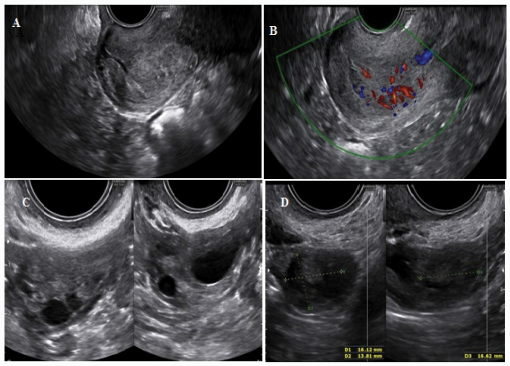

Figure 1: A and B) Gray-scale and color-Doppler ultrasound images of the isoechogenic tissue which infiltrated the posterior cervical stroma. C) Gray-scale ultrasound images of the right and left ovary. At the left ovary, D) A solid unilocular formation with "ground-glass" content. (Class Ultrasound, Fondazione IRCCS Policlinico Universitario A. Gemelli, Rome).

The patient, then undergone to an abdomen and pelvis MRI, which confirmed the uterine lesion that invaded the surrounding myometrium for less than 50% of its thickness with multiple adnexal cystic formations bilaterally (Figure 2). Upon completion of the initial imaging evaluation, a CT-PET scan confirmed the known expansive formation pertaining to the cervix and widespread increase in uptake along the endometrial lumen.

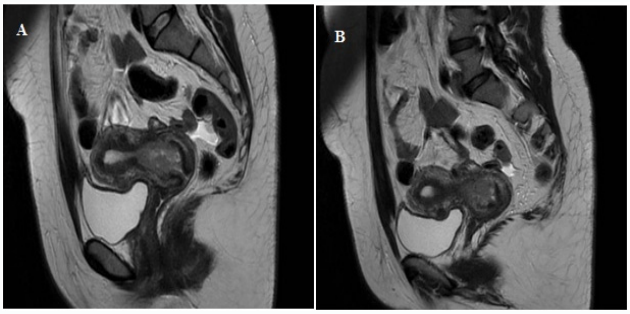

Figure 2: A and B). Sagittal sections of MRI, seq.T2.The hypointense uterine lesion invaded the surrounding myometrium for less than 50% of its thickness. (Fondazione IRCCS Policlinico Universitario A. Gemelli, Rome).

On 21st January 2021, the patient underwent to a laparoscopic radical hysterectomy with bilateral adnexectomy. During the surgery, a suspicious right obturator lymph node package was identified. For this reason, bilateral pelvic lymphadenectomy was performed.

The pathological finding was a moderately-differentiated endometrioid endometrial cancer with stromal cervical infiltration. At the left ovary, an endometriotic cyst with focal transformation into G1 endometrioid adenocarcinoma was detected. For both, uterine and ovarian neoplasia, immunohistochemical staining showed expression of *MLH1*, *MSH6*, focally for *MSH6* but not for *MSH2* as for unstable immuno-phenotype, p53 wild type and ER=1+, 30%, PR=2+, 40% for uterine cancer. All pelvic lymph nodes and the right ovary were free from tumors.

In summary, the histopathological TNM classification was pT2 pN0 G2 (FIGO stage II, LVSI+) and pT1a pN0 G1 (FIGO stage IA) for endometrial cancer and ovarian cancer respectively.

The case was discussed at the multidisciplinary gynecological tumor board in February 2021 with the decision to perform radiotherapy counseling for external beam radiotherapy for endometrial cancer, prior to additional CT-PET scan evaluation, while for ovarian cancer no adjuvant therapy was indicated as per international guidelines [11].

The requested CT-PET scan performed on 18th March 2021 showed a significantly high 18-FDG uptake on the left obturator lymph node (SUV_{max} 20, 22 mm in the short diameter).

The CT-PET finding, associated with the lack of complete surgical staging for ovarian carcinoma, were discussed collectively again at the multidisciplinary gynecological tumor board with the decision to perform pelvic, lumbar-aortic lymphadenectomy, and peritoneal staging for the ovarian neoplasia.

On 6th April 2021, a new surgery was performed with evidence of a left obturator lymphadenomegaly of about 3 cm with hard-ligneous consistency and strongly adherent to the external iliac vessels, obturator nerve, and to the left hypogastric artery. Left obturator lymph node recurrence removal, left pelvic and periaortic lymphadenectomy, total omentectomy, and left ureteral stent placement were achieved.

The pathology report showed an obturator lymph node package with massive adenocarcinoma metastasis with morpho-phenotypic features consistent with endometrioid histotype and carcinoma metastasis in 1/12 isolated pelvic and aortic lymph nodes. The omentum was free of neoplasia (Table 1).

Table 1: Pathological findings and the diagnosis of this case. Final diagnosis was a moderately-differentiated endometrioid endometrial cancer with stromal cervical infiltration. At the left ovary, an endometriotic cyst with focal transformation into G1 endometrioid adenocarcinoma.

Site	Tumor characteristics
Uterus	Moderately differentiated endometrioid endometrial cancer with stromal cervical infiltration and LVSI+
Right ovary	Negative
Left ovary	Endometriotic cyst with focal transformation into G1 endometrioid adenocarcinoma.
Omentum	Negative
Lymphonodes	obturator lymph node package with endometrioid histotype and carcinoma metastasis in 1/12 isolated pelvic and aortic lymph nodes

This anatomical and pathological finding significantly changed the staging of endometrial cancer and consequently the adjuvant therapy of the patient, thus becoming a stage IIIC1 endometrioid endometrial carcinoma.

Chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (area under the curve=5) was started on 5th May 2021 and administered once every three weeks for six cycles until September 2021. CT scans

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with contrast performed during and after the planned six cycles of chemotherapy, showed no evidence of disease.

The patient also underwent external beam radiotherapy with 45 Gy plus two boosts on obturator lymph nodes of 10.8 Gy and brachytherapy with 10 Gy, from November 2021 until January 2022. Subsequent follow-ups, including colonoscopy, resulted negative for disease recurrence.

The immunohistochemistry pathological finding of *MSH2* expression absence, as well as young onset of synchronous endometrial and ovarian cancer, together with the patient's family history of colorectal and gastric cancers, suggested the suspicion of LS (Figure 3). The overall predicted probability of LS by the PREMM5 score model was 34.5% [12].

According to international guidelines, MMR genetic testing was proposed for this young patient, preceded by genetic counseling. As clinically suspected, an unreported *MSH2* pathogenetic variant confirming a defect in the MMR-system (dMMR) was found, defining as clinically suspected LS.

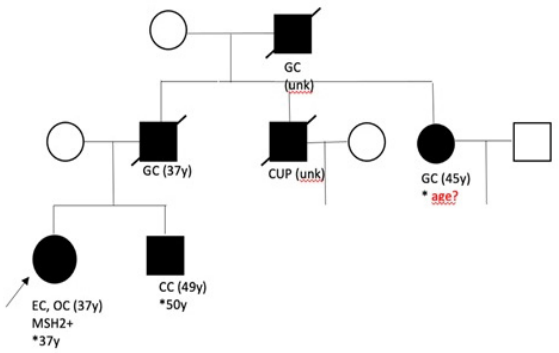

Figure 3: Patient's family pedigree. Arrow designates the proband. Black squares and circles indicate individual with cancer.
GC: Gastric Cancer; CUP: Carcinoma of Unknown Primary Site; EC: Endometrial Cancer; OC: Ovarian Cancer; CC: Colon Cancer.
*indicates current age, () refers to the age at diagnosis.

Pathologic Evaluation

Immunohistochemical analysis

From the radical surgery, uterine and ovarian tissue sections were immunohistochemically investigated. Both tumors share the same profile. Indeed, we reported a loss of the mismatch repair protein *MSH2* and *MSH6* partial expression, whereas *MLH1* and *MSH6* are diffusely conserved. Moreover, they exhibit a strong positivity for estrogen and progesterone receptors, and wild-type p53 staining. Although some authors suggested screening tumors only with antibodies against *MSH6* and *MSH6* proteins (two-stain method) to reduce costs [13,14], it is generally recommended to test the four MMR proteins, since the two-stain immunohistochemical screening may fail to detect mismatch repair deficiency in some LS tumors [15,16] (Figure 4).

Next-Generation Sequencing (NGS): analysis and results

In patients with MMR-d tumors, screening for germline mutations in *MMR* genes is conducted generally by Next Generation Sequencing (NGS). NGS results highlight not only deficiency in *MMR* but also specific pathogenic or likely pathogenic variants, which are helpful

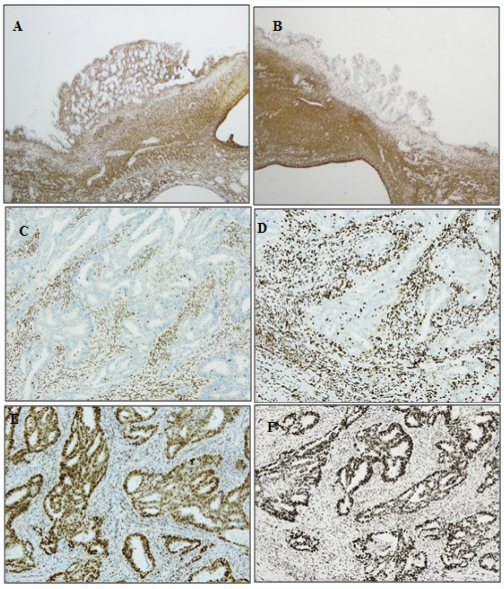

Figure 4: 2MSH2 loss of expression in both lesions (A and B).Tumor cells show loss of expression for *MSH2* (C), focally expression (<10%) for *MSH2* (D), while *MLH1* (E) and *PMS2* (F) are conserved. (Zannoni G., Scaglione G. Fondazione IRCCS Policlinico Universitario A. Gemelli, Rome).

for targeted germline confirmatory sequencing in the affected family.

Genomic DNA was isolated from peripheral blood samples using a Maxwell 16 Blood DNA Purification kit (Promega, Madison, WI, USA) on the automated platform Maxwell 16 MDx AS3000 (Promega). PCR/NGS was carried out using the Hereditary Cancer Solution (HCS) Kit (SOPHIA GENETICS, Saint-Sulpice, Switzerland) on the Illumina MiSeq instrument (Illumina, San Diego, CA, USA). The HCS kit, a NGS capture based target enrichment assay, performs the analysis of 26 cancer related genes (*ATM*, *APC*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *FAM175A*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *MSH6*, *MSH6C*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53*, and *XRCC2*) for sequence and copy number variants detection. Sequencing data were analyzed *via* Sophia DDM® software v.4.2. (SOPHIA GENETICS) [17].

NGS did not reveal any known P/LPVs and bioinformatics prediction was not indicative for the presence of copy number alterations in the investigated genes. However, a nonsense variant p.(Tyr98Ter), c.294T>G, (coverage: 593/1215X), Variant Allele Frequency (VAF): 49%) in the *MSH2* gene was highlighted. The nomenclature of the variant is based on the *MSH2* sequence (NCBI Reference Sequence: NM_000251.2 (LRG_218t1; GRCh37), according to the recommendations of the Human Genome Variation Society (https://www.hgvs.org).

This variant was considered novel since it was not present in the main variant databases investigated as: Clin Var (https://www.ncbi.nlm.nih.gov/clinvar/), Leiden Open-source Variation Database (LOVD) (https://databases.lovd.nl/shared/genes/LDLR), Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org), 1000Genomes (http://www.internationalgenome.org/1000-genomes-browsers/) and Varsome (https://varsome.com/) (last access August 2022). In addition, we did not identify this variant in our cohort of about 200 patients routinely analyzed with the same targeted NGS approach adopted in this study. According to the American College

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of Medical Genetics and Genomics (ACMG) recommendations [18], the novel *MSH2* nonsense alteration was considered as pathogenic variant. In order to confirm the presence of the MSH2c.294T>G variant highlighted by NGS, a targeted Sanger sequencing was performed. Unfortunately, it was not possible to screen the variant in the family members.

Histopathological considerations

Histopathological evaluation of the tumors sections was performed. The hematoxylin-eosin staining of the uterus showed a partially exophytic mass, extending to the isthmus and cervix, characterized by a glandular architecture, composed of cells with moderate atypia and eosinophilic cytoplasm (Figure 5A). The endometrial endometrioid adenocarcinoma exhibited myometrial invasion with a prominent fibromyxoid stroma and isolated glands (Figure 5B), with glands cells appearing with mild to severe atypia. Histologically ovarian lesion corresponds to an endometriotic cyst with a fibrotic wall, endometriotic epithelium, and stroma with an extensive network of arterioles, extravasated erythrocytes, and pigmented histiocytes (Figure 5C and D). In conclusion, the endometrial and ovarian neoplasms showed similar histomorphology and the same immunohistochemical profile, with no precursor lesions neither in the uterus nor in the ovary. The clinical history of the patient, the IHC profile, and the genetical studies, suggest the synchronous origin of these tumors.

Mills et al. [19] showed that more than half of the LS-related endometrial tumors (58%) did not have MSI tumor features, i.e., lower uterine segment location [20], tumor heterogeneity, Tumor-Infiltrating Lymphocytes (TILs), and Peritumoral Lymphocytes (PTLs) [19]. However, a recent study showed a significantly higher density of infiltrating immune cell effectors in LS-associated endometrial cancers compared to sporadic MMR-deficient endometrial cancers, with more CD8+, CD45RO+, and PD1+ T-cells at the invasive margin [21]. Aysal et al. [22] showed that morphologic criteria such as TILs, PTLs, and dedifferentiated morphology are not sensitive enough to detect MSI/dMMR ovarian cancers, as these features are present in only 14% of the MSI/dMMR ovarian cases. However, dMMR ovarian cancers have been shown to exhibit significantly increased CD3+ and CD8+ TILs and PDL1+ intra-tumoral immune cells [23].

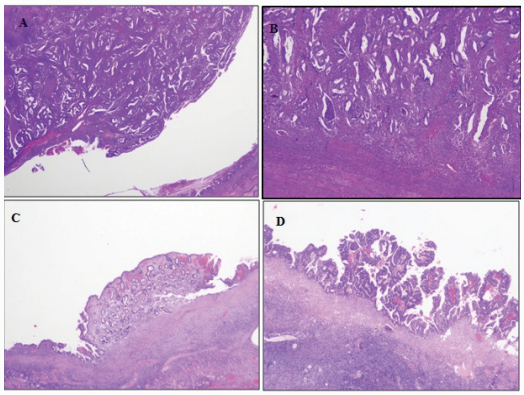

Figure 5: A) Hematoxylin-eosin shows a partially exophythic mass, extending to isthmus and cervix, characterized by a glandular architecture, composed of cells with moderate atypia and eosinophilic cytoplasm. B) Endometrioid adenocarcinoma exhibiting myometrial invasion with a prominent fibromyxoid stroma and isolated glands. C) Ovarian cyst shows a lining epithelium with atypical hyperplasia and (D) Focus of endometrioid adenocarcinoma. (Zannoni G., Scaglione G.Fondazione IRCCS Policlinico Universitario A.Gemelli, Rome).

Discussion

In this case report, we analyzed the histopathological and genetic aspects of low-grade endometrioid endometrial cancer and endometrioid ovarian cancer. Thanks to immunohistochemistry, we found in our young patient the tissue loss of expression of the mismatch repair protein *MSH2* in both endometrial and ovarian cancers. This finding, within the clinical patient's history, increased the suspicion of a genetic syndrome such as Lynch Syndrome, until the confirmation obtained by the NGS analysis result.

From the literature data, endometrial cancer is the most common extracolonic cancer in LS, with lifetime risk estimates of 35%-40% for *MLH1* mutations, 46%-53% for *MSH2*, up to 46% for *MSH6*, and 13% for *MSH6* [24]. As a consequence, tumors from LS patients display Microsatellite Instability (MSI) and a loss of expression of MMR proteins. However, MSI is not restricted to Lynch Syndrome. In fact, only 15%-20% of MSI/MMR-deficient (dMMR) tumors can be attributed to LS, and most MSI/dMMR tumors are sporadic. Among gynecological cancers, synchronous endometrial and ovarian tumors occur approximately in 1%-2% of cases [25].

Endometrial cancer with Lynch syndrome is mainly caused by an *MSH2* or *MSH6* mutation, whereas ovarian cancer with Lynch syndrome is mainly caused by an *MSH2* mutation [26,27]. According to this assertion, in our patient, the immunohistochemical analysis showed the complete absence of expression of *MSH2* in tumors, endometrial and ovarian cancer, and *MSH6* partially expression, whereas *MLH1* and *MSH6* were diffusely conserved.

The interesting aspect of this report is that it brought to the literature a particular and interesting case of a Genetic Syndrome (LS) related to the loss of *MSH2* expression, with a novel pathological variant, and associated with synchronous tumors, initially suspected from the patient's clinical history and IHC, which led us to investigate the family history and perform a more in-depth NGS analysis. This finding, however, has some limitations. First, these limitations are related to the case report itself and its singularity, given the rarity of the event. Furthermore, previous studies are equivocal on the interest to search for LS in the case of synchronous endometrial and ovarian tumors. However, these synchronous tumors seem to be more common among LS-related EC cases [28].

IHC for MMR protein is easily available, generally inexpensive, and a more optimal first-line screening tool than MSI testing for identifying Lynch Syndrome [29]. Considering that IHC is a highly sensitive technique for identifying mutations in MMR genes in Colorectal Cancer (CRC), it could be expected that an IHC-based screening approach could prevent a significant number of LS patients remain undiagnosed.

Wada-Hiraike, et al. [30] found that ER α/β bound to *MSH2* through the *MSH3*/*MSH6* interaction domain of *MSH2*, and, in turn, *MSH2* potentiated the transactivation function of liganded ER α, which was probably related to the pathogenesis of LS-EC. However, there are limited reports on the impact of estrogen and progesterone on the pathogenesis of LS-EC, and thus, further studies are required.

From what have been inferred from literature data and the clinical and oncological history of patients with LS, it appears imperative to consider possible preventive strategies in these women. The role of prophylactic surgery was described by Schmeler et al. [31], who concluded that surgery is an effective strategy to prevent endometrial

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and ovarian cancer in women with LS. It was calculated that six patients need to get a prophylactic hysterectomy and 28 patients need to get bilateral salpingo-oophorectomy to prevent one case of endometrial or ovarian cancer respectively. In addition, it was estimated that annual screening from the age of 30 followed by prophylactic surgery at the age of 40 is the most cost-effective gynecologic cancer prevention strategy in women with LS [32]. However, the disadvantages of radical surgery remain, such as related postoperative complications, the induction of iatrogenic menopause, and the lack of fertility-sparing treatment. In this regard, few studies have emerged concerning the possibility of conservative treatment for eligible patients, but data are unfortunately still scarce and not encouraging [33, 34].

Conclusion

During the last few decades, significant progress has been made in the screening, diagnosis, surveillance, prevention, and treatment of women with LS-correlated cancers [35]. The screening and diagnosis of LS-EC are known to be mainly based on traditional clinical criteria and molecular techniques, including MMR-IHC, MSI testing, *MLH1* promoter methylation testing, and gene sequencing. While there is increased uptake of MSI testing in advanced cancer where immunotherapy is a potential therapeutic option, screening in other clinical scenarios and in non-colorectal Lynch-associated cancers has made little progress [36].

The treatment of LS-EC and OC has been shown to be similar to that of sporadic neoplasia, and immuno-therapy for LS-EC has come into focus in recent years. Pembrolizumab and nivolumab have been shown to be effective and have been recommended by the NCCN guidelines for patients with advanced or recurrent MSI-H/dMMR EC. However, there are still some controversies regarding the pathological feature, prognosis, and management of LS-EC [37]. Furthermore, new changings are arising for ovarian neoplasia [7,38-41]. Emerging data show that universal screening of ovarian cancer identifies cases of Lynch-associated ovarian cancer that would not be identified by clinical criteria alone [42]. Prospective evaluations are ongoing to evaluate risk modification and cost-effectiveness (ClinicalTrials.gov identifier NCT02494791) [43].

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