Endometrioid Cancer Associated With Endometriosis: From the Seed and Soil Theory to Clinical Practice

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Endometriosis is a benign condition characterized by the presence of ectopic endometrial tissue. It is still debated whether endometriosis is a disease that can predispose to the pathogenesis of endometrial cancer outside the uterus. Deficiencies in mismatch repair (MMR) genes are a known risk factor for developing endometrioid cancer. Starting from two cases of patients with abnormal MMR endometrioid carcinoma of the uterus and synchronous endometrioid carcinoma in non-ovarian and ovarian endometriosis, we performed a somatic mutation profile and phylogenetic analysis of the lesions in order to identify if they were metastasis or primary de novo tumors. In the first case, we identified de novo activating mutations in PIK3CA and KRAS in endometrioid cancer lesions but not in endometriosis. Although the acquisition of a de novo mutation in ESR1 and a decrease in mutant allele fraction (MAF) from the endometrial tumor to the localizations in the endometriosis lesions, the clonal relationship was confirmed by the limited number of heteroplasmic mutations in D-loop mitochondrial DNA region. In the other case, the clonal behavior was demonstrated by the overlap of MAF at each site. Our data support the hypothesis of a retrograde dissemination of tumor cells, moving from the primary carcinoma in the endometrium to ectopic sites of endometriosis where localizations of tumor arise.

Keywords: uterine carcinoma, endometriosis, endometrioid adenocarcinoma of the endometrium, mismatch repair (MMR) deficiency, tumor dissemination
INTRODUCTION

Endometriosis is a relatively common disease, characterized by the presence of ectopic endometrial tissue outside the uterus (1). Endometriosis affects 10%–15% of all women of reproductive age (2) and approximately 2%–5% of postmenopausal women, representing a side effect of hormonal replacement therapy or tamoxifen treatment in this population (3). The etiology underlying endometriosis is controversial, but the processes proposed in its development closely resemble those involved in cancer metastasis (4). Ovarian endometriosis has been reported to be associated with an increased risk of epithelial ovarian cancer, representing the direct precursor of clear-cell and endometrioid ovarian carcinomas (5). However, whether extraovarian endometriosis may be an endometrioid cancer precursor remains controversial (6, 7).

Endometrial cancer is a clinically heterogeneous disease. Genomic characterization by The Cancer Genome Atlas (TCGA) classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high (8). Another classification of endometrial cancer differentiates tumors into two subtypes: type I is characterized by a favorable prognosis and represented mostly by endometrioid adenocarcinoma, associated with an unopposed estrogen stimulation, often preceded by endometrial hyperplasia; type II has significantly poorer 5-year survival predominantly represented by non-endometrioid histology, mostly arising in an atrophic endometrium and deriving from intraepithelial carcinoma as a precancerous lesion (9). Since the evidence of activity of immune checkpoint inhibitors in patients with advanced mismatch repair (MMR)-deficient endometrial cancer (10) and considering that Lynch syndrome may account for about 3% of all endometrial cancers (11), it is recommended to screen all endometrial cancer patients with the use of immunohistochemical tests for MLH1, MSH2, MSH6, and PMS2 (12).

Whether patients with endometriosis have increased risks of development of endometrioid tumors or if endometriosis is the soil where endometrioid cancer seeds grow remains unclear. In this study, we report two cases of patients with MMR-deficient endometrioid carcinoma of the uterus and synchronous endometrioid carcinoma in extraovarian and ovarian endometriosis.

METHODS

Tissue Sample and Mismatch Repair Evaluation

Tissue samples were paraffin-embedded archival specimens. Immunohistochemistry was performed at the Pathology Unit. Antibodies against MLH1, MSH2, MSH6, and PMS2 were prediluted according to the manufacturer’s instructions. The expression of MLH1, MSH2, MSH6, and PMS2 was determined qualitatively to be retained or lost, as is standard.

Molecular analyses on genomic DNA extracted from peripheral blood were performed to search for variants in MMR (MLH1, MSH2, and MSH6) genes. Moreover, all coding exons and splice junctions of the MLH1, MSH2, and MSH6 genes were analyzed. The analysis for the identification of variants and genomic rearrangements [copy number variations (CNVs)] was performed by next-generation sequencing (NGS) with Miseq-Illumina sequencer via commercial panel HCS_v1_1 (Sophia Genetics).

Nucleic Acid Extraction and Quantification

Dual DNA and RNA isolation was performed from four formalin-fixed paraffin-embedded (FFPE) tissues using the Maxwell® RSC DNA/RNA FFPE Kit with the Maxwell® RSC Instrument. For each sample, areas were characterized by 100% tumor cells. Nucleic acid concentrations were determined by fluorometric quantitation using Qubit 4.0 Fluorimeter with Qubit dsDNA HS Assay Kit and Qubit RNA HS Assay Kit (Thermo Fisher Scientific, Inc.).

Next-Generation Sequencing

To estimate somatic mutation profiling, NGS was performed with the "Ion Torrent Oncomine Focus Assay" for simultaneous and rapid identification of single-nucleotide variants (SNVs), short insertion and deletions (indels; 35 genes), CNVs (19 genes), and gene rearrangements (23 genes) in 52 cancer genes with therapeutic relevance:

Hotspot genes (35): AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, and SMO.

CNV genes (19): ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, and PIK3CA.

Fusion driver genes (23): ABL1, ALK, AKT3, AXL, BRAF, EGFR, ERBB2, ERG, MET, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PPARG, RAI1, RET, and ROS1.

The Invitrogen SuperScript™ VILO™ cDNA Synthesis Kit (Thermo Fisher Scientific) was used for RNA reverse transcription to cDNA before library preparation.

Libraries were prepared from 10 ng DNA and 10 ng RNA (0.67 ng/µl, 15 µl) with "Oncomine Focus Assay, Chef-Ready Library" reagents on the Ion Chef™ System (Thermo Fisher Scientific). Templating and sequencing were performed using "Ion 510™ & Ion 520™ & Ion 530™ Kit–Chef."

For template preparation, we used Ion 520 chip (up to 5 million reads per chip, 8 samples) on the Ion Chef™ System, while sequencing was completed on the Ion Torrent S5 Plus (Thermo Fisher Scientific). Sequencing data were analyzed using Ion Reporter™ Software that helps to identify and prioritize variants.

To define a reliable variant calling, we have considered two stringent parameters: coverage depth greater than 500× and allele frequency greater than 5%. 

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Phylogenetic Trees
Phylogenetic analysis starting from different tumor populations in the Pathology Unit of Bellaria Hospital (Bologna) was performed as previously described (13, 14). In brief, mitochondrial DNA (mtDNA) D-loop region was sequenced in deep onto MiSEQ (Illumina) and processed by Geneious 9.1.8 (Biomatters Ltd., Auckland, New Zealand) to identify and annotate homoplasmic or heteroplasmic mutations. The 4 consensus sequences representative of each of the four tumor populations were joined and used to construct the phylogenetic tree using Multiple Alignment using Fast Fourier Transform (MAFFT; https://mafft.cbrc.jp/alignment/server/) with the unweighted pair group method with arithmetic mean and the Jukes-Cantor substitution model.

RESULTS
Case Report 1
A 58-year-old woman was diagnosed with a grade 2 endometrioid carcinoma in August 2020. After having ruled out other neoplastic lesions with thorax and abdomen computed tomography (CT) scan and pelvic MRI, the patient underwent a total hysterectomy with bilateral annexectomy and pelvic lymphoadenectomy. During surgery, two peritoneal lesions in the rectouterine pouch were also removed. The diagnosis was of endometrioid carcinoma of the uterus grade 3, with more than 50% invasion of the myometrial wall thickness, 5.2 cm in greatest dimension, with infiltration of the cervix stroma, without lymphovascular invasion, and no pelvic lymph node metastases. The two peritoneal nodules were diagnosed as duplex localization of endometrioid carcinoma grade 3 in endometriosis lesions. In the left ovary, a localization of endometriosis with another endometrioid carcinoma grade 3 lesion was diagnosed [stage pT3aN0M1, Fédération Internationale de Gynécologie et d’Obstétrique (FIGO IVB)]. Using immunohistochemistry, tumor cells were shown to have a normal pattern of expression of p53, MSH2, and MSH6, whereas MLH1 and PMS2 were lost. For this reason, molecular analysis was performed to search for variants in MMR genes on genomic DNA extracted from peripheral blood. The regions of MLH1, MSH2, and MSH6 genes analyzed did not show specific alterations nor partial or complete genomic rearrangements (CNVs).

Five cycles of chemotherapy with carboplatin and paclitaxel were administered. The sixth cycle was omitted for hematologic toxicity (grade 3 anemia and grade 3 thrombocytopenia). Patient then received adjuvant external pelvic radiotherapy at a dose of 45 Gray. Until now, patient is disease-free.

Molecular Profiling
In order to identify if the endometrioid carcinoma lesions in the peritoneum and in the ovary were synchronous tumors that arose in extraovarian and ovarian endometriosis tissue or metastasis, a molecular profiling was performed. Targeted sequencing in primary uterine tumor revealed an activating PIK3CA hotspot exon 2 mutation (c.263G>A) with an allelic ratio of 27% and a KRAS exon 2 hotspot mutation (c.34G>A) with an allelic ratio of 51%. Comparable mutations were found in the tumor lesion of the left paracolpium: PIK3CA exon 2 mutation (c.263G>A) and a KRAS exon 2 mutation (c.34G>A) with an allelic ratio of 12% and 22%, respectively. An activating ESR1 hotspot exon 8 mutation (c.1607T>G) with an allelic ratio of 9% was also identified. The same mutations were detected in the tumor lesion of the left ovary with less allelic ratio: PIK3CA exon 2 mutation (c.263G>A), KRAS exon 2 mutation (c.34G>A), and ESR1 hotspot exon 8 mutation (c.1607T>G) with an allelic ratio of 5%, 12%, and 6%, respectively (Figure 1). No hotspot

FIGURE 1 | Mutations on representative cancer-associated genes of case 1 (A) and case 2 (B). Each color represents a different sample. Triangles represent the mutant allele frequency (MAF), corresponding to those of the vertical axis.
mutations were identified (with a sensitivity of detection of 1%) in the endometriosis nodules without tumor lesions.

The phylogenetic relationship of multiple samples from different tumor regions was also evaluated by sequencing D-loop mtDNA region. We found 6 heteroplasmic mutations, 4 of which were present only in specimen A1, while 2 were present only in specimen A12. The phylogenetic tree is shown in Figure 2. All samples were close to each other, indicating a possible clonal relationship among them.

Case Report 2
In April 2021, a 60-year-old woman was diagnosed with a grade 2 endometrioid carcinoma. Chest and abdominal contrast-enhanced CT scan revealed no metastatic lesions. Patient underwent a total hysterectomy with bilateral annexectomy and low anterior resection of rectum with colostomy. During surgery, a single peritoneal lesion in the rectouterine pouch was biopsied. The surgical specimen of the uterus showed a 50 × 35 mm polypoid tumor. Histopathological diagnosis was grade 2 endometrial carcinoma with more than 50% invasion of the myometrial wall thickness, infiltration of perirectal fat, and lymphovascular invasion. In the left ovary, a localization of endometriosis with another endometrioid carcinoma grade 2 lesion was diagnosed. The peritoneal lesion was positive for endometriosis with grade 2 (stage pT3bNXM1, FIGO IVB). Tumor cells were shown to have a normal pattern of expression of p53 and MLH1 and PMS2 positives at immunohistochemistry. For this reason, molecular analysis was performed to search for variants in MMR genes on genomic DNA extracted from peripheral blood. The regions of MLH1 and MSH6 genes analyzed did not show any specific alteration nor partial or complete genomic rearrangements (CNVs), while MLH2 gene showed a non-classified variant (c.728G>A; p).

Six cycles of chemotherapy with carboplatin and paclitaxel were administered, and adjuvant external pelvic radiotherapy is ongoing. Until now, patient is disease-free.

Molecular Profiling
Also in this patient, a molecular profiling was performed to identify if the endometrioid carcinoma lesions in the left ovary were synchronous tumors that arose in extraovarian and ovarian endometriosis tissue or metastasis.

Targeted sequencing in primary uterine tumor revealed an activating PIK3CA hotspot exon 2 mutation (c.263G>A) with an allelic ratio of 34% and hotspot exon 21 mutation (c.3129G>T) with an allelic ratio of 33%. Furthermore, a variant of uncertain significance of cKIT exon 8 mutation (c.1264G>A) with an allelic ratio of 35% was found. Comparable mutations were found in the peritoneal tumor localization: PIK3CA exon 2 mutation (c.263G>A) and exon 21 mutation (c.3129G>T) with an allelic ratio of 32% and 39%, respectively; cKIT exon 8 mutation (c.1264G>A) with an allelic ratio of 34%. Again, tumor lesion of the left ovary presented PIK3CA exon 2 mutation (c.263G>A) and exon 21 mutation (c.3129G>T) with an allelic ratio of 43% and 46%, respectively; cKIT exon 8 mutation (c.1264G>A) with an allelic ratio of 41%.

DISCUSSION
Although endometriosis is considered to be a benign lesion, malignant transformation in endometriosis-related ovarian neoplasms is possible (15). In recent years, different studies demonstrated that endometriosis (ovarian and extraovarian endometriotic lesions) harbors somatic mutations in cancer driver genes (6, 16). Since somatic mutations are a widespread event in “normal” tissue (endometrial samples included) and most endometriotic lesions harboring cancer-associated genes do not necessarily lead to malignant transformation (17), environmental features protective against malignant transformation or that buffer the effects of such mutations may prevent the progression from endometriosis to gynecologic cancers (16). Moreover, it was
hypothesized that alterations in MMR genes might be involved in the malignant transformation of endometriotic lesions (7).

With these premises, when we faced two similar cases of patients with endometrioid carcinoma of the uterus with MMR deficiency and synchronous endometrioid carcinoma in extraovarian and ovarian endometriosis, the question was whether the latter was subsequent to malignant transformation of endometriotic lesions or to secondary localization. To solve this dilemma, we performed a molecular profile of the cancer and endometriotic lesions of the two cases. In the first case, we identified de novo activating PIK3CA and KRAS mutations in endometrioid cancer lesions but not in endometriosis. This was an unexpected result, since KRAS mutations were associated with endometriosis sustainability (6, 18). Moreover, case 1 showed a decrease in mutant allele fraction (MAF) and the acquisition of a de novo mutation (e.g., ESR1) from primary tumor to distant lesions. For this reason, we performed a phylogenetic relationship of multiple samples from different tumor regions sequencing D-loop mtDNA region. According to this analysis, a limited number of heteroplasmic mutations were found showing a close phylogenetic distance among different tumor populations, demonstrating that peritoneal and ovarian carcinomas are derived from the same endometrial ancestor clone that migrated and settled in endometriotic lesions where the endometrioid tumor arose (Figure 3). In case 2, the MAF was almost the same in all the different lesions, supporting the idea of the clonal relationship between the different tumor localizations.

Both patients had MMR-deficient tumors. MMR alterations may result in genetic tumor heterogeneity (as seen in case 1) but could also be a risk factor for cancer development in endometriotic heterotopic tissue (7, 19). However, our data support the hypothesis of a retrograde dissemination of tumor cells, moving from the primary carcinoma in the endometrium to ectopic sites of endometriosis where localizations of tumor may arise, reinforcing literature data on the origin of endometriosis possibly following retrograde menstruations (20).

A brief comment on ESR1 found in one of our cases is needed. Our results suggest that the ESR1 mutation was a de novo mutation that arose without the selective pressure of a hormonal treatment. This observation suggests that ESR1 may be a biomarker of progression rather than a predictor of endocrine therapy resistance (21) in endometrial cancer. Therefore, characterization only at the time of progression to hormone therapy may be inadequate (22) because ESR1-mutated tumor cells may be the result of a clonal expansion of endometrioid cancer cells primarily refractory to hormonal treatment.

In conclusion, endometrioid tumors, especially if an alteration in the MMR genes occurs, represent a heterogeneous disease, and the acquisition of new mutations is an event that needs to be considered. Although cancer-associated mutations are frequently observed in endometriosis, our study demonstrated that endometriosis-associated carcinoma may arise from cancer seeds that implant in this permissive soil moving in a retrograde way rather than a direct malignant transformation.

FIGURE 3 | The “seed and soil” hypothesis: retrograde flow of endometrial cells already harboring cancer-associated mutation moving from the primary carcinoma in the endometrium to ectopic sites of endometriosis where tumor localizations arise.
How this disease has to be treated and considered (e.g., is really a stage IV endometrial cancer?) is still a matter of debate.

**DATA AVAILABILITY STATEMENT**

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

**ETHICS STATEMENT**

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

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