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# Clonal Evolution and Therapeutic Response in Recurrent Endometrial Cancer with Synchronous Neuroendocrine Tumor under Immune Checkpoint Inhibition

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## Abstract

I The presence of both metachronous and synchronous tumors creates considerable diagnostic and therapeutic complexity, particularly when one exhibits rare neuroendocrine features. We describe a patient with sarcoidosis who had previously undergone treatment for endometrial and ovarian tumors and later developed recurrent lesions with two different histologies: adenocarcinoma and high-grade neuroendocrine carcinoma, both characterized by microsatellite instability–high (MSI-H) status. Comprehensive targeted next-generation sequencing revealed shared synonymous somatic mutations across all three tumors, indicating a common clonal origin. The patient achieved a favorable response to a customized immunotherapy regimen, with only slight exacerbation of sarcoidosis, allowing uninterrupted treatment. This case emphasizes the value of molecular profiling in selecting optimal therapy for complex synchronous tumors and the necessity of close coordination between surgical and medical oncology teams in managing MSI-H cancers.

**Keywords:** Immune checkpoint, Clonal evolution, Endometrial cancer, Ovarian tumors

## Introduction

*Patient story*

Neuroendocrine tumors (NENs) of the cervix and endometrium are exceptionally rare, representing roughly 2% of gynecologic malignancies [1]. Occasionally, these tumors are found alongside a separate histologic type, most often adenocarcinoma. Such synchronous lesions may exist as distinct masses or co-occur within a single biopsy, sometimes classified as mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs). Managing these tumors is particularly complex due to their variable biological behavior, which demands treatment strategies tailored to the aggressiveness of each component. The underlying origin of synchronous tumors remains uncertain; marked differences in morphology and immunohistochemistry raise the possibility that they either arise independently or evolve from a single tumor lineage. Advances in next-generation sequencing now allow detailed molecular comparisons, helping to determine clonal relationships and inform personalized therapeutic approaches.

We present the case of a 45-year-old woman initially diagnosed with endometrial adenocarcinoma (FIGO stage Ia, T1aN0M0) and a concurrent ovarian endometrioid adenocarcinoma (FIGO stage Ic, T1cN0M0), both showing similar histology with approximately 80% tumor cellularity. She underwent complete surgical resection followed by adjuvant carboplatin and paclitaxel. Immunohistochemical testing revealed loss of MSH2 and MSH6, indicative of mismatch repair deficiency. Despite a maternal history of cervical cancer, germline analysis using a 32-gene panel did not reveal pathogenic mutations.

The patient remained disease-free for six years, during which she developed hepatosplenic sarcoidosis, managed with methotrexate and azathioprine. She later presented with abdominal discomfort, and imaging revealed a

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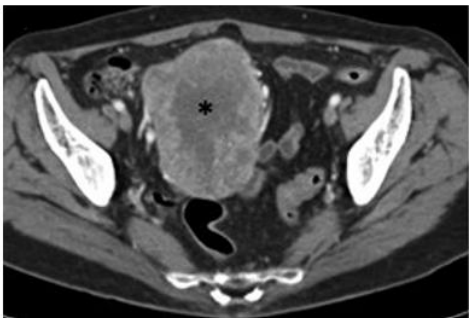
lobulated, enhancing mass in the right hemipelvis along with hypodense liver lesions superimposed on known sarcoidosis (**Figure 1).**

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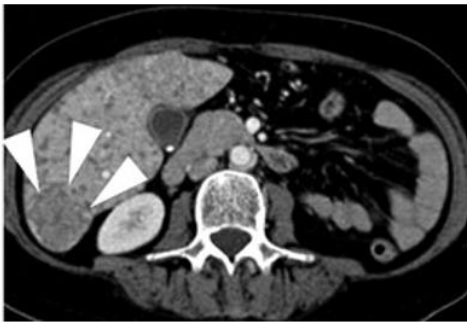

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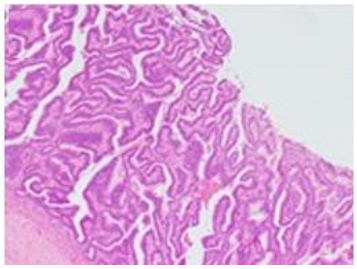
**Figure 1 .**Contrast-enhanced computed tomography at the time of disease recurrence revealed notable findings. (a) Axial imaging demonstrated a lobulated, enhancing mass (*) within the right hemipelvis, which was later confirmed by biopsy as endometrioid carcinoma. (b) A separate hypoenhancing lesion (arrowheads) was identified in segment 6 of the liver, corresponding to a biopsy-confirmed neuroendocrine tumor; additional similar-appearing lesions were observed throughout the liver (not shown). Small hypodense foci in the surrounding hepatic parenchyma were consistent with sarcoid involvement.

*Molecular tumor board findings*

Biopsies were obtained from both the pelvic and hepatic lesions, each exhibiting high tumor cellularity (~70%). Histopathological and immunohistochemical evaluation revealed distinct characteristics between the two sites. The pelvic mass was consistent with recurrent endometrioid carcinoma, demonstrating strong estrogen receptor (ER) expression. In contrast, the liver lesion consisted of nests of relatively uniform neoplastic cells with round nuclei, finely granular chromatin, and moderate eosinophilic to amphophilic cytoplasm, lacking gland formation, marked nuclear atypia, or necrosis. Immunohistochemistry of the liver tumor was positive for chromogranin and synaptophysin, negative for ER, and demonstrated a Ki-67 proliferation index of 40%, supporting a diagnosis of well-differentiated neuroendocrine tumor, WHO grade 3 **(Figure 2 and Table 1).** Notably, no tumor-infiltrating lymphocytes were observed in either biopsy specimen.



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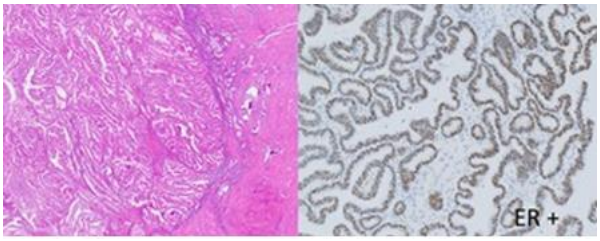


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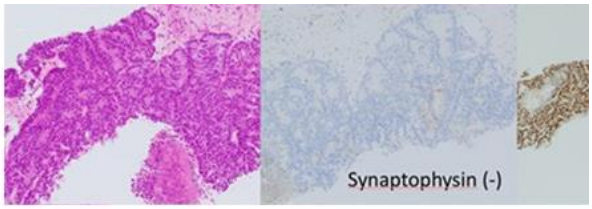


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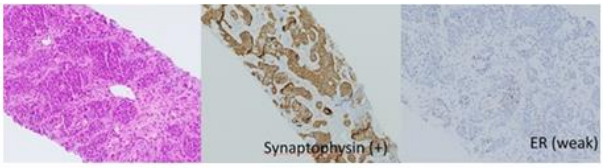



d)

**Figure 2 .**Histologic examination of the initial ovarian and endometrial endometrioid adenocarcinomas revealed closely matching morphology. The ovarian specimen (a) and endometrial specimen (b) both expressed estrogen receptor (ER) and progesterone receptor (PR) but were negative for neuroendocrine markers chromogranin and synaptophysin. The recurrent pelvic tumor (c) demonstrated more complex glandular architecture yet retained a similar histologic pattern and strong ER positivity, with synaptophysin

remaining absent. In contrast, the hepatic lesion (d) consisted of uniform nests of cells with round nuclei, finely granular chromatin, and moderate eosinophilic-to-amphophilic cytoplasm. Immunostaining was strongly positive for synaptophysin, whereas ER expression was weak and patchy.

**Table 1** summary of immunohistochemical findings across all three tumor specimens is provided.

| Specimen | Diagnosis | CK20 | CK7 | CDX2 | PAX8 | PR | ER | Chromogranin | Synaptophysin |
|---|---|---|---|---|---|---|---|---|---|
| **Ovary and uterus** | Endometrial carcinoma | – | Minority + | Weak, focal + | – | + | + | – | – |
| **Liver tumor** | Well-differentiated NET G3 | – | – | Strong, patchy + | – | – | Focal + | Patchy + | Majority + |
| **Pelvic mass** | Metastatic endometrioid carcinoma | – | Rare + | Scattered + | – | N/A | + | N/A | – |

Abbreviations: N/A, not applicable; ER, estrogen receptor; PR, progesterone receptor; NET, neuroendocrine tumor; +, positive; –, negative.

Commercially available targeted next-generation sequencing (NGS; FoundationOne) was carried out on the primary ovarian endometrioid adenocarcinoma as well as the recurrent pelvic and hepatic lesions. All three tumors were found to be microsatellite instability–high (MSI-H) and displayed a high tumor mutational burden. Analysis revealed extensive overlap between the original and recurrent tumors, encompassing both well-characterized mutations and variants of unknown significance **(Table 2).** PD-L1 expression showed a stepwise increase, from absent in the primary tumor to 5% in the recurrent adenocarcinoma and 30% in the neuroendocrine liver lesion. Immunohistochemistry demonstrated concurrent loss of MSH2 and MSH6 in the primary ovarian and endometrial tumors and in the recurrent pelvic lesion, whereas the hepatic neuroendocrine tumor exhibited loss of MSH2 alone. To clarify the tumors' clonal relationships, synonymous somatic mutations were examined, showing that 275 of 292 alterations (94%) were shared across all three specimens.

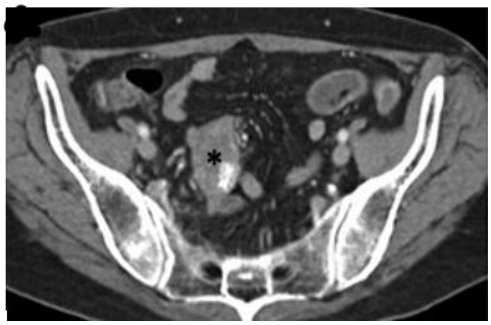
**Table 2.** Summary of next-generation sequencing results, including variant allele frequencies (VAF) for both known pathogenic variants and variants of unknown significance (VUS).

| Specimen (all MSI-high) | Original ovarian and uterine tumor | NEN recurrence | Adenocarcinoma recurrence |
|---|---|---|---|
| **VAF** | | | |
| **APC splice site 423-2A>G** | 38.2 | 30.2 | 31.7 |
| **APC T1556fs*9** | 32.4 | 23.2 | 23.4 |
| **ARID1A G276fs*87** | 33.8 | 24.2 | 30.9 |
| **PD-L1 expression (%)** | 0 | 30 | 5 |
| **TMB** | 32 | 44 | 44 |
| **APC R232*** | 36.4 | 30.2 | 29.1 |
| **ARID1A Q1327fs*11** | | 24.3 | |
| **BCORL1 P1681fs*20** | 35.5 | 26 | 25.3 |
| **ERBB2 R678Q** | 39.9 | 25.9 | 25.3 |
| **MSH2 splice site 942 + 1G>T** | 38.8 | 27.4 | 26.7 |
| **MSH2 C778fs*9** | 34.4 | 23 | 26.9 |
| **ESR1 Y52H** | 16.4 | | |
| **FBXW7 R13*** | 37.2 | 26.8 | 27.3 |
| **FUBP1 Y505fs*20** | 65.3 | 48.3 | 50.5 |
| **MLL2 P647fs*283** | | | 24 |
| **MSH6 F1088fs*5** | 28.5 | | 19.8 |
| **PTEN N323fs*21** | 30.9 | 26.9 | 27.5 |

| | | | |
|---|---|---|---|
| **PTEN R233*** | 36.4 | 28.2 | 27.5 |
| **QKI K134fs*14** | 33.7 | 22.9 | 23.3 |
| **SDHA Q176H** | | | 3 |
| **PBRM1 G677fs*9** | 34.9 | 24.5 | 28.7 |
| **PBRM1 L1349fs*35** | | 27.4 | |
| **PPP2R1A R258C** | 39 | 25.9 | 27.9 |
| **PRKAR1A R368*** | | 26 | |
| **SOX9 V306fs*77** | | 8.7 | |
| **VUS** | | | |
| **ACVR1B R530H** | | + | |
| **ALOX12B F211del** | + | + | + |
| **APC R640Q** | | | + |
| **JAK1 K860fs*16** | | 24.3 | |
| **VHL F136V** | 1.4 | | |
| **ARID1A R811S** | | + | |
| **ATM W2491C** | + | + | + |
| **BRAF R178*** | + | + | + |
| **BRCA2 R1217K** | + | + | + |
| **CARD11 R555fs*45** | | + | + |
| **CBFB F18fs*4** | | + | + |
| **CYP17A1 D289Y** | | + | |
| **ATR T1989A** | | + | + |
| **AXL Q361P** | + | + | + |
| **DOT1L A1448V** | | + | |
| **EP300 A488T and P866H** | | + | |
| **EPHA3 E647fs*9** | + | + | + |
| **IKZF1 D290G** | + | + | + |
| **JAK2 P1002S** | + | + | + |
| **DAXX R291W** | + | + | + |
| **DDR1 R93*** | + | + | + |
| **DDR1 W385fs*75** | | + | |
| **EP300 V2340I** | | | + |
| **KDM6A C468R** | + | + | + |
| **NOTCH1 A2019T** | + | + | + |
| **PDCD1 (PD-1) V43M** | + | + | + |
| **PIK3CA R852Q** | + | + | + |
| **POLD1 D987fs*58** | + | + | + |
| **POLE G1343S** | + | + | + |
| **MED12 C982Y** | | | + |
| **MEF2B I6fs*14** | + | + | + |
| **MEN1 R340W** | + | + | |
| **NBN K156N** | | | + |
| **SMARCB1 K364del** | + | + | + |
| **SRC R271Q** | | | + |
| **SYK A7T** | + | + | + |
| **PTPRO R1082W** | + | + | + |
| **RET L56M and P996Q** | + | + | + |
| **SDHA L204S** | + | | |
| **SMARCA4 V855I** | + | + | + |
| **TSC1 R284C** | | | + |

Abbreviations: VUS, variants of unknown significance; NEN, neuroendocrine neoplasm; +, present; MSI, microsatellite instability; TMB, tumor mutational burden; VAF, variant allele frequency; PD-L1, programmed death-ligand 1.

Following consultation with the gynecologic oncology team, she was initially treated with a combination of carboplatin and etoposide. Although there was a transient response, disease progression occurred after five cycles. Given the tumors' MSI-high status, therapy was switched to pembrolizumab. The patient achieved a partial response in both the adenocarcinoma and neuroendocrine lesions on the first follow-up CT **(Figure 3)**, with continued disease control exceeding one year. Her underlying sarcoidosis showed only mild worsening after starting immunotherapy, managed conservatively with rheumatology guidance. Subsequent restaging scans demonstrated stable sarcoid involvement, ongoing tumor regression at all sites, and the patient remained clinically asymptomatic.

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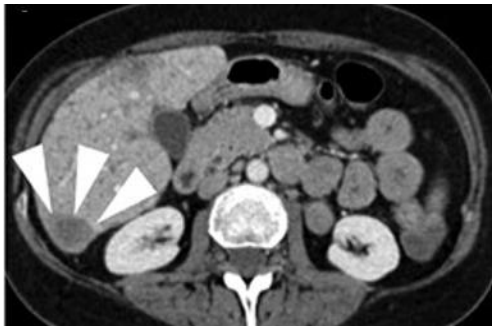

b)

**Figure 3.** Eight months after starting pembrolizumab, contrast-enhanced CT images obtained at comparable levels to those in Figure 1 demonstrate a substantial reduction in both the pelvic and hepatic lesions. The pelvic mass (a) is indicated by an asterisk (*), while the liver lesion (b) is marked with arrowheads. Additional liver metastases also showed a decrease in size (not illustrated).

In this report, we present a patient without a known hereditary cancer syndrome who developed three instances of MSI-high tumors: initially endometrial and ovarian carcinomas treated curatively, followed several years later by recurrent endometrial carcinoma and a liver metastasis. The hepatic lesion was identified as a well-differentiated, grade III neuroendocrine tumor. Genetic profiling, however, suggested a shared clonal origin among all tumor specimens. The patient subsequently received U.S. Food and Drug Administration (FDA)-approved immunotherapy [2], achieving durable clinical benefit without significant exacerbation of her autoimmune condition.

Histopathologic evaluation confirmed that the primary endometrial and ovarian tumors shared similar morphologic features, which were also reflected in the recurrent endometrial lesion. Retrospective immunohistochemical analyses excluded the presence of a mixed neuroendocrine neoplasm (MiNEN) in these specimens. The liver metastasis exhibited focal, weak nuclear ER positivity but strong synaptophysin expression, whereas all other tumors lacked neuroendocrine marker expression. Tumor-infiltrating lymphocytes (TILs) were absent across all samples. Despite histologic differences, next-generation sequencing (NGS) revealed striking molecular similarity, including shared deleterious mutations and variants of unknown significance (VUS), and all tumors retained MSI-high status. Notably, 94% of somatic variants were common across all three tumors, strongly supporting a common origin.

Although synchronous or metachronous multiple tumors are uncommon, their occurrence has been documented, particularly in patients with predisposing germline conditions. Lynch syndrome and other mismatch repair (MMR) deficiencies [3, 4] promote accumulation of DNA replication errors over time. In our patient, despite a maternal history of cervical cancer, comprehensive germline testing—including BRCA, MMR, POLE, and PTEN panels—was negative. The high degree of molecular similarity across tumors further argues against independent tumorigenesis, suggesting clonal evolution rather than three random primary malignancies. Ideally, whole-genome sequencing could provide definitive confirmation, though it was unavailable.

A limitation in interpreting the liver metastasis is the uncertain uniformity of the tumor, given focal weak ER

positivity. Whether this lesion represents exclusively a neuroendocrine tumor or a MiNEN remains unresolved, as only a needle biopsy was available. MiNENs, by definition, contain intermingled histologies with each component representing at least 30% of the neoplasm, while collision tumors (adjacent but independent histologies) and amphicrine tumors (single cells with mixed lineage features) are excluded from this category (WHO 2019: Tumours of the Digestive Tract).

Phenotypic transformation to a neuroendocrine lineage has been documented in other malignancies, though mechanisms remain incompletely understood. Lineage plasticity has been observed in EGFR-targeted lung cancer [5] and long-term androgen-deprived prostate cancer, typically via RB/p53 loss and reduced SOX2 or EZH2 activity [6, 7]. In gastrointestinal [8] and pulmonary [9] MiNENs, molecular and immunohistochemical data suggest a shared origin in amphicrine components. In our case, comparison of key variants in the neuroendocrine component identified emerging mutations in JAK1, PRKAR1A, and SOX9, which have been loosely linked to neuroendocrine differentiation in prior studies [10–13], though tissue specificity and stochastic events cannot be excluded. Determining the full evolutionary trajectory would require larger comparative analyses and assessment of variants lost during tumor progression.

The patient achieved long-lasting clinical benefit from FDA-approved checkpoint inhibition [2], likely aided by the high mutational burden. While Lynch syndrome accounts for fewer than 5% of all endometrial cancers [14], MMR deficiency has been observed in approximately 44% of endometrial MiNENs in a small series, all of which were mixed histologies [15]. Sharabi *et al*. [16] reported an MSI-high cervical neuroendocrine carcinoma responding to stereotactic body radiotherapy combined with nivolumab, noting potential abscopal effects; shared mutations (FBXW7, MSH2, PTEN, QKI, JAK1) mirrored some features in our case, though without mixed histology or separate primaries. With the rise of tumor-agnostic therapies targeting TRK [17], RET, or FGFR, comprehensive mutational profiling is increasingly relevant, especially when multiple, phenotypically divergent tumors are present.

Complicating her course, the patient was diagnosed with systemic granulomatous sarcoidosis involving spleen, lungs, and liver after initial treatment and before recurrence. She had received methotrexate followed by azathioprine, which were discontinued upon cancer diagnosis. Chronic autoimmune disease has been linked to increased cancer risk [18], with sarcoidosis most often associated with gastrointestinal and cutaneous malignancies. Long-term immunosuppressive therapy may elevate the risk of secondary cancers in patients with inflammatory conditions [19, 20]; however, in this case, the recurrence likely represents tumor evolution rather than a new malignancy, though immunosuppression may have facilitated growth.

Upon initiation of pembrolizumab, her pulmonary imaging showed transient worsening, while pulmonary function tests remained stable. The safety of checkpoint inhibitors in patients with pre-existing sarcoidosis is not well established, and treatment decisions were made in consultation with rheumatology. Sarcoid-like reactions have been reported following checkpoint inhibition [21], and patients with sarcoidosis have been safely treated with immunotherapy, with salvage immunosuppression as needed [22, 23]. Management of patients with non-life-threatening autoimmune disease on low or no immunosuppression aligns with National Comprehensive Cancer Network guidelines [24]. To date, no direct association has been established between sarcoidosis and checkpoint inhibitor efficacy; most published cases reflect a selection bias, as only patients who received prolonged immunotherapy are reported.

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**Conflict of Interest:** None

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**Ethics Statement:** None

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