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SYNCHRONOUS ENDOMETRIAL AND OVARIAN CLEAR CELL CARCINOMAS WITH PERITONEAL DISSEMINATION: A CLINICOPATHOLOGIC AND MOLECULAR DIAGNOSTIC DILEMMA

Pathology

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ABSTRACT

Synchronous clear cell carcinomas (CCCs) of the endometrium and ovary are rare and difficult to distinguish from metastatic disease. A 68-year-old postmenopausal woman presented with abdominal pain, anorexia, and bloating. Magnetic resonance imaging demonstrated an endometrial-cavity mass with hematometra, ascites, omental and peritoneal deposits, a suspicious left iliac node, and hepatic subcapsular lesions. Endometrial biopsy showed CCC with AMACR and Napsin A positivity, null-pattern p53, and retained mismatch repair proteins. Cytoreductive surgery identified a 2 cm endometrial CCC without myometrial or lymphovascular invasion and a separate 1 cm left ovarian CCC arising in an endometriotic cyst with ipsilateral tubal involvement. Metastatic CCC involved multiple peritoneal and bowel/mesenteric sites; 20 pelvic nodes and the sampled Glisson capsule were negative. The tumors were staged as pT1a N0 endometrial CCC and pT3b N0 ovarian CCC. Endometrial-tumor sequencing detected truncating TP53 and KDM6A variants; low coverage and lack of paired ovarian sequencing precluded clonality assessment. Five cycles of paclitaxel-carboplatin were administered before grade 4 toxicity and neutropenic sepsis prevented further therapy. PET-CECT showed no residual disease. Morphology and disease distribution favored synchronous primaries with ovarian-origin peritoneal dissemination, although their molecular relationship remained indeterminate.

KEYWORDS

Clear Cell Carcinoma; Endometrium; Ovary; Synchronous Primary Tumors

INTRODUCTION

Clear cell carcinoma (CCC) is an aggressive Mullerian carcinoma characterized by papillary, tubulocystic, glandular, or solid architecture and clear or eosinophilic hobnail cells (WHO Classification of Tumours Editorial Board, 2020). Endometrial CCC is uncommon, whereas ovarian CCC is strongly associated with endometriosis. When morphologically similar tumors occur simultaneously in the endometrium and ovary, distinction between independent primaries and metastatic disease directly affects staging, prognosis, and therapeutic interpretation. Traditional assessment relies on precursor lesions, laterality, depth of uterine invasion, lymphovascular invasion, and the pattern of extrauterine spread; however, molecular studies have demonstrated clonality in many tumors classified morphologically as synchronous primaries (Reijnen et al., 2020).

Case Presentation

A 68-year-old postmenopausal woman presented with abdominal pain, anorexia, and abdominal bloating. Pelvic magnetic resonance imaging dated September 2, 2025 showed an ill-defined 2.3 x 3.1 x 3.2 cm heterogeneous mass within the uterine cavity, associated hematometra, and loss of interface with the adjacent myometrium; the cervix was uninvolved. Moderate ascites, multiple omental and peritoneal nodules, an approximately 1.8 x 2.6 cm left iliac nodal lesion, and two right hepatic subcapsular nodules measuring approximately 1.3 x 1.7 cm and 0.9 x 1.2 cm were considered suspicious for disseminated malignancy. Endometrial biopsy showed a high-grade adenocarcinoma consistent with CCC.

Primary cytoreductive surgery was performed on September 15, 2025 and included hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic nodal dissection, omentectomy, and excision/sampling of peritoneal deposits. The uterus with cervix measured 8 x 5.5 x 4 cm. A 2 cm endometrial tumor and a separate 1 cm left ovarian tumor were identified. The largest omental and lesser-sac deposits measured 2 cm, and the largest right diaphragmatic peritoneal nodule measured 1.6 cm. The endometrial CCC showed no myometrial invasion or lymphovascular space invasion; a benign endometrial polyp was uninvolved. Separate uterine serosal deposits with secondary myometrial involvement were present. The left ovarian CCC arose in an endometriotic cyst containing hemosiderin-laden macrophages and involved the left fallopian tube. Metastatic CCC involved the pelvic peritoneum, omentum, right diaphragmatic peritoneum, falciform ligament with epigastric fat, lesser sac, small-bowel mesentery, small bowel, sigmoid colon, and sigmoid mesentery. The right adnexa and appendix were unremarkable, the sampled Glisson capsule was negative, and all 20 pelvic lymph nodes were reactive (right 0/11; left 0/9). The final report regarded the tumors as synchronous primaries and assigned pT1a N0 to the endometrial carcinoma and pT3b N0 (FIGO IIIB) to the ovarian carcinoma (Mutch & Prat, 2014). Under FIGO 2023, an aggressive endometrial histotype confined to the endometrium is categorized as stage IC (Berek et al., 2023).

Immunohistochemistry on the endometrial tumor showed AMACR and Napsin A positivity, null-pattern p53 expression, and retained nuclear expression of MLH1, PMS2, MSH2, and MSH6; the ovarian tumor also expressed Napsin A. Targeted next-generation sequencing of an FFPE endometrial tumor block with 70% tumor content detected TP53 c.158G>A (p.Trp53Ter; variant allele frequency 19.0%; tier I-B) and KDM6A c.3930G>A (p.Trp1310Ter; variant allele frequency 17.78%; tier II-D). No pathogenic variant was reported in POLE, ERBB2, BRAF, RET, or NTRK genes. Because sequencing coverage was low and the ovarian tumor was not tested, additional variants and the clonal relationship between the two tumors could not be assessed.

Adjuvant paclitaxel and carboplatin were administered for five cycles, the fifth on January 16, 2026. Treatment was complicated by grade 4 toxicity with neutropenic sepsis, electrolyte disturbance, hypoxia, and right lower-lobe consolidation/pulmonary volume overload requiring hospitalization, antimicrobial therapy, filgrastim, oxygen, and supportive care. She recovered but was considered unfit for further chemotherapy. PET-CECT on February 16, 2026 showed no residual disease. At review on April 22, 2026 she had no current complaints, an Eastern Cooperative Oncology Group performance status of 1, and a normal abdominal ultrasonogram performed the preceding day.

Pathological Findings

Microscopically, the endometrial biopsy showed complex papillary, glandular, and tubulocystic structures lined by markedly atypical cells with clear-to-eosinophilic cytoplasm, prominent nucleoli, focal hobnail morphology, and intraluminal eosinophilic material (Figure 1A). In the hysterectomy specimen, tumor was present along the

endometrial surface adjacent to the myometrium without unequivocal contiguous myometrial invasion (Figure 1B). The left ovarian tumor displayed complex papillary and tubulocystic growth within a cystic lesion, with atypical clear and hobnail cells in fibrous ovarian stroma (Figure 1C); endometriotic-type change and hemosiderin-laden macrophages supported origin in an endometriotic cyst. The left fallopian tube was involved by morphologically similar carcinoma (Figure 1D). AMACR and Napsin A showed diffuse cytoplasmic positivity in the endometrial tumor, and the ovarian tumor showed granular cytoplasmic Napsin A expression (Figure 2). These stains supported clear cell differentiation but could not establish the primary site (Pors et al., 2020).

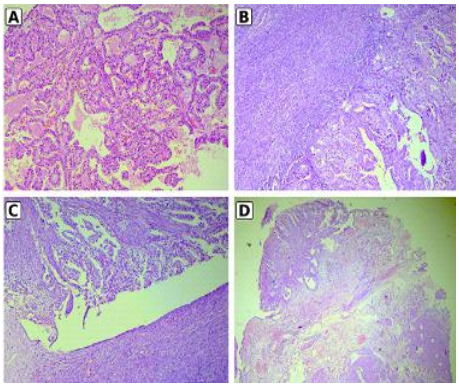

Figure 1. Histomorphology of synchronous clear cell carcinomas. (A) Endometrial biopsy showing papillary and tubulocystic architecture with clear/eosinophilic and focal hobnail cells. (B) Endometrial tumor adjacent to myometrium without definite contiguous myometrial invasion in the illustrated field. (C) Left ovarian CCC with complex papillary and tubulocystic growth in a cystic lesion. (D) Left fallopian tube involved by morphologically similar carcinoma. Hematoxylin and eosin.

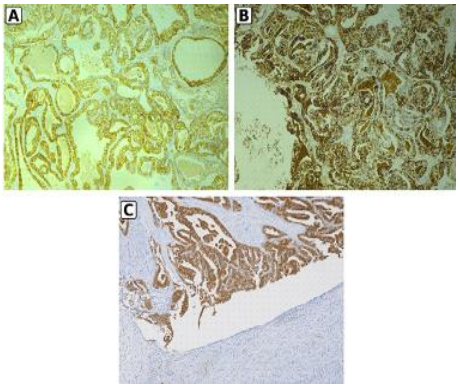

Figure 2. Immunohistochemical findings. (A) Endometrial tumor showing diffuse cytoplasmic AMACR positivity. (B) Endometrial tumor showing strong granular cytoplasmic Napsin A positivity. (C) Left ovarian tumor showing diffuse granular cytoplasmic Napsin A positivity.

DISCUSSION

The central diagnostic issue was whether the ovarian lesion represented metastasis from the endometrial primary or a synchronous ovarian primary. The uterine carcinoma was confined to the endometrium and lacked lymphovascular invasion, whereas the ovarian carcinoma was unilateral, arose in an endometriotic cyst, involved the ipsilateral tube, and was accompanied by extensive peritoneal disease. The contralateral adnexa and 20 pelvic nodes were uninvolved. This distribution, together with the final resection interpretation, favored a uterus-confined endometrial CCC and an independently arising ovarian CCC responsible for the peritoneal dissemination. The radiologically suspicious hepatic subcapsular lesions were not pathologically confirmed because the sampled Glisson capsule was negative.

Nevertheless, identical histotype and immunophenotype at two anatomic sites do not establish independent origin. Molecular profiling has shown that many synchronous endometrial and ovarian carcinomas meeting conventional histologic criteria are clonally related (Reijnen et al., 2020). In this case, TP53 and KDM6A truncating variants were identified only in the endometrial tumor. Paired sequencing of both components, preferably including shared passenger variants and copy-number profiles, would be required to determine clonality and direction of spread. Low sequencing coverage further limited negative interpretation. Napsin A and AMACR are useful markers of clear cell differentiation, but neither distinguishes endometrial from ovarian origin (Pors et al., 2020).

A defensible integrated diagnosis is therefore: synchronous clear cell carcinomas of the endometrium and left ovary, best regarded as dual primaries on clinicopathologic grounds, with peritoneal dissemination staged from the ovarian primary; molecular clonality remains indeterminate. This wording preserves the pathologic staging supported by the resection while acknowledging the limitations of morphology, immunophenotypic concordance, and single-site sequencing. The absence of residual disease on post-treatment PET-CECT is clinically favorable, although continued surveillance is warranted because both p53-abnormal endometrial CCC and advanced-stage ovarian CCC are biologically aggressive.

CONCLUSION

Synchronous endometrial and ovarian CCC requires integrated assessment of precursor lesions, invasion pattern, disease distribution, immunophenotype, and paired molecular testing. Clinicopathologic findings in this patient favored dual primaries with ovarian-origin peritoneal spread, but single-site low-coverage NGS could not resolve clonality.

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