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CASE REPORT

Clear Cell Endometrial Carcinoma: A Case Report and Review of Current Molecular Classification and Management

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Abstract

Introduction: Clear cell carcinoma of the endometrium (CCCE) is a rare but highly aggressive histological subtype of endometrial cancer characterized by early extrauterine spread and poor clinical outcomes. Recent advances in molecular classification have improved risk stratification and may guide individualized treatment strategies. **Case Presentation:** We report the case of a 45-year-old woman diagnosed with advanced clear cell carcinoma of the endometrium. Following comprehensive clinical and pathological evaluation, the patient received palliative systemic chemotherapy with paclitaxel and carboplatin because of advanced-stage disease. Histopathologically, CCCE is classified as a type II endometrial carcinoma and is commonly associated with abnormal *p53* (p53abn) or no specific molecular profile (NSMP), whereas pathogenic POLE mutations and mismatch repair deficiency (MMRd) are relatively uncommon. **Discussion:** Current evidence suggests that the molecular profile of CCCE has important prognostic and therapeutic implications. Tumors with *p53* abnormalities generally exhibit aggressive biological behavior and poorer survival outcomes, emphasizing the importance of molecular classification in treatment planning. **Conclusion:** Clear cell carcinoma of the endometrium is an uncommon but highly aggressive malignancy with an unfavorable prognosis. Early diagnosis, accurate histopathological and molecular characterization, and multidisciplinary management are essential to optimize patient outcomes.

Keywords: Clear cell carcinoma- Endometrial carcinoma- Endometrial cancer- Molecular classification- *p53*- Case report

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Introduction

Clear cell carcinoma (CCC) of the endometrium is a rare histological subtype of endometrial cancer, accounting for approximately 1%–5% of all endometrial malignancies. Despite its low incidence, it is considered one of the most aggressive variants because of its high metastatic potential, frequent extrauterine spread, and poor clinical outcomes compared with endometrioid carcinoma [1, 2].

Historically classified as a type II endometrial carcinoma, clear cell carcinoma is characterized by aggressive biological behavior and limited responsiveness to conventional platinum-based chemotherapy and radiotherapy [3]. Recent advances in molecular pathology have demonstrated that endometrial carcinomas can be classified into distinct molecular subgroups, including POLE-ultramutated, mismatch repair-deficient (MMRd), *p53*-abnormal (p53abn), and no specific molecular profile (NSMP). This molecular classification has become increasingly important for prognostic stratification and therapeutic decision-making [4].

Because of its rarity, the optimal management of clear cell carcinoma remains challenging, and published clinical experience is limited. Reporting additional cases may improve understanding of its clinicopathological characteristics and therapeutic outcomes. We therefore present the case of a 45-year-old woman diagnosed with

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advanced clear cell carcinoma of the endometrium who was managed with palliative chemotherapy.

Case Report

A 45-year-old woman with no significant past medical history presented with a three-month history of abnormal uterine bleeding manifested as persistent menometrorrhagia, without associated pelvic pain. She initially underwent pelvic ultrasonography in August 2022, which demonstrated multiple uterine fibroids. A myomectomy was subsequently performed.

Unexpectedly, histopathological examination of the surgical specimen, supported by immunohistochemical analysis, revealed clear cell carcinoma of the endometrium.

On clinical examination, abdominal palpation demonstrated a pelvic mass, while digital rectal examination identified a firm centrally located pelvic mass measuring approximately 7 cm in diameter. Vaginal examination was not performed because the patient had never been sexually active. Pelvic magnetic resonance imaging (MRI) revealed a large locally advanced uterine tumor infiltrating almost the entire myometrium with extension into the cervix and upper vagina. Multiple pelvic and abdominal wall masses were identified, consistent with secondary peritoneal and cutaneous metastases. MRI also demonstrated a metastatic lesion involving the right iliac wing.

Thoracoabdominal computed tomography (CT) confirmed extensive metastatic disease, including multiple anterior abdominal wall masses extending into the subperitoneal fat and closely abutting the anterior bladder wall. A metastatic liver lesion involving segments V and VIII was identified, together with osteosclerotic lesions affecting the eighth thoracic vertebra and the right iliac wing.

Based on the advanced stage of the disease and the presence of distant metastases, curative surgery was not considered feasible. The patient therefore received six cycles of palliative chemotherapy consisting of paclitaxel and carboplatin. Radiological assessment after completion of chemotherapy demonstrated stable disease according to treatment response evaluation.

Discussion

CCC of the endometrium is an uncommon but highly aggressive histological subtype that accounts for approximately 1%–5% of all endometrial carcinomas. Despite its rarity, CCC contributes disproportionately to disease-related mortality because of its high metastatic potential, early extrauterine dissemination, and poor response to conventional treatment. Consequently, its prognosis is generally less favorable than that of the more common endometrioid subtype [5-9].

The present case illustrates several characteristic features of this rare malignancy. Although the patient was only 45 years old, considerably younger than the typical postmenopausal population affected by endometrial CCC, she presented with locally advanced disease and distant metastases at diagnosis. This finding supports previous reports demonstrating that, although uncommon in younger women, clear cell carcinoma may occur before menopause and can exhibit highly aggressive biological behavior irrespective of age [10].

Abnormal uterine bleeding remains the most common presenting symptom of endometrial carcinoma, including the clear cell subtype. In our patient, persistent menometrorrhagia prompted imaging studies that initially suggested benign uterine fibroids. The diagnosis of clear cell carcinoma was established only after histopathological examination of the surgical specimen with immunohistochemical confirmation. This case emphasizes that persistent abnormal uterine bleeding should always prompt careful pathological evaluation, even when imaging findings appear compatible with benign uterine disease [11, 12].

Radiological evaluation demonstrated extensive local invasion involving the myometrium, cervix, and vagina, together with peritoneal, hepatic, osseous, and abdominal wall metastases. These findings are consistent with the recognized tendency of clear cell carcinoma to spread beyond the uterus at an early stage. Previous studies have shown that patients with advanced-stage disease experience substantially lower survival rates than those diagnosed with localized tumors, highlighting the importance of early detection and comprehensive staging [5, 10].

Histologically, clear cell carcinoma demonstrates papillary, tubulocystic, and solid architectural patterns, frequently accompanied by stromal hyalinization and characteristic clear or eosinophilic cytoplasm. Immunohistochemistry is valuable for confirming the diagnosis and distinguishing CCC from other high-grade endometrial carcinomas (Figure 1). Typical findings include low expression of estrogen and progesterone receptors (Figure 2), variable *p53* expression, and a

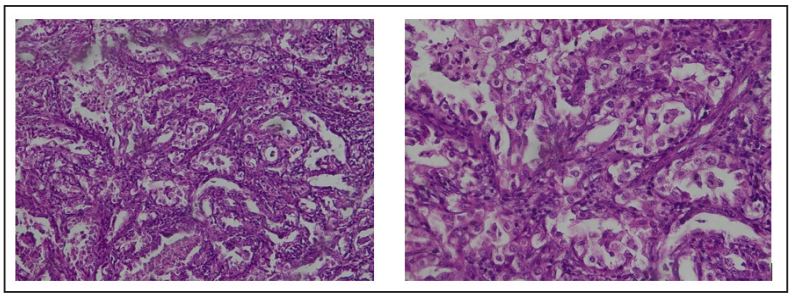


Figure 1. Invasive Adenocarcinoma Proliferation with an Immunohistocheminal Profile Consistent with Clear Cell Carcinoma

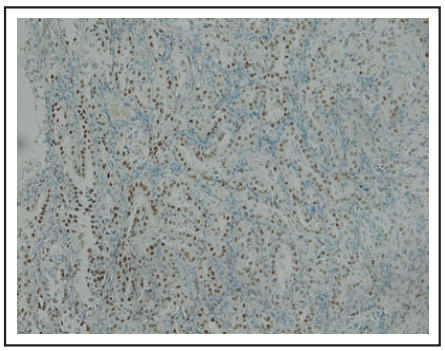


Figure 2. Positive Expression of Tumor Cells by Estrogen Receptors

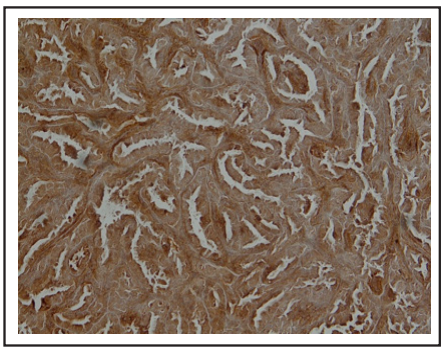


Figure 3. Positive Expression of Tumor Cells by Napsin A

high proliferative index reflected by *Ki-67* positivity (Figure 3) [5, 13].

Current management of endometrial clear cell carcinoma relies on multimodal treatment combining surgery, chemotherapy, and radiotherapy according to disease stage and patient condition. Comprehensive surgical staging remains the standard of care for patients with resectable disease. However, in the present case, widespread metastatic involvement precluded curative surgery, and palliative chemotherapy with paclitaxel and carboplatin was administered. Although radiological reassessment demonstrated stable disease, the prognosis remained poor because of the extensive metastatic burden at presentation.

Recent advances in molecular classification have substantially improved the understanding of endometrial carcinoma and have important therapeutic implications. According to The Cancer Genome Atlas (TCGA) classification, endometrial carcinomas are categorized into four molecular subgroups: POLE-ultramutated, mismatch repair-deficient (MMRd), *p53*-abnormal (p53abn), and no specific molecular profile (NSMP). Unlike traditional histological classification alone, these molecular subtypes provide more accurate prognostic information and increasingly guide treatment selection. Clear cell carcinoma most commonly belongs to the *p53*-abnormal and NSMP molecular groups, both of which are generally associated with less favorable outcomes, whereas POLE-mutated tumors have an excellent prognosis despite aggressive histological features. Recent analyses from the PORTEC-3 trial further demonstrated that patients with *p53*-abnormal tumors derive the greatest benefit from combined chemoradiotherapy, whereas those with MMR-deficient tumors show limited additional benefit from chemotherapy [10, 14, 15].

This case highlights the aggressive nature of endometrial clear cell carcinoma and the challenges associated with delayed diagnosis. It also underscores the growing importance of integrating molecular classification into routine clinical practice to optimize risk stratification and personalize therapeutic strategies.

In conclusion, clear cell carcinoma of the endometrium is a rare but highly aggressive histological subtype characterized by early extrauterine dissemination, poor prognosis, and limited response to conventional therapy. This case highlights the importance of maintaining a high index of suspicion in women presenting with abnormal uterine bleeding and demonstrates the value of prompt histopathological diagnosis and comprehensive staging. Although platinum-based chemotherapy remains a cornerstone of treatment for advanced disease, outcomes remain unsatisfactory in many patients. The integration of molecular classification into routine clinical practice offers new opportunities for individualized risk stratification and treatment selection. Early diagnosis, multidisciplinary management, and molecularly guided therapeutic strategies are essential to improve survival and optimize outcomes in patients with this uncommon malignancy.

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Fatim-Zahra Sabri and Pawendtaoré Esdras Zongo contributed to the conception, data collection, manuscript preparation, and literature review. Halim Sebbar, Sanaa Hachimi, Nissrine Bennani Guebessi, Meryem Belhouari, Hatim Ghita, Tarik Chekrine, Mouna Bourhafour, Zineb Bouchbika, Hassan Jouhadi, Nezha Tawfiq, Souha Sahraoui, and Nadia Benchakroun contributed to patient management, manuscript revision, and approval of the final version. All authors read and approved the final manuscript.

Availability of Data

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

Ethics Approval [AAZ1.1]

Ethical approval for publication of this case was obtained in accordance with institutional requirements. All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for Publication

Written informed consent for publication of this case report and accompanying clinical images was obtained from the patient.

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