Clear cell carcinoma palisading in a focus of endometriosis on the uterine serosa – A case report and review of the literature

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ABSTRACT

Background: Clear cell carcinoma arising from the malignant transformation of endometriosis is a rare but aggressive cancer often diagnosed in perimenopausal women. Malignant transformation constitutes a rare complication of endometriosis, with only a few cases reported in the medical literature. Clear cell carcinoma and endometrioid carcinoma are the two most common histological subtypes associated with malignant endometriosis.

Case Presentation: A 61-year-old Afro-Trinidadian woman underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for a degenerated uterine leiomyoma. Histopathology demonstrated an isolated finding of clear cell carcinoma occurring within an endometriotic cyst on the uterine serosa. Subsequent surgical staging demonstrated early-stage disease associated with a high-risk histological subtype and the patient was referred for adjuvant chemoradiotherapy.

Conclusion: This case highlights the clinical manifestations and treatment modalities employed for an early-stage high-risk subtype of endometriosis-associated cancer. In light of the few publications on this clinical entity, we hope to raise awareness of this unique complication of endometriosis and contribute evidence to the development of standardized treatment protocols.

1. Introduction

Malignant transformation complicates less than 1% of all endometriosis cases [1]. Clear cell carcinoma and endometrioid carcinoma are the two most prevalent histologic subtypes of malignant endometriosis [2]. Although endometriosis-associated neoplasia can affect any site involved by endometriosis, the ovary is implicated in most cases [3]. Rarely, the uterine corpus is involved. Endometriosis-associated clear cell carcinoma typically affects perimenopausal women with a long-standing history of endometriosis, large ovarian endometriomas, and infertility [4].

The clinical features of endometriosis-associated neoplasia are often indistinguishable from other gynaecological cancers [5]. It is important, therefore, to differentiate between the presence of a primary gynaecological malignancy versus endometriosis-associated neoplasia for staging, prognostication, and management purposes [5]. For this reason, Sampson et al described three criteria required for confirming a diagnosis of malignant endometriosis, based on histopathology [6].

Due to the paucity of publications on endometriosis-related clear cell carcinoma, there are no standardized treatment protocols [7]. However, a multimodal approach to treatment that involves surgical staging, adjuvant chemotherapy and considerations for radiotherapy appears to improve patient outcomes [8]. Herein, this case highlights an incidental finding of a high-risk histological subtype of malignant endometriosis arising from the uterine serosa in a postmenopausal woman. The patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for a degenerated uterine leiomyoma. Histopathology demonstrated an isolated finding of clear cell carcinoma arising within a focus of endometriosis on the uterine serosa that satisfied Sampson’s criteria. Surgical staging demonstrated early-stage disease and the patient was referred for platinum-based adjuvant chemotherapy and vaginal brachytherapy based on her high-risk histological subtype.

2. Case Presentation

A 61-year-old woman with a BMI of 24.1 kg/m² presented to the...
Clinical examination demonstrated a mobile, symmetrically enlarged mass that originated from the pelvis and extended to the umbilicus. Speculum examination revealed a normal, healthy cervix associated with postmenopausal changes. Blood investigations inclusive of a complete blood count, and renal and liver function tests were within normal parameters. Pelvic ultrasonography demonstrated an enlarged, retroverted uterus that contained a central cystic structure with low-level internal echoes consistent with a degenerated subserosal uterine leiomyoma. Additionally, a left adnexal mass that contained a solid mural component, likely of an ovarian origin, was noted. The endometrial thickness measured 0.3 cm and there was no evidence of pelvic free fluid. The CA-125 tumour marker was also within the normal range.

A computed tomography (CT) scan of the abdomen and pelvis was requested to further characterize the adnexal mass. Pelvic CT confirmed an enlarged uterus measuring $16.0 \text{ cm} \times 12.7 \text{ cm} \times 10.4 \text{ cm}$, associated with a central degenerated leiomyoma that measured $5.1 \text{ cm} \times 3.9 \text{ cm} \times 3.3 \text{ cm}$ (Fig. 1). The left adnexal mass was predominantly cystic and measured $13.9 \text{ cm} \times 11.9 \text{ cm} \times 14.0 \text{ cm}$. This mass, likely a large ovarian cyst, extended to the umbilicus and displaced the uterus laterally and the urinary bladder inferiorly. There was no evidence of abdominal or pelvic lymphadenopathy and the intra-abdominal organs appeared unremarkable. Further evaluation of the adnexal mass was advised, and the patient was scheduled for surgery.

The patient underwent an uneventful total abdominal hysterectomy and bilateral salpingo-oophorectomy. Intraoperatively, pelvic adhesions and scattered foci of endometriosis involving the ovaries, uterine corpus and bladder peritoneum were noted. These findings were consistent with stage III endometriosis. A solitary anterior degenerated leiomyoma was noted and a well-circumscribed cystic mass arising from the posterolateral surface of the uterine serosa was also observed. Histopathology confirmed an anterior degenerated uterine leiomyoma. However, on cut sections, the posterolateral uterine serosal mass contained degenerated, hemorrhagic material, with an intact serosal surface that measured $11.0 \text{ cm} \times 6.5 \text{ cm} \times 7.0 \text{ cm}$. Histology demonstrated the presence of endometrial-type glands and stroma within the serosal mass that was consistent with an endometriotic-type cyst. Furthermore, nests of prominent and clear eosinophilic hobnail cells were noted among the endometrial-type glands and stroma within the endometriotic serosal cyst (Fig. 2). These cells displayed marked nuclear pleomorphism, atypia, and prominent nucleioli. These findings were consistent with an ovarian-type clear cell carcinoma arising from an endometriotic cyst on the uterine corpus. Histological analysis demonstrated no evidence of disease elsewhere on the surgical specimen.

The patient was referred to the gynaecology-oncology team and her case was discussed at the multidisciplinary team (MDT) meeting, where a recommendation was made for surgical staging to guide adjuvant treatment. Subsequent surgical staging included peritoneal washings and an omentectomy, which demonstrated no evidence of metastatic disease. These findings were consistent with stage 1A ovarian-type clear cell carcinoma arising from an endometriotic cyst on the uterine corpus. Due to the patient’s high-risk histologic subtype, the MDT recommended adjuvant chemoradiotherapy, which comprised a combination of carboplatin and paclitaxel for six cycles with vaginal brachytherapy. The patient was undergoing treatment at the time of writing.

3. Discussion

This case highlights a rare instance of malignant transformation of an endometriotic cyst on the uterine serosa in a postmenopausal patient. While endometriosis affects 10% of women in the reproductive age group, the overall risk of developing an endometriosis-associated neoplasm (EAN) remains low, at approximately 0.7% to 1.9% [1]. A recent prospective study involving 6400 women diagnosed with endometriosis and ovarian endometriomas during a 17-year follow-up demonstrated a standardized incidence ratio of 8.95 for malignant transformation (10). Additionally, perimenopausal women are more frequently affected than women of postmenopausal age [4]. Epidemiological studies describe numerous risk factors for developing an EAN and these include hyperestrogenism, endometriosis diagnosed at an early age, long-standing endometriosis (greater than 10 years), the presence of ovarian endometriomas, and endometriosis-associated infertility [10,11]. Moreover, mutations in the tumour suppressor genes PTEN, KRAS, and p53 have also been implicated [12].

Based on histopathology and molecular patterns, the most common histologic subtype of EAN is clear cell carcinoma (51%), followed by endometrioid carcinoma (43%) [2]. Less common histologic subtypes include low-grade or high-grade serous carcinomas and mucinous carcinomas [2]. In theory, EAN can develop in any location affected by endometriosis. The ovary is implicated in up to 75% of EAN cases while the uterine serosa is rarely involved [3]. Endometriosis-related clear cell carcinoma is similar to clear cell carcinoma of the endometrium, ovary, and cervix as this histologic subtype is highly aggressive, deeply invasive, and poorly sensitive to chemotherapy [13]. Although EAN is a distinct biological entity, its clinical features may be indistinguishable.

![Fig. 1. Axial CT scan of the pelvis demonstrates adnexal mass (white arrow).](image1)

![Fig. 2. Histopathology demonstrates clear cell carcinoma contiguous with endometrial-type glands and stroma.](image2)
from that of non-endometriosis-associated gynaecological cancers [5]. Patients may present with a pelvic mass, abnormal uterine bleeding, weight loss, constipation, and hematuria; in most cases, up to 41.1% of patients may be asymptomatic [5]. Therefore, it is important to differentiate between a primary gynaecological cancer versus malignant endometriosis, for staging, prognostication, and management purposes [5]. For this reason, in 1925, Sampson described three histopathological criteria required for diagnosing an EAN: evidence of endometriosis near the tumour, the absence of another primary site tumour, and histological evidence consistent with an endometrial origin [6]. In 1953, Scott et al added a fourth criterion, which states that EAN must demonstrate a morphological progression from benign to malignant differentiation in a contiguous fashion [14]. In our case, histologic findings satisfied both Sampson’s and Scott’s prerequisites for confirming an EAN.

Currently, there are no standardized treatment protocols for endometriosis-associated clear cell carcinoma; however, a multimodal approach to treatment appears to improve patient outcomes [8]. A total hysterectomy with bilateral salpingo-oophorectomy, combined with platinum-based adjuvant chemotherapy, gives a favourable outcome, particularly when patients are diagnosed with early-stage disease [8,9]. EANs are staged surgically and, at a minimum, should include a total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, omentectomy, and considerations for pelvic/para-aortic lymph node dissection [15]. Stage 1A/1B disease associated with low-risk histology does not require adjuvant treatment [16]. However, the presence of a high-risk histological subtype, such as clear cell carcinoma, is an indication for adjuvant treatment irrespective of the patient’s surgical stage [16,17]. A standard chemotherapeutic regime consists of carboplatin (AUC 6) and paclitaxel (175 mg/m²) used for six cycles [8,18]. Locoregional radiotherapy, particularly vaginal brachytherapy, demonstrates efficacy for early-stage uterine cancer with high-risk histological subtypes and reduces the risk of local recurrence, thus improving the recurrence-free survival [5,19]. Although our patient was diagnosed with an early-stage EAN, her high-risk histological subtype necessitated combined adjuvant chemoradiotherapy to render her disease-free and reduce the risk of recurrence. The overall 5-year disease-free survival rate of early-stage clear cell carcinoma associated with endometriosis is approximately 80–89% [9]. These patients should receive follow-up care for approximately 5 years with a combination of observation, serum CA125 measurements, and imaging [20].

In conclusion, malignant transformation is a rare complication of endometriosis. Moreover, an isolated occurrence of clear cell carcinoma arising from a focus of endometriosis on the uterine serosa is highly unusual. In most cases, patients may be asymptomatic or exhibit clinical features similar to other primary gynaecological cancers. In this regard, histopathologists play a critical role in the detection of cancer, particularly in cases where there is an initial low index of suspicion and where the identified cancer is a high-risk or rare subtype. While standardized treatment protocols are pending, there is mounting evidence to suggest that a multimodal approach to management improves patient outcomes. EAN is staged surgically and a combination of adjuvant chemoradiotherapy is required for high-risk histological subtypes regardless of disease stage.

Contributors

Vishal Bahall conceived, supervised and drafted the manuscript, and performed the surgical staging procedure.

Lance De Barry drafted, edited and revised the manuscript and performed the literature review.

Collin Jaggersnath edited and approved the manuscript and performed the initial total abdominal hysterectomy and bilateral salpingo-oophorectomy.

All authors revised and approved the final manuscript.
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