RESEARCH PAPER

Endometrial Carcinosarcoma: An Unusual Presentation

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ABSTRACT
Objective: To describe the clinicopathological features, diagnostic challenges and management of endometrial carcinosarcoma presenting with unusual clinical manifestations.
Methods: Patients presenting with abnormal uterine bleeding underwent clinical evaluation, imaging and pipelle biopsy. Histopathological examination with immunohistochemistry, including p53, cytokeratin and SMA, was performed. Multidisciplinary management with chemoradiotherapy followed by interval surgery was undertaken.
Results: Histology revealed a biphasic malignant tumor with carcinomatous and sarcomatous differentiation, including heterologous elements. Immunohistochemistry confirmed epithelial and mesenchymal components with high proliferative activity. All patients showed favorable response to neoadjuvant therapy, allowing subsequent surgical staging and cytoreduction.
Conclusion: Endometrial carcinosarcoma can mimic benign conditions, making early diagnosis difficult. Histopathology supported by immunohistochemistry is essential. Combined modality treatment may improve operability and outcomes.
Keywords: *Endometrial carcinosarcoma; biphasic tumor; immunohistochemistry; p53; cytokeratin; SMA*
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INTRODUCTION

Endometrial carcinosarcoma (ECS), also known as malignant mixed Müllerian tumour, is a rare, highly aggressive disease [1]. It accounts for approximately 2%-5% of all uterine neoplasms, causing around 16% of all deaths and is associated with an estimated 5-year overall survival (OS) of 33%-39% [2]. ECS is characterised by a biphasic growth of malignant epithelial (carcinomatous) and mesenchymal (sarcomatous) components, which could be of diverse histological origin: homologous (endometrial stromal sarcoma, fibrosarcoma, leiomyosarcoma) or heterologous (osseous, cartilaginous, and rhabdomyoblastic) cells [3]. Clinically, ECS cannot be distinguished from endometrial carcinoma or uterine sarcoma. The definitive diagnosis can only be made based on histological and immunohistochemical examination [4]. Owing to its microscopic diversity and low frequency of cases, standardised treatment protocols are not available [5, 6]. Proposed treatment includes cytoreductive surgery for medically operable patients and adjuvant therapy that might be radiotherapy or systemic therapy based on surgical and histopathological findings [5, 6].

Because of its rarity, ECS poses significant diagnostic and therapeutic challenges. The clinical and radiological features may mimic endometrial carcinoma or even benign conditions and limited biopsy material may fail to demonstrate the characteristic biphasic morphology, thereby requiring immunohistochemical confirmation. Additionally, in the absence of large prospective trials, the optimal treatment strategy remains controversial. Reporting such unusual presentations adds to the limited body of literature, enhances understanding of tumor behaviour and may contribute to improving future management protocols.

Case Report 1

A 45-year-old woman presented to the Department of Obstetrics and Gynaecology at a Tertiary Care Hospital with a history of heavy and prolonged menstrual bleeding for 15-25 days with passage of clots, accompanied by mild lower abdominal pain for two days. Her obstetric history was G5P4A1 and all were by normal vaginal deliveries. Sterilization had not been performed. Her last childbirth was 15 years earlier. There was no history of medical comorbidities or any relevant family history. General examination revealed pallor and koilonychia, while abdominal examination showed no evidence of masses or organomegaly. Speculum examination demonstrated a polyp measuring approximately 2 × 2 cm protruding through the cervical os with active bleeding. Per vaginal examination revealed an anteverted, bulky uterus with a

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normal cervix. Laboratory investigations indicated anemia, with a hemoglobin level of 8.7 g/dL, MCV of 67 fL, MCH of 38 pg, MCHC of 30% and RDW of 5.8. Serum CA-125 levels were elevated. Ultrasonography revealed a bulky, anteverted uterus with a globular heterogeneous area measuring 9.9 × 7.4 × 6.5 cm, along with heterogeneous myometrium and cystic changes causing loss of the endomyometrial junction. The endometrial thickness measured 18-16 mm. Both ovaries appeared normal and the findings were suggestive of early adenomyosis. Based on these findings, a pipelle endometrial biopsy was performed. The cervical polyp specimen consisted of two grey-white to grey-brown soft tissue fragments, the largest measuring 2.5 × 1.6 × 0.5 cm and the smallest measuring 1.5 × 1 × 0.2 cm, with a homogeneous, firm cut surface. The endometrial biopsy comprised multiple grey-brown linear fragments together measuring 4 × 1.5 × 0.3 cm. Histopathological evaluation of both specimens revealed a high-grade malignant neoplasm composed of glands lined by stratified epithelium exhibiting marked atypia. The stroma showed sarcomatous differentiation with areas of cartilaginous change. Extensive areas of hemorrhage and necrosis were present, favoring a diagnosis of carcinosarcoma (Figure I). Immunohistochemical analysis demonstrated strong p53 positivity in the malignant endometrial glands (90%). Cytokeratin showed strong positivity in the epithelial component (85%) (Figure II), while smooth muscle actin (SMA) highlighted the sarcomatous component (80%) (Figure III), confirming an aggressive biphasic malignancy. The patient was subsequently referred to the oncology department, where she received non-conventional concomitant chemoradiotherapy with favorable oncological response. This was followed by an interval surgical staging laparotomy with lymph node excision. The postoperative recovery was uneventful.

Case Report 2

A 35-year-old woman presented to the Department of Obstetrics and Gynaecology at a Tertiary Care Hospital with a history of heavy and prolonged menstrual bleeding lasting 20 days with passage of clots, accompanied by mild lower abdominal pain for five days. Her obstetric history was G5P2A3, with no associated medical comorbidities or relevant family history. General examination revealed pallor and koilonychia, while abdominal examination showed no evidence of masses or organomegaly. Speculum examination demonstrated a polypoidal growth measuring approximately 3 × 2 cm protruding through the cervical os with active bleeding and per vaginal examination revealed an anteverted, bulky uterus with a normal cervix. Laboratory investigations indicated severe microcytic anemia, with a hemoglobin level of 6.7 g/dL, MCV of 57 fL, MCH of 32 pg, MCHC of 30% and RDW of 6.0, along with elevated serum CA-125 levels. Ultrasonography revealed a bulky, globular, anteverted uterus measuring 10.8 × 8.3 × 5.5 cm, with heterogeneous myometrium and cystic changes causing loss of the endomyometrial junction and an endometrial thickness of 20 mm; both ovaries appeared normal and the findings were suggestive of early adenomyosis. Based on these findings, a pipelle endometrial biopsy was performed. Gross examination of the cervical polyp specimen showed two grey-white to grey-brown tissue fragments with a homogeneous, firm cut surface, while the endometrial biopsy comprised multiple grey-brown linear fragments. Histopathological evaluation of both specimens showed an aggressive malignant tumor composed of admixed carcinomatous and sarcomatous components. The epithelial element formed atypical glandular structures along with the stromal component consisting of pleomorphic spindle cells with areas of heterologous cartilaginous differentiation (Figure IV). Large zones of necrosis and hemorrhage were present. Overall findings favored a diagnosis of endometrial carcinosarcoma. Immunohistochemical analysis demonstrated strong p53 positivity in the malignant glands (92%) (Figure V), cytokeratin positivity in the epithelial component (80%) (Figure VI) and smooth muscle actin (SMA) positivity in the sarcomatous component (80%), confirming the diagnosis of an aggressive biphasic malignancy. The patient was subsequently referred to the oncology department, where she underwent non-conventional concomitant chemoradiotherapy consisting of five cycles of chemotherapy and five cycles of radiotherapy, which resulted in a favorable oncological response. This was followed by an interval surgical staging laparotomy with lymph node excision and the postoperative recovery was uneventful.

Case Report 3

A 28-year-old woman presented to the Department of Obstetrics and Gynaecology at a Tertiary Care Hospital with complaints of infertility and a strong desire to conceive. She reported regular menstrual cycles associated with passage of clots and mild lower abdominal pain for the past five days. Her obstetric history was G2A2 with two missed abortions and there was no history of medical comorbidities or significant family history. General examination revealed pallor and koilonychia, while abdominal examination showed no palpable masses or organomegaly. On speculum examination, a polypoidal mass measuring approximately 1 × 1 cm was seen protruding through the cervical os with active bleeding and per vaginal examination revealed a normal cervix with an anteverted uterus. Laboratory investigations demonstrated severe microcytic anemia with a hemoglobin level of 7.7 g/dL, MCV of 57 fL, MCH of 30 pg, MCHC of 29% and RDW of 5.8, along with elevated serum CA-125 levels. Ultrasonography revealed a bulky, globular, anteverted uterus measuring 8.8 × 7.0 × 6.2 cm, with heterogeneous myometrium and cystic changes causing loss of the endomyometrial junction and an endometrial thickness of 16-18 mm; both ovaries appeared normal and the findings were suggestive of early adenomyosis. Hysterosalpingography demonstrated bilateral tubal blockage, following which a pipelle endometrial biopsy was performed. Gross examination of the cervical polyp specimen showed grey-white to grey-brown tissue fragments with a homogeneous, firm cut surface, while the

endometrial biopsy comprised multiple grey-brown linear fragments. Histopathological evaluation of both specimens demonstrated a biphasic neoplasm with malignant epithelial glands intimately associated with a high-grade sarcomatous stroma. The tumor cells exhibited marked nuclear atypia and mitosis. Foci of cartilaginous differentiation were noted within the mesenchymal component. Extensive hemorrhage and necrosis further supported the impression of carcinosarcoma. Immunohistochemical analysis demonstrated strong p53 positivity in the malignant glands (90%) (Figure VII), cytokeratin positivity in the epithelial component (88%), and smooth muscle actin positivity in the sarcomatous component (85%) (Figure VIII), confirming an aggressive biphasic malignancy. The patient was subsequently referred to the oncology department, where she received non-conventional concomitant chemoradiotherapy comprising five cycles each of chemotherapy and radiotherapy, resulting in a favorable oncological response, followed by an interval surgical staging laparotomy with lymph node excision, after which the postoperative recovery was uneventful.

DISCUSSION

ECS, due its endometrial origin, is staged as an endometrial carcinoma/cancer (EC) rather than a uterine sarcoma [7, 8]. The International Federation of Gynecology and Obstetrics defined the staging system from I to IV according to the extension of the disease [8]. The stage is the most important factor in choosing treatment. For EC stages I-II, surgery is the first treatment, depending on the histopathology classification adjuvant therapies: radiation therapy, chemo or both may be given [9]. On the other hand, as stages III and IV are tumours extending beyond the uterus, usually they are not candidates for surgery as primary treatment; chemo and radiotherapy, as well as hormone or biological therapy are the management strategies with palliative care intentions (to reduce pelvic pain or bleeding) [10]. Even though, in some cases, they can be taken into surgery if debulking is possible and require adjuvant therapy [11].

Despite the fact our patient had an advanced stage ECS, she had good performance status; this was crucial for the multidisciplinary board decision to proceed with a neoadjuvant chemoradiation obtaining promising results. The response to the proposed treatment was a significant shrinkage of the carcinosarcoma from 85.2 × 95.8 × 10.4 mm to 43.4 x 60.7 x 62.7 mm generating the opportunity of a satisfactory cytoreduction surgery. A surgery that was never on the table after the initial diagnosis. Follow-up scans demonstrated a patient in remission, free of disease after a non-standard management of ECS. Due its divergent behaviour and prognosis, the recommendations for managing ECS are scarce, it has been based on expert opinions, small retrospective studies or non-randomised trials potentially biased by unmeasured confounders. There's no consensus in management or standard of care for ECS [12].

Several studies confirm the clear benefit of chemotherapy for ECS on OS in this patient population. Radiotherapy's role, doses and type are still a controversial topic that is under evaluation [5, 6]. The radiation prescription dose in endometrial cancer is commonly 1.8–2.0 Gy daily fractions up to 36–68 Gy (median 54 Gy) [13]. Our patient received VMAT which is a novel radiation therapy technique that delivers the radiation dose continuously as the treatment machine rotates. VMAT allows a reduction dose to organs at risk (bladder, bowel and rectum), with improved planning target volume (PTV) coverage; hence it increases dose homogeneity in the target volume and decreases the treatment delivery time. The benefit of our radiotherapy approach guided by sequencing tomography imaging in each session gave us the opportunity of a novel surgical approach in a non-surgical initial scenario.

The evidence in the use of systemic therapy in advanced stage ECS is a prospective study area. In 2015, a National Cancer Database analysis evaluated the rates of chemo-radiotherapy use as primary treatment in a significant cohort of patients (10,609) with uterine carcinosarcoma with different stages of the disease. The study showed adequate tumour response after the use of chemo-radiation in advanced stages improving the OS (65 months (95% CI: 56–77). Our patient's outcome showed that alternative treatment could impact OS rates despite initial prognosis.

CONCLUSIONS

ECS is an aggressive histopathological presentation tumor with poor OS. The mesenchymal component may contain cell types native to the uterus and resemble high-grade undifferentiated sarcoma or fibrosarcoma; early diagnosis of ECS with IHC helped in the early management and treatment plan. Early diagnosis and approach will help in decision making among conventional and non-conventional treatment plans. Early diagnosis and utilization of recent advance in the diagnosis of the tumour guides us in a good approach of treatment plan which is directly proportional to the survival rate. More studies have to be implemented to standardise this treatment, improve outcomes and to decrease the morbidity.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

FUNDING

None.

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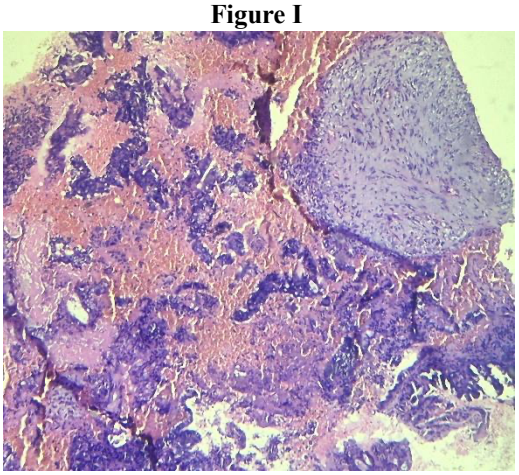
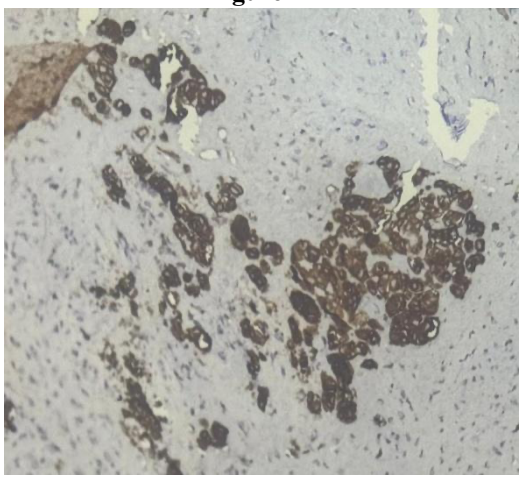
Figure I



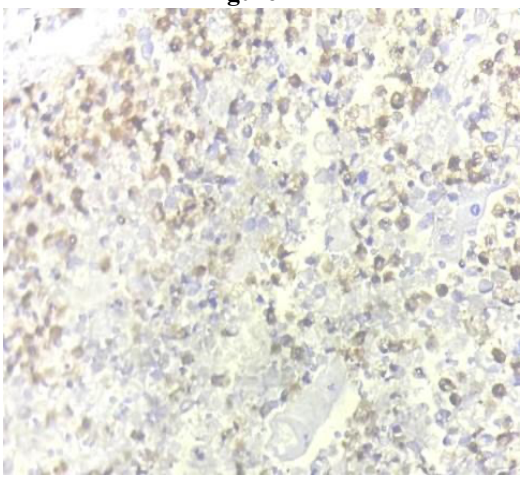
Neoplasm arranged in irregular glandular structures exhibiting marked cytological atypia; intervening stroma shows areas of cartilaginous differentiation (H&E, 10×).

Figure II



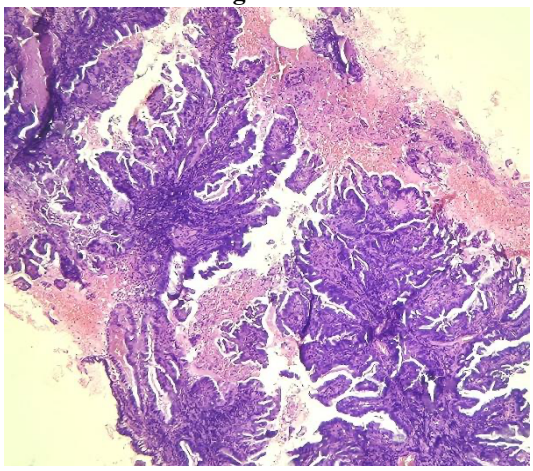
Immunohistochemistry for cytokeratin demonstrates strong positivity (~85%) in malignant endometrial glandular components, confirming epithelial differentiation.

Figure III



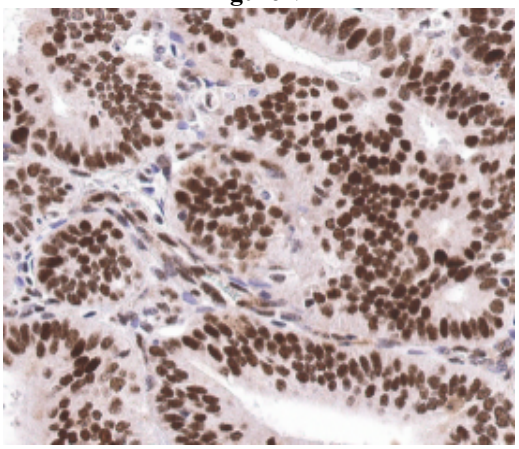
Smooth muscle actin (SMA) immunostaining highlights diffuse positivity (~80%) within the sarcomatous component, supporting mesenchymal differentiation

Figure IV



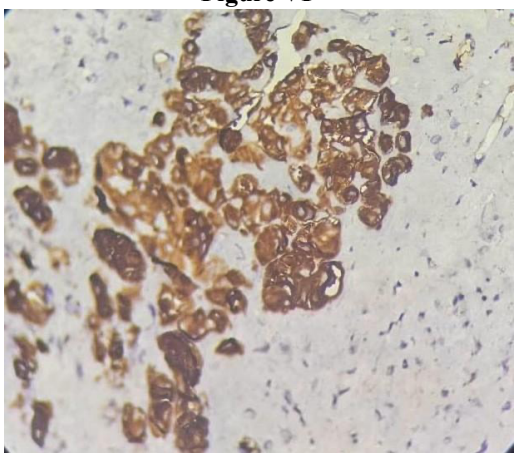
Malignant neoplasm composed of atypical glands lined by stratified epithelium with marked nuclear pleomorphism; surrounding stroma exhibits sarcomatous transformation (H&E, 10×).

Figure V



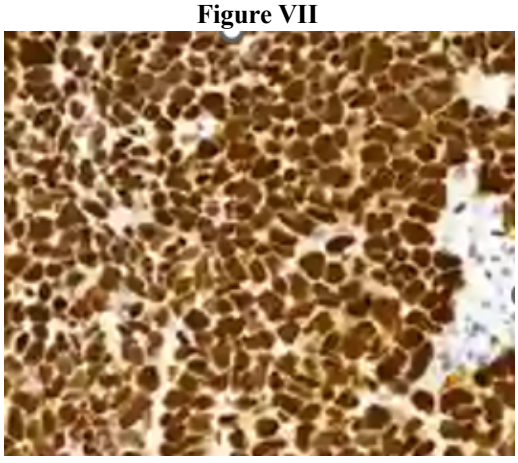
p53 immunostaining shows strong diffuse nuclear positivity (~92%) in both epithelial and sarcomatous components, indicating high-grade tumor biology.

Figure VI



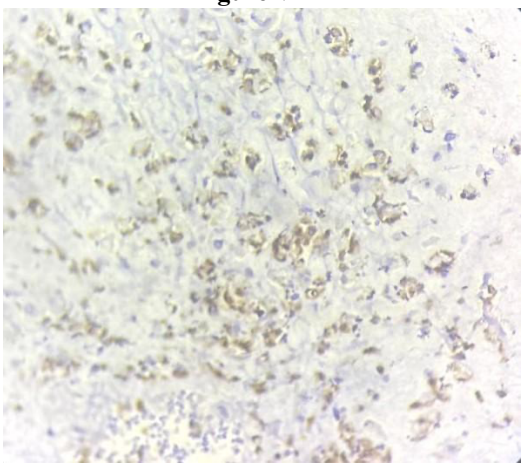
Cytokeratin immunostaining demonstrates strong positivity (~80%) in malignant endometrial glands, reaffirming epithelial origin.

Figure VII



Diffuse strong nuclear p53 positivity (~90%) observed in both glandular and sarcomatous elements, supporting aggressive tumor behavior.

Figure VIII



SMA immunostaining reveals positivity (~85%) in the sarcomatous component with areas of cartilaginous differentiation, consistent with heterologous mesenchymal elements.