

CASE REPORT

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The evaluation, diagnosis, and treatment of malignant mixed Müllerian tumor of the cervix: A case report

Gayathri R Nair, V Jennifer, KVS Latha

ABSTRACT

Introduction: Cervical cancer is the most common gynecologic malignancy in India, the most common histology being squamous cell carcinoma. Malignant mixed Müllerian tumor of the cervix, also referred to as carcinosarcoma of the cervix is an unusual entity. Hence, there is a dearth of literature on evaluation and management of such tumors, which is also reflected in the fact that there are no specific consensus guidelines on the same. We present the case of a 35-year-old woman who was diagnosed to have malignant mixed Müllerian tumor of the cervix.

Case Report: Carcinosarcoma cervix is a rare entity, with postmenopausal women being more commonly affected. This makes our case a very unique one, as our patient is a premenopausal, 35-year-old young woman who presented with abnormal uterine bleeding and was subsequently diagnosed to have carcinosarcoma of the cervix. The clinical presentation and management of the case have been discussed.

Conclusion: Malignant mixed Müllerian tumor is an aggressive and rare tumor which can affect the uterus, ovaries, or the cervix. A negative biopsy may not help

to rule out the diagnosis of the same. Multimodality treatment including surgical intervention, chemotherapy with paclitaxel and carboplatin, and radiotherapy could benefit this subset of patients.

Keywords: Carcinosarcoma, Cervical cancer, Gynecologic malignancies, Malignant mixed Müllerian tumor

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INTRODUCTION

Cervical cancer is the most common gynecologic malignancy in India, the most common histology being squamous cell carcinoma. Malignant mixed Müllerian tumor (MMMT) of the cervix, otherwise termed as carcinosarcoma of the cervix, is an unusual entity, which accounts for only 0.005% of cervical neoplasms [1]. There are less than 100 cases of cervical carcinosarcoma (CCS) being reported so far [2]. The most common symptom of MMT is abnormal vaginal bleeding [3]. Postmenopausal women are more commonly affected [3]. The histological examination of the cervical tumor often reveals that the tumors are comprised of a mixture of malignant mesenchymal and epithelial components [2].

Malignant mixed Müllerian tumor of the cervix is staged similar to staging of carcinoma cervix. In early-stage CCS, aggressive treatment, such as surgery followed by adjuvant radiotherapy with chemotherapy is widely

practiced [4]. Locally advanced MMMT cervix is treated with radical radiotherapy with or without chemotherapy [3]. In cases where metastasis has occurred, palliative chemotherapy and palliative radiotherapy are advisable [5].

CASE REPORT

A 35-year-old premenopausal, multiparous woman, with a body mass index (BMI) of 22, presented with abnormal uterine bleeding for two months to an outside hospital. She was diagnosed to have epilepsy for which she was on carbamazepine. There were no other comorbidities. She attained menarche at the age of 12 years, had regular menstrual cycles lasting for 4–5 days, with cycles every 28 days. There was no history of oral contraceptive pill (OCP) use. She was married at the age of 21 years and had 3 children (full term normal vaginal delivery) with first pregnancy at the age of 23 years, second child born at the age of 26 years, and third child born at the age of 28 years. Postpartum period was uneventful for both pregnancies, and all the three children were breastfed up to one year of age.

The systemic physical examination of the patient revealed no abnormality. An irregular growth of size 3*2 cm in the cervix was detected on per-vaginal examination. Cervical biopsy showed poorly differentiated squamous cell carcinoma. The computed tomography (CT) scans of the abdomen and chest were normal. The CT scan of the pelvis revealed multiple uterine fibroids, and a bulky cervix with enhanced contrast uptake. No other abnormalities were detected on imaging. Thus, she was diagnosed to have multiple uterine fibroids and carcinoma cervix and a clinical stage of IB2 was assigned, in accordance with the International Federation of Gynecology and Obstetrics (FIGO) 2018 guidelines.

The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy with bilateral pelvic lymph node dissection. The post-operative histopathological examination (HPE) was reported as squamous cell carcinoma of the cervix, with a tumor size of 2.9*2*1.6 cm, with a depth of invasion of 2.1 cm. The parametrium was free of tumor. The myometrium revealed presence of multiple fibroids, largest measuring 6 cm in diameter. The endometrium, ovaries and fallopian tubes were reported normal. The patient was referred to our center for further management. At our hospital, a slide review was done of the surgical specimen. The HPE revealed malignant neoplasm of the cervix having a biphasic pattern with the malignant epithelial cells arranged in nests and sheets with moderate eosinophilic cytoplasm and pleomorphic hyperchromatic nucleus (Figure 1). In one focus, there were malignant spindle-shaped cells arranged in diffuse sheets with scant cytoplasm and high-grade nucleus (Figure 2).

There were no heterologous elements seen. The tumor cells had invaded more than two-thirds of the

deeper stroma. No significant pathology was detected in the endometrial tissues. Myometrium revealed presence of fibroids. Ovaries and fallopian tubes were normal. Lymph nodes were not identified. These features were consistent with the diagnosis of MMMT of the cervix-homologous type (Figure 3). She received 6 cycles of adjuvant chemotherapy with injection (Paclitaxel 175 mg/m² and injection, Carboplatin AUC-5, once in 3 weeks). This was followed by adjuvant radiotherapy of 50.4 Gy delivered in 28 fractions. As the margin status was unclear, following external beam radiotherapy (EBRT), she received 2 fractions of vault brachytherapy, 6 Gy per fraction, with a total dose of 12 Gy. She was thereafter kept on surveillance.

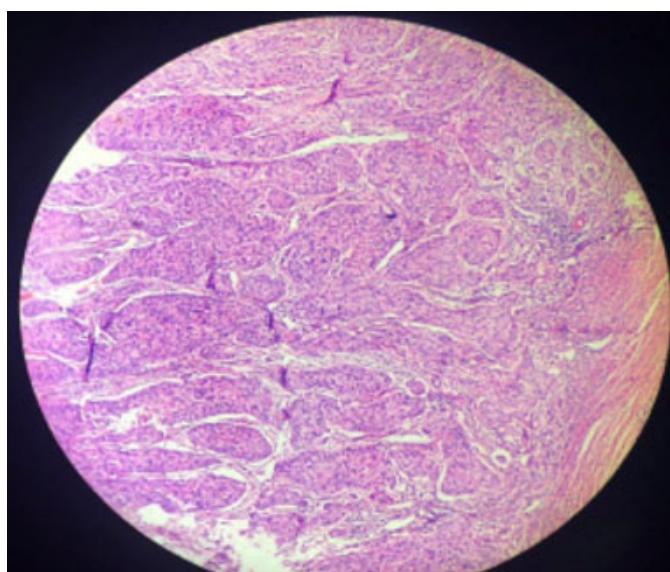


Figure 1: Malignant epithelial cells arranged in nests and sheets—Carcinomatous component of MMMT cervix (Magnification: 40×).

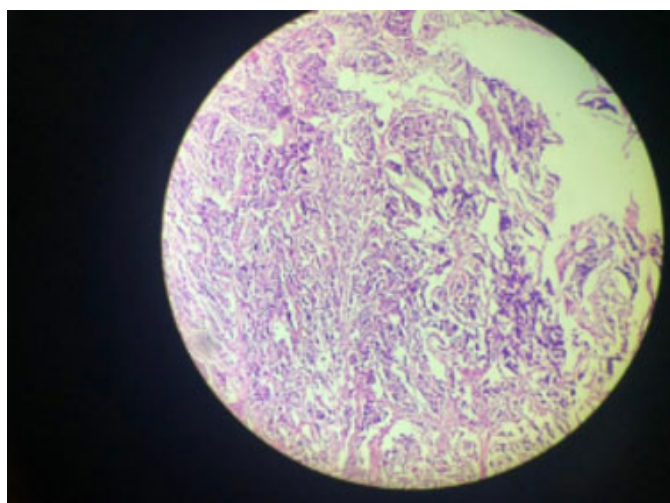


Figure 2: Malignant spindle-shaped cells arranged in sheets—sarcomatous component of MMMT cervix (Magnification: 40×).

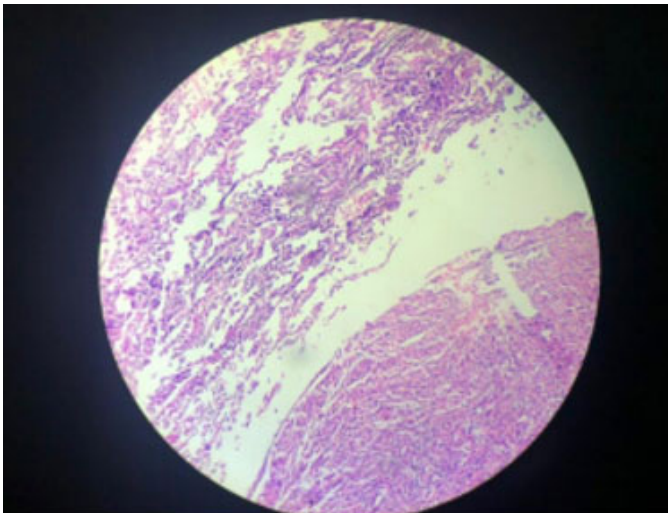


Figure 3: MMTT cervix, a biphasic neoplasm comprised of both malignant mesenchymal and malignant epithelial cells (Magnification: 10×).

DISCUSSION

Carcinosarcomas are tumors with both malignant epithelial and malignant mesenchymal components [2]. It is seen more commonly in the uterine corpus, with primary cervical carcinosarcoma being a rare occurrence [2]. The exact cell of origin and pathogenesis of carcinosarcoma is unclear, with four theories being hypothesized—the collision theory, the combination theory, the composition theory, and the metaplastic theory. The collision theory postulates that the neoplasm arises from two different but synchronous neoplastic cell populations [6, 7]. The combination theory suggests that both neoplastic cell populations originate from a common stem cell. The composition theory infers that paracrine factors generated from the carcinomatous structure induce proliferative response of mesenchymal components. However, this theory has been widely questioned as the sarcomatous component shows the histological features of malignancy [8]. The metaplastic carcinoma theory is favored presently, and it sustains that CCS may stem from the carcinomatous elements and then differentiate into sarcoma components [9–14].

Most women diagnosed with MMTT cervix are between the ages of 12 and 94 years [3], with mid-60s being the average and with most of patients being postmenopausal [15–17]. The patients usually presented with vaginal bleeding as the initial symptom. The most common finding noted on clinical examination was the presence of a cervical mass [3]. The size of the cervical tumor usually ranges from 1.1 to 10 cm in diameter. The cervical tumors often form fungiform, papillary, fungating, polypoid, or pedunculated soft or firm masses. The epithelial component may be an adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma,

basaloid squamous cell carcinoma, adenoid basal carcinoma, adenoid cystic carcinoma, or undifferentiated carcinoma or combination of these subtypes [18]. As per Kimyon et al. [3], the most common epithelial component identified in carcinosarcoma cervix was adenocarcinoma. However, Iida et al. reported same frequency for both squamous cell carcinoma and adenocarcinoma [19].

The sarcomatous components may be homologous to the uterus such as in the case of fibrosarcoma or endometrial stromal sarcoma or heterologous in nature such as when it is foreign to the uterus as in the case of rhabdomyosarcoma or chondrosarcoma. The immunohistochemical analysis may show the presence of epithelial components (positive for CK5, p16, p63, and CK6) as well as sarcomatous components (positive for desmin, smooth muscle actin, and vimentin) [18].

Only 56% of the women with MMTT of the cervix had a preoperative tissue diagnosis being accurately reported as carcinosarcoma [3]. This can probably be attributed to various reasons, including small size of biopsy specimens, experience of pathologists in accurate identification of the sarcomatous component as it may be easily overlooked with usual histology in cervical cancer being squamous cell carcinoma or adenocarcinoma.

The most common stage at presentation was IB [3].

Malignant mixed Müllerian tumor is often associated with resistance to therapies, and high risk of recurrence [3]. As MMTT is an aggressive disease compared to its epithelial and mesenchymal counterparts, the treatment also needs to be equally aggressive.

Surgery has been recommended as the mainstay of treatment for CCS limited to the cervix [20–22]. Radical hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy are the primary surgical modalities [23]. In early-stage CCS, aggressive treatment, such as surgery followed by adjuvant radiotherapy with chemotherapy, was associated with significantly better disease free survival (DFS) than surgery alone. The chemotherapy regimen is usually a platinum based one [4].

In women with locally advanced MMTT, radical radiotherapy with or without chemotherapy is often recommended [3]. Yet, there were several case reports in whom patients with advanced-stage disease underwent primary surgery with adjuvant therapy [19, 24].

In cases where metastasis has occurred, palliative chemotherapy and palliative radiotherapy are advisable [5]. Cisplatin, doxorubicin, ifosfamide, and cyclophosphamide are commonly recommended for metastatic patients with CCS [5]. Stage is the only independent factor for both DFS and overall survival (OS) [3].

CONCLUSION

Malignant mixed Müllerian tumor is a rare tumor which can affect the uterus, ovaries, or the cervix. It is

very important to be aware of this entity, so as to not miss it during routine histopathological examination. In a biopsy specimen, the sarcomatous component may easily be missed, which would in turn lead to the wrong diagnosis of carcinoma cervix, thus emphasizing the need for a careful examination of the slides. In doubtful cases, immunohistochemistry may be used to aid in the diagnosis of carcinosarcoma cervix. The highly aggressive nature of carcinosarcoma, in comparison to carcinoma cervix, mandates the need for an intensive approach to therapy. Various studies have reported better outcomes in patients with early-stage disease who were treated with adjuvant chemotherapy and radiotherapy as compared to surgery alone. A better understanding of the disease pathogenesis, and multimodality treatment including surgical intervention, chemotherapy with paclitaxel and carboplatin, and radiotherapy could benefit this subset of patients.

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Author Contributions

Gayathri R Nair – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

V Jennifer – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

KVS Latha – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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