Primary Ovarian Malignant Mixed Mullerian Tumors Carcinosarcomas: A Clinico-pathological and Immunohistochemical Analysis of Four Cases and Review of Literature

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ABSTRACT

Ovarian carcinosarcomas (OCS), also known as malignant mixed mullerian tumors (MMMTs) are among the rarest and most challenging malignancies arising from the female genital tract. This tumor is estimated to account for only 1-3% of all ovarian malignancies. The influence of proportion of the malignant epithelial or sarcomatous component on the disease progression is a matter of debate. Herein, we analysed clinico-pathological and immunohistochemical features of four cases of ovarian carcinosarcomas diagnosed over a period of seven years from 2008-2014. All the patients were post-menopausal with a mean age of 59.25 years. Carcinomatous component was high grade serous in three cases and high grade endometroid in one case. CK and EMA immunostains were used to highlight carcinomatous component while vimentin immunostain highlighted sarcomatous areas. Two patients had heterologous sarcomatous components; rhabdomyosarcomatous and chondromatous areas which were highlighted by Myogenin, desmin and S-100 respectively. Immunohistochemistry is an essential ancillary technique in highlighting biphasic nature and areas of heterologous differentiation which may have a prognostic impact. The patients were treated with optimal debulking surgery followed by adjuvant platinum/taxane or platinum/ifosfamide combinations based chemotherapy.

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**Introduction**

Carcinosarcoma of the female genital tract, also known as malignant mixed mullerian tumors (MMMTs), are biphasic tumors comprised of varying proportion of both malignant epithelial and mesenchymal (stromal) components. They most commonly are identified in the uterine corpus. Primary ovarian are uncommon and account for about 1-3% of all ovarian malignancies with fewer than 400 cases reported in the literature. The risk factors for MMMTs include obesity, nulliparity, exogenous oestrogen and long-term tamoxifen use. A rare exception aside this is a lesion of postmenopausal women. Carcinosarcomas are composed of two histological subtypes which are classified based on the appearance of the sarcomatous component. The epithelial components in carcinoma are mucinous, serous, squamous, endometrioid, clear cell, transitional or mixture of these types and sarcomatous components may be either homologous (composed of malignant stromal elements native to the ovary such as fibrosarcoma, endometrial stromal sarcoma, or leiomyosarcoma) or heterologous (composed of sarcomatous tissue not normally found in the ovary such as rhabdomyosarcoma, chondrosarcoma, osteosarcoma, or liposarcoma). They are aggressive and have a poor overall survival rate.

Clinical prognostic factors associated with poor survival include advanced stage at presentation, suboptimal debulking, and older age. Patients with carcinosarcoma of the ovary appear to have a higher survival rate if they undergo optimal tumor debulking followed by a platinum based chemotherapy regimen. In the current study, we retrospectively analyzed the data concerning the clinical and pathological characteristics, management and follow up of patients of ovarian carcinosarcoma diagnosed and/or treated at our institute.

**Material and methods**

In this retrospective study, we reviewed clinic-pathological and immunohistochemical features of four cases of carcinosarcoma of ovary diagnosed from 2008-2014. The histological sections were reviewed, with emphasis on type and grade of epithelial and mesenchymal components and their relative percentages of distribution in the tumor sections. The histological features were studied on hematoxylin and eosin stained sections. Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections using standard techniques. The medical records were retrospectively reviewed with emphasis on optimal or sub-optimal surgical debulking, chemotherapy regimens and survival.

**Case history**

Case 1: A 57-year-old postmenopausal multiparous lady presented with pain abdomen, abdominal distension, dysuria and mass per vaginum since 2 months. On examination she had third degree utero-vaginal prolapse with cystocele. Ultrasound abdomen showed complex hypoechoic adnexal mass measuring 12x9x6cm with free fluid in pelvis. Computed tomography scan (CT) showed a large complex mass occupying pelvis mainly right side with multiple pelvic lymph nodes with blurring of fat planes between uterus and urinary bladder. Her CA-125 levels were 236U/L. Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO), infracolic omentectomy and cystocele repair.

Case 2: A 60-year-old postmenopausal lady presented with abdominal distension, urinary retention, mass per vaginum and utero-vaginal prolapse since 6 months. Patient underwent TAH-BSO, omentectomy and repair of cystocele. CA-125 levels were normal.

Case 3: A 65-year-old postmenopausal lady presented with abdominal pain, distension, dysuria and mass per vaginum of 8 months duration. Imaging studies showed complex adnexal mass. Her CA-125 levels were 337 U/L. The patient underwent TAH-BSO.

Case 4: A 55-year-old lady presented with abdominal distension and pain since one month. Ultrasound abdomen showed bilateral complex hypoechoic adnexal mass measuring 12x7x5cm and 9x4x3 cm with multiple pelvic lymph nodes. Patient underwent TAH-BSO, infracolic omentectomy and bilateral pelvic lymphadenectomy. Her CA-125 levels were normal.

**Results**

A total of four cases of primary ovarian carcinosarcomas were identified. The mean age at time of diagnosis was 59.25 years (range 55-65 years). All the patients were post-menopausal at diagnosis. Majority of patients presented with increasing abdominal girth, abdominal pain and distension, urinary retention and mass per vagina and third-degree utero-vaginal prolapse. Radiologically, a complex solid-cystic adnexal mass was demonstrable in all the patients with free fluid in the pelvis. CA 125 level was elevated in two patients preoperatively (236 U/ml and 337 U/ml). International Federation of Gynecology and Obstetrics stage (FIGO) distribution was as follows: Stage IIB, Stage IC in two cases, Stage IIIC. One patient had neo-adjuvant chemotherapy. Table 1 highlights the main clinico-pathological features of the cases.
Histopathology: Grossly, the cut surface of tumors was fleshy with areas of haemorrhage and necrosis (Figure 1a). Tumor size ranged from 12-8 cm with a mean size of 10.5 cm. On microscopic examination high grade serous adenocarcinoma was the carcinomatous component in three cases (75%) and high grade endometroid carcinoma with focal squamous differentiation in one case (25%) (Figure 1b,c). Carcinomatous components showed glands, sheets, nests and complex papillae with fibrovascular core. Individual tumor cells were pleomorphic, with round to oval vesicular nuclei, prominent nucleoli and scant-to-moderate cytoplasm and a high mitotic index (Figure 1d).

The mesenchymal component was homologous in two cases (50%) and showed storiform and fascicular pattern (Figure 2a). Individual tumour cells were pleomorphic, spindle-shaped, polygonal to multinucleated cells, high nuclear-cytoplasmic ratio with scant cytoplasm and 3-5 mitotic figures per high power field (Figure 2d).

Large areas of haemorrhage and necrosis were also seen. Heterologous elements, most commonly cartilaginous and rhabdomyoblastic differentiation were seen in two cases (50%) (Figure 2b,c,e). Epithelial predominance was seen in two cases (> 50% sarcomatous component). Equal epithelial and sarcomatous components were seen in one case. The stage at presentation did not correlate with either epithelial or sarcomal predominance. No germ cell like areas or immature neuroepithelium was seen. Carcinomatous component was the most common metastatising component observed. However one case showed presence of sarcomatous component in the ipsilateral fallopian tube. On immunohistochemistry, the carcinomatous component showed positivity for CK and EMA (Figure 3a). Sarcomatous component showed positivity for Vimentin, smooth-muscle actin (SMA) and desmin (Figure 3b). Rhabdomyoblastic component showed positivity for Myogenin and desmin (Figure 3c,d). Cartilaginous component was positive for S-100. CK-7 immunostain was used to highlight mullerian differentiation. CK-20 was negative (Figure 3e). P53 showed moderate nuclear positivity in both the components (Figure 3f). Omental deposits were seen in one case. No malignant cells were seen in ascetic fluid or peritoneal washings in any case.

All patients were treated with a surgical approach that consisted of a total abdominal hysterectomy with bilateral adnexectomy, omentectomy and peritoneal washings. All the patients were planned for chemotherapy with cisplatin

Table 1: Clinico-pathological features of the cases (n=4)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57</td>
<td>60</td>
<td>65</td>
<td>55</td>
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<tr>
<td>Symptoms</td>
<td>Increase in abdominal girth, abdominal pain &amp; distension, dysuria, mass per vaginum</td>
<td>Increase in abdominal girth, abdominal pain &amp; distension, dysuria, mass per vaginum</td>
<td>Increase in abdominal girth, pain, distension, dysuria</td>
<td>Increase in abdominal girth, abdominal pain, distension, dysuria, mass per vaginum</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>12</td>
<td>8</td>
<td>10</td>
<td>12 &amp; 9</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Epithelial element (type and percentage)</td>
<td>High grade Serous, 55%</td>
<td>High grade Serous, 40%</td>
<td>High grade Serous, 50%</td>
<td>Endometroid with focal squamous differentiation, 60%</td>
</tr>
<tr>
<td>Mesenchymal type element (type and percentage)</td>
<td>Heterologous Rhabdomyosarcoma, with homologous sarcomatous areas 45%</td>
<td>Heterologous chondrosarcoma, 60%</td>
<td>Homologous sarcomatous, 50%</td>
<td>Homologous sarcomatous, 40%</td>
</tr>
<tr>
<td>Omentum</td>
<td>No tumor deposits</td>
<td>No tumor deposits</td>
<td>No tumor deposits</td>
<td>Tumor deposits present</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Involved by tumor with perinodal spread</td>
</tr>
<tr>
<td>CA125 Level (U/ml)</td>
<td>236</td>
<td>337</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td>IIIB</td>
<td>IC</td>
<td>IC</td>
<td>IIIC</td>
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<tr>
<td>Initial Management</td>
<td>TAHBSO+Omentectomy</td>
<td>NACT, TAHBSO+Omentectomy</td>
<td>TAHBSO+Omentectomy</td>
<td>TAHBSO+Omentectomy+pelvic lymphadenectomy</td>
</tr>
</tbody>
</table>

Abbreviations NACT: Neo-adjuvant chemotherapy, ND: Not done, TAHBSO: Total abdominal hysterectomy and bilateral salpino-oophorectomy
Fig. 1: (a) Gross photograph of OCS: Solid, fleshy mass with areas of haemorrhage and necrosis. Microphotographs showing various types of malignant epithelial components; (b) Serous epithelial component (H and E, X200), (c) Endometroid epithelial component with solid areas (H and E, X200), (d) High power view showing increase mitosis and atypia (H and E, X40)

Fig. 2: Microphotographs highlighting various types of sarcomatous components; (a) Homologous sarcomatous component (H and E, X200), (b) Chondrosarcomatous component in opposition to malignant epithelial component (H and E, X200), (c) Rhabdoid differentiation (H and E, X200), (d) Undifferentiated sarcomatous areas with increased mitosis and nuclear atypia (H and E, X200)
and either a taxane or ifosfamide based regimens. One patient with rhabdoid differentiation is on regular follow-up 5 months after the surgery. Other three patients were subsequently lost to follow-up.

**Discussion**

Carcinosarcomas/Malignant mixed Mullerian tumors of the ovary (OMMMTs) constitute an infrequently encountered group of malignant ovarian neoplasms, which comprise 1-3% of all ovarian malignancies. These tumors are highly aggressive and respond poorly to treatment. The relatively low number of reported cases and the difficulty of preoperative diagnosis make it difficult to ascertain the biology of these tumors. Identification of two individual components of carcinosarcomas has sparked theorization to their origin. Various pathogenetic mechanisms have been postulated to explain the biphasic appearance of MMMTs, but the nature of these neoplasms is still unclear. It has been postulated that these tumors arise from pluripotent mullerian mesenchymal stem cells, which undergo divergent differentiation into malignant epithelial and stromal elements (combination theory). Another “collision theory” suggests that the two tumor types, epithelial and sarcoma, evolve independently and then collide, suggesting that the carcinoma and sarcoma are two independent tumors. Current evidence implicates metaplastic transformation of epithelial component, which initiates tumor genesis and gives rise to sarcomatous component and these tumors should be regarded as dedifferentiated carcinomas of the ovary (conversion theory).

The diagnosis of primary ovarian MMMTs (OMMMT) is rarely suspected or confirmed preoperatively, as the clinical presentation and radiology (CT scan) is similar to ovarian epithelial tumors. Tumor markers such as CA-125 may be measured, but they may be raised or may be in the normal range. Even cytological analysis of ascitic fluid in positive cases may yield malignant epithelial components in majority of cases. As widely reported in the literature and similar to several clinico-pathological reports, we found that OMMMT is a rare neoplasm that predominantly affects older and postmenopausal women. All four women in our study were postmenopausal at the time of diagnosis. The median age at presentation had been reported to be 57-65 years, and in the current series it was 59.25 years, with a range of 55-65 years. The gross appearance of the tumors was similar to that of those described in other series; solid, cystic masses with varying degrees of haemorrhage and necrosis. Extraovarian extension of the tumor was noted in two cases (50%). Diffuse implantation

![Fig. 3: Immunohistochemical staining; (a) CK positivity in serous epithelial areas (Indirect immunoperoxidase x 40) (a) Vimentin positivity in sarcomatous stroma (Indirect immunoperoxidase, x 40), (c) Rhabdomyosarcomatous component showing nuclear myogenin and (d) cytoplasmic desmin positivity (Indirect immunoperoxidase, x 40), (e) CK-7 positive and CK-20 negativity highlighting mullerian origin (Indirect immunoperoxidase, x 40), (f) p53 positivity (Indirect immunoperoxidase, x 40)](image-url)
to the peritoneal surface was found in one case. These tumors are typically large, ranging from 15-20 cm in diameter.\textsuperscript{3,11} In the present study tumor size ranged from 12-8 cm with mean of 10.5 cm. The stage distribution is identical to that of serous carcinoma.

The morphology is similar to its uterine counterpart. The characteristic microscopic feature is an intimate admixture of malignant epithelial and stromal elements. In our study, two patients were found to harbour heterologous elements (rhabdomyosarcoma and chondrosarcoma) and two had homologous (fibrosarcoma) elements on review of the histopathology. Epithelial component was high grade serous in three cases (75\%) and endometroid in one case (25\%). In a series of 15 cases, equal representation of the epithelial endometrioid (4 cases) and serous (4 cases) component was observed. The mesenchymal component was largely heterologous which included chondromatous and rhabdomyoblastic differentiation.\textsuperscript{11} In a recent series by Kunkel et al, a vast majority of the cases (57\%) had serous carcinoma as epithelial component with a predominance of heterologous cartilaginous component in 36\% of the cases followed by rhabdomyosarcoma.\textsuperscript{12} In a recent study from North India, endometrioid carcinoma and heterologous rhabdomyosarcoma were the predominant components seen in a series of 27 cases.\textsuperscript{16}

Immunohistochemistry (IHC) staining for cytokeratin and epithelial membrane antigen show diffuse strong staining of the epithelial element, while vimentin exhibits diffuse strong staining of the mesenchymal element.\textsuperscript{17,18} Mullerian origin would be supported by positive CK7 staining and negative CK20 staining. Rhabdomyosarcomatous areas are positive for desmin, myoD1 and myogenin markers, and all chondrosarcomatous, osteosarcoma and lipomatous differentiation can be highlighted by S-100 protein.\textsuperscript{17,18,p53} Immunostain had been reported to show positivity in both carcinomatous as well as sarcomatous areas and therefore the two components of the neoplasm might have undergone a similar carcinogenic event, with the result that carcinosaRcoma can be considered to be monoclonal and originated from a common stem cell, thus supporting “combination theory.”\textsuperscript{19} Additional IHC stains for muscle-specific actin and desmin may help distinguish other “pure” sarcomas with smooth muscle differentiation from ovarian carcinomas (OCS). CD34 staining may help distinguish OCSs from epithelioid sarcomas, which strongly express CD34.\textsuperscript{11,19} Thus, as previously mentioned, we were able to conclude that immunohistochemical staining is a very useful and reliable method for highlighting the biphasic nature of carcinomas and for distinguishing spindle cell carcinoma or undifferentiated carcinoma from carcinosaRcoma.

The significance of sarcomatous component (SC) in predicting outcome in patients with these tumors is still controversial.\textsuperscript{2,10,20,21} Some studies have found a significantly worse prognosis associated with a heterologous SC,\textsuperscript{11,13,16,22} whereas others have not.\textsuperscript{6,7,10,12,14} In a recent study of 47 cases of OMMMTs, features of SC including type of sarcoma, homologous or heterologous, mitotic count, necrosis, and presence of sarcomatous component outside the ovary were studied in relation to disease-specific survival. They concluded that presence of SC outside the ovary was an adverse prognostic factor.\textsuperscript{15} An Indian study had also demonstrated that the sarcoma predominant OMMMTs behave more aggressively (median RFS 10.5 months vs 13 months for epithelial predominant) and optimal debulking of these tumors, delayed the time to recurrence.\textsuperscript{16} Similarly, in the present study, one case had homologous SC outside the ovary, in the ipsilateral fallopian tube. In another study of 34 cases, 17 of which were treated with primary surgery followed by adjuvant chemotherapy for FIGO stage III or IV, statistical analysis showed that stromal predominant tumors, suboptimal debulking, age, and tumors with serous epithelial component were adverse independent prognostic factors.\textsuperscript{21}

Because of the rarity of the disease; no standard treatment has been developed. Many authors have reported a benefit of optimal surgical cytoreduction in patients with OCS.\textsuperscript{2,22,23} Following primary surgical debulking, the consensus has been to recommend adjuvant chemotherapy. Several articles have reported cases obtaining long-term survival with different chemotherapy regimens.\textsuperscript{24,25} Platinum-based regimens have emerged as the most efficacious in several retrospective studies. Historically, treatment regimens have included platinum and/or paclitaxel, platinum and/or ifosfamide, and platinum with doxorubicin and dacarbazine.\textsuperscript{1,26}

**Conclusion**

In conclusion, we have described the clinico-pathological and immunohistochemical features of four cases of primary OCS. Majority of the patients were post-menopausal and elderly. The diagnosis was based on histological identification of both epithelial and sarcomatous component. Immunohistochemical examination is vital to highlight their biphasic nature and areas of heterologous differentiation in undifferentiated cases. Principal prognostic factors are heterologous stromal component and undifferentiated epithelial component. Although present series is too small to draw any significant prognostic conclusions, it does suggest that complete surgery followed by adjuvant chemotherapy with either platinum/taxane or platinum/ifosfamide is the best treatment for
these tumors. Two patients with heterologous SC are on chemotherapy and under close follow up. There is a need for collaborative prospective studies to better understand the molecular changes of MMMTs and to design new therapeutic regimens to improve patients’ survival.

**Conflict of interest**
We have no conflict of interest

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**References**


