

Primary ovarian malignant mixed Müllerian tumor: a rare case report

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Ther Adv Rare Dis

2022, Vol. 3: 1–6

DOI: 10.1177/
26330040221107389

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Abstract: Primary malignant mixed Müllerian tumor (MMMT) of the ovary is an extremely uncommon neoplasm. These tumors show very aggressive clinical course and high mortality as compared to epithelial ovarian neoplasms. The objective of present study is to present a rare case of primary MMMT homologous type of ovary for its aggressive clinical course and immunohistochemistry findings. A 48-year-old woman presented with complaints of lower abdominal pain, dullness of 3 months duration. USG abdomen pelvis revealed bilateral ovarian solid and cystic mass lesion suggestive of malignant potential. Peritoneal fluid cytology reported as positive for malignant cells. Patient underwent exploratory laparotomy which showed large bilateral ovarian masses with extensive nodular deposits all over pelvic-abdominal organs. Optimal debulking surgery was performed and specimen examined for histopathology. On histopathology, it was reported as bilateral ovarian MMMT homologous type. Immunohistochemistry was done which showed the tumor cell expression positive for CK, EMA, CK7, CA-125, and WT1. Also a distinct population tumor cells express Cyclin D1 and focal and patchy expression of CD-10. Tumor was negative for Desmin, PLAP, Calretin, and inhibin. The patient received operative, chemotherapy and adjuvant therapy along with extensive electrolyte, nutritive, and supplementary support. The patient, however, rapidly deteriorated and died within 9 months of postoperative day. Primary ovarian MMMT is an extremely uncommon neoplasm, and it showed extensive aggressive clinical course and even with operative, chemotherapy, and adjuvant therapy, the patient yields poor prognosis.

Plain Language Summary

Primary ovarian malignant mixed Müllerian tumor: a rare case report

Ovarian carcinomas: These are the most common type of ovarian cancer. About two-thirds of these cancers are of epithelial origin.

Obesity, hormone replacement therapy, not having children, and family history of ovarian cancer are risk factors for ovarian cancer.

A neoplasm is a type of abnormal and excessive growth of tissue. Neoplasms arising from more than one cell type or germ layer are called 'mixed tumors'.

Ovarian carcinosarcoma, also known as a malignant mixed Müllerian tumor (MMMT) of the ovary, is a rare, aggressive cancer of the ovary with characteristics of two types of cancer: carcinoma and sarcoma.

In this case, we reported a very uncommon and rapidly progressive tumor with a high chance of death even with an advance treatment protocol.

Because women with this cancer often have no symptoms, more than half of women are diagnosed at an advanced stage.

These cancer cells spread first from surface of the ovary to the lining and organs of the pelvis and abdomen and then to other parts of the body.

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Diagnosis of ovarian cancer starts with a physical examination, a blood test (for CA-125 and sometimes other markers), transvaginal ultrasound, CT scanning, and so on. The diagnosis must be confirmed with surgery to inspect the abdominal cavity and take biopsies for microscopic analysis.

Required advanced ovarian cancer treatment depend on various factors, such as surgery, chemotherapy, radiation, hormonal therapy, and palliative care as per required.

Message: Primary ovarian MMT is an extremely uncommon neoplasm, and in this case we showed a patient with an extensive aggressive clinical course, and even with surgery, chemotherapy, and adjuvant therapy, it showed poor prognosis.

Keywords: adjuvant therapy, chemotherapy in ovarian cancer, malignant mixed Müllerian, primary ovarian tumor

Received: 1 March 2022; revised manuscript accepted: 25 May 2022.

Introduction

Malignant mixed Müllerian tumors (MMMT) are also known as carcinosarcomas. These tumors are defined histologically as the mixture of malignant epithelial and stromal elements. These are exceedingly rare tumors and comprise 1–3% of ovarian malignancies.^{1,2} These cases are extremely rare to detect; therefore, very little is known about its clinical course and outcome. These tumors are of heterologous or homologous type based on the presence or absence of mesenchymal tissue which is not normally found at the primary tumor site.³ Now these tumors regarded as metaplastic epithelial carcinomas as histogenesis of tumor propose a monoclonal histogenesis.⁴

Case report

A 48-year-old woman presented to obstetric gynecology with complaints of dull aching pain in the lower abdominal region for 2 weeks. She had a history of fullness in the pelvic region of 3-month duration. No family, hormonal or any contributory history was noted. Systemic examination was normal. Her obstetric history was G2 L2 A0. Patient was non-diabetic and non-hypertensive.

Ultrasonography (USG) abdomino-pelvis showed bilateral pelvic masses. Right ovarian mass measured 15 × 11.5 × 8 cm, having cystic and solid areas. External surface is nodular. Left ovary measured 3.5 × 2 × 1.0 cm. Uterus with cervix measured 4.1 × 3 × 2.2 cm and grossly appeared normal. Multiple small nodular lesions were noted

over the surface. USG finding was suggestive of bilateral solid cystic lesions with low malignant potential. Routine hematological investigations were normal. Peritoneal fluid for cytology was positive for malignant cells. She underwent emergency exploratory laparotomy procedure as a patient having severe abdominal pain and internal bleeding. The severe pain was related to ischemic changes to ovarian surface nodules and focal bleeding from it. On operative findings, abdomen pelvis showed large right ovarian mass measuring 15 × 12 × 8.5 cm and left ovarian mass measuring 3.5 × 1.7 × 1 cm. Urinary bladder surface, intestine, omentum, and mesentery showed multiple variable size nodules and adhesions. Bilateral fallopian tubes, pelvic wall, and cul-de-sac also showed nodules. The pelvic cavity showed 110 ml hemorrhagic fluid. Optimal debulking surgery was done with excision of ovarian masses, uterus, cervix, and multiple nodules all over omentum, ovarian surface, mesentery, and near urinary bladder which were not adherent.

We received specimen of right ovarian mass totally measuring 14 × 11 × 8.0 cm and weighing 210 gm [Figure 1(a)]. Left ovary measured 3.5 × 1.7 × 1 cm and weighing 140 gm. Cut section of mass was gray white with solid and cystic areas. Large areas of hemorrhage and necrosis were noted. In those areas, the tumor was fleshy. Ovarian capsule was ruptured. Multiple nodular masses largest measuring 1.8 × 1 × 0.8 cm were noted. Cut sections of nodules were gray white, hemorrhagic, and fleshy.

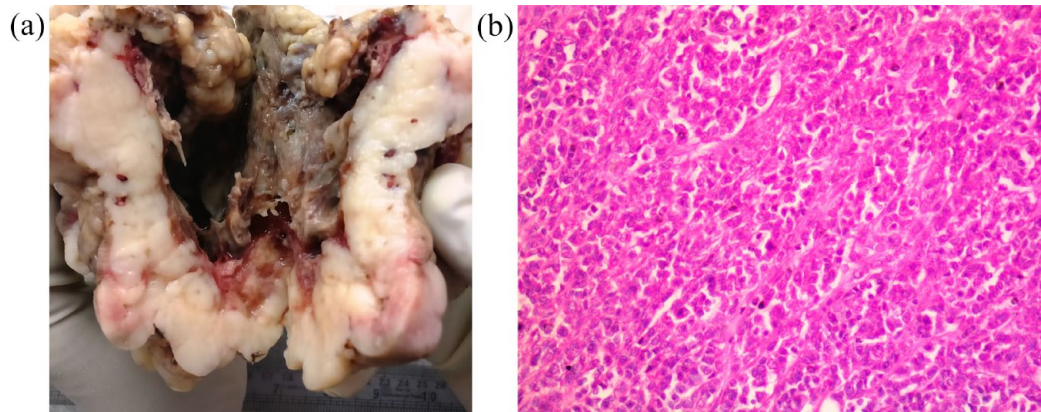


Figure 1. (a) Specimen of right ovarian tumor showing solid cystic areas, tumor was gray white, fleshy with areas of hemorrhage and necrosis. (b). Ovarian tumor composed of cells which were of biphasic malignant epithelial and mesenchymal components (H&E stain 40 \times , 100 \times).

Histopathological examination showed ovarian tumor composed of cells which were of biphasic malignant epithelial and mesenchymal components [Figure 1(b)]. The predominant tumor was a high-grade epithelial carcinoma. Areas of serous and papillary differentiation were noted. The sarcomatous component showed homologous type of tumor having clear cell type with high-grade tumor. Extensive areas of hemorrhage and necrosis were noted. High mitotic activity was noted. Many unusual tumor giant cells were noted. Focal area showed small blue round cell-like tumor. The section from multiple nodular deposits showed similar histological features. On histopathology, it was reported as bilateral ovarian MMT with extensive nodular deposits. The endometrium, myometrium, and cervix on histopathological examination were normal.

In our case, immunohistochemistry (IHC) showed the tumor cell expression positive for CK7, WT1, CA-125, and CK (Figures 2 and 3). Also a distinct population tumor cells express EMA, Cyclin D1, (Figures 4 and 5), and focal and patchy expression of CD-10. Tumor was negative for Desmin, PLAP, calretin, and inhibin.

On the fifth postoperative day, she developed tense ascites and bilateral swelling of her feet. Repeated hemorrhagic ascitic fluid tapping was done. Later, she developed tachycardia and became breathless. The cardio-respiratory care and electrolyte balance was monitored. On the 21st postoperative day, chemotherapy was initiated with cisplatin and carboplatin for 3 months.

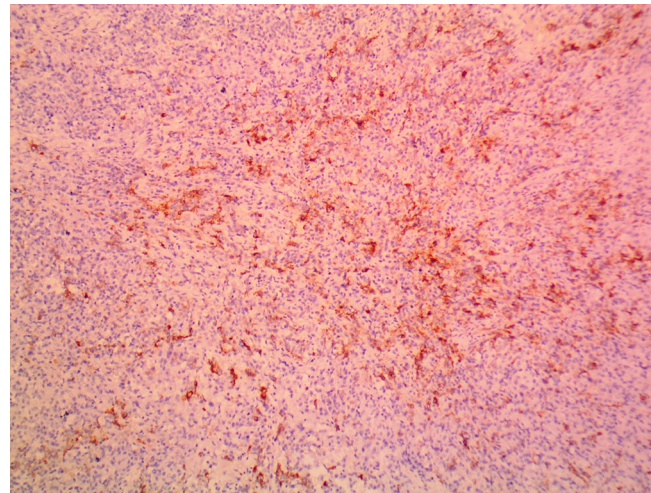


Figure 2. Tumor showing immunoreactivity for CA 125.

Adjuvant treatment of AlbuRel, colony-stimulating growth factors were given. Later, fluorodeoxyglucose (FDG) whole body positron emission tomography (PET) scan was done, which showed multiple solid cystic mass lesions all over the abdomen-pelvic region with extension into mediastinal, left para aortic, left iliac node, and mesenteric node in right iliac fossa. Mesenteric soft tissue mass measuring 9 mm is noted in gastrosplenic ligament. Supraclavicular node and intramammary node deposits were also noted. No liver, lung, and adrenal metastasis were noted.

She started with chemotherapy of docetaxel 80 mg and Graniz 3 mg for 2 months along with

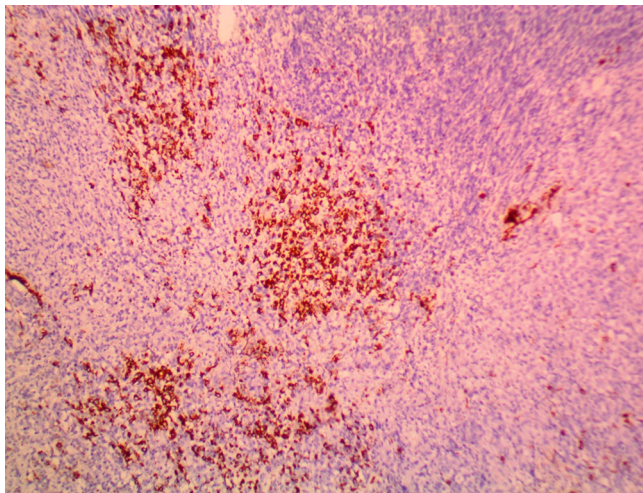


Figure 3. Tumor showing immunoreactivity for CK.

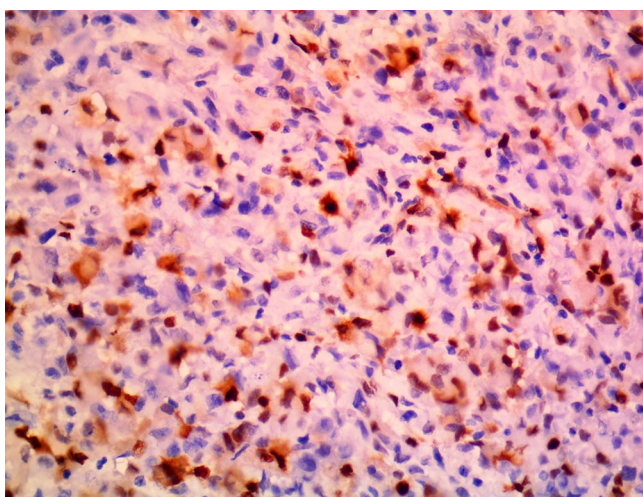


Figure 4. Tumor showing immunoreactivity for Cyclin D1.

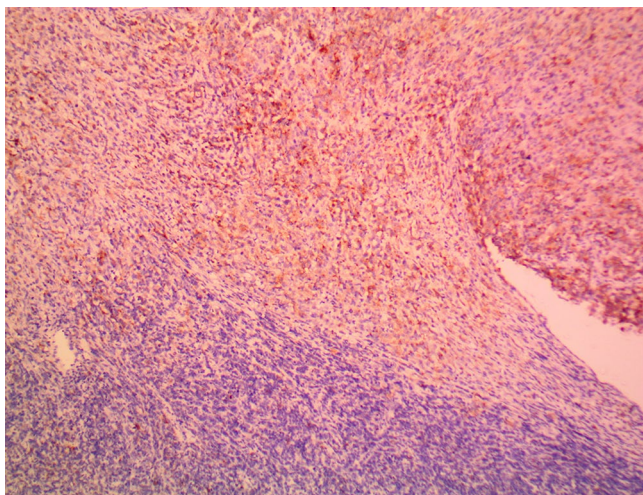


Figure 5. Tumor showing immunoreactivity for EMA.

adjuvant treatment of AlbuRel, growth factor, hematinics, and so on. After completion of chemotherapy (4.5 months) later, she developed severe nausea, vomiting, dehydration, and bony pain: severe muscle wasting was evident. Hemogram showed Hb: 7.1 gm %, TLC: 4900/mm³, platelets count: 7,90,000/mm³, differential leukocyte count: N – 72%, L – 25%, E – 5%. Gradual increase in platelet count upto 11 lakhs was noted. Electrolytes showed hypokalemia and hyponatremia. Even with extensive electrolyte, nutritive, and supplementary support, the patient rapidly deteriorated and died 9 months after the postoperative day.

Discussion

MMMTs are uncommon neoplasms of the female genital tract. It can arise from any genital organ and occurs mainly in the uterus. The occurrence of primary ovarian MMT is extremely rare and shows extensive aggressive clinical course as noted in our case. In 2008 National Comprehensive Cancer Network clinical practice guidelines in oncology, the MMT is classified as carcinosarcoma. Metaplastic transformation of Müllerian-type carcinomas into sarcoma has been suggested on the basis of clonality analyzing.⁵

Various risk factors for the development of these cancers are exogenous estrogen, pelvic irradiation, nulliparity, obesity and human papillomavirus (HPV) infection. In our case, none of the risk factors listed above were noted.⁵

Clinically in our case, there were not any specific signs and symptoms. The patient may remain asymptomatic or may present with non-specific manifestations like pain in the abdomen, fullness, pelvic mass, vaginal bleeding, and so on. Ovarian MMT mostly occurs in postmenopausal women of low parity. The patient initially remains asymptomatic and often presents with disseminated disease.

As carcinosarcomas are categorized into homogeneous type, that is, sarcoma comprised of tissue native to the uterus such as smooth muscle and heterologous type, that is, tumor contains cartilage, skeletal muscle, or bone which is not native to that site. The carcinomatous component may show serous, clear cell type or endometrial tumor

in both type.⁴ On various clinical, pathological, and molecular observations, it has been suggested that these neoplasms are derived from the Müllerian epithelium single stem cell which differentiates or metaplastic to sarcoma.

The ovarian MMMT commonly shows peritoneal seeding and ascites in 67–100% cases.^{2,6} On microscopy, the tumor shows characteristic biphasic morphology of both epithelial and mesenchymal component as two distinct or intermittently mixed. The epithelial tumor shows high-grade carcinoma like serous, endometrioid, papillary, adenocarcinoma, squamous carcinoma, or undifferentiated.^{7,8} IHC plays an important role in differentiating various tumor components.

In our case, 70% areas showed carcinomatous undifferentiated tumor. The remaining 25% showed high-grade sarcomatous homologous elements and focal area 5% showed small blue round cell-like tumor. It has been observed that the presence of predominant malignant stromal component and malignant serous epithelial component in advanced cases have a worse outcome.⁷ In our case, disease was reported as stage IV according to the International Federation of Gynaecology and Obstetrics (FIGO) criteria for ovarian cancer. It is observed that almost 75% of patients were reported in stage III or IV.

The average survival for ovarian MMMT is less than 2 years.⁹ The large residual tumor >2 cm, advance stage are important adverse prognostic factors. There are controversies regarding histological prominent carcinomatous or sarcomatous elements which determines prognosis.

The treatment of this tumor changes as the carcinomatous component being favored as it determines the aggressiveness of tumor.

Surgery remains the primary line of management. Cytoreduction surgery is recommended for advanced-stage disease. A combination of chemotherapy and/or radiotherapy is used to improve survival. To date, no national consensus guidelines have been established for the management of MMMT.¹⁰

The various chemotherapeutic regimens have been used, which consist of cisplatin, ifosfamide, doxorubicin, paclitaxel, sorafenib, and topotecan as single or in combination.¹¹ The standard chemotherapy

regimen is the use of a platinum-based agent and taxane, such as intravenous carboplatin/cisplatin/oxaliplatin alone or in combination with paclitaxel 175 mg/m² for three to nine cycles. After optional cytoreduction surgery, chemotherapy has been shown effective in treatment with good responses. It is observable that despite advances in adjuvant therapy, there is no measurable improvement in survival benefit of the patients.¹²

In this case also, there is no benefit of survival, and the patient died within 9 months. This showed very aggressive behavior of the tumor.

Conclusion

We have an extremely rare case of primary ovarian MMMT homologous type which showed very aggressive clinical course, and even with multifocal treatment approach, prognosis was poor.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was taken from the patient for the publication of this case report.

Author contributions

Sunil V. Jagtap: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Shubham S. Jagtap: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – review & editing.

Rashmi Gudur: Conceptualization; Formal analysis; Investigation; Visualization.

Sonam Billawaria: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

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