

Treatment of Carcinosarcoma of the Fallopian Tube Mimicking Ovarian Cancer: A Case Report and Genetic Analysis

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Carcinosarcoma of the fallopian tube is an exceptionally rare gynecological neoplasm. It tends to have high metastatic potential, to frequently recur, and has a poor prognosis. For these reasons, treatment is difficult and there is no standardized therapy schedule for this disease. Here, we report a case of carcinosarcoma of the fallopian tube mimicking ovarian cancer, initially presenting as a rupture of a growth and subsequent hemoperitoneum. The 55-year-old woman underwent cytoreductive surgery and post-operative conventional platinum-based combination therapy. The anti-angiogenic drug bevacizumab was added, and no evidence of disease was found on follow-up images or tumor markers 51 months after surgical resection. We describe a rare case of carcinosarcoma of the fallopian tube, include an in-depth histopathological review with genetic analysis, and propose treatment with a platinum-based combination therapy including bevacizumab. (*J Nippon Med Sch* 2021; 88: 574–578)

Key words: bevacizumab, carcinosarcoma, fallopian tube, ovarian cancer, platinum

Introduction

Carcinosarcoma, formerly called malignant mixed Müllerian tumors (MMMTs), is a rare gynecological neoplasm that exhibits a characteristic biphasic morphology and is composed of carcinoma and sarcoma components¹. It accounts for fewer than 5% of all gynecologic malignancies and can occur in the endometrium, vagina, uterine cervix, ovaries, or fallopian tubes^{2,3}. Carcinosarcoma of the fallopian tube is extremely rare, and all previous cases are believed to have been reported^{3,4}.

Carcinosarcoma is commonly considered a derivative of carcinoma and is thus treated with the same therapeutic strategy⁵. However, regardless of the significant resemblance between carcinosarcoma and its carcinoma counterpart, prior clinical studies indicate that carcinosarcoma is associated with poorer outcomes⁶. Carcinosarcoma is often diagnosed at a more advanced stage, has a high probability of metastasis, recurs frequently, and has a poor prognosis³. Surgical removal with para-aortic and pelvic lymphadenectomy is considered the first line of treatment, after which chemotherapy with carboplatin

and paclitaxel is recommended. Nonetheless, there are still grey areas that need refinement, including determining the optimal drug schedule, dosage, safety, tolerability, and treatment duration⁷.

Here, we describe a rare case of carcinosarcoma of the fallopian tube, which was initially misdiagnosed as ovarian cancer clinically. We describe the clinical presentation and comprehensive histopathological features, including genetic analysis, and suggest treatment strategies that could improve prognosis.

Case Report

This study was approved by the Research Ethics Committee of Kyung Hee University Hospital (KHUH 2020-06-076). The Review Board and investigation conformed with the principles outlined in the Declaration of Helsinki.

A 55-year-old woman (gravida 2, para 2) with an unremarkable family and past medical history presented to our hospital with severe lower abdominal pain of several days' duration. She experienced menopause at age 53

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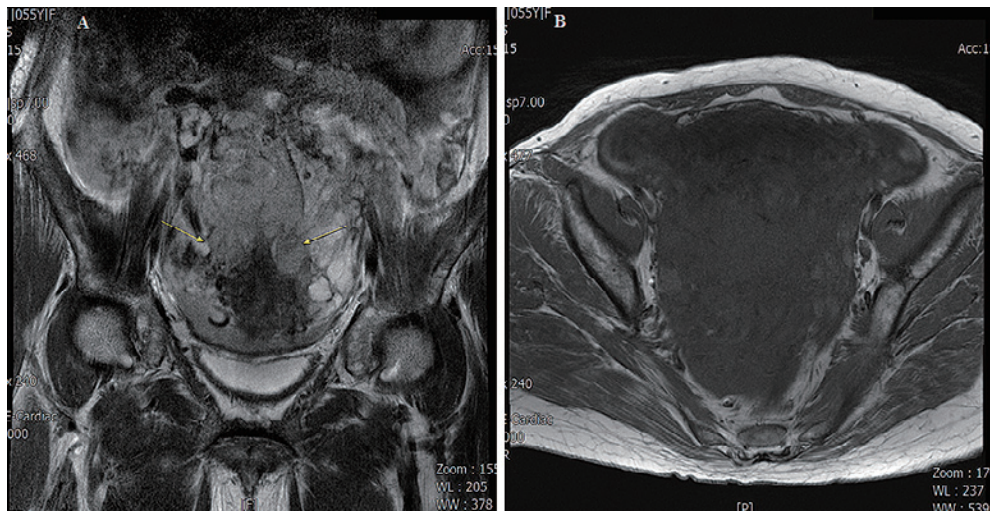


Fig. 1 Pelvic MRI. A: T1-weighted sagittal imaging showing a bilateral ovarian cancer and possible cancer peritonitis and uterine invasion (arrows). B: T1-weighted coronal image showing a complex mass (24×18 cm) in the pelvic region.

Abbreviations: MRI, magnetic resonance imaging

years.

Her physical examination revealed tenderness and rebound in the suprapubic area. Computed tomography of the abdomen and pelvis revealed complex ascites suggestive of hemoperitoneum, with suspected rupture of an ovarian mass as the origin. Pelvic magnetic resonance imaging suggested bilateral ovarian cancer with accompanying cancer peritonitis and uterine invasion (**Fig. 1A**). The cystic locules showed a hyperintense region on fat suppression T1-weighted sagittal imaging (2 arrows). T1-weighted coronal imaging identified a complex mass (24 × 18 cm) in the pelvic region (**Fig. 1B**). Cancer antigen 125 (CA 125) level was 577.5 U/mL and CA 19-9 was within the normal range. Her hemoglobin level was 8.2 g/dL. Other blood tests were all within normal ranges.

We scheduled an exploratory laparotomy, which in this case led to total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal lavage, appendectomy, and pelvic lymph node and para-aortic lymph node dissection.

Pathological Gross Findings

The huge, solid, and cystic mass in the right fallopian tube measured 24 × 18 × 5 cm and contained congested, edematous, and hemorrhagic areas (**Fig. 2A**). The cystic component was completely filled with necrotic tissue. The cut surface was tannish-white with bleeding necrotic foci. The tissue was fragile as a whole. Focal adhesion to the right ovary was present, and the left adnexa showed no macroscopic abnormalities. The uterine cornus had thickened folds and a mass-like appearance at the open-

ing of right salpinx. Adhesion and infiltration of the mass through the uterine serosa was also present. The endometrial cavity and the rest of the uterine body were tumor-free.

Microscopic Findings

The tumor had a principal epithelial component exhibiting features of high-grade serous papillary carcinoma (**Fig. 2B, C**). Microscopy revealed branching papillary fronds, glandular complexity, marked nuclear atypia with marked pleomorphism and prominent nucleoli, and frequent mitoses. The mesenchymal component was an undifferentiated sarcoma (**Fig. 2B, D**) and consisted of intermingled round, spindle, or bizarre cells with marked nuclear anaplasia, variable pleomorphism, frequent mitoses, and prominent nucleoli. The tumor extended superficially and focally to the serosal surface of the right ovary (**Fig. 2E**). The serous tubal intraepithelial carcinoma component found on the fimbriae of the left fallopian tube and admixed to the right tubal mass was strongly positive for P53 (**Fig. 2F**). The endometrium was atrophic.

Microscopically, the uterine serosa, omentum, pelvic peritoneum, and rectum contained metastatic carcinosarcoma. Metastatic carcinosarcoma was found in 9 of 27 pelvic lymph nodes. Ascitic fluid cytology was also positive for malignant cells. The pathologic stage was established as IIIC.

Immunohistochemical Staining

Immunohistochemical analysis showed that the epithelial component was positive for cytokeratin AE1/AE3, estro-

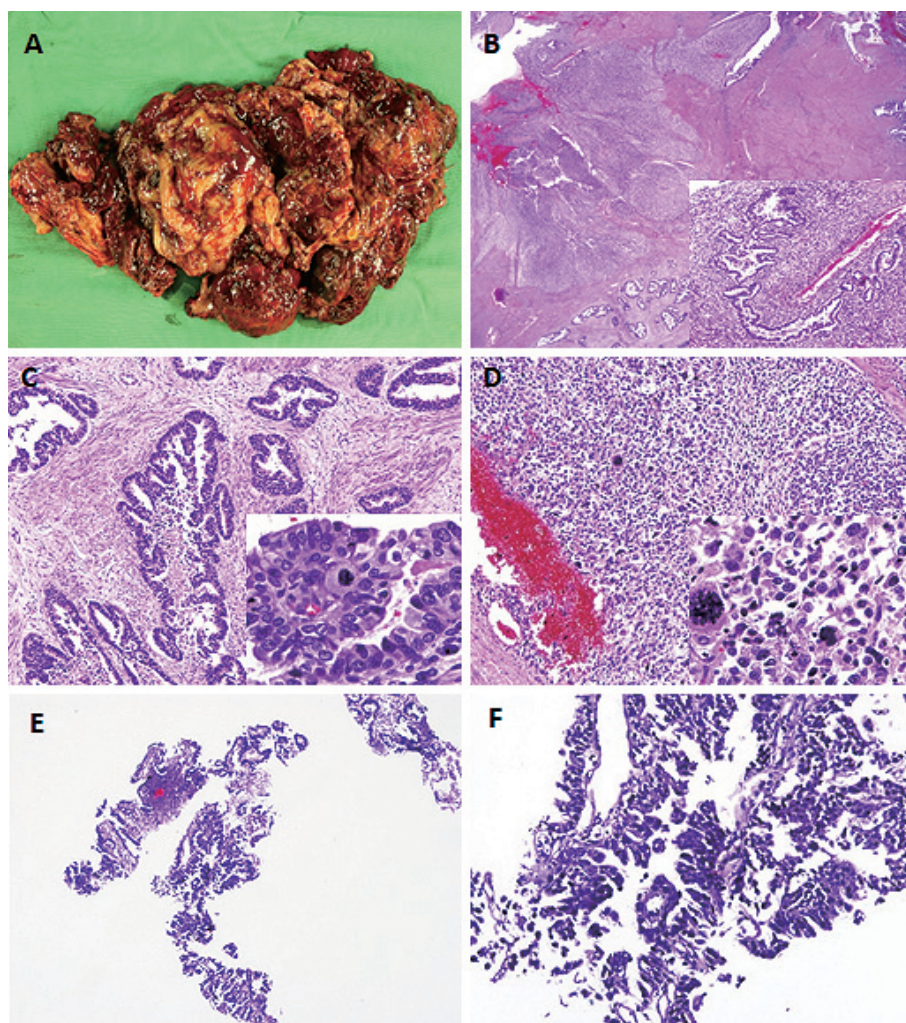


Fig. 2 Representative gross and histological findings. A: A huge, solid, and cystic mass in the right fallopian tube contains congested, edematous, and hemorrhagic areas. B: The tumor consists of an epithelial and mesenchymal component. (H&E, $\times 40$). C: The epithelial component is a high-grade serous papillary carcinoma with features of branching papillary fronds, glandular complexity, and marked nuclear atypia ($\times 40$; inset, $\times 200$). D: The mesenchymal component is an undifferentiated sarcoma with marked nuclear atypia ($\times 40$; inset, $\times 200$). E: The tumor involved the serosal surface of the right ovary ($\times 40$). The ovarian parenchyma is relatively intact. F: A serous tubal intraepithelial carcinoma component on the fimbriae of the left fallopian tube, with strong P53 positivity ($\times 200$, inset, P53).

gen receptors (ER), and P53 (Fig. 3A~C). Vimentin expression was strongly positive in the stromal component and negative in the epithelial component. The mesenchymal component was negative for cytokeratin AE1/AE3, CD10, cyclin D1, and ER in the areas of undifferentiated sarcoma (Fig. 3D~F). Both components were negative for desmin, myogenin, smooth muscle actin, and S100. The serous tubal intraepithelial carcinoma component on the fimbriae of the left fallopian tube and admixed with the right carcinosarcomatous mass was strongly positive for P53.

Molecular Findings

Next generation sequencing was performed on hybridization-captured, adaptor ligation-based libraries using DNA extracted from 4 10- μ m formalin fixed paraffin embedded (FFPE) sections from the present case. In the carcinoma component, a PPP2R1A mutation was detected and involved the P179 hot spot (PPP2R1A, P179R, c.536C>G, 337/1,996, 16.8%); P179 is highly enriched in serous carcinoma and carcinosarcoma. In addition to the PPP2R1A mutation, a TP53 mutation was present (TP53, R273H, c.818 G>A, 889/1,682, 52.7%). In the sarcoma component, the same mutations were detected (PPP2R1

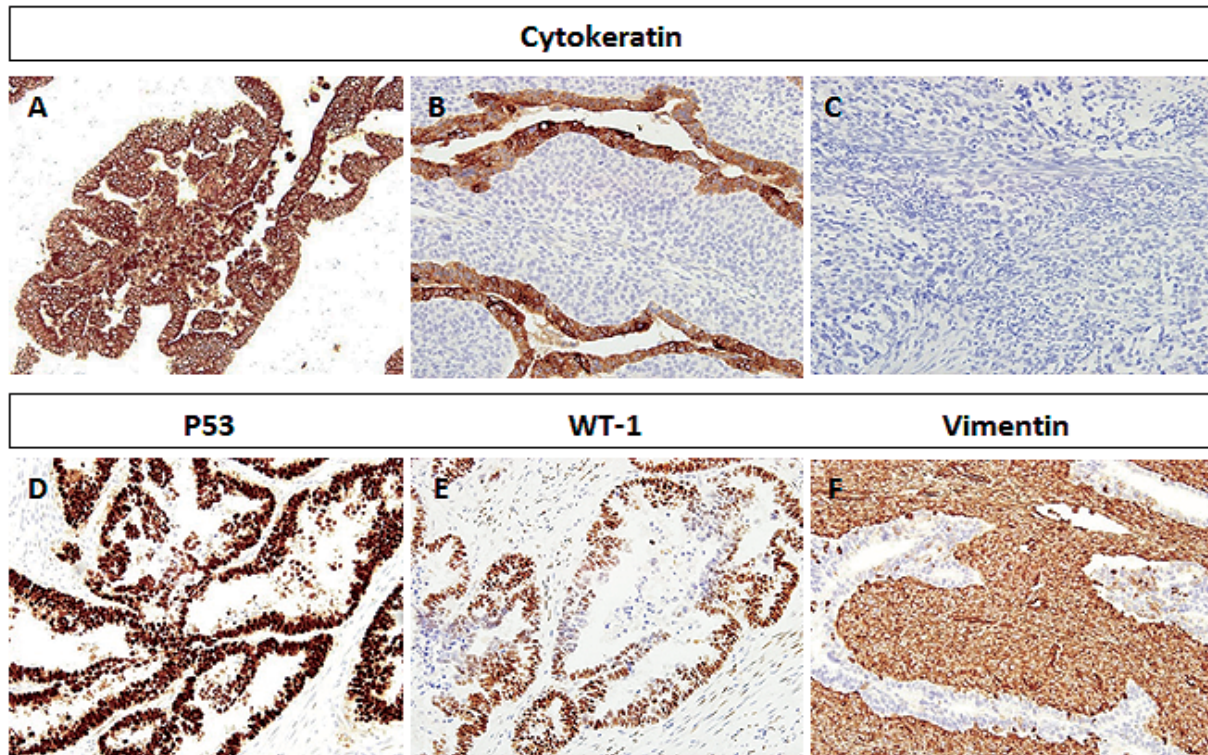


Fig. 3 Immunohistochemical staining. A, B: Representative immunohistochemical stains in the tubal carcinosarcoma. The epithelial component with features of serous carcinoma exhibits strong positivity for cytokeratin AE1/AE3, P53, and WT-1. In contrast, the mesenchymal component with features of undifferentiated sarcoma exhibits negativity for (C) cytokeratin AE1/AE3, focal positivity for (D) P53 and (E) WT-1, and (F) strong positivity for vimentin ($\times 200$).

A, P179R, c.536C>G, 607/1,958, 30%; TP53, R273H, c.818 G>A, 1,383/1,466 94%). Additionally, a TP53 frameshift was found (TP53 V73fs, c.215_216insG, 1,552/1,571, 98%).

After surgery, the patient underwent combination chemotherapy with carboplatin and paclitaxel. Bevacizumab 15 mg/kg was administered every 3 weeks (along with carboplatin and paclitaxel for up to 8 cycles), followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 25 cycles. The patient developed no adverse effects during chemotherapy.

An examination at 51 months after surgical resection showed no evidence of disease on follow-up imaging and no elevation of tumor markers.

Discussion

Carcinosarcoma of the fallopian tube is an extremely rare malignancy that usually develops in postmenopausal women³. It is often fatal and is characterized by high rates of metastasis, frequent recurrence, and a poor prognosis³.

The clinical symptoms for the various sarcomas of the fallopian tube are nearly identical⁶ and include abdominal pain and enlargement, intermenstrual spotting, and

postmenopausal bleeding, all of which are nonspecific. The mass is sometimes misdiagnosed as ovarian cancer, as in the present case, and rupture causes hemoperitoneum.

In our case, the tumor had epithelial and mesenchymal components, including serous carcinoma and undifferentiated sarcoma. Serous carcinomas have an aggressive clinical course, frequently contain a TP53 mutation, and are similarly represented by general aneuploidy⁷⁻¹¹. PPP2R1A mutations are rarely found in the serous subtype of uterine and ovarian cancers and carcinosarcoma¹²⁻¹⁴. PP2A is a broadly expressed serine/threonine phosphatase that may be involved in deregulation of gynecological tumor-related pathways^{14,15}. A recent report suggested a simple classification process, based on the mutational status of major drivers, for serous subtypes, with regards to TP53 and PPP2R1A^{16,17}. Furthermore, Gotoh et al. reported that in carcinosarcoma, both carcinoma and sarcoma components mostly share crucial driver mutations, which supports conversion theories on the pathogenesis of carcinosarcoma^{16,17}. In both the carcinoma and sarcoma components of the present tumor we found PPP2R1A mutations in the hot-spot region of P179. This corroborates the re-

sults of previous studies, and the molecular profiles prove helpful in tumor classification.

A standard therapeutic approach has not been established for fallopian tube carcinosarcoma¹⁸. Postoperative adjuvant therapy to reduce the risks of recurrence and relapse, as well as resection of foci by surgery, is regarded as the principal therapy for carcinosarcoma¹⁸. Thus, the current standard therapy for primary fallopian tube cancer is cytoreductive surgery followed by postoperative combination chemotherapy with paclitaxel and carboplatin, the same regimen used for epithelial ovarian carcinoma¹⁸.

The most important changes in the last few decades have been in the scheduled treatment regime, including the addition of new drugs to first-line therapy. Because of the pathogenetic role of angiogenesis in solid-tumor growth and metastasis, studies have focused on anti-angiogenic drugs⁵. Bevacizumab targets vascular endothelial growth factor receptors and is one of the most promising anti-angiogenic drugs⁵.

There is still doubt regarding the correct drug schedule, dosage, treatment duration, safety, and tolerability for first-line and neoadjuvant chemotherapy treatments. The suggested dosage, according to FDA approval, is 15 mg/kg bevacizumab every 3 weeks, along with traditional 3-weekly carboplatin/paclitaxel, and up to 22 cycles of treatment (15 months)⁵. This schedule has been the standard for many decades. Our patient underwent cytoreductive surgery and postoperative combination chemotherapy with carboplatin/paclitaxel for 8 cycles, with additional bevacizumab treatment for 25 cycles. No evidence of disease was noted on follow-up imaging or tumor markers at 51 months after surgical resection.

In conclusion, we described a rare case of fallopian tube carcinosarcoma, discussed the genetic analysis, and proposed our optimal chemotherapy treatment schedule. Currently, the schedule, dosage, treatment duration, safety, and tolerability of chemotherapy for these cases are not clear. However, for treatment of fallopian tube carcinosarcoma, we recommend a carboplatin/paclitaxel combination, with the addition of bevacizumab, for 22 or more cycles. Other schedules and drug combinations are currently under investigation, some of which may yield even better outcomes for fallopian tube carcinosarcoma.

Conflict of Interest: None declared.

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