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CASE REPORT

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Next-generation sequencing analysis and *TP53* mutation in a rare case of fallopian tube carcinosarcoma

Yoon Young Jeong[1], Sun-Jae Lee[2], Jung Min Ryu[1,*]

[1]Department of Obstetrics and Gynecology, Catholic University of Daegu School of Medicine, 42472 Daegu, Republic of Korea
[2]Department of Pathology, Catholic University of Daegu School of Medicine, 42472 Daegu, Republic of Korea

***Correspondence**
medgirl87@naver.com
(Jung Min Ryu)

Abstract

This report presents a rare case of carcinosarcoma of the fallopian tube, a malignancy with a combination of carcinomatous and sarcomatous components. The carcinomatous element predominantly resembles high-grade serous carcinoma (HGSC), and the sarcomatous element exhibits components from Mullerian structures (homologous) or not normally found in the Mullerian structures (heterologous). The case involved a 75-year-old woman with lower abdominal pain diagnosed with a large tumor in the right adnexa through imaging studies. The final diagnosis was tubal carcinosarcoma (carcinomatous components were composed of HGSC (90%), and sarcomatous components were composed of undifferentiated sarcoma and endometrial stromal sarcoma, *etc.*) without involvement of the ovaries after surgery. The next-generation sequencing (NGS) results identified a *TP53* mutation (NM_000546.5; c.578A>G). The patient underwent chemotherapy and showed no recurrence after 36 months. Here, we describe a rare case of carcinosarcoma of the fallopian tube that did not involve both ovaries and analyzed NGS results.

Keywords

Fallopian tube; High-grade serous carcinoma; Carcinosarcoma; Next-generation sequencing; *TP53* mutation

1. Introduction

Carcinosarcoma of the ovary, also known as malignant mixed mesodermal tumors or malignant mixed Müllerian tumors, is a rare malignancy accounting for only 1–4% of all ovarian cancers. Also, carcinosarcoma of the fallopian tube are extremely rare [1]. These tumors have both carcinomatous and sarcomatous components. The carcinomatous component most commonly resembles high-grade serous carcinoma (HGSC), and the sarcomatous component usually contains hyperchromatic rounded to spindled cells with marked nuclear atypia and a high mitotic index. These tumors are aggressive and behave similarly to HGSC, both in the pattern of spread, response to chemotherapy, and prognosis [2].

Ovarian carcinosarcoma is rare, and tubal exclusive carcinosarcoma, in particular, is even rarer. No next-generation sequencing (NGS) results have been reported for this as of yet. Here, we report a rare case of carcinosarcoma of the fallopian tube, including NGS results to compare with other epithelial ovarian malignancies.

2. Case report

A 75-year-old woman (gravida 3, parity 3) presented to our hospital's gynecology department on 02 November 2020, with lower abdominal pain for 2 weeks as her main complaint. Physical examination revealed tenderness in the suprapubic region. Adequate bowel sounds were noted, and the remainder of the physical exam was negative. Transvaginal ultrasound identified a hyperechoic solid mass of approximately 8 cm in the right adnexa and abundant cul-de-sac fluid collection. Both positron emission tomography (right adnexa maximum standardized uptake value 15.91) and abdominal-pelvic computed tomography (CT) suggested the possibility of primary ovarian cancer with peritoneal carcinomatosis. No abnormal findings were observed on colonoscopy and esophagogastroduodenoscopy. Tumor marker analysis showed elevated cancer antigen 125 (CA 125, 238 U/mL, normal range <35 U/mL), while CA 19-9 (14 U/mL, normal range <37 U/mL) and carcinoembryonic antigen (CEA, 0.67 ng/mL, normal range <8 ng/mL) were within the normal range.

Laparotomy was performed through a high midline skin incision. A large tumor in the right tube, approximately 8 cm, had ruptured, causing bloody ascites. There was tumor involvement in the appendix and mesentery. In addition, there were masses in the small bowel, rectal surface, and omentum. The left fallopian tube and uterus were grossly unremarkable. Based on these findings, the patient underwent bilateral salpingo-oophorectomy with total hysterectomy including cervix and low uterine segment, appendectomy, total omentectomy, tumor reductive surgery, and pelvic lymph node dissections. There was no gross residual disease. Final histopathologic results were confirmed approximately

10 days after surgery. Gross examination revealed a large, multi-fragmented paratubal mass measuring 18.0 × 12.0 × 4.0 cm in aggregates with dilated and edematous fallopian tubes (Fig. 1A,B). The tumor was tan-gray in color and had well-demarcated boundaries. The cut surfaces of the fallopian tube were also filled with the tumor (Fig. 1C). The right ovary was grossly unremarkable.

Histological examination of the surgically resected specimen showed biphasic tumors composed of both carcinomatous and sarcomatous elements. The tumors of the paratubal and tubal areas shared similar appearances (Fig. 2A,B). The tubal mass filled the lumen and bulged out to the fimbrial area. Most of the carcinomatous component was composed of HGSC (90%), clear cell carcinoma (5%), and endometrioid carcinoma (5%). Sarcomatous components were mostly composed of undifferentiated sarcoma and endometrial stromal sarcoma, and focally heterologous components with chondroid differentiation were identified in the intratubal area (Fig. 2B arrow). The metastatic tumors were identified in the appendix, mesentery and rectal serosa; however, bilateral ovaries, contralateral tubes, uterus and omentum showed no indications of malignancy. Immunohistochemical staining showed an aberrantly strong expression of *TP53* in both carcinomatous and sarcomatous elements (Fig. 3). The carcinomatous component was also positive in *WT1* and focally positive for *ER* and Napsin A. Fluid cytology was positive for malignant cells. *TP53* immunohistochemistry (IHC) staining was performed using the assay kit from Leica (cat number NCL-L-p53-D07, Bannockburn, IL, USA), with clone D07 for *TP53* antibody. The antibody dilution was 1:300, and heat-induced epitope retrieval (HIER) was performed using ERII. The Leica Bond III instrument was employed for staining, along with the Leica Bond Polymer Refine Detection Kit (cat number DS9800, Bannockburn, IL, USA) for detection.

A specialized pathologist (S.-J. Lee) identified areas of cancerous tissue, and ten unstained sections with a thickness of 10 μm per subject were prepared for the assay. The entire NGS process, from the extraction of DNA and RNA to data analysis, was outsourced to a commercial laboratory (GC Labs, Yongin, Republic of Korea). Total DNA and RNA were extracted using the RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE from Invitrogen™ (Invitrogen, Life Technologies, Carlsbad, CA, USA) following the manufacturer's instructions. DNA and copy DNA (cDNA) libraries were prepared using the quality-controlled Oncomine Comprehensive Plus Ampilion-based assay panel from Thermo Fisher Scientific (Waltham, MA, USA), which includes a total of 425 tumor-associated genes, according to the manufacturer's standard protocol. Through this NGS technology, a missense mutation in *TP53* (NM_000546.5; c.578A>G) was identified in this rare tumor. NGS testing included HGSC and undifferentiated sarcoma. Clear cell carcinoma and endometrioid carcinoma area account for a very small portion and were therefore not included. Any other variants of clinical significance (tier 1 or 2) were not identified.

In addition, germline *BRCA* testing was conducted by collecting the patient's blood sample and using Polymerase chain reaction DNA sequencing. The result is that no germline BRCA mutation was identified in our case.

The patient's pathologic stage was IIIC. After recovery from surgery, the patient received combination chemotherapy consisting of paclitaxel 175 mg/m^2 intravenous (IV), followed by carboplatin 5 area under the curve IV at three-week intervals for nine cycles. Her pre-operative CA 125 level was elevated at 238 U/mL, which decreased to 13 U/mL following her last chemotherapy. No evidence of tumor recurrence was noted on follow-up imaging or physical examination 36 months after treatment.

3. Discussion

Carcinosarcomas are rare tumors with carcinomatous and sarcomatous components (malignant epithelial and mesenchymal elements). The carcinomatous component of carcinosarcoma is typically serous, endometrioid, clear cell and undifferentiated adenocarcinoma, the most common type of which is HGSC [3, 4]. The sarcomatous component of the tumor is divided into homologous or heterologous. Homologous elements (common components from Mullerian structures) resemble leiomyosarcoma, fibrosarcoma or endometrial stromal sarcoma. Heterologous elements are not normally found in the Mullerian structures (*e.g.*, cartilaginous, osseous, or rhabdomyoblastic) [1]. Carcinosarcomas are known to have a very aggressive progression pattern and also have a very poor prognosis compared to other histologic types in both the uterus and ovary [4]. In particular, ovarian carcinosarcoma has a poorer prognosis than other types of epithelial ovarian cancer, with five-year survival rates of 24.26% in stage III and 12.85% in stage IV [2]. Predictors of recurrence and death for carcinosarcomas include poorly differentiated epithelial or serous histology, rhabdomyosarcomatous components, advanced stage, older age, and lymphovascular space invasion [5].

Primary carcinosarcomas of the fallopian tube are extremely rare. The average age was 59.7 years, and the most common symptoms were atypical vaginal bleeding and abdominal pain with a pelvic mass. It is difficult to predict carcinosarcoma in advance before surgery, and preoperative study is usually based on ovarian malignancy. In most cases, carcinosarcoma is diagnosed through a final biopsy after surgery [6]. One important prognostic factor is the histologic type. The heterologous type of tubal carcinosarcoma may have a negative impact on survival, while conversely, the homologous type is thought to have a positive impact on prognosis [7]. The treatment approach for carcinosarcoma of the fallopian tube is similar to that of ovarian carcinoma. In particular, according to the National Comprehensive Cancer Network guidelines, patients with carcinosarcoma are not candidates for fertility-sparing surgery regardless of age or stage [8]. Optimal surgical debulking and primary chemotherapy regimens used for epithelial ovarian cancer are recommended [9]. For stages II–IV ovarian malignancies, the decision for maintenance treatment with poly ADP ribose polymerase (PARP) inhibitors is determined based on the presence of somatic or germline BRCA mutations. Therefore, even in carcinosarcoma, NGS test results play a vital role in determining treatment [10].

NGS technology is primarily employed in the investigation and interpretation of genetic variations and mutations in gyne-

cological cancers. NGS-based research in gynecological cancers enhances patient-centric medical approaches, contributing to the development of more accurate and effective treatment strategies [11].

Analyzing the tumor's genome through NGS can help determine the unique genetic characteristics of a specific patient's tumor. This forms the basis for developing personalized treatment strategies, including targeted therapies or immunotherapies tailored to specific genetic features. Especially, in ovarian malignancy, when there is a mutation in genes related to DNA damage repair, such as BRCA1 or BRCA2, cancer cells become more sensitive to PARP inhibitors [12]. A PARP is a protein that plays an important role in repairing single-strand DNA damage. When this PARP activity is inhibited, single-strand DNA damage can progress to double-strand breaks, leading to cell death. Individuals with BRCA mutations have dysfunctional homologous recombination repair, which is the primary mechanism for repairing double-strand breaks. Therefore, these BRCA mutations can make PARP inhibitors even more effective. PARP inhibitors are often used as part of combination therapy. The most extensively researched and efficacy-proven representative PARP inhibitors in treatments

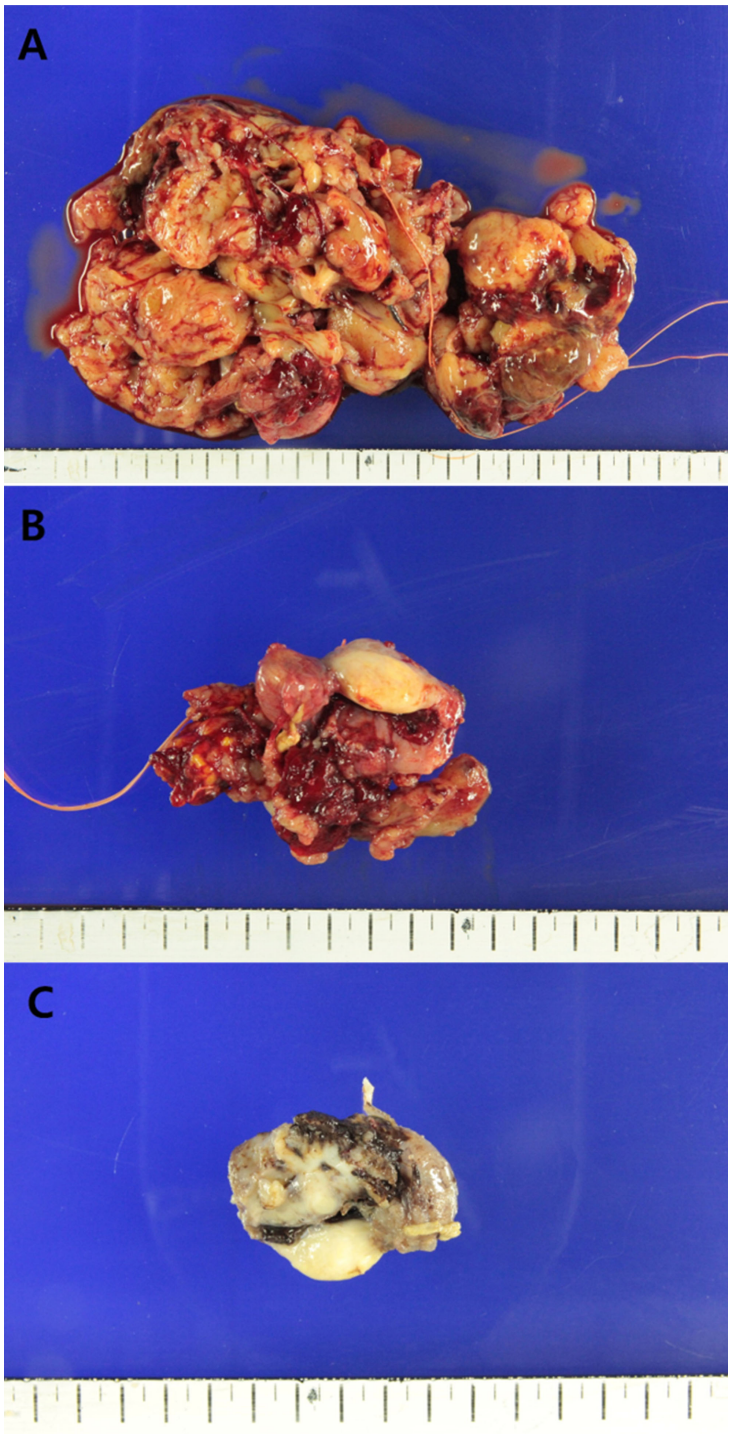

FIGURE 1. Gross appearances of the resected specimen. (A) Mulifragmented paratubal mass. (B) The right salpingo-oophorectomy specimen with unremarkable ovary and congestive fallopian tube. (C) The cut surface of the fallopian tube.

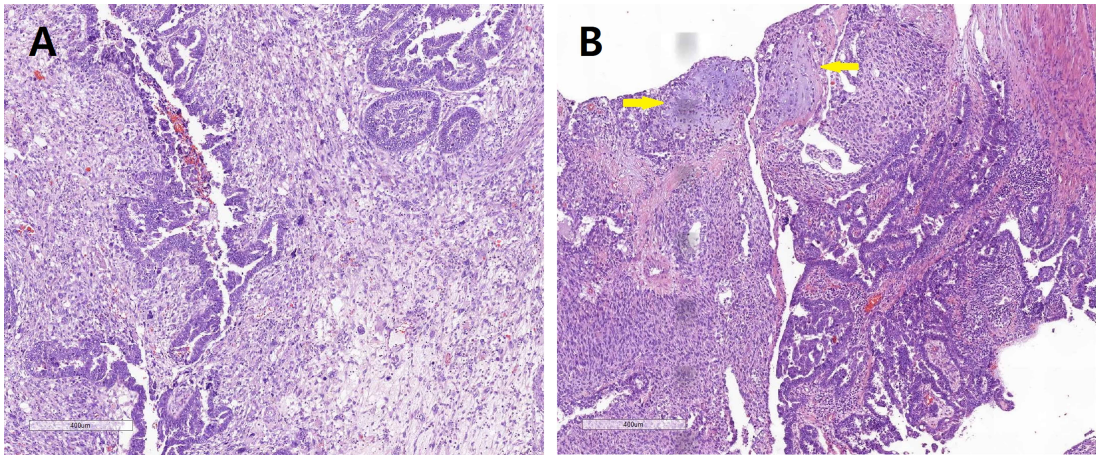

FIGURE 2. Microscopic findings of the tumor (magnification: 40×). (A) Paratubal mass. (B) The mass inside of the fallopian tube. Arrow; chondroid differentiation.

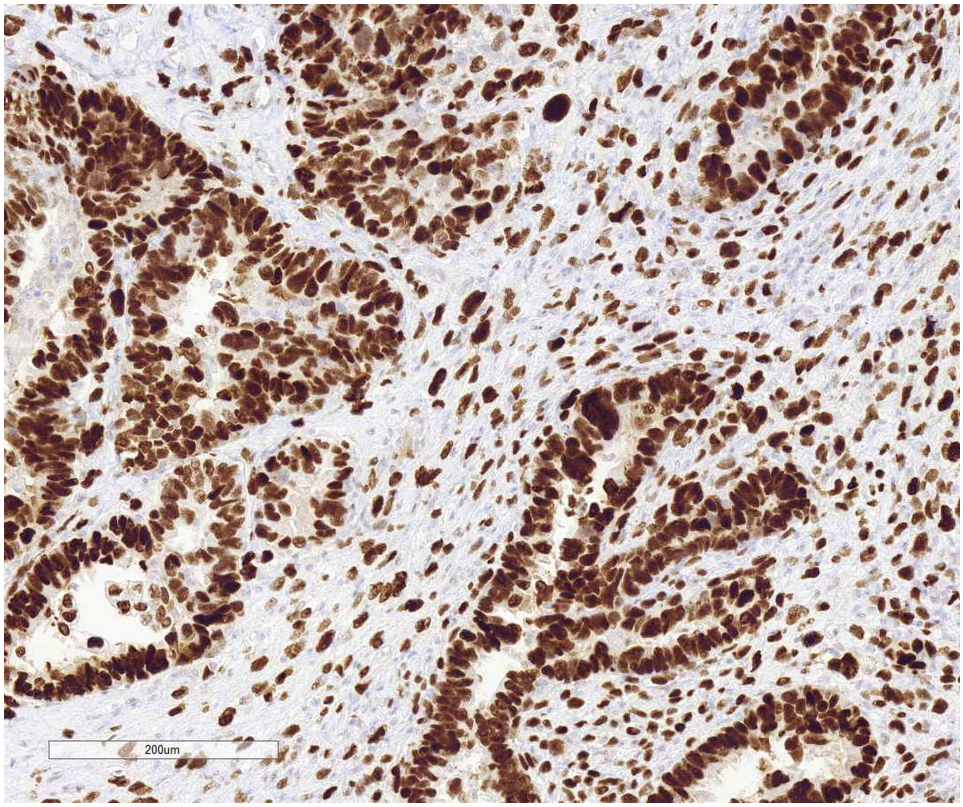

FIGURE 3. Immunohistochemical stain of *TP53* (magnification: 40×).

for ovarian malignancy are olaparib, niraparib, and rucaparib [13].

Elias *et al.* [14] showed that in carcinosarcoma of the ovary, since driver mutations appear to be shared between the carcinoma and sarcoma elements, we expect that PARP inhibitors may have equivalent efficacies against both components.

According to the study by Saotome *et al.* [10], NGS analysis of ovarian malignancies with various histologies revealed that a *TP53* actionable gene variant was identified in 55.6% of HGSC, 13.3% of endometrioid carcinoma, 13.3% of clear cell carcinoma, 33.3% of mucinous carcinoma, 25.0% of undifferentiated carcinoma, and 33.3% in other types. In this study, the "other types" group comprised six cases, among which three included carcinosarcoma [10].

In the NGS analysis from this case, a missense mutation in *TP53* (NM_000546.5; c.578A>G) was identified in this rare tumor using Ion Torrent NGS technology. Any other variants of clinical significance (tier 1 or 2) were specified. Furthermore, no germline BRCA mutation was identified in our case.

Interpreting this in conjunction with the pathological findings, most of the carcinomatous components in our case consisted of HGSC (90%), suggesting an association with *TP53* mutation. Additionally, as the majority of BRCA-associated ovarian/fallopian tube cancers are HGSC, it was essential to verify the NGS results in our patient to determine the efficacy of PARP inhibitors. Based on the analysis of these NGS results, our patient underwent paclitaxel and carboplatin combination

chemotherapy [5].

If DNA damage proves to be irreparable, *TP53* can initiate apoptosis. *TP53* mutations occur early in tumor evolution and may be the main event in ovarian carcinogenesis. This mutation is the most common genetic alteration in epithelial ovarian cancer. Pathogenic *TP53* mutations, known to arise from epithelial secretory cells of the fimbriae, a component of the fallopian tube, have been identified in most HGSCs. However, the clinical application of *TP53* mutational analysis has not yet been achieved. *TP53* mutation is undoubtedly an essential biomarker in terms of therapeutic and prognostic aspects, and ongoing studies are expected to continue advancements in this area [15].

4. Conclusions

In conclusion, in this study, we describe a very rare case of carcinosarcoma of the fallopian tube that did not involve both ovaries, and we analyzed the NGS results. Through our case report, we were able to confirm the presence of *TP53* mutations in the NGS results of tubal carcinosarcoma, most of which consisted of HGSC components. In addition, having examined the NGS analysis results of carcinosarcoma and considering the applications of PARP inhibitors, a more advanced personalized treatment for rare ovarian/tubal cancer types can be developed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SJL—performed the research study and took the pictures; JMR—collected data and wrote the manuscript; YYJ—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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