Clinical History:
A 60-year-old woman presented with abdominal bloating and discomfort. Abdominal/pelvic CT showed a large pelvic mass, ascites, and omental caking. Following three cycles of carboplatin/Taxol neoadjuvant therapy, an exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, omental biopsies, and partial colectomy were performed.
New Frontiers in Pathology
An Update for Practicing Pathologists

Gynecologic Pathology
Case 17

Kathleen R. Cho, M.D.
Department of Pathology
Clinical History

• 60 yo woman presented with abdominal bloating and discomfort

• Abdominal/pelvic CT scan showed a large pelvic mass, ascites, and omental caking

• Based on a cytology diagnosis of “adenocarcinoma c/w Mullerian origin” neoadjuvant therapy with Carboplatin/Taxol was initiated

• Exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, and partial colectomy were performed
Omental metastases include both carcinoma and sarcoma components.
Diagnosis:

Uterus, right and left fallopian tubes and ovaries, and sigmoid colon, total hysterectomy, bilateral salpingo-oophorectomy, and sigmoid colectomy: Carcinosarcoma (malignant mixed Mullerian tumor) with heterologous differentiation, involving the ovaries, uterine serosa, outer myometrium and pericolonic soft tissue. Left fallopian tube with serous tubal intraepithelial carcinoma. Right fallopian tube not identified. Unremarkable portion of large intestine. Unremarkable cervix and endometrium. Myometrium with extensive adenomyosis and leiomyoma.

Omentum #1 and #2, excisional biopsies: Metastatic carcinosarcoma. Angiolympathic invasion identified.
Clinical Course:

- The patient was diagnosed with recurrent platinum-resistant disease a few months after receiving 3 additional cycles of Carboplatin/Taxol

- She was subsequently treated with a number of different drugs, including Ifosfamide/Taxol, Doxil, and Cytoxan/Avastin

- No deleterious mutations were found besides TP53 mutation and TNFRSF14 loss

- The patient died of disease 26 months following her debulking surgery
CURRENT VIEW: MOST HIGH-GRADE SEROUS CARCINOMAS LIKELY ARISE IN THE FALLOPIAN TUBE...

A 64 year old woman presented with a large tumor in the pelvis. Carcinosarcoma with heterologous differentiation was found in the right ovary. Serous tubal intraepithelial carcinoma was found in or near the fimbria of both fallopian tubes. The patient died of recurrent tumor 7 months after primary presentation.
A 69 year old woman presented with a pelvic mass. Both ovaries contained mature cystic teratomas. Carcinosarcoma was also present in the left ovary, while high-grade serous carcinoma was also present in the right ovary. The left fallopian tube contained a 5 mm focus of serous carcinoma with adjacent serous tubal intraepithelial carcinoma. The patient died of progressive disease 12 months post-operatively.
“The identification of intraepithelial carcinoma in this tumor lends support to a role of the epithelial component in fimbrial MMMT histogenesis as seen for MMMT at other anatomic sites.”
Identical TP53 mutations in pelvic carcinosarcomas and associated serous tubal intraepithelial carcinomas provide evidence of their clonal relationship

Laura Ardighieri¹ · Luigi Mori² · Sara Conzadori¹ · Mattia Bugatti¹ · Marcella Falchetti¹ · Carla Maria Donzelli¹ · Antonella Ravaggi³ · Franco E. Odicino⁴ · Fabio Facchetti¹

Case Report

Ovarian Carinosarcoma and Concurrent Serous Tubal Intraepithelial Carcinoma With Next-Generation Sequencing Suggesting an Origin From the Fallopian Tube

Sharlene Helene C. See, MD¹, Amir Behdad, MD¹, Kruti P. Maniar, MD¹, and Luis Z. Blanco Jr, MD¹
But Next-Generation Sequencing Has Shown that Some STICs Likely Represent Metastases!

“Next-generation sequencing also demonstrated unexpected associations between presumed STICs and synchronous carcinomas, providing evidence that some TICs are actually metastases rather than HGSC precursors.”
“Phylogenetic analyses supported STIC as precursor lesions in half of our patient cohort, but also identified STIC as metastases in 2 patients.”
Is there experimental evidence for origin of carcinosarcomas in the fallopian tube?

YES!

Human and mouse ovaries and fallopian tubes are anatomically similar.

From A. Ng and N. Barker, Nat Rev Mol Cell Biol 16:625-638, 2015
TCGA Research Network: Integrated Genomic Analysis of Ovarian Carcinoma (n=316 HGSCs): Genes with statistically recurrent somatic mutations!

Table 2: Significantly mutated genes in HGS-OvCa

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. of mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>302</td>
</tr>
<tr>
<td>BRCA1</td>
<td>11</td>
</tr>
<tr>
<td>CSMD3</td>
<td>19</td>
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<tr>
<td>NF1</td>
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</tr>
<tr>
<td>BRCA2</td>
<td>10</td>
</tr>
<tr>
<td>RB1</td>
<td>6</td>
</tr>
</tbody>
</table>

STICs arise in genetically engineered mice approximately 8 months after induction of tumor formation by inactivation of *Brca1, Trp53, Rb1* and *Nf1* in oviductal epithelium.
Oviductal HGSC and carcinosarcomas arise from STICs in the context of *Brca1, Trp53, Rb1*, and *Nf1* inactivation.
Summary:

• The conclusion that at least some “ovarian” carcinosarcomas likely arise from fallopian tube epithelium is supported by three types of evidence:
  ✓ Histopathological
  ✓ Molecular
  ✓ Animal model systems

• Although STICs are likely precursors of carcinosarcomas, some STICs may represent mucosal metastases from the epithelial component of a carcinosarcoma arising elsewhere
CASE 17

DIAGNOSIS: Ovarian carcinosarcoma with extensive heterologous differentiation, involving right and left ovaries, uterine serosa with extension into outer myometrium, omentum, and pericolonic soft tissue. Left fallopian tube with serous tubal intraepithelial carcinoma.

CLINICAL HISTORY: A 60 year-old woman presented with abdominal bloating and discomfort. Abdominal/pelvic CT showed a large pelvic mass, ascites, and omental caking. Following three cycles of carboplatin/Taxol neoadjuvant therapy, an exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, omental biopsies and partial colectomy were performed. No lymph nodes were sampled.

MICROSCOPIC DESCRIPTION: Sections from the ovaries showed extensive replacement by carcinosarcoma (malignant mixed Mullerian tumor) with prominent heterologous differentiation, primarily chondrosarcoma. The epithelial component showed a mixture of high-grade serous carcinoma and squamous cell carcinoma. The carcinosarcoma also involved the uterine serosa and outer myometrium, peri-colonic soft tissue, and omentum. While the right fallopian tube was not identified, the left fallopian tube showed a focus of serous tubal intraepithelial carcinoma (STIC) characterized by atypical cells with loss of polarity, pleomorphic nuclei, prominent nucleoli and increased mitotic activity. Immunohistochemical staining for p53 and Ki67 were performed on sections from the left fallopian tube, which showed strong and diffuse nuclear expression of p53 and an elevated Ki-67 proliferative index in the atypical cells.

CASE DISCUSSION: Many, if not most, “ovarian” high-grade serous carcinomas (HGSCs) are now believed to arise from precursor lesions in the fallopian tube epithelium, with a predilection for the tubal fimbriae. These precursor lesions, termed STICs, demonstrate cytologic features similar to full-blown HGSC and harbor clonal TP53 mutations, indicating that TP53 mutation is an early event in HGSC pathogenesis. While it is generally accepted that STICs are the direct precursors of many HGSCs previously thought to be ovarian in origin, STIC as a potential precursor of ovarian carcinosarcoma is a more recent concept. Importantly, both uterine and ovarian carcinosarcomas are now thought to represent variants of high-grade serous carcinoma that have undergone epithelial-to-mesenchymal transition and display variable combinations of both carcinomatous and sarcomatous elements. Hence, it is not unexpected that the fallopian tubes might harbor precursors that give rise to either HGSC or carcinosarcoma, with the latter being significantly less common. Although reports are few, primary fallopian tube carcinosarcomas have been described in the literature.

Co-occurrence of STIC with ovarian carcinosarcoma has been reported in several publications, with some of the more recent ones including molecular analysis of the tubal and ovarian lesions. For example, Ardighieri and co-workers identified STIC in association with 10 of 16 pelvic (non-uterine) carcinosarcomas. Clonal TP53 mutations were identified in 8 of the 10 STICs, and all of the associated carcinosarcomas harbored the identical mutation present in the STIC. Similarly, See and colleagues employed next-generation sequencing to identify the same TP53 mutation in STIC and associated carcinosarcoma, with the latter’s carcinomatous and sarcomatous components both showing the identical mutation. The findings described above provide strong molecular evidence that the tube lesions and associated “ovarian” carcinosarcomas
share the same origin, but they do not address the possibility that the STIC could represent a mucosal metastasis from the epithelial component of the carcinosarcoma. Indeed, we and others have shown that metastatic carcinomas to the fallopian tube mucosa can closely mimic STIC 16-18.

Recent studies in genetically engineered mice provide compelling data that transformed tubal epithelial cells can give rise to carcinosarcomas that subsequently metastasize to the ovary and grow as large tumoral masses that mimic an ovarian primary. Specifically, mice can be genetically engineered to develop lesions morphologically identical to human STICs in their oviducts (mouse equivalent to human fallopian tube). When the STICs are allowed to progress, approximately half of the animals develop high-grade serous carcinomas while the other half develop tumors morphologically indistinguishable from human ovarian carcinosarcomas 19. Collectively, these findings provide strong support for the conclusion that at least a subset of “ovarian” carcinosarcomas, likely arise from epithelium in the fallopian tube.

Case follow-up: The patient initially had a favorable response to carboplatin and Taxol chemotherapy but was diagnosed with recurrent, platinum-resistant disease a few months after debulking surgery. She was subsequently treated with Ifosfamide/Taxol, followed by Doxil, and then Cytoxan/Avastin. She died approximately 26 months after debulking surgery.

REFERENCES:


