

CASE REPORT

A Case of High-Grade Serous Tubal Intraepithelial Carcinoma Diagnosed with Adenocarcinoma by Ascitic Fluid Cytology

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ABSTRACT

Fallopian tube cancer is a very rare disease that is difficult to detect in its early stages. To our knowledge, we encountered the first case of serous tubal intraepithelial carcinoma (STIC) diagnosed with ade-

nocarcinoma by ascitic fluid cytology. The patient was a 51-year-old woman who visited our department because of a leiomyoma detected during a uterine cancer screening. Transvaginal ultrasound found multiple leiomyomas and an endometrial cyst of the left ovary. The patients' cancer antigen 125 level was elevated and the leiomyomas showed a tendency to grow. Therefore, surgical treatment was considered to be appropriate. Preoperative imaging showed no evidence of malignancy. We performed abdominal hysterectomy and bilateral salpingo-oophorectomy. The patient had stage IV endometriosis according to the revised American Society of Reproductive Medicine classification, and no macroscopic abnormalities were found in either fallopian tube. Postoperative histopathological findings led to the diagnosis of STIC in the right fallopian tube; cytological examination of the ascitic fluid also confirmed the presence of adenocarcinoma. We performed a staging laparotomy and found no evidence of metastasis to the lymph nodes or the greater omentum; the staging classification was determined to be IC3. After surgery, six cycles of paclitaxel + carboplatin therapy were administered. The patient has since been relapse-free for 15 months to date. Much attention has been directed to the fallopian tubes as the origin of malignant epithelial ovarian tumors, and STIC is now considered to be the origin of high-grade serous ovarian cancer. To avoid overlooking early-stage fallopian tube cancer, surgery for benign disease should also be accompanied by a detailed histopathological examination of the fallopian tubes.

Key words: Serous tubal intraepithelial carcinoma; Ascitic fluid cytology; Adenocarcinoma

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INTRODUCTION

High-grade serous tubal intraepithelial carcinoma (STIC) is a very

rare disease that is difficult to detect in its early stages. The incidence of fallopian tube cancer is said to account for approximately 0.3% of all malignant gynecologic tumors, but no studies have specifically reported the incidence of STIC. In recent years, much attention has been directed to the fallopian tubes as the origin of ovarian cancer, and STIC is now considered to be the origin of high-grade serous ovarian carcinoma. We encountered a case of STIC in which the patient underwent surgery based on a preoperative diagnosis of leiomyomas and endometriosis; she was later diagnosed with adenocarcinoma by ascitic fluid cytology. We herein report our experience.

CASE REPORT

The patient was a 51-years-old woman who underwent an appendectomy at age 12 and a Cesarean section at age 30 (gravida 1, para 1). Nothing significant was noted in her family history. The age of menarche was 12 years and her menstrual cycle was 25 days; her menstrual cycle was regular and she was premenopausal. The patient visited our department because of a leiomyoma detected during uterine cancer screening. The diagnosis was multiple leiomyomas

and an endometrial cyst of the left ovary. We decided to monitor the patient's condition.

Three months later, the leiomyomas showed a tendency for growth; therefore, we decided to proceed with surgical treatment. The uterus was anteverted, anteflexed, and fist-sized with diminished mobility. Transvaginal ultrasound revealed multiple leiomyomas and a chocolate cyst of the left ovary. No ascitic fluid was noted. Cervical cytology was negative for intraepithelial lesions and malignancy, and endometrial cytology was negative. At the initial visit, the patients' cancer antigen 125 level was slightly high at 106.7 U/mL, which increased to 151.7 U/mL at 3 months. Magnetic resonance imaging (MRI) showed multiple leiomyomas, and T1-weighted imaging detected a hyperintense cyst measuring approximately 4×3 cm in the right posterior part of the uterus. These findings were indicative of endometriosis, but no solid part was found (Figure 1). Computed tomography revealed a nodule in the left lung. To further investigate the pulmonary nodule, position emission tomography-computed tomography was performed. No FDG uptake was seen in the left pulmonary nodule. A maximum standardized uptake value of 3.9 was noted in the leiomyomas or the area near the left ovary, but it was not suggestive of malignancy.

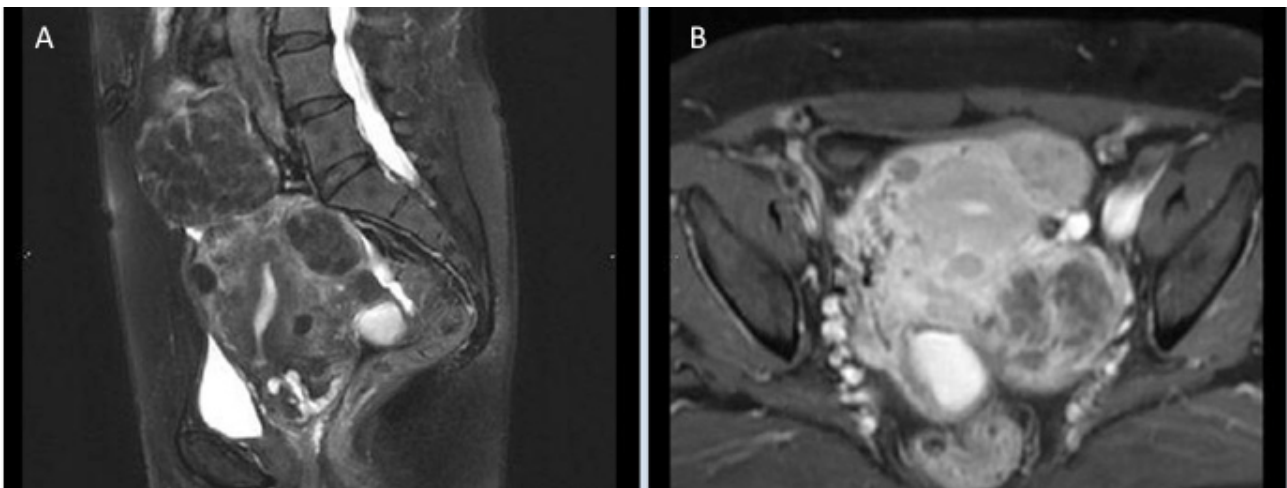


Figure 1 Magnetic resonance imaging (MRI) findings. A: Fat-suppressed gadolinium (Gd)-enhanced T2-weighted MRI, sagittal section. B: Gd-enhanced T2-weighted MRI, transverse section. Leiomyomas of different sizes were found in the uterus. The right ovary was enlarged to approximately 4 × 3 cm in size and an endometrial cyst was suspected. The accumulation of a small amount of ascitic fluid in the pouch of Douglas was noted.

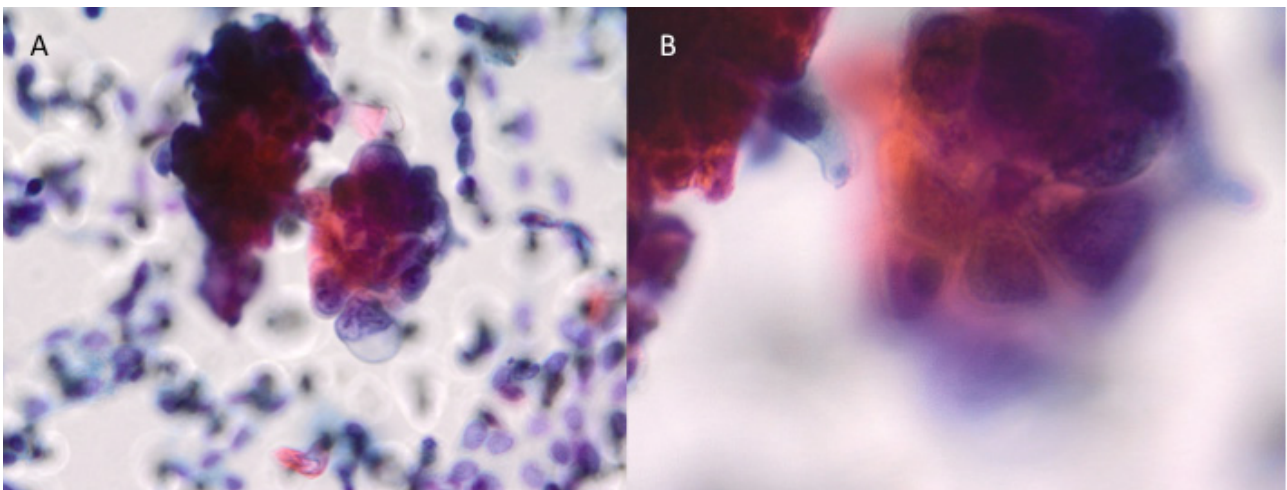


Figure 2 Cytologic findings of ascitic fluid. A: Papanicolaou stain (× 40). B: Papanicolaou stain (× 1000). A single cluster of adenocarcinoma cells was found on the filtered sample. The cancer cell cluster exhibited marked aggregation and prominently atypical cells with nuclei of variable sizes and irregular shapes, resulting in the diagnosis of adenocarcinoma.

Abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. During the surgery, a small amount of yellow-colored clear ascitic fluid was noted. The endometriosis was stage IV according to the revised American Society of Reproductive Medicine classification; no abnormalities were found in either fallopian tube. Ascitic fluid cytology was performed using the membrane filter method (pore filter method: FIL CUP Super), which found a single cluster of adenocarcinoma cells on the filtered sample. The cancer cell cluster exhibited a marked aggregation and prominently atypical cells with nuclei that had variable sizes and irregular shapes (Figure 2).

Histopathological findings led to the diagnosis of multiple leiomyomas and bilateral ovarian endometrial cysts. The endometrium, ovaries, and fallopian tubes did not show any findings suggestive of a cancer cell nest. Therefore, we examined tissue samples from various sites, including the fallopian tube; atypical hyperplasia was found in the epithelium of the fimbria of the fallopian tube. At increased magnification, nuclei were round to oval and irregular shaped; nuclear stratification was also observed. Strong immunohistochemical expression of p53 was confirmed, resulting in the diagnosis of STIC (Figure 3).

After obtaining a thorough informed consent from the patient, we performed a staging laparotomy. There was no evidence of

metastasis to the lymph nodes or the greater omentum. A detailed gastroenterological examination did not find any abnormalities either. Ascitic fluid cytology resulted in the diagnosis of adenocarcinoma, and the condition was treated as stage IC3 fallopian tube cancer. As postoperative adjuvant therapy for fallopian tube cancer, six cycles of paclitaxel + carboplatin therapy (paclitaxel 175 mg/m² and carboplatin AUC 6 mg/mL/min every 21 days) were administered. The patient has since been relapse-free for 15 months and has been receiving follow-up care on an outpatient basis.

DISCUSSION

High-grade serous adenocarcinoma, which accounts for the majority of ovarian serous adenocarcinoma cases, has been traditionally thought to develop in a de novo manner as a result of TP53 mutations in the ovarian surface epithelium. However, a detailed investigation of the entire length of the fallopian tube (including its fimbria) found a high rate of concurrent STIC in patients with ovarian serous adenocarcinoma or peritoneal serous adenocarcinoma, particularly high-grade serous adenocarcinoma^[1]. According to the report, an examination of fallopian tubes resected from patients with ovarian serous adenocarcinoma, serous adenocarcinoma of the fallopian tube,

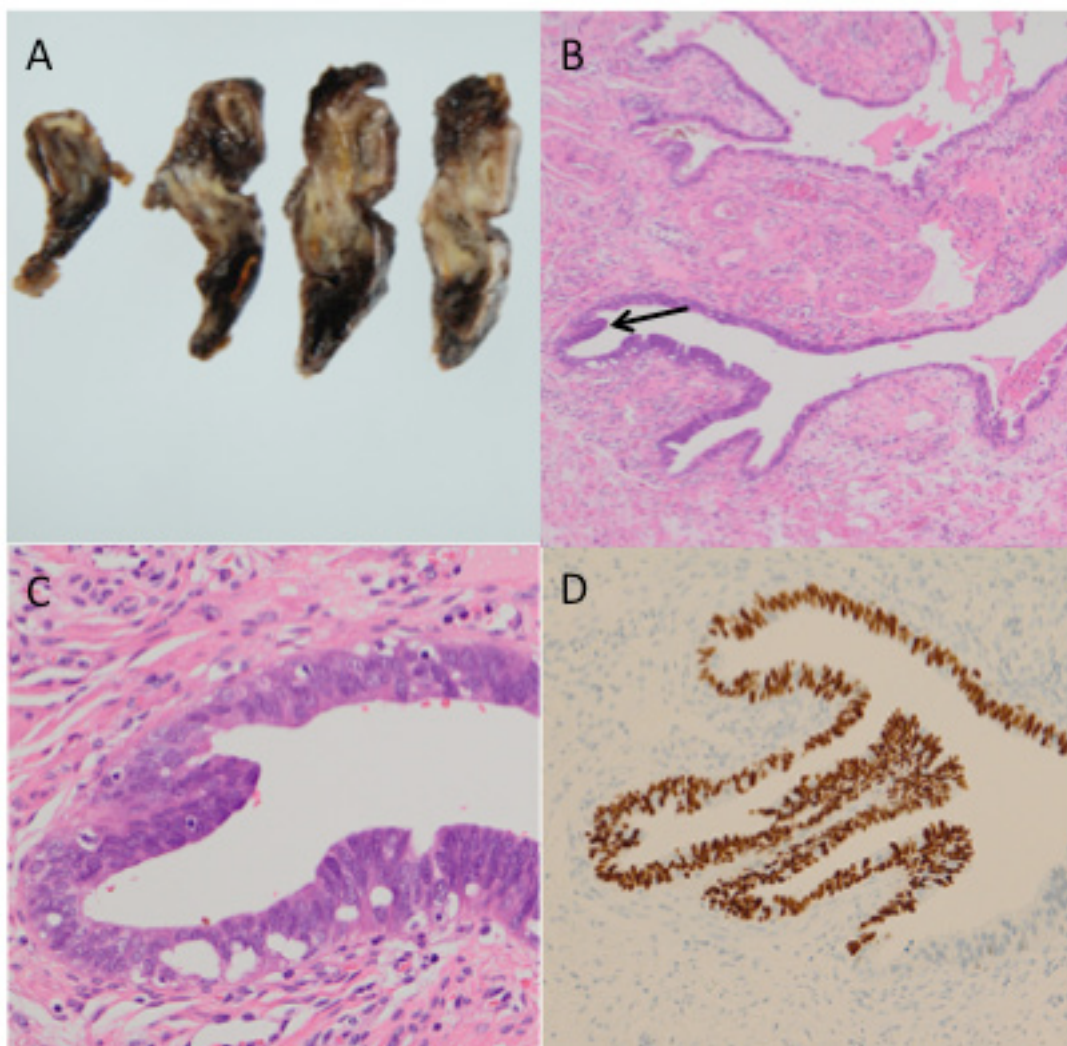


Figure 3 Macroscopic findings and histopathological findings of the resected samples. A: Macroscopic findings of the right fallopian tube. B: Hematoxylin and eosin (HE) stain ($\times 40$). C: HE stain ($\times 100$). Atypical hyperplasia in the fallopian tube epithelium (arrow) was observed. D: p53 stain ($\times 40$). Atypical epithelial cells were positive for p53 on immunohistochemical staining.

or peritoneal serous adenocarcinoma found concurrent STIC in a total of 29 cases (20 of 43 cases with ovarian serous adenocarcinoma, 5 of 5 cases with serous adenocarcinoma of the fallopian tube, and 4 of 7 cases with peritoneal serous adenocarcinoma), of which 27 cases had STIC in the fimbriae of the fallopian tubes.

In recent years, much attention has been paid to the fallopian tubes as the origin of malignant epithelial ovarian tumors, and STIC is now regarded as the origin of high-grade serous carcinoma. Because precancerous lesions in ovarian cancer were thought to be present within the ovaries, pathological examinations of the fallopian tubes have not been actively conducted. However, concurrent STIC has been noted in approximately 50-60% of high-grade serous carcinoma cases^[2], and *p53* gene mutations are frequently identified in both STIC and cancerous parts. Therefore, it is now believed that STIC cells migrate from the fimbria of the fallopian tube and enter through a rupture site on the surface of the ovary, resulting in the development of ovarian cancer as a secondary cancer^[3]. The patient in our case had positive ascitic fluid cytology, strongly suggesting that the epithelium of the fallopian tube was the site of origin of ovarian cancer. Additionally, Rabban *et al.* reported that STIC was found in 4 of 522 cases with benign tumors (0.77%)^[4] and suggested the need for salpingectomy in patients with benign tumors who have no desire to bear children.

In recent years, increasing attention has been paid to hereditary breast and ovarian cancer. It has been reported that 8–62% of people with *BRCA1* or *BRCA2* gene mutations develop ovarian cancer^[5]. In an investigation of 593 patients with *BRCA1/2* gene abnormalities or a family history of breast or ovarian cancer who underwent risk-reducing salpingo-oophorectomy (RRSO), STIC was present in approximately 2% (12 patients); of these, five patients had *BRCA1* mutations, five patients had *BRCA2* mutations, and two patients had a family history of ovarian cancer^[6]. Furthermore, another study reported that STIC was found in approximately 10-15% of patients with *BRCA1/2* gene mutations undergoing RRSO^[7]. In Japan, insurance coverage for RRSO has yet to be approved. However, in the future, it will become necessary to discuss a way to perform salpingectomy only in premenopausal patients with *BRCA1/2* genetic abnormalities to preserve their ovaries.

Through our literature review, we could not find another case report of a patient diagnosed with STIC who had positive ascitic fluid cytology. Our patient with stage IC3 fallopian tube cancer was administered postoperative adjuvant therapy according to ovarian cancer treatment guidelines. For chemotherapy, we chose paclitaxel + carboplatin therapy (paclitaxel 175 mg/m² and carboplatin AUC 6 mg/mL/min every 21 days). No serious adverse events were noted during the treatment, and the patient was able to complete 6 cycles successfully without the need for treatment extension or dose reduction. The patient has since remained relapse-free for 15 months to date.

Our literature review did not find any cases in which a patient was diagnosed with STIC and then with adenocarcinoma by

cytological examination of ascitic fluid, and there are no clear criteria for postoperative treatment in such cases. In the present case, we thoroughly explained the possibility of overtreatment to the patient and obtained her informed consent before initiating chemotherapy. However, the relapse rate for administering chemotherapy in STIC with only positive ascitic fluid cytology is still unknown. In recent years, an increasing number of facilities have been performing salpingectomy. Thus, clear diagnostic criteria need to be developed through the accumulation of clinical data over time.

To our knowledge, we have reported the first case of a patient with tubal intraepithelial carcinoma diagnosed with adenocarcinoma by ascitic fluid cytology. To avoid overlooking early-stage ovarian cancer and fallopian tube cancer, surgery for benign disease should also be accompanied by peritoneal washing cytology and detailed histopathological examination of the fallopian tube.

REFERENCE

- Kindelberger DW1, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, Callahan MJ, Garner EO, Gordon RW, Birch C, Berkowitz RS, Muto MG, Crum CP. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol.* 2007 Feb; **31(2)**: 161-9.
- Callahan MJ1, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, Feltmate CM, Berkowitz RS, Muto MG. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol.* 2007 Sep 1; **25(25)**: 3985-90.
- Robert J. Kurman, M.D. and Ie-Ming Shih, M.D., Ph.D. The Origin and Pathogenesis of Epithelial Ovarian Cancer- a Proposed Unifying Theory. *Am J Surg Pathol.* 2010 Mar; **34(3)**: 433-443.
- Rabban JT1, Garg K, Crawford B, Chen LM, Zaloudek CJ. Early detection of high-grade tubal serous carcinoma in women at low risk for hereditary breast and ovarian cancer syndrome by systematic examination of fallopian tubes incidentally removed during benign surgery. *Am J Surg Pathol.* 2014 Jun; **38(6)**: 729-742.
- King MC1, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003 Oct 24; **302(5645)**: 643-646.
- Stephanie L. Wethington, MD, Kay J. Park, MD, Robert A. Soslow, MD, Noah D. Kauff, MD, Carol L. Brown, MD, Fanny Dao, BA, Ebunoluwa Otegbeye, BA, Yukio Sonoda, MD, Nadeem R. Abu-Rustum, MD, Richard R. Barakat, MD, Douglas A. Levine, MD, and Ginger J. Gardner, MD, Clinical Outcome of Isolated Serous Tubal Intraepithelial Carcinomas (STIC). *Int J Gynecol Cancer.* 2013 November; **23(9)**: 1603-1611.
- Finch A1, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol.* 2006 Jan; **100(1)**: 58-64.

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