American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e921146
DOI: 10.12659/AJCR.921146

Received: 2019.11.03
Accepted: 2019.12.11
Available online: 2020.01.24
Published: 2020.02.08

Incidental Serous Tubal Intraepithelial Carcinoma that Developed into Primary Peritoneal Serous Carcinoma in a Patient without BRCA Mutation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABD 1 Gun Oh Chong
DE 2 Ji Young Park
AEF 1 Hyun Jung Lee

1 Department of Obstetrics and Gynecology, School of Medicine, Kyungpook National University, Daegu, South Korea
2 Department of Pathology, School of Medicine, Kyungpook National University, Daegu, South Korea

Corresponding Author: Hyun Jung Lee, e-mail: obgy1019@hanmail.net
Conflict of interest: None declared

Patient: Female, 62-year-old
Final Diagnosis: Peritoneal high grade serous carcinoma
Symptoms: Serous tubal intraepithelial carcinoma
Medication: —
Clinical Procedure: Total laparoscopic hysterectomy and both salpingo-oophorectomy
Specialty: Obstetrics and Gynecology

Objective: Unusual clinical course

Background: Serous tubal intraepithelial carcinoma (STIC) is proposed as the precursor of ovarian, tubal, and peritoneal high-grade serous carcinoma, but the clinical significance remains unclear, especially in the normal population. We report a rare case of STIC in a patient undergoing non-prophylactic surgery who developed PPSC without a strong family history or BRCA mutations.

Case Report: A 62-year-old woman presented with an abnormal pap smear (ASC-H). She underwent vaginal wall biopsy, endocervical curettage, and HPV testing, which revealed vaginal wall intraepithelial neoplasia 3 and cervical intraepithelial neoplasia 3, HPV 68 positive. Laparoscopic total hysterectomy, including an upper vagina and bilateral salpingo-oophorectomy, was performed. Postoperative histopathologic examination revealed carcinoma *in situ* of the cervix, and, incidentally, a serous tubal intraepithelial carcinoma (STIC) *in situ* of both fallopian tubes. During follow-up, the patient was diagnosed with primary peritoneal serous carcinoma (PPSC), 22 months after the initial operation. BRCA mutations were not detected. The findings in our case, coupled with current evidence, suggest the distal fallopian tube as the source of PPSC.

Conclusions: After an incidental diagnosis of STIC, we recommend surveillance for BRCA mutations. Standard management remains unclear, but further surgical evaluation and/or chemotherapy should be considered in patients with isolated STIC.

MeSH Keywords: Adenocarcinoma • Carcinoma *in Situ* • Genes, BRCA1 • Peritoneum

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/921146

1468 — 2 14

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Serous tubal intraepithelial carcinoma (STIC) is a lesion limited to the epithelium of the fallopian tube and is considered to be the precursor of ovarian, tubal, and peritoneal high-grade serous carcinoma. The incidence of "isolated" STIC has been reported in 0.7–4.0% of BRCA mutation carriers undergoing risk-reducing salpingo-oophorectomy (RRSO), and carcinoma was accidentally found reported in 1–4% of these case [1–6]. The incidence of STICs in women without BRCA mutations was reported by a few researchers and varies depending on the patient population and pathological examination method for fallopian tubes; for example, SEE-FIM (Sectioning and Extensively Examining the FIMbria) protocol versus the classical method.

To date, the literature on STIC mostly focuses on the incidence, as opposed to the management and clinical outcomes. In a patient with isolated STIC without BRCA mutations or risk factors, the necessity for surgical staging, frequency of identifying invasive lesions from staging, and benefit of use of adjuvant chemotherapy have not been determined.

We report the case of a patient without BRCA mutations who developed primary peritoneal serous carcinoma (PPSC) after STIC was incidentally found during non-prophylactic surgery. We also discus optimal management after STIC is incidentally found in patients without BRCA mutations.

Case Report

In May 2014, a 62-year-old woman presented with an abnormal pap smear (ASC-H), which was performed at an outpatient department. She was otherwise healthy, without family or past history of ovarian and/or breast cancer. Upon pelvic examination, she had a normal bimanual examination without tenderness or palpable masses. Transvaginal and abdominal ultrasound scans were unremarkable. She underwent vaginal wall biopsy and endocervical curettage, which revealed vaginal wall and cervix intraepithelial neoplasia 3. The tumor marker cancer antigen-125 (CA125) was present at a concentration of 17.5 U/ml. Laparoscopic total hysterectomy, including an upper vagina and bilateral salpingo-oophorectomy, was performed. Intraoperatively, the appearance of the abdomen, pelvis, and both adnexa were unremarkable. Peritoneal washing cytology was not performed. The patient had an uneventful postoperative course and was discharged on postoperative day 3. Postoperative histopathologic examination revealed carcinoma *in situ* of the cervix, and, incidentally, STIC of both the fallopian tubes. Tumor cells showed hyperchromatic nuclei and nuclear pleomorphism (Figure 1A). In addition, there was strong positive reactivity for p53 (Figure 1B) and an increased proliferative index, as seen with Ki-67 immunostaining (Figure 1C). Both ovaries were free of tumors.

These results were discussed with the patient and she decided on, from among several management options, close follow-up every 6 months with a pap smear, pelvic examination, ultrasonography, and CA125. Ten months after the initial operation, CA125 levels were elevated to 96.3 U/ml and no ascites was found on ultrasonography. Further evaluation was strongly recommended, but the patient refused.

Eleven months later, she presented at the emergency center with severe epigastric pain, and computed tomography revealed peritoneal carcinomatosis and left ureter obstruction. CA125 levels had increased to 556.3 U/ml. The patient underwent open laparotomy with deperitonealization, total omentectomy, and systemic pelvic and para-aortic lymphadenectomy.

The pathology exam reported high-grade serous carcinoma (Figure 2), but BRCA1 and BRCA2 mutations were not

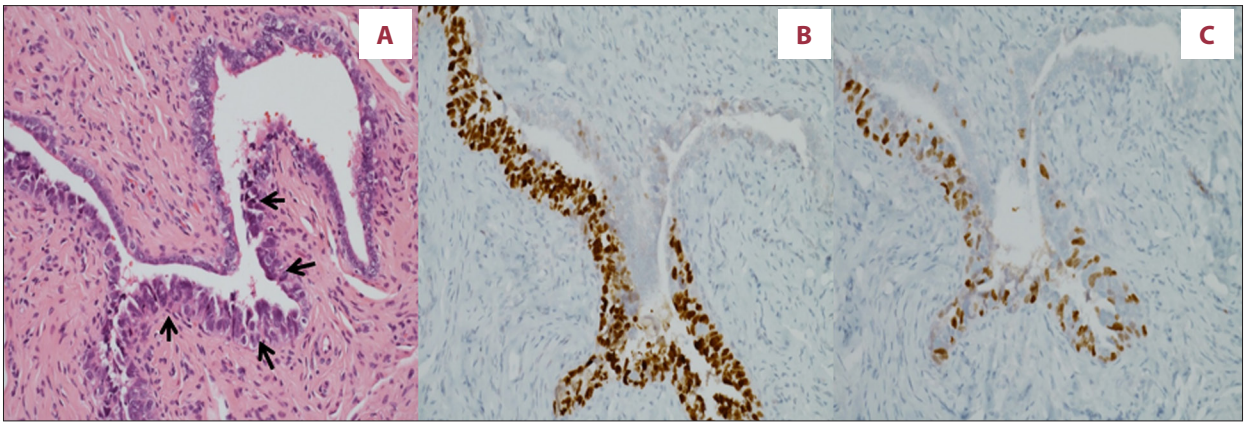

Figure 1. H&E staining of the distal end of the left fimbriae revealed serous tubal intraepithelial carcinoma (**A**). Tumor cells showed hyperchromatic nuclei and nuclear pleomorphism (arrow). There was a strong positive reactivity for p53 (**B**) and an increased proliferative index, as seen with Ki-67 immunostaining (**C**).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

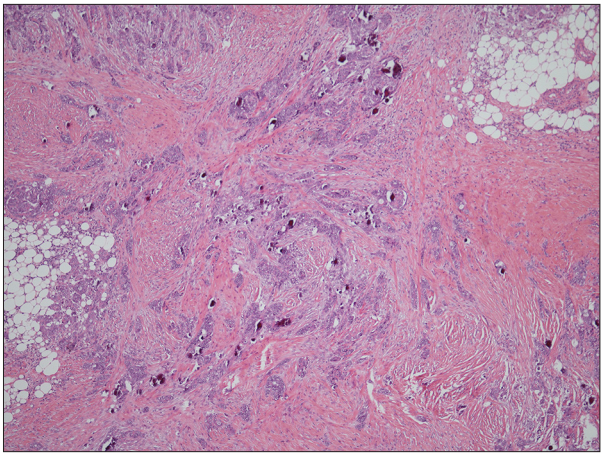

Figure 2. H&E staining of the omentum showed tumor cells with high-grade nuclear atypia and psammomatous calcification, consistent with the high-grade serous carcinoma.

detected. She commenced adjuvant chemotherapy with paclitaxel/carboplatin and bevacizumab as per the standard management of serous high-grade ovarian carcinoma.

Discussion

Serous tubal intraepithelial carcinoma (STIC) was first found in the distal part of fallopian tubes in patients with BRCA mutations had undergone prophylactic risk-reducing salpingo-oophorectomy (RRSO) [7]. For diagnosis of STIC, a combination of morphologic features and immunohistochemical analysis of p53 expression and proliferative activity as assessed by Ki-67 labeling index is necessary. Morphologic features include nuclear enlargement, nuclear rounding, marked nuclear pleomorphism, nuclear molding, hyperchromasia and/or vesicular nuclei with prominent nucleoli, stratification (>2 cell layers), 1 or more mitotic figures, and apoptotic bodies [8,9]. It has been proposed as a precursor of high-grade pelvic serous carcinoma arising in the distal fimbriae of the fallopian tube, but the clinical significance remains unclear. A mechanism detailing how STIC leads to invasive serous carcinoma also has not been defined. However, it has been suggested that cells may fall through the open lumen of the fallopian tube toward the peritoneal cavity. Exfoliated cells may then implant on the ovaries and peritoneal surface and develop into PPSC.

The incidence of STIC has primarily been studied in patients with BRCA mutations or a strong family history of breast or ovarian cancer who have undergone RRSO, and is estimated to be in the range of 0.6% to 6% [4,10,11]. The prevalence of STIC among the general population is unknown. Rabban et al. [12] performed a pathologic evaluation of the fallopian tubes of women at low risk for hereditary breast and ovarian cancer undergoing benign gynecologic surgery; STIC lesions were identified in 3 out of 522 cases (0.76%) and none of them had BRCA mutations. Morrison et al. [13] reported on isolated STIC patients (7/32 patients) but did not describe their BRCA status.

There are a few published studies on the clinical significance and prognosis of patients diagnosed with incidental STIC; however, there is no standard management for these patients. The recommendations for further management have included surgical staging, chemotherapy, and observation/surveillance only. Patrono et al. [14] performed a comprehensive review of clinical outcomes and management in patients with incidental isolated STIC. This study included 103 patients with STIC who were diagnosed from February 2006 to October 2016. The median age for was 53.7 years (range, 37–83). In 80 cases, the STIC lesion was found in patents who underwent RSSO due to BRCA mutations or who had a high-risk personal or family history. In the remaining 23 cases, STIC was detected incidentally after surgery for non-cancerous conditions. The prevalence of "isolated" STIC was 2% and the risk of PPSC in patients with BRCA mutations or high-risk factors was 7.5%. They recommended prompt BRCA mutation screening after diagnosis of STIC because the diagnosis of STIC was associated with the presence of BRCA mutations. Van der Hoeven et al. [6] also reported the outcome and prognostic impact of surgical staging in STIC. They reported that staging procedures were described in 13 out of 82 (16%) patients with isolated STIC undergoing RRSO. The results of peritoneal washing cytology at initial RRSO were positive in 3 out of 13 (23%) patients who underwent staging after an initial diagnosis of STIC. Even though the extent of the staging procedures were not clearly defined, none of the staging procedures reported metastatic or more advanced disease. The estimated risk of recurrence in patients with isolated STIC undergoing RRSO was about 11% after a median follow-up of 42 months. No recurrences were reported in patients with STIC at RRSO who underwent staging or received chemotherapy. Van der Hoeven et al. suggested that additional treatment after RRSO (i.e., staging and/or chemotherapy) was associated with a lower risk of recurrence, despite limited data. However, there were insufficient data to define the extent of the staging procedure and the necessity of reoperation after incidental STIC.

The clinical significance and adjuvant treatment of positive peritoneal cytology in patients with incidental isolated STIC remains undefined. Patrono et al. [7] reported that out of 7 patients with isolated STIC and positive peritoneal cytology, surgical staging was performed in 6 patients and no evidence of disease was found. The aggregate data reported by Wethington et al. [4] showed a 15% rate of positive peritoneal cytology at the time of RRSO. They suggested that peritoneal washing cytology should be done during RRSO. However, the relationship between positive cytology and prognosis was not

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

clearly defined. Van der Hoeven et al. [6] also recommended routine collection of peritoneal washing cytology at RRSO, but they concluded that positive cytology was not a predictor of metastasis or recurrence of disease.

Another question is whether chemotherapy should be recommended after an incidental finding of isolated STIC. In Patrono's review [14], after the diagnosis of isolated STIC, a total of 11 (13.8%) patients received chemotherapy due to positive cytology findings. Of interest, the authors noted that patients who ultimately developed PPSC had not received chemotherapy as an adjuvant treatment after the diagnosis of STIC. However, there is not enough evidence to support whether chemotherapy decreases the rate of PPSC.

Another management option for patients with isolated STIC is close follow-up, but at present there are no standard recommendations. Close follow-up does not guarantee early detection of PPSC and has not been demonstrated to improve survival [14].

Conclusions

To the best of our knowledge, this is the first published case report of a patient with isolated STIC without BRCA mutations who developed PPSC. The findings in our case, coupled with current evidence, suggest the distal fallopian tube as the source of PPSC. After an incidental diagnosis of STIC, we recommend surveillance for BRCA mutations. Standard management remains unclear, but further surgical evaluation and/or chemotherapy should be considered in patients with isolated STIC.

Conflict of interest

None.

References:

1. Poon C, Hyde S, Grant P et al: Incidence and characteristics of unsuspected neoplasia discovered in high-risk women undergoing risk reductive bilateral salpingooophorectomy. Int J Gynecol Cancer, 2016; 26: 1415–20
2. Reitsma W, de Bock GH, Oosterwijk JC et al: Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. Eur J Cancer, 2013; 49: 132–41
3. Sherman ME, Piedmonte M, Mai PL et al: Pathologic findings at risk-reducing salpingo-oophorectomy: Primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol, 2014; 32: 3275–83
4. Wethington SL, Park KJ, Soslow RA et al: Clinical outcome of isolated serous tubal intraepithelial carcinomas (STIC). Int J Gynecol Cancer, 2013; 23: 1603–11
5. Zakhour M, Danovitch Y, Lester J et al: Occult and subsequent cancer incidence following risk-reducing surgery in BRCA mutation carriers. Gynecol Oncol, 2016; 143: 231–35
6. Van der Hoeven NMA, Van Wijk K, Bonfrer SE et al: Outcome and prognostic impact of surgical staging in serous tubal intraepithelial carcinoma: A cohort study and systematic review. Clin Oncol (R Coll Radiol), 2018; 30: 463–71
7. Patrono MG, Iniesta MD, Malpica A et al: Clinical outcomes in patients with isolated serous tubal intraepithelial carcinoma (STIC): A comprehensive review. Gynecol Oncol, 2015; 139: 568–72
8. Visvanathan K, Vang R, Shaw P et al: Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features: A reproducibility study. Am J Surg Pathol, 2011; 35: 1766–75
9. Vang R, Visvanathan K, Gross A et al: Validation of an algorithm for the diagnosis of serous tubal intraepithelial carcinoma. Int J Gynecol Pathol, 2012; 31: 243–53
10. Finch A, Shaw P, Rosen B et al: Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol, 2006; 100: 58–64
11. Manchanda R, Abdelraheim A, Johnson M et al: Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG, 2011; 118: 814–24
12. Rabban JT, Garg K, Crawford B et al: 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; 38: 729–42
13. Morrison JC, Blanco LZ Jr., Vang R, Ronnett BM: Incidental serous tubal intraepithelial carcinoma and early invasive serous carcinoma in the nonprophylactic setting: Analysis of a case series. Am J Surg Pathol, 2015; 39: 442–53
14. Patrono MG, Corzo C, Iniesta M, Ramirez PT: Management of preinvasive lesions. Clin Obstet Gynecol, 2017; 60: 771–79

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]