



Long-term recurrence-free survival of a patient with advanced pure primary ovarian squamous cell carcinoma treated with dose-dense paclitaxel combined with carboplatin

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We describe an extremely rare case of advanced pure primary ovarian squamous cell carcinoma (SCC), treated by adjuvant chemotherapy with dose-dense paclitaxel combined with carboplatin (dd-TC) plus the combination chemotherapy with irinotecan and cisplatin (CPT-P), with long-term recurrence-free survival. A 71-year-old woman complaining of lower abdominal pain was referred to our hospital and a 7-cm-diameter solid tumor was identified. She was diagnosed with a left ovarian tumor that was highly suspicious for malignancy based on ultrasonography, magnetic resonance imaging, and contrast-enhanced computed tomography. Bilateral salpingo-oophorectomy, low-anterior colon resection, and colostomy were performed. Intra- and post-operative histopathological diagnosis revealed International Federation of Gynecology and Obstetrics stage IIIc well-differentiated pure ovarian SCC. As adjuvant chemotherapy, 2 courses of dd-TC were administered, followed by 3 courses of CPT-P; the patient then underwent 4 additional courses of dd-TC. Both regimens were effective and there has been no recurrence or metastasis thus far in the 5 years since the operation.

Keywords: Ovarian neoplasms; Squamous cell carcinoma; Dose-dense therapy; Paclitaxel; Carboplatin

Introduction

Ovarian squamous cell carcinoma (SCC) is a rare entity with several reported etiologies, as follows: 1) malignant transformation of mature cystic teratoma (MCT); 2) differentiation from other ovarian neoplasms (e.g., Brenner tumor, endometrioid adenocarcinoma, and mixed mesodermal tumor); 3) development from ovarian endometriosis; 4) pure ovarian SCC; and 5) metastasis from other organs (e.g., uterine cervix, vagina, lung, esophagus, and neck). Prognosis of ovarian SCC is very poor, and as it worsens with clinical stage, it is especially poor in advanced cases. The present report describes a case of advanced-stage pure ovarian SCC treated by adjuvant chemotherapy with a total of 6 courses of dose-dense paclitaxel combined with carboplatin (dd-TC) and 3 courses of combination chemotherapy with irinotecan and cisplatin (CPT-P) after suboptimal surgery. Fortunately, the patient has maintained long-term recurrence-free survival up to this point. To our knowledge, this is the first reported case of a patient with

advanced ovarian SCC to maintain long-term recurrence-free survival for over 5 years.

Case report

A 71-year-old woman, para 2, with lower abdominal and back pain was referred to our hospital for the evaluation

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and treatment of pelvic cavity tumor that was identified at a nearby clinic. A solid tumor of the left ovary, 70×50 mm in diameter, was identified on transvaginal ultrasonography, magnetic resonance imaging (MRI), and contrast-enhanced computed tomography (CE-CT) (Fig. 1). The tumor seemed to adhere to the uterus and sigmoid colon, but no metastasis to distant organs or lymph nodes was identified. Uterine cervical and endometrial cancer screening demonstrated no evidence of abnormal cytology. Blood and urinary chemistry parameters were all within the normal range. Tumor markers for epithelial ovarian cancer were as follows: carbohydrate antigen (CA) 125, 61.1 U/mL; CA 19-9, 2.1 IU/mL; and carcinoembryonic antigen, 2.0 ng/mL. Upper and lower gastrointestinal tract endoscopy demonstrated no abnormal findings except for a

benign polyp of the colon.

Laparotomy revealed a left ovarian tumor, smaller than fist size, that was adherent to the uterus, peritoneum, rectum, and sigmoid colon. A small amount of ascites was identified and collected. Because of the severe adhesion to the vesico-uterine pouch and pouch of Douglas, due to peritonitis carcinomatosa, optimal surgery for ovarian cancer was thought to be impossible. We first resected the left ovarian tumor, then performed a right salpingo-oophorectomy. Histopathological examination of frozen sections during the operation showed SCC of the left ovary, and cytology of the ascites was positive for SCC. Low-anterior colon resection and colostomy were then performed because the sigmoid colon and its mesentery showed deep and widespread invasion by the carci-

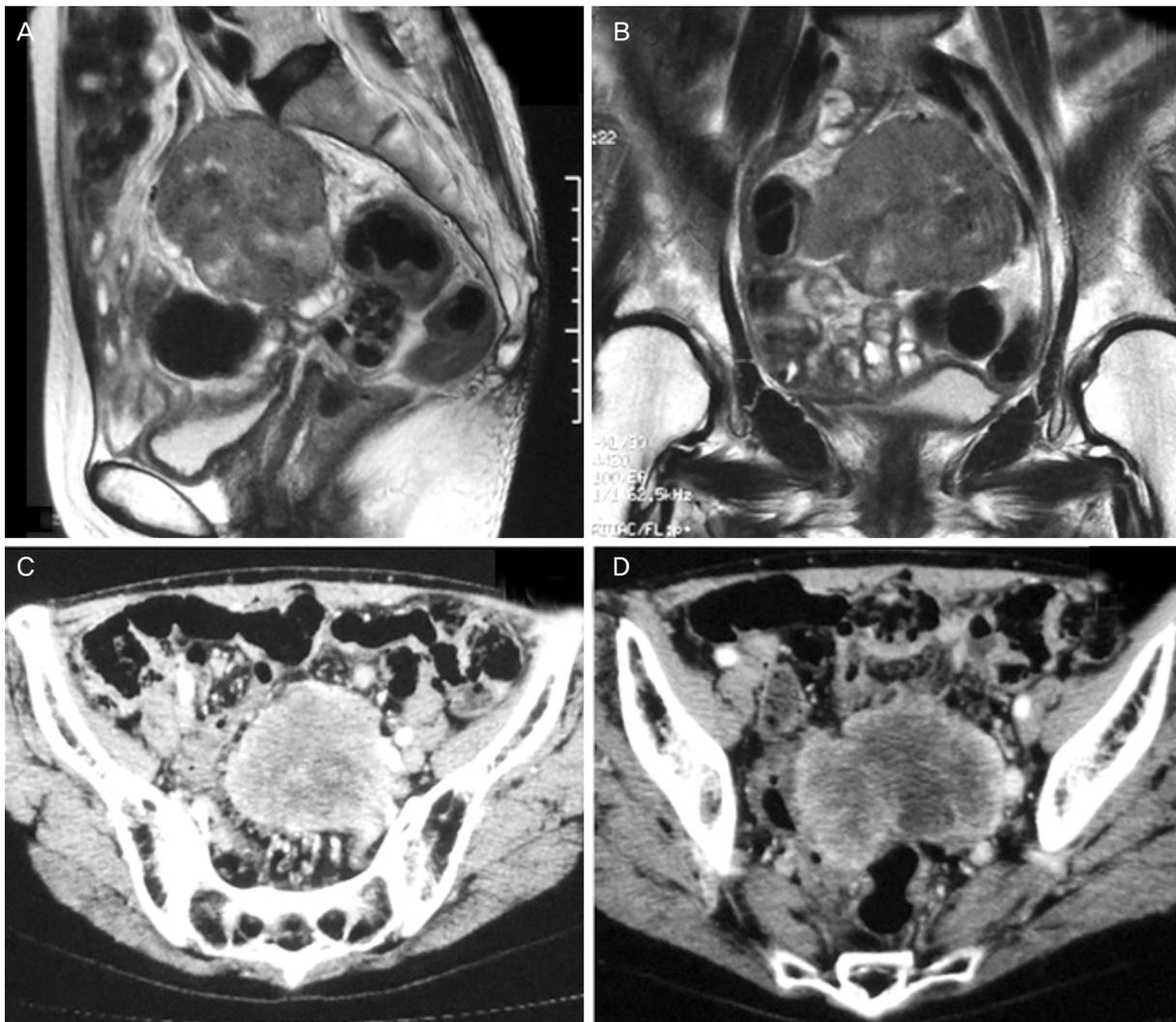


Fig. 1. Magnetic resonance (A-C) and contrast-enhanced computed tomography (D) images revealed a solid tumor of the left ovary, 70×50 mm in diameter. Malignancy and adhesion to the adjacent intestine were highly suspected.

noma, and preservation of these structures was judged to be impossible. There were no obvious tumors on the surfaces of the liver, diaphragm, or omentum in the upper abdomen, although there were some thin remnant tumors >2 cm in size clinging to the surfaces of the peritoneum and mesenterium after the tumor was removed.

The serum level of SCC antigen measured just after the operation was slightly elevated at 3.5 ng/mL. Post-operative histopathological diagnosis revealed well-differentiated SCC of the left ovary, with direct invasion into the submucosal layer of the sigmoid colon (Fig. 2). No other components, such as cystic teratoma, Brenner tumor, endometriosis, or endometrioid adenocarcinoma, were identified, although there was a small mucinous-adenoma-like component that displayed no evidence of differentiation to squamous epithelial cells. Based on these findings, the patient was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIIc pure primary ovarian SCC.

As the first-line adjuvant chemotherapy, 2 courses of dd-TC (paclitaxel, 80 mg/m² [Bristol-Myers Squibb Company, Princeton, NJ, USA] and carboplatin, area under the curve of 5 [Bristol-Myers Squibb Company]) were administered, followed by 3 courses of CPT-P (CPT-11, 48 mg/m² [Pharmacia & Upjohn, Inc., Peapack-Gladstone, NJ, USA] and cisplatin, 48 mg/m² [Bristol-Myers Squibb Company]). Then 4 additional courses of dd-TC were given. After 2 courses of dd-TC chemotherapy, the patient developed ileus that we suspected might be due to the progression of her disease. We therefore switched the regimen from dd-TC to CPT-P. The ileus was managed conservatively and no signs of recurrence were detected. After 3 courses of CPT-P, the patient developed renal dysfunction, and thus we changed the chemotherapy regimen from CPT-P back to dd-TC. Positron emission tomography-computed tomography (PET-CT) performed 10 months after the operation demonstrated no residual tumor, and complete response was considered to have been achieved. We periodically evaluated

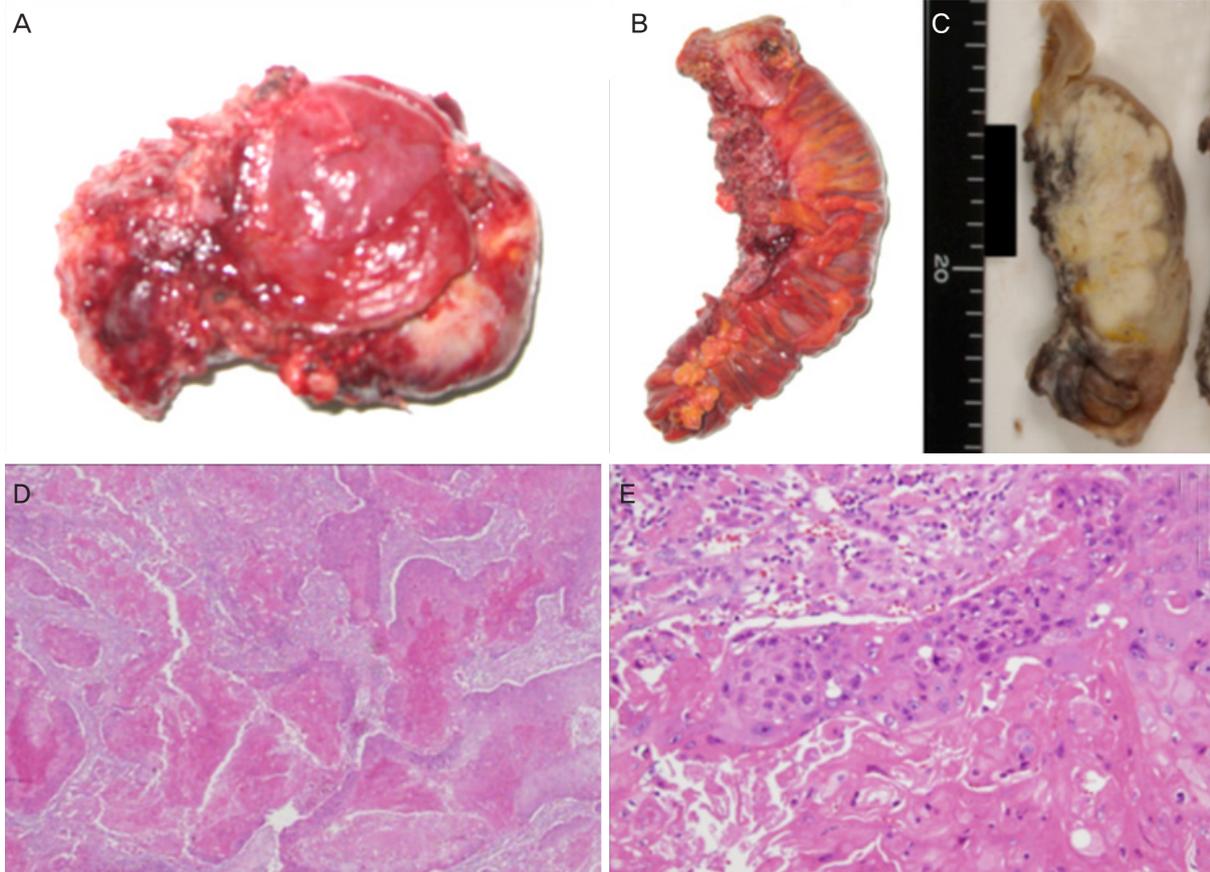


Fig. 2. Macroscopic findings of the left ovary (A) and sigmoid colon (B). Squamous cell carcinoma (SCC) directly invaded the submucosal layer of the sigmoid colon (C). Histopathologic findings of the left ovarian tumor (D, E) (objective magnification $\times 4$ and $\times 20$) revealed well-differentiated pure ovarian SCC.

the status of the patient's disease during and after chemotherapy by imaging and tumor marker measurements, with no signs of SCC recurrence at the time of this writing.

Three years after the operation the patient developed breast cancer, and left mastectomy and sentinel lymph node biopsy were performed at the Department of Surgery of the Fukushima Medical University Hospital. Post-operative histopathological diagnosis revealed invasive ductal carcinoma, papillotubular carcinoma of the left breast, T1cN0M0 stage I primary breast cancer. Pre-operative PET-CT revealed no abnormalities except for the tumor of the left breast, thus confirming the absence of any recurrences of ovarian SCC. Since the breast cancer operation, the patient has been treated with the molecular-targeted agent trastuzumab (Genentech, Inc., South San Francisco, CA, USA).

The patient has been free from recurrence of ovarian SCC for over 5 years since her first ovarian surgery, as determined by extensive evaluations including transvaginal ultrasonography, CE-CT, PET-CT, uterine cervical and endometrial cytology, and tumor marker measurements.

Discussion

Primary ovarian SCC is a rare disease with a very poor prognosis, especially in advanced-stage cases [1]. In our case, although the patient was diagnosed with FIGO stage IIIc advanced ovarian cancer with peritonitis carcinomatosa, she has achieved recurrence-free survival of over 5 years since the initial operation. Although her surgery was suboptimal for ovarian cancer because of severe adhesions in the pelvic cavity, adjuvant chemotherapy with a total of 6 courses of dd-TC and 3 courses of CPT-P was highly effective and resulted in long-term complete response. After 2 courses of dd-TC, ileus occurred but it was successfully managed with conservative treatment. Because we suspected progressive disease at that time, the chemotherapy regimen was changed from dd-TC to CPT-P, although in fact no signs of progressive disease could be identified by later imaging studies or tumor marker measurements. After 3 courses of CPT-P, the patient developed renal dysfunction; thus, we changed the chemotherapy regimen from CPT-P back to dd-TC, as the latter had earlier been considered to be clinically effective. After the first course of this second phase of dd-TC chemotherapy, fever with bone marrow suppression was observed; therefore, the doses were

reduced (paclitaxel, 60–70 mg/m²; carboplatin, area under the curve of 4). We did not perform a second debulking surgery during or after chemotherapy, for several reasons: no remnant tumor was detected by imaging, the surgery would be difficult due to the patient's colostomy, and primarily because she did not desire it.

Most cases of primary ovarian SCCs arise from MCT, although rare cases originate from endometriosis, Brenner tumor, or mucinous adenocarcinoma. MCT is one of the most common benign ovarian tumors, with an incidence of malignant transformation estimated at 1%–2% [2,3]. SCC is the most common transformation, although adenocarcinoma, sarcoma, and carcinoid have also been rarely reported [3]. The prognosis of SCC arising from MCT is strongly dependent on surgical stage. Kikkawa et al. [4] reported that the 5-year survival rate was 95% for stage I patients and 80% for stage II patients, but 0% for stage III and IV patients. Fortunately, over 60% of SCC arising from MCT are identified at stage I or II, because in many cases suspicious morphological changes are detected in MCT during follow-up, resulting in early discovery of malignant transformations. Such transformations are also occasionally identified during the post-operative pathological examination of resected MCT tumors that were considered to be benign.

Recently, the incidence of ovarian carcinoma arising from endometrial cysts was reported as 0.7% by Kobayashi et al. [5]. The most frequent neoplasms arising from ovarian endometriosis are clear cell adenocarcinoma or endometrioid adenocarcinoma, and only rarely SCC [5,6]. The prognosis of SCC arising from ovarian endometriosis is poor because such patients are more likely to have advanced disease at diagnosis (stage III or IV) than patients with MCT. Although a few studies have reported the efficacy of chemotherapeutic regimens such as paclitaxel-cisplatin [7] or weekly paclitaxel-carboplatin [8], there is currently no established effective therapy.

Pure ovarian SCC is extremely rare, with just over 30 reported cases, and its prognosis depends on its clinical stage. The prognosis of patients with advanced-stage disease (stage III or IV) is extremely poor, and most die within 1 year regardless of surgical outcomes or adjuvant chemotherapy regimens [1,9]. There is no evidence that radiation therapy improves survival, and also no established effective chemotherapy regimen [1,9]. The literature contains only 2 case reports of pure ovarian SCCs that responded to adjuvant chemotherapy. One case was treated with weekly paclitaxel combined with carboplatin (TC) [10] and the other with weekly irinotecan [11]; respon-

siveness was maintained for up to 19 and 18 months, respectively. The pathogenetic mechanisms of pure ovarian SCC are unclear. Park et al. [12] posited a relationship between ovarian SCC and human papilloma virus infection, because 11 of 27 patients with ovarian SCC had cervical carcinoma in situ, cervical intraepithelial neoplasia, or vulvar intraepithelial neoplasia [13]. Shimamatsu et al. [14] estimated that the malignant transformation from squamous metaplasia of ovarian epithelial inclusion cysts is one of the causes of ovarian SCC.

Recently, a phase III study performed by the Japanese Gynecologic Oncology Group (JGOG) demonstrated the superiority of dd-CT over TC for stage II–IV epithelial ovarian carcinoma (JGOG3016) [15]. The regimen prolonged both progression-free survival and overall survival in patients with serous or endometrioid adenocarcinoma, although it did not prolong overall survival for clear cell adenocarcinoma or mucinous adenocarcinoma [15]. CPT-P chemotherapy was proven effective for refractory or recurrent ovarian cancer, with an overall response rate of 40% [16]. Although it was unclear whether these regimens would be effective against the SCC of our patient, we selected dd-TC as the first-line chemotherapy and CPT-P as a temporary second-line chemotherapy, and fortunately both regimens performed well in our case.

In conclusion, we report a case of pure ovarian SCC that remarkably responded to adjuvant chemotherapy with dd-TC and CPT-P. To our knowledge, this is the first reported case of a patient with advanced ovarian SCC to maintain long-term recurrence-free survival for over 5 years. Due to the rarity of ovarian SCC, it may be difficult to establish standard treatment protocols by performing randomized trials. We hope that this report will be useful in terms of accumulating cases with positive responses to ovarian SCC in order to establish effective treatment regimens in the future.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Pins MR, Young RH, Daly WJ, Scully RE. Primary squamous cell carcinoma of the ovary. Report of 37 cases.

Am J Surg Pathol 1996;20:823-33.

2. Stamp GW, McConnell EM. Malignancy arising in cystic ovarian teratomas. A report of 24 cases. *Br J Obstet Gynaecol* 1983;90:671-5.

3. Rekhi B, Parikh P, Deodhar KK, Menon S, Maheshwari A, Kerkar R, et al. Squamous carcinoma coexistent with teratoma of ovary: a clinicopathological study of 12 cases diagnosed over a 10-year period at a tertiary cancer referral center. *J Cancer Res Ther* 2015;11:211-5.

4. Kikkawa F, Nawa A, Tamakoshi K, Ishikawa H, Kuzuya K, Suganuma N, et al. Diagnosis of squamous cell carcinoma arising from mature cystic teratoma of the ovary. *Cancer* 1998;82:2249-55.

5. Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, et al. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. *Int J Gynecol Cancer* 2007;17:37-43.

6. Yamakawa Y, Ushijima M, Kato K. Primary squamous cell carcinoma associated with ovarian endometriosis: a case report and literature review. *Int J Clin Oncol* 2011;16:709-13.

7. Eltabbakh GH, Hempling RE, Recio FO, O'Neill CP. Remarkable response of primary squamous cell carcinoma of the ovary to paclitaxel and cisplatin. *Obstet Gynecol* 1998;91:844-6.

8. Ohtani K, Sakamoto H, Masaoka N, Shimada K, Kanada T, Kurihara M, et al. A case of rapidly growing ovarian squamous cell carcinoma successfully controlled by weekly paclitaxel-carboplatin administration. *Gynecol Oncol* 2000;79:515-8.

9. Park JW, Bae JW. Pure primary ovarian squamous cell carcinoma: a case report and review of the literature. *Oncol Lett* 2015;9:321-3.

10. Maruyama T, Sakai K. A case report of pure primary squamous cell carcinoma of the ovary. *Jpn J Gynecol Oncol* 2009;27:69-75.

11. Nakamura Y, Kamei T, Shinagawa M, Sakamoto Y, Miwa I. Case of pure ovarian squamous cell carcinoma resistant to combination chemotherapy with paclitaxel and carboplatin but responsive to monotherapy with weekly irinotecan. *J Obstet Gynaecol Res* 2015;41:809-12.

12. Park JY, Song JS, Choi G, Kim JH, Nam JH. Pure primary squamous cell carcinoma of the ovary: a report of two cases and review of the literature. *Int J Gynecol Pathol*

- 2010;29:328-34.
13. Mai KT, Yazdi HM, Bertrand MA, LeSaux N, Cathcart LL. Bilateral primary ovarian squamous cell carcinoma associated with human papilloma virus infection and vulvar and cervical intraepithelial neoplasia. A case report with review of the literature. *Am J Surg Pathol* 1996;20:767-72.
 14. Shimamatsu K, Iemura A, Nakashima O, Taguchi J, Inoue M, Higaki K, et al. Squamous cell carcinoma of the ovary--a case report. *Kurume Med J* 1994;41:177-82.
 15. Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:1331-8.
 16. Sugiyama T, Yakushiji M, Nishida T, Ushijima K, Okura N, Kigawa J, et al. Irinotecan (CPT-11) combined with cisplatin in patients with refractory or recurrent ovarian cancer. *Cancer Lett* 1998;128:211-8.