Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 609–612

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Research Letter

Primary serous tubal intraepithelial carcinoma with multiple lymph node metastases

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ARTICLE INFO

Article history:
Accepted 18 December 2014

Dear Editor,

A 53-year-old, gravida 2, para 1, woman with no history of major systemic disease, presented to our clinic with a painless right neck mass, which she had noticed 2–3 months previously. She received a health examination and elevated CA-125 level (513 Unit/mL) was found. She then underwent a positron emission tomography–computed tomography (PET/CT) scan, which revealed suspected metastatic lymphadenopathy, including para-aortic, pericaval, and subaortic lymph nodes of the abdomen [maximum standardized uptake value (SUVmax): 6.1], bilateral iliac lymph nodes (SUVmax: 11.1), and right supraclavicular lymph nodes (SUVmax: 7.6) (Figure 1). She visited our ear, nose, and throat clinic and a nodule ~1 cm in diameter over the right side supraclavicular region was found, so excisional biopsy was performed. The pathology revealed metastatic adenocarcinoma, moderately to poorly differentiated; immunohistochemistry stain disclosed CK7 (+), CK20 (−), TTF-1 (−), WT-1 (+) of suspected gynecologic origin.

She was then referred to our obstetrics and gynecology clinic. Bimanual examination revealed a normal-sized uterus and bilateral free adnexa without palpable mass. Ultrasonography only showed small uterine myoma.

Laboratory tests, including a blood cell count, biochemistry, and chest x-ray were all within normal limits, but the CA-125 level was 409 (Unit/mL). Abdominopelvic and chest CT scans were performed, which also revealed multiple retroperitoneal lymph nodes, compatible with the finding of the PET/CT scan. There was no evidence of mediastinal metastasis.

Under the impression of ovarian high grade serous carcinoma with multiple lymph node metastases, the patient then underwent a debulking operation, including total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, para-aortic lymph node sampling, appendectomy, and omentectomy. The size of the uterus was normal with multiple small uterine myomata. On cutting, no obvious endometrial tumor was found. Bilateral ovaries and fallopian tubes were grossly normal. Enlarged, fixed, and firm lymph nodes were found over the bilateral external obturator, common iliac, presacral, precaval, and para-aortic areas up to the level of the renal veins. The largest one measured ~12 × 3 × 3 cm in size (Figure 2). The other pelvic or peritoneal surfaces, including the omentum, large and small intestines, liver, and diaphragm, were free of tumor. There was no ascites, and the appendix looked normal. As there was no gross residual tumor, the procedure was designated as complete debulking. The final pathological diagnosis was primary serous tubal intraepithelial carcinoma (serous carcinoma *in situ*) of the left fallopian tube (Figures 3A and 3B) with multiple lymph node metastases (Figures 4A–4C); the vagina cut end, cervix, uterus, bilateral ovaries, and right fallopian tube were free of tumor.

The patient's stage was assessed as International Federation of Gynecology and Obstetrics (2010) Stage IV. After the first postoperative week, the patient received six consecutive courses of

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http://dx.doi.org/10.1016/j.tjog.2016.06.010

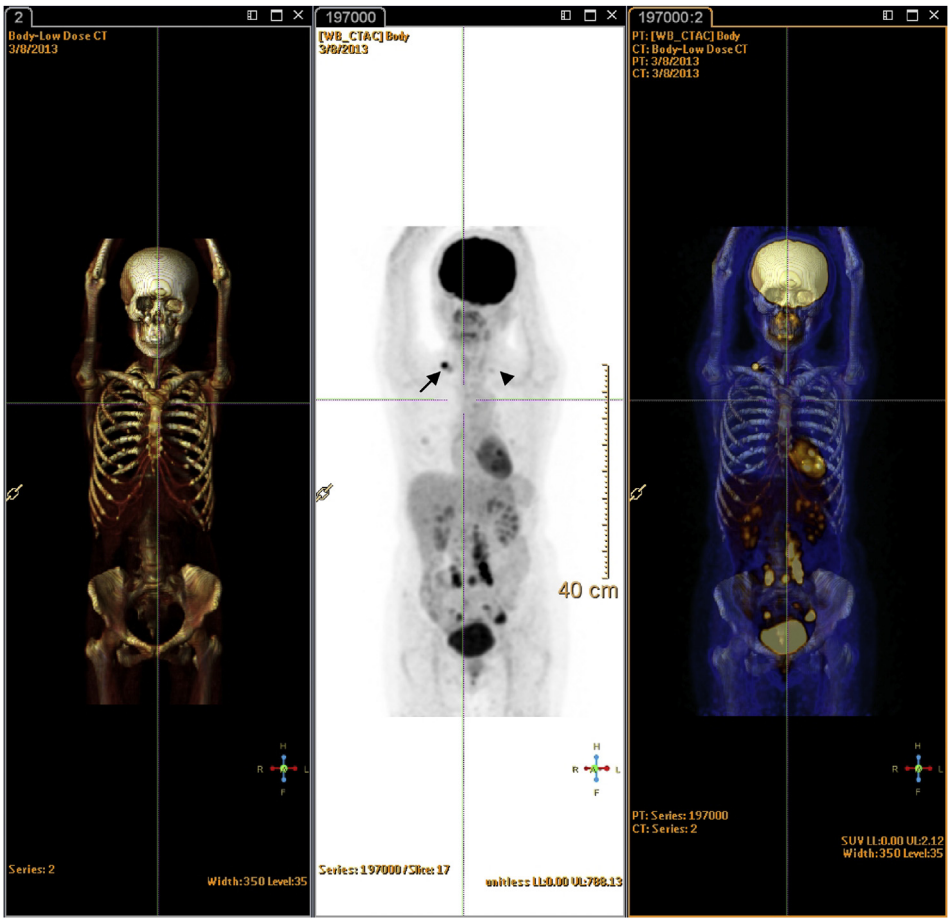

Figure 1. Whole body PET/CT scan. Anterior projection image of PET/CT scan with F-18 fludeoxyglucose (FDG) showed increased FDG activity at the para-aortic, pericaval, and subaortic of abdomen, the bilateral iliac, and the right supraclavicular regions (arrow), indicating metastatic lymphadenopathy. In addition, a metastatic lymph node at the left supraclavicular region was also suspected (arrow head). CT = computed tomography; PET = positron emission tomography.

chemotherapy, consisting of 175 mg/m2 paclitaxel (Taxol, Bristol-Myers Squibb, Wallingford, CT, USA) and carboplatin (Paraplatin, Bristol-Myers Squibb, Princeton, NJ, USA) with an area under the curve of 5 mg/mL/min, administered at 3-week intervals. The patient received regular follow-up at our clinic with pelvic examinations, CA-125 monitoring, chest x-rays, and abdominopelvic CT scans and has been disease-free for ~17 months since surgery.

Serous tubal intraepithelial carcinoma (STIC) presents as a noninvasive, serous carcinoma in the fallopian tube. Besides strong overexpression of p53 mutations, STIC is characterized by increased nuclear/cytoplasmic ratio, enlarged nuclear pleomorphism with prominent nucleoli, and lack of cell polarity without ciliated cells. Lesions with strong p53 expression and less severe atypia are termed serous tubal intraepithelial lesions or low-grade serous tubal intraepithelial neoplasia. Further investigation is needed to differentiate these two atypias from STIC [1,2].

The diagnosis of STIC mainly derives from the pathologic findings of BRCA gene germline mutation carriers who have received risk-reducing salpingo-oophorectomy and the short-term outcome is favorable [2]. Accumulating evidences, based on histology, immunohistochemistry, and molecular changes, indicate that STIC may be the precursor of pelvic high grade serous carcinoma. One of the most important useful markers for STIC is p53, a protein which encoded by the *TP53* gene. It is reported that the mutations of *TP53* gene occur in 96% of pelvic high grade serous carcinoma [3]. In addition to manifestation of p53 mutations, PAX8, a Müllerian marker, is also expressed in ovarian serous carcinoma [4]. Strong expression of p53 and PAX8 of lymph node in this case suggested that STIC is the source of pelvic high grade serous carcinoma.

It has been reported that pelvic high grade serous carcinoma usually presents at an advanced stage, grows rapidly and has poor prognosis. Approximately 10–15% of STIC lesions were detected in BRCA mutation carriers or in patients with a strong history of ovarian cancer who received risk-reducing salpingo-oophorectomy [5]. Besides, a coexisting STIC was found in ~50–60% of sporadic pelvic high grade serous carcinomas [5]. It is proposed that the tumor cells from *in situ* lesions may shed to the ovaries and the surrounding pelvic area, then finally turn malignant [1,5,6]. However, no direct evidence of the mechanism of STIC progression to invasive serous carcinoma has been reported. Since carcinoma *in situ* has no contact with blood vessels, the question of whether *in situ* carcinomas have the ability to shed tumor cells into the blood circulation is still unclear. It is known that the most common type of preinvasive breast cancer is ductal carcinoma *in situ* (DCIS), in which malignant cells proliferate without invasion across the basement membrane. However, recent studies revealed that disseminated tumor cells may

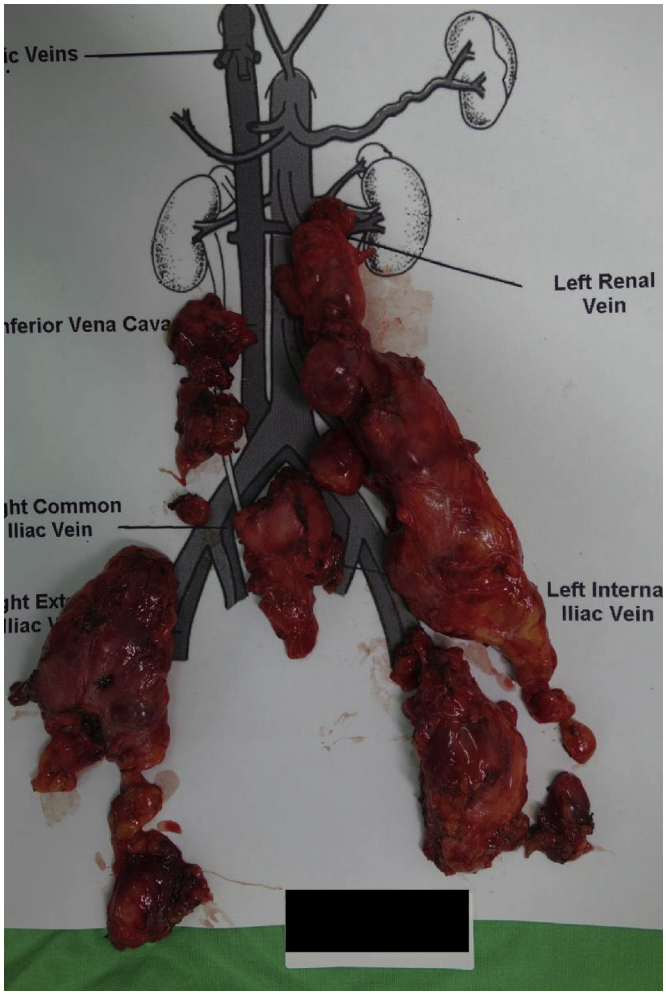

Figure 2. Operative finding. Enlarged, fixed, and firm lymph nodes over the bilateral external obturator, common iliac, presacral, precaval, and para-aortic areas up to the level of the renal veins. The largest one measured ~12 × 3 × 3 cm in size.

be detected in bone marrow or axillary lymph nodes of patients with DCIS [7,8].

The overall survival rate of ovarian cancer when treated in medical centers is 40–50% at 10 years, and the survival rate at Stage IV is less than 6% [6,9]. Our patient has been followed up regularly at our clinic for ~17 months without evidence of recurrence.

To the best of our knowledge, this is the first report of primary STIC with distal metastases but without pelvic serous carcinoma. This case provides further evidence that pelvic serous carcinoma

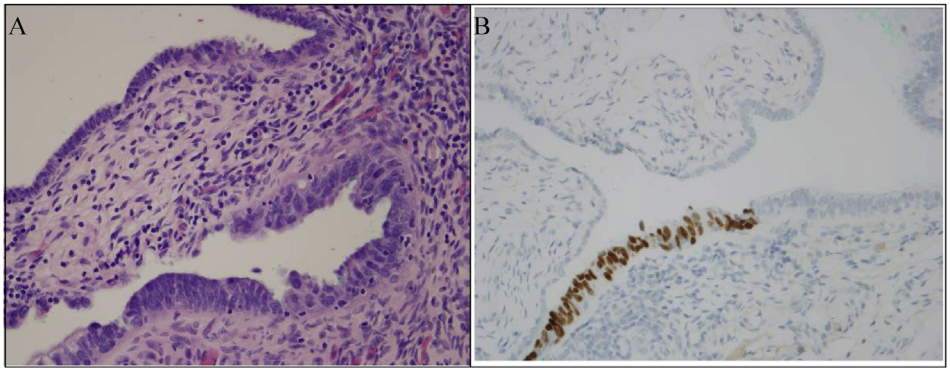

Figure 3. Serous tubal intraepithelial carcinoma (STIC) (400×). (A) 400× Hematoxylin and eosin stain shows that the tubal epithelium is stratified and nonciliated. It also discloses marked nuclear pleomorphism, increased nuclear/cytoplasmic ratio, prominent nucleoli, and loss of cell polarity; (B) strong immunohistochemical staining for p53 protein.

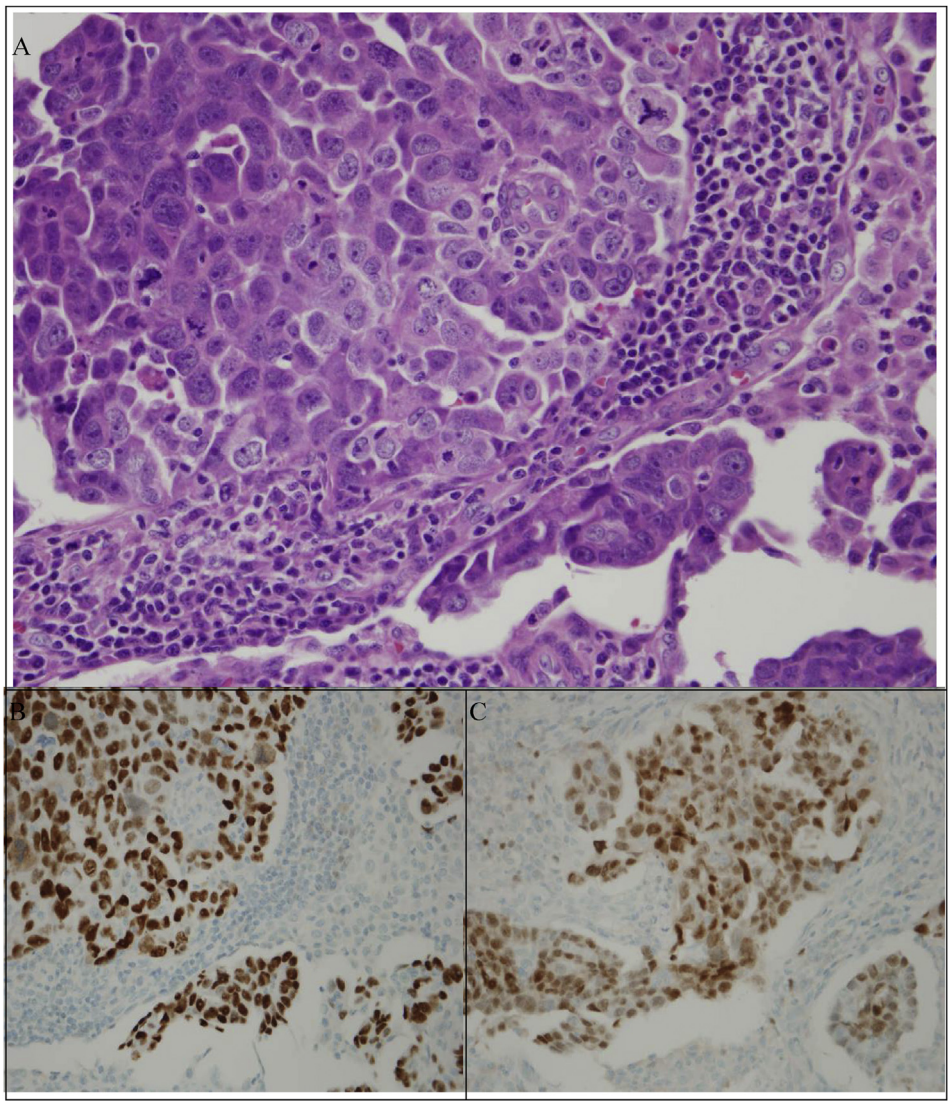

Figure 4. Metastatic adenocarcinoma in neck lymph node (400×). (A) 400× Hematoxylin and eosin stain shows metastatic adenocarcinoma with papillary and micropapillary pattern infiltrates in the neck lymph node; (B) strong immunohistochemical staining for p53 protein; and (C) PAX8 protein.

may originate from STIC. Physicians should always keep in mind that *in situ* carcinoma has the potential of distant metastasis.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Li HX, Lu ZH, Shen K, Cheng WJ, Malpica A, Zhang J, et al. Advances in serous tubal intraepithelial carcinoma: correlation with high grade serous carcinoma and ovarian carcinogenesis. Int J Clin Exp Pathol 2014;7:848–57.
[2] Wethington SL, Park KJ, Soslow RA, Kauff ND, Brown CL, Dao F, et al. Clinical outcome of isolated serous tubal intraepithelial carcinomas. Int J Gynecol Cancer 2013;23:1603–11.
[3] Bell D, Berchuck A, Birrer M, Chien J, Cramer D, Dao F, et al. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609–15.
[4] Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. Am J Surg Pathol 2010;34:433–43.
[5] Dietl J. Revisiting the pathogenesis of ovarian cancer: the central role of the fallopian tube. Arch Gynecol Obstet 2014;289:241–6.
[6] Erickson BK, Conner MG, Landen Jr CN. The role of the fallopian tube in the origin of ovarian cancer. Am J Obstet Gynecol 2013;209:409–14.
[7] Banys M, Hahn M, Gruber I, Krawczyk N, Wallwiener M, Hartkopf A, et al. Detection and clinical relevance of hematogenous tumor cell dissemination in patients with ductal carcinoma in situ. Breast Cancer Res Treat 2014;144:531–8.
[8] Osako T, Iwase T, Ushijima M, Horii R, Fukami Y, Kimura K, et al. Incidence and prediction of invasive disease and nodal metastasis in preoperatively diagnosed ductal carcinoma in situ. Cancer Sci 2014;105:576–82.
[9] Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet 22 April 2014. http://dx.doi.org/10.1016/S0140–6736(13)62146–7.