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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 543–545

www.tjog-online.com

Research Letter

Squamous cell carcinoma arising from an ovarian teratoma related to human papillomavirus infection: Using a PCR-based reverse-blot assay

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Accepted 31 January 2011

Ovarian teratoma is generally a benign disease but secondary malignant transformation within the tumor may take place in postmenopausal women in rare cases. Squamous cell carcinoma (SCC) accounts for approximately 80% of the malignant transformations [1]. A possible connection between SCC arising from an ovarian teratoma and human papillomavirus (HPV) infection was first published by Mai et al. [2]. To the best of our knowledge, there have only been four confirmed cases of the high-risk HPV type in ovarian SCC diagnosed using the HPV typing or staining method [2–5]. Here, we present the case of a woman of childbearing age diagnosed of ovarian teratoma with SCC malignant transformation. The polymerase chain reaction (PCR)-based reverse-blot assay, a highly specific method, showed no expression of HPV in the ovarian SCC but was positive in the cervix.

A 41-year-old woman, with gravida 1, para 1, had experienced lower abdominal pain for 1 week. Pelvic ultrasound showed bilateral ovarian teratomas measuring $7.0 \times 6.0 \times 5.4$ cm on the left side and $12.0 \times 8.7 \times 5.0$ cm on the right. She underwent a laparotomy with bilateral salpingo-oophorectomy in August 2009. Pathology proved mature cystic teratoma of the left ovary, but for the right side it indicated that there was a dermoid cyst with SCC transformation. Tumor markers, such as carcinoma embryonic antigen, cancer antigens 125 (CA125) and 199, SCC antigen, alpha-fetal protein and beta human chorionic gonadotropin, were normal. She subsequently underwent debulking surgery with extrafascial hysterectomy, para-aortic and pelvic lymph node dissection, and partial omentectomy in September 2009.

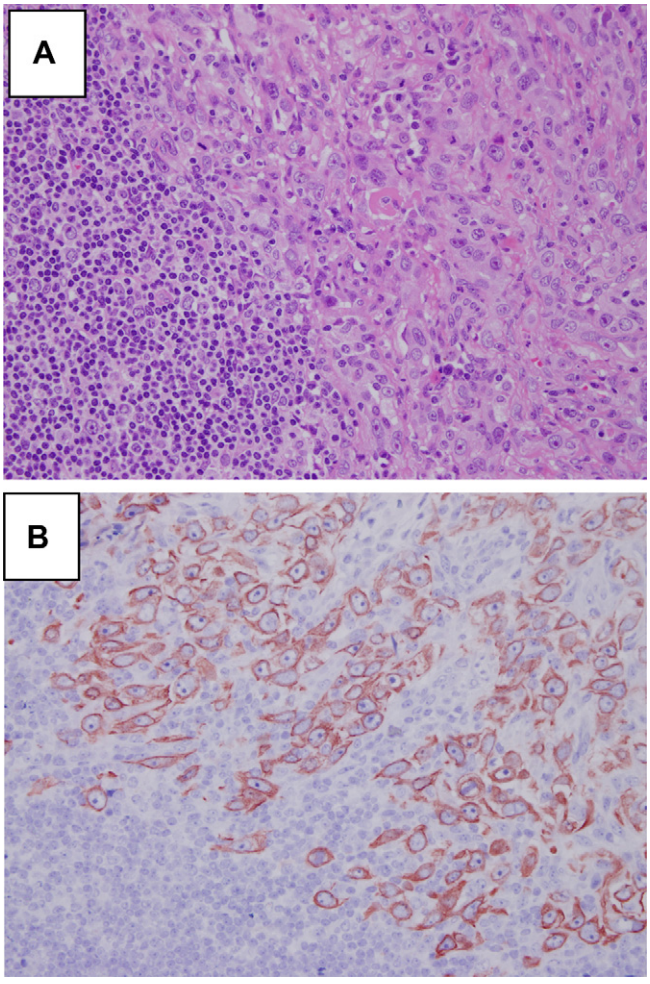

Fig. 1. Lymph node metastases from squamous cell carcinoma. (A) Microscopic sections of lymph node metastases (hematoxylin and eosin 400×). (B) Specific immunostaining is positive for tumor cells (Cytokeratin (CK) 400×).

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doi:10.1016/j.tjog.2011.10.029

The pathology revealed metastatic carcinoma of a para-aortic lymph node (Fig. 1) and no remarkable findings related to the cervix.

The pathologist took some tumor tissue sections from the formalin-fixed, paraffin-embedded (FFPE) tissue blocks of the cervix, the SCC transformation part of the dermoid cyst and the metastatic lymph node for laboratory analysis. We extracted the DNA and used the QIAamp® DNA FFPE Tissue Kit (Qiagen Inc., Venlo, The Netherlands) for further purification. After using PCR to amplify the HPV DNA in the specimen, the HPV PCR products were typed in reverse by using complementary hybridization probes to identify a broad range of genotypes (Easychip® HPV Genotyping Array, King Car, Taiwan) [6]. The cervix had type-11 HPV expression but the other two components failed to demonstrate the presence of any type of HPV (Fig. 2).

The patient had stage IIIc ovarian cancer, so she received adjuvant chemotherapy with cyclophosphamide and carboplatin between September 2009 and January 2010. Regular follow-up, however, showed an elevated SCC antigen level in March 2010. Before a complete study into the suspected ovarian cancer recurrence could take place, the patient died from the disease in April 2010, just 8 months after the diagnosis.

Germ cell tumors account for 20% of all ovarian tumors [7]. Most germ cell tumors are mature cystic teratomas that occur bilaterally in 10.8% of patients [8]. The proportion of mature cystic teratomas that undergo malignant transformation is 0.17% [8]. The secondary malignant transformation arising from an ovarian teratoma often takes time and is most commonly found in postmenopausal women, with the average age at diagnosis being 55 years [1]. It is assumed that pelvic exposure to several carcinogens over time may result in the malignant transformation of mature tissue [9]. SCC is the most common type of malignant transformation and accounts for approximately 80% of cases [1].

The well-known association between cervical SCC and HPV cannot be ignored in any discussion related to SCC of the genital tract. While ovarian SCC is rare, the prevalence of HPV infection and associated cervical SCC is high in sexually-active women. The worldwide prevalence of HPV without cervical pathology is around 10.4%. Regional variations exist and the prevalence of HPV in Asia is 8%. The five leading types of HPV are HPV 16, 18, 31, 58, and 52 [10]. HPV type

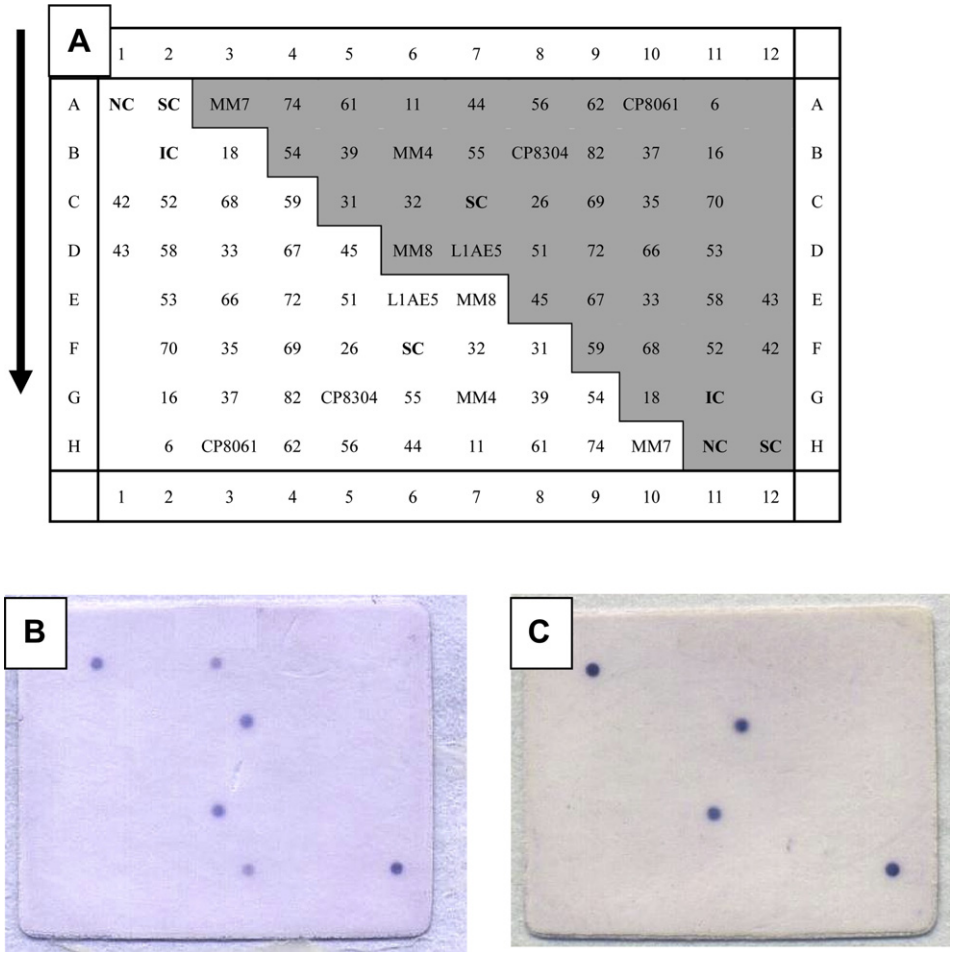

Fig. 2. Polymerase chain reaction-based HPV genotyping array. (A) Chip format of Easychip®. There are four systematic controls (SC), two internal controls (IC) and two negative controls (NC). (B) Light purple spots indicate HPV type 11 infection of the cervix. (C) Only the control spots shown on the plate indicated that the metastatic lymph nodes were negative for HPV infection.

distribution is different in Taiwan and Japan, with HPV 52 being the most common in Taiwan, followed by 16, 51, 35 and 18 [10]. There have been four cases where there has been a positive connection between ovarian SCC and HPV infection, where HPV was present in the ovarian SCC without invasive SCC of the cervix. Some authors concluded that the similarity of the squamous cells may result in HPV having the same carcinogenic effect, with HPV of the cervix reaching the upper genital tract by way of ascending infection [5]. There are also three reported cases that did not find the presence of HPV in ovarian SCC, where HPV staining or type-specific DNA hybridization only capable of detecting five types of HPV was used, yet cervical pathology showed positive HPV expression [11–13]. Mai et al. suggested that the low sensitivity of techniques may result in a failure to demonstrate the presence of HPV in ovarian SCC [2]. To improve of HPV typing and detection, we tried a modified MY11/GP6+ PCR-based reverse-blot array with a reported sensitivity of 96.8% and a type specificity of 91%. The cervix tissue showed expression of HPV 11, but the neoplastic tissues, including the ovarian SCC and the metastatic lymph node, showed no expression of HPV. It has been suggested that HPV may not have had an influence on the ovarian SCC in this case, although the high-risk HPV type for the region may be taken into consideration.

The staging system for mature cystic teratoma is currently the same as the International Federation of Gynecology and Obstetrics (FIGO) classification used for ovarian cancer. Surgical intervention, including hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy, is the mainstay for the disease. Adjuvant chemotherapy is indicated for patients with advanced disease. The chemotherapy regimens are different, however, from those used to treat immature teratoma and epithelial ovarian cancer. The treatment of choice for immature teratoma is a combination of bleomycin, etoposide and cisplatin. The recommended regimens for advanced epithelial ovarian cancer are carboplatin and paclitaxel [14]. For patients experiencing ovarian teratoma with malignant transformation, alkylating agents result in more than double the mean survival rate when compared to other cytotoxic drugs [1]. While the prognosis is fair for early disease, however, it is still poor in the advanced stage. The 5-year survival rates for stages I, II, III and IV disease are 95%, 80%, 0% and 0%, respectively [15].

SCC arising from an ovarian teratoma is rare and more evidence is needed for most effective treatment. The improved HPV typing method we used utilized HPV staining and some type-specific *in situ* hybridization to confirm the negative result for HPV infection of the ovarian SCC and positive result for the cervix. The response to treatment in this case was poor, despite complete surgery and chemotherapy with an alkylating agent for stage IIIc disease. We look forward to acquiring more information about this disease to contribute to our country database. A more complete database will lead to better diagnosis, staging and treatment.

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