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Case Report:

Liquid-based cytology aids in primary fallopian tube cancer diagnosis

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Abstract: Primary fallopian tube carcinoma (PFTC) is a rare malignant carcinoma among all genital tract malignancies. It occurs most commonly in postmenopausal women and is similar to ovarian malignancy historically and clinically. Because of its insidious onset and silent course, the diagnosis is made usually postoperatively. Liquid-based cytology (LBC) is a type of method for cervical cancer screening, but sometimes it may aid in making PFTC diagnosis. We report a 47-year-old woman with PFTC, whose diagnosis was made with the aid of LBC.

Key words: Primary fallopian tube carcinoma (PFTC), Liquid-based cytology (LBC), Diagnosis
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CASE REPORT

A 47-year-old woman had experienced menstrual disorder more than 10 months, and had colporrhagia for 1 month. Her usual menstruation was regular, with moderate amount and sometimes dysmenorrhoea. Since February 2007, her menstrual phase had extended for two weeks, but she did not receive any treatment. On August 23, because of abnormal menstruation, she was referred to our hospital, following a routine collection of cervical exfoliated cells for liquid-based cytology (LBC), which manifested atypical glandular cells suggesting endometrial carcinoma. These cells were arranged in berry-like three-dimensional clusters and had big heteromorphic nuclei (Fig.1a).

Her former LBC was normal. Then she immediately received the hysteroscopy, dilatation and curettage. The pathological result revealed that the glandular cells were assumed to be in the proliferative period. Fortunately, we could exclude the endometrium disease. In the end of August, the ultrasound showed a low echo-level occupier at the posterior wall of the uterus. In September, the computer tomography (CT) revealed that a soft tissue-like tumor grew along the surface at the left of the uterus, 2.5-cm in diameter, moderately reinforced, and some blood vessels around. In November, her menstruation lasted for more than 3 weeks, with lots of leucorrhea and abnormal flavour. In December, the ultrasound showed a 5-cm cystoid and a solid tumor at the left of the posterior uterus, and unclear peplos, inside of which there was blood-like signal. Meanwhile, the magnetic resonance imaging (MRI) manifested a 4.3-cm occupation at the left appendix region, which had an iso-signal and slight sublobe. Pelvic examination showed a normally-sized anteverted uterus, with a 4~5-cm sized mass at the left adnexal region, which was slightly tender. We concluded a malignant fallopian tube tumor lastly. The patient had salpingitis history. Moreover, her family members had various types of malignant tumors, including breast cancer, digestive apparatus cancer, and thyroid carcinoma.

On December 25th, she was received the laparotomy, which revealed that the uterus seemed to be normal and that the left appendix grew like a tumor, which adhered to the Douglas' space and the surface

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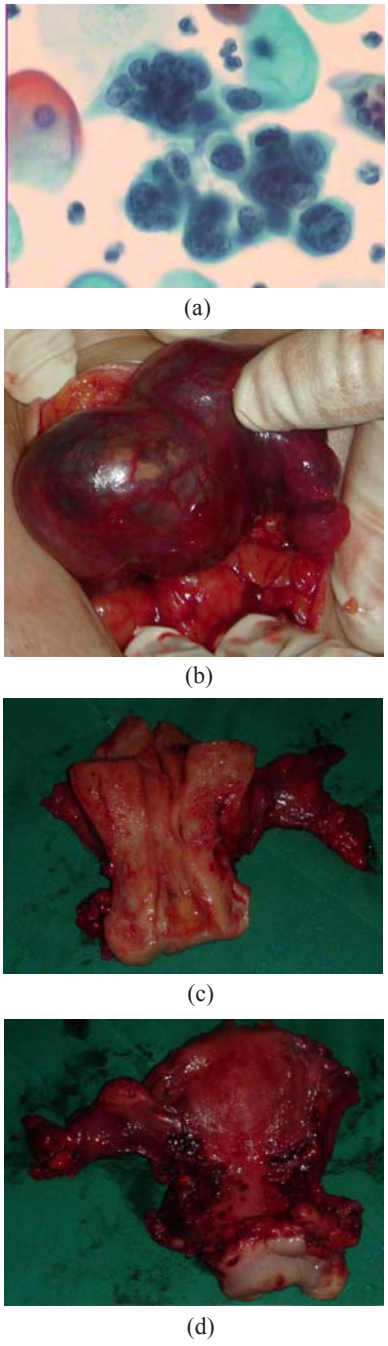
of the rectum (Figs.1b~1d). Following division of the adhesions, surgeons conducted a total greater omentum resection, the whole pelvic lymphadenectomy, and tumor cell clearance. The pathological results revealed transitional cell carcinoma of the left oviduct at stages II~III, and partly low differentiated serous carcinoma invading the whole layer of the oviduct wall, with the encroachment of the fibrofatty tissue of Douglas' space.



(a) (b) (c) (d)

Fig.1 (a) The atypical glandular cells; (b) The fallopian tube cancer profile; (c) Anterior wall of the specimen; (d) Posterior wall of the specimen

DISCUSSION

Primary carcinoma of the fallopian tube is a rare malignancy that accounts for 0.14%~1.80% of all genital tract malignancies (Gadducci *et al*., 2001). A total of 3051 primary fallopian tube carcinoma (PFTC) cases diagnosed and reported from population-based cancer registries from 1998 to 2003 were analyzed in USA, with the incidence rate at 0.41 per 100000 women. White, non-Hispanic women with age of 60~79 years had the highest incidence rate ($P<$ 0.0001). The majority (88%) of PFTCs were adenocarcinomas, of which serous adenocarcinomas accounted for 44% and endometrioid adenocarcinomas for 19% (Stewart *et al*., 2007).

PFTC occurs most commonly in postmenopausal women and is similar to ovarian malignancy histologically and clinically, with the mean age of patients at 55 years old (Pectasides *et al*., 2006). These women usually had infertile and nonparous history. PFTC shares the similar etiology with the ovary carcinoma. Parity was strongly protective and a higher number of deliveries increased the protection (Riska *et al*., 2007). The results of animal studies suggest that progestagen-induced apoptosis of transformed ovarian surface epithelial cells may underlie the observed protective effect of pregnancy on the risk of ovarian cancer (Rodriguez *et al*., 1998). The endosalpingeal lining of the fallopian tube is hormonally reactive and the higher levels of progestagens during pregnancy could lower the risk of PFTC by inducing apoptosis of transformed epithelial cells. And hysterectomy did not give protection against PFTC, but rather it increased the risk insignificantly (Riska *et al*., 2007). The increased risk of PFTC among hysterectomized women could be based on hormonal features, such as raised levels of follicle-stimulating hormone (FSH). High levels of gonadotrophins, mainly FSH, have been hypothesized to stimulate malignant transformation of ovarian epithelial cells and also fallopian tube epithelium in vitro. High concentrations of gonadotrophins may

induce vascular endothelial growth factor expression and accelerate tumor growth, at least in ovarian epithelial cells.

The literature reported that 70% PFTC patients have the chronic salpingitis history, and it was concluded that the chronic inflammation may be the important causative agent (Zhang, 2003). Furthermore, fallopian tube carcinoma should be considered to be a clinical component of the hereditary breast-ovarian cancer syndrome, and may be associated with breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) mutations (Aziz *et al*., 2001).

Nowadays, the collection of cervical exfoliated cells for LBC is the main cervical cancer screening method; especially, the dyskaryotic glandular cells have significant meanings. A retrospective study has showed that the yield for positive pap cervical smear diagnosis in extrauterine malignancies is the best in women with an established diagnosis of a primary neoplasm (Gupta and Balsara, 1999). It has been reported that the use of endometrial cytology and carbohydrate antigen 125 (CA125) measurements aid in the diagnosis (Benjamin *et al*., 2007). In a univariate Cox regression model, tumor stage and serum CA125 level were associated significantly with shortened disease-free survival (P=0.006 and P<0.001, respectively) and overall survival (P=0.03 and P=0.001, respectively). Lymph node involvement, tumor grade, and patient age were not associated with the length of survival. A multivariate Cox regression model showed that in pretreatment the serum CA125 level was a prognostic factor of disease-free and overall survivals, independent of tumor stage (P= 0.005 and P=0.01, respectively). In 90% of the patients, an increase of serum CA125 level preceded the clinical or radiologic diagnosis of recurrent disease with a median lead time of 3 months (range 0.5~7.0 months) (Hefler *et al*., 2000). The elevated serum concentrations of hCGbeta and CA125 predict survival in fallopian tube carcinoma, but in multivariate analyses only hCGbeta is a prognostic factor independent of stage and histology (Riska *et al*., 2006). The serum CA125 level of this patient had been normal since she was finally diagnosed, from which we could anticipate an optimistic prognosis for her.

Pelvic ultrasound, computer tomography (CT), and magnetic resonance imaging (MRI) have been widely used in the field of obstetrics and gynecology. Contrast-enhanced MRI is better than precontrast MRI and transvaginal ultrasound imaging in the diagnosis of adnexal masses and still in the detection of metastasis of lymphoid node. In this patient, imaging was performed before surgery, and we found that the CT and MRI were more meaningful than ultrasound.

PFTC and the ovary cancer have been sharing the same principle of operation and chemotherapy. A Finnish investigation indicated that the median survival time was 27 months and the overall 5-year survival rate 33%, and the stage and size of the residual tumor (<1 vs ≥1 cm) predicted both overall and disease-free survivals (P<0.050) (Riska *et al*., 2006).

The serum CA125 level adequately defines the response to chemotherapy and displays good sensitivity and specificity characteristics during the follow-up of patients with PFTC. Our patient had normal CA125 level all the times, which was proved to be a fine objective index for her.

This patient was the first example in our hospital, whose LBC indicated the dyskaryotic glandular cells before operation, and she was diagnosed with PFTC through pathology at last. As clinicians, we would think of cervical carcinoma and other uterus origin cancer, if LBC showed the dyskaryotic glandular cells. It turned out that the best for the diagnosis would be the combination of using CT and MRI. We must be especially vigilant about the possibility of PFTC to avoid misdiagnosis or delay. Lastly, since there is little difference between advanced ovarian serous and primary peritoneal carcinomas (Jaaback *et al*., 2006; Carlson *et al*., 2008), the dyskaryotic glandular cells may be seen in primary peritoneal carcinomas, so either the appendix carcinoma or primary peritoneal carcinoma should not be ignored.

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