Usefulness of combined PET/CT for patient with epithelial ovarian cancer showing recurrence based on tumor marker CA125

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We report the case of a 41-year-old patient with epithelial ovarian cancer of stage IIIc. One year and nine months after completion of chemotherapy performed after surgery, the level of the tumor marker CA125 began to increase gradually. Conventional computed tomography (CT) and magnetic resonance imaging (MRI) were performed, but the recurrence site could not be determined clearly. However, combined positron emission tomography/computed tomography (PET/CT) revealed a metastasis in the right external iliac lymph node. This allowed commencement of chemotherapy at an early recurrent stage and subsequently the level of CA125 showed a significant decrease.

Key words: tumor marker, CA125, PET/CT, recurrent ovarian cancer

INTRODUCTION

The recurrence rate of epithelial ovarian cancer of stage III - IV within three years after treatment may be as high as approximately 60% [1]. There is no clear evidence of significant prognostic improvement with cytoreductive therapy, but clinical reviews by Harries and Munkarah *et al*. suggest that cytoreductive surgery contributes to prognostic improvement in cases with a disease-free period of over 12 months and a maximum residual diameter of less than 1.5 cm [2, 3].

The tumor marker CA125 is specific to non-mucinous epithelial ovarian cancer and is thought to reflect the disease pathology; therefore, CA125 is useful as a marker for progression or recurrence of the disease [4-6]. However, cases have been reported in which suspected recurrence based on a slight increase of CA125 after treatment could not be confirmed by ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI); such situations are referred to as cases of CA125 tumor-marker recurrence [5].

The Ovarian Cancer Treatment Guidelines define a cut-off value of 35 U/ml for CA125 as a tumor marker, and more than 80% of recurrence cases are CA125-positive at levels higher than this value [5, 7, 8]. In addition, it has been reported that recurrence is likely if an increase of more than 25 U/ml occurs compared to pre-treatment levels, or if two or more consecutive increases in CA125 are observed within one month [6-8]. We have reported that combined imaging using positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has high sensitivity and/or specificity in detection of recurrence [9-11], and therefore is effective in identifying recurrence in tumor-marker recurrent cases in which CA125 is slightly higher than the normal range [9]. Furthermore, several studies have shown that it is possible to detect recurrence sites using combined PET/CT (Table 1).

Table 1 Studies of combined PET/CT for detecting recurrent ovarian cancer.

Year	Author (C)	S-d	NOP	NOS	PE (%)	SE / SP / AC (%)
2006	Chung [12] (Korea)	R-P	77	?	26/77 (34)	93 / 97 / 95
2006	Simcock [13] (Australia)	P-P	56	?	- - - -	- - - -
2005	Hauth [14] (Germany)	P-P	*19	all	5/*11 (45)	- - - -
2005	Nanni [15] (Italy)	P-P	41	?	- - - -	88 / 71 / 85
2004	Sironi [16] (Italy)	R-P	16	all	17/31 (55)	78 / 75 / 77
2004	Pannu [17] (USA)	P-P	31	all	11/16 (69)	73 / 40 / 63
2003	Bristow [18] (USA)	P-P	22	all	18/22 (82)	**84 / - - / 82
2002	Makhija [19] (USA)	R-P	8(tub; 2)	all	5/8 (62)	- - - -

(C): country, S-d: study-design, NOP: number of patients, NOS: number of surgery, PE: pathological evidence, SE/ SP/ AC: sensitivity/ specificity/ accuracy, R-P: retrospective pilot study, P-P: prospective pilot study, tub: fallopian tube cancer, - - : no data, *: 19 patients with suspicious recurrence but 11 patients with positive PET/CT, **: detected recurrent tumor less than 1cm, (This table excepted PET/CT detecting data of limited to retroperitoneal lymph nodes)

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Here, we report a case of ovarian cancer in which CA125 gradually increased after treatment. The recurrence site could not be determined by conventional imaging with CT or MRI, but lymph node metastasis was determined by PET/CT and the CA125 level was subsequently reduced by chemotherapy.

CASE REPORT

A case of CA125 tumor-marker recurrence

The patient was a 41-year-old female who had experienced one pregnancy and a resultant childbirth. She visited our hospital in January 2004 due to the sensation that her abdomen had enlarged, and the presence of a large amount of ascites fluid was confirmed. An aspiration biopsy was performed, and cytology using the ascites fluid gave a diagnosis of class V adenocarcinoma. The pretreatment levels of tumor markers were CA125: 4,749 U/ml (normal <35 U/ml), CA724: 90 U/ml (normal <3.0 U/ml), and CEA: 1.1 ng/ml (normal <5.0 ng/ml). No evidence for an enlarged tumor was seen in imaging, and therefore the lesion was assumed to be an ovarian tumor of normal size. With the aim of controlling the cancerous ascites, intraperitoneal administration of 100 mg/m^2 cisplatin and intravenous drip infusion of paclitaxel 175 mg/m^2 + carboplatin AUC5 (TJ) were performed before surgery. In April 2004, abdominal total hysterectomy + salpingo-oophorectomy + omentectomy + pelvic/para-aorta lymphadenectomy were performed. In a pathological examination, peritoneal dissemination and lymph node metastasis of serous papillary adenocarcinoma originating in the right ovarium were confirmed, abdominal swelling was absent, and advanced ovarian cancer of clinical stage IIIc was determined. The residual tumor could not be found microscopically during surgery, suggesting that optimal conditions (a residual tumor with a diameter of less than 1 cm in the peritoneal cavity) were achieved. After the operation, one course of intraperitoneal administration of 100 mg/m^2 cisplatin and six courses of monthly TJ chemotherapy were performed as adjuvant chemotherapy.

One year and nine months after treatment, the CA125 level began to increase gradually from the normal range, but no abnormalities were found in CT and MRI. However, use of PET/CT revealed a tumor in the right external iliac lymph node (Figs. 1, 2 and 3). After twelve cycles of weekly TJ chemotherapy, the CA125 level subsequently decreased to within the normal range and the recurrent lesion had disappeared in follow-up PET/CT imaging performed after completion of the 12-week course of TJ chemotherapy (Figs. 1 and 4).

Imaging protocol for PET/CT

Combined PET/CT imaging was performed using a PET/CT scanner (Discovery ST, GE Medical Systems). The patient fasted for a minimum of 6 hr prior to

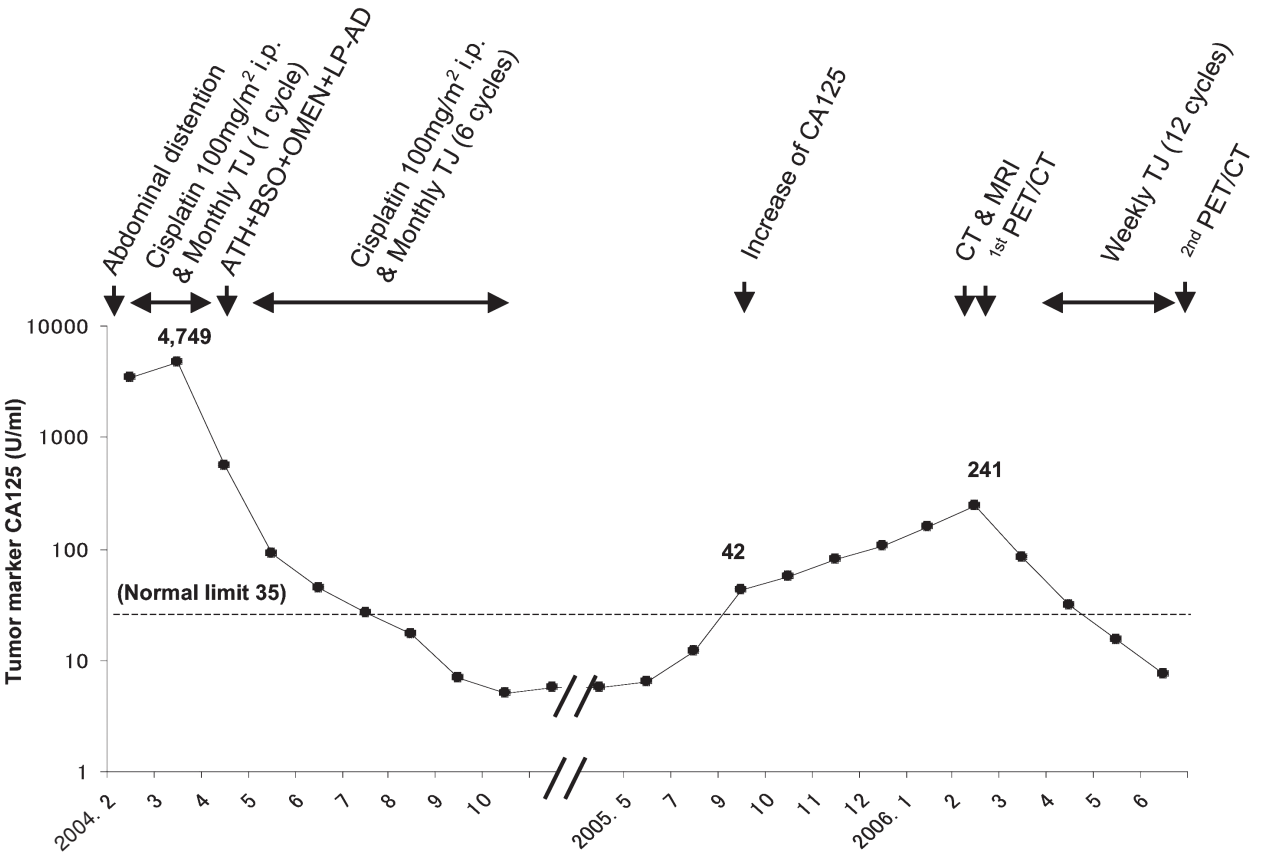

Fig. 1 Clinical time course of the patient.

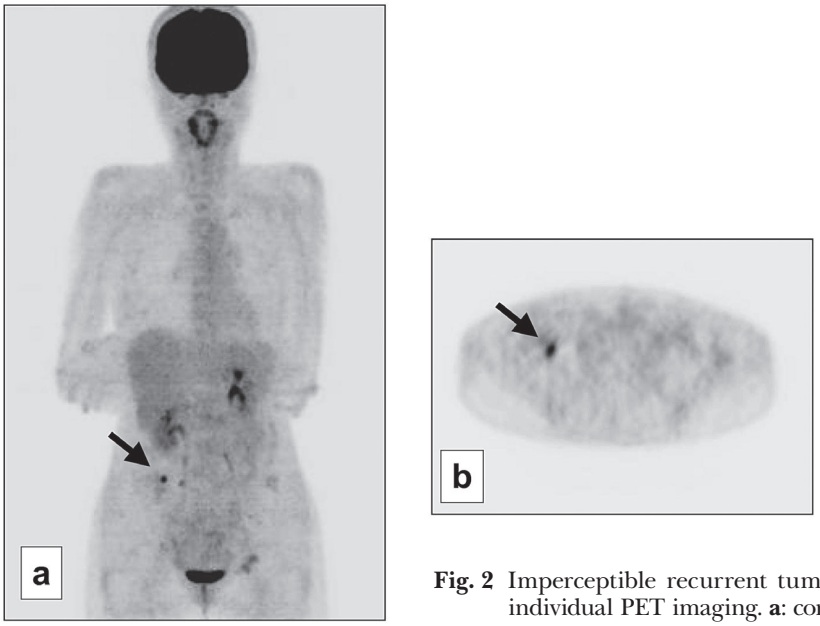

Fig. 2 Imperceptible recurrent tumor of the intraperitoneal cavity in individual PET imaging. **a**: coronary view, **b**: axial view, tumor: →.

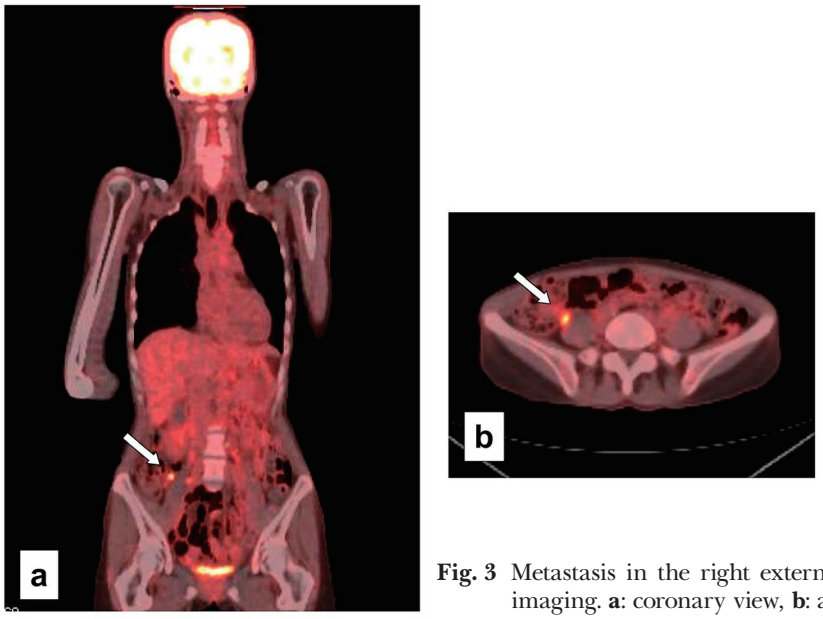

Fig. 3 Metastasis in the right external iliac lymph node on 1st PET/CT imaging. **a**: coronary view, **b**: axial view, tumor: →.

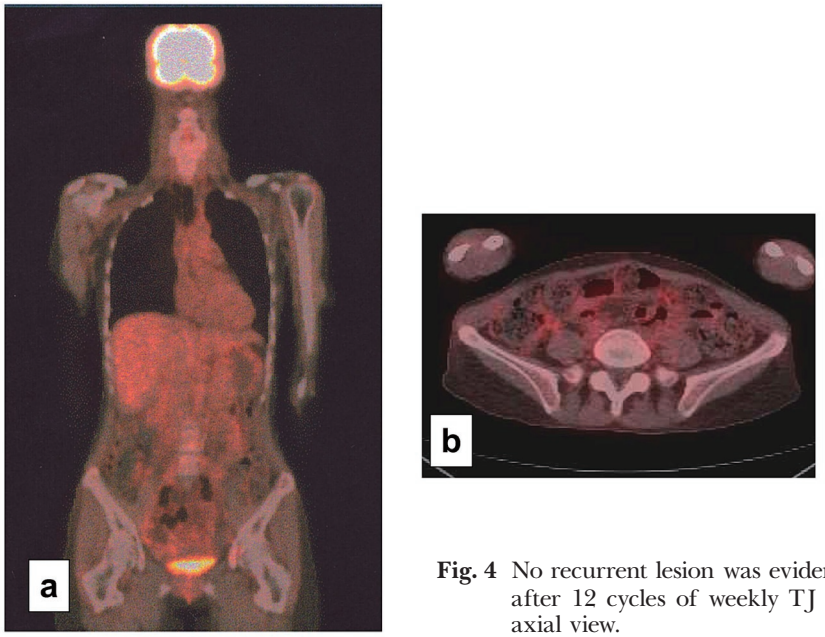

Fig. 4 No recurrent lesion was evident in follow-up 2nd PET/CT imaging after 12 cycles of weekly TJ chemotherapy. **a**: coronary view, **b**: axial view.

PET acquisition. After confirmation of a blood glucose level ≤ 200 mg/dl, sterile 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}FDG) was administered intravenously (average dose: 200 MBq), followed by a tracer uptake phase of approximately 60 min. The patient was voided prior to image acquisition.

DISCUSSION

In treatment of progressive epithelial ovarian cancer, the prognosis is thought to depend largely on whether an optimal initial surgery can be performed to leave no residual tumor, and whether postoperative chemotherapy is effective. In cases of postoperative recurrence, comparatively long-term survival is likely if recurrence is detected at an early stage and effective treatment is provided while the tumor is still small [3, 4, 20]. For this reason, we regularly perform laparoscopy every six months after treatment for patients with advanced ovarian cancer to look for recurrence in the abdominal cavity [21]. Laparoscopy has several advantages: it requires only a short period of hospitalization (three days), observation in pelvic and other abdominal sites can be performed, and an invisible tumor can be found by examining collected ascites. However, with laparoscopy it is difficult to identify recurrence in sites other than the pelvic region, such as those between the diaphragm and the liver, in a twisted intestine, and in a retroperitoneal lymph node; therefore, many cases of recurrence cannot be confirmed at an early stage using this method.

We have used PET with ^{18}FDG for early confirmation of recurrence in cases with tumor-marker recurrence only in which the level of the tumor marker CA125 gradually increases after treatment for ovarian cancer [9]. Such recurrence cannot be shown clearly by CT and MRI: an investigation of the sensitivity/specificity of CT, MRI, US and the tumor marker CA125 in detecting recurrence in 90 patients with progressive epithelial ovarian cancer gave values of 54.3%/84.1%, 57.1%/94.4%, 62.5%/92.9%, and 75.0%/51.7%, respectively. Compared with these data, we have shown that the sensitivity/specificity values of PET were extremely high: 91.3%/100% [9]. In particular, in seven patients in whom CT was negative for recurrence and the level of CA125 was 7-28 U/ml (within the normal range), PET revealed a 1-2 cm peritoneal dissemination in four patients, and a para-aorta lymph node metastasis of 1 cm or smaller in three patients. These sites of recurrence were confirmed in subsequent abdominal operations. In addition, in eight patients with slightly increased CA125 (67-166 U/ml), CT results were negative for five patients, whereas PET results were positive in all eight patients and recurrence in these patients was also confirmed in subsequent abdominal surgery [9].

In recent years, there have been many reports on the usefulness of PET for gynecological cancers [9, 11, 22, 23], and its value for diagnosis of recurrence in other cancers has also been suggested [24-27]. Most recently, the focus has been placed on combined PET/CT for detailed investigation of recurrence in the abdominal cavity and retroperitoneum (Table 1). However, reports on the use of combined PET/CT in this context are still few in number. The results of our case and other pilot studies suggest that a randomized comparative clinical trial with or without use of combined PET/CT should be performed to examine survival benefit through early detection of recurrence.

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