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SHORT COMMUNICATION

Detection of complete response to imatinib mesylate (Glivec®/Gleevec®) with 18F-FDG PET/CT for low-grade endometrial stromal sarcoma

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Abstract Malignant mesenchymal tumors consist of approximately 10% of uterine tumors. The majority of uterine sarcomas are leiomyosarcoma and endometrial stromal sarcoma (ESS). Surgery, radiotherapy, chemotherapy, and hormonal therapy are used for the treatment of ESS. Imatinib mesylate is indicated in the management of gastrointestinal stromal tumor and chronic myelogeneus leukemia. There is an interest to use imatinib mesylate in the treatment of c-kit positive ESS. We reported a case of 42-year-old female low-grade ESS progressed on chemotherapy and presented with objective response to imatinib mesylate. The treatment response was evaluated with FDG PET/CT. Complete metabolic response was detected. FDG PET, a sensitive method for tumor response evaluation on the basis of tumor metabolism changes, is useful for the evaluation of imatinib treatment in low-grade ESS.

Introduction

Malignant mesenchymal tumors consist of approximately 10% of uterine tumors. Uterine sarcomas are endometrial stromal sarcoma (ESS), leiomyosarcoma, and sarcomas arising from other tissues like fibrous tissue, vessels, and lymphatics. However, the majority of uterine sarcomas are leiomyosarcoma and ESS [1]. The initial growth phase of most sarcomas is within the fundal portion of the uterus. Uterine sarcomas have a propensity for dissemination with hematogenous way and pulmonary metastases are most frequently observed. Liver, bone, and brain metastases can also occur.

Endometrial stromal sarcoma is divided into two categories: low-grade stromal sarcoma (50–60% of all ESS), and high-grade stromal sarcoma. Low-grade ESS is associated with good prognosis, long overall survival, and long disease-free survival. Low-grade ESS can arise from extrauterine locations as well [2].

Evaluation of uterine sarcomas are difficult, because the biopsy materials are often fragmented and necrotic. Uterine wall tumors may need laparotomy and hysterectomy for diagnosis. There is no useful tumor marker for the evaluation of endometrial sarcomas, only peritoneal spread of carcinosarcoma tumors may cause an elevation in CA-125 levels [3–5].

Endometrial stromal sarcomas may be misdiagnosed in 40% of patients as uterine leiomyoma, myxoid leiomyoma, cellular leiomyoma, or lymphatic disorder, and the prompt diagnosis of ESS can be made by a pathologist with special interest in gynecological oncology [6].

Surgery, radiotherapy, chemotherapy, and hormonal therapy are used for the treatment of ESS. Endometrial stromal sarcomas are rare tumors and the systemic treatment of ESS is not based on big clinical trials. Moreover, the hormonal receptors might be detected on low-grade ESS (fewer than 10 mitoses per high-power field). Therefore, hormonal therapy may be an option in the treatment scheme.

Imatinib mesylate is indicated in the management of gastrointestinal stromal tumor (GIST) and chronic myelogeneus leukemia (CML). There is an interest to use imatinib mesylate in treatment of c-kit positive ESS. We reported a case of low-grade ESS progressed on chemotherapy and presented with objective response to imatinib mesylate. She

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was evaluated with serial 18F-fluoro-deoxyglucose (FDG)-positron emission tomography and computed tomography (PET/CT) scans.

Case report

A 42-year-old female patient was admitted to hospital with complaints of weakness, abdominal pain, and pelvic mass. Physical examination showed pretibial edema and a palpable mass at the left lower abdominal quadrant. Her medical history revealed subtotal hysterectomy and left unilateral salphyngoophorectomy 2 years ago. The pathological examination was chronic endometritis, serosal congestion at tuba, multiple follicular cysts in ovary, and epitheloid leiomyoma in uterus. After 2 years, however, control abdominal magnetic resonance imaging (MRI) showed hepatosplenomegaly, dilatation at hepatic and splenic veins, thrombus formation in splenic vein, and a mass at left ovary localization ($7 \times 6 \times 6$ cm). There was also a thrombus formation in vena cava inferior which was extending to right atrium. Pulmonary arterial pressure was 70 mmHg. Pelvic mass excision with vena cava inferior and renal vein was performed and the pathological examination showed endometrial stromal sarcoma (low-grade, desmin, actin, vimentin positive, CD-117 focally positive, CD-10 and CD-34 negative, estrogene and progesterone receptors positive) (8×7 cm), tumor thrombus in renal vein and vena cava inferior (Figs. 2, 3, 4, 5). A month after the operation, patient was examined with abdominal computed tomography (CT) and there was a pelvic mass consistent with recurrence. The patient received IMA (Iphosphamide, Mesna, Adriamycine) chemotherapy protocol and leuprolide acetate 11.25 mg for 3 months. However, progression has been detected after six cycles of chemotherapy and GnRH analog. 18F-FDG PET/CT scan was performed with a Siemens Biograph 2 LSO integrated PET/CT camera (Siemens Medical Solutions, Hoffman Estates, IL). The time schedule and semiquantitative results of FDG PET/CT scans are listed in Table 1.

The first PET/CT was performed after the third cycle of IMA chemotherapy and demonstrated mildly increased FDG uptake in the pelvic mass localized at posterior of urine bladder. The maximum standardized uptake value (SUV) was 2.7. The second PET/CT was performed after six cycles of IMA chemotherapy and the maximum SUV in the same pelvic mass was elevated to 3.1. The patient started tamoxifen 20 mg/day for 3 months.

The third PET/CT was performed after tamoxifen and the maximum SUV was 4 which is consistent with progression. The patient started imatinib mesylate 400 mg/day. Three months after initiation of imatinib, ascites was detected. Cytological and microbiological cultures were normal and adenosine deaminase level was within normal limits. The ascites was thought to be related with imatinib mesylate and dose of drug was reduced to 300 mg/day. Furosemide 40 mg/day and spironolactone 100 mg/day were added, but the ascites has not been resolved and serial paracentesis were performed.

The final PET/CT was performed 5 months after imatinib mesylate and demonstrated a complete metabolic response to imatinib mesylate treatment. The maximum SUV was 2.3 in the pelvic lesion which is consistent with a mean decrease of 42.5% in SUV prior to and after treatment.

Because of persistent ascites despite dosage reduction, patient was reexamined with echocardiography and the result was high grade tricuspit deficiency, pulmonary hypertension (PAP 40 mmHg), dilatation at vena cava inferior, hepatic vein, and right heart. The ejection fraction was 60%. Tricuspit valve replacement operation was performed. However, the patient was admitted to coronary intensive care unit because of severe right heart failure, disseminated intravascular coagulopathy, and sepsis. The patient died 50 months after the first diagnosis of ESS.

Discussion

Endometrial stromal sarcomas generally present with abdominal masses. Atypical presentations of ESS may also occur. A case of low-grade ESS with involvement of pelvic veins and inferior vena cava has been reported emphasizing the venous involvement possibility of ESS [7, 8]. Another rare presentation of ESS as a multilocular cystic intrauterine mass mimicking multilocular ovarian cyst has been also reported [9].

Endometrial stromal sarcomas may be diagnosed at earlier ages and a case of high grade ESS in a 10-year-old girl has been reported [10]. Kim et al. [11] reported that the median age of low-grade ESS was 43 years, the median disease-free survival was 111 months (range 6–182 months), and the most common recurrence site was pelvis. The median overall survival of low-grade ESS has been found as 45.35 ± 21 months (range 20–83) in a study with 14 patients and there was a longer disease-free survival in patients with no myometrial invasion and low mitotic count $\leq$5/HPF but the P value was not significant [12]. Overall survival of the present case was 50 months.

The treatment alternatives of ESS are surgery, radiotherapy, chemotherapy, and hormonal therapy. Patients with advanced or recurrent disease frequently experience progressive disease and these women are candidates for new experimental treatment regimes and trials. Low-grade ESS are generally steroid receptor positive tumors and clinical course is mostly with slow tumor progression and high

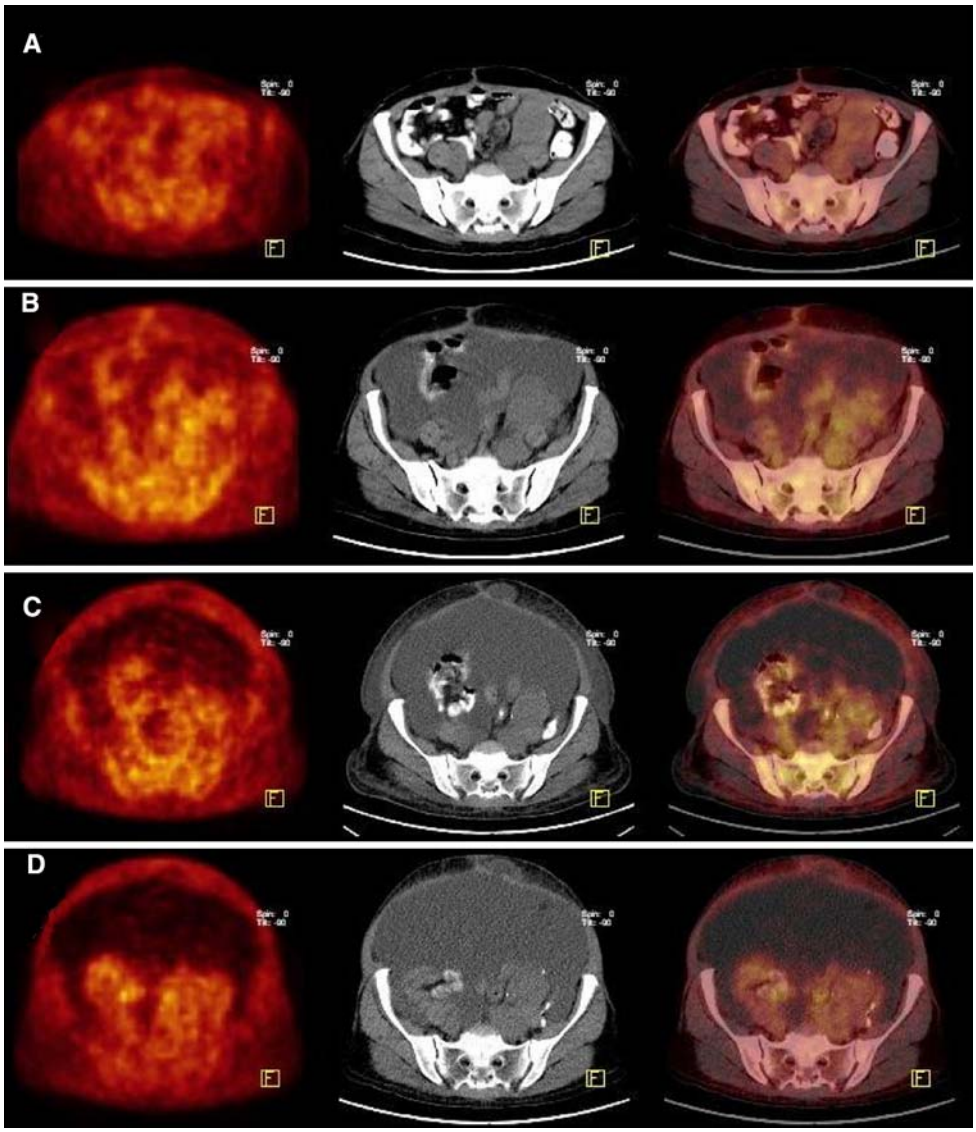

Fig. 1 FDG PET/CT scans after treatments, from left to right axial PET, CT and fused PET/CT images. The first PET/CT scan (**a**, after three cycles of chemotherapy) shows a mild increase of FDG uptake in the pelvic mass (*arrow*); the second study (**b**, after six cycles of chemotherapy) shows a little more increase in FDG uptake; the third study (**c**, after 3 months of hormonotherapy) shows FDG uptake is still high; and the last study (**d**, 5 months after imatinib mesylate) demonstrates a significant decrease in FDG uptake compared with the third scan. An extensive hypometabolism is seen in the abdomen corresponding to massive ascites on CT images (**b**, **c**, **d**)

recurrence rates. In the past, hormonal therapy like progestins was the single alternative approach for hormonal therapy of low-grade ESS. Recently, aromatase inhibitors and gonadotropin-relasing hormone analogs are used as an alternative treatment approach besides radiotherapy and chemotherapy [13].

Endometrial stromal sarcomas can express c-kit which is the target of tyrosine kinase inhibitors. There is a growing interest to use imatinib mesylate in the management of c-kit positive tumors including GIST and CML. Interestingly, a case of c-kit positive high-grade ESS responding to imatinib mesylate has been reported. The patient was a 41-year-old woman with advanced stage ESS. Imatinib mesylate was used at 400 mg/day dosage and the response was evaluated with CT scan. There was a 38% reduction in maximal diameter of the target lesion [14]. In our case, CT did not show a reduction in the tumor size.

The extent of ESS and the response to the management is usually assessed by CT scan. We evaluated the response of the present case to imatinib mesylate treatment with FDG PET/CT. There is no study in the English literature reporting the role of FDG-PET in the evaluation of ESS treatment with imatinib mesylate. FDG PET is an effective method for the response evaluation of solid tumors. There are a number of studies in the literature reporting the role of FDG PET in the treatment evaluation of GIST patients [15–17]. Van Oostren et al. [16] performed FDG PET for treatment response assessment and staging of GIST patients treated with imatinib mesylate. Also Heinicke et al. [17] evaluated the response to imatinib mesylate treatment in GIST. They detected 60% mean decrease in SUV between before and after 1 week of treatment. In our case it was 42.5% mean decrease in SUV between before and after treatment. We have previously published FDG

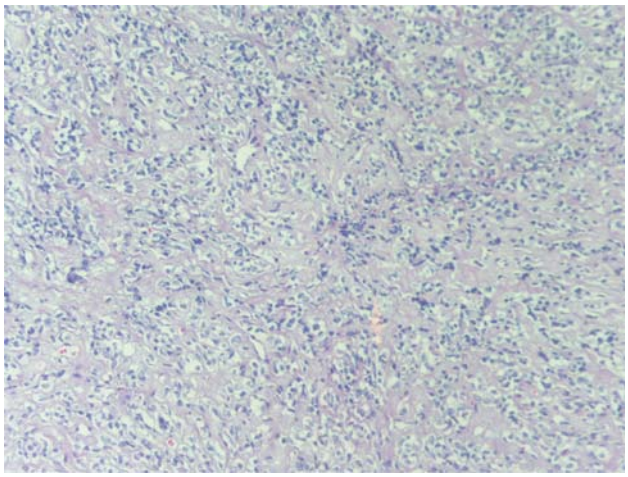

Fig. 2 Low-grade endometrial stromal sarcoma (HE ×40)

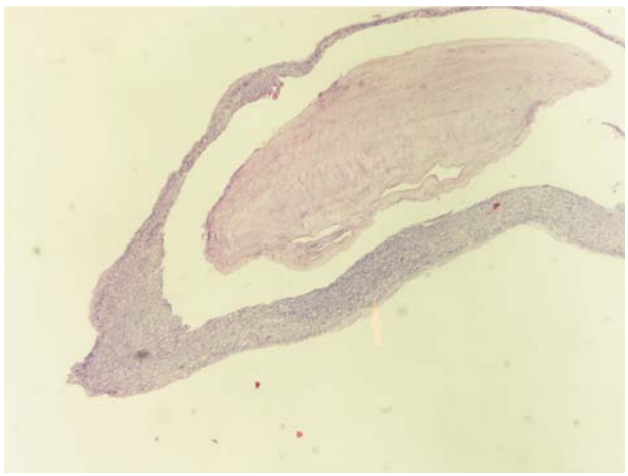

Fig. 3 Low-grade endometrial stromal sarcoma showing vascular invasion in vena renalis (HE ×40)

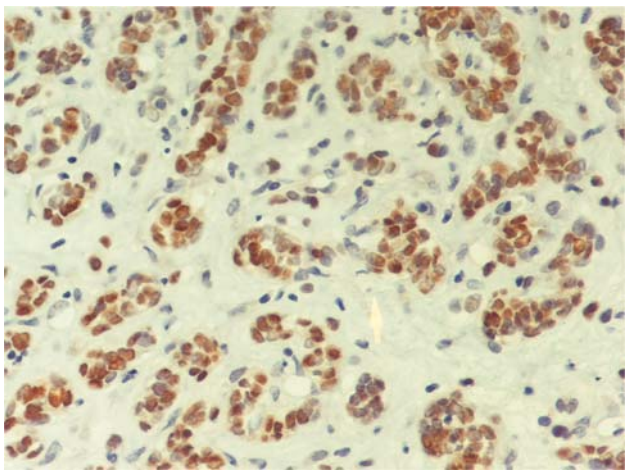

Fig. 4 Progesterone receptor staining (++) in low grade endometrial stromal sarcoma (×100)

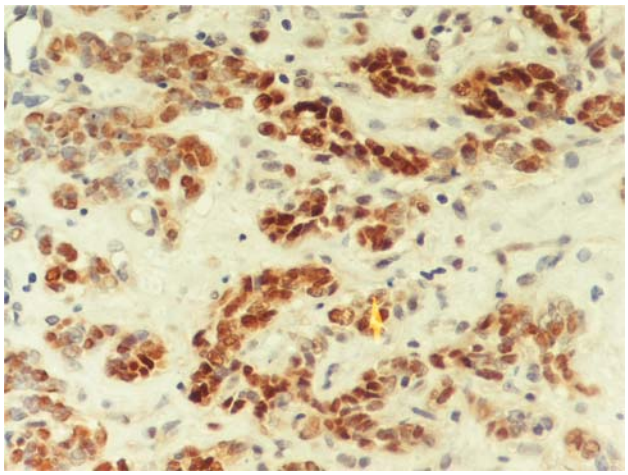

Fig. 5 Estrogen receptor staining(+++) in low grade endometrial stromal sarcoma (×100)

Table 1 The time schedule of FDG PET/CT scans with maximum SUV and HU of the mass

PET/CT	Time of PET/CT	Maximum SUV	HU
Fig. 1a	After three cycles of chemotherapy	2.7	27
Fig. 1b	After six cycles of chemotherapy	3.1	31
Fig. 1c	After 3 months of hormonotherapy	4	34
Fig. 1d	5 months after imatinib mesylate	2.3	37

SUV standardized uptake value, *HU* Hounsfield Units

PET responses to imatinib therapy in GIST patients before and after treatment [18, 19].

In our case, FDG PET/CT scans performed before and after imatinib mesylate treatment, demonstrated complete metabolic response (SUV < 2.5). The previous lesion was evaluated again with CT scan and there was no difference in the size of lesion compared with before and after the treatment of imatinib mesylate. If the tumor was evaluated with RECIST criteria the response should be categorized as stable disease. However, the tumor size evaluation is not a reliable method in the evaluation of response rate for tyrosine kinase inhibitors.

In conclusion, the treatment response evaluation can be performed with different methods. FDG PET is a sensitive method for tumor response evaluation on the basis of tumor metabolism changes. FDG PET is useful for the evaluation of imatinib treatment at low-grade ESS.

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