Case Report

Primary ovarian neuroendocrine carcinoma expressing substantially intense ^{18}F-FDG uptake: A case report[☆],[☆☆]

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ABSTRACT

Ovarian neuroendocrine carcinoma is a rare and aggressive tumor with a poor prognosis. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are often used for diagnosis. However, no specific features exist, and preoperative diagnosis is often difficult. We present a case in which ovarian neuroendocrine carcinoma was diagnosed postoperatively, with the intention to discuss its imaging features on ^{18}F fluoro-deoxy-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). A 70-year-old woman presented to a local hospital with abdominal pain. CT showed a uterine mass and multiple swollen lymph nodes. The mass expanded from the uterus into the left ovarian vessels on dynamic MRI. The SUVmax of the mass and lymph nodes on ^{18}F-FDG PET/CT were notably elevated to 53.2 and 33.0 respectively. Considering the tumor location and high SUVmax, a malignant uterine tumor was suspected. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, and resection of the left ovarian vessels were performed. Histological examination confirmed that the tumor was a neuroendocrine carcinoma derived from the left ovary. To the best of our knowledge, there are only few reports on the ^{18}F-FDG uptake in ovarian neuroendocrine carcinomas. Conversely, in other organs, the carcinomas frequently exhibit markedly elevated SUVmax on ^{18}F-FDG PET/CT. It is possible that ovarian neuroendocrine carcinomas share similar traits, and elevated SUVmax could indicate the potential presence of this histological type.

Introduction

Neuroendocrine carcinoma rarely develops in the gynecological tract. The occurrence rate is approximately 2% of all gynecologic tumors [1]. Progression is rapid, and the recurrence rate is high. In addition, preoperative diagnosis is challenging because of the lack of recognizable imaging traits [2]. The present study outlines a case characterized by notably elevated SUVmax levels on ^{18}F-FDG PET/CT, which ultimately revealed neuroendocrine carcinoma after surgical intervention. This highlights the potential of ^{18}F-FDG PET/CT as a useful modality for differentiating histological types.

Case presentation

A 70-year-old woman (gravida 2, para 2) presented to a local hospital with abdominal pain. Medical history included leiomyoma, appendicitis, chronic glomerulonephritis, asthma, hypertension, hyperlipidemia, and depression. She went through menopause at the age of 55 and smoked for 3 decades. She had no family history of gynecologic cancer.

Contrast-enhanced CT revealed a uterine mass along with multiple enlarged lymph nodes and small pulmonary nodules. Upper gastrointestinal endoscopy was also performed, suggesting no abnormalities. The patient was referred to our institution for further evaluation.

No abnormalities were observed upon speculum examination. Due to the patient's obesity (body mass index, 30 kg/m²), obtaining information via bimanual examination was difficult. A highly echoic mass was observed within the posterior wall of the uterus on transvaginal ultrasound, displaying internal blood flow on color Doppler. Blood test revealed increased D-dimer (2.3 µg/mL). LDH level was within the normal range (199 U/L), and no other noteworthy data were observed. The levels of tumor makers including CEA, CA19-9, and CA125 were not elevated. Cervical and endometrial cytology, endometrial biopsy showed no malignancies. Contrast-enhanced MRI showed a 7 cm mass located near the left uterine horn, which grew along the left ovarian vessels (Fig. 1A). This indicated hyperintensity on T2-weighed imaging, isointensity on T1-weighed imaging (Fig. 1B). Restricted diffusion and gradual enhancement were observed (Fig. 1C and D). Low-grade endometrial stromal sarcoma was suspected owing to the location of the mass within the uterine region and its proximity to the blood vessels. ^{18}F-FDG PET/CT was also performed to evaluate metastases, as there were nodules in the lungs on
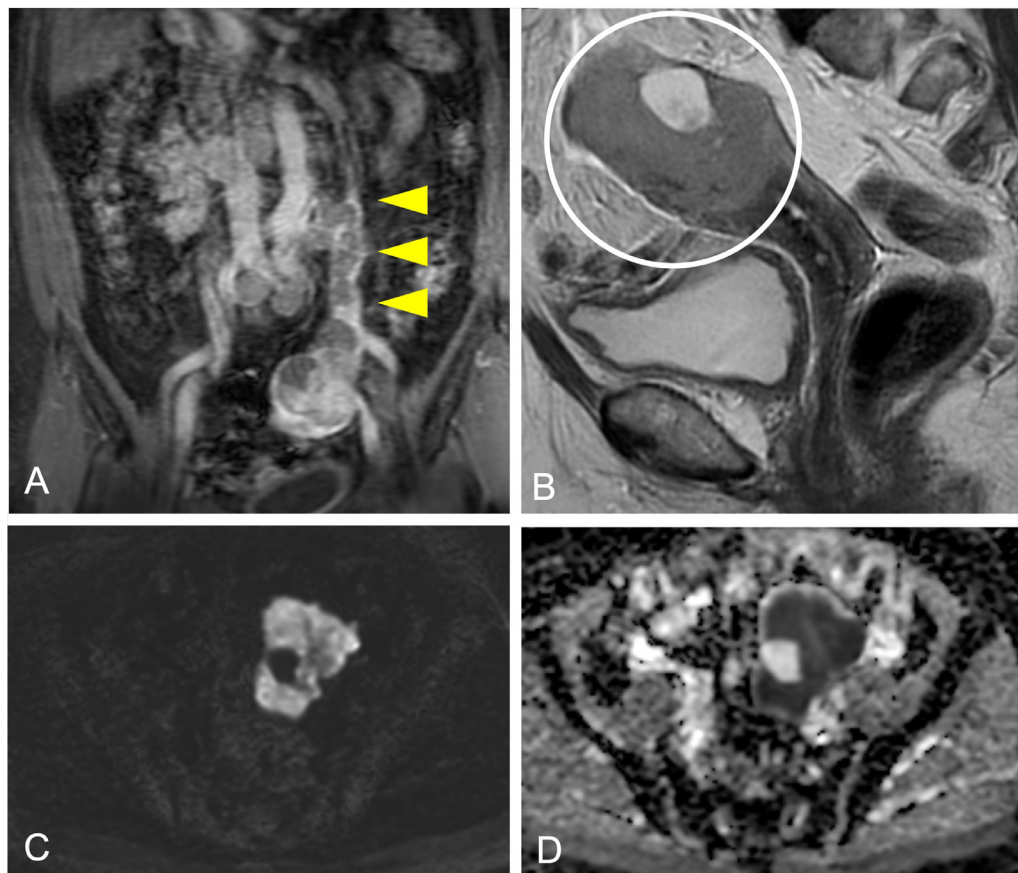

Fig. 1 – Pelvic contrast-enhanced MRI images. The image demonstrated a 7cm mass located near the left uterine horn. Its growth along the left ovarian vessels is depicted in the fat-suppressed 3D T1-weighed coronal image (arrowheads in A). The mass is highlighted in the T2-weighed sagittal image (B). The mass exhibited high signal intensity on diffusion-weighed imaging and low signal intensity on ADC map (C) (D).
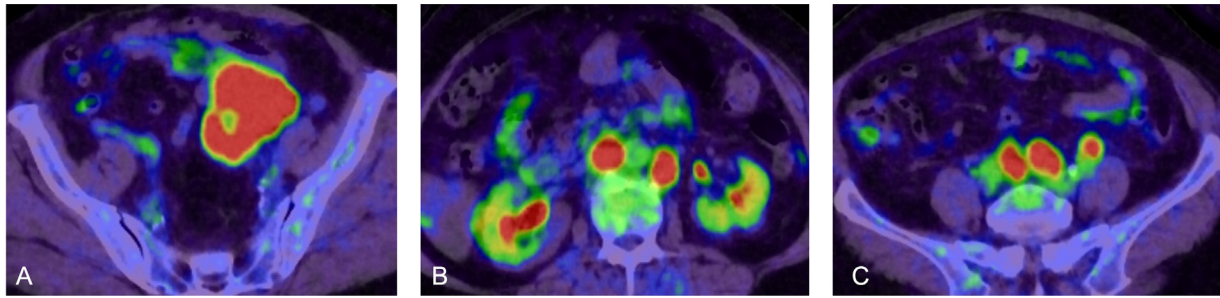
Fig. 2 – ^{18}F-FDG PET/CT images. It showed substantially high ^{18}F-FDG accumulation (SUVmax, 53.2) within the pelvic mass (A). The left common iliac and paraaortic lymph nodes also showed high levels of SUVmax, measuring 33.0 (B) (C).
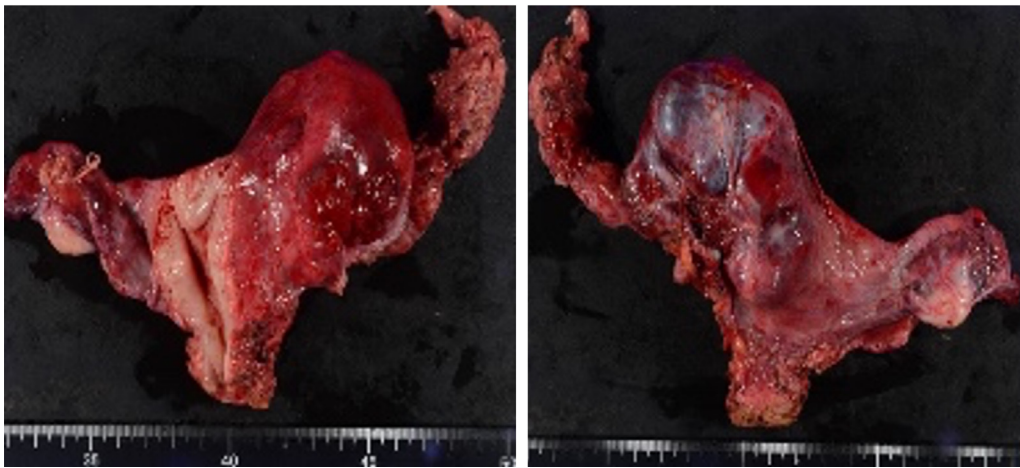

Fig. 3 – Macroscopic finding. The left adnexa were approximately 7cm, adhering to the posterior wall of the uterus.

CT, revealing notably elevated ^{18}F-FDG accumulation within the mass (SUVmax, 53.2) (Fig. 2A). Moreover, pronounced accumulation was observed in the left common iliac, paraaortic, and retrocrural lymph nodes (SUVmax, 33.0) (Fig. 2B and C). In contrast, the pulmonary nodules presented on CT showed low accumulation (SUVmax, 2.7), implying no relationship with the uterine mass. Based on the results of the ^{18}F-FDG PET/CT, mesenchymal tumors such as malignant lymphoma, sarcoma, and neuroendocrine carcinoma were considered.

The patient underwent surgery to remove the lesion and establish a diagnosis. The left adnexa were approximately 7 cm in size and adhered to the posterior wall of the uterus (Fig. 3). As suggested on MRI, it grew adjacent to the left ovarian artery and vein. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, and resection of the left ovarian vessels were performed.

Postoperative histopathology revealed the proliferation of small malignant cells with scant cytoplasm (Fig. 4). Immunohistochemistry showed positive staining for Paired-box gene 8 (PAX 8) and cytokeratin AE1/AE3, along with p53 overexpression, suggesting that the lesion was an ovarian carcinoma. The ovary was identified as the primary lesion because thyroid transcription factor-1 (TTF1) was negative. In addition, synaptophysin was positive. SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (SMARCA4) which often exhibits a loss in small cell carcinoma, hypercalcemic type, was retained (Fig. 5). Glucose
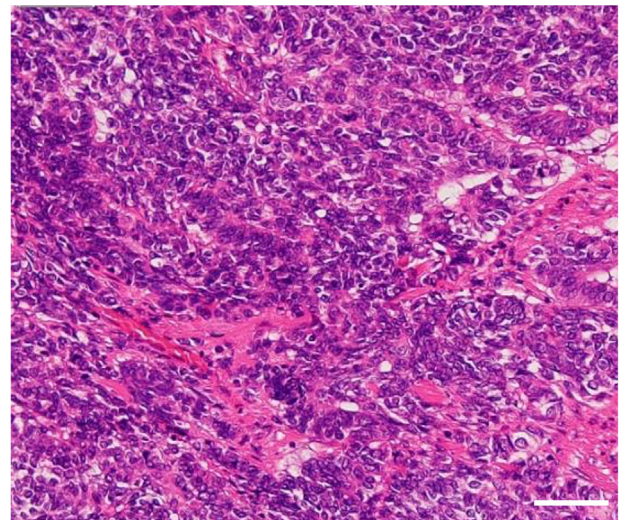

Fig. 4 – Histological finding (H&E staining). It revealed a proliferation of small malignant cells with scant cytoplasm. Scale bar, 50 μm.

transporter 1 (GLUT1) and Ki67 were also immunostained, with positivity rates of 30% and 50%, respectively (Figs. 6 and 7). Malignant cells were present in the omentum and ascites. No lymph nodes were included in the specimen. In
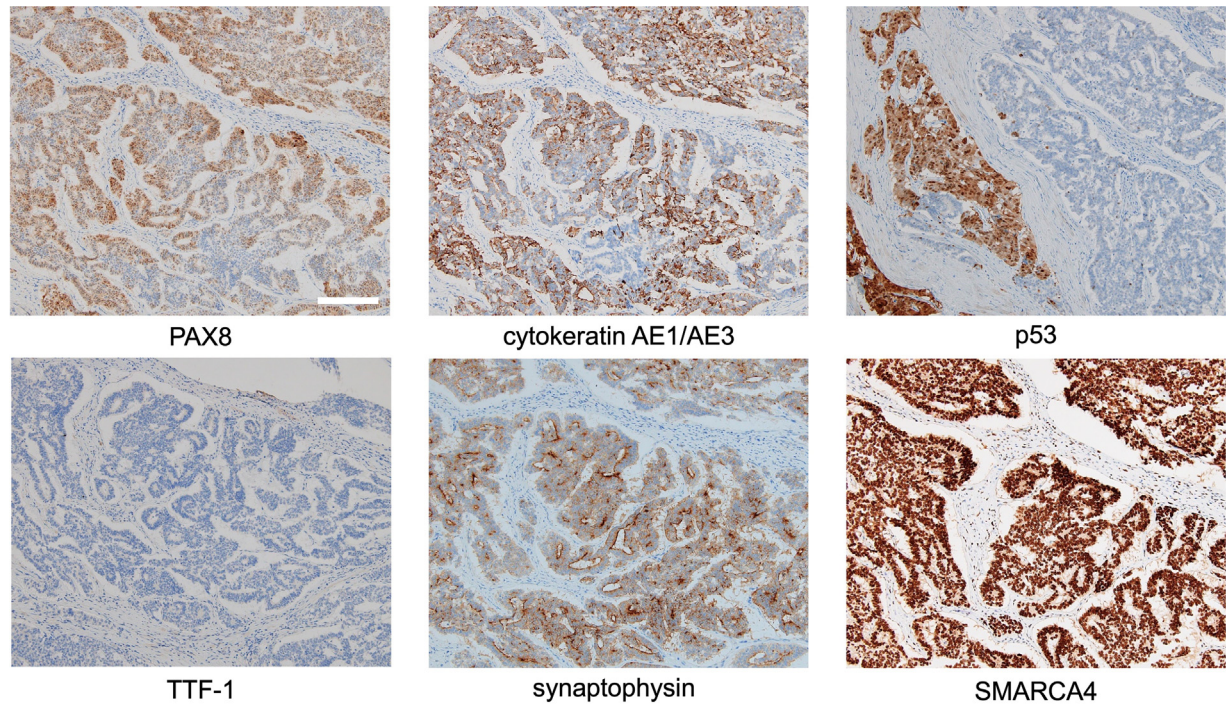
Fig. 5 – Immunohistochemical finding. It suggested that the tumor was a primary ovarian neuroendocrine carcinoma. PAX8 and cytokeratin AE1/AE3 were positive. p53 was overexpressed. TTF-1 was negative, indicating that the primary lesion was the ovary. The detection of synaptophysin positivity supported the diagnosis of ovarian neuroendocrine carcinoma. SMARCA4 did not show a loss, meaning that the tumor was not ovarian small cell carcinoma, hypercalcemic type. Scale bar, 200 μm.
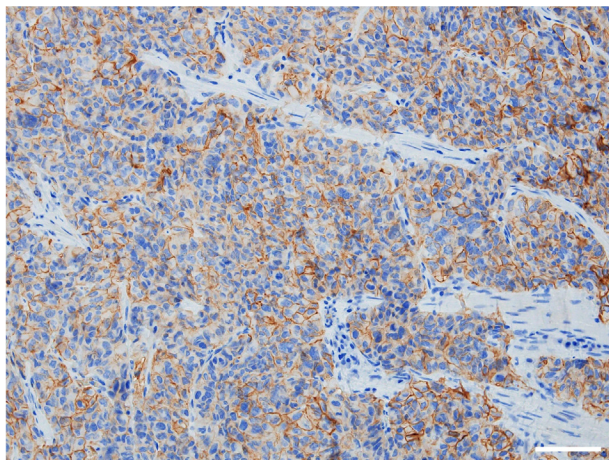

Fig. 6 – Immunohistology of GLUT1. GLUT1 staining was observed in 30% of the tumor cells, which did not demonstrate strong positivity. Scale bar 50 μm.
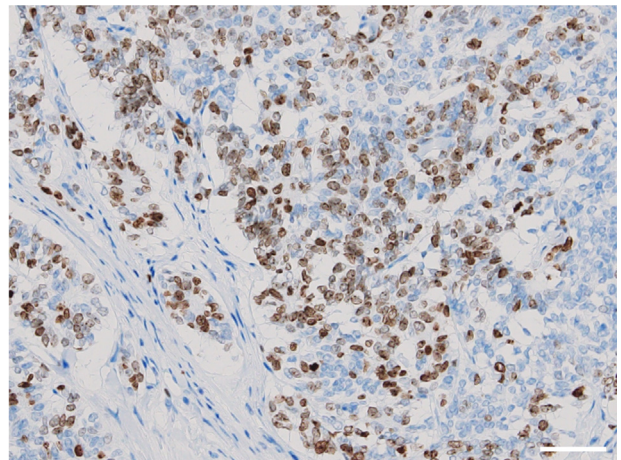

Fig. 7 – Immunohistology of Ki67. Ki67 was approximately 50% positive suggesting high cell proliferation. Scale bar 50 μm.

summary, we diagnosed the patient with primary left ovarian neuroendocrine carcinoma, pT3aNXM0 Stage IIIA2. NSE level was measured after surgery and was elevated to 45.2 ng/mL.

No complications occurred during hospitalization, and the patient was discharged 11 days postoperatively. We intended to begin chemotherapy using etoposide and cisplatin, however she passed away suddenly while bathing at home 47 days after surgery. Autopsy was not performed, at the family's discretion.

Discussion

Neuroendocrine neoplasms are derived from the neuroendocrine cells, and commonly develops in the gastrointestinal tract, pancreas, and lung [3]. They are categorized into well-differentiated low-grade neuroendocrine tumors (NETs)

and poorly differentiated high-grade neuroendocrine carcinomas (NECs) [4]. The incidence of ovarian neuroendocrine carcinoma is frequently observed in perimenopausal and postmenopausal women [2]. Tumor markers, such as NSE, Synaptophysin, and Chromogranin A, are well known [3]. Neuroendocrine neoplasms of the gynecological tracts are rare. The cervix is the most common location accounting for 54% of all gynecological tracts. Sixteen percent of cases develop from the ovary and fallopian tube, and it is said that ovarian neuroendocrine carcinoma is frequently poorly differentiated [2]. Due to its rarity, there are no established diagnostic methods. Ultrasonography, CT, and MRI are often used, however there are no noteworthy features [2].

^{18}F-FDG PET/CT is another imaging modality to consider. It helps evaluate the tumor stage and assess metastases and recurrence [5]. The cutoff value for malignant ovarian tumors is 2.9, however, there are reports indicating that it varies depending on the histology. According to a study based on 160 cases of ovarian carcinoma, the median SUVmax of serous carcinoma (SUVmax, 6.92) and endometrioid carcinoma (SUVmax, 5.90) were relatively higher than those of clear cell carcinoma (SUVmax, 3.52), mucinous carcinoma (SUVmax, 3.42), and metastatic carcinoma (SUVmax, 2.95) [6]. Few studies have investigated the use of ^{18}F-FDG PET/CT and SUVmax in ovarian neuroendocrine carcinomas. Conversely, studies have been conducted on neuroendocrine carcinomas derived from other organs. One study aggregated 15 cases and the mean SUVmax was 10.82±4.50 [7]. This exceeds the SUVmax values observed in the discussed histological types of ovarian carcinomas. Our case exhibited even more higher values. ^{18}F-FDG PET/CT is used to evaluate tissue glucose consumption. ^{18}F-FDG is taken up by cells via glucose transporters (GLUTs), phosphorylated by hexokinases, and accumulates in cells as ^{18}F-FDG-6-phosphate. Malignant cells consume abundant glucose, making them more likely to take up ^{18}F-FDG [8]. Among the 14 types of GLUTs, ovarian carcinoma overexpresses GLUT1 [9], which is similar to neuroendocrine carcinoma [10–12]. We hypothesized that neuroendocrine carcinomas of the ovaries have the same tendency to take up high levels of ^{18}F-FDG. In the present case, the rate of GLUT1 was estimated to be 30% (Fig. 6). This indicates a positivity below the threshold considered strongly positive, which generally requires exceeding 50% [13,14]. However the figure reveals a region with a high density of positive cells, which may account for elevated ^{18}F-FDG uptake. Another factor associated with ^{18}F-FDG accumulation which is cell proliferation. This could be evaluated using Ki67 [14,15]. Ki67 positivity in pancreatic and gastrointestinal neuroendocrine carcinomas is more than 20% [2]. For this case, approximately 50% of the cancerous cells tested positive for Ki67, indicating an association between cellular proliferation and elevated SUVmax (Fig.7). High ^{18}F-FDG uptake could have been an important factor in the histological speculation of our case. The treatment options may not change depending on the histological type; however, we believe it could be helpful when providing information such as prognosis to the patient. Preoperative measurements of tumor markers such as NSE may also be considered if neuroendocrine carcinomas are suspected. Studies on ovarian neuroendocrine carcinomas are scarce; hence, further studies are required.

Conclusion

Malignant tumors show an increased SUVmax on ^{18}F-FDG PET/CT; however, the average level differs depending on the histology. Factors such as GLUTs and cellular proliferation are correlated with ^{18}F-FDG accumulation. Neuroendocrine carcinomas primarily exhibit high levels of GLUT1 and Ki67. Therefore, neuroendocrine carcinomas should be considered when the SUVmax is significantly elevated when differentiating ovarian carcinomas.

Author contributions

Patient consent

Written informed consent was obtained for publication.

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