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Case Report

Case report: diagnosis and treatment of advanced high-grade serous ovarian carcinoma aided by ^{68}Ga-FAPI PET/MR scan

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Abstract: High-grade serous ovarian cancer (HGSOC) is the most common type of epithelial ovarian cancer with insidious onset, rapid growth, and invasive spread. Here, we reported the diagnosis and treatment of a 53-year-old patient with a history of hysterectomy aided by the ^{68}Ga-FAPI PET/MR scan. The patient was first presented to the local hospital with a lump on the left side of the neck with a biopsy suggesting metastatic cancer. Pelvic ultrasonography revealed two irregular masses. After admission, tumor markers, pathology consultation of the biopsy, and the ^{68}Ga-FAPI PET/MR scan were administered. The biopsy of the lump suggested poorly differentiated adenocarcinoma and CA125 was elevated at 530.6 U/ml. The ^{68}Ga-FAPI PET/MR scan showed several abnormal lymph nodes and two soft tissue masses with borders of dispersed restriction displaying internally uneven signals depicted by slightly elongated T1 and T2 signals within the pelvic cavity suggesting that pelvic mass could be the primary lesion. The patient received cytoreductive surgery including bilateral adnexectomy, omentectomy, and appendectomy. Post-surgical pathology suggested left and right HGSOC with left fallopian tube invasion. The patient completed six courses of first-line chemotherapy and remained progression-free for 14 months up to date. To conclude, ^{68}Ga-FAPI PET/MR aids in primary tumor determination and tumor burden assessment and provides a guide for the management of late-stage HGSOC patients.

Keywords: Epithelial ovarian cancer, type II ovarian cancer, ^{68}Ga-FAPI, gynecological malignancy

Introduction

High-grade serous ovarian cancer (HGSOC) is the most common type of epithelial ovarian cancer (EOC) that accounts for nearly 70% of all ovarian cancer [1]. HGSOC is a fast-growing and rapidly spreading cancer that was recently believed to originate from the epithelial cells of the fallopian tubes rather than the ovary [2-4]. Like other ovarian cancers, HGSOC is often diagnosed at a late stage when it has already metastasized to other parts of the body [1]. Similar to other types of cancer, ovarian cancer metastasis can occur through various routes including direct extension, peritoneal seeding, lymphatic spread, and hematogenous spread. The most common routes for ovarian cancer metastasis are through direct extension to nearby pelvic organs and peritoneal seeding [5, 6]. Here, we reported the diagnosis and treatment of a case that developed HGSOC with a hysterectomy history presenting dominant lymphatic metastasis through the aid of a ^{68}Ga-FAPI Positron Emission Tomography (PET) scan.

Case

Patient, Female, 53 years old. Presented to the local hospital due to a lump on the left side of the neck accompanied by pain in the left lower limb. No special examination or treatment was administered. The patient re-visited the local hospital due to slight vaginal bleeding accompanied by abdominal distension a few days later. Pelvic ultrasound revealed two low-echogenic masses in the pelvic cavity measuring 10.5 * 6.2 cm and 5.1 * 4.9 cm with clear borders and irregular shapes, showing blood flow signals in and around them. Examination identified a lump on the left side of the neck, and a biopsy suggested metastatic cancer in the lymph nodes. The patient was referred to our hospital for further evaluation and admitted with the provisional diagnosis of “pelvic mass with undetermined significance”.

After admission, the patient’s medical history was reviewed and comprehensive examinations were conducted. The patient’s medical history included a total abdominal hysterectomy in 2014 due to adenomyosis and denial of a history of smoking, alcohol consumption, exposure to radiation, or any family history of hereditary diseases. Pelvic examination indicated a smooth vaginal remnant with a huge solid pelvic mass extending two fingers above the navel and limited to the pelvic walls with poor mobility. Tumor marker CA125 was elevated at 530.6 U/ml. Considering the biopsy results from the local hospital and clinical presentation, the likelihood of the pelvic mass being a malignant tumor was high. A consultation based on the external biopsy slides suggested a metastatic malignant tumor, which was suspected to be a poorly differentiated adenocarcinoma (**Figure 1A**). A comprehensive assessment of overall tumor burden and metastatic status by ^{68}Ga-FAPI PET/MR scan was scheduled.

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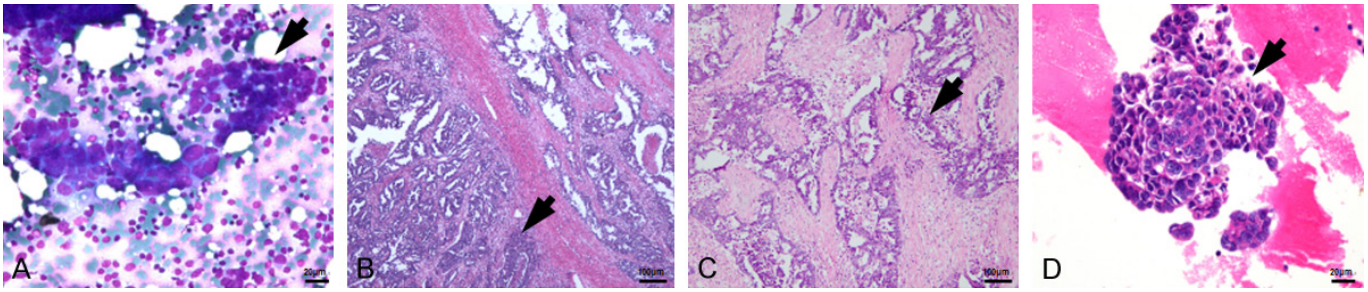

Figure 1. Pathology results of the patients. A. Clusters of cancer cells (arrow) in lymph node collected from the left neck region. B and C. Tumor lesion of HGOSC (arrow) of both left and right ovary. D. Individual small clusters (arrow) of cancer cells were detected in a background of numerous red blood cells.

After intravenous injection of contrast agent followed by 30 minutes rest, a general systematic contrast distribution with T1 and T2 signals was acquired through a full-body PET/MR scan. For specific abdominal/pelvic lesion detection, PET/MR scanning of the abdominal and pelvic regions was performed. For specific chest/lung lesion detection, PET/CT scanning of the lung and chest was performed. PET images were corrected for attenuation and reconstructed using an iterative method. Both PET and MR images were displayed across multiple levels and slices to achieve clear and precise imaging as previously described [7, 8]. According to ^{68}Ga-FAPI PET scan, the radiotracer is notably concentrated in various areas: 1) two soft tissue masses with borders of dispersed restriction displaying internally uneven signals were depicted by slightly elongated T1 and T2 signals within the pelvic cavity (measuring 6.7 × 2.8 cm and 9.5 × 5.8 cm respectively) (**Figure 2A**); 2) multiple abnormal uptake in lymph nodes were observed in the left neck V area and bilateral regions of the clavicle (up to 2.6 × 1.6 cm, SUVmax 3.4-17.9) (**Figure 2B**), mediastinal 3P and right cardiophrenic angle area (up to 1.3 × 0.9 cm, SUVmax 6.9), around the muscles bilaterally, behind the peritoneum, in the mesentery, alongside the iliac vessels bilaterally, inner and outer sides of the ilium, anterior to the sacrum, bilateral pelvic walls, pelvic cavity, right groin area, the inner side of the right gluteus maximus and the lymph node adjacent to the right side of the abdominal aorta lacks distinct separation from the outer limb of the right adrenal gland (up to 3.1 × 2.4 cm, SUVmax 2.6-16.1); 3) multiple nodules with elongated T2 signal are observed near the anterior margin of the spleen and splenic hilum in the pancreatic tail (SUVmax 3.1-5.2) as well as in the right posterior peritoneal area at the L4/5 level (up to 0.7 cm, SUVmax 1.7). Other findings included incidental conditions like brain infarction, thyroid nodules, pulmonary nodules, and mild fatty liver. The absence of the uterus was noted as a post-operative change from the previous hysterectomy.

Based on the comprehensive assessment, the patient underwent laparoscopic exploratory surgery for pathological diagnosis and further treatment. During the surgery, a small amount of clear ascites was observed. The uterus was absent. The rectum closely adhered to the residual vaginal remnant, posterior bladder wall, and pelvic walls. The right adnexa enlarged to a solid mass roughly the size of a woman's fist firmly adhered and fixed to the right pelvic wall. The left adnexa also showed enlargement to a solid mass with a diameter of 10 cm, adhered and fixed to the left pelvic wall and residual vaginal remnant. No significant lesions were detected on the surfaces of the greater omentum, appendix, liver, spleen, intestines, liver diaphragmatic surface, spleen diaphragmatic surface, or liver falciform ligament. The pelvic and abdominal lymph nodes appeared slightly enlarged. The right adnexa was examined through rapid pathology and suggested a poorly differentiated malignant tumor in the right ovary. Cytoreductive surgery involved bilateral adnexectomy, omentectomy, and appendectomy was then conducted and intraperitoneal chemotherapy with 400 mg carboplatin was performed. Additional intravenous chemotherapy (240 mg of paclitaxel + 200 mg of carboplatin) was administered post-surgery.

The postoperative pathology revealed high-grade serous carcinoma in both ovaries and the left fallopian tube (**Figure 1B** and **1C**). A very small amount of cancer cells were observed in the ascites (**Figure 1D**). No cancerous lesions were found in the right fallopian tube, omentum, or appendix. Immunohistochemistry of the tissue indicated a missense mutation in P53. The next-generation sequencing (NGS) gene testing of BRCA1 and BRCA2 revealed no clinically significant point mutations, insertions, or deletions. The patient therefore received five more cycles of carboplatin 500 mg + paclitaxel 240 mg + bevacizumab 400 mg. During the cycles of chemotherapy, the tumor markers and the lung and abdominal CT scans presented normal. The patient received regular follow-ups with normal tumor markers and imaging results and remained progression-free for 14 months.

Discussion

PET scans are valuable in diagnosis, staging, and treatment monitoring of gynecological cancers. Clinically, PET scans aid in determining the primary tumors as well as the extent and spread of cancer, help the oncologist with treatment planning and decision-making, and facilitate treatment evaluation and recurrence monitoring [8, 9]. Several types of cancer including pancreatic, ovarian,

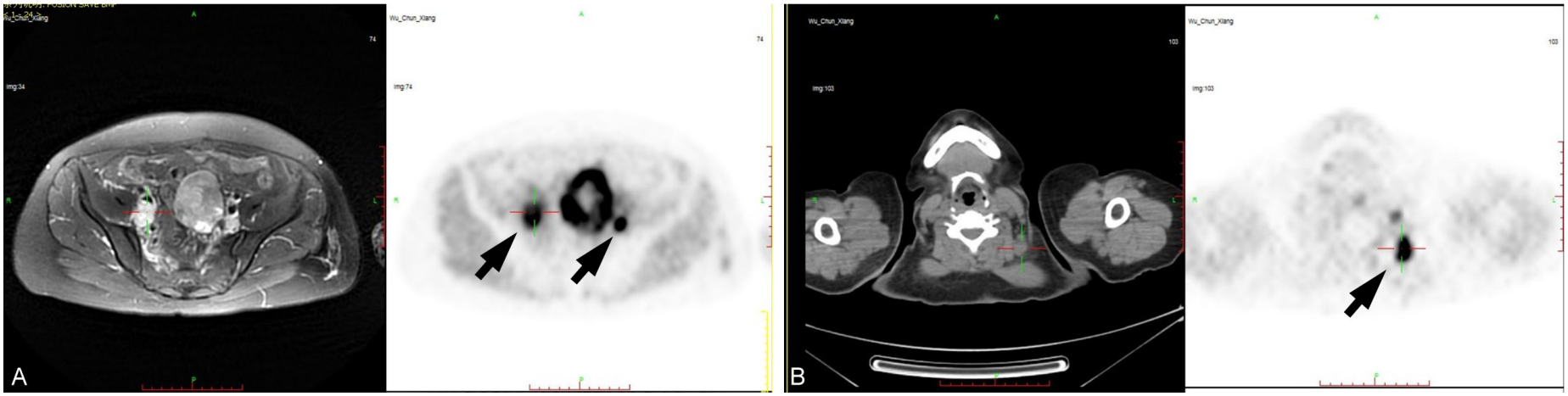

Figure 2. ^{68}Ga-FAPI PET of the case. A. Two slightly elongated soft tissue masses (arrows) with T2 signal in the pelvic cavity. B. A lymph node (arrow) in the left cervical V region.

lung, and liver cancer are noted for insidious onset. Elevated tumor markers or biopsy-proven metastasis followed by PET scans could easily trace the origin of the tumor. In this case, the patient was first presented to the local hospital due to a swollen lump in the region of the left side of the neck accompanied by the left lower limb. The lump was not taken serious attention until the patient was represented to the hospital with vaginal bleeding and pelvic mass revealed by pelvic ultrasonography. A biopsy was then taken to determine the nature of the lump. When the biopsy suggested a malignant tumor, a pre-surgical PET scan was scheduled for further determination of possible primary tumor as well as to evaluate the overall tumor burden and status of lymphatic metastasis. During the follow-up, tumor markers, ultrasonography as well as lung and abdominal CT scans were administered for routine follow-up. A PET scan will be scheduled to identify recurrent lesions when routine follow-up presents abnormality.

We believe that ^{68}Ga-FAPI PET/MR scan provides substantial support for clinical practice in the following aspects. Firstly, the patient recieved a ^{68}Ga-FAPI PET/MR scan for abdominal and pelvic lesions detection instead of ^{68}Ga-FAPI PET/CT. The resolution of PET/MR for soft tissue is conducive to identifying abdominal and pelvic lesions, capturing the shape and the border of the lesion, distinguishing adjacent tissues, and assisting in diagnosis [10]. ^{68}Ga-FAPI PET/MR successfully visualized primary and metastatic ovarian cancer, which was in general accordance with what was observed during surgery. Secondly, we believed the case exihibited outstanding performance of ^{68}Ga-FAPI PET/MR in assisting clinical practice. In this case, the FIGO IVb (the latest stage) HGSOC patient whose first presentation was distant lymph node metastasis in the left neck region. Due to the nature of HGSOC, which includes strong invasiveness, prone to metastasis, and extremely malignant, FIGO IVb patients usually might have multiple organ metastasis and excessive tumor burden, which called for neoadjuvant chemotherapy before tumor debulking surgery. The administration of ^{68}Ga-FAPI PET/MR assisted clinical practice via providing evidence for tumor burden, surgical tolerance, and surgical scope assessment. Guided by ^{68}Ga-FAPI PET/MR, optimal tumor debulking surgery was performed. The patient remained progression-free for 14 months up to date. Last but not least, though ^{68}Ga-FAPI PET/MR had been reported in the detection of ovarian cancer lesions in a few pioneering institutes, the application had not been fully promoted. As HGSOC was a major challenge, we hoped that the case we reported could help to add evidence for the promotion of the application of ^{68}Ga-FAPI PET/MR in the management of HGSOC.

In tumor imaging with PET, several radioactive tracers are commonly used including ^{18}F-fluorodeoxyglucose (FDG), ^{68}Ga-PSMA, ^{68}Ga-FAPI, etc. ^{18}F-FDG is one of the tracers that were first introduced into clinical practice, and for years it has been one of the most widely used PET tracers in cancer scanning [11, 12]. Although ^{18}F-FDG imaging has optimal performances in most cases, it has several drawbacks including false positives due to non-cancerous tissue with increased metabolic activity, false negatives due to cancer cells with low metabolic rates, non-specificity caused by inflammation and infection and limitations in detecting certain types of cancer such as prostate cancer, brain tumors or bone tumors [13, 14]. ^{68}Ga-FAPI was developed and introduced for clinical use around 2017-2018. ^{68}Ga-FAPI targets fibroblast activation protein (FAP), which is overexpressed in cancer-associated fibroblast in tumor microenvironment [6]. Compared to ^{18}F-FDG, the FAP binding ^{68}Ga-FAPI offers better tumor specificity in visualizing certain types of cancers, especially those where FAP is highly expressed, compared to the more generalized uptake of 18F-FDG by various tissues. In some cases, ^{68}Ga-FAPI provided clearer imaging and better differentiation between tumors and surrounding tissues, particularly in cancers where ^{18}F-FDG might not perform as well due to factors like inflammation or overlap in uptake by normal tissues. ^{68}Ga-FAPI has shown promise in detecting distant metastases, especially in tumors that don't typically accumulate ^{18}F-FDG well or in cases where ^{18}F-FDG PET/CT might not provide sufficient information [10, 15, 16]. However, the advantages of ^{68}Ga-FAPI may vary depending on the type and stage of cancer, and it may not necessarily replace ^{18}F-FDG entirely, as both tracers have their specific clinical applications. Although there was still no clear consensus on which tracer had better performance in gynecological cancer imaging, two recent studies suggested superior specificity by ^{68}Ga-FAPI in the diagnosis of ovarian and cervical cancers as well as the identification of metastasis [17, 18].

In this case, the patient received a hysterectomy due to a benign cause in 2014 but retained bilateral fallopian tubes. The origin of ovarian, fallopian tube, and peritoneal cancers has been long debated and was not clearly distinguished during clinical practice according to National Comprehensive Cancer Network guidelines. The theory of "fallopian tube origin" for HGSOC was first put forward in 2010 and reinforced with accumulating evidence [19, 20]. The current widely acknowledged understanding is that EOC originates from both the epithelia of the fimbriated extremity of the fallopian tube and the epithelia of ovaries and EOC was further categorized as type I (originates from ovarian epithelia, including endometrioid, clear cell, mucinous, low grade serous and transitional cell carcinomas) and type II (originate from fallopian tubal epithelia, including high grade serous, undifferentiated and carcinosarcomas) according to tumor origin and molecular backgrounds. In 2015, a population-based cohort study comparing ovarian cancer incidence in patients (N = 251465) who received hysterectomy, salpingectomy, or bilateral salpingo-oophorectomy due to benign causes vs. non-exposed population (N = 5449119) revealed that the risk of developing ovarian cancer in patients retained fallopian tubes was as twice as in

patients with both fallopian tubes removed [21]. Therefore nowadays, salpingectomy is routinely performed in patients who need hysterectomy to reduce the risk of developing ovarian cancer.

Because the ovaries and fallopian tubes are hidden in the abdominal cavity, 80% of all HGSOC are discovered after cancer has widely metastasized. However, in this case, no visible lesions were found during surgery and post-surgical routine pathology did not reveal any omental metastasis. The most prominent metastatic lesions would be the pelvic, abdominal, and distant lymphatic metastasis. It is still not clear whether the slightly different metastatic manifestation of this patient was due to a hysterectomy history. Theoretically, removal of the uterus reduces an important nearby target organ that could be invaded by direct invasion. However, invasions of other pelvic organs including the omentum and peritoneum could be achieved by both direct extension and tumor seeding. According to some studies, hysterectomy might also alter the lymphatic drainage and blood supply. To date, there is still not enough evidence to draw a definitive conclusion on whether a hysterectomy history would alter the pattern of metastasis or prognosis of ovarian cancer patients.

To sum up, PET/MR scan has significant advantages in primary tumor identification, metastasis evaluation, and recurrence determination with tailored tracers. Novel tracers such as ^{68}Ga-FAPI are being tested and gradually introduced. Updated PET technologies are promising aiding in the optimization of treatment plans of gynecological cancers.

Conclusion

^{68}Ga-FAPI PET/MR aids in primary tumor determination and tumor burden assessment and provides a guide for the management of late-stage HGSOC patients.

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Disclosure of conflict of interest

None.

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