Case Report
Case report: [18F]FAPI-42 PET/CT visualize primary adenoid cystic carcinoma not detected by [18F]FDG

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Abstract: Adenoid cystic carcinoma (ACC) is a rare salivary gland cancer. Still, its growth and invasion progress is slow, and its hematogenous metastasis is ACC's most common distant metastasis. Because of the broad expression and low background uptake of fibroblast activation protein (FAP) in tumor stroma, FAPI is considered another potential tracer of ACC in addition to FDG. In this case, we report a patient who was diagnosed with metastatic ACC liver cancer by fine needle aspiration biopsy (FNAB) and underwent PET/CT examination of [18F]FDG and [18F]FAPI-42 to find the primary cancer lesion. Finally, the primary cancer lesion was found in the left submandibular gland and was pathologically confirmed as ACC after resection.

Keywords: [18F]FAPI-42, [18F]FDG, adenoid cystic carcinoma, liver metastase

Introduction

Adenoid cystic carcinoma (ACC) is a rare malignant tumor in the salivary gland epithelium of the respiratory tract, about 1% of all head and neck malignancies [1]. High recurrence rates and distant metastasis are the foremost challenges in managing ACC, occurring in approximately 40% of all ACC patients [2]. Aggressive progression means it has a higher risk of hematogenous metastasis, and local lesions' growth hides its primary lesion. Therefore, many ACC patients are first diagnosed with metastatic ACC. Identifying the primary lesion as soon as possible is essential to improve patient prognosis. This case describes a patient initially found with a liver metastasis lesion who underwent dual PET/CT examination of [18F]FDG and [18F]FAPI-42. Finally, [18F]FAPI-42 PET/CT visualized the primary lesion of ACC located in the left submandibular gland.

Case

A 35-year-old woman are initially diagnosed with liver segment 7 (S7) lesion on upper abdominal CT due to chronic gastritis. The CT plain scan revealed 33×23×38 mm circular mild low-density shadow (CT value 36 HU), which was diagnosed as hepatic ACC through ultrasound-guided puncture. The results of FNAB suggested that the liver lesions were malignant tumors, and the morphology was suspected to be possible ACC. The patient have no positive tumor biomarkers such as AFP, CEA, CA199. To evaluate local and whole-body lesions, this patient underwent whole-body [18F]FDG. [18F]FDG PET/CT imaging showed mild increase in FDG activity foci in the left submandibular gland (SUVmax 3.04), an increase in posterior glandu-

lar density (CT value 119 HU), an increase in FDG activity foci at liver S7 lesions (SUVmax 4.51) and 2-hour delay imaging (SUVmax 4.98) (**Figure 1A**, **1C**, **1E**). In addition, the bilateral palate, sinuses, and salivary glands are of particular concern, all of which exhibit diffuse mild physiological or functional uptake of FDG. Among them, CT plain scan revealed suspicious increased density shadows in the left submandibular gland. Considering that primary ACC in the liver is extremely rare, and CT shows abnormalities in the left submandibular gland, we recommend adding [18F]FAPI-42 PET/CT examination. In [18F]FAPI-42 PET/CT imaging, the liver lesion (SUVmax 3.90) and the left submandibular gland lesion (SUVmax 6.25) show significantly higher abnormal uptake than the background (**Figure 1B**, **1D**, **1F**).

According to the FAPI imaging, left submandibular gland lesion resection was performed, and the pathology was ACC after resection. The tumor cells of left submandibular gland tumor and liver S7 lesion are arranged into small tubular, trabecular and nest like structures, with consistent cell morphology, small, deeply stained nuclei, sparse and unclear cytoplasm. Sieve like structures can be seen in the cell nest, and mucus can be seen in it. The immunohistochemical results of liver lesions are metastatic ACC. Histopathological examination (hematoxylin-eosin 200) of the specimens obtained from the liver segment seven mass revealed positive immunohistochemistry (IHC) stains were observed for CK19(+), CK5/6 (weak positive), CK-pan(+), CD117(+), P63(+), Calponin (weak positive) and S-100 (weak positive) (**Figure 2**). In contrast, negative staining was observed for Hepatocyte(-), Glypican-3(-), GATA-3(-), ER(-), CgA(-), SYN(-), INSM1(-). In addition, the left cervical region I and II lymph nodes dissection were
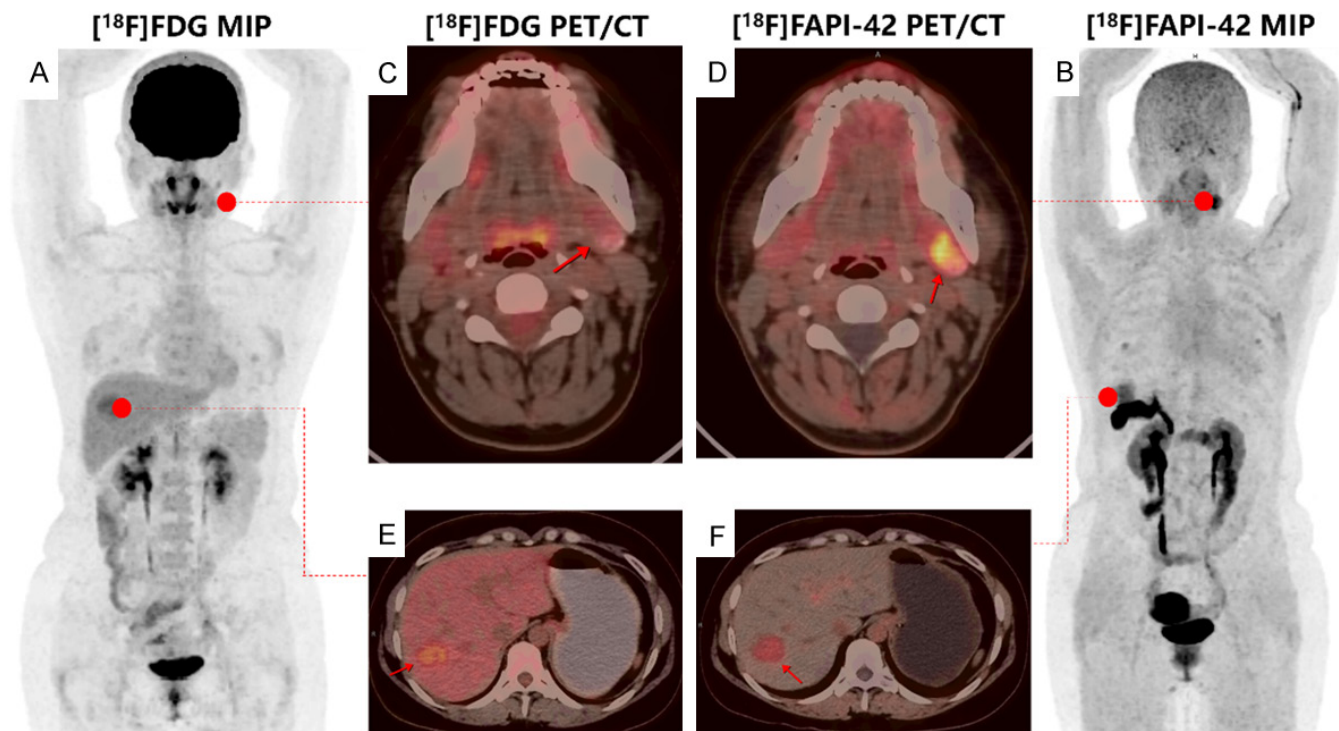
Figure 1. The comparision of the [^{18}F]FDG and [^{18}F]FAPI-42 PET/CT. The [^{18}F]FDG and [^{18}F]FAPI-42 MIP images (A, B). The [^{18}F]FDG and [^{18}F]FAPI-42 PET/CT fusion images of the left submandibular gland in this patient (C, D). The [^{18}F]FDG and [^{18}F]FAPI-42 PET/CT fusion images of the liver S7 in this patient (E, F).

performed in a certain area, which showed no radiographic concentration of [^{18}F]FAPI-42. The pathological results showed no lymph node metastasis. All of the findings were consistent with ACC and liver metastasis lesions. The patient subsequently received radiotherapy treatment.

Discussion

ACC is a malignant tumor originating from the glandular epithelium. It can occur at any age, but it is most common in middle-aged and older adults aged 40-60. There is no significant difference in the incidence between men and women. ACC mainly involves the head and neck salivary glands, and it is rarely found in the gingiva, breast, kidney, bone, lymph nodes, and liver [3-8].

ACC is a rare cancer with a very high degree of malignancy [9]. The symptoms of adenoid cystic carcinoma are not obvious. In the early stage, painless masses are most common, but in a few cases, pain is diagnosed, and the nature of pain is intermittent or persistent. Compared with other types of salivary gland malignancies, ACC is difficult to diagnose preoperatively. The diagnosis of ACC should be considered firstly when pain and nerve palsy occur in the early stage of salivary gland mass. But this patient does not have symptoms of bilateral salivary glands.

In order to further confirm ACC, FNAB can be performed. Under the microscope, the tumor cells are round or ovoid,

like basal cells, and aggregate in a ball shape. The mucus is globular, with one or more layers of tumor cells surrounding it. This unique manifestation is not found in other salivary gland epithelial tumors, which can be diagnosed as adenoid cystic carcinoma. On the ACC of protein level expression, diagnosis of ACC is useful for diagnosis (PS100, Vimentin, CD117, CKit, muscle actin, P63) and for prognosis (Ki-67) [9].

Firstly, although ACC grows slowly and is often not accompanied by lymph node metastasis after initial treatment, it is extremely easy to distant metastasis, even in the case of unknown primary lesions like this case. Without any head or facial symptom, this patient was confirmed to liver S7 metastatic ACC through CT plain scan, ultrasound-guided puncture biopsy and IHC. Then, guidelines recommend [^{18}F]FDG PET/CT for advanced high-grade salivary gland tumors, the FDG uptake of ACC is still lower than other squamous cell carcinoma [10, 11]. Coupled with the physiological uptake of FDG in salivary glands, the identification of ACC lesions becomes more challenging. In addition, some researchers have reported the application of PSMA imaging in ACC. They found that PSMA can find more metastatic lesions compared with FDG [12, 13]. However, the uptake of primary lesions may still be hided due to the widespread expression of PSMA in normal salivary gland epithelium.

Fibroblast activating protein (FAP) is a kind of membrane protease that affects the extracellular matrix degradation
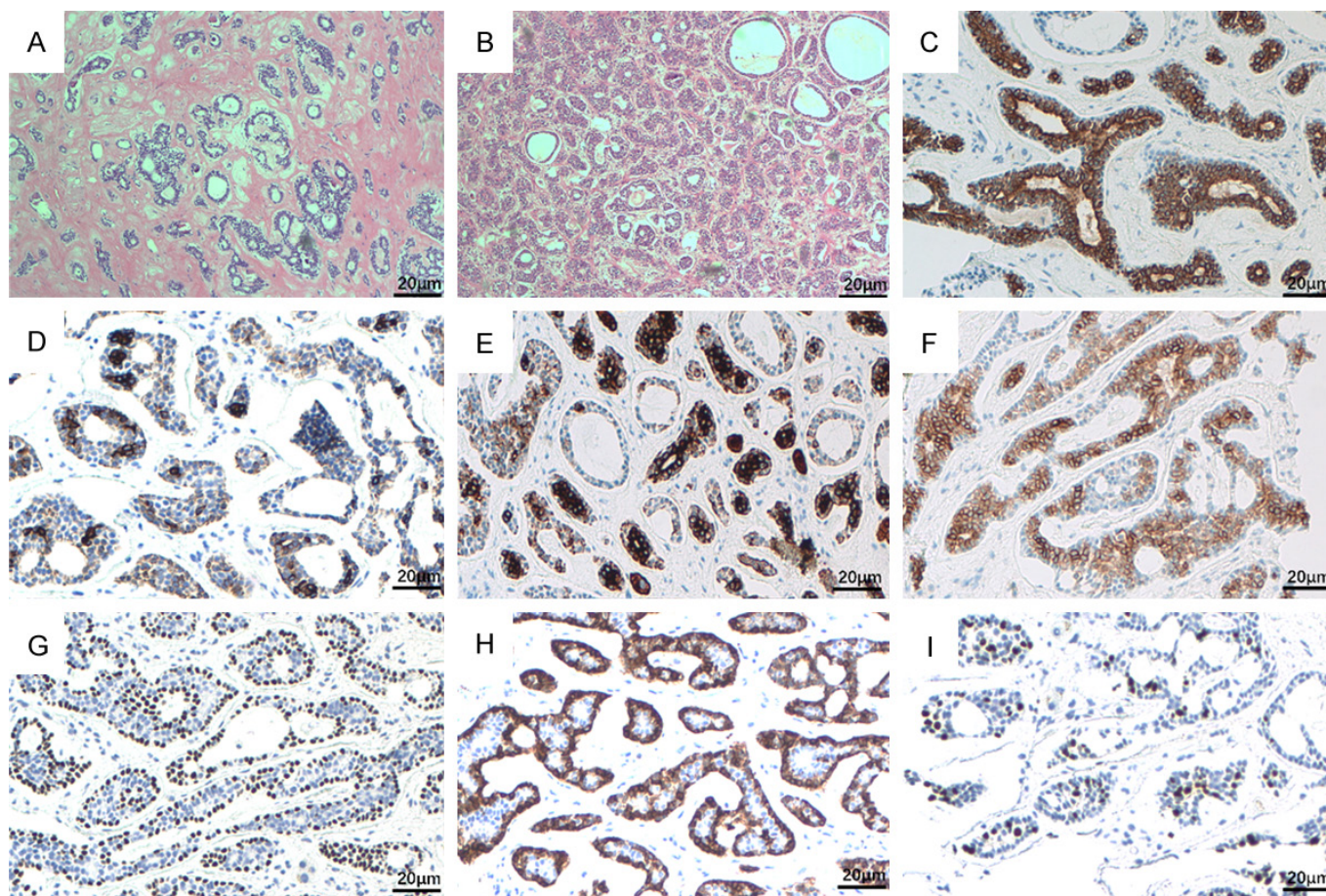
Figure 2. Left submandibular gland lesion (A) and puncture tissue of liver S7 lesion (B) are verified by hematoxylin-eosin staining (HE) and immunohistochemistry (IHC) (C-I). Glandular epithelial component of liver S7 puncture tissue are observed by IHC include CK19(+) (C), CK5/6(partial+) (D), CK-pan(+) (E), CD117(+) (F); while the myoepithelial components of liver S7 puncture tissue demonstrated that P63(+) (G) and Calpon(partial+) (H). The proliferation index-related factor Ki-67 is about 20% (I).

function of tumor cells and is also a new progress in tumor diagnosis and treatment in nuclear medicine. In recent years, FAP-targeted tracers have been proven to have optimistic application prospects in a variety of tumors, including head and neck tumors. The fibrous stroma is also one of the components of ACC tissue, which contains cancer-associated fibroblasts (CAFs) that over-express FAP [14, 15]. Manuel Röhrich also confirmed that ACC contains many FAP-positive stroma [16]. Therefore, FAPI can visualize ACC lesions better, supported by several recent reports [17, 18].

However, it is worth concerned that the literature above all used ^{68}Ga-labelled FAPI. Compared to ^{68}Ga-labeled tracers, ^{18}F-labeled tracers have more accessibility cause of more straightforward and more efficient production, and longer half-life, which makes longer distance transportation possible [19]. Although there are specific differences in biological distribution between ^{68}Ga and ^{18}F, specifically more uptake in parotid and submandibular land for [18F]FAPI-42 [19, 20], its higher tumor background ratio (TBR=1.89) compared to FDG (TBR=1.28), which still helps visualize malignant lesions. Our case demonstrates that commercialized [18F]FAPI-42 is better for

evaluating primary and metastatic ACC in institutions without cyclotrons.

FAP-targeted PET/CT imaging can not only visualize the primary and metastatic lesions of ACC but also improve the accuracy of clinical staging and radiotherapy planning compared to traditional CT and MRI [16]. FAP-targeted radionuclide therapy has resulted in objective responses in challenging to treat end-stage cancer patients such as colorectal cancer, lung cancer, breast cancer, and so on [21]. At present, FAP-targeted radionuclide therapy in ACC has not been reported, but it had a specific therapeutic prospect for FAP-targeted radionuclide therapy in ACC because of its overexpressed FAP protein.

Although we reported only one case, the primary and metastatic ACC lesions were timely detected in the [18F]FAPI-42 PET/CT. Nevertheless, this patient was comfirmed with ACC. Even though ACC has a very low incidence, it is potentially severe owing to the competence of distant metastasis. Therefore, early diagnosis and therapy are essential for the prognosis of ACC patients, and we should consider the possibility of head and neck lesions when a patient presents with isolated distant metastasis without

lymph node metastasis. In this case, [¹⁸F]FAPI-42 PET/CT visualizes primary ACC that are not detected by [¹⁸F]FDG, which compensates for the low TBR of FDG effectively.

Disclosure of conflict of interest

None.

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