Hepatic epithelioid angiomyolipoma mimicking hepatocellular carcinoma on MR and ^{18}F-FDG PET/CT imaging: A case report and literature review

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Abstract
Hepatic epithelioid angiomyolipoma (HEAML) is a rare hepatic mesenchymal tumor with malignant potential. Unlike hepatic angiomyolipoma, HEAML is devoid of adipocytes. Thus, it is easy to be misdiagnosed as other tumors of liver, especially hepatocellular carcinoma (HCC) on preoperative imaging examinations. Herein, we present a case of HEAML mimicking HCC on magnetic resonance (MR) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in a 50-year-old female. After the primary diagnosis of HCC, the patient underwent a laparoscopic resection. The histopathology and immunohistochemical staining helped to reach the final diagnosis of HEAML. The important sign of central vessel can be seen on MRI in this case. The average apparent diffusion coefficient (ADC) value of the HEAML is $0.86\pm0.13\times10^{-3}$mm^2/s, which is lower than that of $0.97\pm0.02\times10^{-3}$mm^2/s of the normal liver. Previous literature on ^{18}F-FDG PET/CT imaging of HEAML is limited to only 2 cases. The ^{18}F-FDG PET/CT images of HEAML with high ^{18}F-FDG accumulation with a maximum standardized uptake value (SUVmax) of 8.88 and extensive necrosis are presented, indicating its malignant potential. This case aims to improve the ability of differential diagnosis from HCC on multimodal imaging, and provides values for further ^{18}F-FDG PET/CT related studies.

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Introduction

Hepatic epithelioid angiomyolipoma (HEAML) is a rare kind of hepatic mesenchymal tumor with potential malignancy. Up to now, most HEAML are reported on basis of individual cases or small samples. As its low incidence combined with nonspecific clinical manifestations and atypical imaging findings, it is easy to be misdiagnosed as other liver tumors with a high rate up to 40.34% (165/409), especially hepatocellular carcinoma (HCC) which topped the list (71/409) [1]. Here, we present a case of HEAML mimicking HCC on magnetic resonance imaging (MRI) and analyze it on positron emission tomography/computed tomography with fluorine-18-fluorodeoxyglucose (^{18}F-FDG PET/CT).

Case Report

A 50-year-old female was admitted to our hospital with 1-month history of abdominal pain and 1-week history of chest pain. Physical examination revealed slightly rebound tenderness at the upper abdomen, accompanied by swelling pain at the manubrium of sternum. For the past medical history, the patient had pulmonary and intestinal tuberculosis for more than 16 years, and a sternum tuberculosis resection for more than 6 years. The patient self-reported the tuberculosis had been cured and no anti-tuberculosis drugs were taken recently. The history of other infectious diseases such as viral hepatitis was denied.

After admission, the patient underwent laboratory examinations, ultrasound, MR and ^{18}F-FDG PET/CT. Laboratory examinations showed that the lactate dehydrogenase was 785IU/L, hepatitis B core antibody was 6.16s/CO and tumor indicators were all negative. Ultrasound revealed mixed echo-mass in left liver and HCC to be suspected. Unenhanced MR images showed the mass located at the left lateral lobe of the liver was measured

about 8.4×6.5cm with hyperintensity on T2-weighted imaging (T2WI, Figure 1A) and hypointensity on T1-weighted imaging (T1WI, Figure 1B). Diffusion-weighted imaging (DWI, Figure 1D) showed a hyperintense mass using a high b value of 800sec/mm^2 and the corresponding ADC map (Figure 1E) showed a decreased signal intensity in the mass. The ADC value of HEAML and the normal liver was measured and calculated as 0.86±0.13×10^{-3}mm^2/s and 0.97±0.02×10^{-3}mm^2/s, respectively. Enhanced MR images (Figure 2) showed the mass was unevenly enhanced in arterial phase and washed out in delayed phase with a low signal relative to the surrounding liver, accompanied by the enhanced pseudocapsule, suggesting an impression of HCC. Fluorine-18-FDG PET/CT images showed the mass accompanied by a ring-shape of high accumulation of ^{18}F-FDG, with a maximum standardized uptake value (SUVmax) of 8.88, was considered as a malignant liver tumor (Figure 3B). Another lesion with high uptake of ^{18}F-FDG is a soft tissue nodule at the right front of the manubrium, with a SUVmax of 10.02 (Figure 3A). Combining with the history of sternal tuberculosis surgery, the soft tissue nodule with calcification was considered as tuberculous infiltration.

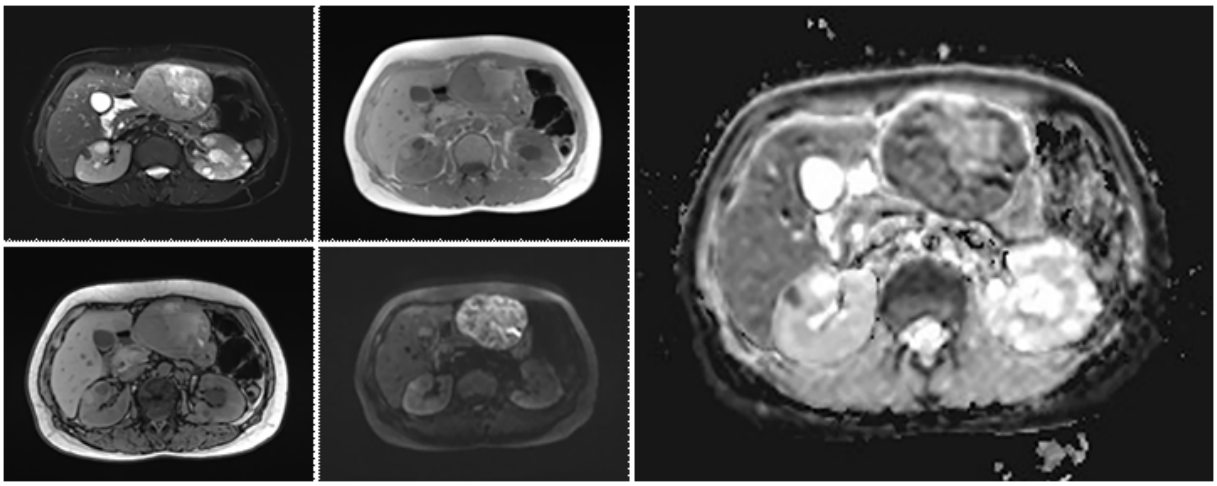

Figure 1. Unenhanced MR imaging. T2WI (A) and T2WI (B) showing large necrosis area with hemorrhage signal. There is no fat attenuation in the in phase (B) and out-phase (C). The DWI (D) and the corresponding ADC map (E).

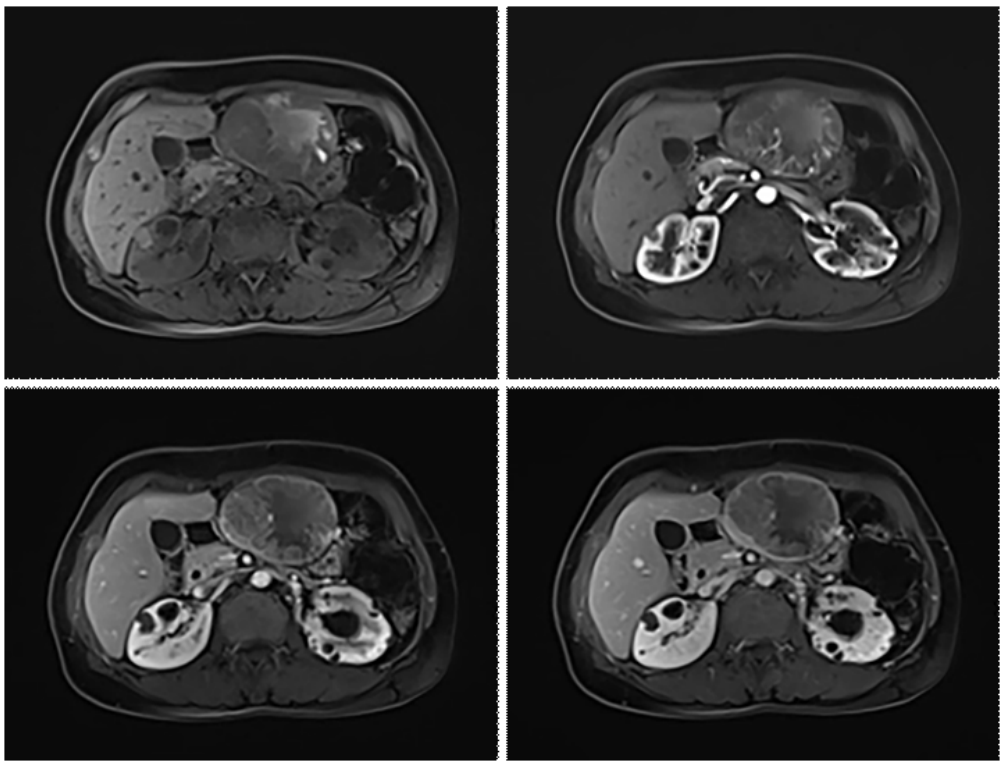

Figure 2. Enhanced MR imaging. (A) The pre-enhanced T1WI with fat suppression. (B) In arterial phase, tortuous vascular enhancement can be observed (red arrow). (C) In portal phase, the tumor is further enhanced. (D) In delayed phase, the tumor enhancement is slightly washed out and lower than the normal liver, with a delayed enhancement of vessels (red arrow).

The impression for the mass tended to be HCC, so the laparoscopic resection of complicated HCC was performed. During the operation, the texture of the liver was normal, and the hard mass was successfully resected. Grossly observed, the tumor was a white grayish yellow mass with a size of about 5×3.5cm. At microscopy, the epithelioid type of tumor cells showed solid nested appearance, with large areas of necrosis, hemorrhage and intravascular tumor emboli. The tumor cells had abundant cytoplasm, large nuclei, obvious nucleoliand some nuclei were malformed (Figure 4B). Immunohistochemistry was displayed as followed (Figure 4C-F): Hepatocyte (-), AFP (-), Arginase-1 (-), Glypican-3 (-), CEA-R (-), CD34 (+), Galectin-3 (-), CK7 (-), CK19 (-), S-100 (-), Melan-A (+), HMB45(+), Ki-67 (7%). The final histopathologic diagnosis was confirmed to be HEAML.

The follow-up at 24 months revealed no evidence of tumor recurrence and metastasis.

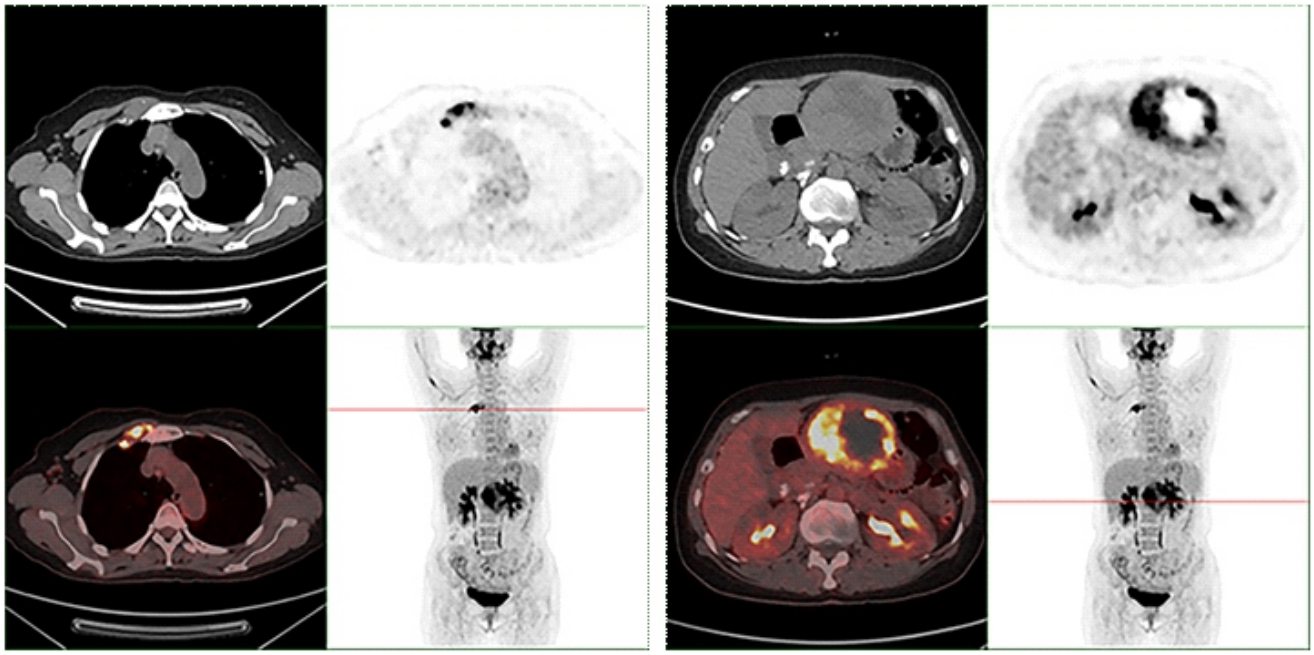

Figure 3. ^{18}F-FDG PET-CT imaging of the soft tissue nodule (A) and the mass in liver (B).

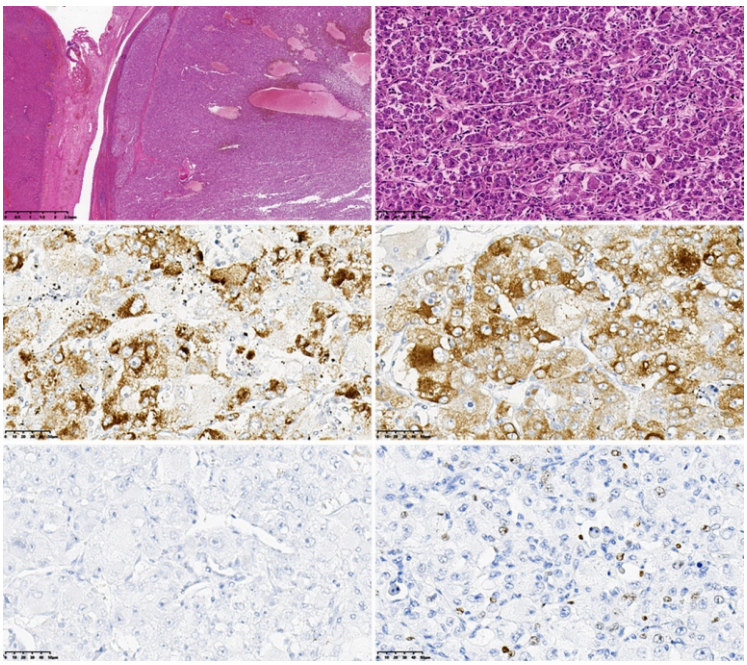

Figure 4. Pathological photographs. (A) Microscopically, the tumor is well defined by extremely pressured normal liver parenchyma. There are large and malformed blood vessels with focal hemorrhage (HE×10). (B) The tumor is almost entirely composed of epithelioid cells without adipose components (HE×200). Immunohistochemistry reveals the cells are positive for HMB-45 (C, magnification × 400), Melan A (D, magnification × 400) and Ki-67 (F, magnification × 400), negative for S-100 (E, magnification × 400). The Ki-67 index is approximately 7%.

Discussion

Angiomyolipoma (AML) is generally regarded as a kind of benign mesenchymal tumor. It is mainly composed of smooth muscle cells, abnormal blood vessels and mature adipocytes in varying proportions. Based on the content of different components, there are multiple histological variations of AML. Epithelioid angiomyolipoma (EAML), as a special variant of AML, is composed almost extensively of epithelioid cells and devoid of adipocytes, which is thought to possess malignant potential [2]. Epithelioid angiomyolipoma is commonly seen in kidney, but is rarely occurred in liver, which is known as HEAML. It tends to occur in young and middle-aged women, with a male to female ratio of 1:4.84 and a median age of 44 years [1]. There are no specific correlations with hepatitis, cirrhosis and family history of tumor. Alpha-fetoprotein (AFP) and other tumor indicators are usually negative [2]. Most of HEAML are usually found occasionally by regular health checkups or examinations for other diseases. When the tumor is large enough, it can be found by complications such as palpable abdominal mass, abdominal pain, and few are treated for tumor spontaneous rupture. In this case, the clinical data are basically consistent with those reported in the literature. There are no special tumor indicators increased, except the elevation of lactate dehydrogenase, which shows nonspecial directivity.

Immunohistochemistry is one of the most important diagnostic methods for HEAML. HEAML is considered as a member of the perivascular epithelioid cell tumor (PEComa) family, which is characterized by the expression of both melanocytic markers of HMB-45 and Melan A [3]. The absent expression of S-100 helps the distinction from malignant melanoma [4]. In this case, the epithelioid cell morphology (Figure 4B), the positive expression of HMB45 and Melan-A, and negative expression of S-100 can make definitive diagnosis of HEAML. Most HEAML are benign, and malignant HEAML are rarely reported. Up till now, definitive criteria for malignant HEAML have not been put forward. Relevant literature suggested large tumor size, cytologic atypia, coagulative necrosis, vascular invasion and metastasis appear to be associated with malignant transformation of HEAML [5]. The case we report contains malformed nuclei, intravascular tumor emboli and large area of necrosis, which suggest it a malignant tendency. However, the patient is free of tumor recurrence and metastasis at a 24-month follow-up, which may be related to the weak expression of Ki-67 of 7% in this case. Weak expression of Ki-67 indicates the tumor is in slow growth and in a non-proliferating phase [5]. The median time of postoperative relapse was reported as 42.5 months [1]. Therefore, whether the tumor is malignant or not needs further follow-up.

Due to the lack of fat in the HEAML, it is difficult to distinguish from other liver tumors on MRI. Additionally, when its enhanced appearance is overlapped with that of HCC, the distinction between the two is particularly difficult. Studies have shown that HEAML is rich in tortuous and dilated vessels with spot-and-strip-shaped vascular enhancement within the tumor, named the central vessel sign, is a characteristic imaging finding of HEAML [6]. In HCC, the tumor supply vessels are mainly hepatic arteries. These vessels are discontinuous and irregular. While in HEAML, the enhanced blood vessels are mainly in venous structures [6], which are tortuous, smooth and varied in thickness. The early enhanced vessels in arterial phase were pathologically proven to be malformed venous vessels (Figure 4A) in our case. Most of these venous vessels in HEAML are connected to drainage veins such as hepatic vein, portal vein or inferior vena cava. Previous literature has reported the rate of early enhanced venous in arterial phase of HEAML is significantly higher than that of HCC with an occurrence rate up to 72.7%, which is called early venous drainage sign of HEAML [7]. It is also an important imaging feature of HEAML. Unfortunately, in this case, this sign is not so obvious. There are still clear enhanced tumor vessels in delayed phase, which may be related to the long retention time of the contrast agent after entering the thick-walled vessels [8].

The enhancement patterns of HEAML are diverse, mainly divided into three types, including fast wash-in and fast wash-out, fast wash-in and slow wash-out, and delayed enhancement [1, 7]. These kinds of radiological variations may be explained with the diversity and variability of tumor components [8]. This case can be described as the fast wash-in and slow wash-out enhancement, which cannot be differentiated from the typical wash-out enhancement pattern of HCC. Hepatocellular carcinoma can also display atypical enhancement patterns of iso-, hypo- or hyper-vascular lesions without wash-out [9]. Moreover, in this case, a ring-shaped enhanced pseudocapsule can be seen in portal and delayed phase. Literature confirmed that when HEAML is large enough, it can compress the surrounding liver parenchyma to form a pseudocapsule [1]. Some studies have demonstrated HAML possessed higher ADC values than HCC [7]. However, in this case, the ADC value of HEAML is lower than the normal liver. This may be due to the intratumoral hemorrhage that reduced the ADC value. Hence, it is extremely difficult to distinguish HEAML and HCC through enhancement pattern, pseudocapsule and ADC value.

As HEAML is a potentially malignant tumor, it is necessary to define the range of lesions. Fluorine-18-FDG PET/CT can detect the distribution of lesions in a larger area. Previous literature on the use of ^{18}F-FDG PET/CT in the assessment of HEAML is limited. Literature has suggested HEAML with intratumor hemorrhage is characterized by high accumulation of ^{18}F-FDG [10]. Necrosis and high ^{18}F-FDG uptake of EAML often indicate the tumor biological aggressiveness [11]. In this case, the PET/CT images show a mass with extensive necrosis and high ^{18}F-FDG accumulation indicating its malignant potential. High ^{18}F-FDG accumulation in tumor is easily confused with other hepatic malignancies, but it has values in differential diagnosis for well or moderately differentiated HCC to some extent. Well or moderately differentiated HCC possess relatively low ^{18}F-FDG uptake due to the low glucose transporter-1 (GLUT1) and high glucose-6-phosphatase (G6Pase) expression [12]. However, high ^{18}F-FDG is accumulated in poorly differentiated HCC, so the high ^{18}F-FDG uptake of the hepatic mass in PET/CT can actually exclude a well differentiated HCC. Nevertheless, the ^{18}F-FDG uptake in HEAML is also variable, and even two lesions in the same liver can have different levels of ^{18}F-FDG uptake [13]. Therefore, ^{18}F-FDG PET/CT for the identification of HEAML needs further studies.

In conclusion, we report a case of HEAML mimicking HCC on MRI and ^{18}F-FDG PET/CT. Although the imaging manifestations of HEAML and HCC overlap, signs of central vessel and early venous drainage on MRI can provide important values for differential diagnosis. The clinical data such as no history of hepatitis and cirrhosis also help to make diagnosis. In addition, the ^{18}F-FDG accumulation on PET/CT also offers some clues for diagnosis. The final diagnosis of HEAML still depends on the histopathologic and immunohistochemical features.

The authors declare that they have no conflicts of interest.

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Author contributions
Siqi Wang consulted the literature and drafted the manuscript. Huawei Xia performed the radiological analysis. Xiangxiang Liu and Yao Liu performed the nuclear medical analysis. Cen Lou read andapproved the final manuscript.

Bibliography

1. Mao JX, Teng F, Liu C et al. Two case reports and literature review for hepatic epithelioid angiomyolipoma: Pitfall of misdiagnosis. *World J Clin Cases* 2019; 7(8): 972-83.
2. Fukuda Y, Omiya H, Takami K et al. Malignant hepatic epithelioid angiomyolipoma with recurrence in the lung 7 years after hepatectomy: a case report and literature review. *Surg Case Rep* 2016; 2: 31.
3. Zhou Y, Chen F, Jiang W et al. Hepatic epithelioid angiomyolipoma with an unusual pathologic appearance: expanding the morphologic spectrum. *Int J Clin Exp Pathol* 2014; 7(9): 6364-9.
4. Ronen S, Prieto VG, Aung PP. Epithelioid Angioleiomyoma Mimicking Metastatic Melanoma in a Liver Tumor. *J Cutan Pathol* 2020; 47(9): 824-8.
5. Nguyen TT, Gorman B, Shields D et al. Malignant hepatic angiomyolipoma: report of a case and review of literature. *Am J Surg Pathol* 2008; 32(5): 793-8.
6. Jeon TY, Kim SH, Lim HK et al. Assessment of triple-phase CT findings for the differentiation of fat-deficient hepatic angiomyolipoma from hepatocellular carcinoma in non-cirrhotic liver. *Eur J Radiol* 2010; 73(3): 601-6.
7. Liu W, Wang J, Huang Q et al. Comparison of MRI Features of Epithelioid Hepatic Angiomyolipoma and Hepatocellular Carcinoma: Imaging Data From Two Centers. *Front Oncol* 2018; 8: 600.
8. Abhirup B, Kaushal K, Sanket M et al. Malignant hepatic perivascular epithelioid cell tumor (PEComa) - Case report and a brief review. *J Egypt Natl Canc Inst* 2015; 27(4): 239-42.
9. Kovac JD, Milovanovic T, Dugalic V et al. Pearls and pitfalls in magnetic resonance imaging of hepatocellular carcinoma. *World J Gastroenterol* 2020; 26(17): 2012-29.
10. Marcuzzi A, Haider EA, Salmi ISA. Hepatic epithelioid angiomyolipoma with renal metastasis: radiologic-pathologic correlation. *Radiol Case Rep* 2018; 13(4): 829-33.
11. Vicens RA, Jensen CT, Korivi BR et al. Malignant renal epithelioid angiomyolipoma with liver metastasis after resection: a case report with multimodality imaging and review of the literature. *J Comput Assist Tomogr* 2014; 38(4): 574-7.
12. Izuishi K, Yamamoto Y, Mori H et al. Molecular mechanisms of ^{18}F-fluorodeoxyglucose accumulation in liver cancer. *Oncol Rep* 2014; 31(2): 701-6.
13. Zhang Y, Li B, Hou J et al. Hepatic Epithelioid Angiomyolipoma and ^{18}F-FDG PET/CT. *Clin Nucl Med* 2018; 43(6): 422-4.