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CLINICAL RESEARCH

Highly metabolic thrombus of the portal vein: ^{18}F fluorodeoxyglucose positron emission tomography/computer tomography demonstration and clinical significance in hepatocellular carcinoma

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Abstract

AIM: To assess the ability of ^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography (^{18}F-FDG PET/CT) to differentiate between benign and malignant portal vein thrombosis in hepatocellular carcinoma (HCC) patients.

METHODS: Five consecutive patients who had HBV cirrhosis, biopsy-proven HCC, and thrombosis of the main portal vein and/or left/right portal vein on ultrasound (US), computer tomography (CT) or magnetic resonance imaging (MRI) were studied with ^{18}F-FDG PET/CT. The presence or absence of a highly metabolic thrombus on ^{18}F-FDG PET/CT was considered diagnostic for malignant or benign portal vein thrombosis, respectively. All patients were followed-up monthly with US, CT or MRI. Shrinkage of the thrombus or recanalization of the vessels on US, CT or MRI during follow-up was considered to be definitive evidence of the benign nature of the thrombosis, whereas enlargement of the thrombus, disruption of the vessel wall, and parenchymal infiltration over follow-up were considered to be consistent with malignancy. ^{18}F-FDG PET/CT, and US, CT or MRI results were compared.

RESULTS: Follow-up (1 to 10 mo) showed signs of malignant thrombosis in 4 of the 5 patients. US, CT or MRI produced a true-positive result for malignancy in 4 of the patients, and a false-positive result in 1. ^{18}F-FDG PET/CT showed a highly metabolic thrombus in 4 of the 5 patients. ^{18}F-FDG PET/CT achieved a true-positive result in all 4 of these patients, and a true-negative result in the other patient. No false-positive result was observed using ^{18}F-FDG PET/CT.

CONCLUSION: ^{18}F-FDG PET/CT may be helpful in discriminating between benign and malignant portal vein thrombi. Patients may benefit from ^{18}F-FDG PET/CT when portal vein thrombi can not be diagnosed exactly by US, CT or MRI.

Key words: ^{18}F-fluorodeoxyglucose; Positron emission tomography/computer tomography; Hepatocellular carcinoma; Portal vein tumor thrombus; Portal vein blood thrombus

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INTRODUCTION

Hepatocellular carcinoma (HCC) carries a high risk of invasion of the portal vein. The detection and etiologic characterization of these thrombi are essential for treatment planning, particularly in patients with hepatic tumors, because malignant thrombosis is a negative factor in terms of prognosis[1,2]. Macroscopic tumor thrombi in the portal vein appear to occur during the terminal stage of HCC. The management of HCC with portal vein tumor thrombosis is complicated and controversial[3,4]. However, benign portal vein thrombi can usually be successfully

managed with early identification[5]. Portal vein thrombosis (PVT) can be diagnosed noninvasively by using either real-time or duplex Doppler sonography, contrast-enhanced sonography, computer tomography (CT) or magnetic resonance imaging (MRI). Typical appearances of venous thrombosis include an intraluminal filling defect, peripheral ring-like enhancement and collateral venous channels[6,7]. Micro-invasive fine-needle aspiration (FNA) of a portal vein thrombus under ultrasound guidance also is an effective, well-tolerated method for the diagnosis of HCC patients with PVT[8,9].

This pattern of ^{18}F-FDG PET/CT has been reported in cases with different kinds of malignant tumor[10], while portal tumor growth and portal vein thrombosis identified by PET/CT in HCC patients have rarely been reported to date. We found highly metabolic thrombi of the portal vein on ^{18}F-FDG PET/CT scans in four patients with HCC. ^{18}F-FDG -avid lesions may represent malignant portal vein thrombosis. The importance of this finding for the diagnosis of and prognosis in HCC and the role of ^{18}F-FDG PET/CT in the diagnosis of PVT are discussed.

MATERIALS AND METHODS

Patients

Between January 2007 and October 2007, five HCC patients with suspected portal vein tumor thrombus (PVTT) were assigned to PET/CT evaluation. Five consecutive patients who had HBV cirrhosis, biopsy-proven HCC, and thrombosis of the main portal vein and/or left/right portal vein on US, CT or MRI, were also studied by ^{18}F-FDG PET/CT. PET/CT. US, CT or MRI results were compared with those at follow-up.

FDG PET/CT technique

The patients were asked to fast for at least 4 h before undergoing PET/CT. The blood glucose levels of these patients should have been within the normal range (0.7-1.2 g/L) prior to intravenous injection of ^{18}F-FDG. The patients received an intravenous injection of 370-666 MBq (10-18 mCi) of ^{18}F-FDG. Data acquisitions by an integrated PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA) were performed within 60 min after the injection. Data acquisition was performed as follows: CT scanning was performed first, from the head to the pelvic floor, with 110 kV, 110 mA, a tube rotation time of 0.5 s and a 3.3 mm section thickness, which was matched to the PET section thickness. Immediately after CT scanning, a PET emission scan that covered an identical transverse field of view was obtained. Acquisition time was 3 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and co-registered images were displayed on a workstation.

Definitive diagnoses of thrombosis and thrombus malignancy

On integrated PET/CT images, thrombi were considered malignant if the maximum standardized uptake value (SUV) was greater than those of normal liver structures with a discrete margin and/or the ^{18}F-FDG uptake was greater than that of the lumen of the descending aorta in the same axial slice. Thrombi were considered benign if the maximum SUV was lower than those of normal liver structures and/or the ^{18}F-FDG uptake was lower than that of the lumen of the descending aorta in the same slice.

All patients were followed-up monthly by US, CT or MRI. Shrinkage of the thrombus and/or recanalization of the vessels on US, CT or MRI during follow-up was considered to be definitive evidence of the benign nature of the thrombosis, whereas enlargement of the thrombus, disruption of the vessel wall, and parenchymal infiltration over follow-up were considered to be consistent with malignancy.

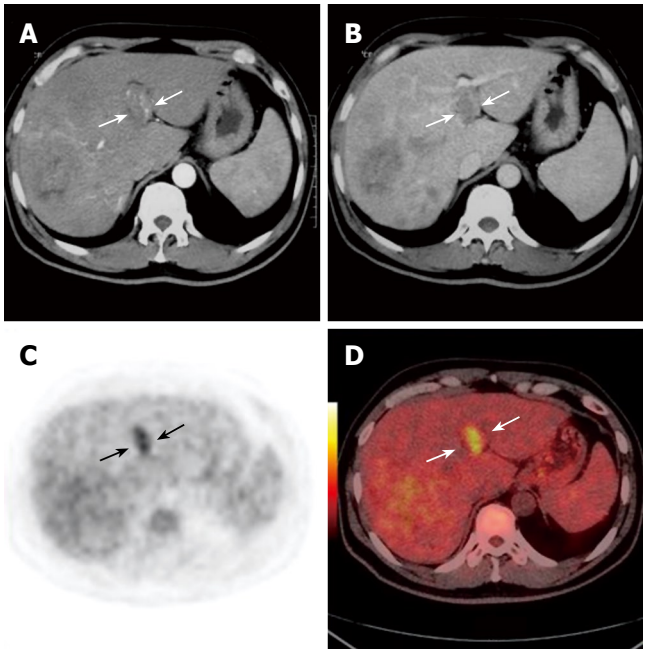

Figure 1 Contrast CT scan showing right lobe and caudate lobe mass and portal vein thrombus in a 55-year-old man. During the arterial phase, the thrombus appears as an iso- to hypodense intraluminal area with dense linear enhancement (white arrows, **A**). A filling defect was detected in the left branch during the portal phases (white arrows, **B**). PET (black arrows, **C**) and PET/CT fused images (white arrows, **D**) reveal a highly metabolic thrombus in the left branch.

RESULTS

Follow-up (1 to 10 mo) showed signs of malignant thrombosis in 4 out of 5 patients. US, CT or MRI produced a true-positive result for malignancy in 4 out of 5 patients, and a false-positive result in 1. ^{18}F-FDG PET/CT was positive in four patients with malignant thrombi, and revealed a true-negative result in the remaining patient. ^{18}F-FDG PET/CT showed highly metabolic thrombi in 4 of the 5 patients. No false-positive result was obtained using ^{18}F-FDG PET/CT.

As shown in Figures 1-5, the four malignant thrombi had SUVs of 3.0-11.5, which were higher than those of the normal liver parenchyma and the lumen of the descending aorta in the same axial slice. The SUVs of these malignant thrombi were lower than those of the HCC mass in the same axial slice. Thrombosis was significantly more common in patients with highly metabolic tumor lesions

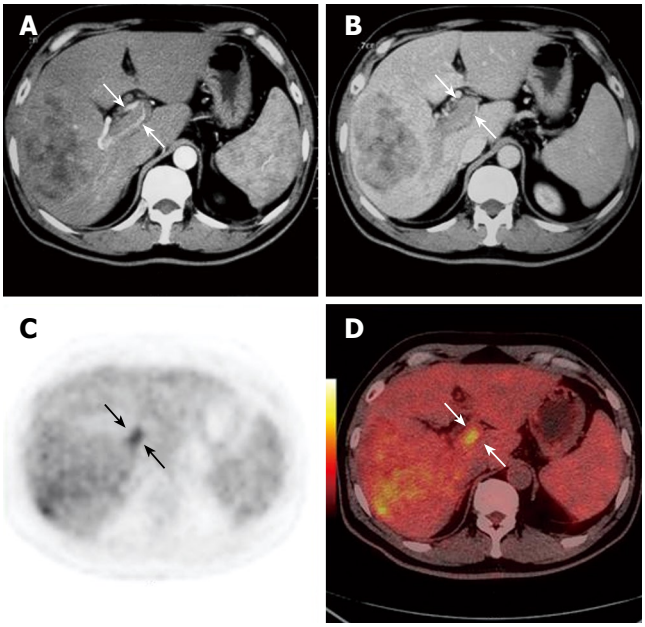

Figure 2 Contrast CT scan showing right lobe and caudate lobe mass and portal vein thrombus of the right branch in the same patient. During the arterial phase, the thrombus appears as an iso- to hypodense intraluminal area with dense linear enhancement (white arrows, **A**). A filling defect was detected in the right branch during the portal phases (white arrows, **B**). PET (black arrows, **C**) and PET/CT fused images (white arrows, **D**) reveal a highly metabolic thrombus in the left branch.

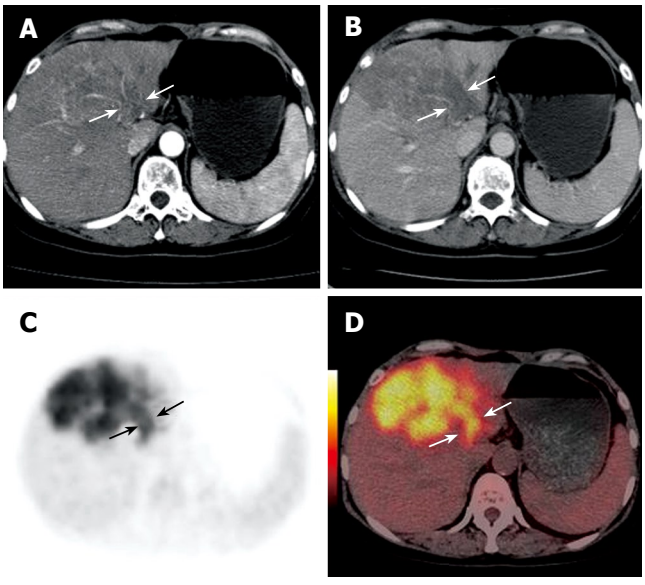

Figure 3 Contrast CT scan demonstrating a left lobe mass and portal vein thrombus in a 60-year-old woman. During the arterial phase, the thrombus appears as a hypodense intraluminal area with dense linear enhancement (white arrows, **A**). A filling defect was detected in the left branch during the portal phases (white arrows, **B**). PET (black arrows, **C**) and PET/CT fused images (white arrows, **D**) reveal a highly metabolic thrombus in the left branch.

than in those with weakly metabolic tumor lesions. All four patients with malignant thrombi had advanced HCC. All of the malignant high metabolism thrombi had discrete margins in PET and PET/CT images.

The remaining patient was shown by ultrasound to have a portal thrombus in the left portal vein 6 mo after HCC

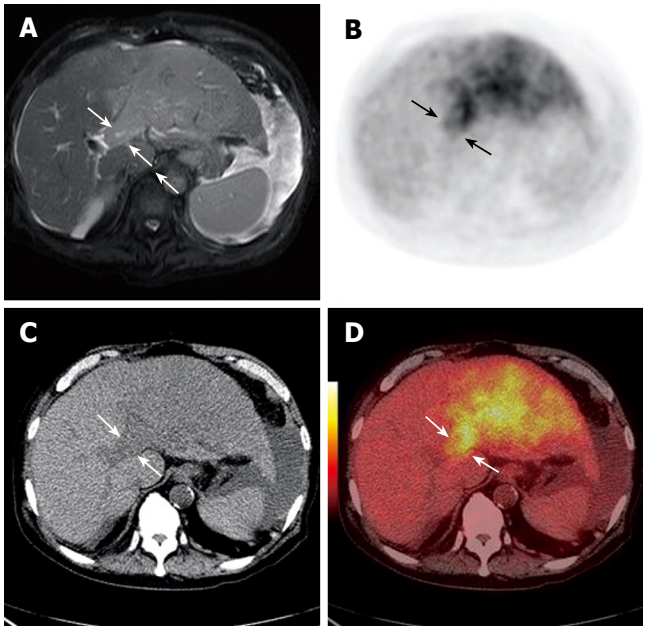

Figure 4 MRI scan showing a left lobe mass and portal vein thrombus in an 80-year-old man (white arrows, **A**). CT detected a low-density lesion in the left branch (white arrows, **C**). PET (black arrows, **B**) and PET/CT fused images (white arrows, **D**) reveal a highly metabolic thrombus in the left branch.

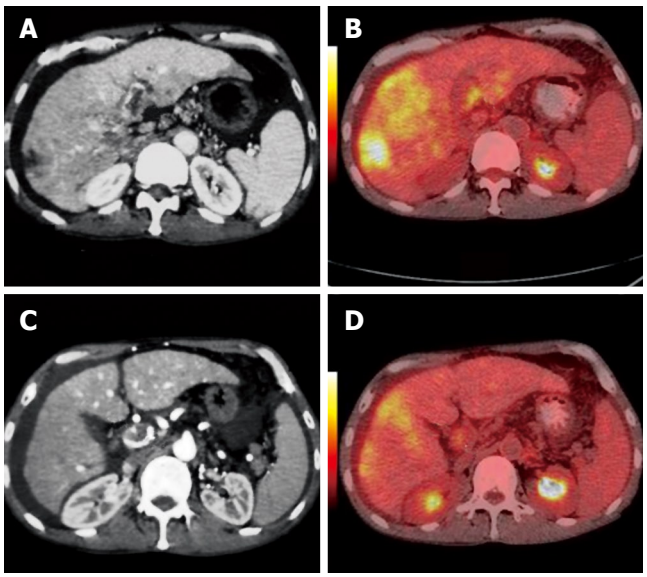

Figure 5 Contrast CT scan showing a diffuse tumor and portal vein thrombus in a 44-year-old man. During the arterial phase, the thrombus appears as a hypodense intraluminal area with mild enhancement at the LV (white arrows, **A**) and PV (white arrows, **C**). PET/CT fused images reveal a highly metabolic mass and a highly metabolic thrombus at the LV and PV, respectively (white arrows, **B**, **D**).

resection. Malignant thrombus was suspected on contrast CT. Contrast-enhanced MRI demonstrated a thrombus in the left portal vein. In the PET/CT examination, the thrombus of the left portal vein had an SUV of 3.0, which was lower than those of the normal liver parenchyma and lumen of descending aorta. ^{18}F-FDG PET/CT found no high ^{18}F-FDG uptake in the left portal vein. The left portal vein was recanalized in the contrast MRI 10-mo follow-up (Figure 6). Finally, diagnosis of the left portal vein blood

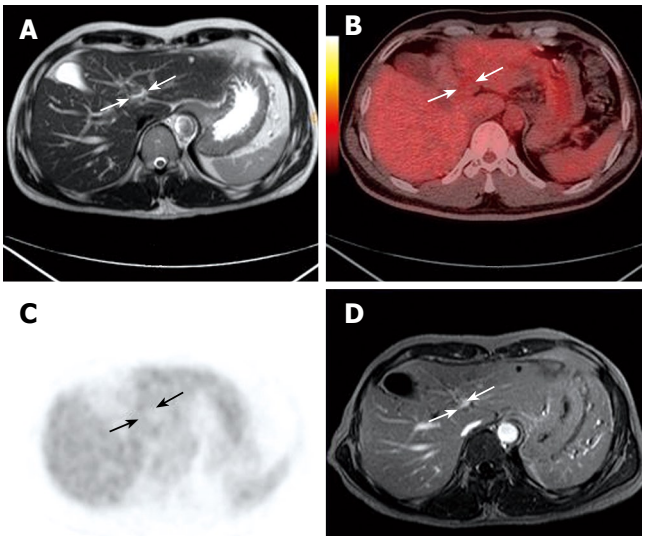

Figure 6 MRI showing a portal vein thrombus in a 44-year-old man six months after HCC resection (white arrows, **A**). PET/CT fused images (white arrows, **B**) and PET (black arrows, **C**) reveal no highly metabolic thrombus in the left branch. LP was recanalized in the contrast MRI at 10 mo follow-up (white arrows, **D**).

thrombus was established. Tables 1 and 2 summarize the clinical and image characteristics of the five patients.

DISCUSSION

HCC tends to invade the intrahepatic vasculature, especially the portal vein. In clinically treated series, the rate of portal invasion is 34%-40%[11-13]. The natural history of untreated HCC is still poor, especially in patients with PVTT; the median survival of such patients was reported to be 2.7 mo, whereas survival in those without PVTT was 24.4 mo. PVTT causes acute portal hypertension, acute upper gastrointestinal hemorrhage, refractory ascites, and finally, acute liver function failure[14-16]. Our findings in the present study confirm portal vein thrombosis is a frequent complication of primary liver tumors, especially those with diameters larger than 3.0 cm, and diffuse tumors.

The reported increased sensitivity of PET/CT over CT has been attributed to the ability of FDG-PET to detect metabolic abnormalities that precede the morphologic changes seen by CT. The global (skull base to proximal thighs) nature of PET/CT study also contributes to increased sensitivity through the detection of distant metastases[17]. ^{18}F-FDG PET/CT has become one of the standard imaging modalities in diagnosing and staging of tumors, and monitoring therapeutic efficacy in hepatic malignancies[18-19]. In this initial clinical experience, ^{18}F-FDG PET/CT appears to be a reliable technique for evaluating the veins of the portal system thrombus. The main advantage of ^{18}F-FDG PET/CT over conventional sonography techniques is its ability to assess the ^{18}F-FDG metabolism activity of portal vein thrombi. Compared with US, the main limitations of no contrast ^{18}F-FDG PET/CT is the absence of ability to observe the portal vein blood stream clearly along the main portal vein and its branch[20,21]. In the fourth patient, arterioportal shunt was confirmed by contrast CT. Thus, when ^{18}F-FDG PET/CT-suspected PVTT is considered, a whole body ^{18}F-FDG PET/CT examination combined with a contrast three-phase liver CT scan in the same PET/CT system is recommended.

Table 1 Clinical data on patients with high and low-metabolism thrombi of the portal vein

Patient	Age (yr)/ sex	Symptoms and signs	Laboratory data	Outcome
1	55/M	No	AFP 5 ng/mL; abnormal HFT	Died of liver failure 2 mo after EPI
2	60/F	Pain in right hypochondriac region	AFP > 1000 ng/mL; abnormal HFT	Died of hepatic failure 3 mo after TACE
3	80/M	Cough	AFP 30 ng/mL; abnormal HFT	Died of renal failure 1 mo after admission
4	65/M	Ascites	AFP > 1000 ng/mL; abnormal HFT	Died of liver failure 1 mo after admission
5	44/M	Six mo after HCC resection	AFP normal; normal HFT	Recanalization

AFP: Alpha-fetoprotein level; HFT: Hepatic function test.

Table 2 Imaging data on patients with high and low-metabolism thrombi of the portal vein

Patient	US, CT, MRI findings		FDG PET/CT SUV ratio		
	Liver tumor location and size	Location of PV tumor thrombus	T/NT	Th/NT	Th/DAo
1	Right and caudate lobe 11 cm × 13 cm	RPV LPV	4.8/3.0 4.8/5.9	5.2/3.0 5.9/3.0	5.2/2.1 5.9/2.1
2	Right lobe 8.4 cm × 9.6 cm	LPV	15.5/2.8	11.5/2.8	11.5/2.7
3	Left lobe diffuse tumor	LPV	9.0/3.6	7.9/3.6	7.9/2.4
4	Both lobes diffuse tumor	LPV PV	5.3/2.7 5.3/2.7	4.9/2.7 3.4/2.7	4.9/2.2 3.4/2.2
5	Six mo after right lobe lesion resection	LPV	-	3. 0/3.0	3.0/2.0

SUV: Standardized uptake value; T: Tumor target; NT: Non tumor target; Th: Thrombi; Dao: Descending aorta; RPV: Right portal vein; LPV: Left portal vein; PV: Portal vein.

Preliminary studies have already highlighted the potential value of ^{18}F-FDG PET/CT in HCC staging and restaging for the TNM stage. It is helpful in early diagnosis and proper treatment, which are very important for patients with PVTT to prolong their lives[22-24]. The reported increased sensitivity of PET/CT over CT has been attributed to the ability of ^{18}F-FDG PET to detect metabolic abnormalities that precede the morphologic changes seen by CT. The global (skull base to proximal thighs) nature of PET/CT study also contributes to increased sensitivity through the detection of distant metastases in HCC patients[25,26].

Dodd *et al*[27] reported that emboli might develop in the portal veins of hepatocirrhosis patients, and that these are mostly portal vein blood thrombi (PVBT), benign hepatic cells, or even bile duct epithelial cells. In recent years, some scholars have found that, during percutaneous ethanol injection, the alcohol that leaks out of the tumor and

flows into the portal vein may cause a benign thrombus. ^{18}F-FDG is not only uptaken by tumor cells, but also by normal cells[28-31] because benign hepatic cells and even bile duct epithelial cells in PVBT can uptake ^{18}F-FDG, which may also have active metabolism in PET/CT images. Thus, further studies are needed to confirm the ability of ^{18}F-FDG PET to discriminate PVTT and PVBT. The potential of this novel approach to characterize the veins of a portal system thrombus should be elucidated in large, ongoing clinical trials.

In conclusion, ^{18}F-FDG PET/CT can be helpful in discriminating between benign and malignant portal vein thrombi. Patients may benefit from ^{18}F-FDG PET/CT when portal vein thrombi can not be diagnosed exactly by US, CT or MRI.

COMMENTS

Background

To select an appropriate treatment regimen, it is essential to accurately characterize the nature of a thrombus in hepatocellular carcinoma (HCC) patients. This study investigated the ability of ^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography (^{18}F-FDG PET/CT) to differentiate between benign and malignant portal vein thrombosis in HCC patients.

Research frontiers

PET and CT are becoming more and more widely available, and their application with ^{18}F-FDG in oncology is beginning to be realized. However, the potential for ^{18}F-FDG PET/CT in the diagnosis of benign and malignant portal vein thrombosis in HCC patients is undefined.

Innovations and breakthroughs

Thrombi with maximum standardized uptake values (SUVs) greater than those of normal liver structures with a discrete margin and/or an ^{18}F-FDG uptake greater than that of the lumen of the descending aorta in the same axial slice were considered malignant. Thrombi with maximum SUVs lower than those of normal liver structures and/or an ^{18}F-FDG uptake lower than that of the lumen of the descending aorta in the same slice were considered benign.

Applications

Our findings can be helpful in discriminating between benign and malignant portal vein thrombi, and can be used to select an appropriate treatment for HCC patients, especially when portal vein thrombi can not be diagnosed exactly by US, CT or MRI.

Peer review

In this study, the authors reported the clinical significance of ^{18}F-FDG PET/CT for the discrimination between benign and malignant thrombi in advanced HCC. This manuscript arouses interest for readers and provides an important clue to diagnose or differentiate portal thrombus characteristics.

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