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*Gastrointestinal Imaging* *Case Series*

# Hepatocellular Carcinoma with Macroscopic Fat Metamorphosis: A Case Series

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## ABSTRACT

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths in the world, with hepatitis B and C as its main causes. HCC can have fat metamorphosis which leads to a better prognosis, though this is more commonly found in lesions smaller than 3 cm in diameter, and usually contains intravoxel fat. In this case series, we present three cases of HCC with macroscopic fat metamorphosis as examined using CT scan and MRI. Macroscopic fat is seen using CT as a hypodense mass with attenuation of −10 to −100 HU, or MRI using fat-saturation technique. Intravoxel fat can be seen on MRI using fat saturation chemical shift technique, appearing as signal loss during opposed phase and increased signal during in-phase. The differential diagnoses of HCC with fat metamorphosis are angiomyolipoma, hepatic adenoma, nodular steatosis, focal nodular hyperplasia, dysplastic nodule, liposarcoma, and hepatic metastasis. Enhancement patterns of the fat and non-fat component; intra-tumoral fat distribution; the presence of cirrhosis; the presence of atoll sign; and history of viral hepatitis are useful clues for differentiation of HCC with other differential diagnoses.

**Keywords:** Hepatocellular carcinoma, MRI, Fat metamorphosis, Focal liver lesion

## INTRODUCTION

The detection and characterization of fat in a liver lesion have an important role on clinical decision making. A fatty liver lesion may have benign or malignant cause, one of which is hepatocellular carcinoma (HCC).[1-3] HCC is the fourth leading cause of cancer-related deaths in the world, with hepatitis B and C as its main causes.[4] Although most HCC do not contain fat, fat within HCC can be found in well-differentiated lesions, arising in 19.6% of lesions smaller than 3 cm in diameter and becoming rarer as the tumor enlarges. Usually, the fat in HCC is intravoxel, but macroscopic fat can also be seen.[3] HCC with fat component may appear like other lesions which can mislead clinicians to other diagnoses and delay treatment. Therefore, being able to detect HCC with fat metamorphosis and distinct it from other diagnoses are very important.

In this case series, we present three cases of HCC with macroscopic fat metamorphosis and review the role of CT scan and MRI to exclude other differential diagnoses.

## CASES

### Case 1

A 64-year-old male presented with chronic diarrhea for 2 months. The patient had a history of hepatitis C and HIV infection but had not undergone any treatment. He also had a history of type 2

diabetes mellitus (DM). Physical examination showed no abnormality. Laboratory examination showed a positive HIV test with absolute CD4 cell count of 360 cells/mm$^3$. The patient underwent multiphase abdominal CT scan which showed a hypodense, heterogenous mass of fat-density (–11 HU) without contrast enhancement in segment VII of the liver. The initial diagnosis of this mass was lipoma. Three months later, a follow-up CT scan showed the mass had enlarged from 0.7 cm to 1.4 cm, leading to a suspicion for malignancy [Figure 1].

Six months after the first CT scan, a follow-up MRI showed an enlarged heterogenous mass of 3.0 cm with increased signal on in-phase and signal loss during opposed phase and T1 fat saturation sequence. The non-fat component of the mass showed contrast enhancement in late arterial phase and no washout during venous phase. Using hepatobiliary-specific contrast, no uptake was seen on the fatty component with uptake on the non-fatty component [Figure 2]. At this time, the patient's serum Alfa-fetoprotein level (AFP) reached 2885 ng/ml. The mass was resected, and core biopsy confirmed that the patient had well-differentiated HCC.

**Case 2**

A 46-year-old male presented with passing black tarry stool for 3 months and weakness. The patient was brought to the hospital to receive transfusion. Pale stool and dark urine were found. There was no history of hematemesis. From physical examination, there was conjunctival pallor. No abnormality was found in abdominal examination. Laboratory examinations showed an increase of hemoglobin (Hb) to 6.8 g/dl and elevation of liver enzymes to AST of 324 and ALT of 64 U/L. The HbsAg examination result was reactive whereas the anti-HCV examination result was non-reactive. The patient's AFP was 8.91 ng/ml.

Upper abdominal CT scan showed liver cirrhosis with a 6.0 cm mass in segment VII of the liver. A hypodense area of fat density that did not enhance after contrast administration was found. Meanwhile, the other part of the mass showed contrast enhancement during late arterial phase without washout during delayed phase [Figure 3]. Upper abdominal MRI examination showed a heterogenous mass on T1 sequence with signal loss on opposed-phase and increased signal on in-phase which indicates the presence of fat. On T2 sequence, there was a hyperintense component which was suppressed when we used fat-saturation technique [Figure 4].

Core biopsy confirmed that the tumor consisted of cirrhotic liver tissue along with micro- and macro-vesicular steatosis, corresponding to well-differentiated HCC.

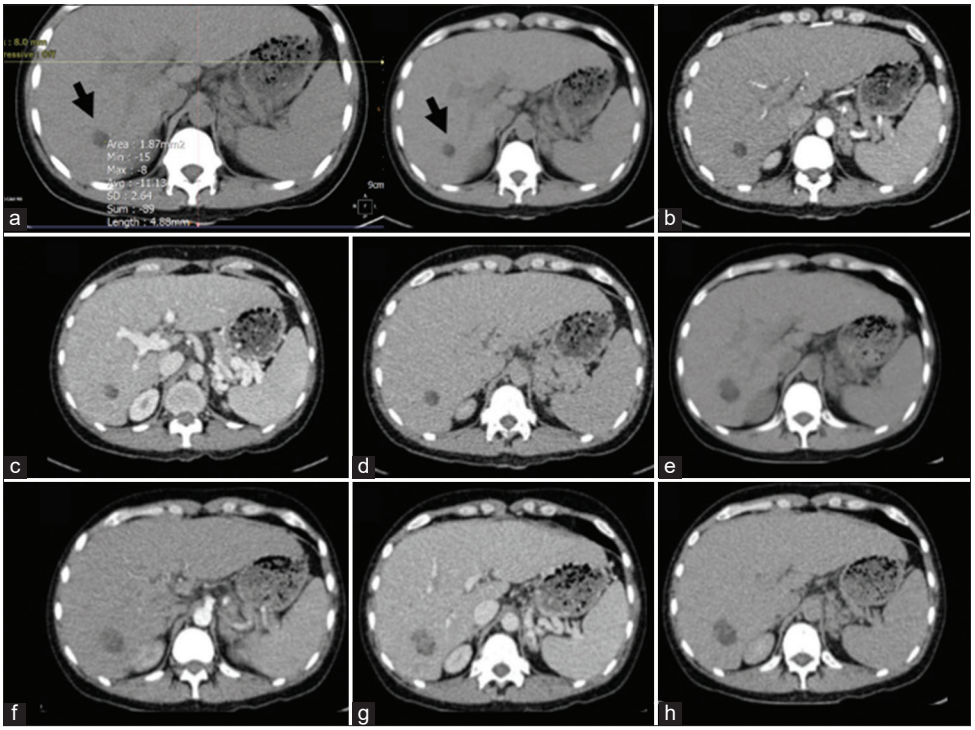


**Figure 1:** A 64-year-old male with hepatocellular carcinoma presenting with diarrhea. (a-d) multiphase abdominal CT scan showed a nodule (arrow) of –11 HU in non-contrast (a), late arterial (b), venous (c), and delayed phase (d and c). (e and d, h and f) Follow-up examination 3 months later showed that the nodule had enlarged in non-contrast (e), late arterial (f), venous (g), and delayed phase (h) with enhancement in late arterial phase (f and e) and washout in the delayed phase (h and f).

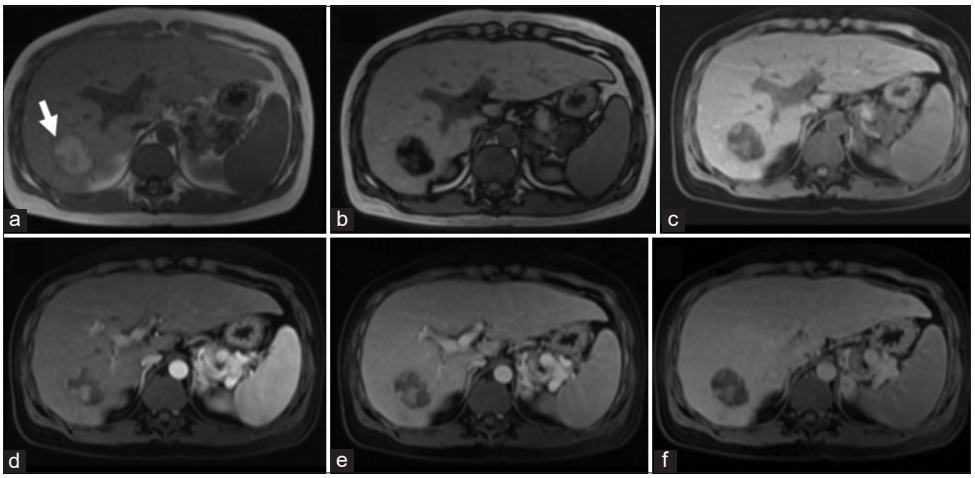


**Figure 2:** A 64-year-old male with hepatocellular carcinoma presenting with diarrhea. (a and b) MRI chemical shift imaging done 6 months after the initial CT scan showed a hyperintense mass (white arrow) during in-phase (a) with signal loss during opposed phase (b). (c) T1 fat-saturation also shows signal loss in the mass. (d and f) Dynamic MR in late arterial (d), venous (e), and hepatobiliary phase (f) showed late arterial phase enhancement that was not followed by washout during venous phase. While there is uptake in the non-fatty component, the tumor's fatty component did not show uptake with hepatobiliary contrast administration.

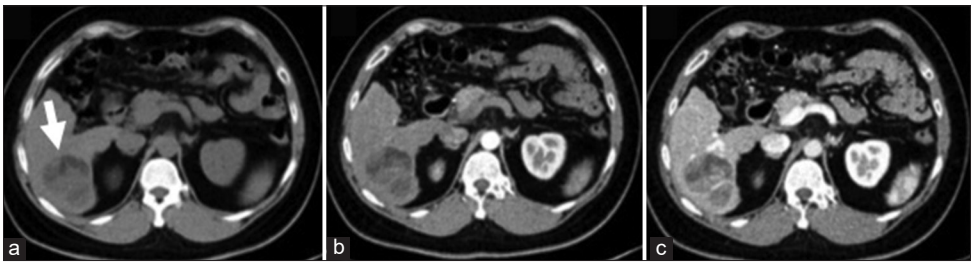


**Figure 3:** A 46-year-old male presented with hepatocellular carcinoma presenting with passing black tarry stool for 3 months. (a-c) Multiphase angiography CT scan in non-contrast (a), late arterial (b), and portal venous phase (c). A liver mass (white arrow) appeared to enhance during late arterial phase (b) followed with isodense appearance during delayed phase (c). The fat-density area did not enhance after contrast administration.

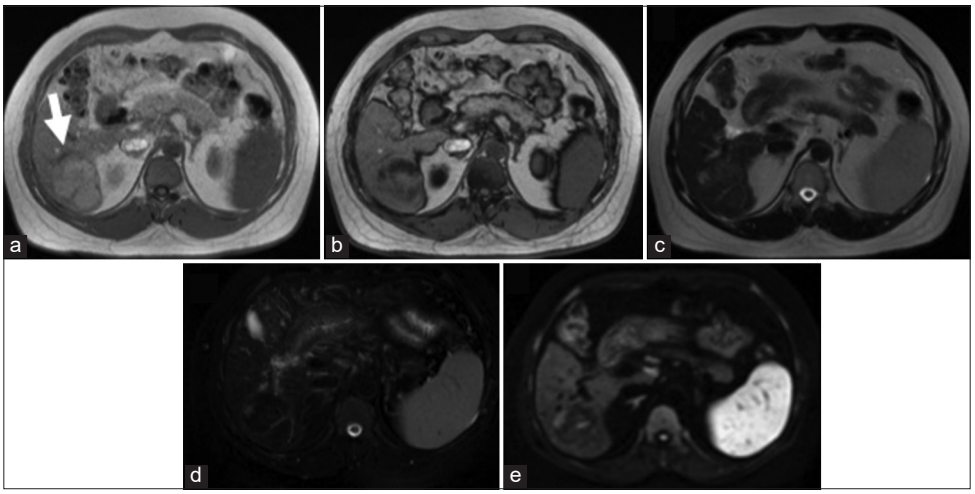


**Figure 4:** A 46-year-old male presented with hepatocellular carcinoma presenting with passing black tarry stool for 3 months. (a and b) T1 chemical shift abdominal MRI showed a hyperintense mass (white arrow) during inphase (a) along with signal loss during opposed-phase (b). (c) Hyperintense component was seen on T2-weighted sequence. (d) The mass appeared to be suppressed during T2 fat saturation technique. (e) On DWI sequence, part of the mass appeared with pathologic diffusion restriction.

**Case 3**

A 67-year-old male presented to the hospital with weakness, nausea, and vomiting for 2 weeks. No history of hematemesis was found. In physical examination, there was no abnormality in the patient's abdomen. Laboratory examination found reactive Anti-HBc and non-reactive Anti-HCV. The patient's AFP level was 1.77 ng/ml.

Multiphase abdominal CT scan showed a 13.0 cm heterogenous mass in the right lobe of the liver. There was a hypodense component that did not enhance with contrast. Meanwhile, the more hyperdense component showed enhancement during late arterial phase followed by washout during delayed phase [Figure 5]. MRI examination showed a mass with similar size and a component with signal loss on both chemical shift imaging and fat-saturation technique, indicating the presence of fat in the mass. Diffusion restriction was seen [Figure 6]. Core biopsy showed the tumor was moderately differentiated HCC.

## DISCUSSION

In this series of three cases of HCC with fatty component, two cases are well-differentiated HCC, and one is moderately differentiated HCC. Two patients have HCC with fat metamorphosis of more than 3.0 cm in diameter, and all have viral hepatitis as their underlying liver disease. One patient has type 2 DM as a comorbidity. The summary of this case series is found in Table 1.

Fat metamorphosis is mostly found in well-differentiated HCC and becomes less common and more focal as the tumor progresses.[5] The mechanism that leads to fat metamorphosis

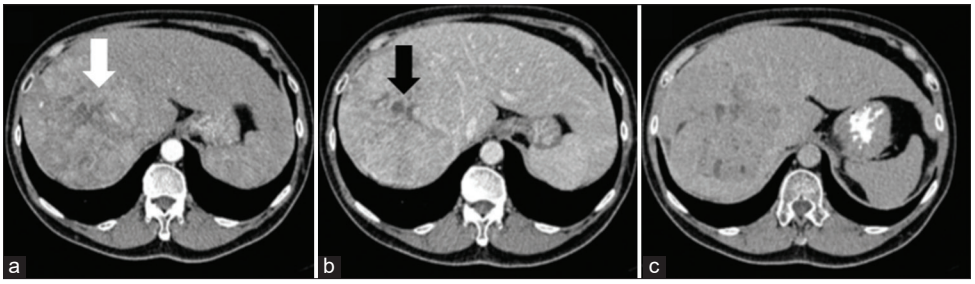


**Figure 5:** A 67-year-old male with hepatocellular carcinoma presenting with weakness, nausea, and vomiting. (a-c) Multiphase abdominal CT showed a hyperdense mass (white arrow) component during late arterial phase (a) that appeared isodense during venous phase (b) and washout during delayed phase (c). A hypodense component (black arrow) that did not enhance with contrast was also seen.

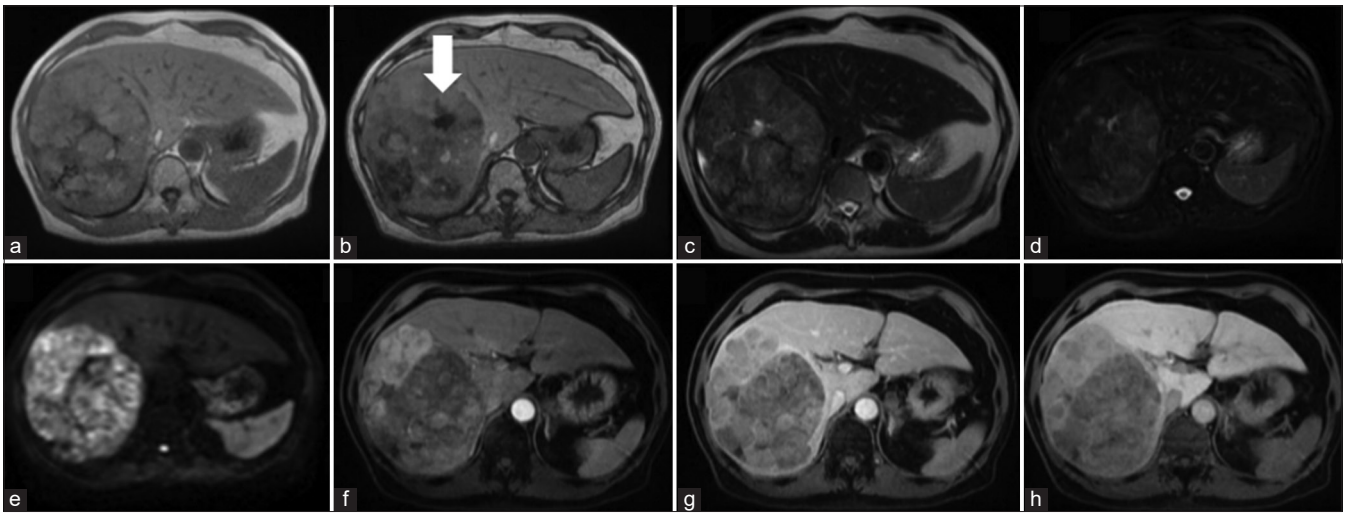


**Figure 6:** A 67-year-old male with hepatocellular carcinoma presenting with weakness, nausea, and vomiting. (a and b) T1 chemical shift abdominal MRI showed a heterogenous mass that appeared iso- to hyperintense during (a) in-phase along with signal loss during (b) opposed-phase (white arrow), indicating the presence of fat. (c) Hyperintense component of the mass was seen on T2-weighted sequence. (d) Part of the mass was suppressed on fat-saturation T2 sequence. (e) On DWI sequence, part of the mass had pathologic diffusion restriction. (f-h) Contrast administration showed enhancement during late arterial phase followed by washout and partly isointense appearance during delayed phase (g) without uptake during hepatobiliary phase (h). No contrast enhancement was found in the fat component.

in HCC is still not fully understood, but one of the factors is the increase of enzymes that synthesize fatty acids such as acetyl-CoA carboxylase.[6] Relative ischemia due to transition from portal venous to arterial blood supply can also enhance fat changes in the lesion. This transition happens in early HCC, which also explains why fatty changes are rarer in larger HCC.[3] Previously, there had been six case reports that described patients with HCC with metamorphosis of more than 3.0 cm in diameter, and only one of the seven patients had viral hepatitis as the underlying disease.[6] The case of HCC with fat metamorphosis is correlated with a better prognosis compared to those without it, according to a study by Siripongsakun *et al*.[7]

Macroscopic fat can be seen on CT as a hypodense mass with attenuation of −10 to −100 HU and MRI.[2] On MRI, macroscopic fat will appear more hypointense in fat-saturated compared to non-fat-saturated image. Lower fat proportion, or intravoxel fat, is not visible on CT, but can be seen on MRI using fat-saturation chemical shift technique, resulting in signal loss during opposed phase compared

**Table 1:** Summary of the findings in this case series.

| Case | Age | Sex | Underlying Liver Disease | Comorbidity | Lesion size (diameter) | HCC differentiation |
|---|---|---|---|---|---|---|
| 1 | 64 | M | Hepatitis C | Type 2 DM | 3 cm | Well-differentiated |
| 2 | 46 | M | Hepatitis B | - | 6 cm | Well-differentiated |
| 3 | 67 | M | Hepatitis B | - | 13 cm | Moderately differentiated |

HCC: Hepatocellular carcinoma, DM: Diabetes mellitus

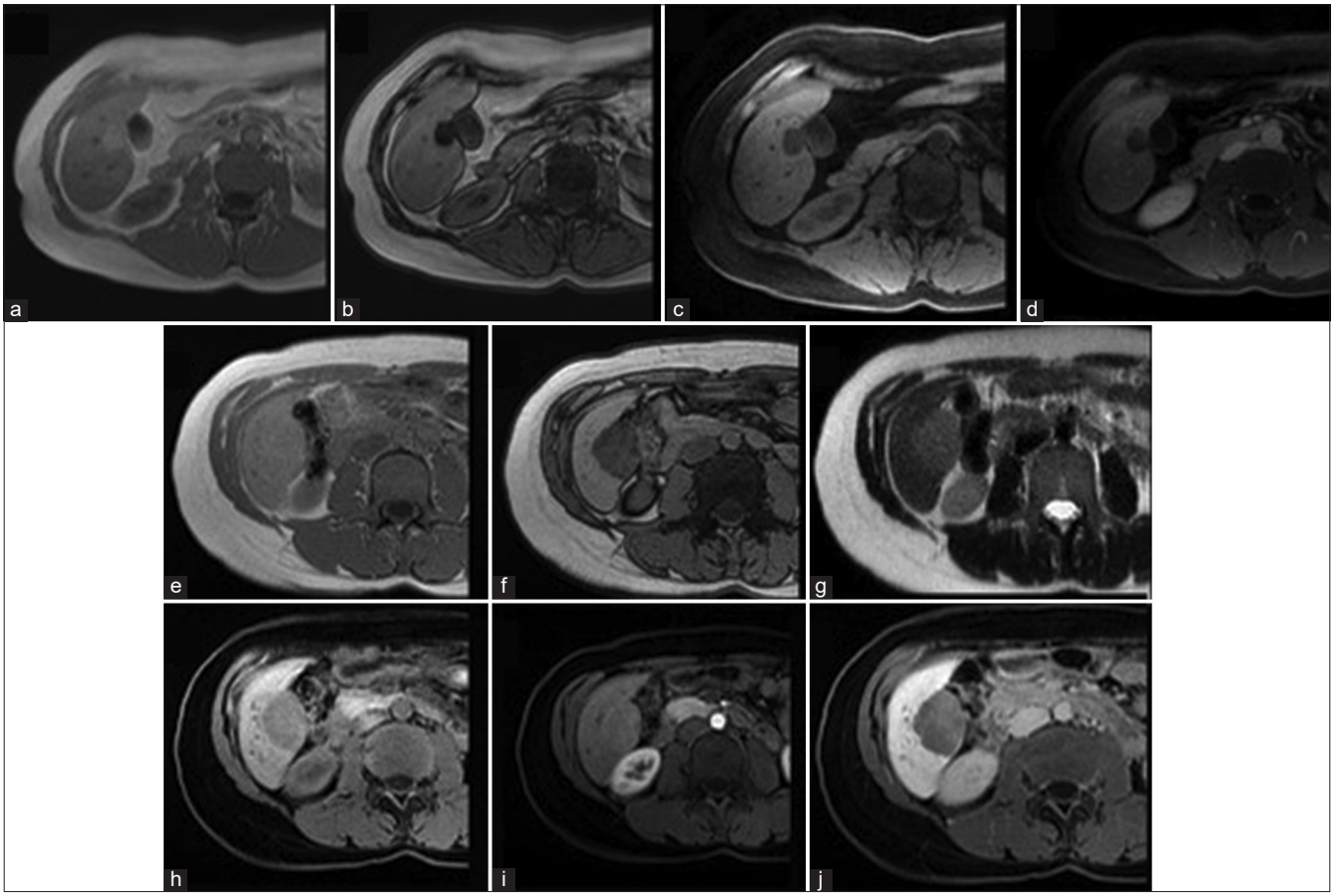


**Figure 7:** (a-d) A 42-year-old female with hepatic angiomyolipoma and (e-j) a 45-year-old female with hepatic adenoma, both incidental findings. (a and b) T1 chemical shift abdominal MRI showed a hyperintense mass during (a) in-phase with signal loss during (b) opposed-phase. (c and d) T1-weighted fat saturation image showing hypointense mass (c) with enhancement after contrast administration (d). (e and f) T1 chemical shift abdominal MRI showed hyperintense mass during in-phase (e) with signal loss during (f) opposed-phase, and with hyperintensity in T2-weighted image (g). T1-weighted sequence (h) showing mild hypointense mass with poor enhancement in late arterial phase (i), followed by washout during delayed phase (j).

to in-phase.[1,3,8] The differential diagnoses of HCC with fat metamorphosis can be benign or malignant. Benign causes include angiomyolipoma (AML), hepatic adenoma, nodular steatosis, focal nodular hyperplasia (FNH), and dysplastic nodule, whereas malignant causes include liposarcoma and hepatic metastasis.[2]

The difference between HCC and AML lies in the vascularization; AML contains better vascularization and thus more contrast enhancement in its fatty component, whereas fatty lesion in HCC is relatively avascular with minimum post-contrast enhancement. Other pathognomonic findings of AML include tortuous vascularity in the central lesion and draining vein that appears on arterial phase.[9] Hepatic adenoma, specifically the HNF1α and inflammatory adenoma subtypes, can also contain fat.[10,11] Its most common subtype, inflammatory adenoma, has focal and heterogenous steatosis, enhances during arterial phase and remains isodense throughout portal and delayed phases. Inflammatory adenomas can show atoll sign, which is the appearance of iso-intense center with peripheral hyperintensity on T2 sequence. Although rare, inflammatory adenoma may also show rapid washout[12] [Figure 7]. In all our cases, the non-fat component showed washout on venous or delayed phase either by CT or MRI whereas the fatty component did not enhance with contrast.

Hepatic steatosis, especially the nodular type, can be distinguished by its typical periligamentous distribution in the 4$^{th}$ segment. FNH can be identified from its characteristic central scar, which appears hyperintense on T2-weighted images with delayed contrast enhancement. The central scar is not seen in HCC other than fibrolamellar HCC. Even so, the presence of fat in FNH is extremely rare.[2] Small dysplastic nodules may also resemble HCC, but they lacks HCC's characteristic hyperintensity during arterial phase and washout during delayed phase.[13]

A fatty liver lesion may arise from liposarcoma, though this is rare. The most common fat-containing malignancy to metastasize to the liver is clear cell renal cell carcinoma. Fatty metastases can be distinguished from HCC by the presence the primary tumor and metastases in other locations, since it usually occurs when the metastasis is already widespread.[3]

The typical appearance of HCC is hyperattenuation during late arterial phase followed by hypoattenuation (washout) during portal venous and delayed phase. However, a study by Lee *et al*. showed 65% of well-differentiated HCC gives atypical enhancement such as iso- or hypoattenuation during arterial phase which continues into delayed phase.[14] If atypical enhancement pattern is found, an additional examination using specific hepatobiliary contrast such as gadoxetic acid (Gd-EOB-DTPA) can be used to detect non-functioning hepatic cells. In HCC, there will be absence of contrast uptake in the fatty component.[12]

## CONCLUSION

HCC may appear with intravoxel and macroscopic fat which shows better differentiation compared to non-fatty HCC. Enhancement patterns of the fat and non-fat component; intra-tumoral fat distribution; the presence of cirrhosis; the presence of atoll sign; and history of viral hepatitis is useful clues for the differentiation of HCC with other diagnoses.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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