

[CASE REPORT]

Hepatic Angiomyolipoma Staining in the Post-vascular Phase of Contrast-enhanced Ultrasound Due to the Presence of Macrophages

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Abstract:

A 47-year-old Japanese man was referred to hospital after the detection of a liver tumor. Dynamic computed tomography and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging were consistent with a diagnosis of hepatocellular carcinoma (HCC). No perfusion defect was observed in the post-vascular phase of contrast-enhanced ultrasound (CEUS). Histopathological staining of the tumor cells was positive for antibodies against HMB-45 and cluster of differentiation (CD) 68, confirming the diagnosis of hepatic angiomyolipoma (HAML). These findings indicated the presence of macrophages in HAML. We herein report a case of HAML explain how macrophages that are present within the tumor affect the staining characteristics in the post-vascular phase of CEUS.

Key words: hepatic angiomyolipoma, macrophage, CD68

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Introduction

Hepatic angiomyolipoma (HAML) is a rare benign mesenchymal tumor. In general, HAML occurs in the non-cirrhotic liver and predominately in women (1). Histologically, HAML is composed of three elements: smooth muscle cells, thick-walled blood vessels, and adipose cells. As the composition of these three elements is diverse in each case, the imaging findings of HAML are highly variable; thus, it is usually difficult to diagnose preoperatively. Furthermore, fat-deficient-type HAML is more difficult to diagnose based on imaging studies, because it lacks fat accumulation, which is one of the characteristic features of HAML (2, 3). Several reports using contrast-enhanced ultrasound (CEUS) have demonstrated that staining in the post-vascular phase is a useful feature for distinguishing HAML from hepatocellular carcinoma (HCC) (4, 5); however, the mechanism underlying these staining characteristics has been unclear.

We herein report a case of HAML and demonstrate that

the presence of macrophages affects the staining characteristics in the post-vascular phase of CEUS.

Case Report

A 47-year-old Japanese man was referred to our hospital with mild liver injury and a liver tumor that had been identified during a general medical checkup. He had no significant medical history, other than the intake of 70 g of ethanol per day.

A physical examination did not show any abnormalities. Laboratory data revealed the mild elevation of his aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase (GGT) levels. There was no evidence of hepatitis B or C virus infection or autoimmune disorder. Thus, his mild liver injury was diagnosed as an alcoholic liver injury. The levels of tumor markers, such as alpha-fetoprotein (AFP), des- γ -carboxy prothrombin (PIVKA II), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9), were within the normal ranges.

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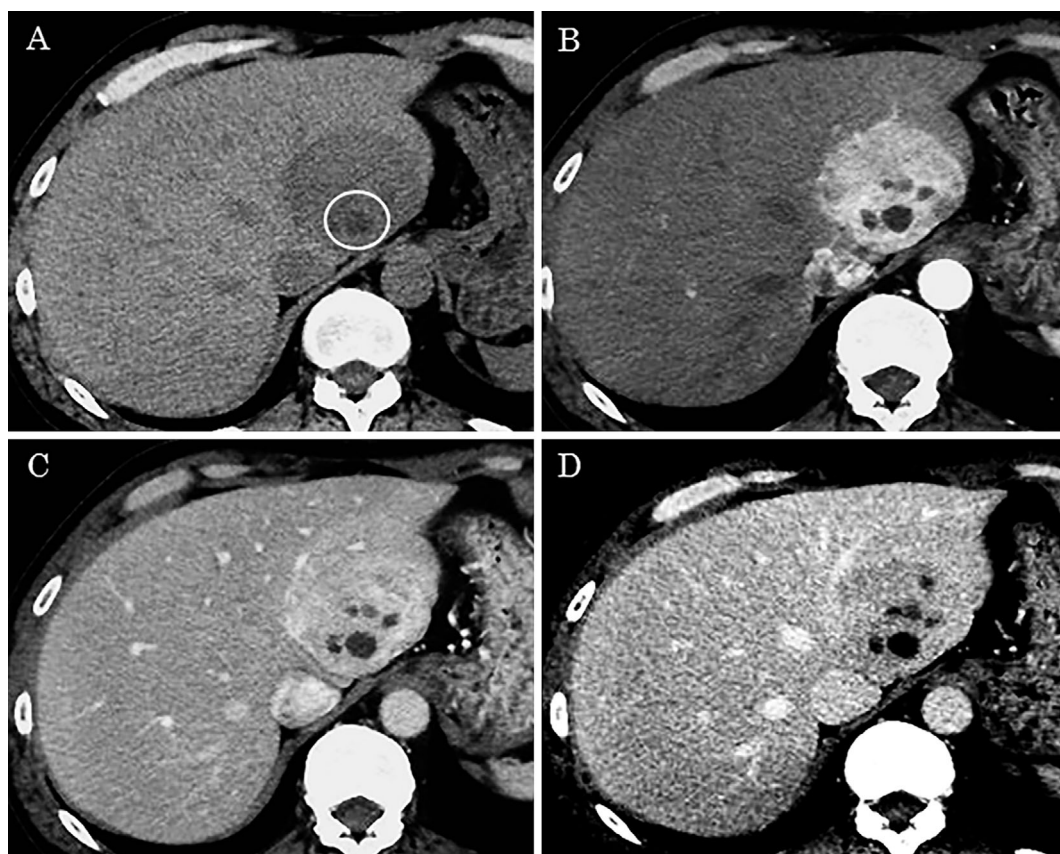


Figure 1. Computed tomography (CT). Unenhanced CT showed a lesion in the left lobe that was hypo-attenuated relative to the surrounding liver. A low-density area that did not match the fat density could be seen within the tumor (CT level 23 HU, circle) (A). Dynamic CT revealed a hypervascular tumor in the left lobe. The tumor was enhanced during the arterial phase (B) and portal phase (C), and then showed slight washout during the equilibrium phase (D).

Abdominal ultrasonography showed a 50-mm tumor in the left lobe of the liver that was almost round, well defined, and unencapsulated. Unenhanced computed tomography (CT) showed a lesion that was hypo-attenuated relative to the liver parenchyma; the presence of fat was not confirmed (Fig. 1A). Dynamic CT demonstrated a heterogeneous hyper-attenuated lesion during the arterial to portal phase with a small unenhanced area, and slight washout during the equilibrium phase (Fig. 1B-D). There were no findings indicative of cirrhosis. Magnetic resonance imaging (MRI) of the mass showed low signal intensity on T1-weighted imaging (WI) and high signal intensity on T2-WI (Fig. 2A and B). The unenhanced area of the mass on enhanced CT showed high signal intensity on both T1-WI and T2-WI. The tumor appeared hypointense in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (Fig. 2C). Contrast-enhanced ultrasound revealed heterogeneous hyper-enhancement in the early vascular phase and prolonged hyper-enhancement in the late vascular phase (Fig. 3A-C). Furthermore, early venous return was seen in the early vascular phase. Perfusion defects were not observed in most of the mass; however, the unenhanced area of the mass on enhanced CT showed a perfusion defect in the post-vascular

phase (Fig. 3D). Based on these imaging findings, we suspected HAML; however, we were not able to rule out HCC. Because of the relatively large size of the tumor, and the risk of rupture due its location on the liver surface with a hump, we decided to perform surgery.

Laparoscopic extended lateral segmental resection of the liver was performed. On gross examination, the tumor was 47×35 mm in size, brownish in color, and clearly demarcated from the surrounding liver tissue. The tumor contained areas of hemorrhage and there was no fibrous capsule (Fig. 4A). Histologically, the tumor was composed of spindle cells, blood vessels, and scant mature fat (Fig. 4B and C). The background liver was almost normal. The tumor cells were immunoreactive to antibodies against melanocytic cell-specific monoclonal antibody (HMB-45) and α -smooth muscle actin (α -SMA), confirming the diagnosis of HAML (Fig. 4D). In addition, the tumor cells were positively stained for cluster of differentiation 68 (CD68) (Fig. 4E) and negatively stained for organic anion-transporting polypeptide 1B3 (OATP1B3) (Fig. 4F). The unenhanced area identified within the tumor on the CT scan was suspected to reflect the presence of hemorrhage, which was not positive for CD68.

These findings indicate that macrophages were present in

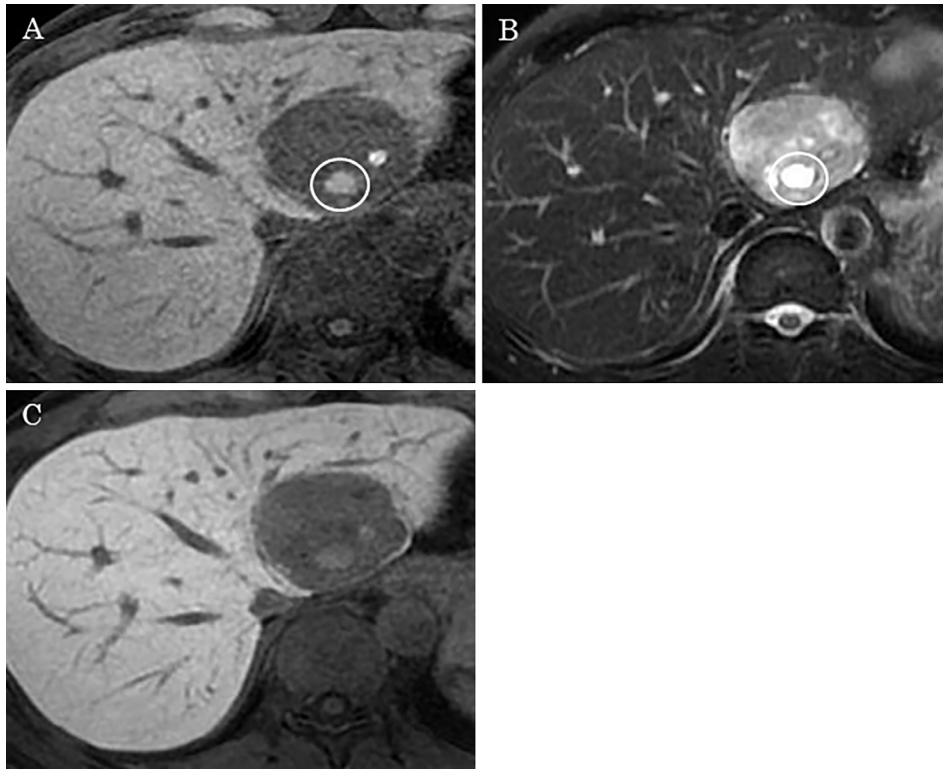


Figure 2. Magnetic resonance imaging (MRI). MRI of the tumor showed low signal intensity on T1-weighted imaging (T1-WI) (A) and high signal intensity on T2-WI (B). The unenhanced area of the mass on enhanced CT showed high signal intensity on both T1-WI and T2-WI (circle). The tumor showed hypointensity in the hepatobiliary phase of Gd-EOB-DTPA (C).

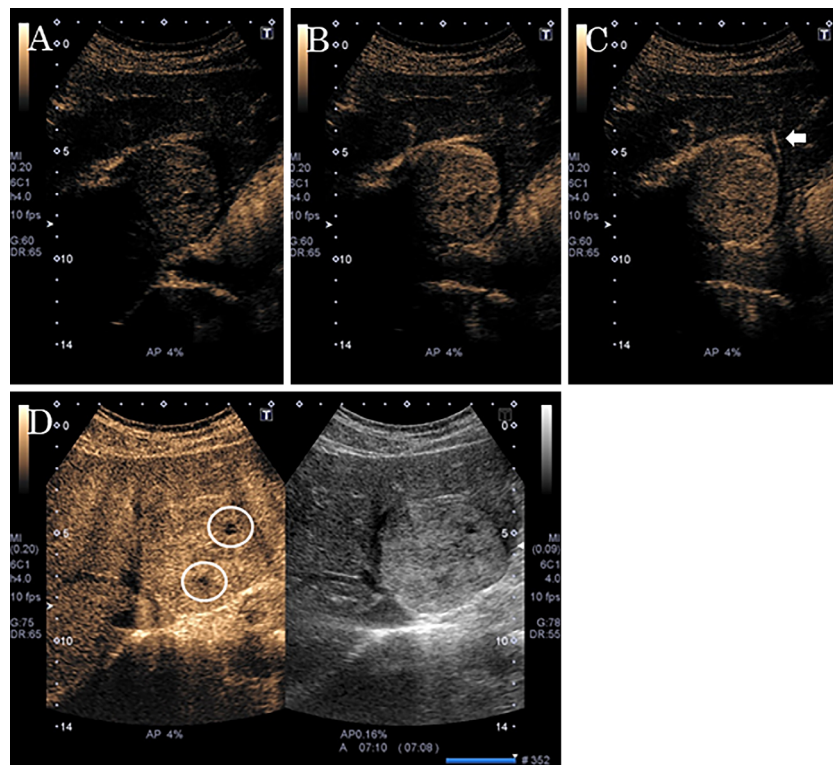


Figure 3. Contrast-enhanced ultrasound (Sonazoid 0.5 mL bolus injection, Toshiba Aplio 500 and 3.75 MHz convex array probe). (A) 14 s. (B) 19 s. (C) 29 s. (D) 7 min. Contrast-enhanced ultrasound showed heterogeneous hyper-enhancement in the early vascular phase and prolonged hyper-enhancement in the post-vascular phase. A small perfusion defect was seen in the mass (circle). Early venous return was seen in the early vascular phase (arrow).

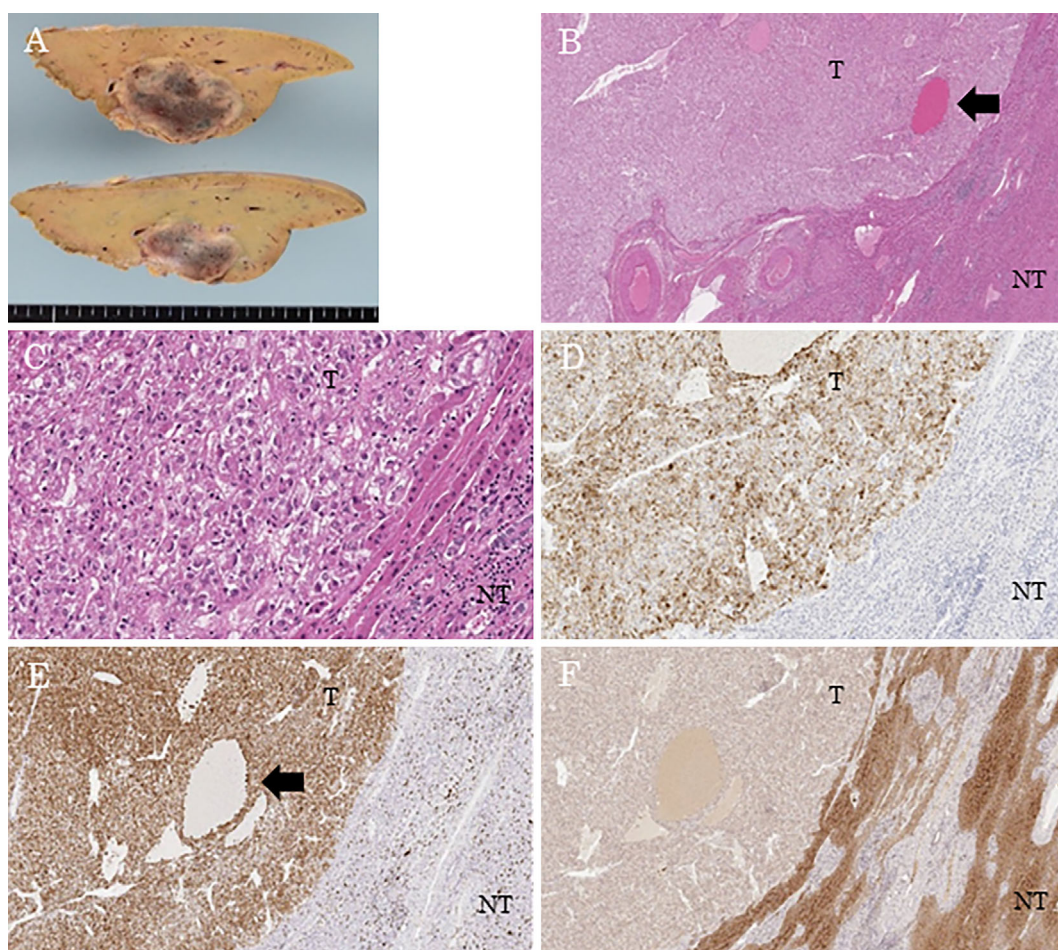


Figure 4. The pathological features of the tumor. (A) The cut surface of the resected specimen showed a brownish-colored lesion that was clearly demarcated from the surrounding liver. The tumor contained hemorrhage (arrow) and no fibrous capsule. (B, C) Low and high power views, respectively, of the borderline area of the tumor (T) and non-tumor (NT) areas (Hematoxylin and Eosin staining $\times 20$, $\times 200$). The microscopic features of the tumor included spindle cells, blood vessels, and scant mature fat. (D) Immunohistochemical staining of the tumor was positive for HMB-45 and CD68 (E). The area of hemorrhage was CD68-negative (arrow). (F) The expression of OATP1B3 was not detected.

the tumor, which lacked normal hepatocytes; thus, the EOB, which was administered for contrast enhancement, was not taken up by the tumor.

Discussion

HAMLs are histologically identified by HMB-45 positivity (6). However, they can be difficult to diagnose HAML clinically because the tumor has variable imaging features that depend on the tissue composition; thus, the accuracy of the preoperative diagnosis is reported to be only 0-40% (7-9). It is especially important to differentiate HAML from HCC because both tumors have similar imaging features (*i.e.*, early-phase enhancement) but significantly different prognoses. Hepatic angiomyolipomas are often misdiagnosed as HCCs, due to overlapping imaging features (3). There are some reports on the differences in the imaging data of HAMLs and HCCs. The presence of an early drain-

age vein and dilated tumor vessels and the absence of a pseudocapsule are reported to be helpful in differentiating HAML from HCC (2, 10-12). Hepatic angiomyolipomas usually show hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, reflecting the absence of normal hepatocytes (3). On the other hand, it has been reported that no defect is observed in the post-vascular phase of CEUS in 67-79% of HAML cases (4, 5). Immunohistochemical staining of the tumor in the present case was negative for OATP1B3 and positive for CD68. Organic anion-transporting poly peptide 1B3 is a transporter in the hepatocyte membrane and plays a role in the uptake of EOB into hepatocytes (13) and CD68 is a specific marker of macrophages, which show the uptake of perfluorobutane contrast medium in CEUS. Thus, although there are no hepatocytes in the tumor, the presence of macrophages is considered to be involved in the mechanism underlying the staining findings that are observed in the post-vascular phase of CEUS

in HAML. It is unclear why a substantial number of macrophages were present in the tumor. It is known that CD68 positive cells are observed not only in hepatic angiomyolipoma (AML) (14) but also renal AML (15, 16). As the presence of macrophages and the absence of hepatocytes in the tumor are reproducible histological features of HAML, the inconsistency between the two abovementioned imaging tests can be useful for differentiating HAML from HCC.

Hepatic hemangioma also showed no defect in the post-vascular phase of CEUS and hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, which is similar to HAML. However, the two tumors can be differentiated by the presence of a fill-in pattern on CEUS or hyperintensity on T2WI, which are characteristic findings of hepatic hemangioma. In addition to HCC, intrahepatic cholangiocarcinoma and metastatic liver cancer also show perfusion defects in the post-vascular phase of CEUS and hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. Thus, the differences in the imaging patterns on dynamic CT and clinical information are helpful for differentiating these malignant tumors.

In summary, we reported a case of HAML and explained that the presence of macrophages in the tumor is associated with the mechanism of staining in the post-vascular phase of CEUS. This finding is a useful feature for distinguishing HAML from malignant liver tumors, which is particularly important in HCC.

The authors state that they have no Conflict of Interest (COI).

References

1. Yang X, Li A, Wu M. Hepatic angiomyolipoma: clinical, imaging and pathological features in 178 cases. *Med Oncol* **30**: 416, 2013.
2. Jeon TY, Kim SH, Lim HK, Lee WJ. Assessment of triple-phase CT findings for the differentiation of fat-deficient hepatic angiomyolipoma from hepatocellular carcinoma in non-cirrhotic liver. *Eur J Radiol* **73**: 601-606, 2010.
3. Kim R, Lee JM, Joo I, et al. Differentiation of lipid poor angiomyolipoma from hepatocellular carcinoma on gadoxetic acid-enhanced liver MR imaging. *Abdom Imaging* **40**: 531-541, 2015.
4. Li R, Tang CL, Cai P, et al. Comparison of CT and contrast-enhanced ultrasound findings in hepatic angiomyolipoma with pathological correlations. *Abdom Radiol (NY)* **41**: 248-256, 2016.
5. Wang Z, Xu HX, Xie XY, et al. Imaging features of hepatic angiomyolipomas on real-time contrast-enhanced ultrasound. *Br J Radiol* **83**: 411-418, 2010.
6. Nonomura A, Enomoto Y, Takeda M, Takano M, Morita K, Kasai T. Angiomyolipoma of the liver: a reappraisal of morphological features and delineation of new characteristic histological features from the clinicopathological findings of 55 tumours in 47 patients. *Histopathology* **61**: 863-880, 2012.
7. Chang Z, Zhang JM, Ying JQ, Ge YP. Characteristics and treatment strategy of hepatic angiomyolipoma: a series of 94 patients collected from four institutions. *J Gastrointest Liver Dis* **20**: 65-69, 2011.
8. Zeng JP, Dong JH, Zhang WZ, Wang J, Pang XP. Hepatic angiomyolipoma: a clinical experience in diagnosis and treatment. *Dig Dis Sci* **55**: 3235-3240, 2010.
9. Yang CY, Ho MC, Jeng YM, Hu RH, Wu YM, Lee PH. Management of hepatic angiomyolipoma. *J Gastrointest Surg* **11**: 452-457, 2007.
10. Iwao Y, Ojima H, Onaya H, et al. Early venous return in hepatic angiomyolipoma due to an intratumoral structure resembling an arteriovenous fistula. *Hepatol Res* **44**: 700-706, 2014.
11. Wang CP, Li HY, Wang H, et al. Hepatic angiomyolipoma mimicking hepatocellular carcinoma: magnetic resonance imaging and clinical pathological characteristics in 9 cases. *Medicine (Baltimore)* **93**: e194, 2014.
12. Wang SY, Kuai XP, Meng XX, Jia NY, Dong H. Comparison of MRI features for the differentiation of hepatic angiomyolipoma from fat-containing hepatocellular carcinoma. *Abdom Imaging* **39**: 323-333, 2014.
13. Narita M, Hatano E, Arizono S, et al. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. *J Gastroenterol* **44**: 793-798, 2009.
14. Tochio H, Tamaki E, Imai Y, et al. CD68-positive cells in hepatic angiomyolipoma. *Oncology* **92**: 35-39, 2017.
15. Tan G, Liu L, Qiu M, Chen L, Cao J, Liu J. Clinicopathologic features of renal epithelioid angiomyolipoma: report of one case and review of literatures. *Int J Clin Exp Pathol* **8**: 1077-1080, 2015.
16. Hohensee SE, La Rosa FG, Homer P, et al. Renal epithelioid angiomyolipoma with a negative premelanosome marker immunoprofile: a case report and review of the literature. *J Med Case Rep* **7**: 118, 2013.

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