

Intrahepatic Extramedullary Hematopoiesis Mimicking a Hypervascular Hepatic Neoplasm on Dynamic- and SPIO-Enhanced MRI

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We present a rare case of a focal intrahepatic extramedullary hematopoiesis (EMH) that mimicked a hypervascular hepatic neoplasm in a 33-year-old woman with idiopathic myelofibrosis. The lesion showed homogeneous and persistent enhancement on both contrast-enhanced CT and gadolinium-enhanced dynamic MR imaging. The lesion did not demonstrate an apparent signal drop on a T2*-weighted sequence following administration of a superparamagnetic iron-oxide agent (SHU 555A). A hepatocellular adenoma was the initial radiological diagnosis. To the best of our knowledge, this is the first report of a histopathologically proven intrahepatic EMH evaluated with dynamic- and SPIO-enhanced MRI.

Index terms:

Liver
Extramedullary hematopoiesis
Magnetic resonance (MR)
Superparamagnetic iron oxide
Kupffer cell

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Extramedullary hematopoiesis (EMH) is a compensatory mechanism by which blood cells are produced outside the bone marrow when marrow production is unable to maintain the needs of the organism (1). It can be seen in a variety of hematological disorders that lack cell formation such as myeloproliferative diseases. EMH usually shows microscopic involvement and its most common sites are the liver, spleen, and lymph nodes (1, 2). In rare cases, such as presented in this report, the involvement can manifest as a mass-like lesion; this uncommon manifestation made it difficult for us to differentiate this disease entity from other focal hepatic neoplasms.

There have been sporadic case reports regarding the radiologic findings of focal intrahepatic EMH (1–9). However, in most reports, only ultrasound (US) and CT findings of this disease have been presented, and there are few reports regarding MRI findings (5, 6, 10). Moreover, to the best of our knowledge, there have been no reports regarding superparamagnetic iron oxide (SPIO)-enhanced MRI findings of this disease entity. Theoretically, as EMH can possess all marrow cells, including reticuloendothelial system (RES) precursor cells, it can be expected that intrahepatic EMH shows a signal drop on a T2*-weighted gradient echo sequence after SPIO administration. In addition, even though there have been a few case reports regarding the enhancement pattern of EMH on CT, most of the reports did not address the dynamic enhancement pattern of EMH on CT or MRI. In this case report, we present contrast-enhanced CT as well as dynamic- and SPIO-enhanced MRI findings of a rare case of intrahepatic EMH and correlate them with the pathology and immunohistochemistry findings.

CASE REPORT

A 33-year-old woman with a five-year history of essential thrombocythemia, was admitted to our hospital after the recent detection of a palpable mass in the left flank.

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Physical examination also revealed a palpable enlarged spleen and liver. Laboratory findings at the time of admission included a hemoglobin level of 14.7 g/dL, a platelet count of $73 \times 10^3/\mu\text{l}$, and leukocyte count of $24,010/\mu\text{l}$. The level of serum alpha-fetoprotein was less than 3 ng/ml. Hepatitis serologic markers such as HBs Ag, HCV Ab, and HAV Ab were all negative. A bone marrow biopsy was consistent with essential thrombocythemia transformed into idiopathic myelofibrosis.

A non-contrast CT scan showed a 2-cm sized, fairly well-defined, and homogeneously low attenuated mass in

segment VI of the liver (data not shown). The liver and spleen were diffusely enlarged. On contrast-enhanced, portal venous phase CT, most of the lesion showed intense enhancement (Fig. 1A). No other focal lesions were identified in the spleen, kidneys or paravertebral region. On MRI, the lesion showed homogeneously low and high signal intensity on T1- (repetition time [TR]/echo time [TE] = 140 msec/2.4 msec, flip angle [FA] = 70°) (Fig. 1B) and fat-saturated T2-weighted fast spin echo images (TR/TE = 12,857.1/100.7) (Fig. 1C), respectively. There was no signal change between the in- and opposed-phase T1-

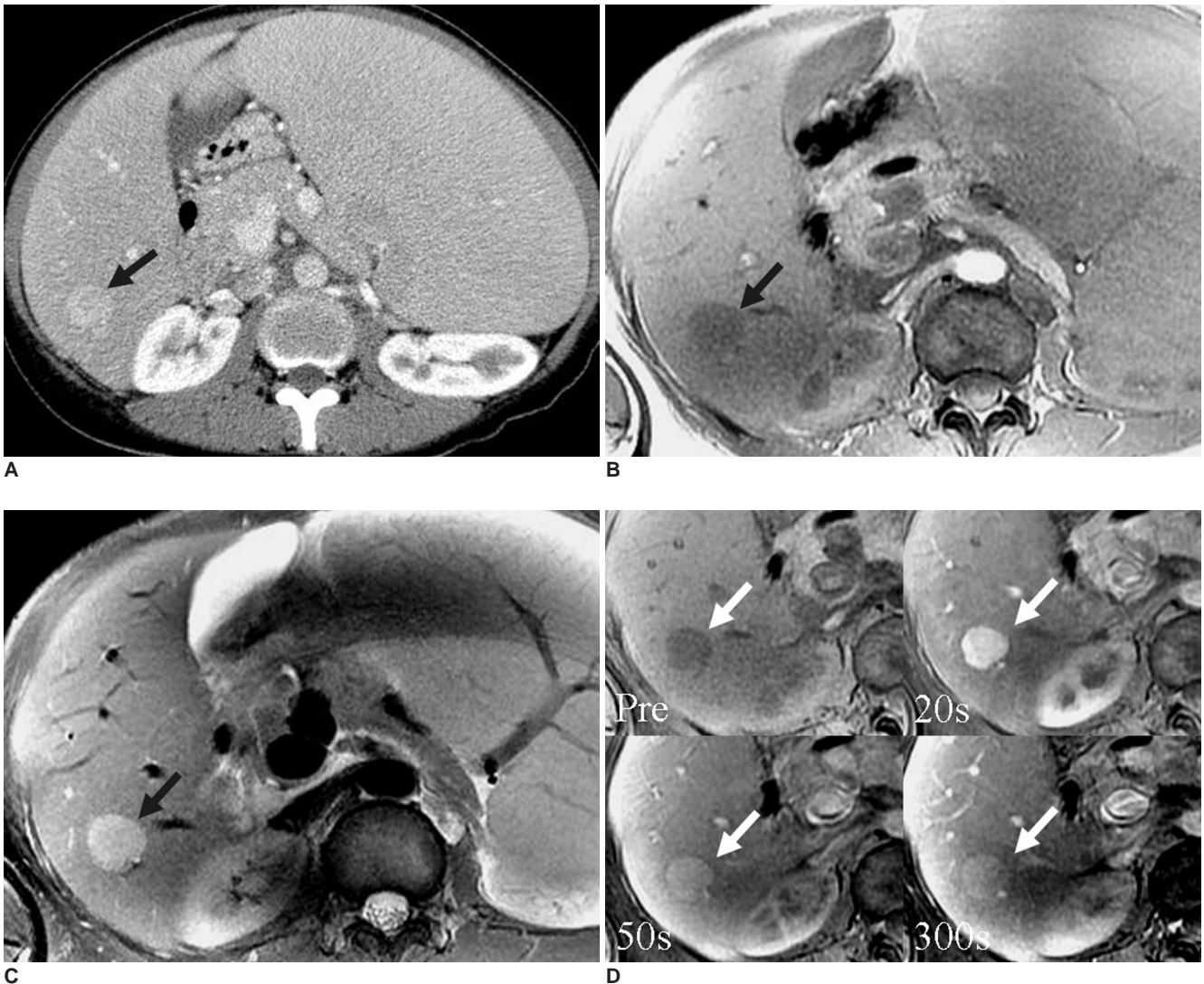


Fig. 1. Intrahepatic extramedullary hematopoiesis in 33-year-old woman.
A. 33-year-old woman with history of idiopathic myelofibrosis. On contrast-enhanced CT obtained in equilibrium phase, 2-cm-sized, well-defined and homogeneously enhancing mass (arrow) is seen in segment VI of liver. Liver and spleen are diffusely enlarged.
B. Lesion (arrow) shows homogeneous low signal intensity on in-phase T1-weighted image (repetition time [TR]/echo time [TE] = 140 msec/2.4 msec, flip angle [FA] = 70°).
C. Lesion (arrow) shows high signal intensity on fat-saturated, T2-weighted fast spin echo image (TR/TE = 12,857.1/100.7).
D. On serial gadolinium-BOPTA dynamic MR scans, lesion (arrows) shows homogeneous and intense enhancement on arterial phase (20 seconds after gadolinium administration, upper right) compared with pre-contrast T1-weighted image (TR/TE = 4.7/2.2, FA = 10°) (upper left); it enhances persistently through portal (50 seconds, lower left) to delayed phases (5 minutes, lower right).

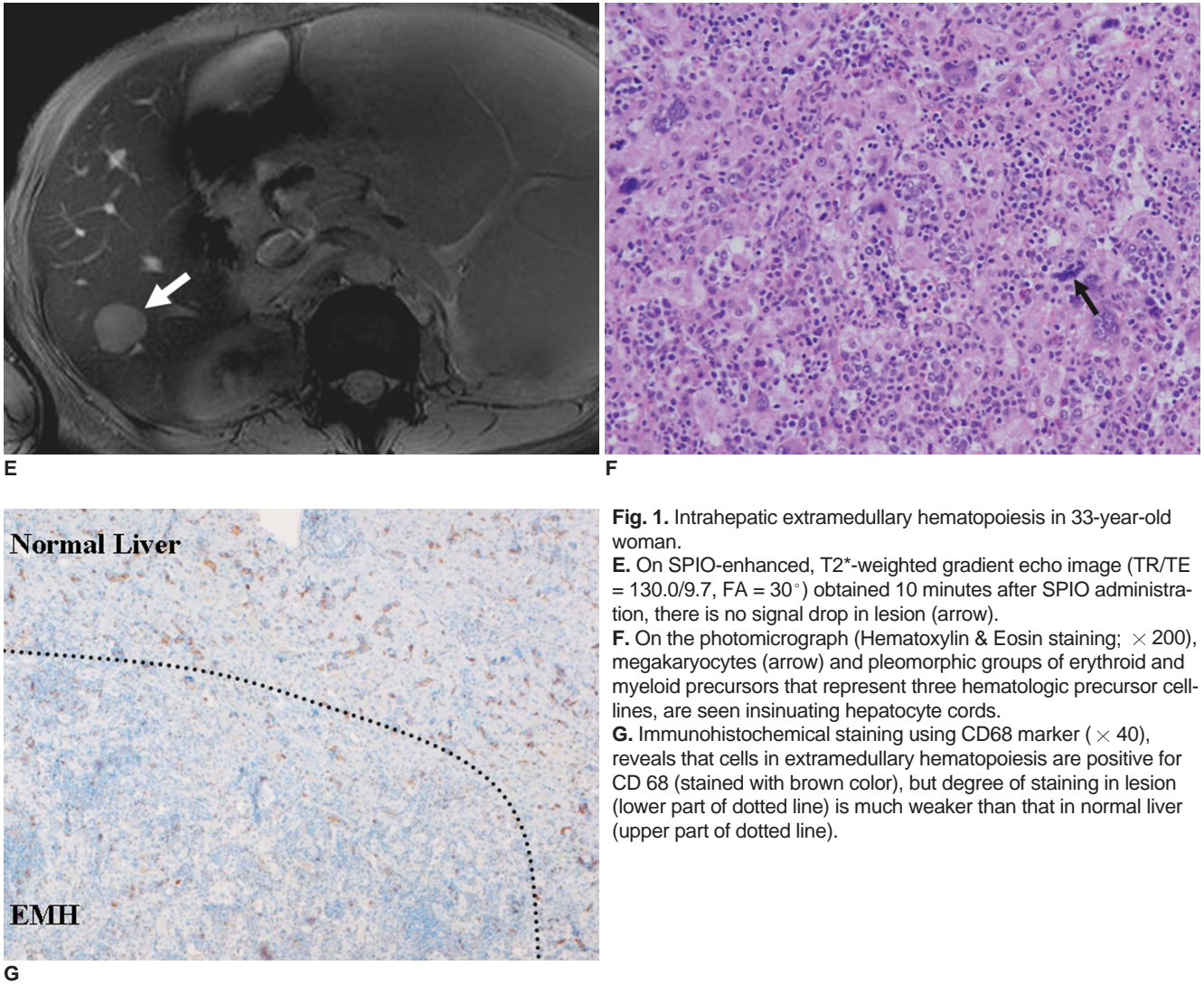


Fig. 1. Intrahepatic extramedullary hematopoiesis in 33-year-old woman.
E. On SPIO-enhanced, T2*-weighted gradient echo image (TR/TE = 130.0/9.7, FA = 30°) obtained 10 minutes after SPIO administration, there is no signal drop in lesion (arrow).
F. On the photomicrograph (Hematoxylin & Eosin staining; × 200), megakaryocytes (arrow) and pleomorphic groups of erythroid and myeloid precursors that represent three hematologic precursor cell-lines, are seen insinuating hepatocyte cords.
G. Immunohistochemical staining using CD68 marker (× 40), reveals that cells in extramedullary hematopoiesis are positive for CD 68 (stained with brown color), but degree of staining in lesion (lower part of dotted line) is much weaker than that in normal liver (upper part of dotted line).

weighted images. After the administration of a dose of 0.5 mmol/kg gadolinium (Gd) (Gd-BOPTA, Multihance, Bracco Imaging, Milan, Italy), the lesion showed homogeneous and intense enhancement on the arterial phase (20 seconds after contrast agent administration) and enhanced persistently until five minutes after Gd administration (Fig. 1D). There was no signal drop in the mass on T2*-weighted images (TR/TE = 130.0/9.7, FA = 30°) obtained 10 minutes following the administration of 1.4 ml of an SPIO agent (SHU 555A, Resovist, Schering AG, Germany) (Fig. 1E).

Considering that the patient had taken an anabolic steroid for the treatment of essential thrombocythemia and the mass had manifested as a well-defined hypervascular lesion, the most probable radiological diagnosis at this point was a hepatocellular adenoma. Differential possibilities also included other hypervascular hepatic neoplasms such as a focal nodular hyperplasia (FNH), hepatocellular

carcinoma (HCC), angiomyolipoma, and a solitary hypervascular metastasis. Although the patient did not have any predisposing factors for HCC, a hepatic tumorectomy was performed, as the possibility of a hepatic malignancy could not be excluded. An splenectomy was also scheduled for the symptomatic splenomegaly regardless of the nature of the hepatic lesion.

The patient underwent the splenectomy and segmentectomy of segment VI of the liver. Grossly, a homogeneously reddish mass without necrosis or hemorrhage was seen in the liver. Microscopically, megakaryocytes and pleomorphic groups of erythroids and myeloid precursors, which are known as the three hematological precursor cell-lines, were seen insinuating into the hepatocyte cords (Fig. 1F). These findings were therefore consistent with a focal intrahepatic EMH. Even though there were some histiocytic cells that are usually considered as precursors of RES cells, no Kupffer cells were found in the lesion by

Hematoxylin and Eosin staining. To investigate the pathological background for the lack of SPIO uptake by the lesion, immunohistochemical staining using the CD68 marker was performed. CD68 is usually positive in histiocytic cells. Immunohistochemical staining revealed that the cells in EMH were positive for CD68, as in the normal hepatic parenchyma. However, the degree of staining in the lesion (weak positive) was much weaker than that in the normal liver (positive) (Fig. 1G).

DISCUSSION

Contrary to previous reports in which focal intrahepatic EMH appeared as a heterogeneously enhancing or non-enhancing mass on contrast-enhanced CT (1–9), this case exhibited homogeneous and persistent enhancement on dynamic Gd-enhanced MRI. We are unable to explain exactly why there was such a discrepancy in the enhancement pattern of the two imaging modalities. However, earlier studies comparing the MRI and CT hepatic imaging of focal liver lesions showed that the use of MRI has several advantages over the use of CT, including greater sensitivity to intravascular contrast agents (Gd-chelate for MRI and iodinated agents for CT) (11). Another theoretical advantage of the use of MRI over the use of CT in terms of contrast enhancement is that the contrast material is delivered in a smaller volume over a shorter period in MR examinations, resulting in a tighter bolus. Considering the greater sensitivity to the contrast agent and tighter bolus injection of the contrast agent on MRI than on CT, the enhancement for a small hepatic lesion might have been more adequately identified on MRI.

Considering the rarity of the EMH disease entity, it may not be included in the initial differential lists of hypervascular hepatic lesions. However, given that almost all patients diagnosed with focal intrahepatic EMH had some underlying hematological disorder as a predisposing factor (9), we believe that it merits consideration in the appropriate clinical setting.

Since the early 1980s, the use of SPIO has been applied to various hepatic and splenic diseases, and many findings for enhanced lesion characterization have been reported (12, 13). Due to the RES tissue specificity of SPIO, it profoundly decreases the signal intensity of the tissues containing RES cells, such as Kupffer cells, but not that of a lesion without RES cells, thereby enabling tissue characterization. There are two commercially available intravenous SPIO agents: AMI-25 (Feridex) and SHU 555A (Resovist). Unlike AMI-25, SHU 555A may be phagocytosed by RES cells, i.e., macrophages, within the bone marrow as well as by RES cells in the liver and spleen due to its smaller size

(14, 15). Theoretically, as EMH can possess all marrow cells, including reticuloendothelial system (RES) precursor cells, it is expected that intrahepatic EMH would show a signal drop on a T2*-weighted gradient echo sequence following SPIO administration. Indeed, in the pathological specimen of the present case, there were many histiocytic cells that were considered as precursors of RES cells as seen by H and E staining. However, contrary to our expectation, the case did not show any signal drop on post-SPIO T2*-weighted MR images. There are several possible explanations for this result. Even though all types of RES cells, including bone marrow cells may uptake SHU 555A particles the strength of the affinity of this contrast agent for each cell is different. SHU 555A has the strongest affinity to Kupffer cells, followed by RES cells in the spleen and macrophages in the bone marrow (14, 15). Therefore, the signal drop induced by SPIO uptake should follow this tendency, resulting in a weak or even no signal drop of the intrahepatic EMH. As the ultra-small SPIO (USPIO) agents can easily cross the capillary wall due to their small size and prolongation of the blood half-life, it is well known that USPIO can be taken up by the RES cells of the bone marrow and lymph nodes (16). If we had used the USPIO agent as a T2- or T2*-contrast agent, we might have observed the signal drop within the EMH in our case. A second possible explanation for the absence of a signal drop in the lesion on post-SPIO T2*-weighted MR images may be the short delay time following SPIO administration. According to previous reports (15), SPIO uptake in the bone marrow and subsequent decreased relaxation time of the tissue usually occur within one to 24 hours, or two hours after SPIO injection. However, in the case of liver MR imaging using SHU 555A, a 10 minute delay is optimal in obtaining a signal drop of the liver and spleen. Therefore, such a short delay time might not be sufficient to induce a signal drop in the histiocyte-precursor cells of the EMH.

As this case study is the first to report the SPIO-enhanced MRI findings of EMH that did not show an apparent signal drop after SPIO administration, we could not generalize our result. However, there have been comparable reports regarding the diagnosis of EMH using Tc-99m sulfur-colloid scintigraphy (6, 17, 18). In addition, of the three reported cases of EMH, one case that was reported by Abbitt et al. (18) showed positive Tc-99m sulfur-colloid scintigraphy whereas the other two cases were negative. Considering the similarity of the enhancement mechanism between Tc-99m sulfur-colloid scintigraphy and SPIO-enhanced MRI, the SPIO-MRI appearance of EMH is also expected to be variable. Therefore, further studies using a large number of cases are warranted to

investigate the SPIO-enhanced MRI findings of EMH in the liver.

In the present case, the correct diagnosis was not originally considered as a focal intrahepatic EMH presenting as a homogeneously and persistently enhancing mass has never been described or included in the differential diagnosis of hypervascular liver lesions. The differential diagnosis for hypervascular liver lesions in a non-cirrhotic liver includes benign tumors such as adenomas, FNH, and occasionally angiomyolipomas. Malignant hypervascular hepatic lesions include an HCC and hypervascular metastasis.

This observation provides further support for the inclusion of an intrahepatic EMH in the differential diagnosis of hypervascular and tumor-like masses without SPIO (SHU 555A) uptake in patients with hematological diseases.

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