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16 December 2014

To whom it may concern,

This letter certifies that the manuscript by Tetsuo Sonomura entitled

Reactive lymphoid hyperplasia of the liver: ring enhancement in the portal venous phase on contrast-enhanced CT and MRI

has been edited by a native-English-speaking scientific editor. The edited text is shown in the following pages of this document.

Yours sincerely,

Aaron Stallard

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Editorial Board
Hepatology Research

2 August 2014

Dear Dr. Takehara,

Please find attached our manuscript entitled "Reactive lymphoid hyperplasia of the liver: ring enhancement in the portal venous phase on contrast-enhanced CT and MRI" by Tetsuo Sonomura, Shinpei Anami, Taizo Takeuchi, Motoki Nakai, Shinya Sahara, Hirohiko Tanihata, Kazuki Sakamoto, and Morio Sato, which we wish to be considered for publication in *Hepatology Research* as a Case Report.

Reactive lymphoid hyperplasia (RLH) is common in the gastrointestinal tract, orbit, lung and skin, but is very rare in the liver. It is difficult to differentiate between RLH of the liver and malignant liver tumors such as hepatocellular carcinoma (HCC), liver metastases, and cholangiocarcinoma. In our case, we observed a liver lesion with characteristic ring enhancement [I have removed the inverted commas throughout because this is a commonly used term.] in the portal venous phase on contrast-enhanced CT and MRI. There are numerous reports in the English literature regarding ring enhancement. [This statement is too vague; please be more specific regarding the aspects of ring enhancement that have been reported (here, and where this sentence appears throughout the manuscript).] We consider that this imaging feature could be a useful clue for identifying RLH in the liver; however, no reports have described the relevance of ring enhancement in the diagnosis of RLH. [Please check that this is your intended meaning, here and elsewhere.] Histological analysis revealed the lesion to be RLH, with prominent sinusoidal dilatation around the periphery. This dilatation is the cause of the ring enhancement, which is useful for the accurate diagnosis of RLH.

The content of this manuscript is original and has not been previously published or accepted for publication elsewhere. No part of the manuscript is currently under consideration for publication elsewhere.

We wish to thank you in advance for considering our manuscript.

Yours sincerely,

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Reactive lymphoid hyperplasia of the liver: ring enhancement in the portal venous phase on contrast-enhanced CT and MRI

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Type of article: Case Report

Running title: RLH of the liver with ring enhancement

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Abstract

We report the case of a 69-year-old woman with reactive lymphoid hyperplasia (RLH) of the liver. She underwent partial hepatectomy under a preoperative diagnosis of hepatocellular carcinoma; however, histopathological analysis revealed RLH. The liver lesion showed the characteristic imaging feature of ring enhancement in the portal venous phase on contrast-enhanced CT and MRI, which enabled the correct diagnosis of the lesion. Histologically, the ring enhancement was compatible with prominent sinusoidal dilatation surrounding the liver lesion.

Keywords: Reactive lymphoid hyperplasia; Liver; Ring enhancement

Introduction

Reactive lymphoid hyperplasia (RLH) is a benign condition of unknown etiology and pathogenesis [1]. It is common in the gastrointestinal tract, orbit, lung, and skin, but very rare in the liver, where it is difficult to differentiate from malignant liver tumors such as hepatocellular carcinoma (HCC), liver metastases, and cholangiocarcinoma. In our case, the liver lesion demonstrated ring enhancement in the portal venous phase on contrast-enhanced CT and MRI. This characteristic imaging feature has been well reported in the English literature [2–6], and could be useful for identifying RLH in the liver. However, no reports have focused on ring enhancement in RLH. [Please check that this is your intended meaning.] Histological analysis revealed prominent sinusoidal dilatation surrounding the liver lesion as the cause of the ring enhancement. This imaging feature and can aid in the accurate diagnosis of RLH.

Case Report

A 69-year-old woman with atrial fibrillation (AF) was being followed up at the cardiology department. Abdominal ultrasonography performed to investigate hematuria revealed the incidental finding of a well-defined hypoechoic lesion in segment 8 of the liver. She had no history of hepatitis, and her liver function was normal. The tumor marker values for HCC were AFP of 4.9 ng/mL and PIVKA-2 of 31000 mAU/mL. We considered that the high PIVKA-2 value was due to the warfarin she was taking for AF. Unenhanced CT showed a liver lesion with subtle low attenuation relative to the liver parenchyma. On triple-phase contrast-enhanced CT, the lesion demonstrated ring enhancement in the portal venous phase and washout of contrast medium in the equilibrium phase. On unenhanced MRI [7], the lesion showed low signal intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging. The lesion showed high signal intensity on diffusion weighted imaging (b = 800 m^2/s, black-and-white inversion), [Or do you mean 'inverted black-and-white gray scale'? If so, please also change in the legend for Fig. 2.] and low signal intensity on the apparent diffusion coefficient map. [Please check that this is your intended meaning.] On gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, there was early enhancement of the lesion in the arterial phase, ring enhancement in the portal venous phase, delayed washout in the late phase image, and low signal intensity in the hepatobiliary phase. Based on the preoperative imaging findings of hepatocellular carcinoma, partial hepatectomy was

performed. A cut section of the resected liver showed a well-circumscribed and yellow–white unencapsulated lesion (15 × 10 mm). However, histopathology confirmed RLH of the liver, characterized by a massive infiltration of mature lymphoid cells, forming lymphoid follicles of various sizes, with germinal centers. Prominent sinusoidal dilatation was seen around the lesion. Immunohistochemical staining was positive for CD10 and negative for Bcl-2.

Discussion

RLH is generally thought to be a benign lesion characterized by hyperplastic lymphoid follicles with reactive germinal centers [1]. Ota et al. [2] and Zen et al. [8] reported a reduction in the size of xxx [Please clarify what is referred to here.] in RLH of the liver; however, the risk of malignant transformation is also reported, namely the development of malignant lymphoma [9]. Although RLH can be found in various organs, including the gastrointestinal tract, orbit, lung, and skin, its occurrence in the liver is rare. It occurs predominantly in middle-aged women (mean age, 54.1 years) [3]. Although the exact etiology remains unknown, associations have been suggested between the development of hepatic RLH and chronic hepatitis [10], autoimmune disease [5,9,11], and malignant tumor [12]. None of these was present in our case.

It is difficult to distinguish between RLH of the liver and malignant liver tumors such as HCC, liver metastases, and cholangiocarcinoma on the basis of the imaging findings. In the present case, the characteristic imaging feature of ring enhancement was evident in the portal venous phase on contrast-enhanced CT and MRI. Ring enhancement is previously described in many papers in the English literature [2–6], and may be a useful aid for identifying RLH in the liver. However, no reports have focused on ring enhancement in RLH of the liver. Among other tumors of the liver, HCCs seldom show ring enhancement in the portal venous phase on triple-phase contrast-enhanced CT or MRI, liver metastases show ring enhancement in three phases, and cholangiocarcinoma shows delayed enhancement in the late phase due to the fibrous tissue in this tumor. Therefore, ring enhancement in the portal venous phase may enable differentiation of liver RLH from malignant liver tumors. In addition, Osame et al. [13] observed a small vessel coursing through a liver lesion (vessel-penetrating sign) on CT, and suggested that this finding may enable malignancy to be excluded. [Please check that this is your intended meaning.]

Histological analysis revealed that the lesion was well-demarcated, with massive infiltration of mature lymphoid cells, forming lymphoid follicles of various sizes with

germinal centers, and with prominent sinusoidal dilatation surrounding the lesion. We consider that the sinusoidal dilatation was the cause of the ring enhancement in the present case. Immunohistochemical staining was positive for CD10 and negative for Bcl-2, which excludes follicular lymphoma of the liver [1].

RLH of the liver is not generally diagnosed until after partial hepatectomy. Some reports [2,4] describe needle biopsy for the diagnosis of RLH; however, this procedure has drawbacks that an insufficient sample may be obtained for diagnosis, and that there is a risk of tumor dissemination in the case of a malignant tumor.

In conclusion, in a middle-aged female patient, RLH should be considered in the differential diagnosis of a small liver lesion that displays ring enhancement in the portal venous phase.

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Figure legends

Fig. 1. Unenhanced and triple-phase contrast-enhanced CT images of the liver, showing a lesion in segment 8 (arrows). [Please note that the arrows are not apparent on the images.] The lesion shows subtle low attenuation relative to that of liver parenchyma on the unenhanced image (a). On contrast-enhanced CT, the lesion was not visible on the arterial phase (b), and showed ring enhancement on the portal venous phase (c) and washout of contrast medium on the equilibrium phase (d).

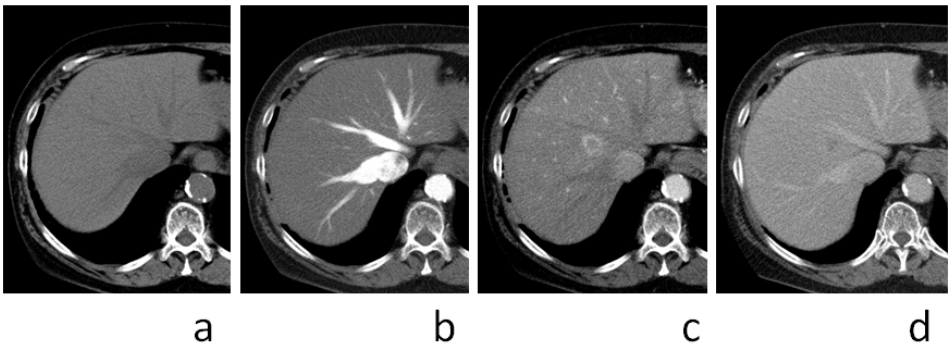

Fig. 2. Unenhanced and Gd-EOB-DTPA-enhanced MRI. The lesion shows low signal intensity on an unenhanced [Please check that this is your intended meaning.] T1-weighted image (a), and high signal intensity on a T2-weighted image (b). The lesion shows high signal intensity on diffusion weighted imaging (c) (b = 800 m^2/s, black-and-white inversion), and low signal intensity on apparent diffusion coefficient imaging (d). On Gd-EOB-DTPA-enhanced MRI, the lesion showed early enhancement in the arterial phase (e), ring enhancement in the portal venous phase (f), washout of contrast medium in the late phase (g), and low signal intensity in the hepatobiliary phase (h) suggesting the absence of normal hepatocytes.

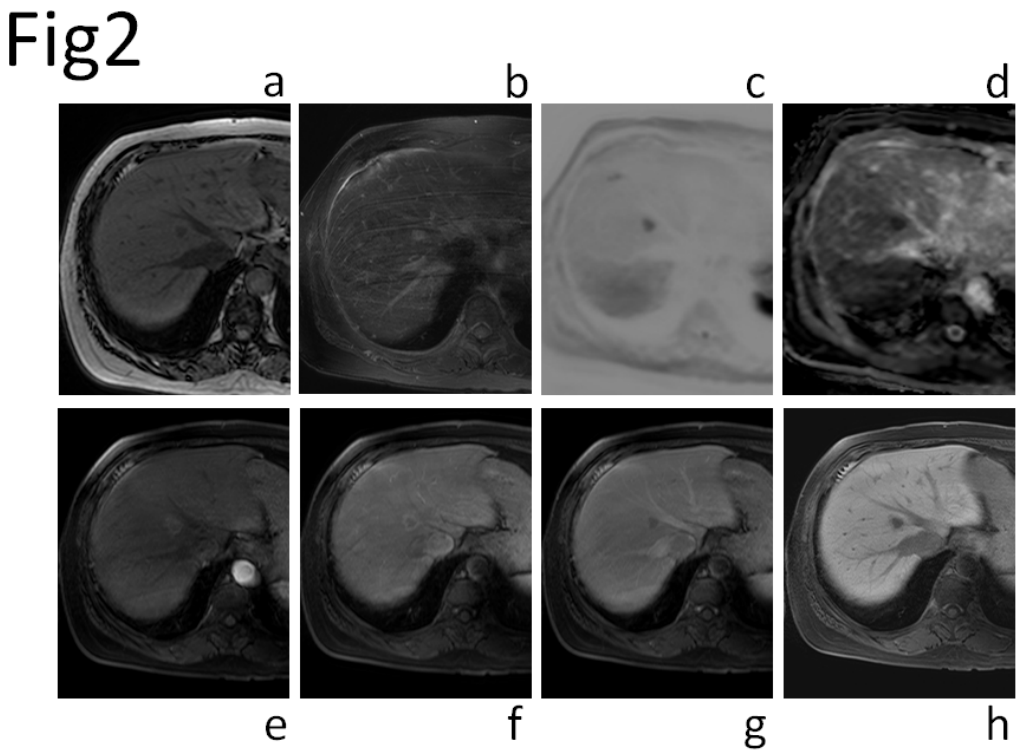

Fig. 3. Cut section of the resected liver. The lesion (15 × 10 mm) is well-circumscribed, yellow–white in color, and unencapsulated.

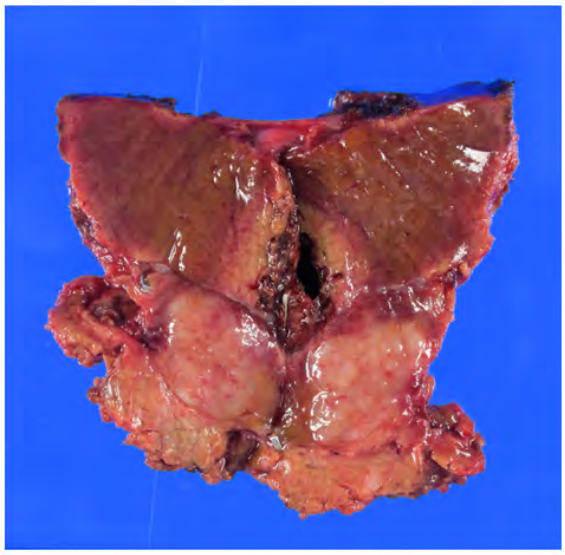

Fig. 4. Histological findings. (a) The lesion is well demarcated and comprises a massive infiltration of mature lymphoid cells, forming lymphoid follicles of various sizes with germinal centers (H & E staining, low magnification). (b) Prominent sinusoidal dilatation seen around the lesion (H & E staining, high magnification) is the likely cause of the ring enhancement observed on the contrast-enhanced imaging examinations. (c) (d) Immunohistochemical staining is positive for CD10, and is negative for Bcl-2. These results exclude follicular lymphoma.