

Case Report

Reactive lymphoid hyperplasia of the liver mimicking hepatocellular carcinoma: incidental finding of two cases

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Abstract: Reactive lymphoid hyperplasia is a rare disease that forms a mass-like lesion and is characterized by the proliferation of non-neoplastic, polyclonal lymphocytes forming follicles. We recently encountered 2 cases of reactive lymphoid hyperplasia of liver, both of which were asymptomatic and mimicked hepatocellular carcinoma by various imaging modalities. Based on the clinical impression of hepatocellular carcinoma, surgical resections were performed. Microscopic findings revealed that both lesions consisted of an aggregation of lymphocytes consisting of predominantly B-cells, with multiple lymphoid follicles positive for CD10 and negative for bcl-2, consistent with the diagnosis of reactive lymphoid hyperplasia. Polyclonality of both lesions was further confirmed by B cell receptor gene rearrangement study. The incidence of reactive lymphoid hyperplasia in the liver is exceedingly rare, and it is difficult to differentiate such lesions from hepatic malignancies based upon clinical grounds. The clinicopathological findings and literature review of this report may be helpful to improve the clinical decision-making.

Keywords: Reactive lymphoid hyperplasia, liver, hepatocellular carcinoma

Introduction

Reactive lymphoid hyperplasia (RLH) is a rare disease that forms a mass-like lesion and is characterized by the proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with an active germinal center [1].

More commonly described in the skin [2] and gastrointestinal tract [3, 4], its occurrence in the liver is exceedingly rare. To date, only 53 cases of reactive lymphoid hyperplasia of liver have been reported worldwide [5-8], and the etiology is still unclear.

Clinically, as a result of shared radiologic features by images, it is very difficult to differentiate hepatic RLH from malignancies in liver, especially hepatocellular carcinoma (HCC). Most of the cases reported were misdiagnosed preoperatively and definitively diagnosed following surgical resection.

In this article, we reported clinical, radiological, histological and immunohistochemical (IHC)

findings of 2 cases of hepatic RLH, both of which were suspicious for HCC before definitive surgery.

Case report 1

A 50-year-old female nurse was referred to us after a routine abdominal ultrasound examination during her annual physical. She had no complaints and no significant medical history. Physical examination revealed no remarkable abnormalities. Laboratory tests, including a complete blood count, liver function tests, and tumor markers (AFP, CEA, CA 19-9 and CA 125) were all within normal limits. In addition, HBsAg, HBcAb and HCV antibody were all negative.

Ultrasound examination identified a hypoechoic solitary nodule in segment 7 of the liver, which was confirmed by CT. Ethoxybenzyl (EOB)-MRI of the liver revealed a 10 mm lesion in segment 7 with low and high signal intensity on T1- and T2-weighted images, respectively (**Figure 1A, 1B**). The lesion was moderately enhanced in the arterial phase (**Figure 1C**) and washed out

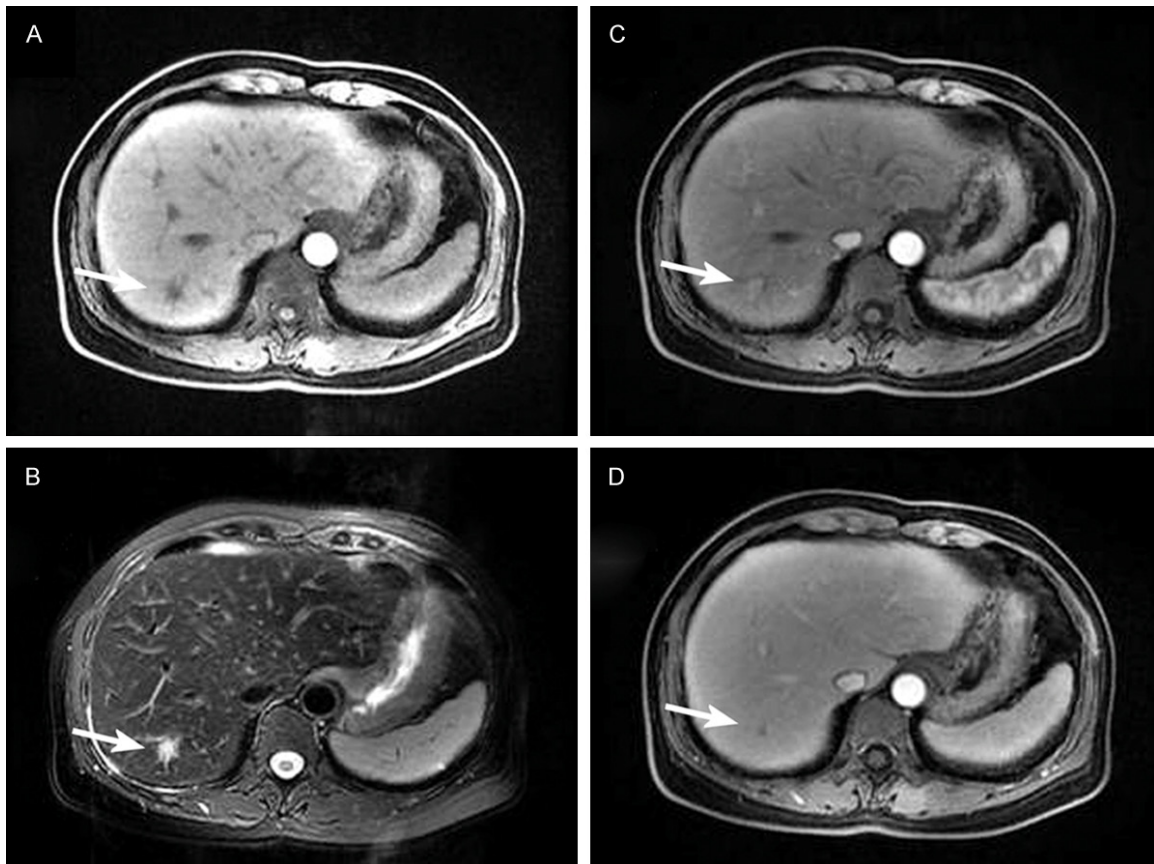


Figure 1. Imaging findings of the lesion in case 1. (A, B) A 10 mm lesion in segment 7 with low and high signal intensity on T1-(A) and T2-(B) weighted images respectively. (C) The lesion was moderately enhanced in the arterial phase. (D) The enhancement washout in the delayed phase.

in the portal venous phase and delayed phase (**Figure 1D**). Furthermore, it was presented as a hypointense and hyperintense signal lesion in the hepatobiliary phase (HBP) and diffuse weighted imaging (DWI). To aid in differential diagnosis, fluorodeoxyglucose-positron emission tomography examination integrated with computed tomography (FDG PET/CT) was performed, which showed no obvious high FDG uptake in the lesion.

Since the radiologic features of the lesion were more in keeping with HCC, surgical resection of the involved segment was undertaken. Grossly, the liver segment showed a grey-white nodule, measuring 10 × 7 × 7 mm. The nodule was firm and well-demarcated from surrounding tissue. Microscopically, the lesion was composed of lymphoid follicles of variable size and shape with expanded germinal centers (**Figure 2A**), indicating active lymphoid follicles. The lymphocytes appear mature and pleomorphic with

scattered tingible-body macrophages, imparting a starry-sky pattern. Lymphocytes from the nodule extended into adjacent liver tissue along hepatic portals. By IHC study, the majority of the lymphocytes were CD20+ B lymphocytes located in the germinal centers (**Figure 2B**) and were positive for CD10 but did not express bcl-2, consistent with a reactive process. No lymphoepithelial lesions were identified. On the basis of the histological and immunohistochemical findings, a diagnosis of hepatic RLH was made and it was confirmed by polyclonality in B cell receptor gene rearrangement study.

No recurrence of the liver nodule was detected during a 3 month medical follow-up.

Case report 2

A 62-year-old woman was found to have a liver lesion by abdominal ultrasound examination during her health check-up. The ultrasonogra-

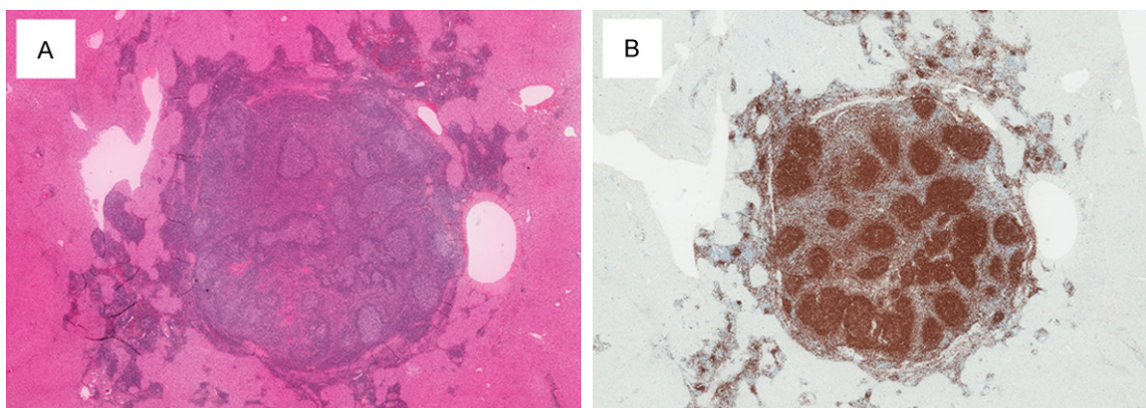


Figure 2. Microscopic findings of the nodule in case 1. A. Lymphoid follicles of variable size and shape were present with expanded germinal centers (H&E). B. CD20 immunostain demonstrates that the majority of lymphocytes were B lymphocytes located in the germinal centers.

phy showed an 11 mm hypoechoic lesion located in segment 7 of the liver.

Her medical history included hypertension, coronary heart disease, and lacunar infarction. Physical examination revealed no obvious abnormalities. Laboratory findings including liver function tests, hepatitis viral associated markers (HBsAg, HBcAb and HCV antibody), and tumor markers (AFP, CEA, CA 19-9 and CA 125) were normal.

The corresponding CT scans revealed a relatively hypodense solid lesion with indistinct borders and peripheral rim enhancement in arterial and portal venous phases. On EOB- MRI, the 14 × 11 mm hepatic lesion was low signal intensity in T1-weighted imaging and high signal intensity in T2-weighted imaging, and low intensity in HBP (**Figure 3A**) and high intensity in DWI (**Figure 3B**). The lesion was hyper-enhanced in the arterial phase (**Figure 3C**), and became equidensity and unclear with an indistinct rim in the portal venous phase and delayed phase (**Figure 3D**). In the FDG PET/CT scanning, the lesion showed a similar standardized uptake value (SUV) with hepatic parenchyma for FDG.

Based upon the radiologic and clinical impression of malignancy, specifically HCC, it was decided to perform surgical resection of segment 7. The liver nodule, 9 × 8 × 8 mm, showed a grey-white solid and firm cut surface. Microscopically, the lesion was composed of dense lymphoid tissue with a hyalinized central area and scattered lymphoid follicles. The ger-

minal centers of the lymphoid follicles were composed of small or large lymphoid cells and tingible body macrophages. An immunostain for CD20 highlighted the presence of reactive follicles (**Figure 4A**) with germinal center B lymphocytes expressing CD10 (**Figure 4C**) and negative for bcl-2 (**Figure 4D**). CD3+ T lymphocytes were mainly located in the interfollicular areas (**Figure 4B**). Polyclonality of the lesion was further confirmed by B cell receptor gene rearrangement study which showed a polyclonal pattern.

Discussion

Reactive lymphoid hyperplasia, also termed as pseudolymphoma, or nodular lymphoid lesion, is an extremely rare disease, especially in the liver. To date, only 53 cases of hepatic RLH have been reported worldwide since the first report in 1981 by Snover et al [5].

After reviewing the literature, we found that hepatic RLH occurs predominantly in females. Out of the 53 reported hepatic cases, only six (11.3%) were male patients, with a male-to-female ratio of nearly 1:8. RLH frequently occurred in 50-70 year old women, and the average age of reported patients was 56.4 years (range: 15-85 years). Hepatic RLH lesions were usually solitary, with multifocal lesions described in only seven cases (13.2%). The size of the lesion was usually less than 20 mm, and the average size was 19 mm (range: 4-105 mm) in the literature reviewed. The clinicopathologic characteristics of our two cases were in accordance with those in the reported literature.

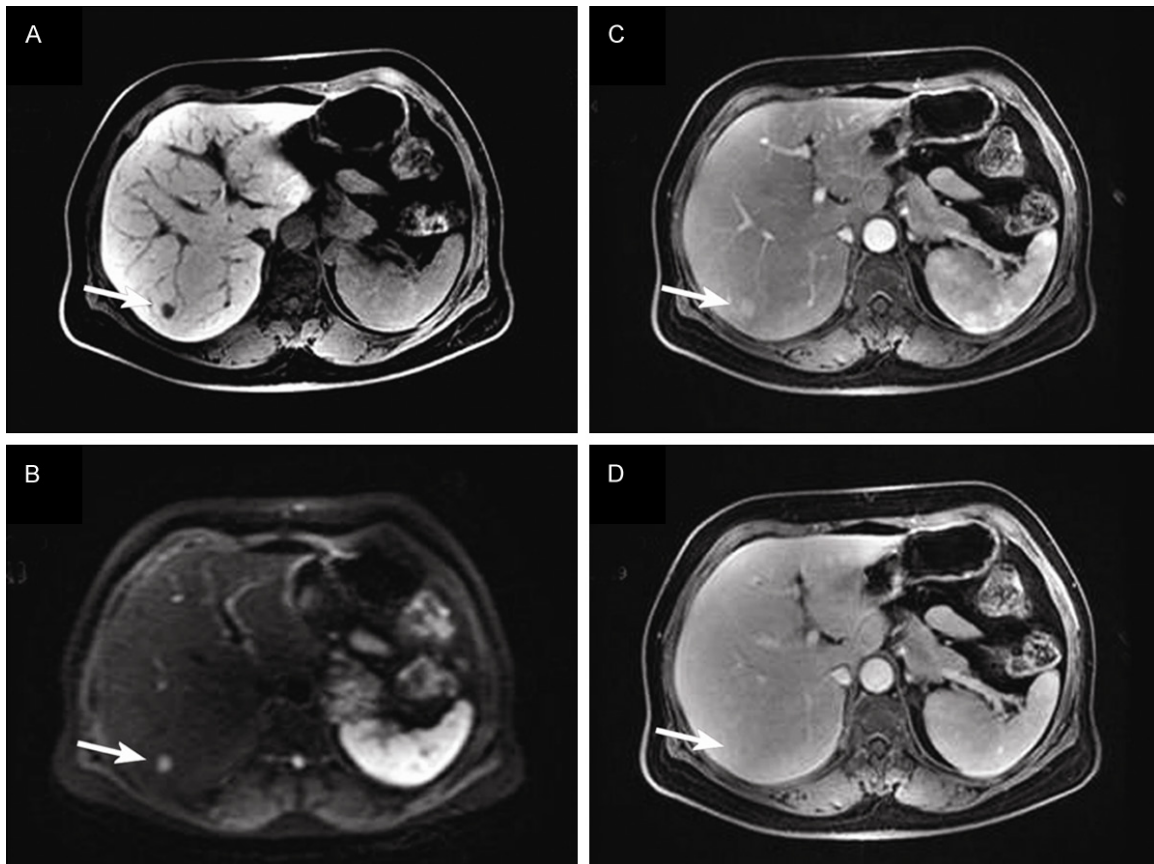


Figure 3. Imaging findings of the lesion in case 2. (A, B) A 14×11 mm lesion in segment 7 with low and high signal intensity in the hepatobiliary phase (A) and diffuse weighted imaging (B) respectively. (C) The lesion is hyper-enhanced in the arterial phase. (D) The lesion became equidensity and unclear with an indistinct rim in the delayed phase.

The etiology of RLH is still unclear. In previous reviews, an association between the development of hepatic RLH and some diseases such as viral hepatitis [9-11], autoimmune diseases [1, 11, 12] and malignant tumors [10, 13, 14] has been suggested; however, such concomitant diseases were found neither in our cases, nor in the largest case series published [6], probably due to the fact that in both reports the lesions were incidentally found from annual ultrasound examinations, which may be performed more common in China.

It is exceedingly difficult to make the diagnosis of hepatic RLH preoperatively, as evidenced by the misdiagnosis made in nearly all cases of this entity, including those reported in the literature. Hepatic RLH was most frequently misdiagnosed as HCC (22/53) in reported cases, and the same misdiagnosis occurred in our two cases. This is predominantly due to the fact that hepatic RLH so closely mimics HCC in vari-

ous imaging modalities, including ultrasound, CT scan, PET/CT, and even EOB-MRI.

EOB-MRI has been the most sensitive method in detection of small HCC until now [15]. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is taken up by hepatocytes and excreted into the biliary tract. Therefore, nodules lacking normal hepatocytes are depicted as low-intensity in the hepatobiliary phase. However, EOB-MRI seems to have failed to provide more help than traditional enhanced MRI in the differential diagnosis between hepatic RLH and HCC, as both lack normal hepatocytes and manifest as low-intensity in the hepatobiliary phase.

Some authors [6] described subtle differences in radiologic findings between hepatic RLH and HCC. They have reported that hepatic RLH becomes unclear in the delayed phase on MRI scan, while HCC is more hypodense in the

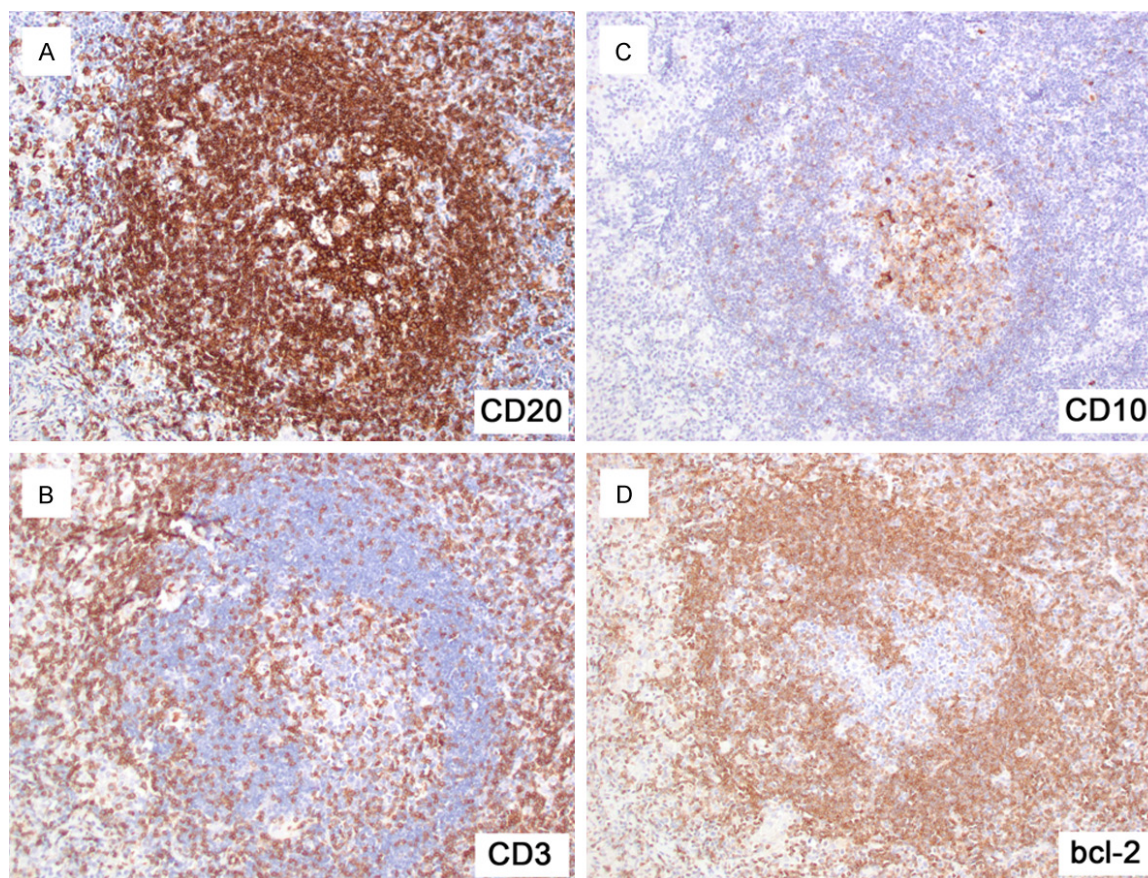


Figure 4. Microscopic findings of the nodule in case 2. (A) Immunostain for CD20 highlighted the presence of reactive follicles. (B) CD3+ T lymphocytes were mainly located in the interfollicular areas. (C, D) The germinal center (B) lymphocytes express CD10 (C) and are negative for bcl-2 (D).

delayed phase. Nonetheless, this described characteristic was not obvious in our cases. After hyper-enhancement in arterial phase of our cases, the case 2 lesion became unclear in both portal venous phase and delayed phase, while the case 1 lesion appeared hypodense in the delayed phase. It indicated that hepatic RLH may have varying radiological enhancement models.

It is worth noting that radiological appearance should be interpreted in the context of other available data, such as biomarkers and the patient's prior probability of developing or having hepatocellular carcinoma. Thus, in patients whose hepatic lesions are < 2 cm, combined with negative HBsAg and HCV antibody and normal serum AFP, although the radiologic appearance may correspond to HCC, the possibility of hepatic RLH should also be considered.

The definite diagnosis of hepatic RLH is difficult not only radiologically, but also histologically. Histologically, hepatic RLH must be differentiated from inflammatory myofibroblastic tumor (IMT) and low grade lymphomas with a nodular growth pattern, primarily marginal zone lymphoma (MZL) and follicular lymphoma. Hepatic IMT are most commonly described as well-defined solitary tumors within the right hepatic lobe [16]. Instead of the pure lymphoid proliferation in RLH, IMT are composed of a spindle cell proliferation with mixed inflammatory infiltrate including plasma cells and lymphocytes. Morphologically, MZL also contain reactive lymphoid follicles. However, lymphoepithelial lesions and cellular atypia were reported to be important diagnostic clues for hepatic MALT lymphoma, features not encountered in hepatic RLH [17]. Follicular lymphoma generally exhibits more densely packed follicles of uniform size and shape and infrequent tingible-body

macrophages. In addition to the morphologic clues, immunophenotyping provides useful information to distinguish reactive from neoplastic proliferations in such settings. The most helpful immunostain to distinguish RLH from follicular lymphoma is bcl-2, which is characteristically absent in reactive germinal center B-cells. Lymphoma also shows a monoclonal population of B lymphocytes as evidenced by light chain restriction or gene rearrangement studies.

In routine practice, if the diagnosis of HCC is highly suspected, preoperative needle biopsy is not usually recommended. However, when a small isolated tumor is discovered in a female patient without typical risk factors for HCC, although the radiologic appearances may correspond to HCC, the possibility of hepatic RLH should also be considered. In this case, a needle biopsy may be a more rational choice. Although, at times the definite diagnosis of hepatic RLH is difficult on small samples, needle biopsy is overall useful in differentiating RLH from epithelial malignancies, such as HCC or metastatic carcinoma. Based on literary review, no local or distant recurrences were identified in any of the resected or conservatively managed cases, within a follow-up period ranging from 3 months to 15 years. In addition, no malignant transformation of RLH in liver to lymphoma has been reported [7]. Thus, RLH is regarded as a benign disorder, to which surgical resection may not be necessary, and close radiologic follow-up is among the recommended management options.

Conclusion

Reactive lymphoid hyperplasia of liver is an extremely rare disease which may show similar radiological features to hepatocellular carcinoma by various imaging modalities. The definite diagnosis of this disease depends upon a combination of morphologic findings, immunohistochemical analysis and molecular studies. It should be considered in the differential diagnosis of small hepatic tumors, especially when a single tumor is found in a female patient with no risk factors of HCC. Considering the biological behavior, a conservative approach, such as needle biopsy and close radiologic follow-up, is among the recommended management options.

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Disclosure of conflict of interest

None.

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