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CASE REPORT

Reactive lymphoid hyperplasia of the liver: A case report and review of literature

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Abstract

A case of a 53-year-old female patient with reactive lymphoid hyperplasia (RLH), clinically designated as pseudolymphoma of the liver is described in this article. The patient was admitted to our hospital for further evaluation of hepatic tumors incidentally discovered at another hospital. Various diagnostic methods, including ultrasonography (US), computerized tomography (CT), magnetic resonance imaging (MRI) and hepatic angiography displayed three small lesions in the liver with outstanding findings consistent with hepatocellular carcinoma (HCC). Surgical resection was performed and the three lesions were microscopically diagnosed as RLH of the liver. The lesions comprised a massive infiltration of lymphoid cells with follicles and hyalinized interfollicular spaces. Immunohistochemical examination revealed that infiltrating lymphocytes had no prominent nuclear atypia and polyclonality. RLH of the liver is a very rare condition and only twelve cases have been reported in the English literature. Majority of the reported cases were middle-aged women and about half of them had some immunologic abnormalities such as autoimmune thyroiditis, Sjogren's syndrome, primary immunodeficiency, primary biliary cirrhosis. Since they are often clinically misdiagnosed as HCC, surgery is the choice of treatment for these patients. Although their pathology resembles malignant lymphoma, the clinical course is completely benign. The authors propose that RLH of the liver can be discriminated from HCC by its clinical features.

Key words: Reactive lymphoid hyperplasia; Pseudolymphoma; Hepatocellular carcinoma; Autoimmune thyroiditis; Immunohistochemistry

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INTRODUCTION

Reactive lymphoid hyperplasia (RLH) is a benign nodular lesion, histopathologically characterized by marked proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with an active germinal center. The lesion is encountered in various organs such as the orbit[1], lung[2], skin[3,4] and gastrointestinal tract[5-7]. However, disease of the liver is quite rare, with only 12 cases reported in the English literature. We have recently encountered a patient with 3 RLH lesions occurred in the liver. In this paper, the clinicopathological and radiographic characteristics of this unique disorder are discussed. Problems in differential diagnosis from malignant diseases, including malignant lymphoma and hepatocellular carcinoma, are also discussed.

CASE REPORT

A 53-year-old Japanese woman with a history of autoimmune thyroiditis was admitted to our hospital for further evaluation of hepatic lesions incidentally discovered on abdominal ultrasonography. The patient was asymptomatic on admission and her condition was generally good. Physical examination revealed no abnormalities. Relevant laboratory tests disclosed slightly elevated lactate dehydrogenase activity (547 IU/L; normal range: 120-245 IU/L), thymol turbidity (7.2 U/L; normal range: 0.0-4.0 U/L) and zinc sulfate turbidity (13.0 U/L; normal range: 4.0-12.0 U/L), although other hepatic function tests including serum asparate aminotransferase, serum alanine aminotransaminase and total bilirubin were within normal range. Levels of serum thyroid-stimulating hormone (10.22 μIU/mL; normal range: 0.35-3.73 μU/mL) and antinuclear antibody (80 ×; normal range: < 40 ×) were elevated due to autoimmune thyroiditis. Both hepatitis B surface antigen and anti-hepatitis C virus antibody were negative. Tumor markers including alpha-fetoprotein and protein induced by vitamin K antagonist-Ⅱ were negative.

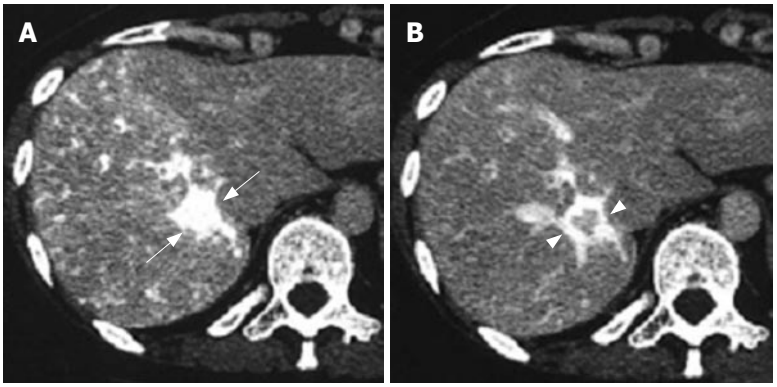

Figure 1 CT angiography showing the conspicuously enhanced lesion in segment 7 through the early phase (arrows) (**A**) and intensified tumor rim enhancement through the delayed phase along with radial enhancement (arrowheads) (**B**).

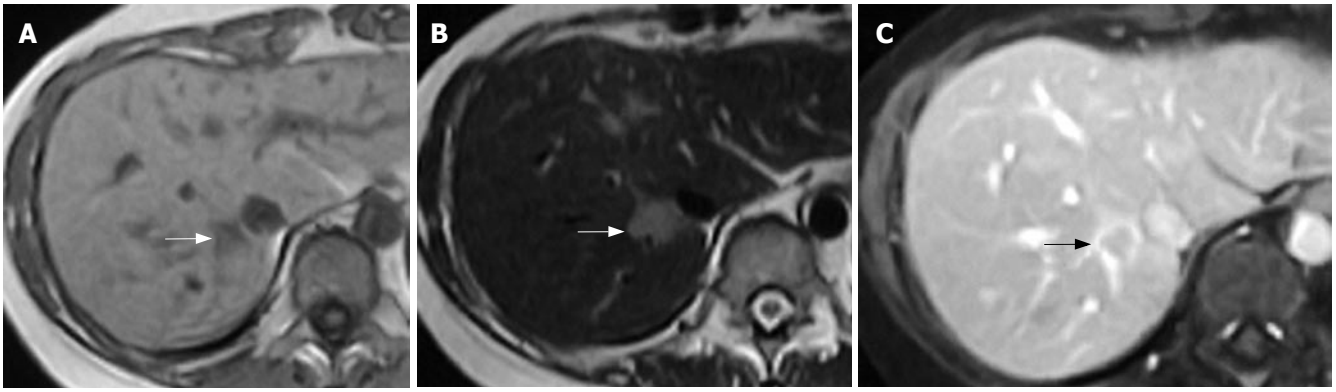

Figure 2 MRI displaying a hypointense signal on T1-weighted imaging (arrow) (**A**), a hyperintense signal on T2-weighted imaging of the lesion (arrow) (**B**), and enhanced tumor rim in the delayed phase of MRI (arrow) (**C**).

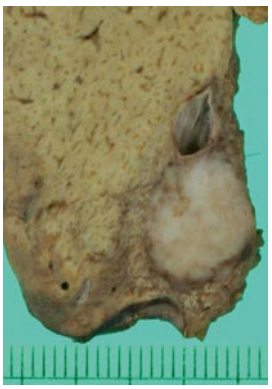

Figure 3 Macroscopy of tumor in segment 7 demonstrating the lesion as a well-circumscribed, white-yellowish nodule on the cut surface.

Precise US examination disclosed 2 hypoechoic nodules in the posterior segment and 1 nodule in the medial segment of the liver (13, 11 and 8 mm in diameter) respectively. Dynamic CT performed in the planes of lesions demonstrated a slight hyperdensity in the arterial phase followed by hypodense areas with pronounced enhancement along the tumor rims in the portal phase. The lesion in segment 7 was conspicuously enhanced through the early phase on CT angiography (Figure 1A). The tumor rim was continuatively intensified through the delayed phase, and radial enhancement toward surrounding liver parenchyma was also recognized (Figure 1B). The lesion was identified as a portal flow defect on CT with arterial portography. On MRI, tumor gave a hypointense signal on T1-weighted imaging (Figure 2A) and a hyperintense signal on T2-weighted imaging (Figure 2B). The tumor rim was underscored as an annular enhancement in the delayed phase, similar to dynamic CT (Figure 2C). Other lesions within segments 4 and 6 showed equivalent hemodynamics to the tumor in segment 7. Hepatic angiography of the 3 lesions also demonstrated distinct tumor staining in the arterial phase, following dense staining along tumor rims in the parenchymal-venous phase. As all images suggested hepatocellular carcinoma, posterior segmentectomy and partial resection of the medial segment of the liver were performed.

The resected liver displayed smooth surfaces and normal appearance. On the cut section, lesions were well-circumscribed, but not encapsulated white-yellowish nodules with irregular shapes (Figure 3). The 3 nodules exhibited similar microscopic findings, comprising a massive infiltration of lymphoid cells with follicles and hyalinized interfollicular spaces at low magnification (Figure 4A). Lymph follicles varied in size and shape with germinal centers composed of small or large lymphoid cells and tingible body macrophages. Interfollicular areas mostly comprised mature lymphocytes with no prominent nuclear atypia and a small amount of infiltrated plasma cells and histiocytes (Figure 4B). Strands of amorphous, somewhat-dense hyalinized material accompanied with capillaries were observed in interfollicular areas (Figure 4C). In some parts, fibrous materials aggregated as nodular structures of various sizes. Bile ductule proliferation was seen along the lesion edges. Portal areas apart from nodules showed irregular expansion with infiltration of small mature lymphocytes (Figure 4D). Immunohistochemical studies on

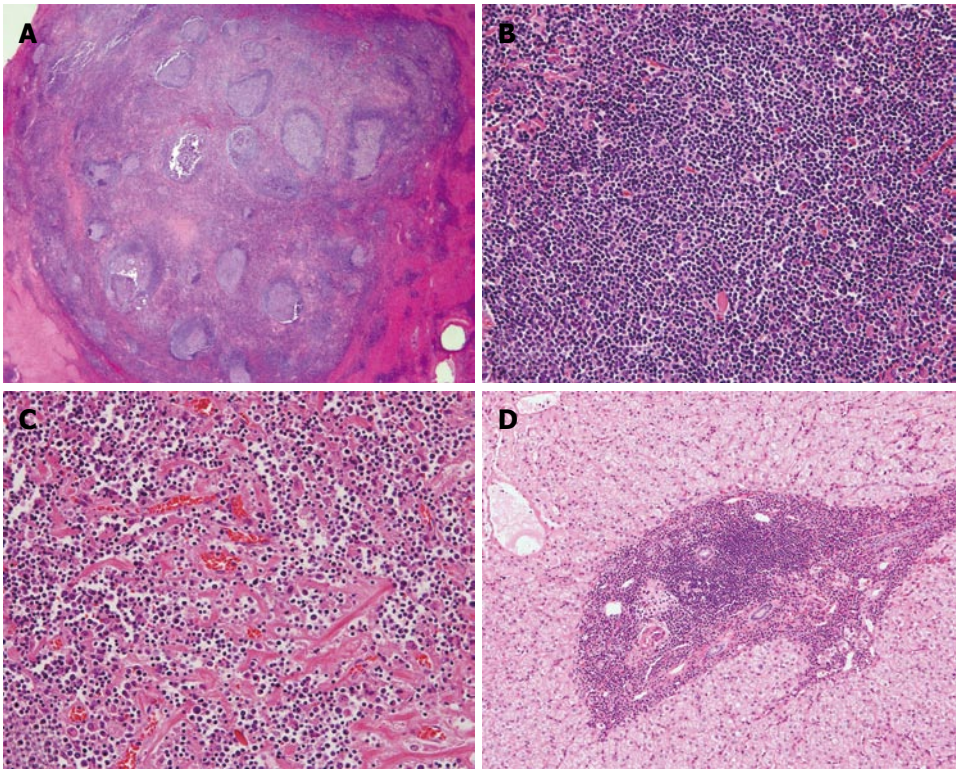

Figure 4 Microscopy revealing lesions comprising massive lymphoid cell infiltration with prominent follicles and hyalinized interfollicular spaces at low magnification (HE, X 2.5) (**A**), interfollicular areas mainly comprising mature lymphocytes with no nuclear atypia (HE, X 50) (**B**), strands of amorphous hyalinized material accompanying capillaries in interfollicular areas (HE, X 50) (**C**), and portal areas apart from the nodules with irregular expansion of infiltration of small mature lymphocytes (HE, X 25) (**D**).

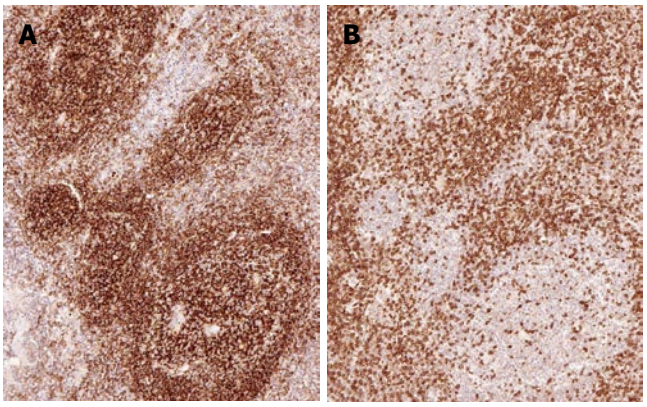

Figure 5 Immunohistochemistry discovering follicles mainly comprising CD20-positive lymphocytes (X 50) (**A**), and interfollicularly and circumferentially distributed CD3-positive cells compared to follicles (X 50) (**B**).

paraffin-embedded tissue sections for CD3, CD5, CD10, CD20, bcl-2 and both κ and λ immunoglobulin light chains were undertaken using the avidin-biotin-peroxidase complex technique. Follicles mainly comprised CD20-positive lymphocytes, while CD3-positive cells were distributed interfollicularly and circumferentially around follicles (Figure 5). Distributions were similar to that seen in reactive hyperplasia of lymph nodes. Lymphoid cells in follicles showed ordinary immunoreactivity, while cells in the mantle zone were positive for CD5 and cells in the germinal center were positive for CD10. Bcl-2 reacted only to lymphocytes in marginal or circumferential areas of follicles, but not in central regions. Scattered plasma cells were positive for both κ and λ light chains at an equal frequency. These immunohistochemical results indicate that lymph follicles were of reactive origin, but not of neoplastic, and that the lesion was composed of polyclonal lymphocytes and plasma cells. A genetic investigation of clonality in the immunoglobulin heavy chains (IgH) using a previously reported polymerase chain reaction method[8] with DNA from paraffin-embedded tissue was also performed. No clonal IgH gene rearrangement was detected with satisfactory negative and positive controls. The 3 lesions were thus pathologically diagnosed as RLH of the liver.

Postoperative course was relatively good and the patient experienced no signs of recurrence for 22 mo.

DISCUSSION

Although RLH can be found in various organs, including the gastrointestinal tract[5-7], orbit[1], lung[2] and skin[3,4], its occurrence in the liver is rare. To the best of our knowledge, only 14 lesions in 12 other cases of hepatic RLH of the liver have been reported in the English literature since the first case report by Snover *et al*[9] in 1981, with this case representing the thirteenth (Table 1). RLH occurs predominantly in middle-aged women, with a mean age of 54.1 years (range 15-72 years, Table 1). Although the pathogenesis remains unknown, an association between development of hepatic RLH and systemic or local immunological abnormalities has been suggested in earlier reports[10,11]. In fact, 6 of 13 patients, including the present, have displayed some immunological complications, such as autoimmune thyroiditis[10], Sjogren's syndrome[11], primary immunodeficiency (PI)[9], and primary biliary cirrhosis (PBC)[12] (Table 1). Two cases have been reported in association with hepatitis B (HB) virus or hepatitis C (HC) virus infection[13,14] (Table 1). The patient with hepatitis B was treated with interferon (IFN)-α[13]. Whether hepatitis viral infection is involved in hepatic RLH remains unclear. However,

Table 1 Reported cases of RLH of the liver

Case	Reference #	Age (yr)	Sex	Complications	Needle biopsy	Preoperative diagnosis	Tumor number	Tumor size (mm)	Treatment
1	9	15	F	PI	Done	Cirrhosis			
2	13	42	F	HB	None	HCC	3	15, 14, and smaller	Resection
3	10	47	F	Autoimmune thyroiditis	None	HCC	1	17	Resection
4	11	49	F	Sjogren's syndrome	Done	Suspicious HCC	1	20	Resection
5	12	52	F	PBC	None	PBC	1	4	Transplantation
6	12	56	F	PBC	None	PBC	1	15	Transplantation
7	12	56	M	Diverticulitis	None	Not reported	1	7	Resection
8	19	59	F	Diabetes	None	Malignant tumor	1	9	Resection
9	16	66	F	Diabetes	Done	Suspicious lymphoma	1	15	Resection
10	17	67	F	None	None	HCC	1	20	Resection
11	18	69	F	Renal cell carcinoma	Done	Metastatic tumor	1	17	Resection
12	14	72	M	Gastric carcinoma HC	None	HCC	1	17	Resection
13	Our case	53	F	Autoimmune thyroiditis	None	HCC	3	15, 12, and 10	Resection

the findings in these patients indicate that continuous stimulation from cytokines such as IFN-α or hepatitis viruses may cause RLH of the liver.

Saltzstein *et al*[15] has defined RLH as propagation of lymph-follicles constructed with lymphoid cells without cytological atypia, accompanied with a conspicuous, reactive germinal center. Katayanagi *et al*[16] and Tanizawa *et al*[17] have also proposed RLH as a localized lesion well-demarcated from the surrounding tissues and characterized by the presence of hyperplastic lymphoid follicles with polymorphic and polyclonal cell populations composed of small mature lymphocytes, mature plasma cells, macrophages and stromal fibrosis. The nodular lesion described herein seems to satisfy these histological criteria.

When RLH is diagnosed, malignant lymphoma must be excluded from the differential diagnosis. In the present case, immunohistochemical examination was performed to rule out malignant lymphoma. Germinal centers were considered non-neoplastic, based on negative results for bcl-2. In addition, lymphoid cells, including plasma cells, proliferating in the interfollicular area displayed polyclonal immunophenotypes. The results of a genetic investigation pertaining to IgH clonality also supported the histological findings. A diagnosis of RLH of the liver thus seems justified.

The lesion has been often misdiagnosed as a malignant tumor, since features are shared with hepatocellular carcinoma on various imaging modalities, namely detection as a hypoechoic mass on US, low density on CT with or without enhancement, low intensity on T1-weighted imaging and high intensity on T2-weighted imaging with magnetic resonance imaging, and tumor staining on hepatic angiography. Distinguishing RLH from hepatocellular carcinoma (HCC) is thus extremely difficult. Hepatectomy has therefore been performed for many patients[10-14,16-19] (Table 1). In the present case, the tumor rim displayed a sustained intensity accompanied with radial enhancement in addition to intratumoral hyperintensity on various imaging modalities. This prominent finding may represent increased capillaries within the nodule and massive infiltration of lymphocytes into portal areas around the lesion. Needle biopsy was indicated for only 4 patients in past reports[9,11,16,18] (Table 1), but it is not helpful for a confident diagnosis of this disease.

In conclusion, accumulation of reported cases with this benign lesion, including our patient, reveals some knowledge concerning the characteristics of this rare condition, such as female predominance, small tumor size, coexistent immunological disorder, and imaging features resembling HCC. The authors would like to emphasize that RLH should be included in the differential diagnosis of small hepatic lesions, particularly in middle-aged women with suspected HCC.

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