World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i10.387

World J Hepatol 2010 October 27; 2(10): 387-391
ISSN 1948-5182 (online)

CASE REPORT

Hepatic reactive lymphoid hyperplasia in a patient with primary biliary cirrhosis

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Received: May 18, 2010 Revised: August 6, 2010
Accepted: August 13, 2010
Published online: October 27, 2010

Abstract

Reactive lymphoid hyperplasia (RLH) of the liver is an extremely rare lesion characterized by the proliferation of non-neoplastic lymphocytes forming follicles. Hepatic RLH is known to be associated with gastrointestinal carcinoma and autoimmune diseases including primary biliary cirrhosis (PBC). We report a case of hepatic RLH in a patient with PBC and gastric cancer. A 68 year old Japanese woman with a 10 year history of liver enzyme abnormality was admitted. Laboratory testing revealed that her anti-mitochondrial antibody was markedly elevated. Five mo after the diagnosis of PBC, she was found to have gastric cancer. Abdominal computed tomography disclosed a liver nodule in S8, suggesting metastatic gastric carcinoma. Histopathologically, the resected liver lesion comprised of a nodular proliferation of small lymphocytes with lymphoid follicles. This is the first reported case of hepatic RLH in a patient with both PBC and gastric cancer. Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult. Therefore, a needle biopsy could be useful to make a diagnosis of hepatic RLH, especially to differentiate from metastatic gastrointestinal carcinoma.

Key words: Reactive lymphoid hyperplasia; Pseudolymphoma; Liver; Primary biliary cirrhosis; Gastric cancer

Peer reviewers: Hatim Mohamed Yousif Mudawi, Associate Professor of Medicine, Department of Internal Medicine, Faculty of Medicine, University of Khartoum, PO Box 2245, Khartoum, Sudan; Can-Hua Huang, PhD, Oncoproteomics Group, The State Key Laboratory of Biotherapy, Sichuan University, No. 1 Keyuan Rd 4, Gaopeng St, High-Tech Zone, Chengdu 610041, Sichuan Province, China

Ishida M, Nakahara T, Mochizuki Y, Tsujikawa T, Andoh A, Saito Y, Yamamoto H, Kojima F, Hotta M, Tani T, Fujiyama Y, Okabe H. Hepatic reactive lymphoid hyperplasia in a patient with primary biliary cirrhosis. *World J Hepatol* 2010; 2(10): 387-391 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i10/387.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i10.387

INTRODUCTION

Reactive lymphoid hyperplasia (RLH) of the liver is an extremely rare lesion characterized by the proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with an active germinal center[1-3]. This lesion has also been reported as pseudolymphoma and nodular lymphoid lesion[4-6]. To the best of our knowledge, only 28 cases of RLH of the liver have been reported in the English literature[7-22].

Herein, we report an additional case of RLH of the liver in a patient with both primary biliary cirrhosis (PBC) and gastric cancer and discuss the clinicopathological features of hepatic RLH and the clinical importance of differential diagnostic consideration of liver lesions in patients with gastrointestinal carcinoma.

CASE REPORT

A 68 year old Japanese female with a ten year history of liver enzyme abnormality was admitted to our hospital for further evaluation of the cause. Laboratory tests disclosed elevated gamma-glutamyl transpeptidase (83 U/L; range 10-47), alkaline phosphatase (568 U/L; range 115-359), leucine aminopeptidase (230 U/L; range 70-180), thymol turbidity (12.2 Kunkel; range 0.0-8.0) and zinc sulfate turbidity (14.1 Kunkel; range 3.0-11.0). Aspartate aminotransferase (28 U/L; range 13-33), alanine aminotransferase (21 U/L; range 6-27), and total bilirubin (0.8 mg/dL; range 0.3-1.2) were within normal ranges. Her serum IgG (1839 mg/dL; range 870-1700) and IgM (306 mg/dL; range 35-220) were slightly elevated. Her anti-mitochondrial antibody (M2) (index 195; range < 7.0) and anti-centromere antibody (index 167; range < 10) were markedly elevated. Both hepatitis B surface antigen and hepatitis C antibody were negative. These laboratory data suggested PBC and a liver biopsy was performed to confirm the diagnosis.

Liver biopsy showed periportal lymphocytic infiltration with bile duct damage (Figure 1). Infiltration of a few eosinophils and neutrophils in the portal area also was observed but granuloma and lymphoid follicle formation were not found. These histopathological findings were consistent with PBC. In addition, no histopathological evidence suggesting liver cirrhosis was seen.

Five mo after the liver biopsy, an upper gastrointestinal endoscopic examination revealed a depressed lesion with spontaneous hemorrhage and irregular margins in the pylorus region of minor curvature (Figure 2). Biopsy of the depressed gastric lesion disclosed signet ring cell carcinoma. Abdominal contrast-enhanced computed tomography (CT) showed a small nodule measuring 2cm with early enhancement in S8 of the liver (Figure 3), suggesting metastatic gastric carcinoma. Serum tumor markers were within normal ranges (CA19-9 17 U/mL; range < 37, carcinoembryonic antigen 2.6 ng/mL; range < 5, alpha-fetoprotein 2.6 ng/mL; range < 20, protein induced by vitamin K absence Ⅱ (PIVKA Ⅱ) 14 mAU/mL; range < 40).

Distal gastrectomy and resection of the liver nodule were performed.

Histopathologically, the gastric carcinoma was a signet ring cell carcinoma invading into the deep submucosa (pT1) (Figure 4A). No lymphatic or vascular invasion was detected by immunostaining of D2-40 or elastica van Gieson stain and no lymph node metastasis was seen (pN0).

Histopathological study of the resected liver lesion disclosed a relatively well-circumscribed nodular proliferation of mature-appearing small lymphocytes with lymphoid follicles (Figure 4B). The lymphoid follicles varied in size (Figure 4B, C). The germinal centers comprised a mixture of small and large lymphoid cells and scattered tingible body macrophages accompanied by a well-developed mantle zone (Figure 4C). Interfollicular areas were mostly composed of small mature-appearing lymphocytes and a small number of infiltrating plasma cells and histiocytes were also found (Figure 4C). No granuloma formation or multinucleated giant cells were observed. Mature-appearing lymphocytes were aggregated in the portal areas around the nodule. No lymphoepithelial lesion of bile

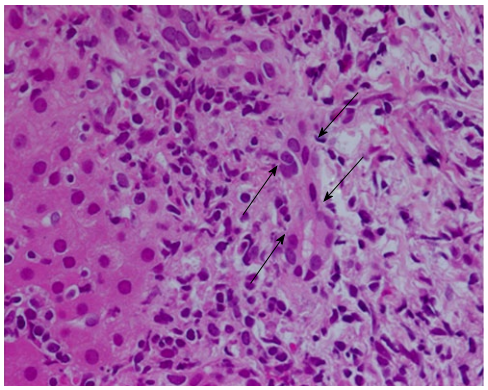

Figure 1 Histopathological findings of the liver biopsy. Periportal lymphocytic infiltration with bile duct damage (arrows: damaged bile duct; hematoxylin and eosin stain, × 400).

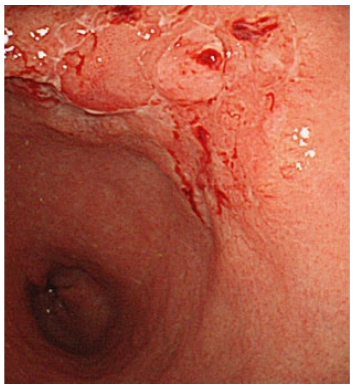

Figure 2 Endoscopic picture of the stomach. The depressed lesion with spontaneous hemorrhage and irregular margins.

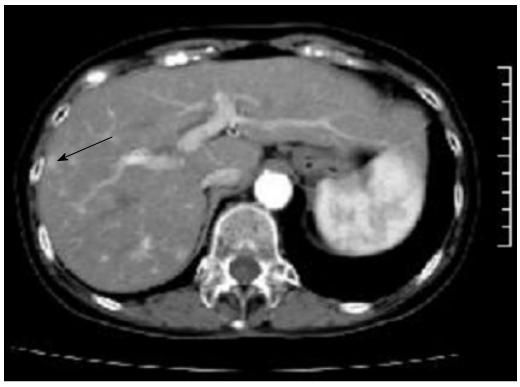

Figure 3 Contrast-enhanced abdominal computed tomography. A well-circumscribed nodule showing early arterial enhancement in S8 (arrow).

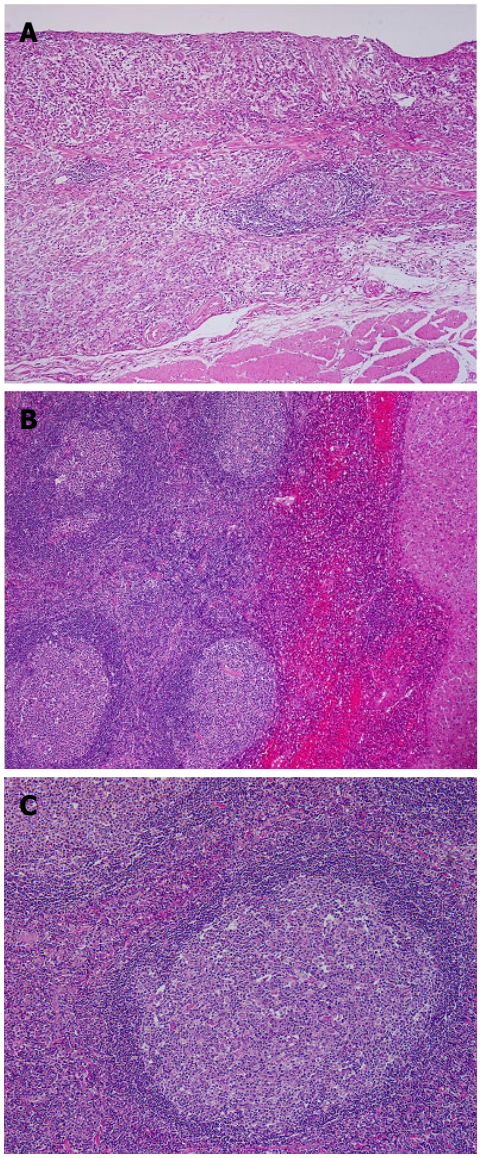

Figure 4 Histopathological findings of the gastric carcinoma and liver nodule. A: Signet ring cell carcinoma of the stomach invading into the deep submucosa (hematoxylin and eosin stain, × 40); B: A relatively well-circumscribed nodular proliferation of lymphocytes with lymphoid follicles in the liver (right: liver parenchyma, hematoxylin and eosin stain, × 40); C: Mantle zone and germinal center are sharply demarcated and a mixture of small and large lymphocytes and scattered tingible body macrophages is observed in the germinal center (hematoxylin and eosin stain, × 40).

duct was observed. In addition, no metastatic gastric carcinoma was disclosed.

Immunohistochemical studies showed that CD3-positive T lymphocytes and CD20/79a-positive B lymphocytes were regularly distributed in the same manner as in the lymph node (Figure 5). Bcl-2 was negative for lymphoid follicles. *In situ* hybridization of immunoglobulin light chains revealed intermixed kappa chain- and lambda chain-positive plasma cells.

Although polymerase chain reaction analysis of the immunoglobulin heavy chain gene was not performed, these histopathological and immunohistochemical findings were consistent with RLH of the liver.

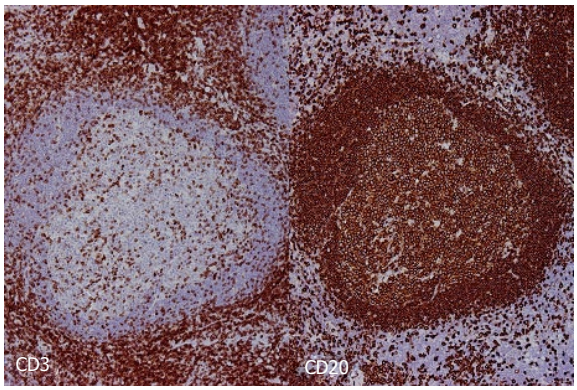

Figure 5 Immunohistochemical findings of the liver nodule. CD3-positive T lymphocytes (left) and CD20-positive B lymphocytes (right) are regularly distributed (× 40).

Post-operatively, no obvious recurrence of the liver no dule was detected during the 3 mo medical follow-up.

DISCUSSION

RLH can occur in various organs such as the gastrointestinal tract[23], lung[24] and skin[25]. RLH of the liver is extremely rare and most previous reports have been one case report, although recently Zen *et al*[5] reported the clinicopathological features of 5 cases of hepatic RLH. We review the clinicopathological features of the 28 cases of hepatic RLH reported previously in the English literature as well as the present case, as shown in Table 1. There is a very high female predominance (4 males/25 females). The youngest patient, reported by Snover *et al*[7], was a 15 year old female who had primary immunodeficiency syndrome. Except for that case, all patients were adult (range 36-85 years; average 59). Six of 29 cases (21%) had multiple lesions (five cases had two and one case had three lesions). The diameter of the lesions ranged from 0.4 to 5.5 cm; however, most were less than 2 cm.

Interestingly, five cases (17%) of hepatic RLH, including the present case, had a history of PBC (Table 1). In addition, six patients (21%) had extrahepatic autoimmune diseases such as Sjögren syndrome[16], Hashimoto thyroiditis[1], Takayasu arteritis[5], antiphospholipid syndrome[5] and CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome[6]; one patient had both PBC and CREST syndrome[6] and one patient had both PBC and chronic thyroiditis[5] (Table 1). The relatively high prevalence of autoimmune disease (approximately 30%) in patients with hepatic RLH suggests that systemic and/or local immunological abnormalities could be associated with the development of hepatic RLH, as suggested by earlier reports[14,16].

Moreover, the prevalence of gastrointestinal carcinoma in patients with hepatic RLH is also relatively high; seven patients (24%) with hepatic RLH had gastrointestinal carcinomas (Table 1). Three patients, including the present case, had gastric cancer and three patients had colon

Table 1 Clinicopathological features of reactive lymphoid hyperplasia of the liver

Case No.	Age	Sex	Number of lesions	Size (cm)	Associated disease	Ref.
1	15	F	1	NA	Primary immunodeficiency syndrome	[7]
2	85	F	2	1.4, 1.8	Gastric cancer	[8]
3	59	F	1	0.9	Diabetes mellitus	[9]
4	42	F	2	1.5, 1.4	Hepatitis B, IFN-alpha therapy	[10]
5	66	F	1	1.5	Diabetes mellitus, non-alcoholic steatohepatitis	[11]
6	67	M	1	2.0	Abnormal liver function	[12]
7	72	F	1	1.7	Hepatitis C, gastric cancer	[13]
8	52	F	1	0.4	Primary biliary cirrhosis	[6]
9	56	M	1	1.5	Primary biliary cirrhosis, CREST syndrome	[6]
10	56	F	1	0.7	Diverticulitis	[6]
11	47	F	1	1.7	Chronic thyroiditis	[14]
12	69	F	1	1.7	Renal cell carcinoma	[15]
13	49	F	1	2.0	Sjogren syndrome	[16]
14	77	F	1	1.5	Colon cancer	[2]
15	64	F	1	0.9	Colon cancer	[2]
16	72	F	1	1.3		[17]
17	36	F	1	1.8	Foca nodular hyperplasia and hemangioma of the liver	[18]
18	75	F	1	1.4	Gastric and colon cancers, liver metastasis (colon cancer)	[3]
19	63	F	1	1.6	Gastric ulcer	[19]
20	53	F	3	1.3, 1.1, 0.8	Autoimmune thyroiditis	[1]
21	67	F	1	1.2	Hypertension	[20]
22	46	F	1	1.0	Renal cell carcinoma	[21]
23	63	F	2	1.3, 0.4	Primary biliary cirrhosis, primary aldosteronism	[4]
24	63	F	2	0.9, 0.5	Primary biliary cirrhosis, chronic thyroiditis, adrenocortical adenoma	[5]
25	40	M	1	2.0	Hepatitis B	[5]
26	81	M	1	5.5	Cholecystolithiasis	[5]
27	64	F	2	3.5, 1.0	Takayasu arteritis, antiphospholipid syndrome	[5]
28	44	F	1	1.5	Colon cancer	[22]
Present case	68	F	1	2.0	Primary biliary cirrhosis, gastric cancer	

NA: not available; Ref: references.

cancer. Sato *et al*[3] reported a case of hepatic RLH in a patient with double carcinomas of the stomach and colon and a metastatic liver lesion from the latter. This is the first case report of hepatic RLH in a patient with both PBC and gastric cancer. Zen *et al*[5] speculated that the antigen from the gastrointestinal tract through the portal vein participates in the pathogenesis of hepatic RLH.

Although the precise mechanism of development of hepatic RLH remains unclear, these results suggest that autoimmune and/or immune reaction to the gastrointestinal malignancies may be involved in its development. In the present case, the patient had both PBC and gastric cancer simultaneously and either one or both may have been associated with the development of hepatic RLH.

Histopathologically, it is important to distinguish RLH from low-grade malignant lymphoma, especially marginal zone B cell lymphoma[5]. In the present case, the resected liver lesion disclosed nodular proliferation of mature-appearing small lymphocytes forming lymphoid follicles with a germinal center and neither lymphoepithelial lesion nor atypia of infiltrative lymphocytes were observed. The diagnosis of hepatic RLH was not difficult in the present case. However, making a diagnosis of hepatic RLH by needle biopsy can be challenging[5]. It has been reported that lymphoepithelial lesions and cellular atypia of infiltrating lymphocytes are important to provide a differential diagnosis[5]. In addition, all of the marginal zone lymphoma in the liver showed a dense portal lymphocytic infiltrate and a nodular proliferative pattern is rare in marginal zone lymphoma[26]. These findings suggest that cellular atypia and infiltrative pattern could be helpful in making a differential diagnosis.

Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult because hepatic RLH has features similar to hepatocellular carcinoma on various imaging modalities; namely a hypoechoic mass on ultrasound, low density on CT with or without enhancement and low intensity on T1-weighted imaging and high intensity on T2-weighted imaging with magnetic reso nance imaging[1,2]. In addition, these diagnostic imaging findings cannot rule out the possibility of metastatic carcinoma in patients with gastrointestinal carcinoma[2]. In the present case, the liver lesion was diagnosed pre-operatively as metastasis of gastric carcinoma. Therefore, a pre-operative liver biopsy could be useful for dis tinguishing hepatic RLH from metastatic gastrointestinal carcinoma and hepatocellular carcinoma, although differential diagnosis from low-grade malignant lymphoma could be challenging.

In summary, we report the first case of hepatic RLH in a patient with both PBC and gastric carcinoma. Pre-operative diagnosis of hepatic RLH by clinical imaging is extremely difficult. Therefore, a needle biopsy could be useful for making a diagnosis of hepatic RLH, especially in differentiating from metastatic gastrointestinal carcinoma and hepatocellular carcinoma, although distinguishing

hepatic RLH from low-grade malignant lymphoma could be challenging.

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S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N