

[ CASE REPORT ]

## Hepatic Pseudolymphoma with an Occult Hepatitis B Virus Infection

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### Abstract:

A 49-year-old woman who was asymptomatic was found to have a small liver tumor on abdominal ultrasonography (US) at her annual health checkup. US revealed a hypoechoic, solid, mass measuring 17-mm in size in segment 6. The tumor markers associated with liver malignancy were negative. An infectious disease screen was negative for hepatitis B surface antigen, but positive for antibody to hepatitis B core antigen. Imaging studies using computed tomography (CT), magnetic resonance imaging (MRI), and CT angiography suggested a malignant liver tumor, such as hepatocellular carcinoma. Partial hepatic resection of the posterior segment was performed. The pathological diagnosis was pseudolymphoma of the liver.

**Key words:** hepatic pseudolymphoma, reactive lymphoid hyperplasia, hepatocellular carcinoma, occult hepatitis B, HBc antibody

(Intern Med 57: 223-230, 2018)

(DOI: 10.2169/internalmedicine.8981-17)

### Introduction

Pseudolymphoma (also referred to as reactive lymphoid hyperplasia or a nodular lymphoid lesion) of the liver is a rare nonspecific, benign lesion characterized by a marked proliferation of polyclonal lymphocytes that form follicles with active germinal centers (1). To date, only 47 cases of hepatic pseudolymphoma have been described in the English-language literature. Pseudolymphoma clinically mimics primary hepatic malignancies, including hepatocellular carcinoma (HCC), malignant lymphoma, and cholangiocarcinoma (CCC). Pseudolymphoma is very difficult to diagnose without performing a histopathological examination. We herein report a case of hepatic pseudolymphoma that was diagnosed preoperatively as HCC in a patient who was positive for antibody to hepatitis B core antigen (anti-HBc).

### Case Report

A 49-year-old woman who was asymptomatic was found to have a small liver tumor in segment 6 on abdominal ultrasonography (US) at her annual health checkup. The patient was admitted for the evaluation of a hepatic lesion. Liver malignancy-associated tumor markers were negative, and the liver function enzymes were within the normal range. An indirect immunoassay test for antinuclear antibodies was positive, with a titer of 1:160, and a speckled pattern of fluorescence. Infectious disease screening was negative for hepatitis B surface (HBs) antigen, hepatitis B virus (HBV)-DNA, and antibody to hepatitis C virus (HCV), and positive for anti-HBc (Table). This means that the patient was in a state of a previous infection with HBV rather than ongoing.

US revealed a markedly hypoechoic, solid mass measuring 17-mm in size mass in S6 of the liver (Fig. 1a). Color Doppler US, and a waveform analysis demonstrated a pulsa-

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Received: February 4, 2017; Accepted: May 17, 2017; Advance Publication by J-STAGE: October 16, 2017

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**Table. Laboratory Data.**

Hematology		Blood chemistry	
WBC	7,000 / $\mu$ L	TP	6.6 g/dL
Neutrophils	51.0 %	ALB	3.9 g/dL
Eosinophils	6.5 %	T.Bil	0.8 mg/dL
Lymphocytes	35.0 %	AST	15 IU/L
Basophils	1.5 %	ALT	12 IU/L
RBC	421 $\times$ 10 <sup>4</sup> / $\mu$ L	LDH	126 IU/L
Hemoglobin	10.1 g/dL	ALP	153 IU/L
Hematocrit	33.8 %	$\gamma$ -GTP	12 IU/L
Platelets	21.7 $\times$ 10 <sup>4</sup> / $\mu$ L	ChE	193 IU/L
Coagulation		T.Cho	164 mg/dL
PT	78 %	TG	65 mg/dL
PT-INR	1.12	BUN	10 mg/dL
APTT	26.8 s	Cre	0.74 mg/dL
Viral marker		ZTT	6.5 Kunkel-U
HBsAg	(-)	CRP	0.03 mg/dL
HBsAb	(+)	ANA	160 Index
HBcAb	(+)	AMA-2	(-)
HBV-DNA	Not detected	AFP	1.2 ng/dL
HCVAb	(-)	AFP-L3	<0.5 %
		PIVKA-II	14 mAU/mL

WBC: white blood cell counts, RBC: red blood cell count, PT: prothrombin time, INR: international normalization ratio, APTT: activated partial thromboplastin time, HBsAg: hepatitis B surface antigen, HBsAb: antibody to hepatitis B surface, HBcAb: antibody to hepatitis B core, HBV-DNA: hepatitis B virus-DNA, HCVAb: antibody to hepatitis C virus, TP: total protein, ALB: albumin, T.Bil: total bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase,  $\gamma$ -GTP: gamma-glutamyl transpeptidase, ChE: cholinesterase, T.Cho: total cholesterol, TG: triglycerides, BUN: blood urea nitrogen, Cre: creatinine, ZTT: zinc sulfate turbidity test, CRP: C-reactive protein, ANA: antinuclear antibody, AMA-2: anti-mitochondrial M2 antibody, AFP: alpha-fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II

tile turbulent blood flow at the periphery of the lesion, with a penetrating vessel branch (Fig. 1b). Contrast-enhanced US using an intravenous ultrasound contrast agent (Sonazoid; Daiichi Sankyo, Tokyo, Japan), which is highly sensitive for detecting tumor vascularity, revealed arteries within the tumor. During the vascular phase, the tumor was enhanced as a real-time finely vascular image (Fig. 1c); and during the postvascular phase (Kupffer phase), the tumor appeared as a perfusion defect (Fig. 1d).

On computed tomography (CT) without any contrast material, the tumor appeared as a slightly low density mass (measuring about 20-mm diameter) in S6 of the liver. During the arterial dominant phase of multiphase CT, the mass showed homogeneous enhancement with dense irregular perinodular enhancement. During the equilibrium phase, the mass demonstrated a low density, with slight perinodular enhancement (Fig. 2).

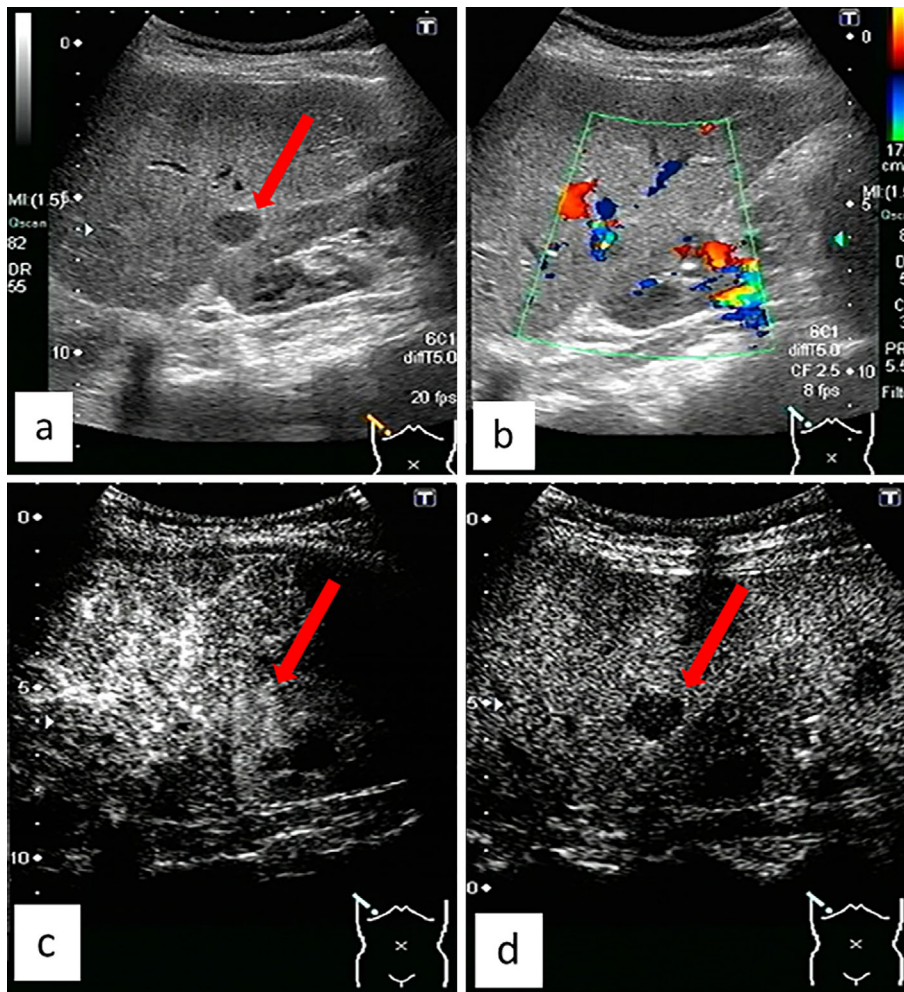
On magnetic resonance imaging (MRI), the mass showed a low signal intensity on T1-weighted imaging (T1WI), high signal intensity on T2WI, and slightly low signal intensity on T1WI on hepatobiliary phase (HBP) of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (Fig. 3a).

On chemical shift MR imaging, the mass showed a low

signal intensity on T1WI during both in-phase and out-of-phase. Clear low conversion to signals in out-of-phase was not accepted. The mass showed a marked high signal intensity on diffusion weighted imaging (DWI). The apparent diffusion coefficient (ADC) value was 0.256, and it accepted strong diffusion restrictions (Fig. 3b). On dynamic MRI, the mass showed the same enhancement pattern as that observed on dynamic contrast-enhanced CT.

Digital subtraction angiography (DSA) of the common hepatic artery revealed tumor staining in S6. CT arterial portography demonstrated a perfusion defect in S6. On CT hepatic arteriography, irregular enhancement of the perinodular liver parenchyma was observed during the early phase, and continued until the delayed phase (Fig. 4).

The differential diagnosis included HCC, peripheral type CCC, combined HCC-CCC, metastatic tumor, and sclerosed hemangioma. Because a malignancy was suspected, we decided to perform partial resection of the posterior segment, with a curative intent. The tumor specimen was a yellowish, clearly demarcated, and uniformly solid 18-mm diameter mass (Fig. 5). Histopathological examination of the resected liver tissue revealed a nodular lesion without a fibrous capsule. The lesion was infiltrated by small lymphocytes and plasma cells, and germinal centers were present. Aggregates



**Figure 1.** Ultrasonography. (a): Conventional ultrasonography (US) findings showing a markedly hypoechoic, solid mass measuring 17-mm in size in segment 6 of the liver (arrow). (b): Color Doppler US revealed the presence of flow in the periphery of the lesion. A doppler waveform analysis further demonstrated the flow to be pulsatile and turbulent. (c): During the vascular phase, this tumor was enhanced as a real-time finely vascular image (arrow). (d): Late phase Sonazoid-enhanced US showed a perfusion defect (arrow).

of histiocytes were also found. Atypical epithelial cells were not detected in the nodular lesion. Small to large lymphoid aggregates occasionally forming lymphoid follicles were present in the non-tumor parts near the nodular lesion, and some fibrosis was seen in the portal areas (Fig. 6a, b).

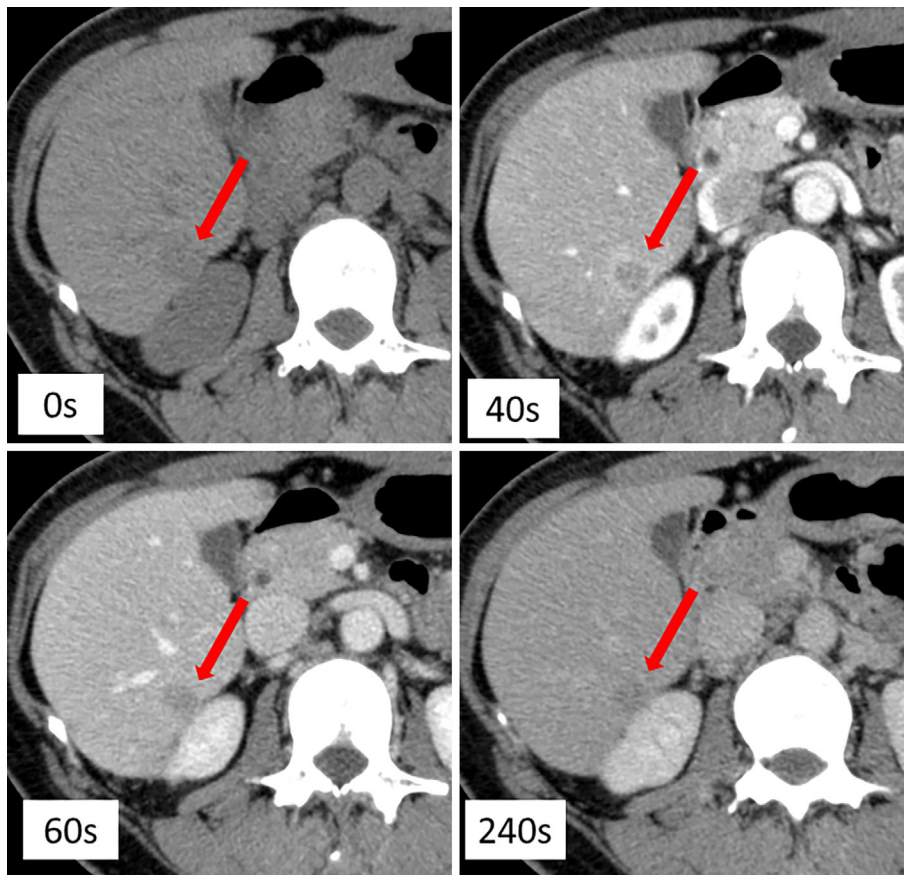
An immunohistochemical analysis of the sections of the specimen revealed many CD20-positive B cells admixed with CD3-positive T cells in lymphoid follicles (Fig. 6e-h). CD10-weakly-positive, Bcl2-negative germinal center cells were detected, indicating that the tumor was not follicular lymphoma. CD79a-positive cells were detected in the germinal centers and mantle zone. The tumor cells were negative for cyclin D1 expression. Aggregates of CD68-positive histiocytes were found in the interfollicular areas. Infiltrating plasma cells showed a polyclonal expression of cellular immunoglobulin (cIg) kappa and lambda chains (Fig. 6i-l). Some IgG4-positive plasma cells were present, and the IgG 4/IgG ratio was less than 5%. Ductal structures positive for CK7 were observed in the periphery of the nodule. A sec-

tion in the periphery of the nodule shows the proliferation of non-neoplastic polyclonal lymphocytes that are forming follicles with active germinal centers.

In liver tissue outside the lesion, the portal areas were focally expanded by lymphocytic infiltrate, and mild fibrosis (ie., F1 in the METAVIR score) was present. Some hepatocytes also showed fatty changes in the lobule (Fig. 6c, d). The final pathological diagnosis was reactive lymphoid hyperplasia (pseudolymphoma) of the liver.

## Discussion

Pseudolymphoma is also called reactive lymphoid hyperplasia (RLH) or a nodular lymphoid lesion. It was first described in the lung as a lymphocytic tumor associated with inflammation and with no evidence of systemic dissemination in 1963 (2). Pseudolymphoma can occur in various locations, including the skin, orbit, thyroid, breast, lung, and gastrointestinal tract; but it rarely occurs in the liver. Since



**Figure 2.** Multidetector-row computed tomography (CT) findings. Unenhanced CT shows the lesion as a slightly hypodense mass (arrow). During the arterial dominant phase of multiphase CT, the mass demonstrates homogeneous enhancement with dense, irregular, perinodular enhancement. The equilibrium phase shows the lesion as a relatively hypodense mass with slight perinodular enhancement.

hepatic pseudolymphoma was first reported as an unusual benign lymphoproliferative lesion in 1981, 47 cases of pseudolymphoma in the liver have been reported in the English-language literature (3, 4).

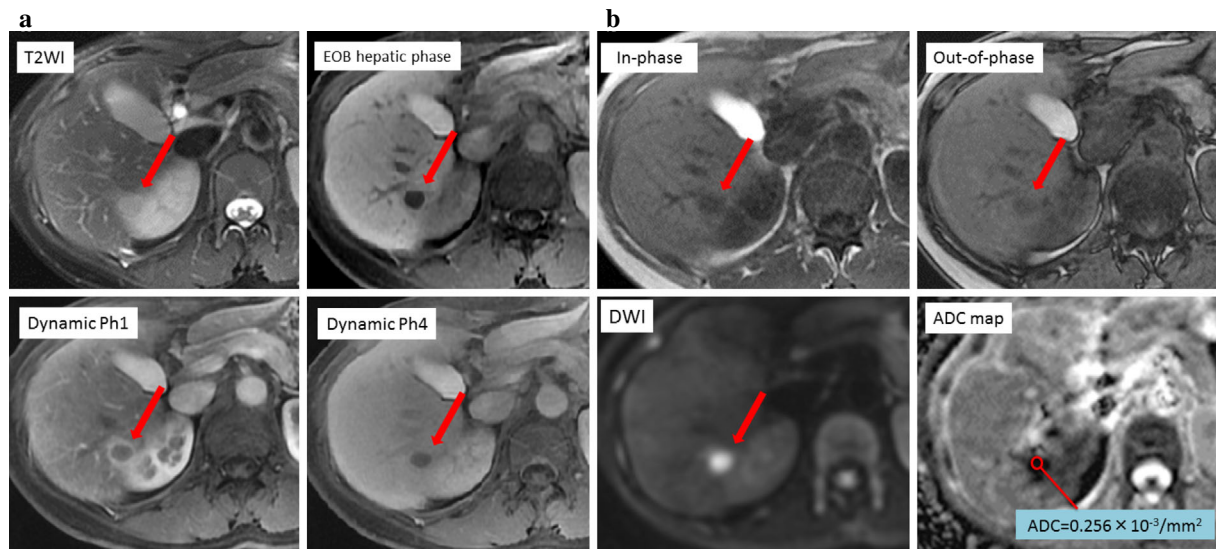
Hepatic pseudolymphoma is characterized by the proliferation of non-neoplastic polyclonal lymphocytes that form follicles with active germinal centers. However, hepatic pseudolymphoma clinicopathologically resembles low-grade lymphomas, including mucosa-associated lymphoid tissue (MALT) lymphoma (5). The differential diagnosis between hepatic pseudolymphoma and primary hepatic marginal zone B cell MALT-type lymphoma is frequently difficult to make. However, in this case, the lesion, unlike MALT lymphoma, did not show any monoclonal population in the germinal centers. The etiology, pathogenesis, and clinical implications of these two disease entities remain to a large extent unknown (5).

The histopathological findings of the pseudolymphoma in this case were compatible with those observed in chronic liver disease-induced pseudolymphoma. Although the etiopathogenesis of pseudolymphoma is unknown, it can develop due to mechanical stimulation in patients with extrahepatic autoimmune disease, such as Sjogren syndrome, Hashimoto

thyroiditis, Takayasu arteritis, and antiphospholipid syndrome, or chronic liver disease such as primary biliary cirrhosis, viral hepatitis, and nonalcoholic steatohepatitis. Pseudolymphomas have been reported to develop after interferon treatment for chronic hepatitis that supports the inflammatory nature of the lesion (2). Although the etiopathogenesis of hepatic pseudolymphoma remains unclear, 27% of the patients had chronic liver diseases including HBV- or HCV-related liver cirrhosis, and 23% had autoimmune disorders in the liver, such as primary biliary cholangitis (PBC), or in extrahepatic organs (5).

There have been 4 reports of pseudolymphoma in association with HBV infection (2). Our case had an occult HBV infection, and uninvolved liver tissue in the resected specimen showed mild fibrosis and mild lymphocytic infiltration on histopathology. However, no histopathological findings suggestive of autoimmune hepatitis (AIH) were seen.

Several reports have focused on the unique clinical manifestation of HBV infection, reflected by detectable HBV DNA in the liver despite the absence of a detectable serum HBs antigen (HBsAg) (6, 7). This unique manifestation is considered to indicate occult HBV infection. In most cases of latent HBV infection, anti-HBc is detectable, and thus



**Figure 3.** (a): On magnetic resonance imaging (MRI), the nodule revealed a high signal intensity on T2-weighted images (T2WIs), and a slightly low signal intensity on T1-weighted images during the hepatobiliary phase of gadolinium ethoxybenzyl diethlenetriamine pentaacetic acid enhanced MRI. Dynamic MRI presented the same enhancement patterns as imaging computed tomography. (b): On chemical shift imaging [T1-weighted images (T1WIs)], the nodule showed a low signal intensity on the T1WIs both during in-phase and out-of-phase (arrows). Clear low conversion to signals in out-of-phase was not accepted. There was a marked high signal intensity on diffusion weighted imaging. The apparent diffusion coefficient value was 0.256.

anti-HBc is considered to be a surrogate marker for patients with occult HBV infection. Most anti-HBc-positive healthy persons have an episomal form of HBV infection accompanied by ongoing viral replication. The HBV genome is frequently detectable in liver tumors in anti-HBc-positive, HBsAg-negative patients (7). Although specimens from our patient were not subjected to an HBV genomic analysis, we could not confirm the presence of active HBV infection.

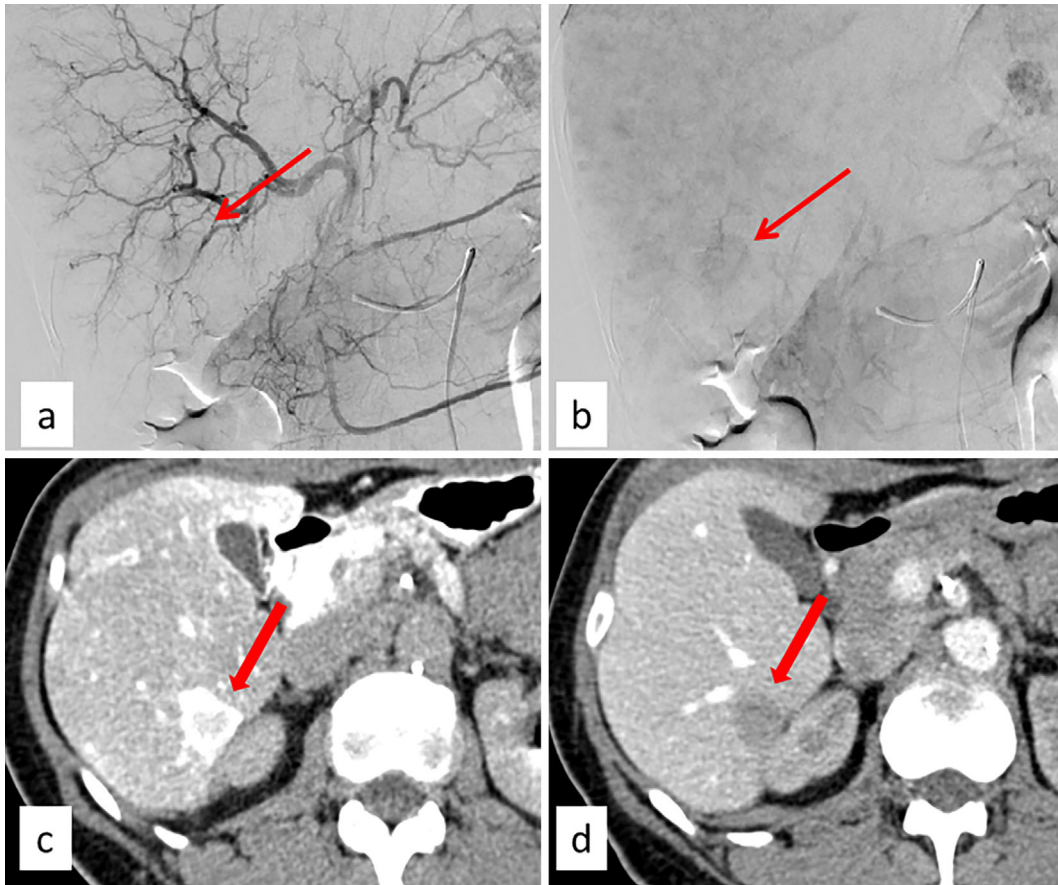
HBV is both a hepatotropic and a lymphotropic virus. Several case-control studies have found a higher prevalence of chronic HBV infection in patients with non-Hodgkin lymphoma (NHL) than in patients of various control groups (historical controls, blood donors, and hospital controls) (8-10). A cohort study from the USA, with a follow-up time of up to 7 years, showed that patients with chronic HBV infection had an increased, almost 3-fold risk of developing NHL (8). A cohort study from South Korea found that HBV infection significantly increased the risk of NHL, suggesting that chronic HBV infection promotes lymphomagenesis (9). The study presented reliable evidence that HBV infection plays an important role in lymphomagenesis. In addition, a cohort study of parous women in Taiwan found that HBV infection was most strongly associated with an increased risk of diffuse large B-cell lymphoma, but not with other specific NHL subtypes. However, the mechanism by which HBV infection may lead to the development of NHL is also not entirely understood (10).

Our pseudolymphoma case occurred in an anti-HBc-positive patient. The patient was presumed to have chronic liver disease, based on the histopathological finding of fibro-

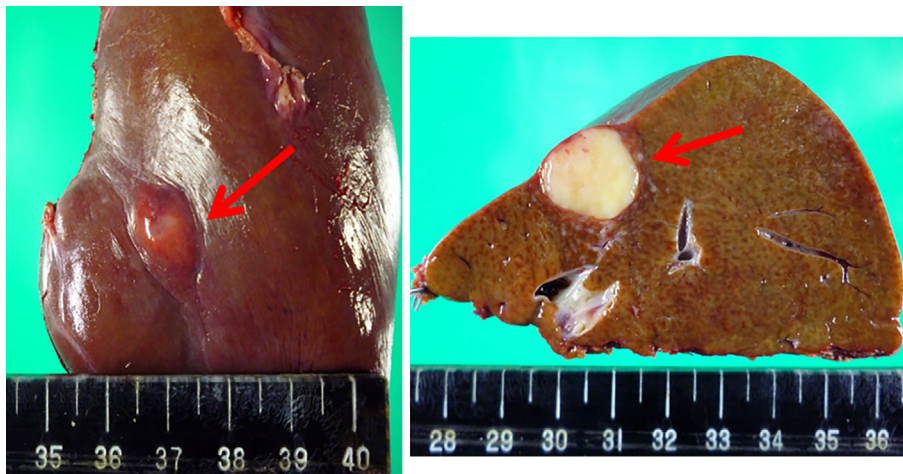
sis in the resected lobule. Talamo et al. speculated that the etiology of hepatic lymphoma may be related to chronic antigenic stimulation from the hepatitis B infection (11). As mentioned previously, we speculated that HBV infection could be related to hepatic pseudolymphoma as well. Although there are no pathological links between chronic hepatitis due to HBV infection and pseudolymphoma, there is an increased possibility that an etiology similar to that proposed by Talamo et al. was involved in the development of pseudolymphoma in our case.

To the best of our knowledge, there have not been any reports of patients with hepatic pseudolymphoma associated with occult HBV infection, and this is the first such reported case. Although an autoimmune and/or immune reaction may have been involved in the development of hepatic pseudolymphoma, the impact of hepatitis B cannot be ruled out.

Clinically, the US, CT, and MRI findings of hepatic pseudolymphoma are similar to those of HCC, CCC, metastatic tumor, and sclerosed hemangioma. A malignant tumor was misdiagnosed in this case based on the imaging findings. One case report emphasized that hepatic pseudolymphoma presented on CT with the vessel-penetrating sign, and that the lesion showed a slight uptake of contrast during the HBP of Gd-EOB-DTPA-enhanced MRI (12). Furthermore, marked enhancement around the lesion on arterial phase of CT or CT-angiography may be of value to differentiate pseudolymphoma from other diseases (13). Since the clinical diagnosis of hepatic pseudolymphoma is often difficult to make, especially during its early stages of development, surgical resection appears to be the mainstay for both diagnosis



**Figure 4.** (a, b): On digital subtraction angiography (DSA) of common hepatic artery, tumor staining was apparent. During the late or capillary phase, the lesion shows apparent ring-like enhancement. (c): On computed tomography hepatic arteriography (CTHA), enhancement of perinodular liver parenchyma and an irregular border was seen during the early phase, which continued until the delayed phase. (d): Computed tomography arterial portography (CTAP) demonstrates a perfusion defect in segment 6 of the liver.

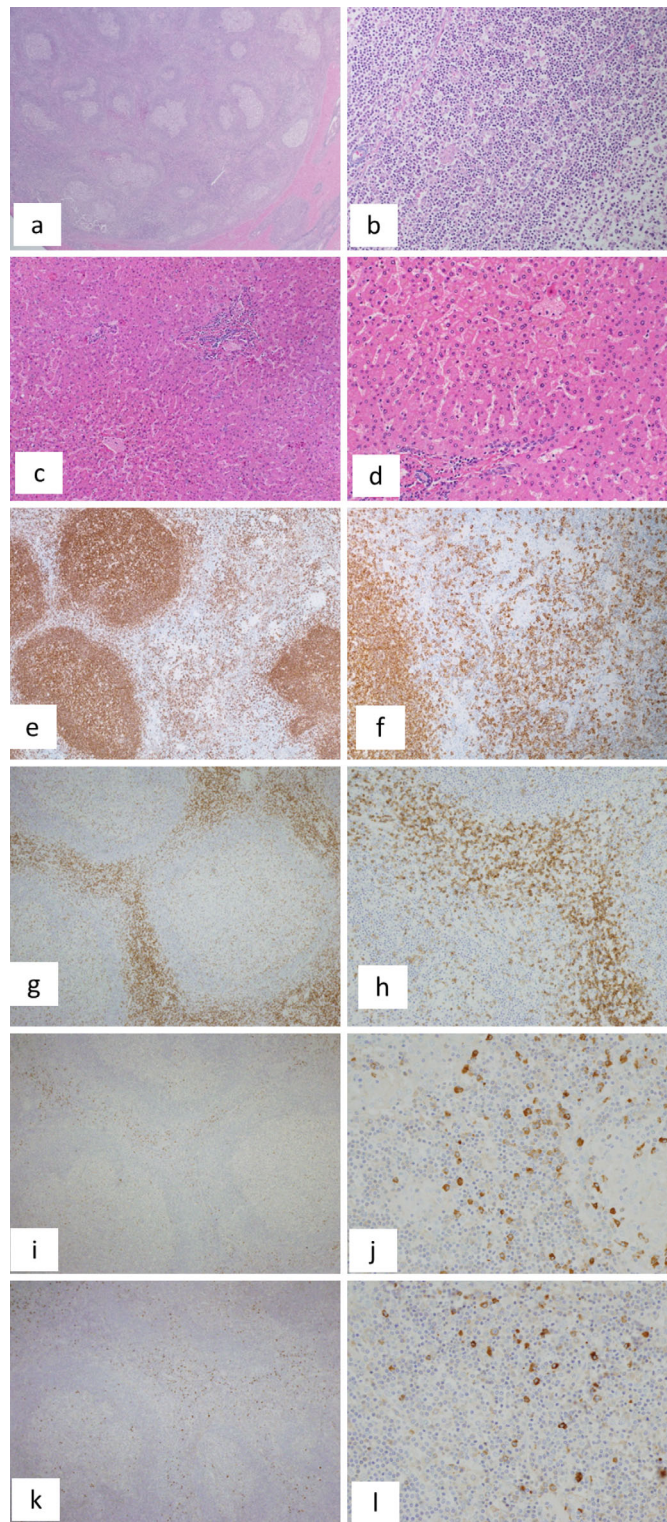


**Figure 5.** Photographs of a partially resected posterior segment of the liver. The tumor was a yellowish, clearly demarcated, and uniformly solid mass (arrow).

and treatment. Furthermore, hepatic pseudolymphoma occurs most commonly in middle-aged women. The diagnosis of a hypervascular tumor of the liver requires particular care in these patients, especially if an extrahepatic malignancy is

present.

In conclusion, hepatic pseudolymphoma occurs very rarely; we herein reported a case of hepatic pseudolymphoma in a patient with occult HBV infection. Hepatic



**Figure 6.** Photomicrographs of resected liver tissue (a, c, e, g, i, k: low-power views; b, d, f, h, j, l: high-power views). (a, b) The sections show a relatively nodular lesion without a fibrous capsule. The lesion shows infiltrates of small lymphocytes and plasma cells, and germinal centers. Aggregates of histiocytes are also seen. Atypical epithelial cells are not seen in the nodular lesion. Near the nodular lesion, small to large lymphoid aggregates with occasional lymphoid follicle formation are present in portal areas. (c, d) In areas outside the tumor lesion, the portal areas are focally expanded by lymphocytic infiltrate, and mild fibrosis (F1) is seen in the lobule. Some hepatocytes show fatty changes. (e, f) Immunostaining shows many CD20-positive B cells in germinal centers. (g, h) Immunostaining shows many CD3-positive T cells in perifollicular and marginal zone. (i, j) Immunostaining shows the polyclonal expression of cellular immunoglobulin kappa chains. (k, l) Immunostaining shows the polyclonal expression of cellular immunoglobulin lambda chains.

pseudolymphoma should therefore be considered in the differential diagnosis of small hepatic tumors, especially when a single hypovascular tumor is found in a patient with HBV infection. Because an accurate diagnosis is difficult to establish, a vigilant follow-up is indicated.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

The authors express their gratitude for the valuable support of Ms. Kyoko Nishizaki, Ms. Miwako Hoshino, Ms. Yuka Sato, Ms. Tomoko Nagaura, Ms. Yuki Nozaki, Ms. Chikako Nishi, Ms. Atsuko Ishibashi, Ms. Eri Yamauchi, and Ms. Motoko Kawashima.

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