

## Differential Diagnosis of Small HCC Focusing on Pseudolymphoma and Bile Duct Adenoma

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### Abstract

With the recent advances in diagnostic imaging, an increasing number of hypervascular hepatic nodules such as Hepatocellular Carcinoma (HCC), Cholangiolocellular Carcinoma (CoCC), Bile Duct Adenoma (BDA) and Lymphoproliferative Disorders (LPD) including pseudolymphoma have been detected. We encountered two cases of pseudolymphoma of the liver and two of bile duct adenoma features of which were compared with those of HCC. Imaging studies of pseudolymphoma of the liver in a 57-year-old woman who had Sustained Virological Response (SVR) to Interferon (IFN) treatment of Hepatitis C Virus (HCV), and a bile duct adenoma in a 39-year-old man, who had sustained SVR by treatment of HCV with Pegylated (Peg) IFN plus ribavirin were analyzed through imaging modalities and histochemical studies. Discussed here is the differential diagnosis of HCC in terms of pseudolymphoma and bile duct adenoma and the importance of avoiding overtreatment of benign lesions.

**Keywords:** Bile Duct Adenoma; Chronic Hepatitis C; Hypervascular Nodule; Pseudolymphoma; Small Hepatocellular Carcinoma

### Introduction

With the recent advances in diagnostic imaging [1-6], an increasing number of hypervascular hepatic nodules such as Hepatocellular Carcinoma (HCC), Cholangiolocellular Carcinoma (CoCC), hemangioma, adenoma, Focal Nodular Hyperplasia (FNH), Bile Duct Adenoma (BDA) and Lymphoproliferative Disorders (LPD) including pseudolymphoma have been detected. In general, the incidence of BDA and LPD is relatively small compared to other hypervascular liver tumors such as HCC, CoCC, hemangioma, adenoma and FNH. However, the precise diagnosis in BDA and LPD should be performed by imaging findings and histopathological analyses in order not to be overtreated, especially infected with HCV cases. Taken together with previous cases, two cases of pseudolymphoma of the liver and two of bile duct adenoma analyzed by imaging modalities are described and compared with small HCC. Discussed here is the differential diagnosis of small

HCC through imaging studies focused on pseudolymphoma and bile duct adenoma.

### Case Report

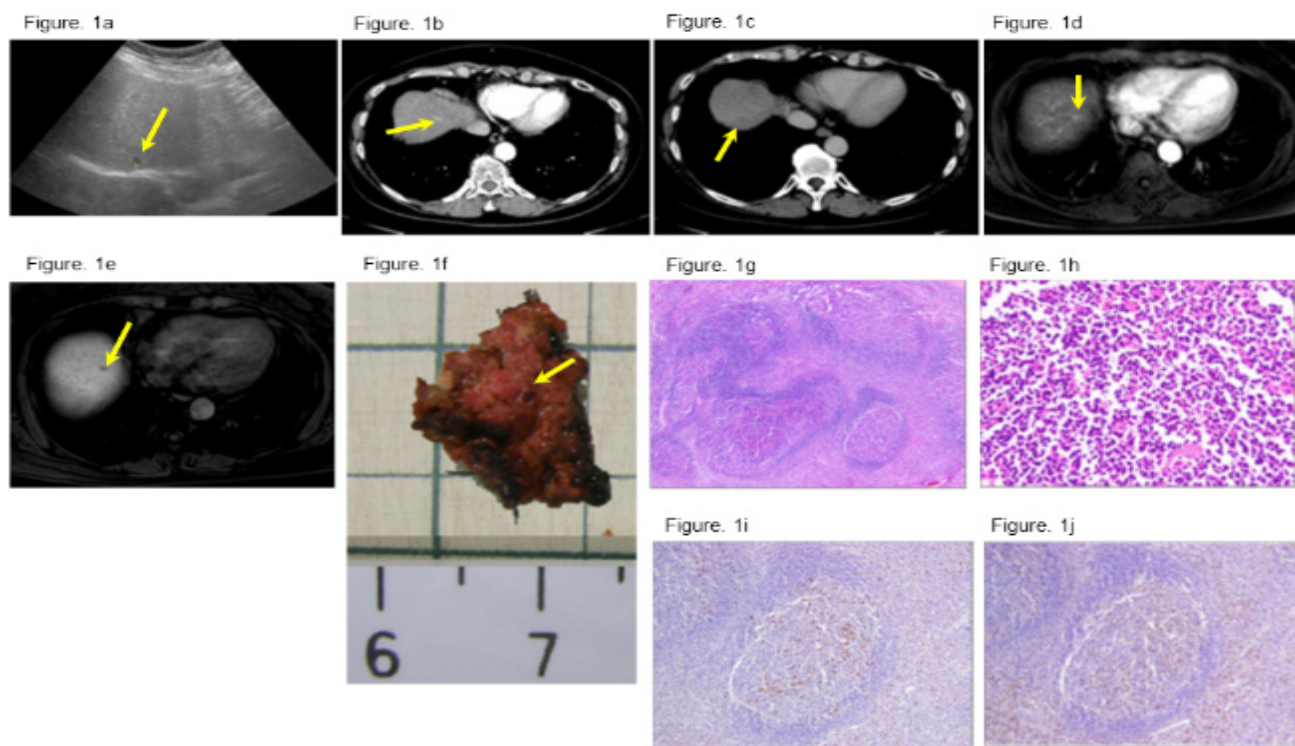
#### Case 1

Laboratory examinations at follow-up of a 57-year-old woman, who had achieved Sustained Virological Response (SVR) after treatment of Hepatitis C Virus (HCV) with Interferon (IFN), revealed the following: Immunoglobulin G (IgG) 863 mg/dL (normal, 1125~1737mg/dL), IgA 178 mg/dL (179-349mg/dL), IgM 42 mg/dL (126-252mg/dL), CEA 1.8 ng/ml (< 5.0ng/ml), Alpha-Fetoprotein (AFP) 9.7 ng/ml (0-20), protein induced by vitamin K absence or antagonist II (PIVKA II) 21 mAU/ml (0-40), Carbohydrate Antigen 19-9 (CA19-9) 5 U/ml (0-37), Interleukin-2 (IL-2) 466 U/mL (145-519). Antinuclear, anti-mitochondria, anti-smooth muscle, anti-liver kidney microsomal autoantibodies, and lupus erythematosus tests were negative. Routine Abdominal Ultrasonography (US) revealed a 10mm hypoechoic nodule in Segment Seven (S7) (Figure 1a), and Sonazoid Contrast-Enhanced US (CE-US) revealed, hypervascularity in the early vascular phase

and defect in the post-vascular phase. Computed Tomography (CT) disclosed no nodule. CE-CT revealed a hypervascular nodule (Figure 1b) in the early phase and low density nodule in the late phase (Figure 1c). Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid Magnetic Resonance Imaging (Gd-EOB-DTPA MRI) showed a hyper vascular nodule in the early phase and defect in the hepatobiliary phase (Figure 1d, e). CT During Arteriography (CTA) revealed hyper vascularity at the early phase, and CT During Arterial Portography (CTAP) revealed perfusion defect (Table 1).

Based on the patient's choice and under informed consent, the nodule was resected. Grossly, the lesion was a relatively poorly-defined yellowish white nodule with a soft rubbery consistency (Figure 1f). Histological analysis disclosed atypical lymphocytic proliferations forming follicles comprising numerous germinal

centers (Figure 1g). B cells positive for Cluster of Differentiation (CD) 10 and CD20, and negative for bcl-2 were distributed mainly in the germinal centers. The CD21-positive follicular dendritic cell networks were well preserved in the germinal centers while T cells positive for CD3 were distributed in the interfollicular zones. (Figure 1h) Infiltrating plasma cells in the lymphoid follicles stained positive for both immunoglobulin kappa and lambda light chains at sequential frequencies, indicating polyclonal and benign features (Figure 1i, j). The background of the liver revealed chronic persistent hepatitis. Molecular biology with the use of Polymerase Chain Reaction (PCR) proved the nodule was polyclonal not monoclonal, indicating benign features of lymphoid cells. (Data not shown) Based on the above findings, the nodule was finally diagnosed as pseudolymphoma or reactive lymphoid hyperplasia.



**Figure 1: Case 1**

- (a) US, 10mm hypoechoic nodule in segment seven.
- (b) CE-CT, hypervascularity in the early phase.
- (c) CE-CT, low density nodule in the late phase.
- (d) Gd-EOB-DTPA MRI, hypervascularity in the early phase.
- (e) Gd-EOB-DTPA MRI, defect in the hepatobiliary phase.
- (f) Gross appearance of the nodule, 10mm relatively poorly-defined yellowish white nodule.
- (g) Atypical lymphocytic proliferations forming follicles comprising numerous germinal centres. (HE stain).
- (h) Mainly of marked proliferation of atypical lymphoid cells. (HE stain).
- (i) Kappa chain positive plasma cells in the germinal centre.
- (j) Lambda chain positive plasma cells in the germinal centre.

## Case 2

Laboratory examination at follow-up of a 39-year-old man who had attained SVR after treatment of HCV with Pegylated (Peg) IFN plus ribavirin disclosed the following: AFP 7.2 ng/ml (0-20), PIVKA II 23 mAU/ml (0-40). A routine US examination revealed an 8mm hypoechoic nodule in Segment 6 (S6) (Figure 2a). CE-US revealed a hypervascular nodule in the early vascular phase, and defect in the post-vascular phase; Gd-EOB-DTPA-MRI revealed a hypervascular nodule in the early phase (Figure 2b) and defect in the hepatobiliary phase (Figure 2c); CE-CT disclosed a hypervascular nodule in the early phase and isovascular nodule

in the delayed phase. CTA revealed hypervascularity at the early phase (Figure 2d) and CTAP revealed perfusion defect (Figure 2e) (Table 1). Over a period of three months, US guided biopsy was carried out three times. Only one of 28 specimens revealed proliferation of small bile ducts with slight cellular and structural atypia within a loose fibrous stroma (Figure 2f). Initially, BDA was suspected from the histological findings, however, CoCC needed to be ruled out, and because of the very tiny specimen immunohistochemical analysis could not be done. The nodule finally was diagnosed as BDA through only Hematoxylin Eosin (HE) staining of the specimen by an expert hepatopathologist.

Figure. 2a

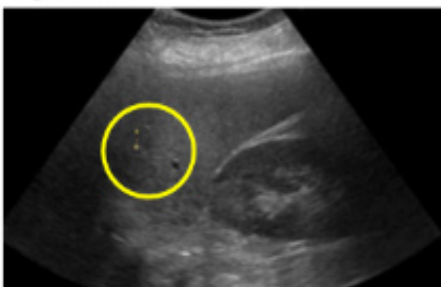


Figure. 2b

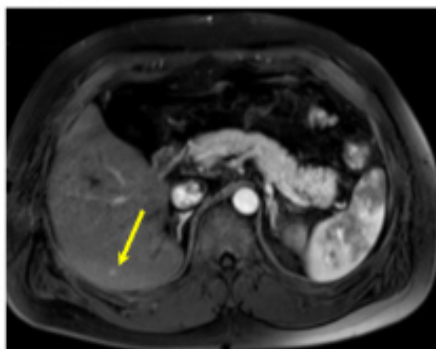


Figure. 2c

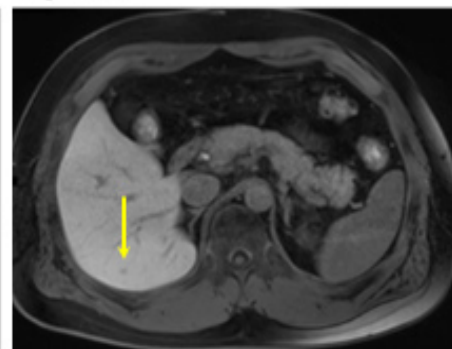


Figure. 2d

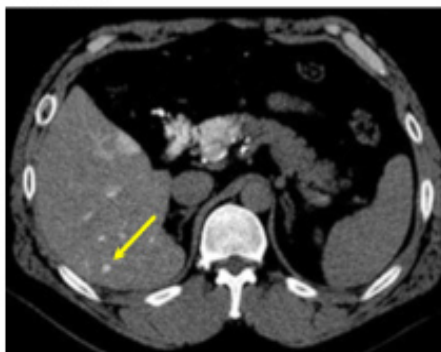


Figure. 2e

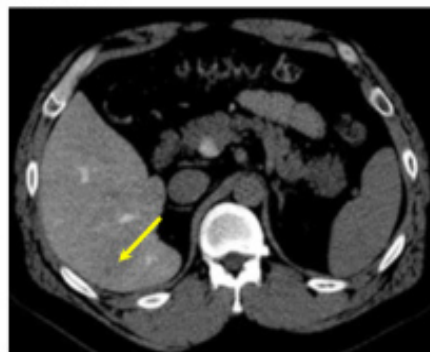
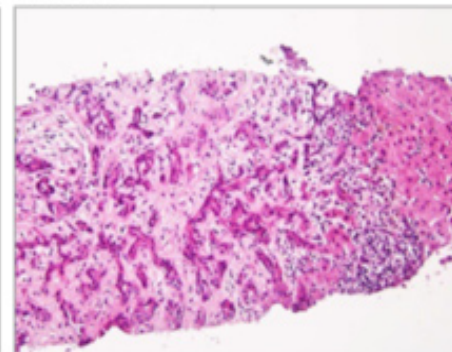


Figure. 2f



**Figure 2: Case 2**

- (a) US, 8 mm hypoechoic nodule in segment six.
- (b) Gd-EOB-DTPA MRI, hypervascular nodule in the early phase.
- (c) Gd-EOB-DTPA MRI, defect in the hepatobiliary phase.
- (d) CTA, hypervascular nodule at the early phase.
- (e) CTAP, perfusion defect
- (f) Proliferation of small bile ducts with slight cellular and structural atypia within a loose fibrous stroma (HE stain).

	Case 1	Case 2
US	Hypoechoic, 10mm sized in S7	Hypoechoic, 8mm sized in S6
CE-US	Hypervascularity in the early vascular phase  Defect in the post-vascular phase	Hypervascularity in the early vascular phase  Defect in the post-vascular phase
CE-CT	Hypervascularity in the early phase  Low density in the late phase	Hypervascularity in the early phase  Isovascularity in the delayed phase
Gd-EOB-DTPA MRI	Hypervascularity in the early phase  Defect in the hepatobiliary phase	Hypervascularity in the early phase  Defect in the hepatobiliary phase

**Table 1:** Imaging findings of two cases.

Discussion

We have previously described a 15×17mm pseudolymphoma in the liver of a patient with chronic hepatitis C [7] and a 7mm bile duct adenoma in a patient with chronic hepatitis C [8]; imaging studies of both nodules were compatible with HCC. In brief, CE-CT revealed early-phase hypervascularity and late-phase washout in both the pseudolymphoma and the bile duct adenoma [7,8]. In the present study, imaging analyses of a 10 mm pseudolymphoma and an 8 mm bile duct adenoma confirmed that the nodules were compatible with HCC. Pseudolymphoma is common in the gastrointestinal tract, orbit, lung, skin, pancreas, and thyroid, but relatively rare in the liver [7]. It is recognized as a mass with histologic features of diffuse reactive lymphoid proliferation, and is 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. More than 50 cases reported in the literature are compatible with pseudolymphoma as determined by immunohistochemical findings such as positivity of B cells in the germinal centers for CD10 and CD20, positivity of T cells in the interfollicular zones for CD3 and positivity of infiltrating plasma cells in the lymphoid follicles of both immunoglobulin kappa and lambda light chains [9].

The use of PCR demonstrates a polyclonal immunoglobulin heavy chain gene rearrangement, which confirms diagnoses [10,11]. In the present case, the diagnosis of pseudolymphoma was confirmed by not only histological findings including immunohistochemistry, but also the biomolecular method of

PCR. BDA has previously been called cholangioma, benign cholangioma, or cholangioadenoma, and simply BDA; it is also often confused with bile duct hamartoma; however, it has now been established as a pathologically distinct entity [12]. Most cases of BDA, a rare benign tumor composed of bile duct cells, are found incidentally during laparotomy or at autopsy [12]. Clinical, gross, and histopathologic features of 152 cases reviewed and found asymptomatic, have been discovered incidentally during intra-abdominal surgery (103 cases) and at autopsy (49 cases) [13]. BDA appears as a small whitish nodule measuring < 2 cm (mostly 5 mm to 1.0 cm in diameter) and locates immediately below the liver capsule. It is usually found in the normal liver, but on rare occasions also in the cirrhotic liver. Histologically it reveals a nonencapsulated tumor composed of a proliferation of small bile ducts within a fibrous stroma [14]. It also needs to be differentiated from CoCC.

Morphometrically, the size of small bile ducts ranged between 15 and 30 μm; in the present case, however, that of the non-neoplastic interlobular ducts and cholangioles of the background was 15~30 μm and less than 15 μm, respectively, and the size of the small bile ducts of the nodule was almost the same as that of the interlobular bile ducts in the background. Immunohistochemical stains positive for p16INK4a and negative for EZH2 have been significantly useful in differentiating between BDA and CoCC [14]. In the present case, absence of significant structural and cellular atypia and stromal invasion was observed, although immunohistological analysis could not be carried out due to the very tiny specimens. The diagnosis of BDA was confirmed by only HE staining by an expert hepatopathologist. Nonetheless, the nodule was treated by Radiofrequency Ablation (RFA) in compliance with the patient’s choice, regardless of its being benign. The definitive diagnosis of nodular lesions, detected by imaging modalities in the liver with cirrhosis, remains a critical challenge for clinicians.

The issue is particularly complicated for small (1-2 cm) nodules, many of which may be preneoplastic with uncertain malignant potential [15], such as macrorenerative nodules, Low-Grade Dysplastic Nodules (LGDN) or High-Grade Dysplastic Nodules (HGDN), or more rarely, hemangiomas that are found in up to 42% of explanted livers [16-18]. EASL and AASLD have issued the guidelines for the diagnosis of HCC [19-22]. EASL–EORTC Clinical Practice Guidelines recommend as follows. In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed up every 4 months during the first year and with regular check-up every 6 months thereafter (evidence 3D; recommendation 2B). In cirrhotic patients, diagnosis of HCC for nodules 1-2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. In the latter case, it is recommended that biopsies be assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement

patterns identified during follow-up.

Non-invasive criteria can only be applied to cirrhotic patients and should be based on imaging techniques obtained by a 4-phase multidetector CT scan or dynamic CE-MRI. Diagnosis should be based on the identification of typical hallmarks of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging modality is required for nodules beyond 1 cm in diameter (evidence 2D; recommendation 2B), a more conservative approach with 2 modalities is recommended in suboptimal settings. The role of CE-US and angiography is controversial. PET-scan is not accurate for early diagnosis [19]. AASLD recommendations are as follows [20, 21]. Diagnosis of HCC should be based on imaging techniques and/or biopsy. The 2005 diagnostic algorithm has been validated and the diagnostic accuracy of a single dynamic technique showing intense arterial uptake followed by “washout” of contrast in the venous-delayed phases has been demonstrated [20]. CE-US may offer false positive HCC diagnosis in patients with cholangiocarcinoma and thus, has been dropped from diagnostic techniques. The application of dynamic imaging criteria should be applied only to patients with cirrhosis of any etiology and to patients with chronic hepatitis B who may not have fully developed cirrhosis or have regressed cirrhosis.

Interpretation of biopsies and distinction between high-grade dysplastic nodules and HCC is challenging. Expert pathological diagnosis is reinforced by staining for glypican 3, heat shock protein 70, and glutamine synthetase, because positivity for two of these three stains confirms HCC [21]. In addition, Bruix et al. has described evidence-based diagnosis [23]. Lesions identified by surveillance must be characterized. In any cancer-screening program, there is the possibility of overdiagnosis. To minimize this risk, a recall algorithm has been developed and validated. Lesions < 10 mm are unlikely to be HCC and thus require only a short-interval follow-up period, such as every 3 months for at least 2 years. Lesions > 10 mm are more likely to be HCC. If CT or MRI evaluations show typical features of HCC, no further investigation is required. If the features are not typical, alternate imaging procedures can be implemented or a biopsy specimen can be collected and analyzed [23]. EASL and AASLD recommendations are reasonable. Three problems, however, should be pointed out. First is the size of nodule: even when less than 1 cm, typical findings such as hypervascularity in the early phase and washout in the late phase by CT and MRI have been demonstrated in some HCC cases [24].

Second is the sensitivity of imaging modalities for small HCC: the superiority of arteriportal angiography such as CTA and CTAP to CE-CT in the diagnosis of HCC in nodules smaller than 2 cm has been demonstrated [25,26]. In our study (case 2), positive findings of arteriportal angiography with positive

findings of CE-US and Gd-EOB-DTPA MRI were observed irrespective of negative findings such as lack of washout in the late phase at CE-CT. Third is the background of the nodule: even with a non-cirrhotic background, such as chronic hepatitis C together with chronic hepatitis B, the occurrence of HCC including small HCC < 2 cm has been described [27]. With the above, some small HCCs with a background of chronic hepatitis C show typical imaging findings. It is important, therefore, that clinicians in the field of hepatology be vigilant when encountering benign nodules such as pseudolymphoma and BDA imaging studies of which can be compatible with small HCC. In order not to mistake benign nodules for malignant ones with histopathological analyses and to avoid overtreatment or wrongfully treating them by RFA [28-32], surgery or transplantation [17,18,33-37], clinicians in the field of hepatology need to differentiate such nodules from small HCCs. Further studies are needed on a larger number of pseudolymphoma and BDA cases imaging findings of which display features compatible with HCC.

## Abbreviation

HCC: Hepatocellular Carcinoma; Cocc: Cholangiolocellular Carcinoma; BDA: Bile Duct Adenoma; LPD: Lymphoproliferative Disorders; FNH: Focal Nodular Hyperplasia; HCV: Hepatitis C Virus; SVR: Sustained Virological Response; Peg INF: Pegylated Interferon; Ig-G: Immunoglobulin G; Ig-A: Immunoglobulin A; Ig-M: Immunoglobulin M; AFP: Alpha-Fetoprotein; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; PIVKA II: Protein-Induced By Vitamin K Absence II; CE-US: Contrast Enhanced Ultrasonography; CE-CT: Contrast Enhanced Computed Tomography; CTA: CT During Arteriography; CTAP: CT During Arterial Portography; Gd-EOB-DTPA-MRI: Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction

## Author Contributions

Kim SK conceived the case and wrote the manuscript; Kim SR and Imoto S observed the clinical course of the patient and made the figures; Fujii T, Fujii Y, Yuasa K and Ohtani A observed the clinical course of the patient; Kobayashi H conducted the radiological examinations; Koma Y performed the autopsy and examined histology of the specimen; Kudo M interpreted the imaging findings.

## Conflict of Interest Statement

Masatoshi Kudo received financial support from Taiho Pharmaceutical CO., LTD., Taiho Pharmaceutical CO., LTD., Chugai, Otsuka, Takeda, Sumitomo Dainippon, Daiichi Sankyo, grants and personal fees from MSD, Eisai, Bayer, Abbvie, Medico's Hirata, Astellas Pharma, Bristol-Myers Squibb.

The other authors have no conflicts of interest to declare.

## Informed Consent

Informed patient consent was obtained for publication of the case details.

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