

# Potential value of apparent diffusion coefficient in the evaluation of hepatic pseudolymphoma

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## Introduction

Hepatic pseudolymphoma, also called reactive lymphoid hyperplasia or nodular lymphoid lesion, is a rare benign non-neoplastic lesion that is histopathologically composed of lymphoid follicles, densely-infiltrated lymphoplasmacytic cells and epithelioid cells (1). The incidence of this disease among females is nine times that of males, which shows a significant gender preference (2). Most hepatic pseudolymphomas are asymptomatic, with an average onset age of 50 years (2).

Due to the confusing imaging features of hepatic pseudolymphoma with hepatocellular carcinoma (HCC) or hepatic metastasis (3), the final pathological diagnosis of hepatic pseudolymphoma in clinic depends on surgical resection. Given the benignity of hepatic pseudolymphoma, the possibility of obtaining pathological tissues by a more minimally invasive approach should be explored so as to avoid unnecessary surgical management.

Herein, we reported a case of hepatic pseudolymphoma confirmed by ultrasound-guided biopsy and fully illustrated its performance by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT. Finally, the imaging differential diagnosis of hepatic pseudolymphoma was analyzed so as to minimize misdiagnosis and inappropriate clinical management.

## Case presentation

A 50-year-old asymptomatic female was found with a hepatic

lesion during a routine health check and was thus admitted to our institution for further assessment. Laboratory examination indicated the liver function was in the normal range. The elevated hepatitis B virus indicator showed an infection with hepatitis B virus, but the patient had been regularly taking antiviral medication. She had undergone two operations, including subtotal thyroidectomy 7 years ago (a benign lesion) and cholecystectomy due to gallstones ten years ago. The patient had no other chronic diseases, such as hypertension and diabetes, and had no harmful health habits, such as smoking or drinking. Clinical/imaging evaluation of the liver showed normal liver morphology with smooth margin and homogeneous texture, balanced ratio of hepatic lobe to hepatic dysmorphism, and no obvious signs of cirrhosis or portal hypertension.

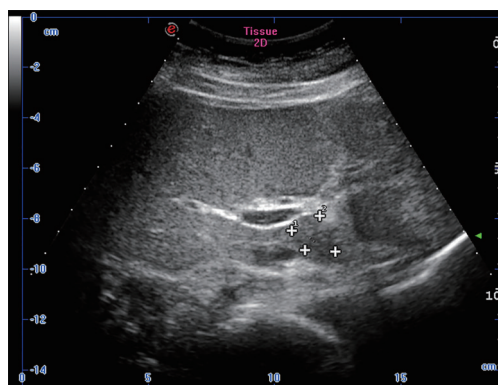
Hepatic ultrasonography showed a hypoechoic nodule in segment 1 with clear boundary (*Figure 1*). Non-enhanced CT indicated a homogeneously hypoattenuating lesion (45.7 HU,  $1.7 \times 2.5 \text{ cm}^2$ ) in segment I. Hepatic contrast-enhanced CT revealed a hypoattenuating nodule (61.9 HU) with minimal perinodular enhancement during the arterial phase. The lesion was also hypoattenuating during the portal and delayed phases (79.8 and 81.5 HU, respectively; *Figure 2*).

Conventional MRI of the hepatic lesion showed hypointense signals on T1-weighted images (T1WI) and hyperintense signals on T2-weighted images (T2WI) with clear boundaries. In the out phase, the signals of the lesion were without any deficiency. The diffusion weighted imaging (DWI) sequence of the lesion showed hyperintense

signals with a low apparent diffusion coefficient (ADC) ( $0.95 \times 10^{-3} \text{ mm}^2/\text{s}$ ) at  $b=0$ ,  $1,000 \text{ mm}^2/\text{s}$ , which indicated the diffusion restriction of water molecules. Contrast-enhanced MRI showed a heterogeneous enhancement of the lesion during the arterial phase and mildly hyperintense signals during the portal and delayed phases (Figure 3), which suggested a prolonged enhancement pattern. Moreover, no enlarged lymph node was found in the hilar and retroperitoneal region.

The hepatic lesion was further evaluated by non-enhanced PET/CT scan (Siemens Medical Solutions USA, Inc., Malvern, PA, USA), which showed an irregular hypoattenuating lesion with ill-defined boundary and an increased radioactive uptake (SUVmax 6.4) (Figure 4). No abnormal ( $^{18}\text{F}$ )s-fluorodeoxyglucose (FDG) metabolism was found in other parts of the body.

An ultrasound-guided needle biopsy was further performed for diagnosis. Pathological tissues were successfully obtained. The pathological results revealed the



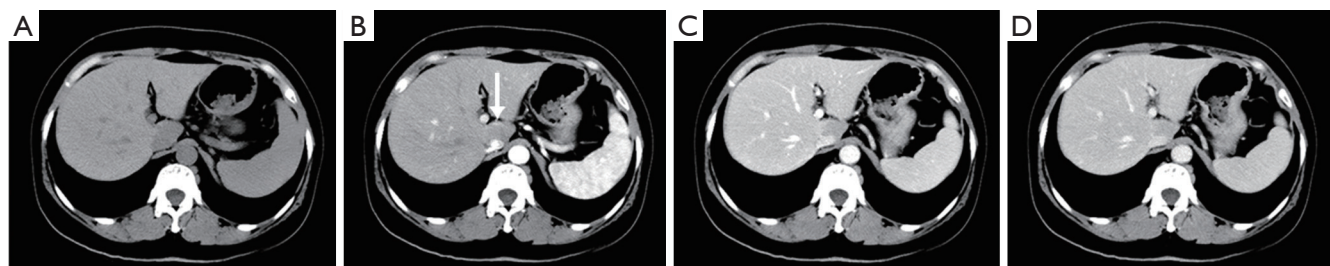
**Figure 1** Abdominal ultrasonography showed a hypoechoic lesion of the caudate lobe, with clear boundary.

infiltration of numerous B lymphocytes and the involvement of T lymphocytes into the hepatic cells, but no hepatocyte lobular structure (Figure 5). Immunohistochemistry showed hepatocyte (+), CK19 (+), CD20 (+), CD3 (+), AFP (–), CD34 (–), GPC-3 (–), TDT (–), CD1a (–), and Ki-67 (low). The pathological diagnosis suggested hepatic pseudolymphoma and low-grade B-cell lymphoma, and was then confirmed by a clonal gene rearrangement test, which showed “negative”. Finally, the morphology, immunophenotype, and clonal gene rearrangement test results together confirmed the diagnosis of hepatic pseudolymphoma. During 23 months of follow-up, the patient did not complain about any apparent discomfort. The patient underwent imaging examinations several times, including recent hepatic ultrasound, which indicated no significant change in lesion size.

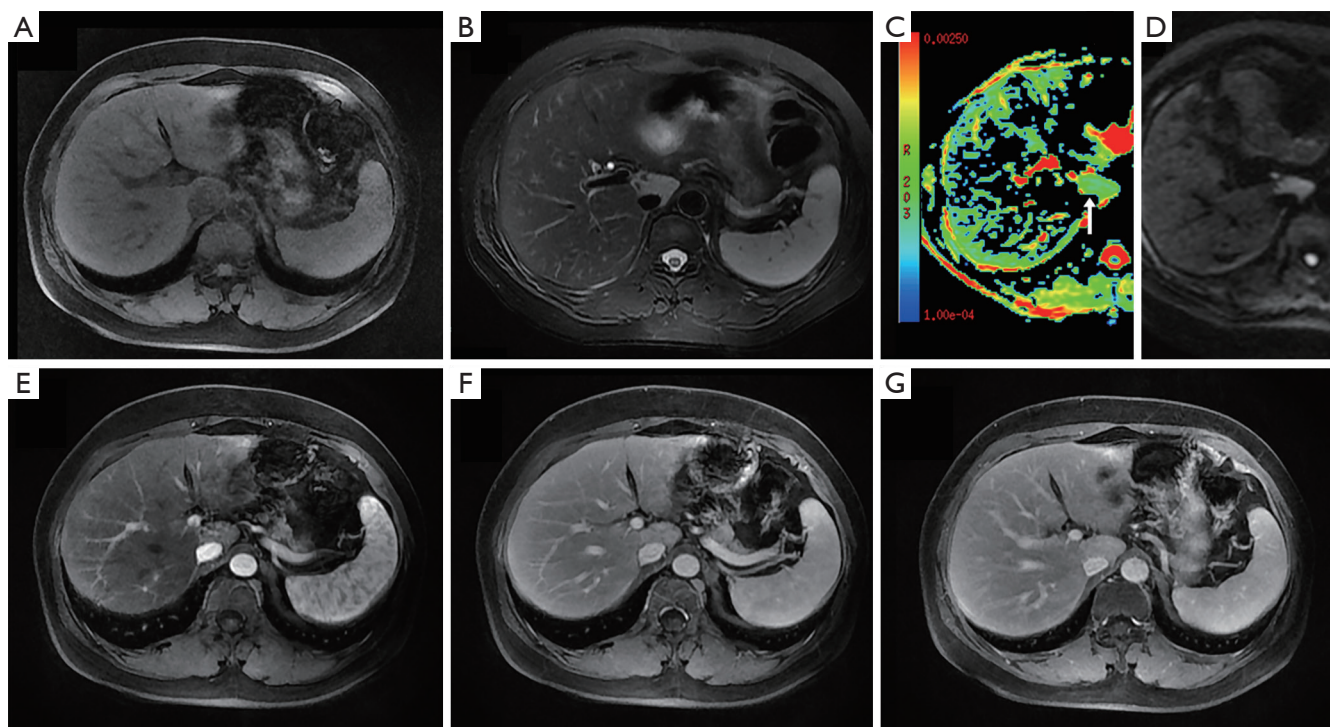
## Discussion

Pseudolymphoma is a proliferative disorder of lymphoid tissues and can attack various parts of the body, including the intestine, lungs, skin, eye orbits, thyroid and less commonly, the liver (2). Since the first report of hepatic pseudolymphoma in 1981 (4), about 50 cases of sporadic hepatic pseudolymphomas have been reported (5). Pathologically, the differential diagnosis of hepatic pseudolymphoma from low-grade B-cell lymphoma is often challenging and should be assisted by gene rearrangements and *in situ* hybridization (6). In the present case, however, the histopathology of tissues obtained by biopsy failed to distinguish these two lymphomas. Nevertheless, a definitive diagnosis was finally confirmed by clonal gene rearrangement test.

The etiology of hepatic pseudolymphoma remains unknown, but a significant proportion of these patients



**Figure 2** Non-enhanced CT showed a homogeneously hypoattenuating lesion of the caudate lobe (A). Contrast-enhanced CT indicated subtly peripheral enhancement of the lesion during arterial phase, and poor enhancement during portal vein phase and delayed phase (arrow, B-D).



**Figure 3** Conventional MRI showed hypointense signal on T1WI (A), slightly hyperintense signal on T2WI (B), high signal on DWI (D), and low signal on ADC (arrow, C). Contrast-enhanced MRI indicated hypervascularity of the lesion during arterial phase, and mildly hyperintense signal during portal phase and delayed phase (E-G).

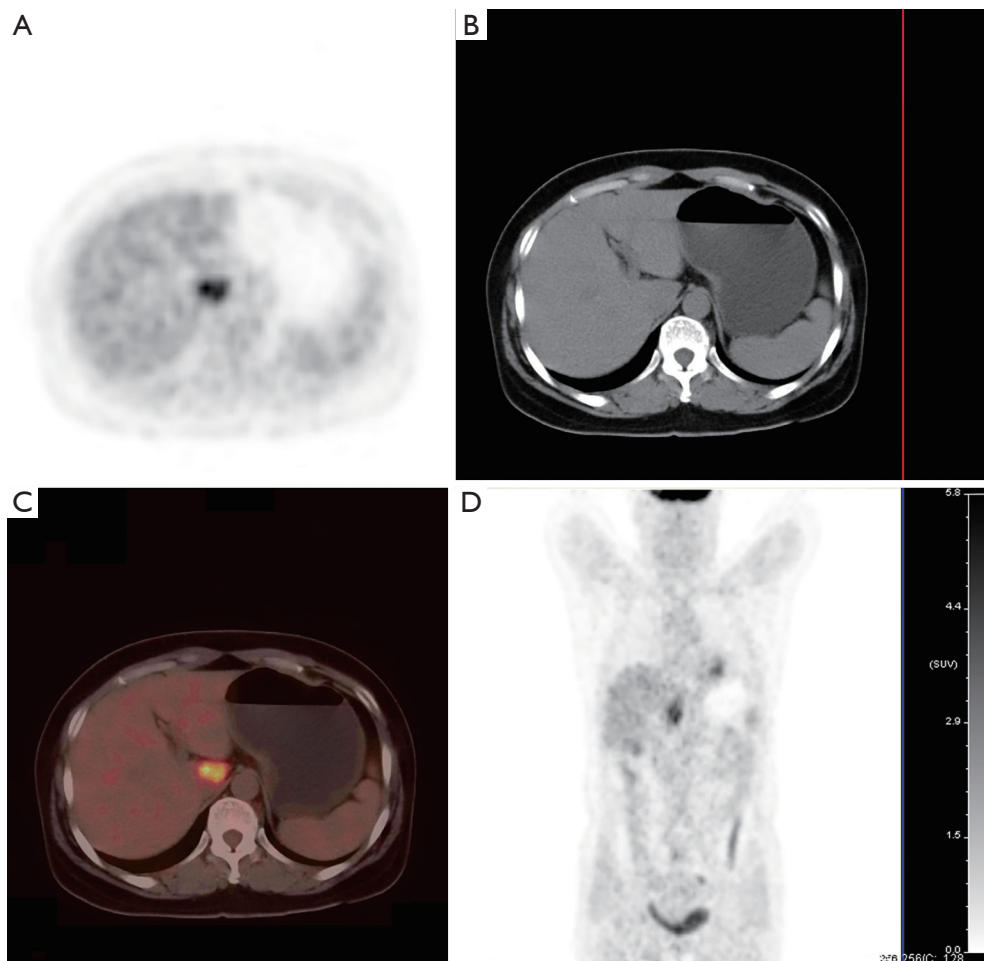
are combined with hepatic diseases, including hepatitis virus infection, primary biliary cirrhosis, and non-alcoholic steatohepatitis (2,5). Patients with hepatic pseudolymphoma are prone to autoimmune diseases, including autoimmune thyroiditis, Sjogren's disease, antiphospholipid syndrome, CREST syndrome, and Takayasu disease (2). Interestingly, the present patient suffered from chronic hepatitis, but not autoimmune disease. In brief, the specific molecular mechanism of hepatic pseudolymphoma may be critically related to hepatitis virus infection, and intrahepatic and external autoimmune processes, but still requires further exploration.

Hepatic pseudolymphoma, usually in diameter of less than 2 cm, is often solitary and occasionally in group (5). Ultrasonography indicated a hypoechoic lesion had surrounding vascular signals (1,2,7). Contrast-enhanced ultrasonography showed a wash-out enhancement pattern of the lesion, which may be misdiagnosed as HCC (7). Non-enhanced CT of lesions showed hypodensity. The abundant vascularity, ring enhancement and vessel-penetrating sign on contrast-enhanced CT were considered to be diagnostic clues (8,9). Conventional MRI showed the lesion was

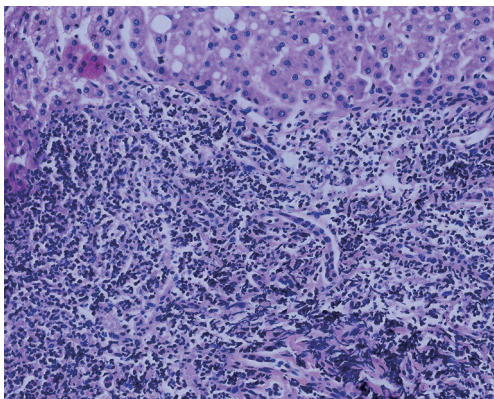
round with homogeneously hypointense signals on T1WI and hyperintense signals on T2WI (5,7,10,11). The DWI sequence of the tumor showed hyperintense signals with significantly low ADC (5,7,10,11). Contrast-enhanced MRI revealed the most common pattern was ring enhancement, the pathological basis of which was lymphocytic infiltration around the nodule (5,7,10). Moreover, pseudocapsules were reported (5).

Because more than one-quarter of hepatic pseudolymphomas are associated with tumors (mainly gastric cancer and colon cancer), ring-enhanced hepatic pseudolymphomas could be easily misdiagnosed as metastatic tumors. In our case, the lesion showed a prolonged enhancement on contrast-enhanced MRI. As reported, lesions during Gd-EOB-DTPA or Eovist-enhanced hepatobiliary phases showed hypointense signals (2,7,9,11) or slightly hypointense signals due to less uptake of the contrast agent (8). Therefore, liver-specific contrast agents may limit the diagnostic value for hepatic pseudolymphoma. The intense uptake of hepatic pseudolymphomas on non-enhanced PET/CT may lead to misdiagnosis of hepatic malignancy (12). In our case, despite





**Figure 4** PET images (A and D); CT images (B); fusion images (C).  $^{18}\text{F}$ -FDG PET/CT showed intense uptake in the lesion of caudate lobe.



**Figure 5** Pathological results of liver lesion showed a large number of B lymphocyte infiltration, without significant nuclear polymorphism (HE,  $\times 200$ ).

the intense FDG uptake, the hepatic pseudolymphoma was still at a lower metabolism compared with the well-differentiated HCC (13).

We emphasize the diagnostic value of ADC in differentiating hepatic pseudolymphoma from hepatic neoplastic lesions. Studies demonstrate hepatic pseudolymphoma should be differentiated from HCC and hepatic metastases (5,11). A study of hepatic pseudolymphoma confirmed that the diffuse infiltration of small lymphocytes resulted in a significantly limited diffusion of water molecules with an ADC of  $(0.82 \pm 0.45) \times 10^{-3} \text{ mm}^2/\text{s}$  ( $b=0, 500 \text{ mm}^2/\text{s}$ ) (5). Although the  $b$  value differed, ADC in our case still fell in the scope of the above research. Moreover, lymphoid tissue-derived hepatic lymphomas with low ADC ( $0.83 \times 10^{-3} \text{ mm}^2/\text{s}$ ) can be significantly

differentiated from benign disorders ( $1.40 \times 10^{-3} \text{ mm}^2/\text{s}$ ), such as hepatic focal nodular hyperplasia and adenomas, and from malignant tumors ( $1.06 \times 10^{-3} \text{ mm}^2/\text{s}$ ), such as hepatocellular cancer, cholangiocarcinoma, and metastatic tumors (14). Therefore, low ADC may be an important clue in the diagnosis of hepatic pseudolymphoma.

However, ADC is unable to distinguish between hepatic pseudolymphoma and hepatic lymphoma because ADC is low in both cases due to the monoclonal or polyclonal dense lymphocytes. We believe these two lymphomas may be feasibly differentiated by size and enhancement pattern. Hepatic pseudolymphomas are generally smaller (less than 2 cm in diameter) than hepatic lymphomas, which often lump together. Also on contrast-enhanced CT and MRI, hepatic pseudolymphomas usually show marginal enhancement, compared with the less marginal enhancement of hepatic lymphomas. In addition, clinical characteristics also may help with the differentiation, since hepatic pseudolymphomas are generally asymptomatic without abnormal laboratory indicators, whereas hepatic lymphomas are symptomatic with abnormal laboratory indicators.

At present, the clinical application of quantified ADC is limited by the difficulty of re-emergence. On the one hand, the acquisition of ADC is affected by many factors, including hardware devices (e.g., 1.5 and 3 T field strength), scan sequence parameters (e.g., b-values) and biological factors (e.g., benign and malignant liver diseases). On the other hand, different ADC thresholds are used in different studies for the differential diagnosis of benign and malignant liver lesions (15). These factors render the absence of ADC in the 2017 Version of LI-RADS (16). Nevertheless, DWI sequences including ADC are useful complements to conventional MRI sequences in clinical evaluation of hepatic tumors (17).

Hepatic pseudolymphoma is usually pathologically diagnosed by surgical resection, which also helps to achieve therapeutic goals (5,6). In a few cases, pathological tissues were obtained by liver biopsy for the final diagnosis (1,6). In the follow-up cases, the diameter of hepatic pseudolymphomas generally decreased. Since hepatic pseudolymphoma is free from malignant transformation (3), unnecessary surgical treatment should be avoided. In the present case, due to the possibility of benignity, pathological tissues were obtained through biopsy for a final diagnosis, which helped the patient avoid surgery. Therefore, we suggest biopsy as a diagnostic procedure and encourage follow-up for such tumors so as to avoid unnecessary

surgical resection.

Generally, the imaging characteristics of hepatic pseudolymphoma are diverse, but the ADC of DWI sequence may help to narrow the differential diagnosis range. The size and enhancement pattern of the lesions may contribute to the differentiation between hepatic pseudolymphoma and hepatic lymphoma. A biopsy is the appropriate way to obtain a final diagnosis of hepatic pseudolymphoma.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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