Clinics and Research in Hepatology and Gastroenterology (2015) **39**, 435—442

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MINI REVIEW

Diagnostic imaging of hepatic lymphoma

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Available online 23 December 2014

Summary Hepatic lymphoma is a rare disease with poor prognosis because of delayed diagnosis. The disease comprises primary, metastatic, and intravascular hepatic lymphomas. The pathological characteristics of lymphomas differ contributing to difficulty in early diagnosis. Early diagnosis and appropriate treatment result in improved prognosis; therefore, diagnostic radiology and its development with various contrast agents are critical for improving disease outcomes. Herein, we review hepatic lymphomas and summarize the results of imaging studies in correlation with pathological characteristics. The information provided will help physicians in early diagnosis and thereby improving prognosis.

Introduction

Liver tumors encounter a large variety of hepatic lesions. Although the liver biopsy is the gold standard for diagnosis, diagnostic radiology plays an important role in monitoring the clinical course of tumors (change of sizes, vascularity, etc.), detection of potential malignant transformation, and new lesions in chronic liver diseases. To date, significant development of imaging modalities such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), in combination with various contrast agent has increased the diagnostic relevance in the context of additional information from the physical examination and biochemical analysis [1]. Developments in imaging include:

- a dynamic study of CT and MRI to determine the vascularity, enhancement pattern of the lesion, and to suggest the malignant potential of the lesions;
- a newly developed MRI contrast agents, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA) which is taken up by the hepatocytes in later phases (hepatobiliary phase), is used to find the malignant hepatic lesions. In addition, diffusion-weighted images show the difference between benign and malignant liver tumors showing the possibility of contribution to distinguish the malignant lesion by quantifying diffusion effects

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http://dx.doi.org/10.1016/j.clinre.2014.11.001
2210-7401/

via apparent diffusion coefficient (ADC) measurements [2—6];
- contrast agent for US, including perflubutane, used for real-time imaging of hepatic tumors in a non-invasive manner can be used for detection at initial diagnosis as well as the clinical follow up of tumorous lesions;
- 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) to detect and diagnose the stage of the disease [7,8].

The combination of these multi-modalities can be helpful for detection and diagnosis of the new lesions as well as screening for liver diseases. Furthermore, with early diagnosis of malignant tumors, the prognosis can be improved [9,10]. For example, successful chemotherapy after the diagnosis in early stages of intravascular hepatic lymphoma (IVL) increases the 3-year overall survival rate to 33% which show the poor prognosis of few months of survival [9]. In this review, we have focused on hepatic malignant lymphoma, which demonstrates an aggressive clinical course that is often related to the difficulty of the diagnosis. Because the appropriate diagnosis and treatment can improve the prognosis [11], it is necessary to establish the diagnosis using multiple imaging modalities. To enable this, clinicians must be aware of the clinical characteristic of the various types of the disease and the associated imaging patterns, particularly the use of contrast-enhanced US (CEUS) to detect and follow the clinical course of hepatic lymphoma.

Classification of hepatic lymphomas

Malignant lymphomas are categorized as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) [12,13]. The distinction between the two categories is based on the pathological findings of Hodgkin and Reed—Sternberg cells in HL that occupies less than 10% of malignant lymphomas, all others are NHL [11,13]. Lymphomas arise from either lymph nodes (nodular) and extranodular organs. NHL includes nodal- or extranodular disease types. Approximately 40% of NHL are extranodular and involve lung, breast, thymus, liver, spleen, etc. [11]. It is important to distinguish primary extranodular NHL from secondary extranodular NHL that is metastatic lymphoma from nodular NHL. They are also classified by other clinical findings, such as the organs involved, leading to the diagnosis of lymphomas. The prognosis of NHL varies depending on the stage and other factors [14]; however, the recent total 5-year overall diffuse large B-cell lymphoma (DLBCL) survival rate has been reported to be 30—50% after successful chemotherapy [10].

Hepatic lymphoma is a rare disorder [1,15—17] that can be classified into primary hepatic lymphoma (PHL), metastatic hepatic lymphoma (MHL), and intravascular lymphoma (IVL). PHL and IVL are extranodular, and MHL can be either nodular- or extranodular lymphomas. Most PHL and IVL have the characteristic pathological findings of NHL, whereas MHL can be either NHL or HL. The poor prognosis is due to the difficulty in accurate diagnosis based on the various patterns of the imaging studies and non-specific symptoms. Therefore, an early diagnosis using imaging modalities is essential and the summary of these imaging studies shown in this review (Table 1) will aid clinicians in making accurate diagnosis of diseases with suspicion and thereby resulting in improved prognosis.

PHL

Frequency

PHL is an extranodular lymphoma, which is confined to the liver with no evidence of lymphomatous involvement in the spleen, lymph node, bone marrow, and other lymphoid structures [15,18—22]. It is a rare type of NHL representing less than 1% of all extranodular lymphoma [16]. PHL can occur in any age groups and 21% of patients are complicated by hepatitis C viral (HCV) infection indicating the relationship with HCV [23,24]. Furthermore, co-infections of hepatitis B virus, Epstein—Barr virus, and human immunodeficiency virus have been reported [25—27].

Clinical character

In these cases with complications, the prognosis is poor with a median survival of 15.3 months. [28] Approximately one-third of the patients have clinical symptoms of lymphoma with fever and weight loss as well as night sweats. Abdominal discomfort is the most commonly reported clinical symptom. Laboratory examinations show increased transaminases, alkaline phosphatase, and bilirubin in approximately 70% of the patients [23,25,28,29]. Soluble interleukin-2 receptor (sIL-2R) can be a serum tumor marker for disease progression in some cases [30].

Character of imaging studies

Pathological examination reveals either mass-forming or infiltrating growth patterns of tumor progression. The mass-forming type shows an expansive and destructive growth pattern, whereas the infiltrating type shows infiltration of tumor cells into the portal tracts as well as sinusoids. These pathological characteristics are significantly reflected in the imaging studies of CT and MRI [5]. Mass-forming growth patterns have been observed in 66%, whereas infiltrating pattern have been observed in 34% of cases [31]. Characteristic findings of imaging studies are summarized in Table 1. And representative images of PHL are shown in Fig. 1 and Fig. 2. The imaging studies of mass-forming growth type shows various patterns. The hepatosplenomegaly can be detected multiple modalities. US study showed hypo-iso echoic mass lesion. CEUS using perflubutane showed ring-like enhancement (Fig. 2a) and vascular penetration in the tumor (Fig. 2b) in vascular phase, and hypoechoic lesion in Kupffer phase indicating the mass forming of lymphoma cells (Fig. 2c). CT showed low-density mass with no enhanced plain studies (Fig. 1a). Contrast-enhanced dynamic study showed vascular penetration inside the tumor (Fig. 1b), ring-like enhancements in the edge of the tumor (Fig. 1c), and no distribution of contrast agent in the tumor (Fig. 1d). MRI shows hypointense on T1-weighted and dynamic study using gadoxetic acid (Fig. 1e—g)