Case Report
Primary hepatic lymphoma: a rare case report and literature review

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Abstract: Primary hepatic lymphoma (PHL) is a rare malignancy, which only occupies about 0.4% of all primary extra-nodal non-Hodgkin lymphomas (NHLs) and 0.016% of all NHLs [1]. It includes B-cell lymphoma, T-cell lymphoma, and others. A seventy-one year old man first went to visit the doctor because of pneumonia and then he was diagnosed with PHL of diffuse large B-cell lymphoma with no virus hepatitis or other typical symptoms. PHL is a rare disease, which is very difficult to diagnose due to non-specific clinical manifestations and accessory examinations. This case may help clinicians to improve their understanding of this disease.

Keywords: Lymphoma, non-Hodgkin, lymphoma, large B-cell, diffuse, liver neoplasms

Introduction
The liver is infiltrated by lymphoma either as a result of its wide spread or by the primary location of the lymphoma. Primary hepatic lymphoma (PHL) is a very rare malignancy, which only comprises about 0.4% of all primary extra-nodal non-Hodgkin lymphomas (NHLs) and 0.016% of all NHLs [1]. It is generally defined as one that only involves the liver and/or lymph nodes in the porta hepatitis, without infiltration of other locations [2, 3]. PHL of diffuse large B-cell lymphoma (PHL-DLBCL), a type of B-cell lymphoma, occurs most frequently among these cases [4]. In this study, we want to improve clinicians’ understanding of this disease by reporting a case of PHL-DLBCL in an individual who visited the hospital because of pneumonia.

Case report
A seventy-one year old man, who had a past medical history of hypertension and pneumonia but with no immunodeficiency diseases, visited our hospital because of a fever. He mainly had mild fever in the afternoons with axillary temperature fluctuated between 37.1-37.3°C, while sometimes it reached higher than 38°C with the highest axillary temperature at 39°C, but it returned to normal at night. Simultaneously he also experienced night sweats, obvious fatigue, and weight loss of approximately more than 10% in the recent six months.

A physical examination found a rough-sounding breath of the lung. Laboratory data on admission are presented in Table 1. Ultrasonography (Figure 1) found a hypoechoic lesion (sized 2.6×2.4 cm with clear boundaries) in the right anterior section of the liver with peripheral hyperecho and blood flow signals. Meanwhile, there were no signs of lymphoma infiltration in sites such as the neck, supraclavicular region, axilla, inguinal region, and retroperitoneal lymph nodes. Computerized tomography (CT) showed that there were stripes on the superior lobe of the right lung and inferior lobe of the lungs. The abdominal CT (Figure 2) showed that the liver had uneven reduction in density and multiple patch-shaped low-density areas with unclear boundaries that had a maximum size of 58×53 mm. While, there were no abnormal lymph nodes in the chest, abdominal and pelvic cavity from the CT results. Hepatic magnetic resonance imaging (MRI) and its enhanced pattern (Figure 3) showed that there were multiple patches of slightly high T2 signal and slightly low T1 signal and an abnormal enhancement in the arterial phase of the enhanced scan with no obvious enhancement was found at the venous
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Table 1. Comparison of the main indexes before and after the treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before chemotherapy</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
<th>Sixth</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>101</td>
<td>120</td>
<td>122</td>
<td>126</td>
<td>126</td>
<td>140</td>
<td>142</td>
<td>130-175</td>
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<tr>
<td>WBC (10^9/L)</td>
<td>7.63</td>
<td>3.43</td>
<td>5.86</td>
<td>6.21</td>
<td>6.53</td>
<td>6.77</td>
<td>7.62</td>
<td>3.50-9.50</td>
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<tr>
<td>ESR (mm/h)</td>
<td>54</td>
<td>20</td>
<td>12</td>
<td>17</td>
<td>15</td>
<td>22</td>
<td>3</td>
<td>0-15</td>
</tr>
<tr>
<td>Alb (g/L)</td>
<td>34.3</td>
<td>39.9</td>
<td>41.4</td>
<td>42.5</td>
<td>41.5</td>
<td>43.7</td>
<td>43.4</td>
<td>40-55</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>31</td>
<td>21</td>
<td>17</td>
<td>17</td>
<td>20</td>
<td>22</td>
<td>21</td>
<td>9-50</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>27</td>
<td>19</td>
<td>20</td>
<td>23</td>
<td>23</td>
<td>26</td>
<td>27</td>
<td>15-40</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>127</td>
<td>99</td>
<td>82</td>
<td>76</td>
<td>73</td>
<td>80</td>
<td>81</td>
<td>45-125</td>
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<tr>
<td>LDH (U/L)</td>
<td>243</td>
<td>273</td>
<td>308</td>
<td>364</td>
<td>353</td>
<td>303</td>
<td>232</td>
<td>135-226</td>
</tr>
<tr>
<td>β2-MG (mg/L)</td>
<td>2.6</td>
<td>2.80</td>
<td>3.40</td>
<td>3.60</td>
<td>3.30</td>
<td>2.80</td>
<td>2.60</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Ultrasound

Liver: Hypoechoic lesion, sized 2.6×2.4 cm with clear boundary, peripheral hyperecho and blood flow signal

MRI and its enhanced pattern

T2 slightly high signal and T1 slightly low signal; at arterial phase: abnormal enhanced, 30 mm-round T2 slightly low signal with enhancement

Meanings of some important symbols in Table 1. N: Normal. (-): This examination was not performed. Abbreviations: Hb: hemoglobin; WBC: white blood cell; ESR: erythrocyte sedimentation rate; Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin.
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Figure 1. Ultrasound scanning found a hypoechoic lesion (sized 2.6×2.4 cm with clear boundaries) in the right anterior section of liver with peripheral hyper-echo and blood flow signals (the left one).

Figure 2. Computed tomography scanning (CT) of abdomen showed that the density of liver had uneven reduction and the liver also had multiple patch shaped low-density areas with unclear boundaries. The size of the maximum one was 58×53 mm (the right one).

and late phases. Roundish patches of slightly low T2 signal with diameters of almost 30 mm were found in parts of the lesions, and their images were enhanced on MRI enhancement scans. No signs of lymphoma infiltration were found in bone marrow morphology. The pathological results of this case (Figure 4) with percu-
taneous trans-hepatic biopsy using B-mode ultrasound showed large, heteromorphic lymphocytes in the hepatic tissue. The nuclei were round or oval-shaped with single or multiple nucleoli. The nuclear mitotic figure was common. Regarding immunohistochemistry, cluster of differentiation (CD) 20 and B-cell lymphoma (BCL)-2 were diffusely positive; BCL-6, multiple myeloma-1 (MUM-1), and CD5, were positive; and c-myc as locally positive (20%). CD21 was suspected to have a slight follicular dendritic cell (FDC) net and the Ki-67 labeling index was about 70%; CD10, CD23, CD56, CD3, cyclin D1, and AE1/AE3 were negative. On the basis of these clinical manifestations, auxiliary examinations, and pathological results, the patient was diagnosed with primary hepatic NHL with a type of DLBCL in stage IV B (Ann Arbor-Cotswolds staging system), non-germinal center B cell-like (DLBCL, non-GCB), and an International Prognostic Index (IPI) scored of 3, which indicated that he was in a moderate- to high-risk group. As soon as this diagnosis was established, the patient was treated with R-CHOP scheme chemotherapy (vincristine, 2 mg, d1; cyclophosphamide, 600 mg, d1-2; epirubicin, 50 mg, d1-2; rituximab, 600 mg, d3; and prednisone, 15 mg, d1-5; 21 d as a period) and he has received six cycles of the chemotherapy period up to date with his various indicators gradually improving (Table 1).

Literature review

PHL-DLBCL is a frequent type of PHL and was found in our case. Patients who develop this
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disease are mainly 50 to 60 years of age and men are 2 to 3 times more likely than women to develop this disease with varied and non-specific clinical manifestations [5]. Abdominal pain is the most common symptom, generally complicated with general malaise [6]. The pathogenesis of PHL is still not clear. It has been suggested that viral infection and immunodeficiency disorder are important causes of PHL [7, 8]. However, our patient in our case was a 71 year-old man who was diagnosed with PHL-DLBCL based on histology without suggested potential causes.

While accessory examinations including laboratory index and image tests are beneficial for assessing a patient’s condition, changing the therapeutic regimen, and prognosis, they have little significance on the diagnosis of PHL. It is suggested that serological lactate dehydrogenase (LDH) is a diagnostic marker of PHL [9]. In addition, LDH and β2-microglobulin (β2-MG) are two important prognostic factors of PHL [10, 11]. It has been demonstrated that when LDH and β2-MG levels approach the normal range, patients with PHL have a longer survival time and better health conditions [4]. Considering this patient as an example, his LDH level was increased slightly at first, and then it gradually decreased to the normal range as a result of the therapy. In addition, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in this patient were both within the normal range, which meant that there was very little injury or maybe no damage at all to the liver at its early detection. Although the image findings were very atypical, they may help to detect and evaluate the size of lesions and may help for follow-up purposes. A hypoechoic lesion can first be detected by ultrasound, CT, and MRI, from which the enhanced pattern could clearly reveal the location, number, and blood supply of the tumor, and this information would have been acquired to establish a diagnosis. It has been reported that hepatic lymphoma shows an equivalent or low T1 signal and high T2 signal on MRI [12]. Its enhanced scan shows a slight patch or peripheral ring enhancement, which is similar to the “vessel penetration sign” in the lesion [13]. For the patient in our case, the results from the ultrasound and CT all appeared negative after two cycles of chemotherapy and the enhanced MRI pattern of the lesions appeared to be smaller with the treatment. This suggests that MRI and its enhanced pattern are important for evaluating the effectiveness in curing hepatic lymphoma.

Liver tissue biopsy is the “gold standard” for establishing a correct diagnosis of PHL in this case with immunohistochemistry, which is the foundation of PHL’s classification. In this case, CD 20, BCL-6, and MUM-1 were all positive but
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CD10 was negative, which could cause it to be diagnosed as DLBCL, non-GCB. The prognosis of non-GCB is not as good as that of GCB. Rosenwald et al. [14] reported that the 5-year overall survival rate of GCB was 76% but the 5-year overall survival rate of non-GCB was only 34%. The patient in our case was found with BCL-2, which had been reported as an unfavorable factor of non-GCB. Likewise, Ki67 staining and the IPI score of 3 (moderate-high group) also indicated his poor prognosis [15].

Rituximab, a monoclonal antibody, was proven to be the first safe and effective treatment against B cell lymphoma, by significantly improving the prognosis and overall survival rate of patients with non-GCB receiving the CHOP scheme [16, 17]. R-CHOP, an anthracycline-based regimen, is the most frequently used chemotherapy regimen worldwide [18]. The patient in our case was also administrated the R-CHOP chemotherapy regimen. In addition to this kind of therapy, surgical treatment, radiotherapy, and chemotherapy have also been used alone or in combination for treating PHL based on its macroscopic characteristics, which are divided into solitary nodule (60%), multiple focal nodules (35%), and diffuse infiltration without nodules (5%) [19]. Our patient could be considered as having multiple focal nodules based on the CT, MRI, and its enhanced pattern and therefore, he was treated with the R-CHOP chemotherapy regimen. After 6 cycles of chemotherapy, hemoglobin (Hb), and serum albumin (Alb) levels had increased to the normal range and the erythrocyte sedimentation rate (ESR) and LDH levels had decreased to a normal range as well. In addition, imaging findings including those of ultrasound, CT, and MRI were also improving.

Conclusion

PHL is a rare disease, which is very difficult to diagnose due to non-specific clinical manifestations and accessory examinations. Our case should be considered as a possible diagnosis when solid nodules are found in the liver using imaging texts with high LDH, normal alpha fetoprotein (AFP), and carcinoembryonic antigen (CEA). If there is no invasion to other organs or tissues, liver biopsy should be performed for further verification. Once a patient is diagnosed with PHL, the R-CHOP chemotherapy scheme should be administered as soon as possible to improve patient prognosis.

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Disclosure of conflict of interest

None.

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References