Case Report

Primary hepatic extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type is associated with chronic inflammatory process

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ABSTRACT

Primary hepatic extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type lymphoma is very rare disease. We reported two cases of primary hepatic MALT lymphoma associated with chronic inflammatory disorder. One case was a 74-year-old female complicated with asymptomatic primary biliary cirrhosis. Another case was a 73-year-old man presented with a mild hepatitis C. Both biopsy specimens showed diffuse infiltration of small atypical lymphoid cells that were phenotypically CD20+, CD79a+, CD5- and CD10-. Patients were received r-THP-COP (rituximab, pirarubicin, cyclophosphamide, vincristine, predonisolone) and achieved complete remission. Primary hepatic MALT lymphoma may be strongly associated with chronic inflammation, especially hepatitis C virus infection. However, the relationship between primary hepatic MALT lymphoma and PBC is still controversial, because the lymphoma complicated with PBC is extremity rare and there is no immunological and genetical study about it. We discuss the pathogenesis and clinical manifestation of this rare disease.

CASE REPORT

Primary hepatic lymphoma (PHL) comprises less than 1% of all malignant lymphomas [1]. The most common histological type is diffuse large B-cell lymphoma (DLBCL) [2,3]. Other histology has been reported extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type [4,5], follicular lymphoma [6], Burkitt’s lymphoma [7] or Hodgkin’s lymphoma...
Primary hepatic MALT lymphoma is reported to occur in only 3% of PHL cases. The etiology of this lymphoma is unknown, but most seem to be associated with chronic inflammation. We report two cases of primary hepatic MALT lymphoma associated with chronic inflammation of the liver.

In the first case, a 74-year-old woman reported general fatigue and weight loss in 2007. Abdominal ultrasonography and computed tomography (CT) identified multiple liver masses, and she was referred to our hospital. There was no evidence of hepatosplenomegaly or superficial lymphadenopathy. Blood cell counts and serological findings were all within normal ranges, except gamma-glutamyl transpeptidase (G-GTP), which was elevated. Viral markers, including those of hepatitis B and C, were negative. Serum IgM was elevated (420 mg/dl) and anti-nuclear antibodies, anti-mitochondria M2 antibodies and anti-centromere antibodies were positive. This finding was clinically considered as asymptomatic primary liver cirrhosis (PBC). Upon tumor biopsy, histological findings showed diffuse infiltration of small atypical lymphoid cells with lymphoepithelial lesions (LEL; Fig.1 a, b, and c). The phenotype of these cells was found to be ...

Figure 1. (a) A dense infiltration of small centrocytic lymphoid cells can be seen around the bile duct (case 1; H&E stain; x 400); (b) These abnormal lymphocytes stain positive for CD20. Note that these cell infiltrated into the epithelial cells of bile duct (arrow). (case 1; x 400); (c) lymphoepithelial lesions (arrows) in the bile duct are highlighting by staining AE1/AE3 (case 1; x 400); (d) a diffuse infiltration of lymphocytes can be seen in the liver (case 2; H&E stain; x 100); (e) Many small centrocytic and monocytoyid lymphocytes infiltrated to liver tissue. In this case, lymphoepithelial lesion was not observed. (case 2; H&E stain; x 400); (f) These abnormal lymphocytes stain positive for CD20 (case 2; x 400).
CD20+, CD79a+, bcl-2+, CD5-, CD10-, and bcl-6- Immunoglobulin heavy chain rearrangement by polymerase chain reaction showed monoclonality (Fig.2). There was no finding of tumor cell infiltration in bone marrow biopsy (data not shown). Thus, we made a diagnosis of MALT lymphoma. Slight lymphocyte infiltration around periportal region was noted in the non-tumorous liver tissue. Chronic non-suppurative destructive cholangitis was noted. The patient was treated with 6 cycles of rituximab-THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisolone) [9]. Complete remission (CR) was achieved and retained it until now.

In the second case, a 73-year-old man presented with a mild case of hepatitis C. A routine abdominal ultrasound examination in April 2008, had identified multiple liver nodules, but the patient was asymptomatic and physical examination revealed no abnormal abdominal findings. Blood cell counts and serology (including liver enzymes and LDH) were all within normal limits. A CT scan showed multiple, enhanced hepatic masses, but there was no evidence of regional lymphadenopathy and no other sites of malignancy were identified. Upon tumor biopsy, histological findings showed diffuse infiltration of small atypical lymphoid cells without LEL (Fig.1 d, e, and f). These cells had the phenotype CD20+, CD79a+, bcl-2+, Cyclin D1-, CD5-, CD10- and CD23-. A diagnosis of MALT lymphoma was also made, but further chromosomal and genetic analysis could not be performed because we were unable to obtain sufficient tissue. The histological findings in the non-tumorous tissue showed portal inflammation and lobular inflammation with mild focal hepatocellular necrosis. Enlarged fibrotic portal tracts were noted. These findings were consistent with the pathological feature of chronic hepatitis. There was no finding of tumor cell infiltration in bone marrow biopsy. The patient was treated with 6 cycles rituximab-THP-COP [9]. CR was once achieved, but he relapsed in December 2009. Then, He received 6 cycles of rituximab-fludarabine and achieved re-remission.

Cases of PHL associated with PBC are extremely rare. Panjala et al reported a lymphoma frequency of 0.6% (13/2192 cases) [10] and, to the best of our knowledge, there have been only five reports of primary hepatic MALT lymphoma associated PBC [11-15]. Lymphomagenesis in MALT lymphoma is strongly associated with autoimmune diseases, such as Sjogren’s syndrome and Hashimoto’s disease [14]. In PBC, a prolonged immune response is directed toward the ductal epithelial cells, causing a chronic, non-
Lymphomas associated with hepatitis C virus (HCV) infection are commonly of the B-cell type, and the most common histological subtypes are DLBCL, MALT and lymphoplasmacytic lymphoma [2,3]. Previous studies report the prevalence of HCV infection in PHL as approximately 60% [2,3]. Recently, some groups confirmed an association between HCV infection and non-Hodgkin’s lymphoma in large case-control studies [16,17]. In these studies, the number of HCV carriers was significantly larger in the non-Hodgkin’s lymphoma group than in the control group. However, the prevalence of HCV carriers within the PHL population is much higher [3]. The exact pathogenic role of HCV in systemic and non-systemic B-cell lymphoma remains unclear, as HCV does not integrate into the host genome and does not contain any obvious oncogenes. However, it has been suggested that chronic HCV-driven antigenic stimulation triggers the proliferation of B-cell clones in these lymphomas. Therefore, it is reasonable to suppose that chronic inflammation of the liver, which is a common target organ of HCV infection, is strongly associated with the pathogenesis of PHL.

In conclusion, in the same way that gastric MALT lymphoma is associated with Helicobacter pylori infections, primary hepatic MALT lymphoma may be strongly associated with chronic inflammation. However, the pathological mechanism is still unclear, because this lymphoma is very rare entity. And this type lymphoma is relatively good prognosis, but has not established standard treatment yet. Further studies are required to establish the relation between with chronic inflammatory process and lymphomagenesis in primary hepatic MALT lymphoma.

**LIST OF ABBREVIATIONS**

PHL – Primary hepatic lymphoma  
DLBCL – diffuse large B-cell lymphoma  
MALT – extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue  
CT – computed tomography  
G-GTP – gamma-glutamyl transpeptidase  
PBC – primary liver cirrhosis  
LEL – lymphoepithelial lesions  
HCV – hepatitis C virus

**REFERENCES**


