Case Report

Remission of splenic marginal zone lymphoma in a patient treated for hepatitis B: a case of HBV-associated lymphoma

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Splenomegaly is a common finding in chronic hepatitis B infection. We present the case of a man with an acute flare of chronic hepatitis B infection, where splenomegaly in absence of portal hypertension led to the diagnosis of splenic marginal zone lymphoma (SMZL) with bone marrow involvement. Adequate suppression of the hepatitis B virus (HBV) viral load with tenofovir resulted in complete remission of the lymphoma.

Keywords: Chronic hepatitis B, SMZL, Splenic marginal zone lymphoma, Antiviral therapy, B-cell non-Hodgkin lymphoma

Introduction

Splenic marginal zone lymphoma (SMZL) is a distinctive and well-characterised B-cell neoplasm. Indolent B-cell lymphomas derived from the marginal zone include three specific entities: extranodal marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue (MALT), nodal marginal zone lymphoma (NMZL) and SMZL.1 It is estimated that less than 1% of non-Hodgkin lymphoma (NHL) are SMZL. The median age of patients is 68 years (range 22–79 years) with a male-to-female ratio of 1:1.8. Characteristic features are splenomegaly, moderate lymphocytosis with villous morphology, an intrasinusoidal pattern of involvement of various organs, especially bone marrow, and a relatively indolent course.2 Although SMZL is accepted as a specific entity in the World Health Organization (WHO) classification, its lymphomagenesis remains obscure.3 Long-standing antigenic stimulation explains how lymphoid infiltrates may appear in extranodal sites that are normally devoid of lymphoid tissue. At least six microbial species are associated with MALT lymphoproliferations: Helicobacter pylori, Helicobacter heilmannii, hepatitis C virus (HCV), Campylobacter jejuni, Borrelia burgdorferi and Chlamydia psittaci.1 Hepatitis C virus is also associated with SMZL. Recently, the role of chronic hepatitis B virus (HBV) infection in the pathogenesis of B-cell lymphomas is receiving more attention. We report a case of remission of SMZL in a patient who received treatment for chronic active hepatitis B.

Case Report

A 56-year-old Lebanese man was evaluated for abdominal discomfort, weight loss of 6 kg, fatigue and fever at our outpatient clinic in Aruba. He reported night sweats and intermittent nausea. A year before presentation, he had had a gastroduodenoscopy for dyspeptic symptoms. Antrum biopsy demonstrated H. pylori-associated antral gastritis for which he received eradication therapy. There were no signs of H. pylori-associated gastric MALT lymphoma. Also noteworthy, there were no oesophageal varices. His medical history was otherwise unremarkable.

Physical examination showed no abnormalities, except for a splenomegaly. Laboratory results showed lymphocytosis (12.5 × 10⁹/l), thrombocytopenia (112 × 10⁹/l [145–392 × 10⁹/l]) and elevated liver enzymes (aspartate aminotransferase, 375 U/l [v 31 U/l], alanine aminotransferase, 694 U/l [< 60 U/l], total bilirubin 34 μmol/l [5.1–20.5 μmol/l], direct bilirubin 11 μmol/l [1.7–8.6 μmol/l], alkaline phosphatase 136 U/l [< 121 U/l]; gamma-glutamyl transferase 57 U/l [< 64 U/l]).
Serological testing indicated an infection with HBV (HBsAg positive, HBeAg negative). Hepatitis B virus viral load (HBV-DNA) was 20 700 IU/ml. The HBV genotype was genotype D, consistent with the geographic genotype distribution of HBV in the Middle East. Other causes of viral and nonviral hepatitis were excluded, although we did not test for superinfection with hepatitis delta virus (HDV). At this stage, the working diagnosis was a flare of perinatally acquired chronic hepatitis B. An HIV test was negative.

Ultrasound imaging of the abdomen confirmed the presence of splenomegaly, measuring a splenic length of 24 cm. However, signs of portal hypertension were absent.

Ascites was not detected, and Doppler ultrasound demonstrated a normal direction of the portal blood flow.

Six months later, the chronic HBV infection had shifted from an immune active to an inactive phase. However, the fatigue and night sweats persisted and the splenomegaly had not subsided. The findings on ultrasound remained unchanged.

A liver biopsy showed normal architecture of the portal triangles, without fibrosis or bridging and no signs of inflammation.

Lymphoma was suspected. Bone marrow biopsy revealed intrasinusoidal small lymphoid cells, a highly characteristic feature of SMZL. Immunohistochemical staining showed that B-cell lymphocytes were positive for CD20 and CD79 and negative for CD5, cycline D1, CD23, CD10 and Bcl-6. On histologic sections, there was lymphocytic infiltration into the bone marrow (Fig. 1).

**Treatment**

Our patient had an HBeAg-negative chronic HBV infection with a high HBV-DNA viral load and a SMZL with bone marrow involvement. HBV infection treatment started using a nucleotide reverse-transcriptase inhibitor, tenofovir disoproxil fumarate 245 mg once daily. Within 3 months, the HBV viral load was undetectable. Clinically, the fatigue and night sweats resolved. The patient regained his weight and the splenomegaly resolved.

A bone marrow biopsy was repeated 6 months after initiation of antiviral treatment and showed no signs of lymphoma. The patient remained in complete remission during 12 months of follow-up. Antiviral treatment is continued indefinitely to suppress HBV-DNA and to reduce the risk of antiviral resistance.

**Discussion**

Primary splenic lymphoma is rare and defined as lymphoma restricted to the spleen or splenic hilar lymph nodes. Most cases are B-cell NHLs that are classified by the current WHO classification. A significant association between hepatitis C virus (HCV) infection and B-cell lymphoma has been reported in epidemiological studies. Most of them describe a strong relationship between indolent lymphomas and HCV.

Furthermore, antiviral therapy results in HCV-RNA clearance and consequent tumour regression in most patients with HCV-related indolent NHL. It should be noted here that, in contrast with the suppression of HBV-DNA in HBV-treatment, the goal of antiviral therapy in HCV-infection is eradication of HCV. Successful eradication is associated with improved overall survival. Retrospective analysis also identified a positive correlation between persistent HBV infection and NHL. An adjusted hazard ratio of 2.80 (95% confidence interval [1.16–6.75]) was found for HBV-infected persons to develop NHL, when compared to non-HBV-infected subjects. To our knowledge, we present the second case of clinically documented lymphoma remission after antiviral HBV therapy.

Two mechanisms of oncogenesis are proposed. First, viral production and release of haematopoietic tumour growth factors, lead to lymph cell proliferation. Second, HBV-DNA integrates in the host genome and this could lead to over-expression of cellular oncogenes or to downregulation of the expression of tumour suppressor genes. This second pathway is also known as chronic antigenic stimulation and explains how lymphoid infiltrates may appear in extranodal sites that are normally devoid of lymphoid tissue.

We recognise that HCV contributes to the pathogenesis of mixed cryoglobulinemia (MC) and that the odds of developing NHL are high in patients with HCV-MC. A similar association is not established for HBV-related cryoglobulinemia. Testing for cryoglobulinemia was not performed in our laboratory, but the thought that cryoglobulins play a role in the pathogenesis of HBV-related lymphoma merits further study.

Figure 1 Bone marrow with a paratrabecular focus of predominantly small lymphoid cells.
The overall prognosis of SMZL is good.\textsuperscript{2} There are four main treatment strategies: no treatment, splenic irradiation, chemotherapy and splenectomy. Recently, the effects of splenomegaly on survival outcomes were evaluated; a significant impact of the procedure on the risk of lymphoma-related death or overall survival was not detectable. With the availability of safe and effective alternatives, splenectomy should no longer be considered the treatment of choice in SMZL.\textsuperscript{6}

Treatment of the underlying chronic infection may cause regression of SMZL.

When concomitant chronic HBV infection is present, antiviral therapy leads to suppression of the virus and its associated oncogenes or tumour growth factors, and subsequently to inhibition of antigenic stimulation. Although a direct association of HBV with SMZL cannot be asserted, its role in lymphoma genesis warrants further investigations. We hypothesise that a causal association exists between chronic HBV infection and SMZL, as a complete remission of the lymphoma was attained after successful suppression of the HBV viral load with tenofovir.

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References