Splenic Marginal Zone Lymphoma in a Chronic Hepatitis B Patient: A Rare Case Report and a Literature Review

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Abstract

BACKGROUND: Hepatitis B virus (HBV) is an important global public health problem with significant morbidity and mortality. Chronic HBV infection is a dynamic process with the risk of progression to cirrhosis and hepatic carcinoma (HCC). Although HCC is currently the main concern for diagnosed chronic hepatitis B (CHB), these patients are also considered in high risk for developing B-cell non-Hodgkin lymphoma (B-NHL). The increased risk for B-NHL is well-documented in chronic hepatitis C patients, while in HBV patients are still subject of studies and the most common form of B-NHL reported in these studies is diffuse large B-cell lymphoma (DLBCL).

CASE REPORT: We are reporting the case of a patient with chronic HBV infection complicated with a rare type of B-NHL, a splenic marginal zone lymphoma (SMZL) and through a literature review aim to assess the importance of being aware of the increased risk of lymphoproliferative disorders in chronic HBV patients, assess the role of laboratory follow-up for the early diagnose of this complication, and also recommend testing for HBV infection in all patients diagnosed with B-NHL not only in DLBCL forms but also in rare forms like SMZL.

CONCLUSION: CHB infection has an increased risk for B-NHL not only for the aggressive DLBCL form which is the most common form encountered but also for SMZL which is a rare indolent form of B-NHL with a better prognosis. Laboratory monitoring has a great value to the early detection of B-cell clonal expansion. In all SMZL, patients are recommended screening for HBV, because treatment with antivirals may regress lymphoma and also prevent readvication of HBV in case of chemotheraphy, especially rituximab.

Introduction

Although national vaccination programs, infection with hepatitis B virus (HBV) remains an important global public health problem, with significant morbidity and mortality. Approximately 240 million people are chronic HBV surface antigen (HBsAg) carriers. Countries regional variation of HBsAg positive patients varies between low endemicity levels (<2%) and high endemicity levels (>8%) [1, 2]. Approximately a quarter of these carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and hepatic carcinoma (HCC) [3]. HCC is currently the main concern for diagnosed chronic hepatitis B (CHB) patients and may develop even in patients who have been effectively treated [4, 5]. In fact, studies have shown that HBV may promote carcinogenesis not only in hepatocytes but also in B-cell lymphocytes inducing B-cell non-Hodgkin lymphoma (B-NHL). The most common form encountered in HBV patients is the aggressive diffuse large B-cell lymphoma (DLBCL) form [6], [7], [8], [9], while few cases are reported in the literature with splenic marginal zone lymphoma (SMZL) [10], [11], [12].

Case Report

Patient 64 years old, hypertensive, diagnosed from several years in the service of Hepatology and Gastroenterology UHC “Mother Teresa” with chronic HBV infection, with moderate splenomegaly in abdominal echography and in treatment with tenofovir from several years. The liver and renal functions were within normal values. During follow-up examinations for chronic HBV treatment, it was noticed an elevation of white blood cells with lymphocytosis. The microscopic examination of the peripheral blood smear revealed lymphocytic elements mostly atypical with eccentric nuclei and dense chromatin with basophilic cytoplasm, in which some cases presented fine extensions in the form of villous projections. Based on these considerations, the diagnosis of SMZL was suspected (Figure 1).

The patient has performed further examinations in Italy near San Matteo Polyclinic in Pavia to establish the diagnoses. In the laboratory examinations, it was noticed hypergammaglobulinemia with monoclonal components IgM kapa. Serology for HIV and HCV was negative. The cytfluorimetry of medullary blood revealed a B-cell clonal expansion of 41% of mononuclear cells, staining
CD 19+ with clonal restriction for the light chains (kappa phenotype), CD 5−, CD 23−CD 20+, partial expression of CD200, CD24, CD79b, FMC7 and staining negative for CD10, CD11c, CD25, CD103, and CD38. There were no phenotypic expressions and cytometric distributions clearly referable to hairy cells or villous lymphocytes. The further examination performed was the osteomedullary biopsy which established the diagnose. The osteomedullary biopsy revealed a 40% not homogeneous cellularity, discrete interstitial lymphoid infiltrates and also in the center lacunar and paratrabeicular nodules. These infiltrates were composed of small elements similar to lymphocytes staining CD20+, CD79a+, CD5−, CD23−, bcl1/cyclin D1−, bcl6−CD138−, and p53−. Occasionally were seen suggestive images for intra-sinusoidal localizations. It was noticed a modest 5–10% plasmocellular content with polytypic expression of light chains of Immunoglobulin. The osteomedullary biopsy has shown clearly a medullary involvement in the course of a lymphoproliferative form, with a low degree of cytological malignancy, with B-cell CD 20+ phenotype and morphological and phenotypical characteristics of marginal derivation.

Based on considerations, the patient was diagnosed with a B-cell NHL type indolent, a marginal splenic lymphoma type, with medullary involvement, splenomegaly, and in association with monoclonal component IgM kappa.

Our patient is on treatment with Tenofovir for CHB, in biochemical remission with normal levels of transaminases and without specific treatment for SMZL. He is in good clinical conditions and under periodical controls for chronic HBV infection and SMZL disease.

**Discussion**

There are more than 60 types of NHL classified in indolent and aggressive subtypes. The most common type is the aggressive diffuse large B-cell lymphoma making up about 30–58% of all lymphomas, while SMZL is a chronic B-cell lymphoproliferative disorder characterized by splenomegaly and a clonal expansion of B-cells with villous projections in peripheral blood, characterized by slow progression and an indolent course [13], [14], [15]. It was described firstly in 1992 and was included in the WHO 2016 classification of hematopoietic tumors as a distinct entity, although very rare accounting for 1–2% of all NHL [16].

Definitive diagnosis of SMZL relies on spleen histology and if that is not available, diagnosis requires integration of blood marrow histology with cell morphology and immunophenotype [17]. Pathological cells of SMZL are small-to medium-sized mature B-cells with round or oval nuclei and condensed chromatin with basophilic cytoplasm. Most of the cases present villous cells which are cells with typical unequal membrane projections (villi). Blood marrow infiltration can be nodular, interstitial, or intra sinusoidal. There is no specific immunophenotypic pattern for SMZL. Pathological cells are usually positive for CD19, CD20, CD22, CD79a, CD79b, FMC7, and IgM and negative for CD5, CD10, CD43, BCL6, cyclin D1. CD11c, and CD25 are sometimes positive, but CD103 and CD123 are almost always negative. Bone marrow immunohistochemistry analysis reveals mostly positivity for CD45RA, CD45RB, CD19, CD20, CD79a, Pax5/BSAP, IgD, Bcl-2, DBA-44 (CD72), and CD38 [16], [17], [18], [19].

Several important studies have reported the increased risk of NHL in patients infected with hepatitis C virus as an extrahepatic manifestation of HCV chronic infection and in the majority of cases as a progression of mixed cryoglobulinemia [20], [21]. The most encountered type in HCV patients appears to be peripheral B-cell derived indolent NHL, while viral hepatitis C has been reported in 10−16% of SMZL patients [22]. Reports indicate that marginal splenic lymphoma has been regressed after antiviral therapy in hepatitis C patients in spite of previous ineffective chemotherapy. This is in favor of the hypothesis that stimulation of marginal zone B-cells in the spleen by persistent viral antigens, particularly the E2 viral antigen, could be implicated in the pathogenesis of SMZL [23], [24], [25]. On the other hand, the risk of HBV infection for NHL as we pointed out above is still the subject of epidemiological and case−control studies. Meta-analyses of these studies have shown that patients infected with HBV have a two to three-fold higher risk of developing NHL and the most common type reported is DLBCL form [6], [7], [8], [9]. Few studies have reported an association of chronic HBV infection with SMZL and most of them are only case reports emphasizing that patients would achieve remission with HBV eradicating therapies [10], [11], [12], [26]. Two large studies have evaluated the prevalence of HBS Ag positivity in SMZL patients. One study reported...
a significantly positive association between HBV and SMZL, with an approximately three-fold risk compared to the general population and with a 18.8% prevalence of SMZL in HBs-Ag-positive patients [27], while another recent study in Romanian patients reported a prevalence of HBV in SMZL patients nearly 17.7% [28]. The specific mechanisms by which HBV induces the initiation and promotes the progression of NHL remain unknown, although some mechanisms of oncogenesis are proposed like the integration of HBV DNA in the host genome which can cause chronic antigenic stimulation and viral production and the release of hematopoietic tumor growth factors which lead to lymph cell proliferation [29].

Consensus guidelines recommend treating SMZL only in the presence of symptomatic splenomegaly, cytopenia, systemic symptoms, or progressive nodal disease and there is a wide range of therapeutic options including splenectomy, chemotherapy, and rituximab alone or with chemotherapy [17], [30], [14]. The prognosis seems to be very good after treatment for viral hepatitis B and C and there have been series, where the survival rates at 5 years were approximately 80% [23], [24], [25], [29], [30], [14]. In addition, the antiviral therapy should be among the therapeutic options for the curative purpose of SMZL in patients with concomitant chronic B and C viral hepatitis; therefore, in all SMZL, patients are recommended the test for hepatitis B and C, because the effective antiviral treatment leads to a better prognosis of SMZL. In fact, all patients diagnosed with NHL should be tested for HBV prior treatment, because they have an increased risk of HBV reactivation and this risk is amplified in those receiving anti-CD20 antibodies such as rituximab. The current guidelines recommend screening any patients receiving anti-CD20 antibodies for HBV, and any patients found to be seropositive for HBV (HBsAg and/or anti-HBc) should be treated prophylactically and for 6–12 months until after cessation of anti-CD20 therapy. Recent trials have demonstrated greater efficacy of entecavir and tenofovir as first-line antivirals for the prevention and treatment of HBV reactivation [4], [31].

Conclusion

CHB infection has an increased risk for B-NHL not only for the aggressive DLBCL form which is the most common form encountered but also for SMZL which is a rare indolent form of B-NHL with a better prognosis. Laboratory monitoring has a great value to the early detection of B-cell clonal expansion. In all SMZL, patients are recommended screening for HBV, because treatment with antivirals may regress lymphoma and also prevent reactivation of HBV in case of chemotherapy, especially rituximab.

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