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CASE REPORT

Hepatitis C Virus Infection and Locally Advanced Splenic Marginal Zone Lymphoma

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Splenic marginal zone lymphoma (SMZL) is a rare malignant B-cell neoplasm, usually with an indolent clinical course and favorable prognosis. Treatment options include chemotherapy, surgery, radiation and immunotherapy. In some recent studies an increased incidence of hepatitis C virus (HCV) infection in patients with SMZL was reported and its possible role in lymphomagenesis was emphasized. A 66-year-old woman with twelve-year history of HCV infection was admitted due to locally advanced abdominal tumor involving the spleen and the left part of the diaphragm. Transaminase serum levels were not elevated. Neither peripheral lymphadenopathy nor bone marrow pathology was found. Absolute blood lymphocyte, erythrocyte and platelet counts were normal. A splenectomy with partial diaphragm resection in one block was performed. Recovery was uneventful. Pathologic examination with immunohistochemistry revealed SMZL and confirmed a neoplastic infiltration of the resected diaphragm. Following surgery, chemotherapy (CHOP regimen) and immunotherapy (anti-CD20 antibody) were given. At the last follow-up 15 months after surgery, the patient was free of any symptoms of lymphoma. Surgical resection of even locally advanced SMZL with involvement of adjacent tissues can be performed as a diagnostic and therapeutic procedure. Splenectomy is especially indicated in symptomatic patients without other sites of the disease. HCV infection may result in increased risk of SMZL due to the induction of B-cell lymphoproliferation. Because of possible lymphoma regression following anti-viral therapy, a systematic screening for HCV in patients with SMZL seems to be valuable and helpful for treatment planning. (Pathology Oncology Research Vol 13, No 4, 382–384)

Key words: hepatitis C, splenic neoplasm, marginal zone lymphoma

Introduction

SMZL is a rare subtype of marginal zone-derived malignant B-cell neoplasms (<1% of all lymphoma cases). They show some heterogeneity. The modality of spread, clinical diagnostic criteria and prognostic factors remain a matter of debate.[7] The great majority of patients are over 50 years of age.[1,4] SMZL is an indolent malignancy and probably takes years for full clinical manifestation. Most patients are asymptomatic and the disease presents as an incidental finding. No standard treatment is established and prospective studies are lacking. Therapeutic options are heterogeneous, including alkylating agents, purine analogues, immunotherapy with anti-CD20 antibody, splenic irradiation and splenectomy.[1,4,7] Surgical treatment is especially indicated for patients with abdominal symptoms, spleen enlargement and cytopenias.[1,7] Up to 20% of patients could be monitored using a watch-and-wait policy because of an indolent course of disease.[4] The prognosis is usually favorable, median survival is 9-13 years and most disease-related deaths are associated with transformation to diffuse large cell lymphoma.[7] Recently, an association of hepatitis C virus (HCV) infection with B-cell lymphomas is emphasized and its direct role in the pathogenesis of these malignancies is suggested.

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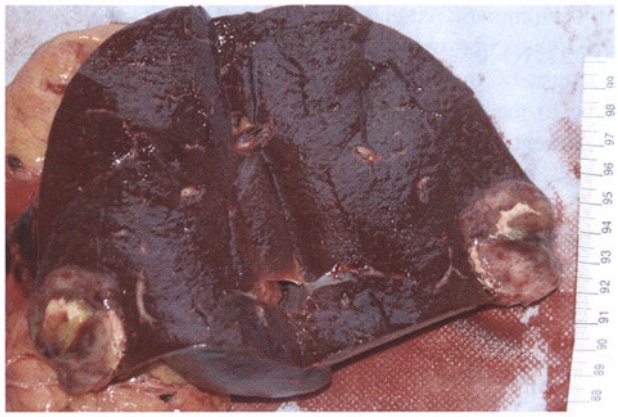

Figure 1. *Picture of the excised specimen. The gross tumor size was measured to be 42x30 mm.*

Case report

A 66-year-old woman with twelve-year history of HCV infection was admitted due to intermittent abdominal pain. Abdominal ultrasound and CT scanning revealed a hyperechogenic mass at the upper part of the spleen, infiltrating the diaphragm. Neither enlarged lymph nodes nor other pathology at abdomen or retroperitoneal region were diagnosed. No symptoms of liver dysfunction were noticed. The patient did not report any HCV-related therapy in the past. Transaminase serum levels were not elevated. Absolute blood lymphocyte, erythrocyte and platelet counts were normal. Neither peripheral lymphadenopathy nor bone marrow pathology was found. Following these investigations surgery was made. During laparotomy a splenic tumor involving the diaphragm was found. In addition, multiple uterine myomas were noticed. Direct visual and digital examination did not show any other intra-abdominal lesions. Splenectomy with partial resection of the diaphragm in one block was performed (*Fig. 1*). Pathologic report with immunohistochemistry revealed the splenic marginal zone lymphoma (Bcl-2+, CD20+, CD79a+, CD23-) and confirmed the presence of neoplastic infiltration of the diaphragm (*Fig. 2*). Resection was confirmed microscopically as R0. No pathological finding in lymph nodes at the hilar area of the spleen was reported. Recovery was uneventful. At the time of lymphoma

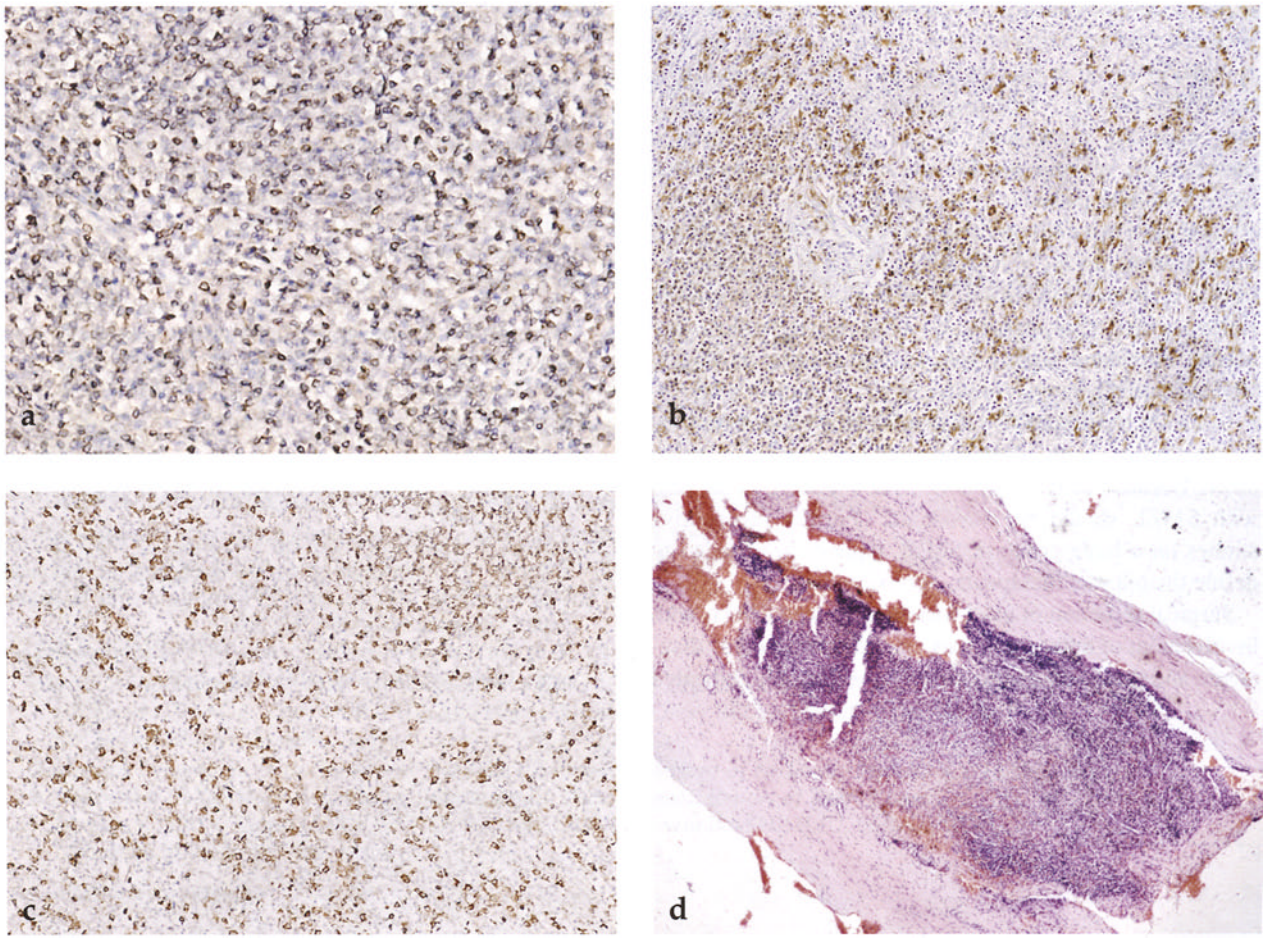

Figure 2. *Immunopositive reactions for* ***a)*** *Bcl-2, B) CD20 and* ***c)*** *CD79a antigens.* ***d)*** *Lymphoma infiltration of the diaphragm.*

diagnosis the patient was HCV antibody-positive, but HCV RNA-negative, therefore, anti-HCV therapy was not administered. Following surgery, polychemotherapy (CHOP regimen) and immunotherapy (anti-CD20 antibody) were administered. At the last follow-up 15 months after surgery the patient was free of any symptoms of the disease.

Discussion

In the last years the high prevalence of chronic HCV infection among patients with B-cell lymphoma is emphasized. In 16-35% of patients with lymphoproliferative disorders, including SMZL, a HCV-positive serology was found.[1,4] Results of these studies suggest an important etiologic role for HCV infection in the development of SMZL. The mechanism of induction of B-cell lymphoproliferative disorders by HCV is not fully elucidated. It is probably due to antigen-driven processes.[7,10] HCV drives the monoclonal expansion and, occasionally, the malignant transformation of B cells producing a poly-reactive natural antibody commonly encoded by the VH1-69 variable gene.[2] The preferential usage of this segment in the majority of HCV-positive lymphoma cases suggests the presence of a common antigen, probably a HCV antigen epitope, involved in B-cell selection.[6] The molecular basis for virally induced lymphomagenesis is still unclear. HCV may stimulate monoclonal B-cell proliferation through their specific receptor on the cell surface. Binding of the HCV envelope proteins to a cellular ligand, CD81, may also enhance this antigen-driven process.[10] The causal relationship between HCV infection and marginal-zone lymphoma is strongly supported by regression of the neoplasm following anti-viral therapy. In some recent studies virological and hematologic responses and lymphoma regression after treatment with interferon-alpha alone or with ribavirin were reported.[1,3,5,8,9] Thus, anti-HCV treatment may be an alternative to other therapeutic strategies in these cases. Because of these findings, HCV testing in patients with SMZL should be considered.[8] Further prospective studies on a large group of SMZL patients are needed to define the optimal therapeutic approach.

Surgical resection of even locally advanced SMZL with involvement of adjacent tissues can be performed as diagnostic and therapeutic procedure. It is especially indicated in symptomatic patients without other sites of the disease. HCV infection may result in an increased risk of SMZL because of the induction of B-cell lymphoproliferation. Due to the reported lymphoma regression after antiviral treatment, a systematic screening for HCV in patients with SMZL may be helpful for the optimal management.

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