Lacrimal Gland Marginal Zone Lymphoma: Regression after Treatment of Chronic Hepatitis C Virus Infection: Case Report and Review of the Literature

Adil Coskun¹, Ozden Yukselen², Vahit Yukselen¹ and A. Onder Karaoglu¹

Abstract

A 43-year-old woman was first admitted to the ophthalmology clinic with the complaint of a mass compressing the right eye. Based on clinical and laboratory examinations she was diagnosed as having marginal zone lymphoma (MZL) of the right lacrimal gland in addition to hepatitis C virus (HCV) infection. After the treatment for HCV infection with pegylated interferon plus ribavirin, a radiographic response of the MZL was obtained; she remains in remission through thirty months of clinical follow-up. In this case, the treatment of HCV infection led to regression of MZL suggesting the necessity of testing for HCV infection and treatment of the HCV infection should be highly considered in all HCV-positive patients with MZL's.

Key words: hepatitis C virus, marginal zone lymphoma, lacrimal gland lymphoma, pegylated interferon


Introduction

The extranodal marginal zone B-cell lymphoma of mucosa-associated tissue (MALT lymphoma) represents the most common lymphoma subtype in the ocular adnexa (1, 2). Ocular adnexal lymphomas, which arise in the conjunctiva, lacrimal gland, eyelid, and orbital connective tissue, account for 8-12% of all ocular adnexal tumors (3, 4), and 8% of all extranodal non-Hodgkin lymphomas (NHL) (5). Although the results of several studies are conflicting, hepatitis C virus (HCV) has been suggested to be a cause of NHL. HCV has been shown to sustain clonal expansion of B lymphocytes in HCV-infected patients (6). The persistent antigenic stimulation caused by chronic HCV infection was suggested to be in association with NHL (7). Moreover HCV infection is most frequently encountered in the patients with lympho-plasmacytoid lymphoma. Marginal zone lymphomas of the lymph node and diffuse primary hepatosplenic B-cell lymphomas have also been reported to be related to HCV infection (8, 9). In the literature a case of MALT lymphoma of the left lacrimal and mammary glands in a patient with liver cirrhosis caused by HCV infection was also reported (10). We herein report a patient with extranodal marginal zone lymphoma of the right lacrimal gland who achieved both a complete clinical remission and a complete radiological response after the successful treatment of chronic HCV infection.

Case Report

A 43-year-old woman was initially admitted to the ophthalmology department with swelling of the upper eyelid and exophthalmia on the right side eight months previously. A computed tomography (CT) scan revealed a soft tissue mass (18×11×20 mm), which did not involve the adjacent bone tissue (Fig. 1a). During pre-operative examinations the laboratory tests revealed elevated levels of liver enzymes. Therefore, the patient was referred to our gastroenterology department. On admission an analysis of the liver enzyme levels showed alanine aminotransferase (ALT) at 138 IU/L and aspartate aminotransferase (AST) at 132 IU/L; the subsequent two controls were higher than the upper normal limit. A histopathological examination of the mass showed

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that the lacrimal gland tissue was diffusely infiltrated by a marginal-zone lymphoma (Fig. 2). The immune phenotypic features were positive for CD20 and BCL-2, and negative for CD3, CD10 and BCL-6. Staining for immunoglobulin kappa and lambda chains did not reveal a monoclonal predominance. Unfortunately, we were technically unable to study HCV-RNA in the mass by PCR at the time of diagnosis, as the patient refused bone marrow aspiration and biopsy could not be performed. The CT scans of the neck, chest, abdomen and pelvis showed no lymphadenopathy. The liver and spleen were both within the top normal size range. At presentation she denied a history of weight loss, fatigue, night sweats, and fever. Her past medical history included a thyroidectomy operation 10 years earlier, and a tooth extraction 2 years previously. On physical examination, there was no palpable lymphadenopathy, splenomegaly or hepatomegaly. Table lists the patient’s laboratory values before and after treatment. Her hepatitis screening panel revealed an antibody to HCV, and her hepatitis C viral load analyzed by PCR was 5,876,000 copy/mL, and HCV genotype was 1b. A liver biopsy to assess the degree of fibrosis before the start of treatment confirmed active chronic hepatitis with fibrosis stage II and severe piece-meal necrosis, significant portal inflammation, and rare spotty necrosis with a histological activity index of 10/18 according to Knodell’s classification.

The patient was started on combination therapy for her chronic HCV infection (peginterferon α-2b 100 μg once a week via subcutaneous injection and ribavirin 1,000 mg orally a day). She experienced some adverse effects including mild pancytopenia and slight fatigue at the beginning, but a dose reduction was not necessary. She worked and performed routine daily activities throughout the treatment period. At the third month of the treatment, her ALT and AST levels decreased to within normal limits and the HCV-RNA level was undetectable by PCR. Therefore, the treatment achieved early viral response for HCV infection. She was administered the 12-month standard therapy for HCV genotype 1b. At the end of therapy, a successful end of treatment viral response was achieved (HCV-RNA level was undetectable by PCR at the end of the therapy, at the 12th month), and the CT scans of the lacrimal gland revealed a complete resolution of the mass (Fig. 1b). She declined a bone marrow biopsy to confirm a complete response. The patient was followed by physical examination and laboratory studies every three months which included PCR for HCV viral load every six moths, and CT scans on a regular basis (the first year every 3 months, and then biannually). Thirty months later, she clinically remains in remission without any evidence of lymphoma based on laboratory and radiographic.

Table. The Patient’s Laboratory Values before and after Treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (N: 9-36 U/L)</td>
<td>151</td>
<td>33</td>
</tr>
<tr>
<td>ALT (N: 10-28 U/L)</td>
<td>155</td>
<td>25</td>
</tr>
<tr>
<td>ALP (N: 42-141 U/L)</td>
<td>103</td>
<td>108</td>
</tr>
<tr>
<td>GGT (N: 9-30 U/L)</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>LDH (N: 230-460U/L)</td>
<td>316</td>
<td>298</td>
</tr>
<tr>
<td>Hg (N: 11,7- 15,5gr/dL)</td>
<td>11,8</td>
<td>12</td>
</tr>
<tr>
<td>HCT (N: % 37-44)</td>
<td>33</td>
<td>36,4</td>
</tr>
<tr>
<td>White cells (N: 4,1-11,2 10³/μL)</td>
<td>3900</td>
<td>4100</td>
</tr>
<tr>
<td>PLT (N: 150-350 10³/μL)</td>
<td>189000</td>
<td>154000</td>
</tr>
</tbody>
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studies, and HCV-RNA by PCR continues to be undetectable.

**Discussion**

There have been several epidemiological studies, and in particular those from Italy have reported an increased HCV prevalence in patients with NHL, showing 9-37% in NHL cases vs. 3-10% in control group (11, 12). Zuckerman et al. found HCV infection in 22% of cases with NHL and in only 5% of controls with other medical conditions (Odds ratio 5.4) (8). HCV infection was especially common (46%) among cases with “monocytoid B-cell lymphoma”, now classified as marginal zone lymphoma. Similarly, an association between HCV infection and NHL was reported in a large multi-center U.S. population based case-control study (13). In that study, Engels et al. reported that 3.9% of the NHL patients and 2.1% of the controls were infected with HCV, and a positive association was noted for marginal zone lymphoma with OR 3.99 (13). On the other hand, some reports did not confirm this association (14, 15). Rabkin et al. also described a negative association between HCV and NHL in a case-control study nested within large cohort followed in California (16). To some extent, the discrepancy across geographic regions might be explained by the differences of the prevalence of HCV between the regions studied.

Although the mechanism by which HCV infection leads to the development of NHL remains to be determined, several lines of biological evidence indicate that HCV is a cause of NHL. HCV has been detected not only within the infected hepatocytes, but also in blood cells, such as lymphocytes (17). HCV infection is also demonstrated nearly universally in patients with essential mixed cryoglobulinemia, which is a low-grade lymphoproliferative disorder (18, 19). HCV virus has been shown to sustain clonal expansion of B lymphocytes in HCV-infected patients (6). There is some evidence that HCV can directly infect lymphocytes. HCV envelope protein E2 binds human CD81; this specific receptor allows the internalization of the virus to be also expressed on the lymphocyte B surface (20). Moreover, Zuckerman et al. found an increased prevalence of t(14,18) translocation and clonal immunoglobulin gene rearrangement (immunoglobulin heavy chain gene, IgH) in HCV-infected patients for which these biological markers disappeared following successful interferon treatment (21). These findings suggest that anti-viral therapy may also be indicated in HCV-infected patients with evidence of the clonal expansion of B cells to decrease the risk for developing lymphoma (21). Hernine et al. also reported that interferon was only effective in the splenic lymphoma if associated with HCV infection (22). In this study, when HCV infection was not present no hematological response to the interferon treatment was obtained. These results suggest that systematic screening for HCV infection should be performed in patients with splenic lymphoma, because for some patients the treatment of HCV infection may be an alternative to splenectomy, chemotherapy or both. Other studies have also reported the regression of splenic and nodal marginal zone lymphomas or HCV-associated immunocytoma after treatment of HCV infection by interferon (23, 24). These reports are in agreement with the findings of the present case. Furthermore, the reappearance of translocated B-lymphocyte clones is observed in patients whose HCV infection initially responded to interferon treatment and then relapsed. This confirms the hypothesis that the expanded B-lymphocyte clone needs persistent treatment of the infective stimulus (25-27).

HCV has also been demonstrated in tissues that might be relevant in site-specific lymphocyte proliferation, such as the gastric mucosa. HCV was detected in a patient with gastric MALT lymphoma who did not respond to anti-*Helicobacter pylori* treatment (28). Tursi et al. also treated HCV infection in patients with gastric MALT lymphoma who were *Helicobacter pylori* negative and in whom anti-H. pylori treatment did not achieve disappearance of gastric MALT lymphoma. They obtained disappearance of gastric MALT lymphoma in all patients in whom HCV was cured successfully (68.75%) (29).

In conclusion, various treatment modalities have been employed for marginal zone lymphomas (chemotherapy, radiation therapy, antibiotics in the case of *Helicobacter pylori* associated gastric MALT lymphoma, and monoclonal antibody treatment etc.). We herein described a case of lacrimal gland marginal zone lymphoma in a patient with asymptomatic chronic HCV infection. By resolving the HCV infection we obtained the disappearance of the marginal zone lymphoma of the lacrimal gland, and a complete clinical and radiological remission was achieved. Taken together, this report and the findings of previous reports, suggest the importance of testing all patients with all types of marginal zone lymphoma for HCV infection. Treatment of the underlying chronic HCV infection may result in the clinical remission of marginal zone lymphoma as long as the HCV infection remains in sustained remission.

The authors state that they have no Conflict of Interest (COI).

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