Case Report

Hepatitis C-Induced Hepatitis Flare in a Patient with Non-Hodgkin B-Cell Lymphoma Treated by Rituximab Including Chemotherapy (Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin - Vincristine, Prednisolone) Regimen

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Abstract
Hepatitis virus infections can lead to more critical outcomes such as severe hepatic dysfunction, failure, and fulminancy in the immunosuppressive patients other than immunocompetent individuals. It is globally accepted that reactivation of both hepatitis B virus and hepatitis C virus (HCV) occurs after chemotherapy and miscellaneous antibody treatments of malignant diseases or solid organ/bone marrow transplant in recipient patients. Especially among B-cell non-Hodgkin lymphoma (NHL) patients, according to various studies, the seroprevalence of HCV is higher than that of the general population. On the other hand, the role of HCV in the pathogenesis and etiology of NHL has been suggested. Today, cytotoxic drugs, corticosteroids, rituximab (RTX), and hepatotoxic regimens are administered to NHL patients. Specifically, it has been emphasized that the utilization of RTX (Anti CD20 antibody) regimens for B-cell NHL patients may result with flares in HCV patients conspicuously. Here, we report the case of an acute flare up due to HCV infection in a patient who underwent a 4 month course of RTX, containing chemotherapy against a B cell NHL (CD20+) disease and a dramatic recovery from HCV infection at the end.

Introduction
Hepatitis C is known to be one of the main leading causes of liver failure worldwide. About 60-85% of people who are exposed to hepatitis C virus (HCV) will go on to develop chronic hepatitis C (1,2). It is globally accepted that reactivation of both hepatitis B virus (HBV) and HCV occurs after immunosuppressive treatments especially after chemotherapy. In addition, mortality rates related to reactivation in patients with oncologic and hematological malignancies who are receiving intensive chemotherapy regimens is higher than that observed in the general population. HBV reactivation was reported in patients receiving chemotherapy to vary between 14% and 72% (3). On the other hand, HCV reactivation is observed rarely, and the result of HCV reactivation has the modest results (3). According to various studies in non-Hodgkin lymphoma (NHL) patients, the seroprevalence of HCV in NHL patients is higher than the general population. Today, cytotoxic drugs, corticosteroids, rituximab (RTX), and hepatotoxic regimens are administered to NHL patients (4). Especially, utilization of RTX regimens for NHL patients may result with flares in HCV patients. Here, we report a case of an HCV-infected patient with NHL and after 4 months of this RTX regimen, an acute flare up of HCV occurred.

Case Report
A 58-year-old female patient was admitted to the oncology outpatient clinic with complaints of axillary...
swelling measuring about 3 cm × 3 cm. After differential diagnosis, histopathological examination of excised biopsy material revealed diffuse large B cell lymphoma and the immune phenotypic feature was positive for CD20 (CD20+). The chemotherapy regimen RTX, cyclophosphamide, hydroxydaunorubicin, oncovin - vincristine, prednisolone (R-CHOP) was initiated in April 2011. During routine controls after the fifth cycle, approximately 10-fold increase in liver enzymes, alanine aminotransferase (normal value 40> IU/ml), and aspartate aminotransferase (normal value 40> IU/ml) levels was observed (Table 1). After detecting elevated liver enzymes, chemoimmunotherapy was stopped. There was an important point that should be indicated is that before starting chemoimmunotherapy, HBV, and HCV serology testing was not conducted leaving the HBV vaccination status of the patient unknown. Current Laboratory investigations revealed HBV-related serum markers and serum HBV-DNA titers to be negative. An enzyme-linked immunosorbent assay testing for HIV was also normal. Serology was positive for hepatitis C, and her HCV-RNA titer was found to be about 17,796,000 IU/ml. Further investigation into her medical history showed that, there were no related exposure (such as injecting drug use, tooth extraction, high-risk sexual practices, blood transfusion, and surgical operations) and the patient was evaluated as a flare of chronic HCV infection. Liver needle biopsy was performed, and histopathological examination of biopsy material revealed chronic hepatitis C with 5/18 histological activity index and 2/6 of fibrosis. A genetic type of HCV was found to be genotype 1. Peginterferon (PEG-IFN) alfa-2b 100 mcg/week subcutaneously + ribavirin 1000 mg/day perorally treatment was commenced. After 4 weeks of antiviral therapy, rapid virologic response was observed, and her HCV RNA levels were undetectable. Antiviral therapy was completed in about 48 weeks. After treatment, there was no recurrence in HCV, serological virologic response occurred and oncological monitoring has still been underway with remission.

Discussion

Today, about 200 million of people are infected by HCV virus in worldwide. The prevalence of this disease ranges from 0.4% to 3% in Western Europe while Egypt has the largest burden of HCV infection in the world with a 9% prevalence of chronic HCV infection (5). In Turkey, the prevalence of this infection varies between 0.5% and 1% and this rate reaches 1.9% in Southeastern Anatolia region (6). Abnormal liver function tests are

| Treatment course/laboratory values | 1st month of chemotherapy (end of 1st cycle) | 2nd month of chemotherapy (end of 2nd cycle) | 4th month of chemotherapy (end of 5th cycle, acute flare) | 6th month after hepatic flare | 4th week of antiviral therapy | 24th week of antiviral therapy | Normal range |
|-----------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------|
| WBC                              | 13.7                                        | 6.30                                        | 4.52                                        | 4.79                                        | 4.30                                        | 6.07                                        | 4.0-10.5×10³/mm³ |
| PLT                              | 457                                         | 479                                         | 389                                         | 222                                         | 176                                         | 196                                         | 150-450×10³/mm³ |
| HB                               | 12.4                                        | 11.4                                        | 11.9                                        | 14.1                                        | 12.5                                        | 12.6                                        | 13.5-18 g/dL |
| ALT                              | 36                                          | 31                                          | 158                                         | 372                                         | 50                                          | 15                                          | 5-40 U/l |
| AST                              | 32                                          | 33                                          | 149                                         | 392                                         | 56                                          | 19                                          | 5-40 U/l |
| T. Bil                           | 1.02                                        | 0.62                                        | 0.57                                        | 1.21                                        | 1.01                                        | 0.71                                        | 0.2-1.2 mg/dL |
| I. Bil                           | 0.22                                        | 0.15                                        | 0.13                                        | 0.45                                        | 0.36                                        | 0.15                                        | 0.1-0.3 mg/dL |
| Urea                             | 20                                          | 21                                          | 22                                          | 24                                          | 26                                          | 27                                          | 15-44 mg/dL |
| Creatinin                        | 0.74                                        | 0.77                                        | 0.65                                        | 0.79                                        | 0.80                                        | 0.80                                        | 0.6-1.4 mg/dL |
| Albumin                          | 3.61                                        | 3.64                                        | 3.67                                        | 3.98                                        | 4.15                                        | 3.96                                        | 3.5-5 g/dL |
| PT                               | 11.4                                        | 10.3                                        | 11.4                                        | 10-14 sec                                    | 10-14 sec                                    | 10-14 sec                                    | 10-14 sec |
| INR                              | 1.07                                        | 0.94                                        | 1.26                                        | Positive                                    | Positive                                    | Positive                                    | 0.8-1.2 |
| ANTIHCV                          | Positive                                    | Positive                                    | Positive                                    | Positive                                    | Negative                                    | Negative                                    | IU/mL |
| HCV-RNA                          | 17,796.000                                  | 11,560.000                                  | Negative                                    | Negative                                    | IU/mL                                       | IU/mL                                       |
| AFP                              | 15.5                                        | 4.71                                        | 2.36                                        | 1.71-3.71                                   | 0.70-1.48                                   | 1.48 pg/mL                                   |
| T3/T4                            | 3.47/1.23                                   | 3.43/1.46                                   | 6.40/1.72                                   | 3.71-7.0/1.48                               | 1.48 pg/mL                                   | 1.48 pg/mL                                   |
| TSH                              | 0.39                                        | 0.82                                        | 1.73                                        | 0.36                                        | 0.05                                        | 0.35-4.94 IU/mL                              |

Table 1. Laboratory findings of the patient before and after the antiviral therapy.

WBC: White blood cell, PLT: Platelet, HB: Hemoglobin, T. Bil: Total bilirubin, I. Bil: Indirect bilirubin, PT: Prolongate time, AFP: Alpha-fetoprotein, HCV: Hepatitis C virus, INR: International ratio, AST: Aspartate transaminase, ALT: Alanine transaminase
usually seen in patients undergoing immunosuppressive therapy with cytotoxic drugs. In addition to the effects these treatments might cause, other primary or secondary hepatotropic viruses such as HBV, HCV, cytomegalovirus, and herpes simplex virus could affect the liver depending on the immunosuppressive state of the patient. Specifically, as a consequence of HBV and HCV replication or reactivation, severe hepatic failure in the form of fulminancy could also be seen. A study comparing the incidence of hepatitis infection in patients undergoing chemotherapy by Kawartani et al. showed a higher incidence of severe liver dysfunction in patients infected with HCV or HBV when compared to those who were non-infected [35%, 0%]. Severe liver dysfunction was reported more in patients infected with HBV than those infected with HCV (75%, 18%) (7). Although not clearly understood, HCV flare in patients following chemotherapy was found to be less common than that of HBV infection. Destruction in T cell function during HCV infection is thought to be responsible for a weak immune response leading to the lower incidence of disease reactivation (8). Especially, a higher prevalence of HCV is seen among B-cell NHL patients. In a meta-analysis study by Gispert et al., the mean HCV prevalence in patients with B-cell NHL was found to be around 15% compared to a mean prevalence of 2.9% in patients diagnosed with other hematological malignancies and 1.5% among the general population (9).

The structural features of the HCV enable it to create a chronic stimulus on the immune system, a mechanism which leads to an abnormal clonal selection and development. Previously conducted experimental studies have confirmed the role of HCV in the pathogenesis of B-cell NHL as an activator of the common CD81 receptor found in hepatocytes and B-lymphocytes (9). A normal liver enzyme panel prior to the start of immunosuppressive therapy and the unremarkable risk history raise the suspicion of HCV-related activated B cell lymphoma in our patient.

RTX is a mono-clonal antibody used in the treatment of CD20 positive B-cell NHL. Its role as a revolutionary drug in the treatment of these types of hematological malignancies is well-recognized. However, reports from various studies conducted globally have confirmed severe HCV reactivation post RTX regimens. In a study conducted by Marignani et al., RTX treatment was given to two different groups of B-cell NHL patients thus those who tested HCV positive and negative, respectively. Hepatic flare was observed in three of nine HCV positive patients while none of the 95 HCV-negative patients enrolled into the study reported HCV reactivation after RTX treatment (9). The study concluded that HCV infection should be considered as a potential risk factor for hepatic flare in B-cell NHL patients undergoing RTX including chemotherapy as part of their treatment regimen (9). These patients were recommended for evaluation for possible HCV infections. Furthermore, the study highlighted an increase in liver enzymes to be clinically nonsignificant (9). In our case, hepatic flare was observed in a CD20+ B cell NHL patient undergoing five cycles of R-CHOP treatment. Her abnormal liver enzymes returned to normal 4 weeks following a combination therapy of PEG-IFN alfa-2b and ribavirin.

As a conclusion, a high index of clinical suspicion of HCV reactivation is warranted in B-cell NHL patients taking RTX as part of their chemotherapy treatment regimen. Pre-treatment evaluation of patients which should include investigation of hepatic markers, under the supervision of a team of the infectious diseases specialists, gastroenterologists, and medical oncologists is highly recommended.

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