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CASE REPORT

Rituximab-induced hepatitis C virus reactivation in rheumatoid arthritis

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The B-cell depletion agent rituximab (RTX) is used in lymphoma and rheumatoid arthritis (RA), and there have been several case reports of an RTX-induced reactivation of hepatitis C virus in patients with lymphoma. However, there have been no papers detailing hepatitis C virus reactivation after RTX therapy in a patient with RA. Here we report a case of RTX-induced hepatitis C virus reactivation in a patient with RA. Physicians should be aware that a close follow-up of liver function and viral load is mandatory after RTX therapy in patients with RA and concomitant hepatitis C.

Introduction

Rituximab (RTX), a chimeric monoclonal antibody against CD20 on B—cells, is one agent used synergistically against lymphoma. Due to complement-associated and antibody-dependent cellular cytotoxicity related to a depletion of B-cells, this drug has recently been used for rheumatoid arthritis (RA).[1] However, RTX is considered to be associated with immunosuppression, reactivation of hepatitis B,[2] and increased complications of cytomegalovirus infection.[3]

In addition, increasing serum hepatitis C virus (HCV) RNA levels in patients with B-cell non-Hodgkin's lymphomas undergoing treatment with RTX combination chemotherapy have been reported.[4,5] So far, there have been no reports on the adverse effects of RTX therapy in RA patients with concomitant hepatitis C. Here we describe the case of a patient with RA who was refractory to anti-tumor necrosis

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factor (TNF) therapy and experienced HCV reactivation upon receiving RTX therapy.

Case report

A 51-year-old woman presented with symmetric arthritis affecting her hand joints and involving more than three joint areas, with marginal erosion of the affected hand joints, and morning stiffness since 2003. Her serum was positive for rheumatoid factor, and the level of anticyclic citrullinated peptide antibodies was more than 340 U/mL. She subsequently received combination therapy comprising several nonbiological disease-modifying antirheumatic drugs (DMARDs), including hydroxychloroquine, methotrexate, azathioprine, leflunomide, sulfasalazine, and cyclosporine, but all these therapies failed to relieve her symptoms.

In April 2004, during the treatment with DMARDs, serological tests revealed an elevation of alanine aminotransferase (ALT) level to 80 U/L (normal $<$ 36 IU/L). Serum was positive for anti-HCV antibody, and negative for hepatitis B surface antigen. Furthermore, liver sonography revealed parenchymal liver disease. From March 2005, the patient received etanercept 25 mg twice a week to prevent hepatotoxicity induced by methotrexate-based DMARDs and to control the persistent and active polyarthritis.

Etanercept was administered for two and half years, and a serial follow-up of ALT levels during that period revealed intermittent elevation of liver function to about two times the upper limit of normal. In addition, the treatment was not effective in controlling the patient's RA activity. Therefore, in January 2008, the treatment was shifted from etanercept to B-cell depletion therapy (RTX, two 1000 mg intravenous infusions with a 2 week interval). However, no obvious improvement was detected 3 months after beginning of this RTX treatment in terms of Disease Activity Score 28 (DAS28).

A baseline survey of liver function performed in December 2007, before RTX therapy was administered, revealed serum aspartate aminotransferase (AST) and ALT levels of 34 U/L and 41 U/L, respectively. In addition, the viral load of genotype 1b HCV RNA was 0.015512 $\times$ 10^6 IU/ml by BAYER quantitative analysis (BAYER System 340 bDNA Analyzer, US). Follow-up assessment of the AST/ALT and HCV RNA levels (5.99454 x 10^6 IU/mL) in April 2008 revealed a marked elevation of all three parameters (Fig. 1).

To assess the patient's immune status, the lymphocyte count was measured before RTX therapy and on the 132nd day after RTX treatment. Lymphocyte counts were 2376/μL and 2332/μL, respectively. The medications administered concomitantly during this period were hydroxychloroquine 400 mg/d, the non-steroidal anti-inflammatory drug celecoxib 200 mg once daily, and prednisolone 5 mg/d. The drugs and their dosages were the same as those administered before RTX treatment.

After the diagnosis of reactivation of hepatitis C in September 2008, the patient received weekly injections of subcutaneous peginterferon α-2a (180 μg) plus oral ribavirin (1000 mg daily). The patient's DAS28 score for RA markedly decreased from 6.73 to 4.4 over a period of 2 months. At the same time, liver function also returned to the normal range, and HCV RNA was undetectable 2 months later. Subsequently, the subject received a 6-month course of antiviral therapy.

Discussion

B-cell depletion therapy is considered to be safe in RA patients with concomitant hepatitis C.[6] RTX has also been used for the treatment of HCV-associated cryoglobulinemia and its complications,[7,8] In patients with non-Hodgkin's lymphoma, a deterioration in liver function has been shown to occur when RTX is used in combination with other chemotherapeutic agents rather than when used separately.

In the case of our RA patient, elevated HCV RNA titer, AST and ALT levels developed after one course of RTX therapy. It remains to be clarified whether the difference

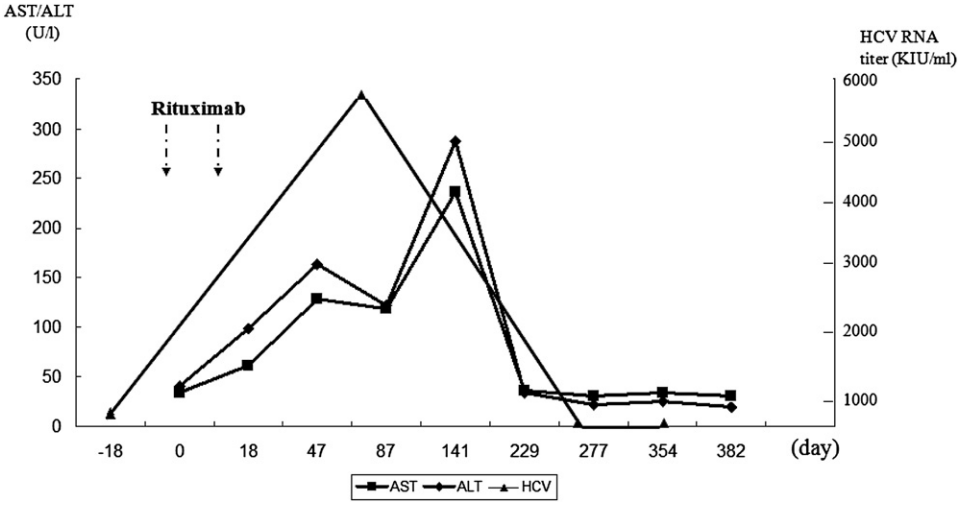

Figure 1. Changes in the liver function and viral load of hepatitis C virus (HCV) following rituximab therapy. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

in susceptibility to hepatitis C reactivation between patients with RA and with non-Hodgkin's lymphoma is related to the dose of RTX administration or to the underlying disease. B-lymphocytes are supposed to shield against HCV[9]; thus, it could be speculated that the elevated HCV viral load reflects virus spreading from RTX-related B-cell cytotoxicity. Otherwise, B cells serve as antigen-presenting cells to $CD4^+$ helper T-cells which respond against HCV. The B cell number may be reduced and their function may be affected due to the impact of RTX on B-cell activity.[10]

There are several limitations to this case report. First, we cannot completely exclude HCV reactivation related to the natural course of infection or to toxicity from other drugs, although there was an improvement in liver function and constant medication in the 3 months prior to RTX administration. As a result of the improvement in liver function in the patient's history and because of the change in HCV RNA viral load after RTX use, we are still highly suspicious that RTX-induced HCV reactivation indeed occurred.

The second limitation is that the patient's HCV RNA level did not follow-up during the anti-TNF therapy. There were some episodes of mildly elevated liver function tests, which returned to baseline spontaneously or when the doses of the hepatotoxic agents were reduced. We therefore suggest that this indirectly reflects the relative clinical stability of HCV infection during anti-TNF therapy.

In addition, a decreased DAS28 score was noted after antiviral therapy. There is in fact no evidence-based rationale to explain why disease activity was decreased, as indexed by DAS28, after withdrawal of RTX. We hypothesize that the active arthritis occurring before RTX withdrawal was associated with HCV-related extrahepatic manifestations, including arthritis. The decreased disease activity may partially relate to the response to antiviral therapy.

Based on our experience with this patient with RA and hepatitis C reactivation after RTX monotherapy, we suggest that a close follow-up of liver function, viral load, or both is mandatory after RTX therapy in RA patients with concomitant hepatitis C.

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