Hepatitis C Virus (HCV) Reactivation Caused by Steroid Therapy for Dermatomyositis

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Abstract

A Japanese woman was treated with injectable methylprednisolone and oral prednisolone for dermatomyositis. On admission, her serum was positive for anti-hepatitis C virus (HCV) antibodies, although HCV RNA was undetectable on polymerase chain reaction. Glucocorticoid therapy improved the dermatomyositis; however, the serum alanine aminotransferase levels rapidly increased, with positive serum HCV RNA and a high viral titer. Both parameters decreased in association with prednisolone tapering, whereas dermatomyositis subsequently recurred and the administration of glucocorticoid therapy was repeated. The serum alanine aminotransferase and HCV RNA levels subsequently increased in a similar manner to that observed after the first course of therapy. Liver enzymes and the viral load should be monitored in anti-HCV-positive patients receiving immunosuppressives, even if serum HCV RNA is negative.

Key words: hepatitis C virus, methylprednisolone, myositis, reactivation, steroids

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are serious health problems worldwide; more than 350 million people are infected with HBV and >170 million are infected with HCV (1, 2). Both types of hepatitis virus may induce chronic liver infection and potentially death due to liver failure and/or hepatocellular carcinoma (3). Recently, the potential for reactivation of HBV during chemotherapy or immunosuppressive therapy has also become a major concern. In contrast to that observed for HBV, the frequency of HCV reactivation is low. HCV reactivation may occur as a consequence of the loss of host immune control over the virus (4, 5); however, little is known about the overall frequency and mechanisms of HCV reactivation (6). HCV reactivation is commonly defined as a three-fold or greater increase in the serum alanine aminotransferase (ALT) level in patients without tumor infiltration to the liver who have not received hepatotoxic drugs and have no recent history of blood transfusions or other systemic infections in addition to HCV. Changes in the liver enzyme levels may be accompanied by the reappearance of HCV RNA and/or a sudden increase in the serum HCV RNA level of >1 log₁₀ IU/mL (7).

Dermatomyositis and polymyositis are classified as idiopathic inflammatory myopathies characterized by the presence of inflammatory infiltrates primarily affecting the skeletal muscle and skin (8, 9). Although HCV is responsible for a variety of extrahepatic virus-associated autoimmune disorders (10), HCV infection associated with polymyositis/dermatomyositis is less common. Intensive immunosuppressive therapy is often required in the initial stage of treatment for several collagen diseases, including dermatomyositis, although there are few reports of HCV reactivation in such individuals. Hence, whether the administration of corticosteroid therapy alone stimulates the reactivation or acute exacerbation of HCV infection remains unclear. We herein report a case of HCV reactivation caused by treatment with steroid therapy for dermatomyositis.
Case Report

A 76-year-old woman was admitted for a fever, erythematous rash over the upper eyelids, muscle pain in the lower extremities and progressive proximal muscle weakness in February 2012. The onset of symptoms had occurred 10 days prior to admission. The patient had a history of blood transfusion during surgery for lung tuberculosis at 37 years of age, and, in 2003, she has been diagnosed as being positive for anti-HCV antibodies (Abs) [123.34 S/CO by enzyme immunoassay (EIA); normal, <100]. The HCV RNA was identified as genotype 2 at a level of 1.0 KIU/mL according to the COBAS AMPLICOR HCV MONITOR version 2.0. She declined to receive antiviral therapy because the ALT level remained within the reference range. However, in 2006, the serum HCV RNA level spontaneously decreased below the detectable limit based on a branched DNA probe assay. Upon admission, a physical examination demonstrated a heliotrope rash on the upper eyelids, erythema on the dorsum of the hands and the V-sign on the anterior cervical to thoracic regions. Manual muscle tests revealed the following muscle strengths: 4/5 bilateral pectoralis major and 3/5 bilateral proximal lower extremities. The findings of a mental status examination, cranial nerve testing and deep tender reflexes were normal; however, the serum activities of myositis-associated enzymes were elevated, as follows: creatine kinase (CK), 3,142 IU/L (range, 45-163 IU/L); lactate dehydrogenase, 514 IU/L (range, 119-229 IU/L); aldolase, 25.0 IU/L (range, 2.7-7.5 IU/L); aspartate aminotransferase, 197 IU/L (range, 13-33 IU/L); ALT, 86 IU/L (range, 8-42 IU/L); white blood cell count, 4.6x10^3/mm^3 (range, 2.9-8.5x10^3/mm^3); red blood cell count, 4.54x10^6/mm^3 (range, 3.7-4.9x10^6/mm^3); and platelet count, 130x10^3/mm^3 (range, 200-400x10^3/mm^3). Autoantibodies, including antinuclear Abs, anti-Jo1 Abs, anti-Mi-2 Abs, antiribonucleoprotein Abs, anti-double stranded DNA Abs, antisignal recognition particle Abs and other disease-specific autoantibodies, were negative. Although a muscle biopsy revealed no characteristic features, electromyography showed myogenic changes in the right quadriceps, and magnetic resonance imaging indicated the presence of pronounced inflammation in the bilateral proximal thigh muscles (Fig. 1) with hypointense areas on both T2-weighted images with fat suppression and inhomogeneous contrast enhancement on T1-weighted images with fat suppression. The patient was therefore diagnosed with probable dermatomyositis. No signs of complications, such as interstitial pneumonia, pulmonary hypertension or malignancy, were observed.

On admission, the HCV Ab level was 15.9 S/CO according to the COBAS AMPLICOR HCV MONITOR version 2.0.

Figure 1. Enhanced magnetic resonance imaging indicated findings consistent with myositis in the thigh muscles: vastus lateralis, vastus medialis and semimembranosus. A) T2-weighted image with fat suppression showing an inhomogeneous high-intensity area. B) Enhanced T1-weighted image with fat suppression showing inhomogeneous increased areas.
The patient’s clinical course was as follows (Fig. 2). Methylprednisolone (m-PSL) pulse therapy was administered at a dose of 500 mg/day for three days, followed by oral prednisolone (PSL) at a dose of 50 mg/day. The dose of PSL was subsequently increased to 60 mg/day following an increase in the CK level, after which the patient’s symptoms improved and the myositis-associated enzyme levels decreased. The serum CK level continued to decrease; however, the ALT level increased again three weeks after the end of treatment. Although HCV RNA had been undetectable prior to the start of m-PSL pulse therapy, the patient subsequently tested positive for HCV genotype 2b, with a high level of viremia (>7.8 log IU/mL), according to TaqMan PCR at week 7 of treatment. HCV core antigens examined at a later date were also positive. A detailed interview revealed no incidents of sexual contact, needle-stick accidents, acupuncture, tattoos or history of injection of blood derivatives or blood transfusions after the current admission. We therefore initiated treatment with 600 mg/day of ursodeoxycholic acid orally in association with the intravenous injection of neo-minophagen C. Consequently, the serum ALT and HCV RNA levels gradually decreased, and the patient was discharged at week 12 of treatment. Following tapering of the dose of PSL, the serum HCV RNA level decreased to 4.2 log IU/mL at week 25 of treatment, and the ALT level remained within the reference range. The dose of PSL was then tapered to 5 mg/day at week 46 of treatment, and the HCV RNA level decreased to 2.0 log IU/mL at week 62 of treatment. However, the patient was again hospitalized due to the exacerbation of myositis at week 62 of treatment. Because the HCV RNA level had increased during the previous administration of m-PSL pulse therapy, a second cycle of m-PSL pulse treatment was administered at a lower dose of 250 mg/day for three days, and the dose of PSL was tapered to 30 mg/day. Although the myositis exhibited a tendency to improve, the ALT level increased to 128 IU/L one week after the second cycle of pulse therapy; in addition, the HCV-RNA level increased to 6.0 log IU/mL and the HCV core antigen titer increased to 853 fmol/L. Following the completion of PSL tapering, the serum ALT...
and HCV RNA levels decreased, displaying a similar clinical course to that observed after the first cycle of steroid pulse therapy.

Discussion

In the current case, the HCV RNA level increased markedly after the administration of systemic steroid pulse therapy for dermatomyositis. To our knowledge, this is the first report of HCV reactivation caused by a single administration of steroid therapy for collagen disease. HCV reactivation is associated with the use of various immunosuppressive and chemotherapeutic agents, including busulfan, cytarabine, cyclosporine, gemcitabine, methotrexate, rituximab and vincristine (5-7, 11-16). Many patients who exhibit HCV reactivation during treatment with one of these drugs are simultaneously treated with corticosteroids (11, 12). Among these agents, rituximab is reported to be a high-risk drug related to HCV reactivation during treatment with one of these drugs are simultaneously treated with corticosteroids (11, 12). Among these agents, rituximab is reported to be a high-risk drug related to HCV reactivation (13). Several pathogenic mechanisms involving the association between steroids and HCV reactivation have been postulated, including enhanced HCV infectivity due to an upregulated expression of viral receptors on the surface of hepatic cells (17) and enhanced viral replication both in vitro and in vivo (4). HCV genotype 2, in particular, may be a risk factor for reactivation (18). Antibody responses to hypervariable region 1 of the HCV envelope glycoprotein E2 are more vigorous in HCV genotype 2-infected subjects than in those with genotype 1 infection (19, 20). This suggests the presence of stronger antibody-mediated immune pressure on the genotype 2 virus and may explain the difference in HCV kinetics observed among genotypes.

The health consequences of HCV reactivation appear to be less severe than those of HBV reactivation because ALT elevation is usually mild and transient in most patients with HCV reactivation (14). As in most previous reports, the ALT levels in this case increased in association with the HCV RNA level following the administration of systemic corticosteroid pulse therapy, and the HCV RNA level decreased gradually as the dose of steroids was tapered. However, the mortality rate is reportedly similar between HBV- and HCV-infected patients with severe hepatitis (15), and several studies have shown that hepatic dysfunction caused by HCV reactivation may lead to frequent modifications and interruptions in therapy for the primary disease, thereby worsening the overall outcome (13, 16). Furthermore, the long-term impact of chronic HCV infection can be serious, as cytotoxic and immunosuppressive treatment may accelerate progression to cirrhosis (15).

Most reports of HCV reactivation have involved chronic hepatitis C or anti-HCV Ab-positive patients without HCV RNA data. However, there are case reports describing the recurrence of HCV after clinical HCV resolution. For example, one report discussed a patient who received immunosuppressive therapy after achieving an apparent sustained viral response (21), and another report discussed a patient with hypogammaglobulinemia who was treated with corticosteroids 8.5 years after the resolution of acute hepatitis C (22). It has also been reported that a low level of HCV RNA is detectable in the liver and peripheral blood mononuclear cells of anti-HCV Ab-positive patients years after the elimination of HCV (23). These data suggest that achieving the clearance of serum HCV RNA does not result in the full restoration of antiviral immunity and that sterilizing the immune system with the complete elimination of the virus is unlikely. Therefore, it is possible that many patients who have apparently achieved clearance of HCV may suffer from HCV reactivation and liver injury if they receive strong immunosuppressive treatment.

HCV and HBV reactivation is known to occur in older patients treated with prednisolone therapy and is a potential cause of reactivation in our patient (24, 25). We are convinced of the diagnosis of HCV reactivation in the present case for several reasons. First, the previously detected genotype 2 infection was consistent with the genotype 2b detected at our hospital. Second, HCV reactivation occurred again after the second cycle of steroid pulse therapy. Third, no etiologies other than HCV reactivation adequately explains the occurrence of the two ALT flares. In order to distinguish whether this case involved HCV reactivation or a new HCV infection, detailed interviews were conducted with the patient as well as her family members and attending medical staff. Consequently, no episodes associated with new HCV infection, such as sexual contact, needle-stick accidents, acupuncture, tattoos or a history of injection of blood derivatives, were reported.

The Roche Cobas AmpliPrep/Cobas TaqMan HCV assay (CAP/CTM) is the most widely used assay for HCV-RNA quantification worldwide, although it may underestimate the HCV RNA levels in a number of patients with HCV genotypes 2 and 4 due to a mismatch between the primers or probes and the viral sequence (26). However, the possibility of a false-negative result for HCV RNA on CAP/CTM is remote in this case, as repeat measurements of the HCV RNA levels with the CAP/CTM, Abbott Real-Time HCV (ART) and ARCHITECT Anti-HCV (CMIA) assays using the stored serum samples obtained at the first visit revealed that the patient was negative for HCV RNA.

In the present case, antiviral therapy has not yet been administered because the patient strongly hopes to treat the hepatitis C successfully without interferon. It is possible that the natural resolution of HCV by the immune response may drive the level of viremia below the limit of detection, whereas interferon treatment may result in the sustained inhibition of viral replication and achievement of complete elimination. Therefore, treatment with interferon appears to be preferable in cases of HCV reactivation.

In summary, our findings indicate that greater attention should be paid to the possibility of HCV reactivation in any patient with a history of HCV infection undergoing immunosuppressive therapy. Currently, no reliable methods exist to predict an individual’s risk of HCV reactivation, and
unlike that observed for HBV reactivation, no drugs are currently approved to prevent HCV reactivation. A dramatic increase in the number of patients with a sustained viral response is expected in association with the use of direct-acting antiviral drugs, although the true frequency and severity of HCV reactivation in patients with occult HCV infection remains unclear. Prospective studies are thus needed to provide clinical evidence and determine the pathogenesis of HCV reactivation in both patients with chronic HCV infection and those with occult HCV infection.

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

References


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