Purpura with Ulcerative Skin Lesions and Mixed Cryoglobulinemia in a Quiescent Hepatitis B Virus Carrier

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Abstract

Mixed cryoglobulinemia is occasionally seen in patients with hepatitis B virus (HBV) infection. This report presents the case of a quiescent HBV carrier who had type II mixed cryoglobulinemia, protracted purpura, ulcerative skin lesions and advanced chronic kidney disease. The cutaneous manifestations of the patient improved along with a decrease in the serum cryoglobulin and HBV-deoxyribonucleic acid levels following the initiation of oral entecavir in combination with plasmapheresis. However, the patient ultimately required prednisolone due to the limited benefits of these treatments. We also discuss various concerns regarding steroid treatment in patients with mixed cryoglobulinemia complicated by HBV infection.

Key words: purpura, mixed cryoglobulinemia, hepatitis B, entecavir, reactivation

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Introduction

Cryoglobulinemic vasculitis is an immune complex-mediated disease involving vascular injuries that may manifest various complications, including purpura with or without ulcerative lesions, renal involvement, peripheral neuropathy and gastrointestinal bleeding (1, 2). Steroids and immunosuppressive agents have been used as treatments with a view to suppressing B-cell clonal expansion and the intrinsic production of cryoglobulins with varying degrees of success (1). However, the indications for such agents in the treatment of symptomatic cryoglobulinemia among hepatitis B virus (HBV) carriers should be determined carefully, as immunomodulatory treatments may enhance viral replication and precipitate hepatic flares due to reactivation of hepatitis (3, 4). In this report, we describe the case of a quiescent HBV carrier with mixed cryoglobulinemia, protracted purpura and ulcerative skin lesions on the lower extremities who was treated with oral entecavir, prednisolone (PSL), and plasmapheresis.

Case Report

In August 2010, a 71-year-old woman was found to be positive for HBsAg, anti-HBV envelope (HBe) antibodies, anti-HBV core (HBc) antibodies and cryoglobulin when a local physician confirmed the presence of chronic renal dysfunction with a serum creatinine (Cr) level of 2.1 mg/dL. The asparate aminotransferase (AST) and alanine aminotransferase (ALT) levels were within the normal ranges, and the patient was negative for HBe antigens (HBeAg), anti-HBs antibodies and antibodies to hepatitis C virus (HCV). A serological workup revealed a detectable level of serum HBV-deoxyribonucleic acid (DNA) of 2.4 log copy/mL, as determined by a polymerase chain reaction assay, and the patient was confirmed to be negative for antineutrophil cytoplasmic antibodies and anti-glomerular base-
ment membrane antibodies. Two months after the diagnosis, a palpable nonpruritic petechial rash gradually appeared over the distal portion of a lower extremity along with deterioration of the renal function, and periodic hemodialysis treatment was commenced in late January 2011. The petechial rash persisted, and cutaneous ulcerations developed in the distal portion of a lower extremity along with a marginal change in the cryocrit level (Fig. 2). Three months with gradual relief of pain, despite the cessation of entecavir and plasmapheresis at the end of September 2011 due to a relapse of the ulcerative purpura (Fig. 1D), while relapse of the ulcerative purpura (D) was seen in the middle of December 2011.

Table. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell</td>
<td>2,500/L</td>
<td>C-reactive protein</td>
<td>1.75 mg/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>31%</td>
<td>IgG</td>
<td>485 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.5 g/dL</td>
<td>IgA</td>
<td>134 mg/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>11.1 × 10^4/L</td>
<td>IgM</td>
<td>261 mg/dL</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>36 mg/dL</td>
<td>C3</td>
<td>55 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>4.08 mg/dL</td>
<td>C4</td>
<td>1.0 mg/dL</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>2.8 g/dL</td>
<td>Cryocrit</td>
<td>2%</td>
</tr>
<tr>
<td>AST</td>
<td>12 U/L</td>
<td>ALT</td>
<td>4 U/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>207 U/L</td>
<td>HBsAg (+)</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>135 mmol/L</td>
<td>HBeAg (+)</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>4.2 mmol/L</td>
<td>anti-HBc (+)</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mmol/L</td>
<td>anti-Hbe (+)</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.6 mg/dL</td>
<td>anti-HBs (-)</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.4 mg/dL</td>
<td>HBV-DNA (2.3 log copy/mL)</td>
<td></td>
</tr>
</tbody>
</table>

At the time of admission, the patient had a temperature of 36.5°C, a pulse of 82 beats/min and a blood pressure of 129/69 mmHg. Her height and weight were 153 cm and 40.5 kg, respectively. A physical examination revealed palpable purpura with painful cutaneous ulcerative lesions (Fig. 1A). The laboratory data obtained on admission are summarized in Table. The cryoprecipitate was characterized by immunoelectrophoresis, which showed that the proteins included polyclonal immunoglobulin (Ig) G and κ-type monoclonal IgM, and was negative for rheumatoid factor, suggesting the presence of type II mixed cryoglobulinemia (1). A peripheral blood smear was unremarkable, and the absence of atypical plasma cells was noted. A bone marrow biopsy confirmed that there were no increases in the area of plasma cells (approximately 5%). The patient was subjected to additional cycles of cryofiltration on days 1 and 6, and treatment with oral entecavir at a dose of 0.5 mg/week was initiated two days after the second cycle of cryofiltration. Due to a significant decrease in the serum IgG level to 214 mg/dL after cryofiltration, we performed plasma exchange (PEX) as an alternative apheresis treatment, which replaced three liters of plasma with the same amount of fresh frozen plasma (FFP), once a week for a total of five treatments (Fig. 2). Although the patient’s renal function did not recover, the cryocrit and HBV-DNA levels became undetectable five weeks after admission, and the ulcerative lesions continued to improve for at least two months with gradual relief of pain, despite the cessation of entecavir and plasmapheresis at the end of September 2011 (Fig. 1B, C).

The patient was finally treated with oral PSL at a dose of 20 mg/day (0.5 mg/kg) starting in the middle of December 2011 due to a relapse of the ulcerative purpura (Fig. 1D) and a slight increase in the cryocrit level of 2%, despite the resumption of oral entecavir and PEX. This was followed by partial resolution of the cutaneous manifestations, with a marginal change in the cryocrit level (Fig. 2). Three months later, the patient died of acute cardiac failure when the dose of oral PSL was gradually tapered to 5 mg/day. The patient’s relatives declined a postmortem autopsy.

Discussion

Cryoglobulins are heterogeneous serum immunoglobulins that precipitate at low temperature and are resolubilized by warming. They are classified into three types: type I cryoglobulins are single monoclonal immunoglobulins, and types II and III are mixed cryoglobulins, composed of different immunoglobulins, with a monoclonal component being present in type II and polyclonal immunoglobulins exclusively comprising type III (1). The cryoglobulins may be found in

![Figure 1. Changes in the ulcerative lesions before and after the initiation of treatment with oral entecavir combined with plasmapheresis. Severe ulcerative lesions observed on admission (A) were improved four weeks after treatment (B). Further resolution was also noticed at the end of October 2011 (C), while relapse of the ulcerative purpura (D) was seen in the middle of December 2011.](image)
ultimately required PSL due to the limited therapeutic benefits. The pathogenesis of mixed cryoglobulinemia associated with HBV has also been demonstrated (10, 11). Therefore, it may not be surprising that the cutaneous manifestations observed in the current patient apparently improved along with a decrease in the serum cryoglobulin and HBV-DNA levels following the initiation of oral entecavir in combination with plasmapheresis. However, the clinical impact of antiviral treatment with entecavir in symptomatic HCV-related cryoglobulinemia has been found to be associated with chronic HCV infection, and antiviral treatment with interferon in combination with ribavirin has been shown to have a clinical benefit in patients with symptomatic HCV-related cryoglobulinemia (2, 6, 7). On the other hand, a few investigators have shown the significance of HBV infection in the development of mixed cryoglobulinemia (8, 9), and a beneficial effect of antiviral treatment with entecavir on symptomatic cryoglobulinemia associated with HBV has also been demonstrated anecdotally (10, 11). Therefore, it may not be surprising that the cutaneous manifestations observed in the current patient apparently improved along with a decrease in the serum cryoglobulin and HBV-DNA levels following the initiation of oral entecavir in combination with plasmapheresis. However, the clinical impact of antiviral treatment with entecavir in subjects with HBV-related mixed cryoglobulinemia should be evaluated more carefully, since our patient ultimately required PSL due to the limited therapeutic benefits of entecavir combined with plasmapheresis.

Although the pathogenesis of mixed cryoglobulinemia in patients with HBV remains to be delineated, similar processes to those proposed in cases of hepatitis C, such as the emergence of B-cell populations producing polyclonal cryoglobulins and the subsequent positive selection of B-cells releasing monoclonal cryoglobulins, may be involved (1, 2). Indeed, a potential association between the development of lymphoproliferative disorders and HBV infection has been demonstrated (12). Otherwise, there may be a common pathological background, such as genetic susceptibility or decreased hepatic clearance of abnormally produced cryoglobulins, among subsets of patients with viral hepatic injuries (1, 13, 14). Although the resolution of cryoglobulinemia by abrogation of viral replication is not exceptional (1, 2, 10, 11, 15, 16), it is reasonable to consider that our patient may have acquired a monoclonal B-cell population whose production of cryoglobulins was no longer suppressed by the antiviral treatments.

The use of corticosteroids with or without immunosuppressants has been of interest in controlling life-threatening cryoglobulinemic inflammatory manifestations before the administration of antiviral agents, especially in cases complicated by HCV (1, 2, 17, 18). Some of the reasons for the deferred administration of antiviral agents include the risk of increased drug toxicity and exacerbation of the underlying vascular injuries due to the immunomodulatory and antiangiogenic effects of the drugs. Therefore, it is currently recommended that antiviral treatment should be commenced after an acute flare of the disease has been suppressed (18). One may argue that such therapeutic regimens may accelerate HCV replication, with potentially detrimental effects on the underlying liver disease; however, the relationship be-

Figure 2. The time course of the patient. The height of the upper gray area in the plot demonstrates the arbitrary severity of the ulcerative lesions. The corresponding time points of each panel in Fig. 1 are also demonstrated at the top. Note that the decreased levels of serum C3 and C4 were maintained throughout the observation period despite the fluctuation of the ulcerative skin lesions. The date of admission to our hospital in August 2011 was defined as clinical day 0. CRP: C-reactive protein, UD: undetectable.
between immunosuppression and HCV reactivation is less clear than that for HBV infection (19, 20). Indeed, the reactivation of HBV replication in patients receiving immunosuppressive treatment is a well-recognized and often reported serious complication of clinical importance (3, 4). Consequently, the treatment of cryoglobulinemic vasculitis with corticosteroids and immunosuppressants in patients with HBV infection may be more deleterious than when it is performed in cases complicated by HCV. Moreover, steroid-mediated HBV reactivation and replication have been suggested to occur via specific glucocorticoid response elements in the HBV genome, further emphasizing the growing scope and complexity of this problem (21). In this regard, it is strongly recommended that prophylactic antiviral agents should be administered to HBV carriers starting treatment with immunosuppressive therapy (3, 22, 23). The appropriate duration of antiviral treatment in patients with various types of rheumatic diseases and chronic HBV infection remains to be delineated; however, an agent with a low risk for HBV resistance, such as entecavir, is preferred in cases requiring long-term immunosuppression (3, 22-25). Finally, the clinical impact and optimal point of administration of antiviral treatments in cryoglobulinemic patients with hepatitis B and those with hepatitis C should be evaluated separately.

Currently, it remains unclear whether entecavir is also beneficial for the treatment of quiescent HBV carriers with symptomatic cryoglobulinemia. Nevertheless, the clinical course of the current patient is compatible with the concept that antiviral treatment with entecavir is not only an acceptable first-line choice for the treatment of cryoglobulinemic vasculitis, but should also be considered to be a mandatory prophylactic agent that should be administered prior to steroid treatment (3, 10, 11, 22). Otherwise, in this case, the use of rituximab combined with a prophylactic antiviral agent may have been useful as an alternative therapeutic option (4), since the PSL given for the relapsed purpura seemed to have limited benefit in the current patient. It may not be surprising that the decreased levels of serum C3 and C4 were maintained throughout the observation period, despite the fluctuation of the ulcerative skin manifestations, since the poor relationship between the degree of hypocomplementemia and clinical vasculitis is not exceptional (26, 27). At present, there is insufficient evidence regarding the ideal agent among subjects similar to our patient who require additional immunosuppression due to persistent cutaneous lesions.

There have been several reports demonstrating the therapeutic benefits of plasmapheresis in subjects with cryoglobulinemic vasculitis (2, 5, 17, 28). The monotherapeutic cryofiltration performed in the current patient did not improve her deteriorated renal function, which should be related to her cryoglobulinemic glomerular injuries (4, 28); however, it did seem to have at least some benefit for the cutaneous lesions. Nevertheless, the significant reduction in the serum IgG level confirmed in our patient during treatment with cryofiltration, which has been linked to a significant risk of various types of infections (29), led us switch to PEX, since FFP supplies normal plasma constituents, including globulins, that can induce beneficial immunomodulatory effects, such as alterations in the idotype/anti-idotype antibody balance (30). However, there is no information available regarding the appropriate mode of plasmapheresis for the treatment of cases of mixed cryoglobulinemia. Consequently, the optimal management of cryoglobulinemic patients complicated by HBV can be determined only when more experience with cases similar to ours has accumulated.

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

References
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