Hepatitis C Virus-associated Neuropathy Accompanied by Eosinophilic Vasculitis and Granuloma Formation

Natsuko Yuki1, Akira Yoshioka2, Rei Yasuda1, Takuma Ohmichi1 and Nobuyuki Oka3

Abstract

We herein report the case of a patient with hepatitis C virus (HCV)-associated neuropathy with atypical pathological findings of a biopsied sural nerve. A 48-year-old man was admitted for a gait disturbance. Purpura and edema on the legs and hyperalgesia on the distal extremities were noted. The plasma HCV viral load was high, and cryoglobulin was positive. In the biopsied sural nerve, perivascular eosinophilic infiltration was associated with extravascular granuloma formation in the epineurium. The patient’s symptoms disappeared following treatment with interferon-α and ribavirin. The present case suggests that HCV infection can lead to peripheral neuropathy associated with eosinophilic infiltration and granuloma formation.

Key words: hepatitis C virus, neuropathy, eosinophilic vasculitis, granuloma formation, eosinophilic granulomatosis with polyangiitis

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Introduction

Hepatitis C virus (HCV)-associated neuropathy is a common neurological complication in HCV-infected patients (1, 2). It is often associated with mixed cryoglobulinemia (MC), and small-sized vessel vasculitis is usually observed on nerve biopsies (3-5). The vascular deposition of HCV viral particles containing MC and perivascular inflammatory infiltrates has been postulated as a disease mechanism (5-8). HCV is a lymphotropic virus, and the inflammatory cells usually consist of monocytes and lymphocytes (3, 9). We herein report the case of a patient with HCV-associated neuropathy with atypical pathological findings (perivascular eosinophilic infiltration associated with extravascular granuloma formation in a sural nerve biopsy specimen).

Case Report

A 48-year-old Japanese man with no previous history of bronchial asthma, allergies or drug use was found to have liver dysfunction at 17 years of age. The patient noticed purpura and edema on both legs on colder days in February 2006, as well as paresthesia of the right arm and bilateral legs. Although the purpura and edema disappeared spontaneously, the paresthesia remained. In November 2007, he experienced severe diarrhea, accompanied by pain and edema of the legs. His symptoms developed gradually over three weeks in association with hematuria. In December, the patient was admitted to our center due to a gait disturbance associated with pain and edema of the legs, diarrhea and hematuria. A physical examination revealed purpura and edema of the legs. The patient exhibited no disturbance of consciousness or cranial nerve involvement, although he displayed dysesthesia, hyperalgesia and pallhypoesthesia of the distal lower extremities. The sensation of touch and position was preserved. No muscular weakness or atrophy were noted in the limbs, and deep tendon reflexes were normal. Babinski’s sign was absent. A urinalysis showed no proteinuria or hematuria. The creatinine clearance was 110.5 mL/min, and urinary sediment was unremarkable. Hematological studies showed a white blood cell count of 5,300/μL, with an eosinophil fraction of 355.1/μL. The serum IgG and IgE levels were 1,248 mg/dL and less than 25 IU/mL, respectively. Other tests included the following results: blood glu-
cose, 238 mg/dL; C-reactive protein, 1.22 mg/dL (normal range <0.3 mg/dL); erythrocyte sedimentation rate, 23 mm/h (normal range, 1-7 mm/h); rheumatoid factor, 141 U/mL (normal range <20 IU/mL); CH50, 15 U/mL (normal range, 30-45 U/mL); C3, 80 mg/dL (normal range, 86-160 mg/dL); and C4, 2 mg/dL (normal range, 17-45 mg/dL). Anti-nuclear antibodies were negative, as were myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibodies. Cryoglobulin was positive; however, the quantity of cryoglobulin was too small to be able to determine its type. Anti-HCV antibodies were positive. The plasma HCV viral load determined using polymerase chain reaction was high (626.0 IU/mL), and the HCV genotype was 1b. Cerebrospinal fluid findings were unremarkable. Nerve conduction studies revealed decreased sensory nerve action potentials of the sural nerves and increased motor distal latency of the tibial nerves bilaterally (Table). Magnetic resonance images of the ral nerves and increased motor distal latency of the tibial nerves also showed these findings. These symptoms resolved by maintaining a warmer temperature. He was treated with interferon-α and ribavirin from February 2008 to January 2009. The HCV viral load and level of cryoglobulin became undetectable in May 2008 and January 2010, respectively. Although the purpura and severe paresthesia of the legs relapsed on colder days until the winter of 2008, these symptoms disappeared starting in the winter of 2009. There was no improvement in nerve conduction studies (Table). While the very mild paresthesia and hyperalgesia of the legs persisted, the patient’s clinical status stabilized.

On a histopathological examination of a sural nerve biopsy specimen, perivascular infiltration of eosinophils and mononuclear cells was observed in the epineurium (Figure A). The diameter of most of the involved vessels was less than 100 μm. No necrotizing angiitis or infiltration of polymorphonuclear neutrophils was observed. Granuloma formation included epithelioid and mononuclear cells, and eosinophils were detected in the epineurium (Figure B). Epineurial vessels obstructed by the infiltration of cells into the vessel walls were noted (Figure C). A paraffin section doubly immunostained with both anti-CD68 and anti-human smooth muscle actin antibodies (Dako Japan Co., Kyoto, Japan) showed intra-intimal infiltration of macrophages and vascular recanalization (Figure D). A toluidine blue-stained section showed a decrease in the number of myelinated fibers with a predominance of larger diameter fibers (larger myelinated fiber density, 390/mm²; smaller myelinated fiber density, 2,540/mm²; normal control values for larger and smaller myelinated fiber densities are 3,340±490/mm² and 4,370±720/mm², respectively) (Figure E) (10). Some myelin ovoids and regenerating clusters were noted (Figure F). No eosinophilic infiltrates were observed in the endoneurium.

Except for the paresthesia of both legs, the patient’s symptoms resolved by maintaining a warmer temperature. He was treated with interferon-α and ribavirin from February 2008 to January 2009. The HCV viral load and level of cryoglobulin became undetectable in May 2008 and January 2010, respectively. Although the purpura and severe paresthesia of the legs relapsed on colder days until the winter of 2008, these symptoms disappeared starting in the winter of 2009. There was no improvement in nerve conduction studies (Table). While the very mild paresthesia and hyperalgesia of the legs persisted, the patient’s clinical status stabilized.

Discussion

HCV-associated neuropathy is divided into the following two categories: sensory predominant symmetrical polyneuropathy and mononeuritis multiplex-type neuropathy (11-14). Sensory predominant symmetrical polyneuropathy is usually related to MC, in which the biopsied nerve shows perivascular infiltrates composed of monocytes and lymphocytes surrounding small vessels without vessel wall necrosis (11, 12). On the other hand, patients with mononeuritis multiplex-type neuropathy exhibit severe multifocal or diffuse weakness and more frequently have systemic diseases, such as cerebral infarction, abdominal ischemia and/or mesenteric infarction associated with abdominal arterial microaneurysms and renal infarction (11, 13, 14). On nerve biopsies, vasculitis involves medium-sized arteries with the mixed inflammatory infiltration of monocytes, lymphocytes and neutrophils associated with necrotizing angiitis (11, 13, 14). Rarely, HCV infection is also associated with other types of peripheral neuropathy, such as demyelinating polyneuropathy or polyradiculoneuritis (5, 15-17). Peripheral neuropathy

**Table. Results of the Motor and Sensory Nerve Conduction Studies before and after Treatment**

<table>
<thead>
<tr>
<th>Nerve Conduction Study</th>
<th>Median Nerve</th>
<th>Tibial Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>Left</td>
<td>Normal Range</td>
</tr>
<tr>
<td>Distal latency (ms)</td>
<td>3.7 (4.0)</td>
<td>3.2 &lt;4.0</td>
</tr>
<tr>
<td>CMAP (mV)</td>
<td>8.2 (11.1)</td>
<td>12.5 &gt;5.0</td>
</tr>
<tr>
<td>MCV (m/s)</td>
<td>61.6 (59.6)</td>
<td>62.7 &gt;47.0</td>
</tr>
<tr>
<td>F-wave occurrence (%)</td>
<td>100 (44)</td>
<td>- &gt;50</td>
</tr>
<tr>
<td>Minimal F latency (ms)</td>
<td>27.6 (28.4)</td>
<td>- &lt;29.0</td>
</tr>
</tbody>
</table>

**Sensory Nerve Conduction Studies**

<table>
<thead>
<tr>
<th>Nerve Conduction Study</th>
<th>Sural Nerve</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>Normal Range</td>
<td>Left</td>
</tr>
<tr>
<td>SNAP (μV)</td>
<td>17.5 (9.7)</td>
<td>27.4 &gt;4.5</td>
</tr>
<tr>
<td>SCV (m/s)</td>
<td>57.6 (54.7)</td>
<td>65.1 &gt;45.0</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity, -: not examined, n.e.: not evoked

Data are before treatment (after treatment).
associated with perivascular eosinophilic infiltration and granuloma formation, as documented in the present case, has not been previously reported in a patient with HCV-associated neuropathy.

Similar histological findings, including angiitis with eosinophilic infiltration and granuloma formation, are observed in patients with eosinophilic granulomatosis with polyangiitis (EGPA). However, the present patient had no history of bronchial asthma, eosinophilia or any drug use. Moreover, his clinical signs resolved following treatment with interferon-α and ribavirin. Therefore, HCV infection itself seemed to play a role in the development of neuropathy in this case. Persistent HCV infection has been suggested to be a mechanism of EGPA (18). Some EGPA patients have been reported to have HCV infection (18-20). While the antigen responsible for EGPA has not been identified, it is suggested that an allergic background and hypereosinophilia may be induced by the persistent activation of CD4+ T cells (21, 22). HCV chronically infects B and T cells, stimulates the production of autoantibodies and activates cytotoxic mechanisms (18). Therefore, it is possible that, although MC may be the origin of the present patient’s vasculitis, activation of T cells by HCV infection may have resulted in eosinophilic vasculitis. Hence, granuloma formation may be associated with HCV infection and detected in patients without full manifestations of EGPA.

We herein reported the case of a patient with HCV-associated neuropathy with atypical pathological findings in a sural nerve biopsy specimen. The present case indicates that HCV infection can induce eosinophilic infiltration and granuloma formation, thus broadening the clinical spectrum of HCV-associated neuropathy.

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

References

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