Chronic Inflammatory Demyelinating Polyradiculoneuropathy in a Patient with Crohn’s Disease

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Abstract

Crohn’s disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that is frequently accompanied by systemic complications. Neuropathologies have not been well investigated as extraintestinal manifestations of CD. We herein report the case of a 36-year-old man with CD who presented with progressive weakness and numbness. A neurological examination and the results of a nerve conduction study and a sural nerve biopsy led to a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Plasma exchanges were initially effective; however, the effects gradually declined starting 10 days after the plasma exchange (PE). These results suggest that humoral factors may play an important role in CIDP associated with CD.

Key words: chronic inflammatory demyelinating polyradiculoneuropathy, Crohn’s disease, inflammatory bowel disease, extraintestinal manifestations, neurological complications, humoral factors

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Introduction

Crohn’s disease (CD) is a relapsing transmural inflammatory disorder that can affect the entire gastrointestinal tract from the mouth to the anus. It is considered a systemic disease because it is frequently accompanied by extraintestinal manifestations, including uveitis, arthritis, ankylosing spondylitis, primary sclerosing cholangitis and erythema nodosum, among others (1, 2). Neurologic complications can also occur; however, the exact prevalence of neurologic involvement associated with CD, including peripheral neuropathy, is unknown (3). Recently, immune-mediated neuropathy has been reported in patients with CD, and this etiology is supported by the occurrence of clinical improvement following the administration of immunomodulatory agents (4-6). Neuropathies caused by vitamin deficiencies or metronidazole treatment have also been reported (7, 8). A few cases of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been reported (4-6, 9) as a disturbance of the peripheral nerves associated with CD; however, the clinical and pathological features of CIDP associated with CD remain incompletely understood. We herein report the case of a 36-year-old man with CD suffering from CIDP that was confirmed on electrophysiological and sural nerve biopsy studies.

Case Report

A 36-year-old man was admitted to our hospital with progressive weakness and numbness of the extremities. Numbness in the fingers and toes had emerged one year before his admission and had progressed to the wrists and groins over the three months before admission. The muscle weakness also gradually progressed in both of the patient’s upper and lower limbs, followed by instability of gait and standing. The patient’s symptoms deteriorated until he had difficulty both elevating his arm and gripping objects, while he was...
also unable to walk.

Four years before admission, the patient was diagnosed with CD based on radiological and colonoscopy findings accompanied by noncaseating granuloma in a biopsy specimen. His Crohn’s disease was moderately to severely active with small and large bowel involvement and multiple strictures as well as perianal fistulas with no history of bowel resection. The patient had been treated with mesalazine, metronidazole, ciprofloxacin, azathioprine and infliximab. Although no typical extraintestinal complications had been observed, he felt numbness in his fingers and toes beginning one year before admission. Ciprofloxacin, azathioprine and metronidazole were discontinued at that time due to the possibility for the development of peripheral neuropathy as an adverse event of these drugs. Infliximab was discontinued five months before admission due to a severe acute infusion reaction and secondary failure; however, mesalazine was continued and levofloxacin and methotrexate were added. The patient had no family history of either neurological or gastrointestinal disorders.

On admission, the patient was afebrile, and a general physical examination revealed emaciation (body mass index: 14.0) and mild tenderness in the right lower-quadrant of the abdomen. A neurological examination showed symmetric distal atrophy and weakness of the extremities (Medical Research Council grade 2/5); the right and left grip strengths were both 4 kg. Deep tendon reflexes were absent. Pinprick and temperature sensations were reduced in a stocking and glove pattern. Vibration and position sensations were reduced at the ankle and knee joints. The patient could not walk due to muscle weakness and sensory disturbance and became wheelchair-dependent. A complete blood count, liver function tests and the electrolyte levels were normal; however, the CRP level was elevated to 2.22 mg/dL and the erythrocyte sedimentation rate was raised to 52 mm/h. A cerebrospinal fluid analysis showed elevation of the total protein concentration (113 mg/dL) without pleocytosis. Extensive laboratory investigations of the patient’s serum, including the levels of immunoglobulin and vitamin B1 and the thyroid function, showed normal results, and tests for anti-nuclear antibodies, hepatitis B virus surface antigens and antibodies against hepatitis C virus, human immunodeficiency virus, anti-ganglioside, myelin-associated glycoprotein and sulfatide were negative. Magnetic resonance imaging of the spinal cord showed no abnormal findings. A nerve conduction study showed marked prolongation of distal motor latencies and minimal F-wave latencies and a conduction delay. The conduction delay was more prominent at common entrapment sites, such as the carpal tunnel, cubital tunnel and Guyon tunnel (Table, Figure). A left sural nerve biopsy revealed a moderate reduction in myelinated fiber density, increased numbers of thinly myelinated fibers and subperineurial edema. Neither inflammation nor amyloid deposition were found. A teased-fibers preparation showed frequent segmental demyelination. The patient was diagnosed with CIDP based on the criteria of the European Federation of Neurological Societies and the Peripheral Nerve Society (10).

Two sessions of therapeutic plasma exchange (PE) were performed. PE was performed consecutively for three days as one session using an albumin preparation as replacement. Throughout the entire treatment regimen, the volume of one treatment was 3,000 mL/one therapy. No problematic adverse events occurred during PE. On the third day after the first session of PE, weakness of the extremities was improved, and grip strength increased to 12 kg on both sides, but thereafter it gradually declined to 6 kg by 10 days after the treatment. The second PE session also increased the grip strength, followed by a decrease over a similar time course. A nerve conduction study conducted 20 days after the second PE session showed increased motor and sensory potential sizes with resolution of the conduction delay and shortening of the distal motor latencies (Table, Figure). There were no obvious correlations between the symptoms of CD and neuropathy. Intravenous immunoglobulin therapy (0.4 g/kg per day for five consecutive days) had the same effect as PE, resulting in increases in grip strength to 15 kg on both sides and the ability of the patient to walk with crutches. However, the patient felt fatigability and his grip strength declined to 10 kg two weeks after the administration of intravenous immunoglobulin therapy. Corticosteroid therapy, including prednisolone at a dose of 60 mg/day, as induction with maintenance therapy slowly tapered to 30 mg/day over three months achieved improvements in weakness of the extremities and grip strength to 16 kg on both sides. A nerve conduction study performed 14 weeks after the second PE, while the patient was undergoing corticosteroid therapy, showed further increases in motor and sensory potential sizes with shortening of the distal motor latencies (Figure).

Discussion

Neuropathologies as extraintestinal manifestations of CD have not yet been well investigated, although some studies have suggested that medical treatments for CD or vitamin deficiencies caused by malabsorption might be causes of neurologic disorders in patients with CD (7, 8). Peripheral neuropathy is one of the most frequently reported neurologic complications of CD (3, 11). In one study, 30% of 33 patients suffering from neuropathy associated with inflammatory bowel disease had demyelinating forms of neuropathy (4). Only six cases of CIDP have been reported in patients with CD (4-6, 9). In four of these cases, the development of CD preceded the onset of CIDP by one to 23 years, and one patient developed CD and CIDP around the same time; no information on timing was available for the sixth patient. Most patients were treated with immunotherapies such as intravenous immunoglobulin, glucocorticoids or cyclophosphamide; however, the therapeutic efficacy, and therefore the CD activity at the onset of CIDP, varied.

PE involves the removal of plasma, including antibodies and soluble mediators such as cytokines and cell growth fac-
The therapeutic effects of PE in patients with autoimmune diseases are primarily based on modulation of the humoral immune system and elimination of pathogenic autoantibodies, complement and cytokines. In addition, the removal of humoral factors may modulate cellular immunity (12). The modulatory effects of PE on the immune system do not persist over time. Indeed, our patient’s grip strength declined within 10 days of each session of PE. Currently, the pathophysiology of CD is believed to involve inappropriate inflammatory responses to intestinal microorganisms in genetically susceptible hosts (1). The components of the type 17 helper T-cell pathway are features of this inflammatory response (1), which involves proinflammatory mediators produced by immune cells in the intestines such as tumor necrosis factor-α (TNF-α), interleukin-1β, -6, -12, -23 and chemokines. These factors overlap with those responsible for the pathogenesis of CIDP (13, 14) and may modulate T-cell activation involving the peripheral nervous system to generate inflammatory lesions. The early improvement and subsequent worsening of grip strength after PE in our patient suggests that pathogenic humoral factors are crucial for the development of CIDP associated with CD.

In the present case, the electrophysiological findings characterized by nerve conduction delay at distal terminals and common entrapment sites strongly support the involvement of humoral factors in CD-associated CIDP. Nerve conduction delays at distal terminals are considered to be caused by vulnerability of the sites to humoral factors due to relative blood-nerve barrier deficiencies (15). Minor compression or trauma at common entrapment sites will cause nerve injuries and impair the blood-nerve barrier function. Few reports have previously described electrophysiological studies in patients with CIDP associated with CD; however, the electrophysiological features observed in this case suggest a vulnerability to humoral factors.

There have been several reports of peripheral neuropathy associated with TNF-α antagonist therapy, although the mechanisms underlying this phenomenon are not well understood (16). In most cases, the patients responded to withdrawal of the offending agents, and additional immunosuppressive therapy was seldom required (17-19). Nerve conduction potentials (CMAPs) and sensory nerve action potentials (SNAPs) of the median nerve before the first PE, at 20 days after the second PE and at three months after the second PE during corticosteroid therapy were recorded. Median nerve CMAPs were recorded after stimuli at the wrist, the elbow, and the axilla. Median nerve SNAPs were recorded after stimuli at the wrist.

Table. Nerve Conduction Findings before and after Plasma Exchange

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<thead>
<tr>
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<th>Plasma exchange</th>
<th>Normal limit</th>
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<tr>
<td></td>
<td>Before</td>
<td>After 20 days</td>
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<tr>
<td>Median nerve CMAP</td>
<td></td>
<td></td>
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<tr>
<td>Amp (mV)</td>
<td>12.7</td>
<td>12.7</td>
</tr>
<tr>
<td>NCV (m/s)</td>
<td>16.5</td>
<td>10.5</td>
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<tr>
<td>Tibialis nerve CMAP</td>
<td></td>
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<tr>
<td>Amp (mV)</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>NCV (m/s)</td>
<td>29.2</td>
<td>39.0</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>18.4</td>
<td>14.9</td>
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<tr>
<td>Median nerve SNAP</td>
<td></td>
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<tr>
<td>Amp (μV)</td>
<td>N.R.</td>
<td>3.3</td>
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<tr>
<td>NCV (m/s)</td>
<td>N.R.</td>
<td>25.0</td>
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<tr>
<td>Sural nerve SNAP</td>
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<tr>
<td>Amp (μV)</td>
<td>5.3</td>
<td>9.3</td>
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<tr>
<td>NCV (m/s)</td>
<td>35.7</td>
<td>50.4</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
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<td>12</td>
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<tr>
<td>ISS</td>
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<td>3</td>
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Values in boldface type are abnormal results.


The skin temperature was kept above 32°C. Median nerve CMAPs and SNAPs were recorded with stimulus sites at the wrist, the elbow, and the axilla. Tibialis nerve CMAPs were recorded at the ankle and the knee.

Figure. Compound motor action potentials (CMAPs) and sensory nerve action potentials (SNAPs) of the median nerve before the first PE, at 20 days after the second PE and at three months after the second PE during corticosteroid therapy. Median nerve CMAPs were recorded after stimuli at the wrist, the elbow, and the axilla. Median nerve SNAPs were recorded after stimuli at the wrist.
duction studies performed in those patients who developed neuropathy in response to TNF-α antagonist therapy shared no common characteristic features (18). In our patient, the neuropathy was unlikely to be an adverse event of infliximab because the neurologic symptoms worsened two months after the discontinuation of infliximab.

The exact pathophysiological and genetic connections between CIDP and CD are not completely understood. The clinical and electrophysiological responses to PE observed in our case indicate that humoral factors are important in the pathogenesis of CD-associated CIDP. However, additional cases of CIDP in patients with CD are required in order to fully understand the pathogenesis and relationship of these two diseases.

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

References