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【 CASE REPORT 】

Repeated Acute Exacerbations of Chronic Inflammatory Demyelinating Polyradiculoneuropathy Accompanied by Pain and Swelling in Distal Extremities

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Abstract:
An 81-year-old man experienced acute progression of weakness in the extremities accompanied by a fever, tenderness, and swelling in distal parts of the extremities. He had flaccid tetraparesis with fasciculations and general hyporeflexia. Nerve conduction studies indicated demyelinating sensorimotor neuropathy. A cerebrospinal fluid examination revealed elevated proteins without pleocytosis. Immunological treatments were effective, but his symptoms exhibited repeated relapse and remission phases. He was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with an acute onset. The highlight of this case is pain with inflammatory reaction recognized as red flags of CIDP, with the clinical course and electrophysiological findings compatible with CIDP.

Key words: chronic inflammatory demyelinating polyradiculoneuropathy, nerve conduction studies, red flags, fever, pain

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Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is clinically characterized by chronically progressive (over eight weeks), recurrent proximal and distal muscle weakness of all extremities accompanied by sensory disturbances (1). Several CIDP variants have been recognized, showing heterogeneous clinical features (2). Some CIDP cases present with acute progression within four weeks, which resembles Guillain-Barré syndrome (GBS) (3, 4). Other neurological disorders should be ruled out, such as motor neuron disease, diabetic neuropathy, Charcot-Marie-Tooth (CMT) disease, and systemic disorders with neuropathy, including POEMS syndrome, paraneoplastic syndrome, and vasculitic neuropathy. Especially in cases accompanied by pain symptoms and other systemic features, the clinician should reconsider an alternative diagnosis (5).

We herein report a case of recurrent acute exacerbation of CIDP accompanied by atypical physical symptoms that responded well to immunotherapy.

Case Report

An 81-year-old man with a history of prostate cancer and radiation therapy 15 years previously and no history of exposure to toxic materials noticed weakness in his bilateral arms. Ten days later, he was admitted to a city hospital and received daily oral prednisolone (15 mg/day). However, the weakness progressed rapidly, and he could not move the extremities by himself. He was transferred to our hospital for a further evaluation at three weeks after the symptoms first appeared.

On an examination, the body temperature was elevated (38.2°C) with tenderness and swelling in the distal parts of the extremities (Fig. 1), but his general medical condition was otherwise normal. No skin lesions, such as livedo reticularis, were observed. Neurological examinations revealed

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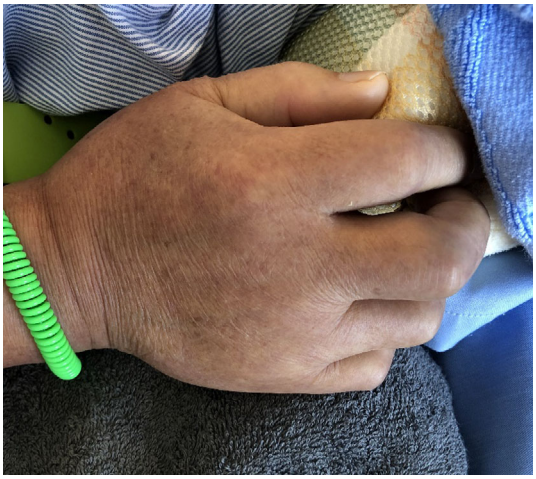

Figure 1. Swelling on the right hand. The patient also experienced tenderness in distal parts of the extremities.

alert consciousness and intact cranial nerves. He had flaccid tetraparesis (grade 1 in the biceps brachii, quadriceps, tibialis anterior muscles, and 1+ in the deltoid, adductor muscles on the Manual Muscle Strength Testing) with fasciculations in the extremities. Deep tendon reflexes were generally decreased. Vibratory sensations were decreased, whereas superficial sensations were intact. He did not have bladder or rectal disturbance. The Hughes functional grading scale was grade 4, and the inflammatory neuropathy cause and treatment overall disability sum scale (INCAT-ODSS) was 10.

Laboratory tests revealed elevated C-reactive protein (CRP; 13.12 mg/dL) and erythrocyte sedimentation rate (93 mm/h), while blood cell counts were normal. Anti-nuclear antibody and anti-neutrophil cytoplasmic antibody (ANCA) were negative. Immunoelectrophoresis detected no monoclonal gammopathy. The serum level of vascular endothelial growth factor (VEGF) was normal (402 pg/mL), and human immunodeficiency virus antibody and hepatitis C virus were negative. Anti-GM3 IgG antibody was positive, but anti-contactin-1, anti-neurofascin-155, anti-myelin-associated glycoprotein, and anti-sulfated-glucuronyl-paragloboside antibodies were negative. PMP22 gene duplication or deletion was not detected. Next-generation sequencing analyses did not reveal any pathological CMT-related gene mutations. Elevated protein (131.4 mg/dL) and a high IgG index (0.89) were detected in the cerebrospinal fluid, but no pleocytosis or malignant cells were found. Truncal computed tomography produced no findings of inflammation, malignancy, or organomegaly.

Nerve conduction studies (NCSs) produced findings of demyelinating sensorimotor neuropathy in the median, ulnar, tibial, and sural nerves (Fig. 2A-C, Table). Needle electromyography at the biceps brachii and vastus lateralis muscles revealed polyphasic and long-duration motor unit potentials. Fasciculation potentials were present at rest. Median nerve short-latency somatosensory evoked potentials (SSEPs) did not reveal any component (Fig. 3A). Magnetic resonance imaging revealed enlargement of the cervical spinal roots and brachial plexus.

We first considered a diagnosis of GBS due to the acute progression of weakness and general hyporeflexia. He was treated with immunoadsorption plasmapheresis (IAPP) followed by intravenous immunoglobulin (IVIg; 0.4 g/kg over 5 days). His motor symptoms generally improved, and he was able to walk with the aid of a walking frame. The Hughes grade was 3, and the INCAT-ODSS was 6. The decreased vibratory sensations remained unchanged. The fever, tenderness, and swelling in the distal extremities gradually disappeared. Inflammatory findings in the laboratory tests also improved. Follow-up NCSs and SSEP evaluations still produced findings for demyelination, but their amplitude and latency showed clear improvements (Fig. 2D-F, 3B).

However, 10 days after terminating the immunotherapy, muscle weakness accompanied by pain reappeared in the extremities, and he was again unable to walk. We diagnosed the patient with acute exacerbation of CIDP despite having a fever with pain and swelling in the distal extremities. He received IAPP, IVIg, and intravenous methylprednisolone (mPSL) pulse therapy (1 g over 5 days), after which his condition improved. He was started on oral administration of prednisolone (60 mg/day), but the muscle weakness acutely relapsed 10 days after the end of the mPSL pulse treatment. He was administered cyclosporine (200 mg/day) followed by IAPP and IVIg treatments, and the weakness again improved. He was discharged from the hospital and continued on regular IVIg as a maintenance treatment in our outpatient clinic, and he continued to live in his home with tapering dosages of prednisolone and cyclosporine for more than two years. The INCAT-ODSS improved to 3. Regular imaging studies did not disclose any malignancy.

Discussion

The electrophysiological findings in this patient met the criteria of definite CIDP, but these were accompanied by atypical clinical features, such as a fever, pain, and swelling in the distal extremities. These physical symptoms are usually recognized as red flags for a CIDP diagnosis and are observed in conditions mimicking CIDP, such as paraneoplastic syndrome, POEMS syndrome, and vasculitic neuropathy (5). This patient had serum VEGF levels within the normal range and no organomegaly, which did not support POEMS syndrome. We regularly followed this patient over two years and did not detect malignancy, so paraneoplastic syndrome was deniable. We did not perform a nerve biopsy and started immunotherapy immediately due to the rapid progression of muscle weakness. We were therefore unable to completely rule out the possibility of vasculitic neuropathy, which can present with clinical features mimicking CIDP.

Tanaka et al. reported a case of microscopic polyangiitis resembling CIDP with positivity for perinuclear ANCA (6). Because ANCA was negative in our patient, we considered our case to be compatible with CIDP. This diagnosis was

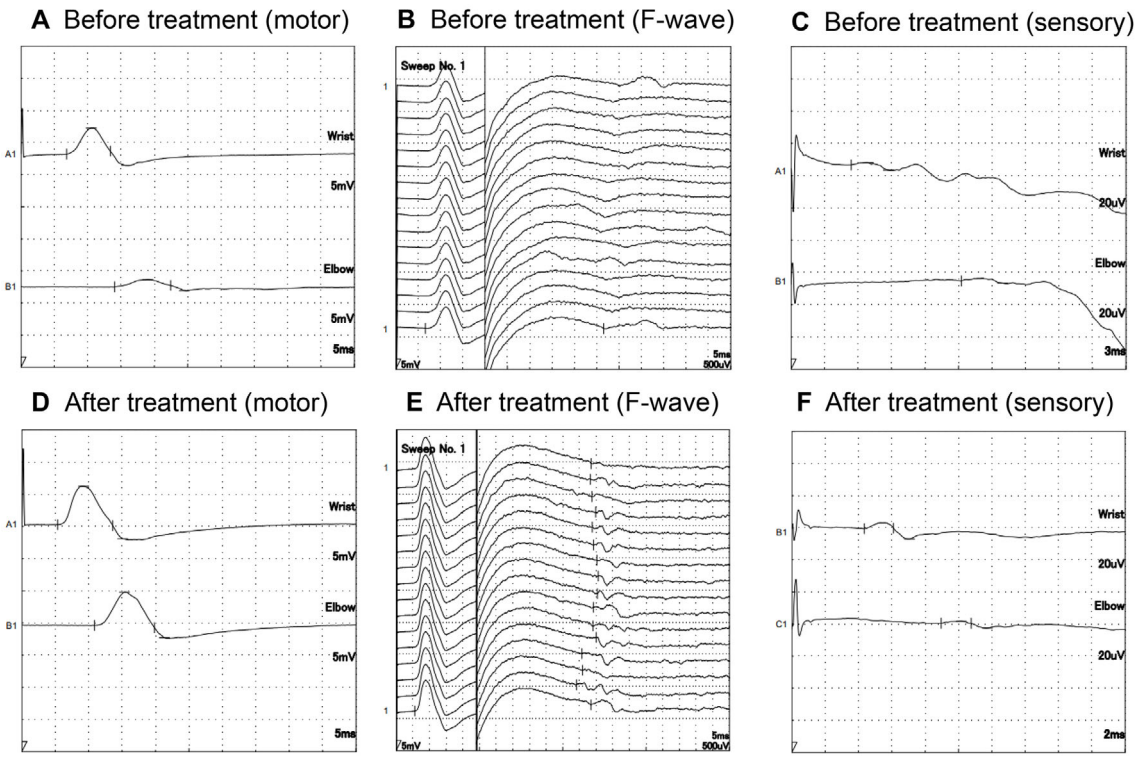

Figure 2. **Left median nerve conduction study findings before (A-C) and after (D-F) treatment. (A) Prolongations of motor distal latency and distal compound motor action potential duration, reduction of motor conduction velocity, and motor conduction block were evident. (B) An F-wave was not evoked. (C) Sensory distal latency prolongation and reductions in sensory nerve action potential and sensory conduction velocity were found. (D) Motor distal latency prolongation and conduction block were improved. (E) F-waves were observed, but the latency was prolonged after treatment. (F) Sensory distal latency prolongation and reduction of sensory nerve action potential were improved.**

Table. **Nerve Conduction Study.**

Motor nerve	Distal latency (ms)	CMAP amplitude (mV) Distal	CMAP amplitude (mV) Proximal	MCV (m/s)	F-wave latency (ms)
Left median	**6.9**	5.8	**1.7**	**26.4**	**Not evoked**
Left ulnar	**5.5**	7.8	**2.0**	**17.6**	**Not evoked**
Left tibial	**7.9**	**5.4**	**1.1**	**16.4**	**Not evoked**
Sensory nerve	**Distal latency (ms)**	**SNAP amplitude (μV)**		**SCV (m/s)**	
Left median	**5.4**	**4.5**		**25.9**	
Left ulnar	4.2	**3.6**		**33.6**	
Left sural	**4.9**	**13.6**		**30.9**	

Abnormal data is shown in bold font. CMAP: compound muscle action potential, SNAP: sensory nerve action potential, MCV: motor conduction velocity, SCV: sensory conduction velocity

also supported by demyelinating neuropathy findings in NCSs and remarkable responses to immunotherapy without any clinical findings of vasculitis, such as skin hemorrhaging or nephritis, for more than two years.

Another unique clinical feature in our case was the rapid exacerbation of muscular weakness during the relapse phases. Some patients with CIDP are known to show acute progression, and a diagnosis of GBS may subsequently be revised to CIDP (3, 4). Compared with GBS patients, acute CIDP patients are less likely to have autonomic dysfunction, facial weakness, preceding infectious symptoms, or a need for mechanical ventilation (7). These clinical signs were not observed in our patient, so he was diagnosed with acute CIDP rather than GBS.

The clinical courses and findings of examinations in our patient were similar to those in previous cases of CIDP showing repeated relapses triggered by a fever (8, 9). Mazzucco et al. reported a case of subacute-onset tetraparesis

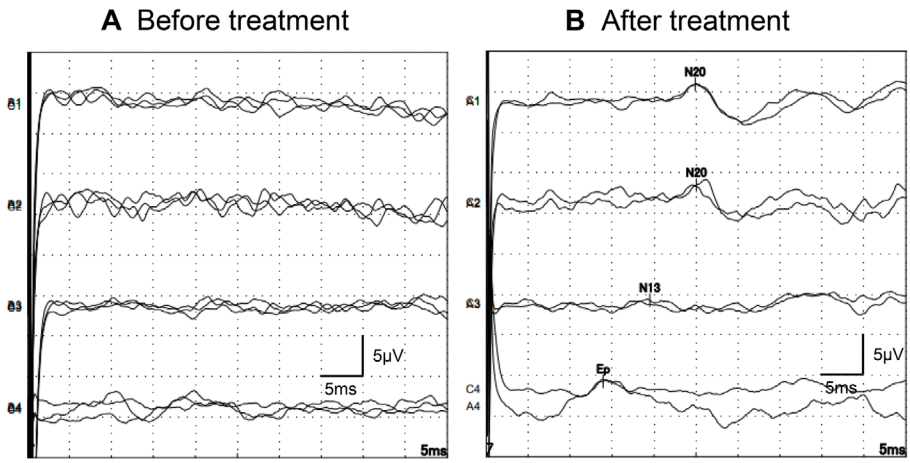

Figure 3. **Left median nerve somatosensory evoked potential findings before (A) and after (B) treatment. (A) No components were evident before treatment. (B) Components appeared, but their latencies were prolonged in the peripheral nerve after treatment.**

triggered by pyrexia in which NCSs disclosed sensorimotor demyelination, which was confirmed by a sural nerve biopsy (9). A patient reported by Ueda et al. showed acute-onset limb muscle weakness with sensory disturbance preceded by pyrexia. NCSs confirmed sensorimotor demyelination, and laboratory tests revealed that CRP and serum levels of tumor necrosis factor-α were increased in the relapse phase and decreased in the remission phase (8). Recently, Horiuchi et al. reported an atypical CIDP case showing pyrexia-associated relapses and disappearance of symptoms after improvement of a fever. The authors discussed the existence of fever-induced reversible conduction block in demyelinated fibers (10). Clinical episodes of relapses after pyrexia in these three cases were explained by Uhthoff's phenomenon. Pyrexia-triggered relapses in our patient might be due to similar mechanisms, in which a fever associated with inflammation in the peripheral nerves was able to induce reversible conduction block in the demyelinated nerves.

The supposed pathophysiology of the present case should be discussed. Although our patient presented with atypical clinical symptoms, neurological features and electrophysiological findings were compatible with typical CIDP. The antibody-mediated mechanism is thought to be a pathogenesis of typical CIDP (11). We speculated that undetermined autoantibodies might lead to inflammation and reversible conduction block in demyelinated neurons. The efficacy of IAPP and IVIg treatments support this mechanism. Another mechanism might be the existence of cell-mediated immunity, in which T-cell-induced inflammatory cytokines breakdown the blood-nerve barrier on the peripheral nerves. This mechanism is supported by the effectiveness of corticosteroids and cyclosporine in our patient.

Our case presented with atypical clinical signs of a fever, tenderness, and swelling in the distal extremities, which constitute red flags of CIDP. However, the clinical course and electrophysiological findings were compatible with a CIDP diagnosis. Although a clinical diagnosis is practically challenging in cases accompanied by atypical features matching the red flags of a clinical diagnosis, an immediate and accurate diagnosis is crucial due to CIDP being a treatable neurological disease.

Written informed consent was obtained from the patient for the publication of this case report.

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

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