INTERNAL MEDICINE

□ CASE REPORT □

Polyethylene Glycol Interferon α-2b-induced Immune-mediated Polyradiculoneuropathy

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Abstract

Polyethylene glycol-interferon α (PEG-IFNα) has been used as the standard treatment for hepatitis C virus (HCV) infection. There have been no previous reports of polyradiculoneuropathy with anti-ganglioside antibodies induced by PEG-IFNα-2b. We report a 59-year-old man who developed polyradiculoneuropathy during treatment with PEG-IFN α-2b for chronic HCV infection. Serum levels of anti-asialo-GM1 (GA1) and anti-GM1 antibodies were elevated. Cessation of therapy with double filtration plasmapheresis resulted in marked improvement in his symptoms accompanied by a reduction in the antibody level. PEG-IFN α-2b may induce peripheral neuropathy mediated by anti-GA1 and anti-GM1 antibodies.

Key words: pegylated interferon alpha, hepatitis C infection, polyradiculoneuropathy, anti-ganglioside antibody

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Introduction

There are millions of patients worldwide with chronic hepatitis C virus (HCV) infection. The current standard care for chronic hepatitis C is combined therapy with ribavirin and interferon. Recently, the pegylated form of interferon α (PEG-IFN α) has become the mainstream treatment for chronic hepatitis C in place of other forms of IFN α. An enhanced IFN molecule produced by covalent attachment of a polyethylene glycol moiety to IFN α shows more sustained virological responses than unmodified IFN α (1). Two types of PEG-IFN, PEG-IFN α-2a and PEG-IFN α-2b, are currently available, and both have been shown to have significantly superior efficacy to non-pegylated interferons (1). Treatment with non-pegylated type IFN has been reported to be complicated by various types of peripheral neuropathy, including demyelinating polyneuropathy, axonal neuropathy, and vasculitic neuropathy (2-4). However, PEG-IFN-related neuropathy is rare, and anti-ganglioside antibodies induced by PEG-IFN treatment have not been reported (5-7). Here, we report the first case of polyradiculoneuropathy with anti-ganglioside antibodies induced by PEG-IFN α-2b.

Case Report

A 59-year-old man was diagnosed as having chronic hepatitis type C in 1993 at age 47. No improvement was observed with non-pegylated type IFN α therapy in 1993 or with non-pegylated type IFN α-2b and ribavirin combined therapy in 2003. These therapies did not have any adverse effect. The patient began a third round of combined therapy consisting of PEG-IFN α-2b (100 μg, once per week) and ribavirin (800 mg/day) in March 2005 at age 59. In June, ribavirin was reduced to 200 mg/day because of pancytopenia. During these treatments, the patient had not suffered from any other infectious disease. In September, the patient developed muscle weakness in the legs, which progressed gradually and in November he sometimes fell while walking. On admission to the Orthopedics Department of our hospital with leg injury after falling in December, he was found to have muscle weakness in the bilateral arms as well as legs, and dysesthesia in the distal parts of the extremities. He became wheelchair-bound in late December

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Table 1. Results of Nerve Conduction Studies

	Motor nerve conduction studies							
	median (right)		ulnar (right)		tibial (left)		peroneal (left)	
	initial	follow up	initial	follow up	initial	follow up	initial	follow up
Distal latency(ms)	3.8 (<4.0)	3.42	2.9 (<3.5)	2.76	**8.25** (<5.1)	4.26	**5.60** (<4.8)	**4.88**
Distal CMAP(mV)	10.82 (>3.5)	11.72	11.21 (>2.8)	10.33	**2.21** (>2.9)	4.40	3.80 (>2.0)	2.19
Proximal CMAP(mV)	10.39	11.41	10.32	10.10	2.97	2.62	2.23	1.95
Conduction verocity(m/s)	54.8 (>48)	57.2	**46.9** (>50)	57.0	**38.9** (>41)	43.6	**30.1** (>42)	**36.2**
Minimum F-wave latency(ms)	30.78 (<31)	25.34	**33.60** (<32)	28.60	42.8 (<58)	53.7	**59.1** (<57)	55.1
F-wave ocurrence(%)	**37** (>62.5)	100	**18** (>62.5)	68	87 (>62.5)	81	**18** (>62.5)	81

	Sensory nerve conduction studies					
	median (right)		ulnar (right)		sural (right)	
	initial	follow up	initial	follow up	initial	follow up
SNAP peak latency(ms)	3.2 (<3.7)	3.38	2.98 (<3.2)	3.26	NR(<4.5)	4.42
SNAP amplitude(μV)	**5.29** (>10)	19.8	8.00 (>8)	17.39	NR(>5.0)	**2.50**
Conduction velocity(m/s)	58.4 (>51)	53.9	63.7 (>50)	52.1	NR(>34)	**33.9**

Abnormal values in bold. Normal values in parentheses. CMAP, compound muscle action potential; SNAP, sensory nerve action potential; NR, no response. The initial studies were performed prior to the cessation of PEG-IFNα-2b, and the follow-up were performed 2 month after.

2005, and was transferred to the Neurology Department in early January 2006.

Neurological examination revealed moderate proximal dominant weakness (2-3/5 on the Medical Research Council Scale) in all extremities, which was more prominent in the lower limbs, with slight atrophy. Tendon reflexes were reduced and absent in the upper and lower extremities, respectively. He could not stand or walk without assistance. Sensory examination revealed mild hypesthesia in a glove and stocking distribution. On blood analysis, rheumatoid factor and antinuclear antibodies were negative, creatine kinase was not elevated (174 IU/L; normal, 86-287 IU/L), erythrocyte sedimentation rate was prolonged (68.0 mm in an hour), and cryoglobulins were positive (type not determined). Hepatitis C virus RNA was positive (6.1 KIU/mL; normal, <5.0 KIU/mL) and liver enzymes were elevated with serum aspartate aminotransferase of 87 IU/L (normal, 10-48 IU/L), alanine aminotransferase of 99 IU/L (normal, 3-50 IU/L), and gamma-glutamyltranspeptidase of 77 IU/L (normal, 11-48 IU/L). Serological tests for anti gangliosides antibodies by enzyme-linked immunosorbent assay (ELISA) (8) indicated that anti-asialo-GM1 (anti-GA1) IgM antibody was strongly positive (OD 0.984; normal, <0.4), and that anti-GM1 IgM antibody was mildly positive (OD 0.293; normal, <0.1). IgG type anti-GM1 and anti-GA1 antibodies, and other anti-ganglioside antibodies including IgG and IgM type GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1 b, and Gal-C were all negative. Cerebrospinal fluid analysis revealed slight elevation of protein concentration (45 mg/dL; normal, 10-40 mg/dL) without pleocytosis. Electrophysiological studies indicated prolonged distal motor latency in the peroneal and tibial nerves, reduced motor conduction velocities in the ulnar, tibial, and peroneal nerves, reduced occurrence rates of F-waves in the median, ulnar, and tibial nerves, and absent sensory nerve action potentials in the sural nerves (Table 1); there were no conduction blocks or temporal dispersion. Needle EMG demonstrated long duration, high amplitude, and polyphasic potentials in the adductor magnus and tibialis anterior muscles. Sural nerve biopsy revealed no inflammatory infiltrates or vasculitis in Hematoxylin and Eosin stained specimens, but mild axonal degeneration (2.8%) and demyelination (6.4%) in teased fiber preparations.

We diagnosed his illness as PEG-IFN α-2b-induced polyradiculoneuropathy, and discontinued PEG-IFN and ribavirin combined therapy on January 5, 2006. The limb weakness showed gradual improvement after cessation of therapy. As elevation of anti-ganglioside antibodies suggested the neuropathy to be immune-mediated, we performed double filtration plasmapheresis (DFPP) three times beginning in early February 2006. Improvement of the patient's symptoms was accelerated after DFPP treatment. He became able to walk without assistance by March 2006, and the results of nerve conduction studies also improved (Table 1). In late March, serum IgM type anti-GA1 antibody titer measured by ELISA was found to be reduced (OD 0.596; normal, <0.4), and anti-GM1 antibody became negative (OD <0.1). These titers were confirmed by concurrent measurement of pre- and post-treatment serum. He was discharged from our hospital at the end of March, and there has been no recurrence of the neuropathy for more than one year. In March 2007, serum IgM type anti-GA1 antibody was further reduced (OD 0.255; normal, <0.4), and anti-GM 1 antibody was still negative (OD <0.1).

Discussion

The neurological disorders after the PEG-IFN α-2b and ribavirin combined therapy in this patient were characterized by clinical and electrophysiological findings compatible with polyradiculoneuropathy and the presence of IgM type anti-GA1 and anti-GM1 antibodies that paralleled the disease activity. Although this patient had cryogloblinemia, his sural nerve biopsy findings and electrophysiological findings were not compatible with vasculitic neuropathy, and he did not have any other autoimmune disease.

The patient's polyneuropathy progressed gradually during the period of treatment with PEG-IFN α-2b, and the cessation of the therapy resulted in improvement of the symptoms and electrophysiological abnormalities. Moreover, this patient had not developed polyneuropathy after the previous treatment with non-pegylated type IFN α-2b and ribavirin. These findings suggest a diagnosis of immune-mediated polyradiculoneuropathy induced by PEG-IFN α-2b, but not by IFN α-2b itself or ribavirin, although the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP) occurring in association with, but not caused by PEG-IFN treatment (6) cannot be ruled out.

Antibodies to GA1, a type of neutral glycolipid, have been reported to be found in some patients with neuromuscular diseases, including Guillain-Barré syndrome (GBS) (9), multiple motor neuropathy (MMN) (10), CIDP (11), and ataxic neuropathy (12). However its pathological implications are not well understood. As the GA1 epitope is contained in the myelin of the peripheral nervous system (13), anti-GA1 antibody could be associated with demyelination of peripheral nerves. Antibodies to GM1, an acidic glycolipid, are detected in various peripheral neuropathies, including CIDP, GBS, and MMN (14-16). Both IgG and IgM type anti-GM1 antibodies are related to peripheral neuropathies; the latter is related to MMN (15) and the former to GBS (16). Since the titers of both IgM type anti-GA 1 and anti-GM1 antibodies paralleled the disease activity in this patient, it could be possible that anti-GA1 antibody and/or anti-GM1 antibody were associated with motor-dominant polyradiculoneuropathy. There have been no previous reports of patients positive for anti-GA1 or anti-GM1 antibodies in neuropathies with hepatitis C infection or IFN treatment.

Non-pegylated type IFN may induce autoantibodies or trigger autoimmune disease (17). Neuropathies that may become exacerbated or develop further during treatment with non-pegylated type IFN include demyelinating neuropathy (2), axonal neuropathy (4), and vasculitic neuropathy (3). In the patient reported here, we speculate that the anti-GA1 and GM1 autoantibodies induced by PEG-IFN α-2 b played a role in the pathogenetic mechanism of demyelinating neuropathy. The mechanism underlying the generation of these autoantibodies would be related to an epitope formed by pegylation of IFN α-2b, because only pegylated type IFNα-2b, but not non-pegylated type, caused neuropathy in this patient. The covalent attachment of a PEG moiety to IFNα-2b may cause the conformational change, which would stimulate the immune system to produce anti-glycolopid antibodies. The improvement of the clinical findings and the electrophysiological data suggested that this patient had a demyelinating disorder. There was no evidence of vasculitis associated with cryoglobulinemia in this patient. The effectiveness of drug withdrawal and plasmapheresis supported this speculation regarding the pathomechanism, i.e., PEG-IFN α-2b-induced, immune-mediated demyelination, in which anti-GM1 and GA1 antibodies were involved.

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