

CASE REPORT

Acute inflammatory demyelinating polyneuropathy associated with pegylated interferon α 2a therapy for chronic hepatitis C virus infection

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Abstract

The combination of pegylated interferon (Peg-IFN) and ribavirin is the standard of care for chronic hepatitis C virus (HCV) infection treatment. In general, common side effects related to this combination therapy are mild and are very well tolerated. However, peripheral neuropathy including demyelinating polyneuropathy related to Peg-IFN is extremely rare. We present the first case of an acute inflammatory demyelinating polyneuropathy (AIDP) associated with Peg-IFN- α 2a (Pegasys) after 16 wk of a combination therapy with Pegasys and ribavirin in a 65-year-old woman with chronic HCV infection. She developed tingling, numbness, and weakness of her upper and lower extremities and was hospitalized for acute neurological deficits. Her clinical course, neurological findings, an electromyogram (EMG), nerve conduction studies (NCS), muscle biopsy, and a sural nerve biopsy were all consistent with AIDP likely related to Pegasys use. The patient recovered completely with the use of intravenous immunoglobulin (IVIg) including physical therapy and neurological rehabilitation. It is very important that gastroenterologists and/or hepatologists recognize this rare neurological complication related to Peg-IFN treatment very early, since it requires a prompt discontinuation of therapy including an immediate referral to a neurologist for the confirmation of diagnosis, management, and the prevention of long-term neurological deficits.

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INTRODUCTION

The combination of Peg-IFN and ribavirin has been shown to be an effective treatment for chronic hepatitis C. Overall, the common side effects associated with these two drugs are well known. The common side effects of IFN include flu-like symptoms and psychiatric symptoms such as depression, suicidal ideation, irritability, nervousness, and insomnia^[1-3]. Less common side effects include hematopoietic suppression, reversible hair loss, hearing loss, retinopathy, dermatitis, seizures, and the development or exacerbation of autoimmune diseases such as thyroid dysfunction, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, vitiligo, type 1 diabetes, and myasthenia gravis^[1-5]. Neurological complications, however, are rare. Only some publications reported on IFN-related peripheral neuropathy including sensory neuropathy^[6,7]. In addition, rare neurological complications such as vasculitic neuropathy, autonomic neuropathy, Bell's palsy, and chronic inflammatory demyelinating neuropathy (CIDP) related to IFN use have also been documented in the literature^[1,5,8,9]. Here we present the case of a severe AIDP that developed at wk 16 of Pegasys therapy.

CASE REPORT

A 65-year-old white female presented to liver clinic at the University of Chicago Medical Center for chronic hepatitis C treatment. The initial physical examination was unremarkable with the exception of spider angiomas in her neck and face, and bilateral palmar erythema. Initial liver profile included aspartate aminotransferase (AST) 56 (8-37) IU/mL, alanine aminotransferase (ALT) 67 (8-35) IU/mL,

total bilirubin 0.6 mg/dL, alkaline phosphatase 77 IU/mL, albumin 4.8 g/dL, and prothrombin time (PT) 13.1 s. Serum viral load was estimated to 2414896 IU/mL with a genotype 1a. A liver biopsy examination revealed a grade I and stage III liver disease with a focal bridging fibrosis. The patient participated in a clinical trial for chronic hepatitis C and received Pegasys 180 µg subcutaneously per week and ribavirin 1000 mg/d in divided doses orally. HCV RNA levels decreased to 416 IU/mL after 12 wk of therapy, indicating an early viral response (EVR).

Approximately 13 wk after start of the treatment, the patient presented to the University of Chicago hospital with a 24 h onset of fever, chills, nausea, vomiting, headache, and fatigue. Her chest X-ray and CT scan of chest demonstrated a right upper lobe pneumonia. A cerebrospinal fluid (CSF) analysis revealed the presence of single WBC (monocyte), glucose levels of 74 mg/dL within the normal range, and a protein level of 15 mg/dL. However, her sputum culture grew pneumococci requiring treatment with vancomycin, ceftriaxone, and moxifloxacin for pneumonia. Pegasys and ribavirin treatment thus was temporarily discontinued. The patient was discharged home with oral moxifloxacin medication and recovered from pneumonia. However, shortly after discharge, the patient developed a macular rash on the anterior and posterior chest wall with an extension of rash into the anterior abdominal wall, which was attributed to the use of antibiotics. Two weeks after the onset of pneumonia (wk 15), the patient was restarted with Pegasys and ribavirin. Unfortunately, she reported tingling, numbness, and weakness of her lower extremities 3 wk later (wk 16). Her neurological symptoms progressed rapidly over the course of 1 wk to the point of losing the ability to ambulate, and she became wheelchair bound. In addition, the patient also complained of tingling and numbness in the upper extremities involving the fingers and wrists bilaterally. Pegasys and ribavirin were discontinued due to an acute onset of weakness of upper and lower extremities. The patient was hospitalized again. The neurological examination revealed normal cranial nerves with normal bulk of muscles and tone; but a weak muscle strength (4/5) in the upper extremities as well as in hips, knees, and ankle dorsiflexion and ankle plantarflexion bilaterally. Other muscle groups were even weaker (3/5) including ankles and toes. Tendon reflexes were diminished significantly. Sensory examination revealed decreased light touch, pinprick, and temperature sensation from the feet to mid-calves as well as hands except vibratory sense. A clinical diagnosis of acquired, acute demyelinating sensorimotor polyneuropathy was made. Other laboratory tests included a normal complete blood count, chemistry profile, erythrocyte sedimentation rate, and C-reactive protein. Antinuclear antibodies, rheumatoid factor, human immunodeficiency virus (HIV) test, anti-GM1 (ganglioside) antibodies, serum cryoglobulin level, Epstein-Barr virus serology, and cytomegalovirus serology were tested negative. A second CSF analysis was acellular again with protein (29 mg/dL) and glucose (60 mg/dL) levels within the normal range. In addition, myelin associated glycoprotein antibody was tested negative, and immunoglobulin A level was normal including negative immunoelectrophoresis for monoclonal antibodies in CSF.

Table 1 EMG/Nerve conduction studies

	Distal latency (m/s)	Conduction velocity (m/s)	Amplitude (µV (sensory) mV (motor))
Sensory			
Right sural	NR	NR	NR
Left sural	NR	NR	NR
Motor			
Right peroneal	8.9	27	0.6
Right tibial	9.5	27	1.4
Left tibial	7.9	30	1.1
Right ulnar	6	37	3.9
Right median	7.6	49	2.4
Left median	7.8	48	1.1
F wave			
Right tibial	Unclear		
Right ulnar	42.6		
Right median	54.8		
Left median	Unclear		

NR: No response obtainable.

An EMG, NCS, and Sural nerve biopsy were consistent with an AIDP (Table 1). The patient was treated with a course of IVIG at a dose of 0.4 g/kg per day. Unfortunately, she was only able to complete 4 d of treatment due to the development of a rash and leukopenia from IVIG. The patient was subsequently discharged for physical therapy and neurological rehabilitation where she had some improvement in her ability to write, to use utensils, and to ambulate with a walker.

Even though her neurological symptoms somewhat improved after a short course of IVIG, the patient developed bilateral foot drop, loss of finger grips, and a progressive weakness and numbness in both her hands and feet four weeks later. A neurological examination revealed decreased muscle bulks in the upper and lower extremities distally. Muscle strength was weaker (3/5) in finger abduction, plantar flexion and dorsiflexion bilaterally with bilateral foot drops. Tendon reflexes were 2/4 in the upper extremities but diminished significantly in the lower extremities, including absent reflexes at patella and achilles bilaterally. Remainders of motor examinations were normal. Sensory examination revealed normal sensation in the upper and lower extremities except absence of all modalities of sensation at her toes excluding sense of vibration and decreased pinprick sensation below the knees. Laboratory findings were again negative including anti-Sjogren's syndrome A (SSA) and Sjogren's syndrome B (SSB). Subsequently, a sural nerve biopsy and a gastrocnemius muscle biopsy were obtained and findings were consistent with an AIDP without showing any vasculitic features (Table 1). The patient was treated with 5 d of 2nd course of IVIG and the symptoms of weakness and bilateral legs numbness markedly improved over two months. Six months after the completion of the 2nd course of IVIG, the patient felt very well and neurological symptoms and signs resolved completely without having any residual neuromuscular deficits.

DISCUSSION

Peripheral neuropathy is a rare and uncommon side effect

seen in patients treated with IFN- α . In recent years, a variety of peripheral neuropathies have been reported in patients treated with IFN including sensory neuropathy, autonomic neuropathy, Bell's palsy, and more recently, CIDP^[6-12]. As an example, one patient who received multiple cycles of IFN- α developed paresthesias of both legs and was diagnosed with sensorimotor polyneuropathy due to high cumulative effect of IFN- α ^[6]. IFN- α 2a has also been shown to have caused peripheral sensory neuropathy given for a period of twenty months^[7]. In this case, when IFN- α 2a was discontinued for 4 wk, peripheral neuropathy resolved. However, upon reinitiating the IFN- α 2a, the peripheral neuropathy re-appeared suggesting IFN-related neuropathy. Furthermore, Lapinski *et al* reported a case of peripheral polyneuropathy in a patient who received Pegasys for 1 mo followed by pegylated IFN α -2b (Pegintron) for 3 mo that resulted in paresis of hands and legs leading to a CIDP confirmed by an EMG^[9].

The more probable etiologies in our patient included infectious processes, toxins and/or drugs, and immune-mediated processes leading to demyelinating neuropathies^[13]. Viral infections such as HIV and CMV have been described to cause demyelinating neuropathy^[14,15]. HIV infection can lead to peripheral neuropathy that can rapidly progress to either acute or chronic demyelinating neuropathy due to macrophage-mediated immune attachment within the endoneurial parenchyma^[16]. Since HIV test was negative in our patient this was not the cause of her neuropathy. A CMV infection in a patient with chronic HCV can present as an acute Guillain-Barre syndrome (GBS)^[15]. It has been hypothesized that host immune system mistakenly attacks own nerve cells that expressed similar epitope as of HCV or CMV antigen. Our patient had multiple CSF analysis that failed to detect CMV DNA. Therefore, our patient also did not have CMV-related demyelinating neuropathy.

Toxins and/or drugs are also common etiologies for demyelinating neuropathies, which can be acute or chronic in nature. Common toxins/drugs are barbital, sulfonamides, phenytoin, nitrofurantoin, heavy metals, carbon monoxide, industrial poisons, and certain AIDS drugs (e.g., zalcitabine, didanosine)^[13]. Our patient had no exposure to any of these above toxins or drugs other than Pegasys, ribavirin, and moxifloxacin. There are several reported cases of moxifloxacin induced peripheral sensory neuropathy including an evidence of a tendon rupture without showing demyelinating neuropathy^[17]. Similarly, ribavirin also has not been associated with any type of reported neuropathy. But Pegasys including IFN- α has been implicated to cause immune mediated CIDP during chronic hepatitis C treatment^[5,8] due to cytokine-induced apoptosis in the myelin-producing oligodendrocyte resulting in inhibition of central nervous system remyelination thus causing demyelinating neuropathy^[5,18,19]. To the contrary, IFN- α has also been shown to be a successful treatment in patients with CIDP^[8]. However, if a patient develops demyelinating neuropathy secondary to IFN use, it should be discontinued immediately since it may cause irreversible nerve damage due to inhibition of remyelination process. Two cases of CIDP have been described either with Pegasys or IFN- α use^[5,8]. In both

cases, paresthesia and muscle weakness developed 6 wk after therapy and lasted more than 8 wk suggesting CIDP. It has been shown that patients with CIDP respond to prednisone, plasma exchange, and IVIG^[5,20,21]. The time course for our patient's symptoms was not long enough to meet the criteria for a CIDP. The criteria for CIDP usually include the clinical deterioration of neurological symptoms for a period of greater than 8 wk as opposed to AIDP and/or GBS, which usually has deterioration over a period of approximately 4 wk or less^[21]. Furthermore, immune-mediated AIDP of GBS type has been reported after infection, post-vaccination, or surgery and also accounts for a significant portion of demyelinating polyneuropathies^[13]. In our patient, there was an initial high suspicion for AIDP of GBS type due to a pneumonia prior to neurological symptoms and signs. Her time course fit an acute demyelinating neuropathy given that it developed approximately 3 wk later. A typical presentation of GBS includes a significant motor weakness along with mild to moderate paresthesias. The muscle weakness typically starts in the distal muscles of the lower extremities and weakness ascends rapidly involving upper extremities. In addition, CSF analysis usually reveals an elevated protein level with normal white blood cell count. Even though our patient's presentation was suggestive of a GBS due to a preceding pneumonia, CSF analysis on multiple occasions revealed a normal CSF protein. Furthermore, our patient had significant painful paresthesias that are not commonly seen in GBS. Thus, the clinical course including normal CSF protein and painful paresthesias was not suggestive of a typical GBS, but rather suggestive of an acute immune mediated process related to Pegasys use as AIDP. The pathogenesis of AIDP related to Pegasys use is thought to be an acute immune-mediated process similar to GBS. The precise and exact immune regulatory function of IFN- α including Peg-IFN is not well understood and it is likely similar to mechanism associated with IFN induced CIDP described above^[5,18,19]. In addition, IFN- α has been reported to enhance *in vivo* and *in vitro* autoantibody production and may upregulate transcription of genes associated with class I major histocompatibility complex (MHC) antigens^[22]. It is likely that the levels of proinflammatory cytokines may trigger autoimmune phenomena in immunologically predisposed individuals when IFN is administered. Therefore, the immune system mistakenly attacks the host's nerve tissue after recognizing a molecular epitope similar to a foreign antigen and may result in acute inflammatory neuropathy^[23]. Immunomodulation with plasma exchange or IVIG usually shortens the disease process and provides the best outcome^[23]. Our patient fit this clinical picture of an acute inflammatory neuropathy and showed a quick response to IVIG therapy.

One other possible immune-related process as the etiology of the demyelinating neuropathy would be IgM binding to Myelin-Associated Glycoprotein (MAG). Demyelinating polyneuropathy with monoclonal IgM is often associated with anti-MAG autoantibodies^[24]. Our patient was negative for this antibody including negative immunoelectrophoresis suggesting this is not the case.

Vasculitic neuropathy, an autoimmune process may

also occur in association with chronic HCV infection. Generally, patients may develop a chronic symmetrical axonal sensorimotor peripheral polyneuropathy due to a necrotizing vasculitis^[25]. Subsequent treatment with IFN- α can worsen vasculitic neuropathy^[25]. In addition, there have been multiple reported cases of GBS associated with HCV related to cryoglobulinemia^[26,27]. However, our patient had an undetectable cryoglobulin level on multiple occasions, which rules out a possibility of cryoglobulin induced demyelinating neuropathy.

In conclusion, the treatment of chronic HCV infection has come a long way in recent years. Physicians and other medical providers must be aware of possible side effects, including demyelinating neuropathy in patients who are treated with IFN and/or pegylated IFN in addition to HCV/cryoglobulin related neuropathy. As we learned from our case, Pegasys may cause neurological symptoms including AIDP. In addition, it is imperative on the part of the health care providers recognize AIDP very early for the diagnosis and treatment including the prevention of a long-term neurological complication by obtaining a neurology consultation.

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