

Pericarditis and chronic inflammatory demyelinating polyneuropathy during therapy with pegylated interferon alfa-2a for chronic hepatitis C

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Abstract

We report a case of pericarditis and chronic inflammatory demyelinating polyneuropathy with biological signs of a lupus-like syndrome due to pegylated interferon alfa-2a therapy during treatment for chronic hepatitis C. The patient developed moderate weakness in the lower limbs and dyspnea. He was hospitalized for congestive heart failure. An electrocardiogram showed gradual ST-segment elevation in leads V₁ through V₆ without coronary artery disease. A transthoracic cardiac ultrasonographic study revealed moderate pericardial effusion with normal left ventricular function. Anti-DNA antibody and anti-ds DNA IgM were positive. Neurological examination revealed a symmetrical predominantly sensory polyneuropathy with impairment of light touch and pin prick in globe and stoking-like distribution. Treatment with prednisolone improved the pericarditis and motor nerve disturbance and the treatment with intravenous immunoglobulin improved the sensory nerve disturbance.

INTRODUCTION

Therapy with interferon alpha is widely accepted for the treatment of chronic hepatitis C. Secondary effects on the cardiovascular and neurological systems are rare. Acute pericarditis complicating interferon therapy has been described previously^[1-5]. Some reported interferon-related peripheral neuropathy^[6-9].

We report a case of acute pericarditis and chronic inflammatory demyelinating polyneuropathy (CIDP) with biological signs of a lupus-like syndrome during the treatment of hepatitis C infection in which standard dosage levels of pegylated interferon alfa-2a (PEG-IFN-2a) were used. We also review interferon alpha therapy and hepatitis C virus side effects on the cardiovascular and neurological systems.

CASE REPORT

In November 2009, a 67 year old man was referred to our hospital because of hepatitis C virus (HCV) infection.

Chronic active hepatitis C without signs of fibrosis was diagnosed. Chronic HCV serology was positive while HBsAg and human immunodeficiency virus (HIV) serology was negative. The patient received therapy with PEG-IFN-2a, 180 µg a wk from November 5th 2009 until November 19th 2009, because of high HCV infection. The treatment with PEG-IFN-2a was discontinued because of leg edema on December 3rd 2009. Chest radiographs showed mild cardiomegaly (CTR = 0.52). A transthoracic cardiac ultrasonographic (UCG) study showed that the size of the left ventricle and systolic function was normal. The estimated ejection was 56.1%. The early diastolic filling wave/atrial filling wave (E/A) was 1.27. Computed tomographic (CT) scanning of the chest showed no congestion, pleural effusion or pericardial effusion. Treatment with furosemide 10 mg per day and eplerenone 25 mg per day was started.

The patient was admitted to our hospital because of dyspnea, edema and paraesthesia on January 18th 2010. Blood pressure was 123/69 mmHg, pulse 101 beats/min temperature 36.9°C, respiratory rate 22/min and oxygen saturation 97% (room air). A portable chest radiograph revealed pulmonary vascular congestion without pleural effusion. An electrocardiogram (ECG) showed no ST segment elevation or T-wave abnormality. The UCG study revealed moderate pericardial effusion with normal left ventricular function. The CT scan of the chest revealed pulmonary vascular congestion, pleural effusion and pericardial effusion. An injection of furosemide 40 mg per day and carperitide 0.05 γ (µg/kg per min) were given for congestive heart failure. ECG showed gradual ST-segment elevation in leads V₁ through V₆ without elevated myocardial enzyme. After treatment of congestive heart failure, coronary angiography (CAG) was performed. The CAG showed that there was no significant coronary arterial stenosis. The left ventricular ejection fraction was 60.5% and the left ventricular end-diastolic pressure was 10 mm Hg. Right-sided cardiac catheterization revealed a right atrial pressure of 14 mm Hg, right ventricular pressure of systolic 46/diastolic 10/mean 44 mm Hg, pulmonary arterial pressure of systolic 40/diastolic 20/mean 40 mm Hg, pulmonary-capillary wedge pressure of 16 mm Hg, cardiac output of 6.9 liters per minute and cardiac index of 4.1 liters per minute per m². These data suggested diastolic heart failure.

The blood sample examination showed no minor inflammatory syndrome (CRP = 0.1 mg/dL, normal value 0-0.3 mg/dL). The hepatic enzymology was normal. The pair viral serologies (influenza, echo, coxsackie, polio and mumps) proved negative. The anti-nuclear antibody, LE test, anti-ds DNA IgG, anti-CCP antibody, anti-RNP antibody, anti-Sm antibody, anti-SS-A antibody, anti-SS-B antibody, anti-Scl-70 antibody, anti-Jo-1 antibody, anti-centromere antibody and lupus anticoagulant proved negative but anti-DNA antibody and anti-ds DNA IgM were positive. Cryoglobulin and M-protein were negative. The polymerase chain reaction (PCR) for Mycobacterium tuberculosis proved negative in the sample from stomach. A diagnosis of autoimmune pericarditis was made.

The patient became unable to walk and stand. Neurological examination revealed moderate weakness in lower limbs and a symmetrical predominantly sensory polyneuropathy with impairment of light touch and pin prick in globe and stoking-like distribution. Tendon reflexes were absent in all extremities. Romberg's test was positive. Electrophysiological studies revealed normal motor conduction velocities in the median nerves but absent in the tibial nerves and normal sensory nerve action potentials in the median nerves but absent in the tibial nerves. There was cytoalbuminologic dissociation in the cerebrospinal fluid (CSF). The protein content was elevated (68 mg/dL) although the cell count was normal (9 lymphocytes per 3 fields) in the CSF. The limbs weakness showed gradual progression after cessation of PEG-IFN-2a.

After discontinuation of interferon and initiation of prednisolone 10 mg per day, the pericardial effusion resolved within 16 d. The patient was treated with a course of intravenous immunoglobulin (IVIg) of at a dose of 0.4 g per kg per day for 5 d. The treatment with prednisolone improved the motor nerve disturbance and the treatment with IVIg improved the sensory nerve disturbance.

DISCUSSION

We report the case of a 67 year old man who developed congestive heart failure, acute pericardial effusion and gait disturbance during treatment with PEG-IFN-2a for chronic active hepatitis C viral infection.

The most common secondary effects with interferon alpha include influenza-like symptoms, headache, fatigue, fever, rigors, myalgia, thrombocytopenia and induction of autoantibodies, reported in over 30% of cases. Reported with rarer frequency are polyneuropathy, paranoia and suicidal thoughts, diabetes mellitus, retinopathy, optical neuritis, diminution of hearing, seizures, loss of libido and cardiotoxicity^[10].

The cardiac toxicity of interferon alpha is well known and uncommon. Most frequently, cardiac adverse effects of interferon alpha for HCV hepatitis are arrhythmia (atrial fibrillation, sinus bradycardia, atrioventricular block and ventricular fibrillation), ischemic cardiomyopathy, cardiomyopathy, myocardial infarction and pericarditis^[11,12]. Interferon alpha is the most cardiotoxic of the three interferons, followed by interferon beta and interferon gamma. Toxicity does not depend on the daily dose, the total amount or the duration of treatment. There are no established predisposing factors for interferon cardiotoxicity. The mechanism of interferon cardiotoxicity is unclear and probably multifactorial. Interferon evokes the release of several cytokines including tumor necrosis factor alpha and interleukin 1, 2 and 6. There is a high degree of individual variation in toxicity but most adverse events are reversible upon cessation of interferon.

A high prevalence of HCV infection has recently been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and myocarditis^[13]. Chronic infection with HCV is sometimes associated with clinical

and biological manifestation of auto-immune pathologies such as cryoglobulinemia, membranoproliferative glomerulonephritis, Sjögren syndrome, rheumatoid arthritis and systemic lupus erythematosus (SLE)^[14]. Okanou *et al* reported autoimmune phenomena in 987 patients treated with interferon alpha for HCV hepatitis^[15]. 12 patients developed hyperthyroidism, 6 hypothyroidism, 3 interstitial pneumonia, 2 rheumatoid arthritis, 2 autoimmune hepatitis, 1 SLE and 1 autoimmune thrombocytopenic purpura. Interferon alpha 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 antigens^[16]. It is likely that the levels of proinflammatory cytokines may trigger autoimmune phenomena in immunologically predisposed individuals when interferon is administered. Therefore, the immune system mistakenly attacks the host's tissue after recognizing a molecular epitope similar to a foreign antigen and may result in acute inflammation.

Peripheral neuropathy is a rare and uncommon side effect in patients treated with interferon alpha. A variety of peripheral neuropathies have been reported in patients treated with interferon including sensory neuropathy, autonomic neuropathy, Bell's palsy and chronic inflammatory demyelinating neuropathy (CIDP)^[17-22]. PEG-IFN-2a, including interferon alpha, has been implicated in causing immune mediated CIDP during chronic hepatitis C treatment^[6,23] due to cytokine-induced apoptosis in the myelin-producing oligodendrocyte, resulting in inhibition of central nervous system remyelination thus causing demyelinating neuropathy^[23-25]. Interferon may evoke potential immune disease.

To the contrary, interferon alpha has also been shown to be a successful treatment in patients with CIDP^[6]. 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. It has been shown that patients with CIDP respond to prednisone, plasma exchange and IVIG^[23,26,27]. 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 Guillain-Barre syndrome (GBS) which usually has deterioration over a period of approximately 4 wk or less^[27]. The pathogenesis of CIDP related to PEG-IFN-2a use is thought to be an immune-mediated progress similar to GBS^[23-25].

Gressens *et al*^[3] also reported a case of pericarditis during the treatment of chronic infection with HCV complicated polyneuropathy. The case of pericarditis without tamponade outside the context of a lupus-like syndrome emerged in the course of the fourth month of remission during treatment with interferon alpha in classical dosage levels. Acetylsalicylic acid had been initiated for acute pericarditis and neurological improvement was achieved through the administration of vitamin B in that case. Boonen *et al* reported a case of pericarditis during the treatment of chronic infection with HCV. This pericarditis

emerged as part of a lupus-like syndrome with clinical and biological manifestations of autoimmune pathologies^[1]. The patient was treated with chloroquine 250 mg per day and prednisone 40 mg per day in that case.

This case of pericarditis which we are reporting on emerged with resultant lupus-like syndrome caused by PEG-IFN-2a. The biological markers of autoimmune pathologies (anti-DNA antibody and anti-ds DNA IgM) were positive. Any effect from the HCV itself is quite unlikely; virus activity must have been low because the transaminases had normalized. We excluded other viral causes by the fact that pair serological tests were negative. We may reasonably attribute the diastolic heart failure to PEG-IFN-2a and the pericarditis to lupus-like syndrome. This case was simultaneously complicated by CIDP of the lower limbs.

In conclusion, pericarditis and CIDP developed during the interferon therapy with an increased protein concentration in the CSF and steroid and IVIG seemed to result in improvement. We suggest that interferon may induce an immune mediated pericarditis and peripheral neuropathy. Cardiac monitoring may be well advised including demyelinating neuropathy when using treatments based on interferon for chronic HCV infections.

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