

CASE REPORT

Severe Mononeuritis Multiplex Associated with Peginterferon-Ribavirin Therapy of Chronic Hepatitis C

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Vasculitis is a common extrahepatic manifestation of chronic hepatitis C virus infection and could be either associated with cryoglobulinemia or not.

The mechanism of peripheral neuropathy seems to be vasculitic in both cryoglobulinemic and non-cryoglobulinemic patients. Antiviral therapy with peginterferon and ribavirin usually improves symptoms of virus-induced neuropathy. Herein, we reported on a rare case of hard mononeuritis multiplex triggered by antiviral therapy in a patient without neurological symptoms before the treatment.

Keywords: Hepatitis C, Peginterferon, Mononeuritis Multiplex, Cryoglobulinemia

Introduction

Combination therapy with peginterferon and ribavirin is now the standard treatment for chronic hepatitis C virus (HCV) infection. Therapy is long-term and lasts 24 to 48 weeks depending on the virus genotype ⁽¹⁾. Myalgia, arthralgia, back pain and headache are the prominent neuromuscular and neurological adverse events of the treatment. However, they are usually not reasons for dose modification and discontinuation of therapy. Mononeuritis multiplex is a painful asymmetric asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least two separate nerve areas. Mononeuritis multiplex is associated with systemic disorders such as diabetes, vasculitis, amyloidosis, direct tumor involvement, polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, and paraneoplastic syndromes, also may be associated with some infections as Lyme disease, leprosy and acquired immunodeficiency syndrome (AIDS). Chronic hepatitis C, especially with cryoglobulinemia, may cause mononeuritis multiplex ⁽²⁾. The following case report describes a patient with severe mononeuritis multiplex during antiviral therapy of chronic hepatitis C.

Case report

A 60-year-old woman, on a routine blood test, had elevated serum alanine aminotransferase (ALT) of 78 IU/L (normal: 0-41), and serum aspartate aminotransferase (AST) of 54 IU/L (normal: 0-31). HCV antibody (anti-HCV) was positive; polymerase chain reaction (PCR) revealed 1,560,000 copies/mL of HCV RNA, genotype 1b. Her blood sugar, vitamin B12, serology for Lyme disease, antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), antineutrophil cytoplasmic antibody (ANCA), cryoglobulins, hepatitis B surface antigen (HbsAg), antibody to

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human immunodeficiency virus (anti-HIV) were all within normal limits. Physical and neurological examination were also normal. Liver biopsy showed moderate inflammatory activity and severe fibrosis. Antiviral therapy started with pegylated interferon alfa-2a, 180 µg subcutaneously (sc) once weekly and ribavirin, 1000 mg daily. During the first three months of therapy, there was no adverse events but flue-like symptoms at the beginning. PCR for HCV RNA, after three months became negative (early virological response). In the fourth month of therapy, the patient began to feel burning and tingling in her feet and right hand. The pain intensified in her legs so markedly that she was not able to walk and admitted to hospital in the fifth month of antiviral therapy. On admission, physical examination was normal. Neurological examination revealed distal weakness and decreased sensation in the thumb and side fingers of both hands; she had right foot drop and weakness of right foot eversion. Sense of vibration was depressed in both legs to the level of knees. The deep tendon reflex were normal. At that time, she had an erythrocyte sedimentation rate (ESR) of 75 mm after the first hour, white blood cell (WBC) count of $2.25 \times 10^9/L$, AST of 58 IU/L, and ALT of 45 IU/L; ANA, ANCA, complement, cryoglobulins, rheumatoid factor, blood urea nitrogen (BUN), creatinine, and protein/24 h urine were negative or within normal limits. Electroneurography revealed mixed sensory-motor neuropathy of both median nerves and right tibial and peroneal nerves. These abnormalities were consistent with mononeuritis multiplex. Antiviral therapy was discontinued and she was treated with repeated doses of intravenous immunoglobulin (IVIG), gabapentin and later on with physical therapy with improvement of neurological symptoms, despite reappearance of HCV RNA two months after cessation of antiviral therapy.

Discussion

It is well-known that vasculitis is a common extrahepatic manifestation of chronic HCV infection (2, 3). Vasculitis of vasa nervorum usually causes neuropathy. Vasculitis is either caused by mixed cryoglobulinemia or is non-cryoglobulinemic. Detectable cryoglobulins are present in about 50% of patients with HCV infection although most of them do not have symptoms related to cryoglobulinemia (4). Most patients with HCV infection and neuropathy are cryoglobulinemic. Nonetheless, Nemni *et al.*, reported that mononeuropathy or multiple

neuropathy developed more frequently in HCV-positive non-cryoglobulinemic patients than HCV-positive cryoglobulinemic patients (5). Interferon-based therapy in most cases leads to improvement of vasculitic symptoms (6, 7). Its antiviral effects decrease viral load and its antiproliferative effect could reduce cryoglobulin production by B lymphocytes. In rare cases, interferon therapy may lead to exacerbation or even a new onset of neuropathy. Its immunomodulatory effect could stimulate immune reactions with worsening of the disease. Pacifi *et al.*, had doubts about the role of interferon in acute third cranial nerve ophthalmoplegia (8). Acute autonomic and sensory neuropathy have been described after interferon alfa-2b therapy (9). It is speculated that peripheral neuropathy in HCV-positive patients treated with interferon, may also be due to direct neurotoxic effects of interferon alone. However, Brianiet *et al.*, assessed possible peripheral neurotoxicity of pegylated interferon alpha and did not find any associated occurrence (or worsening) of peripheral neuropathy or antibodies to peripheral nerve antigens in patients with HCV infection (10). Our patient had no signs of neuropathy before the treatment and developed severe mononeuritis multiplex during the therapy. She was non-cryoglobulinemic before the therapy, as she was when she developed neuropathy. In that time, there was no detectable virus in her blood. Probably, interferon modulated the immune system and caused neuropathy. It was very hard to make a decision about continuation of the antiviral therapy when the first neurological symptoms appeared. The early virological response was achieved in the patient with advanced fibrosis; but the rapid neurological deterioration was the reason for termination of the treatment. The decision about continuation of the treatment when neuropathy occurs is complex, and depends on the severity of symptoms, stage of liver disease and predictable factors for sustained virological response. Our patient improved, but peripheral neuropathy may worsen after cessation of interferon therapy (11). The clinical course of neuropathy and other vascular complications of interferon-based therapy is variable and ranges from improvement despite continuation of the therapy to severe worsening albeit termination of the treatment. In some cases, additional immunosuppressive therapy, after discontinuation of interferon therapy, leads to regression of symptoms with the risk of increased virus replication. The precise connection between HCV infection, mixed cryoglobulinemia, and neuropathy, has not been found yet; no significantly effective treatments were also found. But, we are

sure that as more people are diagnosed with HCV neuropathy, our knowledge increases. This case is very instructive for all hepatologists treating chronic HCV infection.

References

1. Hadziyannis SJ, Sette H, Jr., Morgan TR, *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med.* 2004;**140**(5):346-55.
2. Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinaemia, and vasculitis: immune complex relations. *Lancet Infect Dis.* 2005;**5**(4):227-36.
3. Cacoub P, Costedoat-Chalumeau N, Lidove O, Alric L. Cryoglobulinemia vasculitis. *Curr Opin Rheumatol.* 2002;**14**(1):29-35.
4. Lunel F, Musset L, Cacoub P, *et al.* Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. *Gastroenterology.* 1994;**106**(5):1291-300.
5. Nemni R, Sanvito L, Quattrini A, Santuccio G, Camerlingo M, Canal N. Peripheral neuropathy in hepatitis C virus infection with and without cryoglobulinaemia. *J Neurol Neurosurg Psychiatry.* 2003;**74**(9):1267-71.
6. Trebst C, Wedemeyer H, Manns MP, Tillmann H, Windhagen A. Treatment of hepatitis C virus-associated inflammatory polyneuropathy with pegylated interferon-alpha and ribavirin. *Eur J Gastroenterol Hepatol.* 2007;**19**(1):91-2.
7. Zoras C. [Therapy with peginterferon alfa in a patient with polyneuropathy caused by hepatitis C-associated vasculitis]. *Med Klin (Munich).* 2006;**101**(3):243-7.
8. Pacifici L, Passarelli F, Papa G, Cannone L, Rossini PM. Acute third cranial nerve ophthalmoplegia: possible pathogenesis from alpha-II-interferon treatment. *Ital J Neurol Sci.* 1993;**14**(7):579-80.
9. Irioka T, Yamada M, Yamawaki M, Saito Y, Mizusawa H, Miura H. Acute autonomic and sensory neuropathy after interferon alpha-2b therapy for chronic hepatitis C. *J Neurol Neurosurg Psychiatry.* 2001;**70**(3):408-10.
10. Briani C, Chemello L, Zara G, *et al.* Peripheral neurotoxicity of pegylated interferon alpha: a prospective study in patients with HCV. *Neurology.* 2006;**67**(5):781-5.
11. Lidove O, Maisonnobe T, Servan J, *et al.* [Peripheral neuropathy and hepatitis C virus infection: more than cryoglobulinemia]. *Rev Med Interne.* 2001;**22**(10):939-47.