



Short communication

Tumefactive multiple sclerosis and hepatitis C virus 2a/2c infection: Dual benefit of long-term interferon beta-1a therapy?



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ABSTRACT

Hepatitis C virus (HCV) infection has been implicated in triggering acute disseminated encephalomyelitis but not tumefactive multiple sclerosis. We report the case of a 17-year-old female who presented with a 5-day history of left hemiparesis and hemisensory loss followed by a right third nerve palsy. Tumefactive multiple sclerosis was diagnosed based on the absence of encephalopathic signs, the presence of tumefactive brain lesions, the exclusion of neoplastic and infectious causes of the lesions by biopsy, and the occurrence of relapse after a period of remission. The patient was at risk for HCV infection due to parenteral drug abuse and multiple sexual partners. Serial HCV antibody tests and RNA polymerase chain reaction assays revealed acute HCV infection and genotyping showed HCV genotype 2a/2c. She was treated with high-dose methylprednisolone and discharged with only mild left hand weakness. Interferon beta-1a 30 mcg was administered intramuscularly once a week. Remission from HCV infection was achieved in three years without standard anti-HCV therapy. This case suggests that CNS myelin is a potential target of the immune response to HCV 2a/2c infection, the HCV 2a/2c virus may be involved in triggering autoimmune tumefactive brain lesions, and interferon beta-1a is effective against HCV 2a/2c infection. We recommend serial HCV antibody testing and HCV RNA PCR assay, preferably with HCV genotyping, in all patients with acute inflammatory demyelinating diseases of the CNS.

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1. Introduction

Clinically isolated syndrome (CIS) is diagnosed when a person shows signs and symptoms of multiple sclerosis (MS) for the first time and dissemination in time is not yet evident [1]. In the vast majority of these patients, magnetic resonance imaging (MRI) will show typical MS lesions in the brain. Rarely, atypical white matter lesions are seen that are large, oval-shaped, well circumscribed, and ring-enhancing. These lesions resemble tumors or abscesses and are referred to as *tumefactive lesions*. A person with tumefactive brain lesions who experiences one or more relapses is said to have *tumefactive MS* [2]. The most important differential diagnosis of CIS with tumefactive lesions is acute disseminated encephalomyelitis (ADEM). ADEM is a monophasic inflammatory disease characterized by multifocal poorly circumscribed and non-tumefactive demyelinating brain and/or spinal cord lesions [3].

The latest expert consensus requires the presence of encephalopathic symptoms to diagnose ADEM [4].

A variety of viruses have been implicated in triggering ADEM, including varicella, mumps, measles, rubella, influenza, Coxsackie B virus, herpes simplex virus, Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) [5]. To our knowledge, there is still no evidence of a link between viruses and tumefactive MS.

The etiopathogenetic status of tumefactive MS relative to ADEM and typical MS remains unclear. Tumefactive MS has been viewed as a distinct variant of MS [6], as a recurrent disseminated encephalomyelitis [7], and as a disorder that is intermediate between MS and ADEM [8]. A more recent study of 168 patients with biopsy-confirmed tumefactive demyelinating disease suggests that these cases represent a part of a heterogeneous clinical and radiographic spectrum of MS [9]. Here we report a case of tumefactive MS in the setting of acute HCV 2a/2c infection.

2. Case description

The patient is a 17-year-old female with a 6-day history of left hemiparesis, left upper extremity numbness, and diplopia. She had multiple sexual partners and injected illicit drugs but her HIV and hepatitis

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virus tests were negative in the past. On admission, she was afebrile with normal vital signs and no meningismus. Physical exam revealed an awake and attentive patient with a right third nerve palsy and left face, sternocleidomastoid, and trapezius weakness. Distal muscle weakness was noted in the left upper (3/5) and lower (4/5) extremities. Sensation to pinprick was also reduced over the left upper extremity. Routine blood tests were normal, except for elevated transaminase levels (AST = 789 U/L, ALT = 1186 U/L). Brain CT scan was normal. Cerebrospinal fluid (CSF) was clear with 1 WBC/ μ L, 14 RBC/ μ L, and normal protein (28 mg/dl), glucose (49 mg/dl), and LDH (14 U/L). CSF bacterial, fungal, and viral studies were all negative. Screening tests for HAV, HBV, and HCV were also negative.

Brain MRI revealed multifocal round or oval-shaped lesions in the subcortical and upper brainstem white matter with minimal involvement of adjacent gray matter structures (Fig. 1). Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping showed increased diffusivity in most and restricted diffusion in a few lesions. Some lesions also showed ring enhancement with gadolinium. Cervical cord MRI was normal. Magnetic resonance angiography (MRA) of the brain and the neck was unremarkable. Electroencephalography showed multifocal slow waves and no epileptiform activity.

Viral hepatitis was suspected based on exposure history and asymptomatic serum transaminase elevation. Serial HCV antibody tests and HCV RNA polymerase chain reaction assays were performed. The HCV antibody test was initially negative but HCV RNA was detected and the assay showed a viral load of 15,217 IU/mL. HCV genotyping revealed genotype 2a/2c. Other potential etiologies for hepatitis were excluded.

Stereotactic biopsy of an accessible tumefactive lesion in the right anterior frontal lobe showed reactive gliosis, microgliosis, scattered gemistocytes, and glial atypia (Fig. 2). These findings, especially microgliosis, are consistent with multiple sclerosis. Neoplastic cells, HSV, CMV, and other infectious agents were not detected. Infectious agents such as HIV, HSV, West Nile and other arboviruses, bacteria, and toxoplasma were also ruled out by microscopy, cultures, and/or immunological tests of blood and/or CSF. Tests to detect autoimmune disorders such as ESR, RPR, ANA, anticardiolipin antibodies, and lupus

anticoagulant were all within normal limits. CSF myelin basic proteins was normal (0.5 ng/ml) and oligoclonal bands were absent. The CSF IgG synthesis rate was mildly elevated (4.4 mg/day). Intravenous methylprednisolone 1000 mg per day for seven days resulted in dramatic improvement. On the day of discharge, she only had mild left hand weakness.

The patient was incarcerated and her medical care was continued in prison. Interferon beta-1a (Avonex®) 30 mcg was administered intramuscularly once a week. This was the only MS disease-modifying therapy in the prison formulary. HCV antibody testing 60 days after disease onset was highly reactive. She remained positive for HCV RNA and the assay showed a viral load of 33,651 IU/mL, which is a greater than two-fold rise in titer compared to the initial assay. Follow-up MRI three months after disease onset did not show any active or new lesions. However, two years after disease onset, she experienced numbness and paresthesia of the left upper extremity. This lasted three weeks and resolved spontaneously. While she never received anti-HCV specific treatment, her HCV antibody and RNA PCR tests became non-reactive indicating complete remission from HCV infection three years after disease onset.

3. Discussion

This is the first report of a possible link between tumefactive MS and acute HCV infection. Hepatitis C virus infection has been linked to various autoimmune disorders [10], including ADEM [11,12]. Sacconi et al. reported the case of a 46-year-old woman who presented with altered mental status, seizures, hemiparesis and hemianopia seven weeks after surgery and blood transfusion. MRI revealed multifocal brain lesions typical for ADEM. HCV infection was diagnosed based on anti-HCV IgM antibodies and HCV RNA polymerase chain reaction (PCR) [11]. Sim et al. described the case of a 47-year-old woman who manifested dysarthria and left hypoesthesia followed by right hemiparesis; there is no information regarding mental status. The patient had a remote history of blood transfusion during C-section. MRI showed multiple brainstem, thalamic, and cord lesions consistent with ADEM. Serum and CSF anti-HCV antibody tests were positive and PCR showed markedly elevated

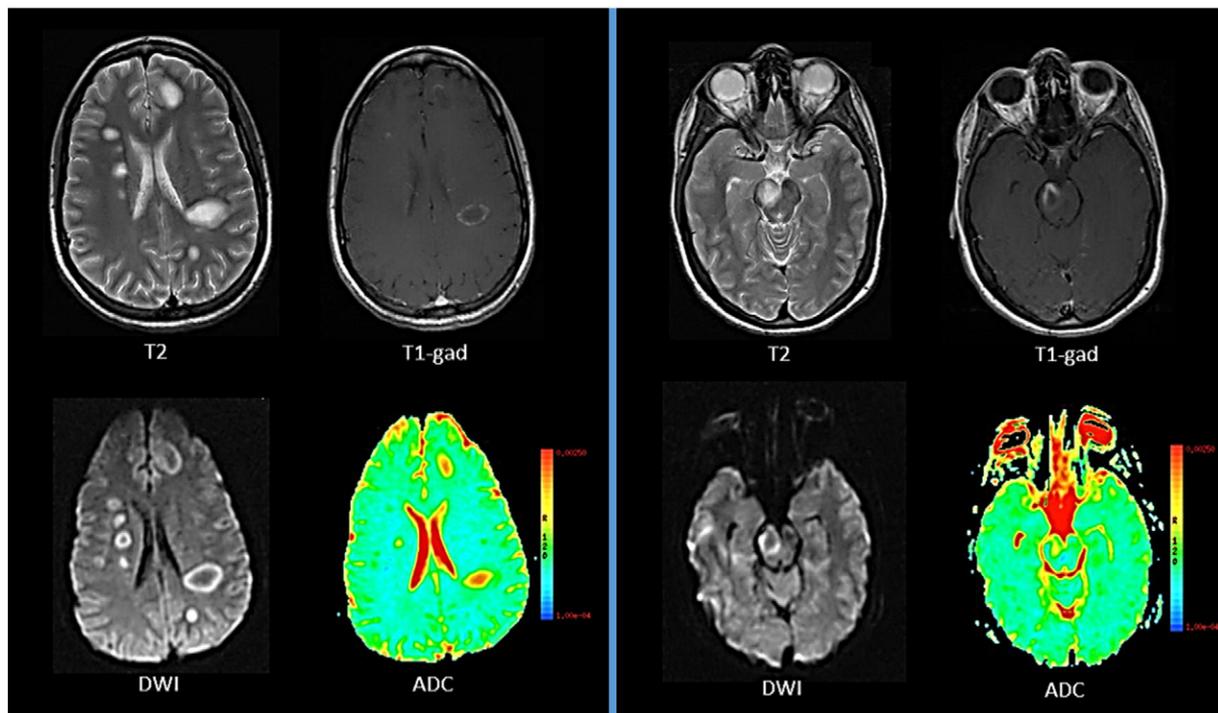


Fig. 1. Brain MRI T2-weighted images show hyperintense white matter lesions in the subcortical and upper brainstem with spread to adjacent gray matter. There is increased diffusivity in most of the lesions on diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps (see color scale). Slight gadolinium enhancement was seen in some of the lesions on T1-weighted images (T1-gad).

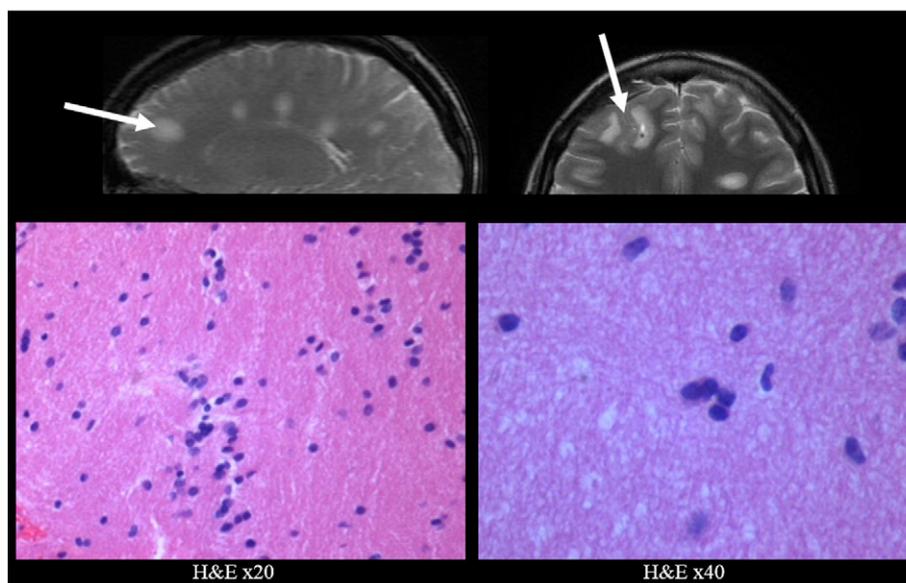


Fig. 2. Pathology of an active tumefactive brain lesion. The arrow on the left points to the biopsied lesion in the right anterior frontal lobe and the arrow on the right shows the same area after biopsy. The sections shown were hematoxylin–eosin (H&E) stained and magnified 20 \times (left) and 40 \times (right). The most notable findings are reactive gliosis, microgliosis (glial cell proliferation and increased cellularity), scattered gemistocytes (reactive and hyperplastic astrocytes), and glial atypia (multinucleation). These findings (especially microgliosis) are consistent with chronic inflammatory processes of the central nervous system, such as multiple sclerosis.

HCV RNA titer [12]. Prior to these reports, HCV-related CNS inflammation was attributed to CNS vasculitis in the setting of cryoglobulinemia [13]. As a rule, CNS vasculitis is a late complication of HCV infection occurring months or years after the acute phase of the infection [14].

Our patient had acute HCV infection and MRI showed multifocal white matter brain lesions that are consistent with tumefactive MS. The lesions are oval-shaped and well circumscribed with minimal surrounding edema; some lesions are also ring-enhancing. By contrast, ADEM lesions are usually poorly demarcated with irregular margins and surrounding edema [3,15]. The pathology of ADEM consists of sleeves of demyelination and extensive inflammatory infiltrates, often dominated by macrophages [15]. The patient's biopsy revealed microgliosis and reactive astrocytes with no significant inflammatory infiltrates – findings which are more consistent with a chronic inflammatory process, such as MS, than an acute inflammatory process, such as ADEM or viral encephalitis. Moreover, our patient did not manifest encephalopathic symptoms, which is now required by some experts to diagnose ADEM [4]. There were no signs of vasculitis on MRI/MRA. Blood, CSF, and microbiological studies did not show alternative etiologies. Two years after disease onset, the patient developed left upper extremity numbness and paresthesia which resolved completely in three weeks. The patient was in prison and MRI was not performed, but the authors consider these symptoms as symptoms of MS relapse, which would then be another argument in favor of tumefactive MS [2].

HCV infection is usually suspected based on a history of exposure. Our patient was most likely infected through self-injection of illicit drugs or sexual contact. Screening is performed with an anti-HCV antibody test [16]. Since seroconversion may take 6 to 12 weeks to occur, the screening test can be falsely negative if the infection is acute or recent [17]. HCV RNA reverse transcription PCR is used to confirm HCV infection and to assay for virus load [18]. The results of serial HCV antibody tests and RNA PCR assays indicate that our patient had acute HCV infection when she presented with tumefactive brain lesions.

There are 11 known HCV genotypes (denoted by numbers) and each genotype is further divided into subtypes (denoted by alphabets). For example, genotype 2 has three known subtypes: 2a, 2b, and 2c [19]. It is possible to be infected with more than one HCV genotype; this is most likely among injection drug users. Two HCV genotypes were identified in our patient – 2a and 2c. HCV genotypes differ in terms of their

geographical distribution, pathogenicity, and interferon sensitivity [20]. HCV genotype 1 is prevalent in North America and Japan, genotype 3 in the Indian subcontinent, and genotype 4 in Africa and the Middle East; genotype 5 is found in South Africa and genotype 6 in Southeast Asia [21]. Pathogenicity varies among the different genotypes; e.g. genotype 3 is associated with a higher risk of liver steatosis [22] and genotype 1 with development of hepatocellular carcinoma [23]. HCV sensitivity to peginterferon therapy also depends on genotype [24].

It is not clear whether HCV genotypes differ in their immunopathogenicity. In one study, HCV genotype 2c was found to be a major risk for developing extrahepatic autoimmune diseases while genotype 1b seemed to prevent these complications [25]. The mechanism by which viruses trigger inflammatory demyelinating diseases of the CNS remains unknown. Presumably, certain viral antigenic components that resemble myelin epitopes induce a humoral and/or cell mediated response directed towards CNS myelin [2]. Since host genetics also have a role in the pathogenesis of autoimmune diseases, the right match between host and virus genetics may be crucial in triggering autoimmunity. Therefore, the HCV genotype is and of itself a clue to understand how HCV triggers ADEM, tumefactive MS, and other autoimmune diseases.

Interestingly, the patient achieved remission from HCV infection even though she did not receive sofosbuvir and ribavirin, the recommended treatment for HCV genotype 2 [26]. Because of the initial concern of tumefactive MS, she received weekly interferon beta-1a injections for 12 months. There are publications alluding to the efficacy of interferon beta-1a in inducing remission in HCV infection [27–29]. There is also one report of a patient with MS and HCV infection who obtained dual benefit from interferon beta-1a injections [30]. On the other hand, studies demonstrating interferon beta-1a efficacy against HCV infection were mostly conducted on patients with well-established chronic HCV infection [31]. Moreover, spontaneous remission from HCV infection is well known [32]; approximately 15% of acute HCV infections recover spontaneously [33].

4. Conclusion

This case suggests that CNS myelin is a potential target of the immune response to infection with HCV genotype 2a/2c but it does not exclude the possibility that other HCV genotypes may also trigger tumefactive

multiple sclerosis or other autoimmune disorders. It also suggests that interferon beta-1a may be an effective treatment for HCV genotype 2a/2c infection. Serial HCV antibody testing and HCV RNA PCR assay, preferably with HCV genotyping, should be part of the work-up of acute inflammatory demyelinating diseases of the CNS. Knowing the genotypes of viral triggers may enhance our understanding of the immunopathogenesis of autoimmune diseases.

Disclosure

The authors declare that they have no competing interests.

References

- [1] Lublin FD, Reingold SC, Cohen JA, Cutter GR, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* Jul 15 2014;83(3):278–86.
- [2] Rahmlow MR, Kantarci O. Fulminant demyelinating diseases. *Neurohospitalist* Apr 2013;3(2):81–91.
- [3] Menge T, Hemmer B, Nessler S, Wiendl H, Neuhaus O, et al. Acute disseminated encephalomyelitis: an update. *Arch Neurol* 2005;62:1673–80.
- [4] Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* Sep 2013;19(10):1261–7.
- [5] Tenembaum S, Chitnis T, Ness J, Hahn JS, International Pediatric MS Study Group. Acute disseminated encephalomyelitis. *Neurology* Apr 17 2007;68(16 Suppl. 2):S23–36.
- [6] Poser S, Luer W, Bruhn H, Frahrn J, Bruck Y, Felgenhauer K. Acute demyelinating disease: classification and non-invasive diagnosis. *Neurol Scand* 1992;86:579–85.
- [7] Brinar VV. Non-MS recurrent demyelinating diseases. *Clin Neurol Neurosurg* 2004;106:197–210.
- [8] Kepes J. Large focal tumor-like lesions of the brain: intermediate between multiple sclerosis and acute encephalomyelitis: a study of 31 patients. *Ann Neurol* 1993;33:18–27.
- [9] Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. *Brain* Jul 2008;131(Pt 7):1759–75.
- [10] McMurray RW. Hepatitis C-associated autoimmune disorders. *Clin Rheum Dis Clin North Am* May 1998;24(2):353–74.
- [11] Sacconi S, Salviati L, Merelli E. Acute disseminated encephalomyelitis associated with hepatitis C virus infection. *Arch Neurol* Oct 2001;58(10):1679–81.
- [12] Sim JE, Lee JB, Cho YN, Suh SH, Kim JK, Lee KY. A case of acute disseminated encephalomyelitis associated with hepatitis C virus infection. *Yonsei Med J* Jul 1 2012;53(4):856–8.
- [13] Acharya JN, Pacheco VH. Neurologic complications of hepatitis C. *Neurologist* May 2008;14(3):151–6.
- [14] Cacoub P, Saadoun D, Limal N, Léger JM, Maisonneuve T. Hepatitis C virus infection and mixed cryoglobulinaemia vasculitis: a review of neurological complications. *AIDS* Oct 2005;19(Suppl. 3):S128–34.
- [15] Hu W, Lucchinetti CF. The pathological spectrum of CNS inflammatory demyelinating diseases. *Semin Immunopathol* Nov 2009;31(4):439–53.
- [16] Albeldawi M, Ruiz-Rodriguez E, Carey WD. Hepatitis C virus: prevention, screening, and interpretation of assays. *Cleve Clin J Med* Sep 2010;77(9):616–26.
- [17] Kaźmierczak J, Pawełczyk A, Cortes KC, Radkowski M. Seronegative hepatitis C virus infection. *Arch Immunol Ther Exp (Warsz)* Apr 2014;62(2):145–51.
- [18] Irshad M, Mankotia DS, Irshad K. An insight into the diagnosis and pathogenesis of hepatitis C virus infection. *World J Gastroenterol* Nov 28 2013;19(44):7896–909.
- [19] Zein NN. Clinical significance of hepatitis C virus genotypes. *Clin Microbiol Rev* Apr 2000;13(2):223–35.
- [20] El-Shamy A, Hotta H. Impact of hepatitis C virus heterogeneity on interferon sensitivity: an overview. *World J Gastroenterol* Jun 28 2014;20(24):7555–69.
- [21] Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006;3:41–6.
- [22] Rubbia-Brandt L, Leandro G, Spahr L, Giostra E, Quadri R, Malé PJ, et al. Liver steatosis in chronic hepatitis C: a morphological sign suggesting infection with HCV genotype 3. *Histopathology* 2001;39:119–24.
- [23] Bruno S, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007;46:1350–6.
- [24] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580–93.
- [25] Giannitti C, Morozzi G, D'Alfonso S, Bellisai F, Galeazzi M. Viral genotype and HLA class II alleles influence on extra-hepatic manifestations of chronic HCV infection. *Reumatismo* Jul-Sep 2008;60(3):192–8.
- [26] American Association for the Study of Liver Disease. Recommendations for testing, managing, and treating hepatitis C. Last updated 04/03/2014; source URL: <http://www.hcvguidelines.org/full-report>.
- [27] Habersetzer F, Boyer N, Marcellin P, Bailly F, Ahmed SN, Alam J, et al. A pilot study of recombinant interferon beta-1a for the treatment of chronic hepatitis C. *Liver* Dec 2000;20(6):437–41.
- [28] Cheng PN, Marcellin P, Bacon B, Farrell G, Parsons I, Wee T, et al. Racial differences in responses to interferon-beta-1a in chronic hepatitis C unresponsive to interferon-alpha: a better response in Chinese patients. *J Viral Hepat* Sep 2004;11(5):418–26.
- [29] Pellicano R, Craxi A, Almasio PL, Valenza M, Venezia G, et al. Interferon beta-1a alone or in combination with ribavirin: a randomized trial to compare efficacy and safety in chronic hepatitis C. *World J Gastroenterol* Aug 7 2005;11(29):4484–9.
- [30] Tan FU, Cetinkaya H, Erden E, Ulkatan S, Aydin N. Dual benefit from intramuscular interferon-beta treatment in a patient with multiple sclerosis and chronic hepatitis-C virus infection. *Hepatogastroenterology* Nov-Dec 2002;49(48):1686–7.
- [31] Nomura H, Miyagi Y, Tanimoto H, Yamashita N. Interferon-beta plus ribavirin therapy can be safely and effectively administered to elderly patients with chronic hepatitis C. *J Infect Chemother* Aug 2014;20(8):489–92.
- [32] Wietzke-Braun P, Manhardt LB, Rosenberger A, Uy A, Ramadori G, Mihm S. Spontaneous elimination of hepatitis C virus infection: a retrospective study on demographic, clinical, and serological correlates. *World J Gastroenterol* Aug 21 2007;13(31):4224–9.
- [33] Pham T, MacParland SA, Mulrooney PM, Cooksley H, Naoumov NV, Michalak TI. Hepatitis C virus persistence after spontaneous or treatment-induced resolution of hepatitis C. *J Virol* Jun 2004;78(11):5867–74.