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BRIEF REPORT

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Papillitis and vasculitis of the arteria spinalis anterior as complications of hepatitis C reinfection after liver transplantation

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Abstract It is well known that hepatitis C virus (HCV)-related chronic liver disease may be associated with various immunological disorders including mixed cryoglobulinemia, which is accompanied by cutaneous vasculitis, arthralgias, membranoproliferative glomerulonephritis, and neuropathy in association with cryoprecipitable immune complexes in serum. We describe here the first case of central nervous system HCV infection with evidence of the virus in the cerebrospinal fluid in association with cryoglobulinemia in a patient who developed recurrent episodes of papillitis and vasculitis of the arteria spinalis anterior after liver transplantation.

Key words Hepatitis C reinfection, papillitis arteria spinalis anterior, liver transplantation · Papillitis arteria spinalis anterior, liver transplantation, hepatitis C reinfection · Liver transplantation, hepatitis C reinfection, papillitis arteria spinalis anterior

Introduction

Frequent and various immunological abnormalities have been reported in patients with chronic hepatitis C [4]. The prevalence of cryoglobulinemia in patients with chronic HCV infection is more than 50 %. It has been suggested that HCV plays a major role in the pathogenesis of cryoglobulinemia. The underlying mechanism is thought to be the formation of aggregates consisting of HCV virions and HCV antibodies complexed with rheumatoid factors within cryoglobulins [1].

Cryoglobulinemia is usually present at low levels and does not cause symptoms in patients with chronic hepatitis C. However, cases of severe cryoglobulinemia, characterized by cutaneous involvement or by renal or neurological involvement or both, have been reported in patients with chronic HCV infection [6, 7]. Furthermore, 40 % of HCV-infected patients with mixed cryoglobulinemia show deposition of HCV antigens in skin biopsies [9].

Post-transplant cryoglobulinemia was recently described in three patients presenting clinically with either glomerulonephritis or cutaneous vasculitis or both after orthotopic liver transplantation [5].

We report here the first case of a liver transplant patient who developed recurrent episodes of papillitis and vasculitis of the arteria spinalis anterior due to HCV reinfection and cryoglobulinemia with evidence of HCV in the cerebrospinal fluid.

Case report

In November 1989, a 43-year-old male patient underwent liver transplantation at the University Hospital Innsbruck for decompensated non-A-non-B cirrhosis. The post-transplant course was complicated by an acute organ rejection 1 week after transplantation and a surgical revision of the choledochal duct due to stenosis at the site of anastomosis 5 weeks later. Two months after transplantation, the patient was discharged in good condition. He received triple immunosuppressive drug therapy (cyclosporin, prednisolone, and azathioprine) and his aminotransferases levels were within the normal range. In a retrospective analysis, including a pretransplant serum, all of his sera tested positive for HCV antibodies (Second generation ELISA, Abbott Laboratories, Chicago, Ill., USA) and HCV RNA (Quantiplex, Chiron, USA).

Sixteen months later, under immunosuppressive treatment (cyclosporin 280 mg, azathioprine 50 mg daily), the patient suddenly complained about loss of vision in his left eye. Opthalmological examination showed evidence of papillitis. All possible causes of opticus neuritis, such as a frontal lobe mass, sinusitis, multiple sclerosis, and infectious meningitis, were excluded. Azathioprine treatment was stopped and steroid therapy was initiated (40 mg methylprednisolone for 14 days, then stepwise reduction), which completely resolved the symptoms. Two months later, a sudden increase in aminotransferases levels (AST 59 U/l, normal 2–18 U/l; ALT 293 U/l, normal 2–22 U/l) prompted a liver biopsy that showed histological evidence of acute viral hepatitis without signs of organ rejection. According to Simmonds' HCV-genotyping classification, HCV-subtype 1 b (INNO-Lipa, Innogenetics, Belgium) was identified [10]. Throughout his disease, cryoglobulins (type II) tested positive, whereas autoimmune markers and CMV remained negative.

Four months later, a relapse of opticus neuritis once more prompted methylprednisolone therapy, which again was successful. Because transaminase elevation (AST 38 U/L; ALT 100 U/l) persisted for more than 6 months, the patient was given 5000000 IE of α-interferon three times a week subcutaneously over 4 months. This not only brought down his transaminase levels, but also decreased HCV viremia (Fig. 1). A control liver biopsy after interferon therapy showed minimal hepatitis.

Three and a half years after liver transplantation, the patient suddenly developed paraplegia and hypoesthesia of both legs in association with disturbances of the bladder and bowel functions. Neurological examination revealed a transverse lesion of the spinal cord. Myelography excluded intra- or paramedullar masses; a CT scan of the thoracic spine was normal. Spinal tap showed a normal cell count, normal protein concentration, normal IgG production, and oligoclonal banding in his cerebrospinal fluid. However, HCV antibodies as well as HCV-RNA, tested by means of a nested in-house PCR and confirmed with the Amplicor assay (Hoffmann-La Roche, Switzerland) at a low titer ($< 3.5 \times 10^5$ mEq/ml; Quantiplex, Chiron, USA) in the cerebrospinal fluid, were positive. Magnetic resonance imaging (MRI) showed evidence of an inflammatory process in the region of the arteria spinalis anterior at segment 5/6 of the thoracic spine. An echocardiogram and carotid artery Doppler were performed to rule out embolism from the heart or an atherosclerotic plaque. Five courses of plasmapheresis and high-dose methylprednisolone therapy (80 mg daily) completely resolved the neurological symptoms.

To date, the patient is suffering from histologically proven mild chronic hepatitis C infection with minimally elevated transaminase levels, but he has had no further episodes of neuritis or vasculitic complications. He has been kept on cyclosporin monotherapy since the last complication.

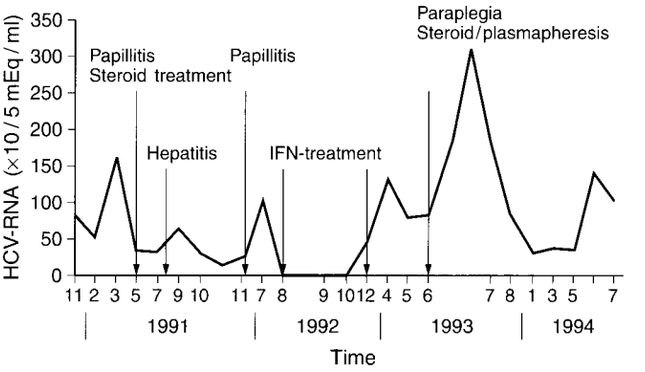

Fig. 1 HCV-RNA levels during the observation period after liver transplantation and episodes of papillitis, acute hepatitis C reinfection, alpha-interferon treatment, paraplegia, and plasmapheresis

Discussion

Most cases of post-transplant hepatitis C are caused by recurrent infection, and nearly all patients undergoing transplantation for hepatitis C develop recurrent viremia. Circulating virions are found in peripheral blood mononuclear cells and are suggested to be the source of recurrent infection. In addition, the HCV subtype 1 b appears to pursue a more aggressive clinical course in patients after transplantation than other genotypes [3]. Patients infected with subtype 1 b are twice as likely to develop acute hepatitis and three times as likely to develop chronic hepatitis as those infected with other genotypes. Furthermore, the genotype 1 b is associated with higher RNA levels and a lower response to interferon therapy.

The clinical course of our patient after liver transplantation is extraordinary for several reasons:

1. We found evidence of HCV infection in cerebrospinal fluid by detecting HCV antibodies as well as HCV-RNA. At present, the hypothesis that HCV causes central nervous system infection is still under discussion. Recently, a case of a young patient with anicteric hepatitis A encephalitis coexistent with HCV infection was reported [11]. In this case report, the authors concluded that a para-infectious encephalitis due to hepatitis A or C was responsible for inducing immune complex vasculopathy. As an alternative hypothesis, the authors also suggested that the observed neurological symptoms were due to a neurotropic infection or neuronal lytic effect. However, the cerebrospinal fluid in that patient was not examined for the presence of hepatitis A virus or HCV. In the case of our patient, antibody tests enabled us to demonstrate the presence of HCV and HCV-RNA in the cerebrospinal fluid. It is, however, not clear whether the presence of the virus is the result of chronic HCV infection, the immunosuppressive ther-

apy following liver transplantation, or immune complex vasculitis causing damage to the blood/brain barrier. As normal cerebrospinal fluid contains mononuclear cells and immunoglobulins in small amounts, evidence of HCV antibodies and HCV-RNA may also simply be a manifestation of HCV viremia.

2. Recurrent episodes of papillitis and vasculitis of the arteria spinalis anterior after liver transplantation have not been described yet. Previous studies have shown a high prevalence of cryoglobulinemia in chronic HCV infection. In our patient, mixed cryoglobulinemia and HCV reinfection after transplantation strongly suggest papillitis and vasculitis of the arteria spinalis anterior as central nervous system immune complex complications; multiple sclerosis and other causes of encephalitis could be excluded by a normal cerebrospinal fluid IgG concentration and oligoclonal banding, by MRI excluding lesions that correspond to pathologically proven multiple sclersosis plaques, and by a negative bacterial cerebrospinal fluid culture.

3. Another interesting finding in our patient was that papillitis and vasculitis developed only after liver transplantation and not before, even though the cryoglobulins and HCV were present all the time. The dramatic increase in HCV viremia after transplantation in the presence of cryoglobulins may lead to enhanced immune complex formation. Expression of HLA class I and II antigens after transplantation, together with enhanced expression of HCV antigens, causes antibody production against HCV antibodies, leading to immune complex production. Furthermore, allograft rejection can additionally increase immune complex production [5]. In all three reported cases, as well as in our patient, post-transplant immune complex complications developed in the presence of high HCV viremia under immunosuppressive drug therapy [5]. One might predict that immunosuppressive agents could lead to long-term amelioration of disease because these drugs have been shown to be an effective therapy for cryoglobulin-associated vasculitis. However, cyclosporin A has been said to damage vascular endothelium, and chronic administration of cyclosporin A has been found to be associated with arteriolar damage [8].

4. No correlations between HCV-RNA levels and episodes of neuritis/vasculitic complications were found. During the entire observation period after liver transplantation, high HCV-RNA levels were observed. The highest levels were detected before the first episode of papillitis, after the second course of steroid therapy, 4 months after interferon treatment, and during successful plasmapheresis and the third course of steroid therapy, reaching levels up to 3×10^7 mEq/ml. One may speculate that during plasma exchange HCV antibodies are eliminated, which could also lead to high virus replication and viremia. However, the lack of correlation between HCV-RNA levels, neuritis, and vasculitis suggests that it is not the virus alone that is responsible for these complications, but rather the cryoglobulins that lead to central nervous system immune complex neuritis and vasculitis.

5. High-dose prednisone treatment and plasmapheresis, in addition to immunosuppressive drug therapy, resolved the neurological symptoms. Two episodes of papillitis were treated with 40 mg methylprednisolone therapy, fortunately without persistent loss of vision or visual disturbances. During the episode of paraplegia, plasmapheresis was successfully instituted. As with other immunocompromised patients with cryoglobulinemia, our patient's course stabilized following intensive plasma exchange; paraplegia, hypoesthesia of both legs, and disturbances of the bladder and bowel functions were completely resolved [2]. Since plasmapheresis does not suppress cellular immune function, it appears to be the safest therapeutic option for patients with severe immune complex complications who are receiving immunosuppressive drug therapy.

In conclusion, we report here the first case of recurrent episodes of papillitis and vasculitis of the arteria spinalis anterior in a liver transplant patient in association with hepatitis C reinfection and cryoglobulinemia. Immunosuppressive drug therapy and repeated, additional methylprednisolone treatment certainly complicate the interpretation of our patient's course. Whether it was the more aggressive HCV genotype 1 b, or the fluctuating emergence of a quasispecies, in association with high post-transplant HCV-RNA levels and cryoglobulinemia leading to immune complex neuritis and vasculitis which, in turn, caused damage to the blood/brain barrier, or rather the immunosuppressive drug therapy that encouraged penetration of the virus into the neuronal system demands further investigation. Nonetheless, despite the severe complications of central nervous system immune complex neuritis and vasculitis, treatment with methylprednisolone and plasmapheresis was successful.

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