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CASE REPORT

Systemic lupus erythematosus following virological response to peginterferon alfa-2b in a transplanted patient with chronic hepatitis C recurrence

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Abstract

Autoimmune manifestations are common both in patients chronically infected by hepatitis C virus, and in patients transplanted for non-autoimmune diseases. A correlation between interferon based treatment and autoimmune diseases or the development of autoantibodies is well established in non-transplanted patients, but few data are available about transplanted patients. It is unclear whether interferon may increase the incidence of acute cellular rejection and there are few reports on the development of atypical autoimmune manifestations during post-liver transplantation interferon or pegylated interferon treatment. We describe a case of systemic lupus erythematosus following treatment with pegylated interferon alfa-2b in a transplanted patient with recurrence of chronic hepatitis C. Our experience suggest that pegylated interferon may induce autoimmune diseases in the immunosuppressed host, different from acute cellular rejection and call for a great attention to possible autoimmune disorders development during interferon based treatments in liver transplanted patients.

Key words: Hepatitis C virus; Liver transplantation; Autoimmunity; Immunosuppression; Systemic lupus erythematosus

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INTRODUCTION

Autoimmune manifestations are common in patients chronically infected by hepatitis C virus (HCV)[1]. On the other hand, tissue autoantibodies are common in liver recipients transplanted for non autoimmune diseases and may be associated with negative graft outcome[2,3]. The safety and efficacy of interferon (IFNs) and the newest pegylated interferons (Peg-IFNs) for the treatment of recurrent hepatitis C in transplanted patients are still debated[4,5]. In particular, it is unclear whether IFN may increase the incidence of acute cellular rejection (ACR) and there are no reports on the development of atypical autoimmune manifestations during post-liver transplantation (LT) IFN or Peg-IFN treatment.

We report a case of severe autoimmune disease, different from ACR, during treatment with Peg-IFN alfa-2b in a transplanted patient with recurrence of chronic hepatitis C (CHC).

CASE REPORT

A 55-year-old man, underwent LT in March 2001 for HCV genotype 1 liver related cirrhosis. Acute immunosuppressive (IS) schedule was cyclosporine, azathioprine (AZA) and steroids. According to the Transplantation Unit IS protocol, AZA and steroids were stopped 3 wk and 1 year after LT, respectively. Screening tests for LT revealed the presence of cryoglobulins with a cryocrite of 8% and antinuclear antibodies (ANA) at low titre (1/160) with homogeneous pattern. After LT, clinical outcome was regular until January 2002, when the patient showed a persistent mild increase of transaminases (ALT 115 U/L and AST 103 U/L) with high viral load (17.5 MEq/mL, Versant HCV-RNA 3.0 bDNA, Bayer). Liver histology showed mildly active chronic hepatitis with severe fibrosis, presence of lymphocytes and macrovescicular steatosis, sug-

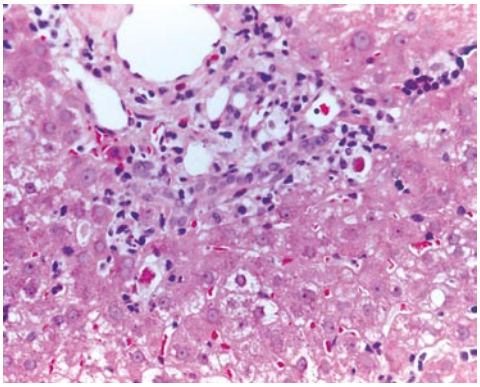

Figure 1 Liver histology before starting antiviral treatment.

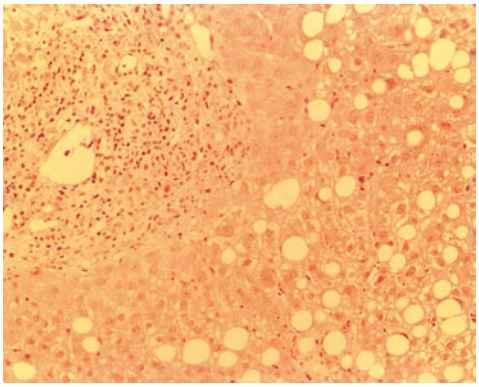

Figure 2 Liver histology after stopping antiviral treatment.

gestive of HCV recurrence (Figure 1).

In October 2002 the patient started a cycle of Peg-IFN alfa-2b (1.1 mcg/kg per week) and Ribavirin (6.4 mg/kg per day). After 4 wk of treatment transaminases were normal. HCV-RNA showed a 2 log fall (0.01 MEq/mL) at wk 12; became undetectable by branched DNA, but still positive by polymerase chain reaction (TMA test, Versant HCV-RNA, Bayer) at wk 24 and finally negative by PCR at wk 36.

At wk 44 the patient presented migrant arthritis and the following biochemical parameters: normal transaminases, CyA 240 ng/mL, increased gamma-glutamyltransferase (γGT), alkaline phosphatase (ALP) and bilirubin (384 U/L, 690 U/L and 1.69 mg/dL, respectively), gamma-globulins 30%, Waaler-Rose 1/1280, ANA 1/640 and anti-DNA positive. No vascular or biliary complications were revealed by ultrasound and computed tomography, nor any signs of infectious diseases were present. Suspicion of an immune mediated manifestation, prednisone 10 mg/d was started. However, despite the presence of signs of autoimmunity we decided to complete the Peg-IFN cycle in consideration of the fact that we were almost at the end of the planned 48 wk of treatment with the patient responding to Peg-IFN.

At wk 48 the patient was asymptomatic, transaminases and bilirubin were normal, HCV-RNA negative by PCR, while ALP and γGT were decreased (ALP 350 U/L and γGT 94 U/L). Peg-IFN was stopped and steroids were maintained.

One month later, the patient developed pleuro-pericardial effusion and ascites. Liver function tests (LFTs) were normal, HCV-RNA was negative (PCR) and CyA within the therapeutic range; ANA was very high (1/1280) as well as perinuclear anti-neutrophil cytoplasmatic antibodies (pANCA) (1:320). Therefore, our patient developed a syndrome characterised by high titre autoantibodies, migrant arthritis and serositis. Following the current criteria, the diagnosis of systemic lupus erythematosus could have been made[6,7]. Prednisone was increased to 15 mg/d and diuretics introduced, resulting in the remission of liquid effusions and a progressive reduction of autoantibodies (ANA 1:160 and pANCA negative). We did not increase further the prednisone dosage in consideration of the possibility of an HCV re-activation in an already immunosuppressed patient and because of the initial clinical remission of autoimmune manifestations.

In March 2004, four months later, the patient presented an important increase of all LFT (GOT 257 U/L, GPT 197 U/L, ALP 438 U/L, γGT 356 U/L, total bilirubin 20.35 mg/dL, with direct bilirubin 17.20 mg/dL) with normal eosinophils, serum HCV-RNA positive at low titre (2.96 MEq/mL). CyA was close to the lower limit of the therapeutic range (100 ng/mL). Liver biopsy revealed the presence of interface hepatitis, numerous rosettes, cholangitis with ductular proliferation and biliocytes regression (Figure 2). Histological findings were not suggestive for HCV recurrence and did not fulfil the standard criteria for acute or chronic rejection[8]. Therefore, International Criteria for Autoimmune Hepatitis (AIH score)[9] were applied, according to which the patient was categorized as positive for "probable AIH" (score + 11). Consequently, steroid treatment was increased and the patient was switched from cyclosporine to tacrolimus. Response to immunosuppressive treatment was slow but progressive until normalization of LFTs.

DISCUSSION

It is well known that treatment with IFN may cause autoimmune diseases or the development of autoantibodies in non transplanted patients[10-13] while few data are available on transplanted ones. In particular, to the best of our knowledge, it has never been described the development of SLE after LT during interferon treatment. Only two cases of SLE have been described during IFN treatment in immunocompetent patients treated for HCV infection[12]. In a series of 677 patients treated for HCV infection, 4% developed autoimmune diseases, the majority (62%) being represented by thyroid dysfunction; only 1 patient developed an SLE-like syndrome with an incidence of 0.15% in the study population[14]. Alfa-IFN therapy has been moreover associated with the development of idiopathic thrombocytopenic purpura, myasthenia gravis, Addison's disease, diabetes, COELIAC disease, rheumatoid arthritis, primary biliary cirrhosis, polymiositis, psoriasis[12,15-23].

Antiviral actions of alfa-IFN include the induction of several proteins, such as protein kinase (PKR) and 2',5' -oligoadenylate synthetase, important in viral dynamics[24]. Moreover, IFNs induce the expression of MHC both on antigen presenting cells (APC) and hepatocytes, resulting in a virus-specific lysis of infected cells mediated by cytotoxic T-cell response[25]. Thus, IFNs may lead to the development of autoimmune diseases by the up-regulation of MHC in both transplanted and non transplanted patients.

Moreover, the interaction of IFN activities in a particular pathway, such as in the immunosuppressed host, may lead to severe autoimmune manifestations that can compromise the graft survival. A relation between virological response and ACR was suggested in a recent study. Authors supposed that viral eradication improves microsomial function leading to a decrease of IS drugs levels[4]. The same mechanism may play a role in the induction of other autoimmune diseases such as that occurred to our patient who developed an SLE. Furthermore, our patient was on treatment with calcineurin inhibitors that have been thought to predispose to autoimmunity by interfering with T cell maturation and developing autoaggressive T-cells clones[26]. It is therefore possible that various mechanisms contribute to the development of autoimmune manifestations after liver transplantation.

In conclusion, the clinician should be aware of the possible development of autoimmune disorders, different from ACR, during interferon based treatment in LT patients, especially if signs of autoimmunity are present before starting IFN.

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