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CASE REPORT

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Antimitochondrial antibody serocoversion post-liver transplant during hepatitis C treatment with peginterferon α, ribavirin and telaprevir

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ABSTRACT

Pegylated interferon alpha (PEG-IFN α), a key component of chronic hepatitis C therapy, has been linked to the development of auto-antibodies and autoimmune disease. We report the first case of antimitochondrial antibody (AMA) seroconversion during PEG-INF α based therapy after liver.[1-4] transplantation. A fifty-seven year-old man five months after liver transplantation was initiated on hepatitis C triple therapy with PEG-INF α, ribavirin and telaprevir. He had failed previous PEG-IFN α and ribavirin 12 years pre-transplant and his AMA remained negative pre-transplant. After twelve weeks of antiviral therapy, he developed elevated liver enzyme tests associated with an AMA seroconversion to seropositivity. A liver biopsy failed to show histological evidence of primary biliary cirrhosis or graft rejection. He was initiated on urseodeoxycholic acid with subsequent improvement of his liver enzymes. This case demonstrates that despite adequate immunosuppression, AMA seroconversion may occur post-transplant during interferon-based therapy. As AMA seroconversion did not occur during the pre-transplant PEG-IFN therapy, we speculate that donor allograft antigens in combination with PEG-IFN may have been a factor in the post-transplant seroconversion.

Key words. Peginterferon. Hepatitis C. Liver transplantation. Antimitochondrial antibody. Seroconversion.

INTRODUCTION

Pegylated interferon alpha (PEG-IFN α) remains a key component of effective therapy for the treatment of hepatitis C infection. There are several reports of the immunomodulatory effects of interferon alpha and it is known that it can exacerbate autoimmune diseases.[1-4] There is also a single report of antimitochondrial antibody (AMA) seroconversion during treatment with interferon-α.[3] We report the first case of AMA seroconverion during PEG-IFN α-based treatment for chronic hepatitis C (HCV) in a patient on immunosuppressants after liver transplantation.

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CASE REPORT

We report a 57 year old man who was transplanted for end-stage liver disease secondary to chronic hepatitis C, with a 4.5 cm hepatocellular carcinoma. His HCV genotype was 1b and attempted treatment with peginterferon and ribavirin 12 years prior to transplantation, but discontinued due to an esophageal variceal bleeding. During his pre-transplant assessment, his antinuclear antibodies and AMA were negative. The anti-smooth muscle antibodies were weakly positive at a titer of 1:80. He underwent an orthotopic liver transplant from a deceased donor who was HBs antigen negative and HBc antibody positive with no significant post-operative complications and was discharged home on his post-operative day 11. He received standard immunosuppression with mycophenolate mofetil, tacrolimus and intravenous methylprednisolone followed by oral prednisone. Prophylactic lamivudine, valgancyclovir and cotrimoxazole were also started for hepatitis B, cytomegalovirus and *pneumocystis jirovecii* prophylaxis respectively. Two months after transplantation,

a liver biopsy was obtained to assess an increase in his liver enzymes revealingvmild rejection with a rejection activity index (RAI) score of 3 and no appreciable fibrosis. Five months aftertransplant, his liver enzymes were: AST 659 IU (normal < 40 IU/L), ALT 643 IU (normal < 60 IU/L), GGT 151 IU (normal < 55 IU/L), alkaline phosphatase 490 (normal < 110 IU/L), total bilirubin of 9 μ mol/L (normal < 22 μ mol/L). A FibroScan showed a score of 12.4 Kpa, consistent with an F2-F3 stage fibrosis. The patient was switched from tacrolimus to oral cyclosporine in preparation of starting treatment for his hepatitis C recurrence with combination of telapravir, peginterferon and ribavirin. Serum HCV RNA levels were 24 534 447 IU/mL prior to treatment initiation and less than 15 IU/mL after four weeks of therapy. The serum HCV RNA levels became undetectable at week 8 and remained so at week 12. All the liver enzymes normalized at week 6 of therapy. After 22 weeks of treatment, a new elevation in liver enzymes was observed with alkaline phosphatase 3-4 times the upper limit of normal. A repeated measurement of immunological markers at week 31 of therapy revealed a positive AMA with a titer of 1:160. Antinuclear antibodies, extractable nuclear antibodies and double-stranded DNA antibodies remained negative. A liver biopsy performed at week 36 of therapy, while the HCV RNA remained undetectable, showed changes consistent with recurrent hepatitis C, no allograft rejection, but no histological evidence of primary biliary cirrhosis. He started therapy with urseodeoxycholic acid at 15mg/kg/day with subsequent improvement of his liver enzymes.

DISCUSSION

Chronic HCV is associated with a high prevalence of auto-antibodies. One study compared the prevalence of autoantibodies in chronic HCV to autoimmune hepatitis (AIH). The prevalence of antinuclear, anti-smooth muscle and antimitochondrial antibodies was 63%, 65% and 4% in patients with HCV compared to 63, 65 and 50% in AIH respectively.[5] Another study in 58 patients with chronic HCV receiving interferon-α therapy found at baseline a prevalence of 11.3, 37.9 and 1.7% for antinuclear, anti-smooth muscle and antimitochondrial antibodies, respectively.[3] In one study the sera of 460 patients with untreated HCV were tested for AMA using indirect immunofluorescence and 7 (1.5%) were found to be positive; none had PBC. All patients were treated with IFN-alpha for six months. Only one of the seven patients achieved SVR and AMA became undetectable. The others remained HCV RNA and AMA positive.[6]

We report a patient without any evidence of autoimmune liver disease prior to the post-transplant initiation of treatment for hepatitis C. During the course of treatment, the initial normalization of the liver enzymes was followed by an increase in the ALT and alkaline phosphatase levels, associated with a seroconversion of AMA, that partially responded to therapy with ursodeoxycholic acid. However, the liver biopsy failed to show histological evidence of primary biliary cirrhosis. This, however, may be because the disease was at a very early stage or because of sampling error. Therefore, with a positive AMA and a liver biochemical pattern that can be consistent, we cannot absolutely exclude a diagnosis of PBC. D'Amico, *et al*. published the case of a woman who developed overlap syndrome of AIH and PBC shortly after completing treatment with interferon-α.[2] This was the first case report of interferon treatment inducing PBC with biochemical, immunological and histological evidence. Other studies have shown AMA seroconversion during treatment with interferon. Imagawa reported in a cohort of 58 patients one case (1.7%) of *de novo* AMA appearance during treatment with interferon-α and one case with worsening of liver enzymes during treatment in a patient with pre-existent AMA.

Interferon-α has cytokine activity and stimulates the production of T-helper (Th) cells, more specifically Th-1 cells that produces interferon-γ and interleukin-2 (IL-2) over Th-2 cells that produce IL-4 and IL-5.[7] On the other hand, calcineurin inhibitors (CNI) are inhibitors of IL-2 and interferon-γ transcription, thus interfering with T-cell co-stimulation and clonal expansion. In the case of our patient, it would be expected that the stimulatory effects of interferon-α on T-cells would be directly counterbalanced by the inhibitory effect of CNI. One study in 15 renal transplant patients with hepatitis C receiving interferon-α treatment evaluated the impact of therapy on several autoantibodies. Five patients developed autoantibodies (Antinuclear 1, smooth-muscle 1, antithyroid microsomes 3). None of the 15 patients had pre-existing or developed antimitochondrial antibodies.[8] It is interesting that this patient's AMA did not seroconvert during his initial pegIFN

treatment 12 years pre-transplant and only occurred post-transplant. It is possible that the antigenic stimulation from the donor allograft, in combination with the immunostimulatory properties of pegIFN, may have been a factor in the seroconversion. If this is the case, the seroconversion could be considered an unusual serologic variant of allograft versus host interaction that has not affected graft function or histology.

In summary, this is the first reported case of AMA seroconversion in a patient undergoing PEG-IFNα based treatment for HCV after liver transplantation. This occurred despite immunosuppressive treatment with a CNI and mycophenolate and demonstrates that AMA-seroconversion may occur after transplant during interferon-based therapy. Although routine screening of autoantibodies may not be warranted,[9] one should entertain the possibility of a de novo primary biliary cirrhosis-like process in a patient with an unexplained increase in alkaline phosphatase levels during PEG-IFNα therapy as an AMA seroconversion may alter the clinical management.

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