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Post-transplant plasma cell hepatitis in a liver transplant patient treated with pegylated interferon plus ribavirin

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ABSTRACT

The recurrence of hepatitis C after a liver transplant remains an important cause of graft loss and retransplant. Antiviral therapy with peginterferon plus ribavirin (PEG-INF/RBV) can achieve a sustained viral response and histological improvement in a high percentage of cases. However, this treatment is not exempt from important side effects or from the possibility of precipitating rejection, with the resulting graft loss. We report the case of a liver transplant patient who received treatment with PEG-INF/RBV and developed plasma cell hepatitis as the presenting form of rejection.

Keywords: Liver Transplantation; C Hepatitis Treatment; Plasmatic Cells; Allograft Rejection; Autoinmune Response

1. INTRODUCTION

Despite the fact that new triple therapy with the association of proteasa inhibitor has achieved satisfactory response rates for HCV-Genotype 1, even in liver transplant patient, the treatment combination of peginterferon plus ribavirin (PEG-INF/RBV) was the best treatment available in our daily clinical practice in 2010 for relapse of hepatitis C virus (HCV) in liver transplant patients. However, its efficacy and tolerability are somewhat less than in non-transplant patients, and special consideration must be given to the frequency and severity of its side effects, as they may cause important morbidity, which can even lead to graft loss [1,2]. Acute or chronic rejection in association with this treatment is potentially severe, though controversial complication, and rates vary considerably between the different studies (0% - 25%) [2-5]. Diagnosis of this complication is often difficult because of its form of presentation and the existence of histological features that are superimposed on other entities, such as recurrent hepatitis C or autoimmune hepatitis [3,6]. We report the case of a patient who developed plasma cell hepatitis after treatment with PEG-INF/RBV, which we believe was an unusual form of presentation of acute rejection leading to graft loss and the death of the patient.

2. CASE REPORT

A 61-year-old man underwent liver transplantation in January 2010 due to hepatic cirrhosis associated with HCV and hepatocarcinoma. When he was enlisted for liver transplantation presented Child-Score of B-7 and MELD-Score of 13, laboratory findings of hypertension portal as well as splenomegaly and pancytopenia that was decisive for not treating with antiviral therapy HCV infection before liver transplantation. After transplantation, immunosuppression theraphy consisted of neoral cycolosporine and steroids that were gradually tapered during the first year. In the immediate post-transplantation liver (LT) period the pacient was keeping a good liver function until the 30th day post-transplantation when laboratory findings reported the result of HCV-RNA 9,290,000 copies per mililiter. Eventually, there was a progressive biochemical and virological worsening which was decisive to perform a liver biopsy in 21th month post-LT, this reported the histological relapse. In that moment, laboratory findings included AST (aminotransferase) 239 IU/L (15 - 35); ALT (alanine aminotransferase) 427 IU/L (30 - 65); Ɣ-GT (gamma-glutamiltransferase) 185 IU/L (15 - 85); AP (alkaline phosfatase) 208 IU/L (50 - 135); and HCV RNA, 16,353,000 copies per milliliter (**Figure 1**). Histologically, a mild interfase hepatitis was reported with focal apoptotic bodies and portal-portal linkage distorsion with periportal fibrosis,

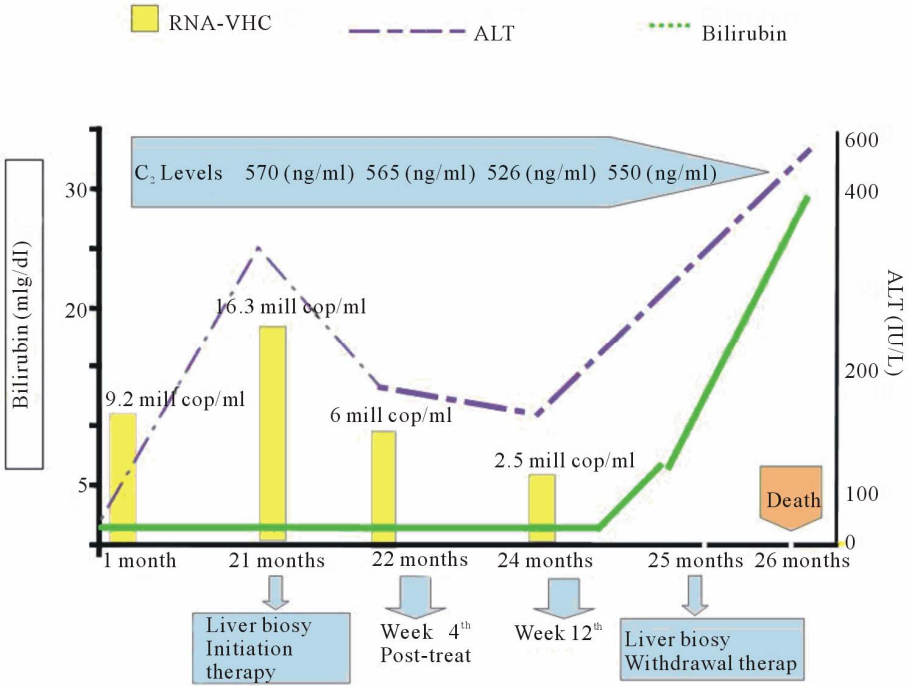

Figure 1. Clinical and analitical secuence after liver trasplantation.

but not cirrhosis (Grade 2 Metavir stage II) (**Figure 2**).

Treatment was started with subcutaneous PEG-INF α2a at a dose of 180 µg per week and ribavirin, 1200 mg per day. Initial side effects were asthenia and hemolytic anemia, necessitating reduction of the dose of ribavirin. A control blood test during treatment week 16 showed hemoglobin 10.5 g/dL (12 - 16), platelets 101,000/µL (140,000 - 350,000), leukocytes 3400/µL (4000 - 11,000 /µL), AST 577 IU/L (15 - 35) , ALT 523 IUL/(30 - 65) Ɣ-GT 449 IU/L (15 - 85), AP 538 IU/L (50 - 135), TB (total bilirrubin) 7 mg/dL (0.3 - 1.5), DB (direct bilirrubin) 5 mg/dL (0.1 - 0.5), INR 1.97, prothrombin time 37.8% (70% - 130%), associated with a poor general state, intense asthenia, fever, reduced consciousness, renal impairment and jaundice. During the treatment viral load decreased but never became negative and ciclosporine levels (CsA) remained the whole time within therapeutic range (levels C_2: 500 ng/ml +/− 120) (**Figure 1**).

The patient was admitted to hospital and antiviral therapy was withdrawn. He was diagnosed with extrahospital pneumonia caused by *Streptococcus pneumoniae* that was treated with amoxicillin-clavulanic acid during 14 days with good response, as well as an urinary tract infection cause by *Echerichia coli* which initially responded well to ciprofloxacin therapy. However, the liver profile still showed marked cytolysis and a progressive increase in bilirubin, which reached 30 mg/dL. Abdominal-pelvic ultrasound and computed tomography ruled out the presence of vascular or biliary alterations and other pathological findings. Antigen assays and polymerase chain reaction for CMV were also negative. Viral markers for HAV-IgM and HBV, as well as ANA, AMA, ASMA and antiKLM antibodies, were all negative. Gamma-globulin/IgG levels were normal.

A liver biopsy revealed a severe portal and periportal lymphoplasmocytic infiltrate (interphase hepatitis), hepatocyte necrosis and periportal fibrosis with no data indicative of rejection, thus suggesting an autoimmune or toxic hepatitis (**Figure 3**).

Finally, the patient experienced progressive worsening of liver function with no response to extracorporeal cleansing techniques (MARS) and died.

3. DISCUSSION

Acute rejection is a potentially serious adverse effect in patients with a recurrence of hepatitis C after liver transplantation and who are receiving treatment with interferon (interferon or peginterferon, with or without ribavirin), and which can even lead to graft loss [1,2]. Although the association between interferon therapy and acute rejection in liver transplantation is not as well-documented as it is for kidney transplantation, the immunomodulatory and immunostimulatory effects of interferon have been suggested as possible mechanisms leading to acute rejection in liver-transplant patients [1, 3].

In our case, and given the initial suspicion of acute rejection, we performed a liver biopsy, which only showed the presence of a severe portal and periportal lymphoplasmocytic infiltrate (interphase hepatitis), with no

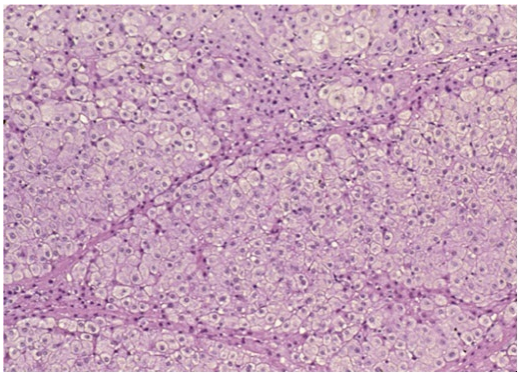

Figure 2. Septal fibrosis and disarranged lobular structure.

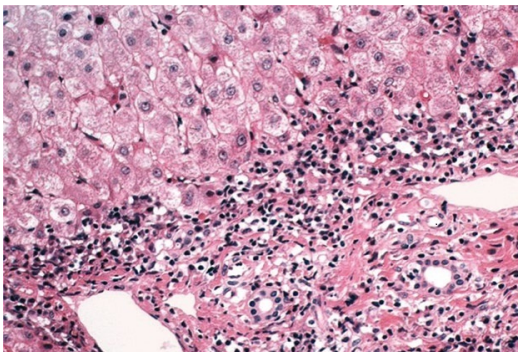

Figure 3. Lynphoplasmocitic interfase hepatitis.

other relevant histological findings.

The differentiation between acute cellular rejection, recurrence of HCV or autoimmune hepatitis can often be difficult, due to the superimposition of the histologic findings [3]. The absence of findings suggestive of acute or chronic cellular rejection (no eosinophils, bile duct lesions or endothelialitis), together with the exclusion of other causes of graft dysfunction, suggests a *de novo* autoimmune process. Liver graft dysfunction in transplant patients treated with PEG-INF/RBV who develop similar autoimmune phenomena to a *de novo* acute autoimmune hepatitis (AIH) has been described in various recent reports [7,8]. The patient histologically presented an interfase hepatitis, with no biliary lesions or granuloma, as well as no genetic liver disease (normal values of alpha 1-anti-trypsin, serum ceruloplasmine, iron and ferritin levels). Biochemically, there was a predominant serum aminotransferase abnormality (AST 557 IU/L ALT 523 IU/L). Additionally, no toxic or alcohol injury was reported. But, on the other hand, he lacked the rest of the criteria necessary for *de novo* AIH, such as the absence of autoantibodies (ANA, SMA, anti-LKM1, AMA) and normal levels of globulin, gamma-globulin or immunoglobulin G [9]. Considering all of these and the presence of HCV, we believe that it concerned an unusual form of presentation of rejection, triggered by the treatment with PEG-INF/RBV, that mimics AIH. Fiel *et al*. [10] recently published a series of cases of liver transplant patients with HCV who had a severe plasma cell infiltrate simulating AIH and which they called post-transplant plasma cell hepatitis. The authors related the entity to subtherapeutic levels of immunosuppression and considered it to be a variant of acute rejection. Although these authors did not associate the situation with the use of interferon, the known association between this drug and autoimmune phenomena suggests the need for further study to define the role of PEG-INF in the development of plasma cell hepatitis and to establish its relation with rejection or AIH [11].

In our patient, an increase in immunosuppression and treatment with steroids may have been indicated [12]. However, this was impeded by the concurrence of severe acute infectious processes, extrahospital pneumonia and urinary tract infection, so that we could not therefore evaluate any possible response to this.

In conclusion, treatment with interferon in liver transplant patients who experience a relapse of HCV may trigger autoimmune phenomena which can, unusually, lead to potentially severe side effects, including graft loss. This, together with the difficulty differentiating between rejection, recurrence of HCV and AIH, necessitates adequate evaluation of the treatment requirements in patients with recurrent HCV.

Withdrawal of therapy and the possible use of steroids should be considered as the first line of therapy.

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ABBREVIATIONS

PEG-INF: pegylated interferon;
RBV: ribavirin;
CMV: cytomegalovirus;
HCV: hepatitis C virus;
HAV: hepatitis A virus;
HBV: hepatitis B virus;
ANA: antinuclear antibody;
AMA: antimitocondrial antibody;
ASMA: anti-smooth muscle antibody;
antiKLM: anti-liver/kidney microsomal antibody.

