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CASE REPORT

Severe sirolimus-induced acute hepatitis in a renal transplant recipient

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Summary

Sirolimus is currently used as an immunosuppressive agent in kidney transplantation due to its lack of nephrotoxicity and antiproliferative properties. However, a large number of side effects has been described with the use of m-Tor inhibitors. Most are reversible when treatment is withdrawn. Hepatotoxicity is one of these side effects, considered as a benign condition and resulting generally in a transitory and small increase in transaminase levels. We report here, to the best of our knowledge, the first case of severe sirolimus-induced acute hepatitis confirmed by liver biopsy, in a renal transplant recipient. This condition was completely cured in few weeks after sirolimus withdrawal.

Introduction

Sirolimus is a macrocyclic triene antibiotic which has antifungal, immunosuppressive and potent antitumoral properties. Treatment with sirolimus has been associated with inhibition of graft-specific histological changes, with evidence suggesting a benefit in prevention and treatment [1] of interstitial fibrosis and tubular atrophy in renal transplant patients, inhibition of bronchiolitis obliterans in lung transplant patients [2] and reduction of hepatic fibrosis in a rat model [3]. However, the combination of sirolimus with mycophenolate mofetil (MMF) does produce a side effect profile somewhat different to that observed with calcineurin inhibitors-based regimens [4]. Hepatotoxicity is one of these side effects resulting generally in a transitory and small increase in transaminase levels and is considered as a benign condition [5]. We report here, to the best of our knowledge, the first case of severe sirolimus-induced acute hepatitis confirmed by liver biopsy, in a renal transplant recipient.

Case report

A 54-year-old man with end stage renal failure due to IgA glomerulonephritis was admitted to our unit in August 2007 for his first renal transplantation. His past history was uneventful. The donor was a 66-year-old woman and there were three human leucocyte antigen donor-recipient mismatches. Initial immunosuppression consisted of a sequential quadruple therapy using induction by anti-interleukin 2 receptor antibodies followed by steroids, cyclosporine A and MMF.

During month 2 post-transplantation, toxic agranulocytosis (neutrophils count = 780/mm^3) most probably due to the association of MMF and valaciclovir occurred. This episode was resolved after valaciclovir withdrawal, MMF dose reduction and granulocyte colony-stimulating factor administration.

During month 3 post-transplantation, the patient received steroid pulses for subclinical rejection diagnosed with a protocol biopsy.

During month 7 post-transplantation, he was treated for cytomegalovirus infection and in month 7 post-transplantation for severe pneumocystosis.

Finally, epidermoid carcinoma of the face occurred in month 10 post-transplantation and was surgically treated.

In September 2008, due to skin cancer and bad renal function (creatinine = 21.6 mg/l) associated with vascular lesion on graft biopsy, ciclosporine A was withdrawn and sirolimus was introduced (3 mg/day) in association with prednisolone (5 mg/day) and MMF (500 mg twice daily). Target blood levels were between 8 and 12 ng/ml. The rest of the treatment was: omeprazole 20 mg/day, alfuzosine 10 mg/day, irbesartan 150 mg/day, hydrochlorothiazide 12.5 mg/day, trimethoprim-sulfamethoxazole 400 mg/day, atenolol 50 mg/day, epoetin β 5000 IU/week. The use of nonprescription agents and complimentary and alternative medicines were ruled out after questioning the patient.

During the first month of treatment, sirolimus was well tolerated. In the second month after switch of treatment, the patient was readmitted for fatigue. Clinical examination was normal. Biological testing (Fig. 1) showed acute hepatitis with an increase in alanine aminotransferase (ALT) levels from 14 to 609 IU/l (normal < 42 IU/l), aspartate aminotransferase (AST) levels from 13 to 861 IU/l (normal < 38 IU/l), and γ-glutamyl transpeptidase levels from 50 to 1043 IU/l (normal 8–61 IU/l). Total bilirubin was 92 μmol/l. There was sign of hepatic insufficiency (prothrombin index of 60%). C-reactive protein level was slightly elevated at 29 mg/l. Serum creatinine level was 23.8 mg/l. Haemoglobin level, leukocyte and platelet counts were normal. Blood and urine culture were negative. There was no significant proteinuria or haematuria. Mushroom consumption was ruled out after questioning the patient. Abdominal ultrasonography was normal, with no evidence of obstruction of the biliary duct. Serologic testing for HBV and HCV was negative, as was HAV immunoglobulin M. Polymerase chain reaction (PCR) for B, C and E hepatitis virus, cytomegalovirus, Epstein–Barr virus and human Herpes virus type 6 were negative. Testing for autoimmune hepatitis was also negative (anti-mitochondria and anti-LKM1 antibodies). Sirolimus blood level was 10 ng/ml at the time of liver biopsy. No overdose was noted prior the occurrence of acute hepatitis.

Liver biopsy (Figs 2 and 3) was then performed showing cytolytic and cholestatic hepatitis with lymphocytes and eosinophil infiltration in the portal space without

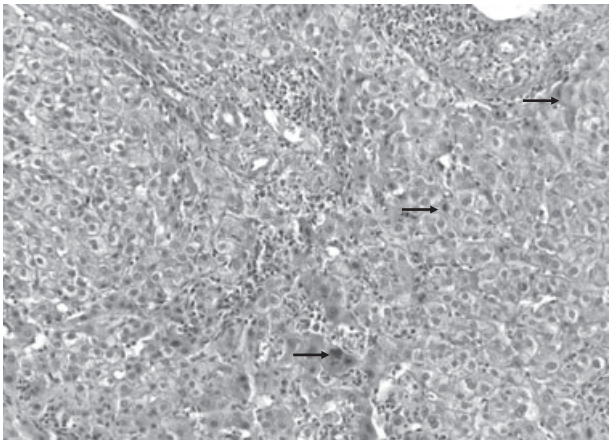

Figure 2 Haematoxylin-eosin stain × 200 showing cytolytic and cholestatic hepatitis with lobular infiltrate of lymphocytes and hepatocyte necrosis (black arrows).

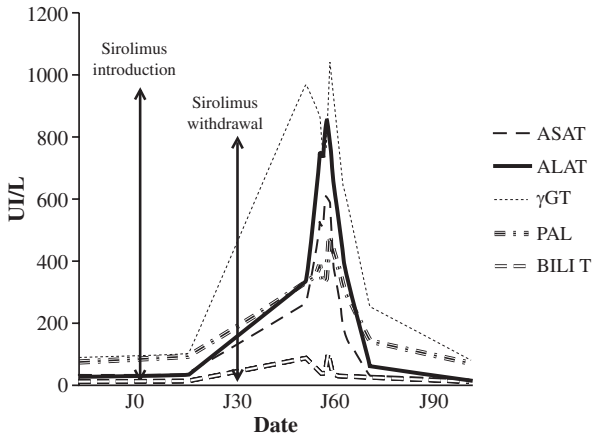

Figure 1 Outcomes of liver enzyme during hepatitis episode. (AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase).

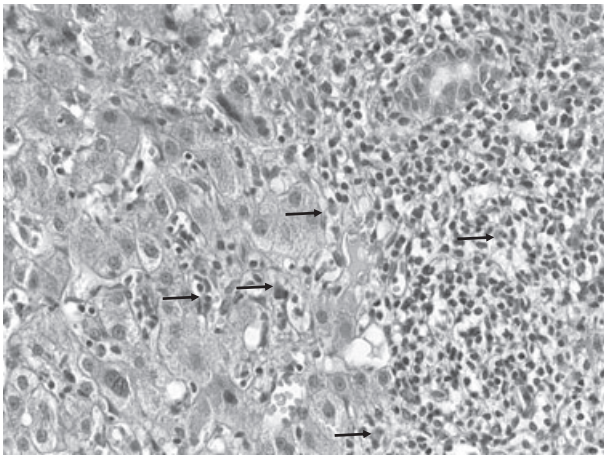

Figure 3 Haematoxylin-eosin stain × 400 showing polymorph infiltrates in portal space with lymphocyte, plasma cells and eosinophil (black arrows).

granuloma, consistent with drug-related hepatitis. Sirolimus being the only drug recently introduced, sirolimus-induced hepatitis was therefore suspected. Sirolimus was withdrawn and cyclosporin reintroduced leading to a dramatic decrease in transaminase levels with normalization within 5 weeks.

At this time, 9 months after the hepatitis episode, the patient clinical examination is normal with no recurrence of skin cancer, hepatic tests are in the normal range and creatinine level is 26.1 mg/l.

Discussion

Sirolimus is a potent immunosuppressant with a mechanism of action that is distinct from that of either calcineurin inhibitors (CNI) or antimetabolites [6]. It is now used as the basis for therapies that spare or avoid these nephrotoxic drugs [7,8]. The adverse event profile observed with sirolimus clearly differs from that seen with CNI [4]. The major side effects reported with increasing frequency are dyslipidaemia, bone marrow suppression (anaemia, leukopenia and thrombocytopenia), delayed wound healing, pneumonia and proteinuria [4,9,10]. There are also several uncommon but nevertheless significant side effects such as skin rashes, peripheral oedema and oral mucosal ulcers. Except for pneumonia, most of these side effects respond to a reduction in dose.

Hepatotoxicity is also a side effect reported with the use of sirolimus resulting generally in a transitory and small increase in transaminase levels and is considered as a benign condition [5]. Groth *et al.* have reported an incidence of 17% for increase in transaminases levels in patients under sirolimus therapy compared to 3% in patients under cyclosporine therapy [5]. No case of severe acute hepatitis has been described in this study.

We report the first case of sirolimus-induced severe hepatitis in a renal transplant recipient, confirmed by liver biopsy for whom sirolimus withdrawal leads to a dramatic normalization of hepatic tests within 5 weeks. The ocurrence of hepatitis following the introduction of sirolimus, the absence of others drug recently introduced, the negativity of the extensive check-up for other cause of hepatitis, the result of liver biopsy and the rapid normalization of liver tests after sirolimus-withdrawal prove the diagnosis of sirolimus-induced hepatitis.

One other case of sirolimus-associated hepatotoxicity has been described after renal transplantation [11]. However, in this case, liver biopsy was not contributive and other drugs could be incriminated. Moreover, the evolution of hepatotoxicity was quite slow (several months) whereas in our case, hepatic tests were normal during the first 2 months of treatment and acute hepatitis developed rapidly in 3 weeks during the third month of therapy.

Some cases of sirolimus-related hepatotoxicity have also been reported following liver transplantation [12] leading to drug discontinuation.

There have been cases report of mycophenolate-induced hepatotoxicity [13,14]. When taking a patient off of cyclosporine MMF AUC is increases by approximately 25% due to an increase in the enterohepatic circulation of MPA-glucuronide. However, in our case, MMF AUC performed 3 weeks before the occurrence of hepatitis and 15 days after the introduction of sirolimus was 18.6 mg h/l. So, MMF hepatotoxicity due to high exposure could not be incriminated in this case.

This observation is important for renal transplantation but also for liver transplantation. Indeed, cytolysis is frequent after liver transplantation and in this situation; potential sirolimus toxicity must be considered in the same way as acute rejection or vascular problems.

The exact mechanisms of sirolimus hepatotoxicity are unknown. The presence of eosinophilia on liver biopsy could be consistent with an allergic drug reaction leading to hepatocyte necrosis. Moreover, rapamycin may induce reduction of hepatocytes regeneration by an increase sensitivity of hepatocytes to TGF-β antiproliferative effects and to TRAIL/TNF and interferon-induced apoptosis [15].

In conclusion, clinicians must be aware that sirolimus may induce severe toxic hepatitis. A liver biopsy is generally necessary to confirm the diagnosis due the absence of specific symptoms. Prompt withdrawal of the drug is then necessary.

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