CASE REPORT

Sirolimus-induced drug fever and ciclosporin-induced leukencephalopathy with seizures in one liver transplant recipient

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Abstract

We describe the first case of sirolimus-induced drug fever in a female liver transplant recipient, with a history of hepatitis C-induced end-stage liver cirrhosis in 1999. In 2005, six years after transplantation, she developed calcineurin inhibitor-induced renal function impairment. Immunosuppression was switched from tacrolimus to sirolimus. Two days after the intake of sirolimus, she developed daily fever spikes, but no infectious focus was found. Antibiotic therapy had no influence on the fever. After fourteen days, sirolimus was switched back to tacrolimus and the fever disappeared. In history, the patient developed ciclosporin-induced generalized seizures eleven days after liver transplantation, followed by the development of a motoric speech disorder. Magnetic resonance imaging (MRI) findings were consistent with leukoencephalopathy, therefore immunosuppressive therapy was changed from ciclosporin to tacrolimus and the neurologic symptoms improved significantly. Our case is the first reported case of sirolimus-induced drug fever. In addition, the patient showed the rare occurrence of ciclosporin-induced leukencephalopathy with seizures.

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Key words: Liver transplantation; Immunosuppression; Side effects

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INTRODUCTION

Ciclosporin and tacrolimus are very potent immunosuppressive drugs which have been used in organ transplantation for more than 10 years. Both are calcineurin-inhibitors and have the same mode of action. They are mainly metabolized by cytochrome P450 3A4 in bowel and liver^[1]. The main side effects of ciclosporin and tacrolimus are renal toxicity, neurotoxicity, arterial hypertension, diabetes mellitus and hyperlipidemia^[2]. Combination therapy of these two drugs is therefore not useful. Until now, many immunosuppressive regimens contain either ciclosporin or tacrolimus in combination with other immunosuppressive drugs. For several years, the mammalian target of rapamycin (mTOR) inhibitor, sirolimus (Rapamune®), has also been used as an immunosuppressive drug in organ transplantation. Similar to ciclosporin, it is also metabolized in bowel and liver by cytochrome P450 3A^[1]. The main advantage of sirolimus is its virtual lack of nephrotoxicity. The main side effects are hyperlipidemia, anemia, and thrombocytopenia. Ciclosporin and sirolimus are substrates of the efflux-transporting pump P-glycoprotein, which is among others localized in gut and liver^[3]. Ciclosporin and sirolimus have different modes of action and synergistic effects^[4]. Therefore, in patients with renal impairment, combination therapy allows a dose reduction of both drugs which results in reduced side effects, especially on renal toxicity. Ciclosporin, tacrolimus as well as sirolimus can be given as monotherapy or in combination with other drugs. Patients with progressive impairment in renal function due to ciclosporin- or tacrolimus-induced nephrotoxicity can be switched to sirolimus monotherapy to prevent further loss of renal function^[5].

CASE REPORT

We present the case of a 63-year-old female patient, who was first diagnosed with chronic hepatitis C virus infection in 1996 (genotype 1b). Infection was most likely due to several blood transfusions which were necessary after resection of a cyst of the left ovary in 1973. In 1997

Figure 1 Magnetic resonance imaging (MRI) of the head showing almost symmetric periventricular white matter lesions consistent with leukoencephalopathy and a beginning encephalitis (FLAIR TR 8000 ms, TE 110 ms).

histopathological liver examination was performed for the first time and showed inflammation grade IV, as well as fibrosis grade III (Ishaak-Score). Therefore, interferon monotherapy was given for one year (relapse after end of treatment). Six months later, she presented with decompensated liver cirrhosis and esophageal bleeding due to varices grade III. After re-compensation she was listed for liver transplantation in January 1999. Neurologic status was normal prior to liver transplantation. Liver transplantation was successfully performed in August 1999. The explanted liver demonstrated complete cirrhosis (716 g). The liver graft showed no histological damage and normal perfusion as judged by duplex sonography. Immunosuppressive therapy was started with a combination therapy of ciclosporin, azathioprine and steroids. Eleven days after the start of immunosuppressive therapy, she developed a generalized seizure, which could be stopped with diazepam. Several focal and generalized epileptic fits followed and the patient developed a motoric speech disorder which finally resulted in dysarthria and complete aphasia. The patient showed no other neurologic symptoms. A magnetic resonance imaging (MRI) of the head showed periventricular white matter lesions consistent with leukoencephalopathy and a beginning encephalitis (Figure 1). The described symptoms were interpreted as side effects of ciclosporin medication. Therefore, immunosuppressive therapy was changed from ciclosporin to tacrolimus (FK 506, Prograf®) and antiepileptic therapy was initiated with 400 mg gabapentin four-times a day. The dysarthric disorder improved significantly, but residuals still existed with no occurrence of further seizures at the time when this report was written. During the treatment with steroids and tacrolimus, the patient developed an insulin-dependent diabetes mellitus.

In December 1999, transplant reinfection with hepatitis C virus was diagnosed. In July 2001, liver histology showed a beginning fibrosis of the liver graft with little infiltration of inflammatory cells, corresponding to chronic hepatitis (Yano classification: grading 4, staging 3). Therefore, antiviral therapy with interferon alpha (1.5 Mio units/wk) and ribavirin (600 mg/d) was initiated. Due to pancytopenia azathioprine medication, ribavirin was stopped one year later. Hepatitis C virus re-infection was controlled by 90 µg pegylated interferon alpha 2a once a week subcutaneously. In 2003, a control MRI showed no deterioration of leukoencephalopathy.

In September 2005, the patient presented with progressive renal impairment and peripheral oedema.

Serum creatinine (193 µmol/L, normal range 44-80 µmol/L) and urea levels (15 mmol/L, normal range 2.0-8.3 mmol/L) were elevated. Urinary tests confirmed chronic renal failure with a creatinine clearance of only 20 mL/min. Therefore, immunosuppressive therapy was changed from tacrolimus (Prograf®) to sirolimus (Rapamune®). Two days after starting sirolimus, the patient developed fever of 38°C, which reached up to 39°C on the next day. No reason for the fever was found either with blood cultures or with urine examination, or with X-rays. The patient showed no other specific clinical symptoms (e.g. diarrhea, skin lesions, pharyngitis). Leucocytes (3.8/nL, normal range 4.8-10.8/nL) and thrombocytes (96/nL; normal range 130-440/nL) were reduced, most likely due to interferon therapy and splenomegaly. Erythrocyte sedimentation rate (ESR) and C-reactive protein were normal and cytomegalovirus and Epstein Barr virus screening was negative. Antibiotic therapy with piperacilline and sulbactame was given for 6 d, but did not result in any improvement of the daily spikes of fever, which occurred every evening (Figure 2). After 14 d, the fever disappeared when sirolimus was switched back to tacrolimus in combination with mycophenolate mofetil. Thus, sirolimus-induced drug fever was diagnosed.

At the time when we wrote this report, the patient was in a good clinical condition, neurologic status remained stable but dysarthria still existed, and renal function (133 µmol/L serum creatinine) improved with dose reduction of tacrolimus and intake of 3 litres fluid per day.

DISCUSSION

The clinical and radiological features demonstrated in this patient are consistent with those of leukoencephalopathy, a rare condition previously described in patients treated with ciclosporin and tacrolimus^[6,7]. In our patient as in most patients previously described, leukoencephalopathy associated with immunosuppression occurred early during therapy and was reversible with good recovery. One case of late-onset leukoencephalopathy with a fatal outcome has been reported^[8]. In the reported case, the symptoms due to leukoencephalopathy improved after withdrawal of ciclosporin, but unfortunately, did not completely disappear. The patient also suffered from seizures, which disappeared after withdrawal of ciclosporin and initiation of antiepileptic therapy with gabapentin.

Neurologic symptoms represent serious complications following orthotopic liver transplantation and may be caused by various perioperative factors or may develop due to drug-specific toxicity of immunosuppression. The incidence of neurotoxicity seems to be higher in patients treated with tacrolimus than in patients treated with ciclosporin in the early postoperative period, after retransplantation as well as in the late phase^[9]. Watson *et al*^[10] described two patients who suffered from neurological events, one with encephalopathy and the other with recurrent seizures. Both patients were on sirolimus and ciclosporin after orthotopic liver transplantation and stabilized after withdrawal of ciclosporin. Choi *et al*^[11] reported that of the 367 patients who received OLT, 48 suffered from neurological complications, 17

Figure 2 Temperature curve before, during (14 d) and after sirolimus therapy. Antibiotic therapy with piperacilline and sulbactame given from d 3 to 9 showing no effect. m: morning; e: evening.

developed seizures (status epilepticus occurred in two patients, generalized tonic-clonic seizures in five patients). Although neurotoxicity is not a frequent side effect of ciclosporin medication, the described cases in the reports are in accordance with our patient's symptoms (seizures and consecutive motoric speech disorder) which could be interpreted as side effects of ciclosporin medication. The motoric dysarthric disorder improved significantly after a change of the immunosuppressive regimen, but residuals still existed.

Idilman *et al*^[12] described two cases of reversible posterior leukoencephalopathy manifested as headache, nausea and seizures associated with the use of immunosuppressive drugs following liver transplantation. One case of a 29-year old patient treated with ciclosporin after a liver transplant for primary sclerosing cholangitis showed late-onset progressive leukoencephalopathy due to immunosuppressive therapy and died three years later. These reports suggest that neurological side effects should be cautiously observed when alteration of immunosuppressive therapy is considered.

Although ciclosporin is an immunosuppressive agent widely used in the management of liver transplant recipients, neurological complications have been described in only few cases. The two different neurological side effects found in our patient are probably associated with ciclosporin medication.

Side effects of sirolimus include delayed wound healing, oral ulcers, hypertension, interstitial pneumonitis, infections, and most importantly, hyperlipidemia and myelosuppression^[13]. Concerning the central nervous system, it has been shown that sirolimus can alter cell metabolism of primary astrocytes, thus resulting in similar neurotoxicity as experienced by tacrolimus and ciclosporin^[14]. Perhaps the greatest potential benefit of sirolimus for liver transplant recipients is its lack of nephrotoxicity as compared to calcineurin inhibitors^[15,16].

At present, no single immunosuppressive regimen can offer a clear advantage over another with regard to prevention of cellular rejection, graft survival, and patient survival^[17]. In our patient, immunosuppression was switched from ciclosporin to sirolimus due to nephrotoxicity of ciclosporin. We clearly could show that the fever in our patient was not related to infection, but most likely to sirolimus. Two days after starting immunosuppression with sirolimus, our patient developed fever with no infectious focus found in blood cultures, urine tests or in radiologic examinations. Even the antibiotic therapy did not show any improvement of the daily spikes of fever in the evening. Due to the diagnosis of sirolimus-induced drug fever, the immunosuppressive medication was changed back to tacrolimus in combination with mycophenolate mofetil and no more fever spikes occurred. To our knowledge, this is the first reported case of drug-fever obviously related to sirolimus. Two years ago, Dorschner *et al*^[18] described a 2-year drug-related fever caused by everolimus, a sirolimus-derived immunosuppressant (Certican®). Their patient was 66 years old and received a cardiac transplant due to dilatative cardiomyopathy. The immunosuppressive regimen consisted of steroids, ciclosporin, and everolimus. Two weeks after the replacement of everolimus with azathioprine, all the patient's symptoms disappeared.

This is the first report of a liver transplant recipient with rare immunosuppressant-induced side effects. Until now, we could not unravel the mechanism(s) responsible for these side effects. A mutation in cytochrome P450 3A or FK-binding protein 12 (FK-BP12) seems to be unlikely, because our patient had no side effects under medication with tacrolimus, which is also metabolised by cytochrome P450 3A and bound to FK-BP12. Since ciclosporin, tacrolimus and sirolimus are substrates of the ATP-binding efflux pump P-glycoprotein, located in several organs like bowel and liver, it seems to be impossible that this protein might cause the several drug-side effects in our

patient. Therefore, we speculate that immunosuppressant drugs may have some influence on proteins in the central nervous system.

In conclusion, ciclosporin is an immunosuppressive agent widely used in the management of solid organ transplantation. Sirolimus is a powerful immunosuppressant used to prevent acute rejection episodes in patients who have undergone transplantation, particularly when nephrotoxic effects of calcineurin inhibitors become problematic.

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