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Letter to the Editor

Probable sirolimus-induced rupture of arterial anastomosis after liver transplantation in a patient intolerant of tacrolimus

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To the Editor:

Liver transplantation remains the only cure for end-stage liver disease. Tacrolimus is widely used as a first-line immunosuppressive drug to prevent organ rejection after liver transplantation [1–3]. However, tacrolimus has a narrow therapeutic index and wide inter-individual variability in pharmacokinetics, which can result in underimmunosuppression or toxicity. Orally administered tacrolimus is rapidly absorbed from the distal gastrointestinal tract and extensively metabolized in the liver and intestinal walls by cytochrome P450 (CYP) 3A4 and 3A5 [2,4,5]. The activity of these enzymes has significant influence on the pharmacokinetics of tacrolimus. *CYP3A5* polymorphism roots the individual differences in tacrolimus bioavailability [1]. Due to the drug's narrow therapeutic range, dosage adjustments to achieve the desired blood concentration are challenging. Serum concentrations above the therapeutic range may result in nephrotoxicity and neurotoxicity [5]. An alternative to tacrolimus is sirolimus, a newly developed immunosuppressive agent for use in organ transplant recipients [6,7]. However, sirolimus is known to impair wound healing, which limits its early clinical application [8,9]. We report a case of probable sirolimus-induced rupture of arterial anastomoses after liver transplantation in a patient intolerant of tacrolimus.

A 54-year-old woman with hepatocellular carcinoma underwent liver transplantation. The liver graft (1600 g) was from a brain death donor. The recipient's and donor's common hepatic arteries were anastomosed in an end-to-end fashion by 7–0 PROLENE interrupted sutures (Ethicon; Johnson & Johnson, New Brunswick, NJ, USA). The total operation time for the recipient was 345 min. The anhepatic phase time and warm and cold ischemic times were 47 min, 0 min, and 166 min, respectively. Estimated blood loss was 2500 mL. Intraoperatively, 4 units of packed red blood cells and 1920 mL fresh frozen plasma were transfused. Intraoperative and postoperative Doppler ultrasound confirmed complete patency of the anastomoses of the hepatic artery, portal vein, and hepatic vein.

The postoperative course was uneventful. Induction immunosuppressive therapy was with basiliximab for 2 days. Tacrolimus (3.5 mg twice a day) and mycophenolate mofetil (MMF; 250 mg twice a day) were administered orally from postoperative day (POD) 3 onward. The patient was discharged 1 week after the surgery.

She presented with elevated serum levels of creatinine (141 μmol/L; normal: 44–97 μmol/L) and tacrolimus (24.7 ng/mL; normal: 4–6 ng/mL) 20 days after the surgery in a routine follow-up visit (Fig. 1). Acute kidney injury was diagnosed and tacrolimus was stopped, following which serum creatinine level began to decline. After serum creatinine returned to normal, tacrolimus (2 mg twice a day) was reintroduced. She was discharged on POD 26 after her general condition was improved.

On POD 30, the patient was readmitted with severely elevated serum levels of creatinine (268 μmol/L) and tacrolimus (19.2 ng/mL). Doppler ultrasound showed no abnormalities in the transplanted liver or the portal and arterial anastomoses. Gene sequencing revealed heterogeneous mutation of *CYP3A5*3*. On POD 31, tacrolimus was discontinued, and the immunosuppressive regimen was changed to MMF (500 mg twice a day) and sirolimus (loading dose: 6 mg once a day for 2 days; maintenance dose: 2 mg once a day). On POD 34, the serum sirolimus level was 13.9 ng/mL. On POD 37, serum hemoglobin level dropped suddenly to 59 g/L (normal: 120–150 g/L). Computed tomography showed multiple peritoneal hematomas (Fig. 2). Emergency laparotomy revealed rupture of the arterial anastomosis, with large amounts of blood and clots in the peritoneal cavity. Peritoneal lavage and reanastomosis of the left gastric artery and the donor proper hepatic artery were performed. The patient survived the operation but died of multiple organ failure on POD 45.

Tacrolimus, a calcineurin inhibitor, is among the most effective immunosuppressive drugs used after liver transplantation [4,10,11]. However, toxicity can occur at concentrations slightly above or even within its therapeutic range. The drug has been reported to cause nephrotoxicity, neurotoxicity, diabetes, and gastrointestinal disturbances, and to increase the risk of infections and malignancies [4,5,12].

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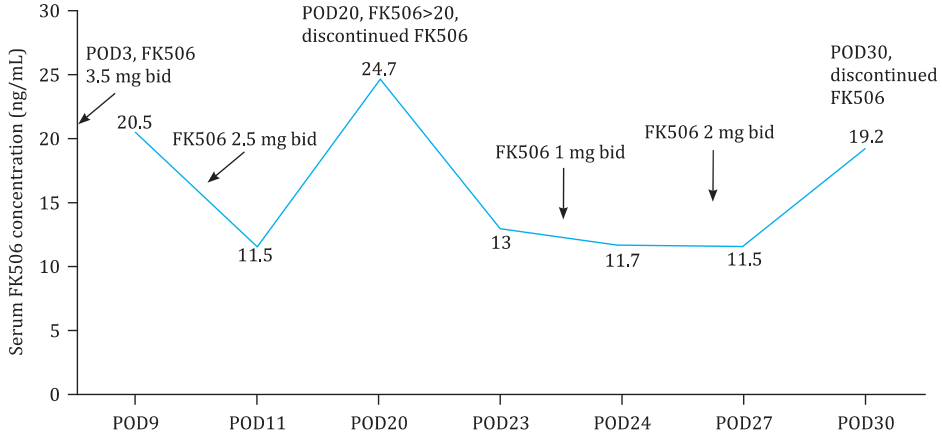

Fig. 1. The serum tacrolimus (FK506) level was detected after orally administering tacrolimus.

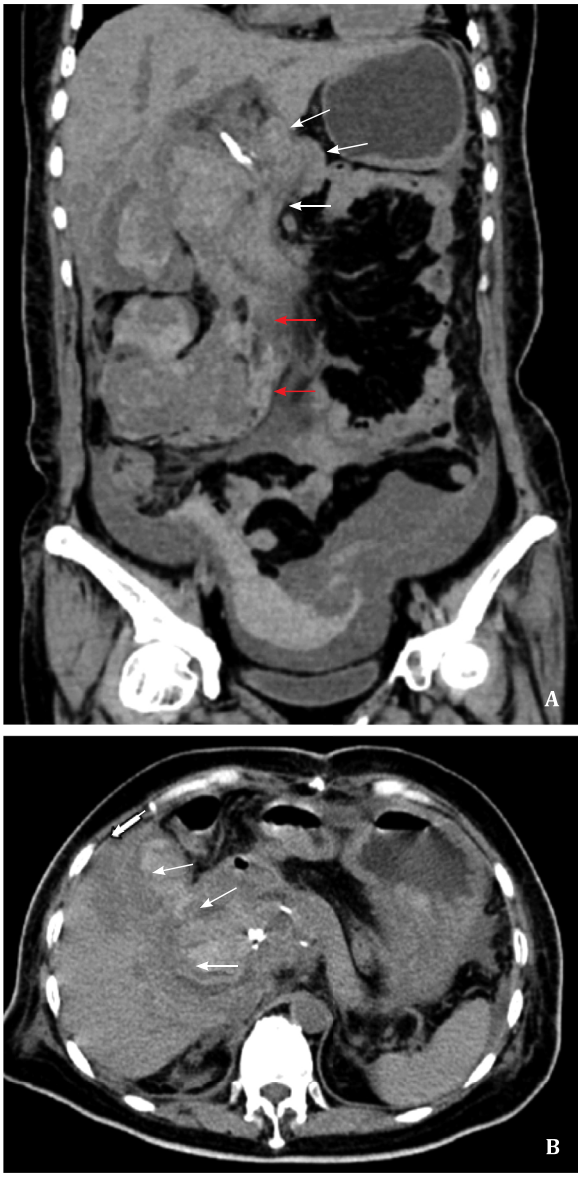

Fig. 2. Computed tomography performed on postoperative day 37. **A:** In the coronal plane, computed tomography indicated perihepatic hematoma (white arrows) and multiple hematomas in the abdominal cavity (red arrows); **B:** In the horizontal plane, computed tomography indicated perihepatic hematoma (white arrows).

Two factors probably contributed to the elevation of serum tacrolimus level in our patient. First, decreased enzymatic activity of CYP3A may have led to the accumulation of tacrolimus in the body. CYP3A, a monooxygenase found in liver and intestine, is one of the key proteins involved in tacrolimus metabolism [1,4,13,14]. *CYP3A5*, a member of the subfamily of CYP3A enzymes, accounts for 6%–99% of the total hepatic CYP3A content [5]. *CYP3A5* polymorphism (*CYP3A5*3*, 6986A>*G*), which is due to a splicing defect, can lead to loss of *CYP3A5* activity [1,3–5,13,14] and thus to tacrolimus toxicity. Second, elevation of serum tacrolimus level may also have been caused by hepatic dysfunction. Tacrolimus is mainly metabolized by the liver. Hepatic dysfunction, which is common after liver transplantation, can decrease tacrolimus clearance and increase the elimination half-life, and thus result in toxicity [5].

Tacrolimus can cause severe tubular and interstitial fibrosis, as well as focal hyalinosis of small renal arteries and arterioles [12], leading to acute and chronic kidney disease after liver transplantation [5]. In our patient, we substituted tacrolimus with sirolimus at first suspicion of acute renal injury. Sirolimus has a more favorable safety profile and is less likely to cause nephrotoxicity and neurotoxicity [6,7]. However, impaired healing has been reported in 20%–50% of solid organ transplant recipients treated with sirolimus [6,7,15]. This effect may be due to the antiproliferative actions of sirolimus. It has been shown to impair epithelial healing, prevent cholangiocyte regeneration, impede fibroblast proliferation, and inhibit angiogenesis [15–17].

The patient underwent a successful liver transplantation, whereas the postoperative course was uneventful. Postoperative Doppler ultrasounds performed every 2–3 days confirmed patency of the anastomoses of the artery and the veins within 1 month after liver transplantation. There was no sign of abscess or pseudoaneurysm of the arterial anastomosis at that time. And rupture of the arterial anastomosis happened suddenly just days after the initiation of sirolimus. Therefore, sirolimus would be a possible trigger of the devastating rupture of arterial anastomosis. Moreover, mTOR inhibitor inhibits cell proliferation and angiogenesis. Although there is no robust data available concerning the influence of mTOR inhibitors on wound healing after transplantation, some trials have indicated that wound healing may be affected in transplant patients receiving a loading dose of sirolimus and/or high exposure levels [9]. Albano et al. [18] suggested that late conversion to sirolimus at 3 months post-transplant does not affect the occurrence of wound complications. Considering its possible adverse effect on wound healing, it's reasonable to avoid using sirolimus at the early stage after LT. Unfortunately in this patient, due to tacrolimus toxicity, she received sirolimus 6 mg for 2 days as a loading dose and 2 mg as a maintenance dose just one month

after LT. The loading dose and high exposure levels of sirolimus potentially impaired the stability of the arterial anastomosis and finally led to the rupture.

Immunosuppressive drugs used after organ transplant have various serious adverse effects. We report a liver transplantation patient with *CYP3A* mutation who developed acute renal injury due to tacrolimus toxicity. However, substitution with sirolimus led to arterial anastomosis failure. Further studies are necessary to clarify the safety profile of sirolimus.

Contributors

LTB proposed the study. LMY and MT performed the research and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts. LTB is the guarantor.

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Ethical approval

An informed consent was obtained from the patient.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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