



Tacrolimus (FK 506) induced thrombotic thrombocytopenic purpura after ABO mismatched second liver transplantation: salvage with plasmapheresis and prostacyclin

WING Y. AU,* ALBERT KW LIE,* CLARENCE CK LAM,° SHEUNG-TAT FAN,# CHI-LEUNG LIU,# KARL YOUNG,® CHUNG-MAU LO#

Departments of *Medicine, °Pathology, and #Surgery and ®Intensive Care, Queen Mary Hospital, Hong Kong, China

ABSTRACT

We report the course of thrombotic thrombocytopenic purpura (TTP) in a patient receiving tacrolimus (FK506) immunosuppression for an ABO mismatched second liver graft. A Chinese woman with fulminant hepatitis-B reactivation failed a living-related orthotopic liver transplantation (OLT) due to portal vein thrombosis. An ABO mismatched cadaveric OLT (group A to O) was performed, with peri-operative plasmapheresis to reduce anti-A hemagglutinin titers. On day 30, she developed fever, hemolysis, thrombocytopenia and neurologic dulling. Prominent microangiopathic features in peripheral blood film, and characteristic brain lesions on magnetic resonance imaging confirmed TTP. She responded initially to intensive plasmapheresis with cryosupernatant replacement, and withdrawal of FK506. An attempted reintroduction of FK506 for threatened rejection led to TTP exacerbation. This was controlled with prolonged plasmapheresis and a ten-day infusion of prostacyclin. Immunosuppression was changed to mycophenolate mofetil. By day 53, the peripheral film and lactate dehydrogenase level had returned to baseline and plasmapheresis was stopped.

©2000, Ferrata Storti Foundation

Key words: tacrolimus, TTP

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare microvascular hemolytic disease. The central feature in the pathogenesis of TTP is abnormal platelet aggregation in the microcirculation, secondary to abnormal platelet endothelial interaction.¹ Recent evidence has shown that many primary cases are of immune-mediated etiology.^{2,3} However, in secondary cases, an immune etiology may or may not be implied.^{4,5} A large number of drugs have been implicated as causative agents.⁶ Some, such as cyclosporin and alkylating agents, have both been implicated as cause and also used for

treatment. TTP has rarely been reported in the setting of orthotopic liver transplantation (OLT).^{7,8} The prognosis of TTP is often poor, partly due to delayed diagnosis and definitive therapy, and partly due to the serious nature of the underlying conditions.⁹ We report a case of tacrolimus (FK506) induced TTP after ABO mismatched second OLT. The disease ran a protracted clinical course, but the patient was successfully salvaged with intensive plasmapheresis, and prostacyclin infusion after FK506 withdrawal.

Report of a case

A 44-year old Chinese woman (blood group O) underwent OLT from an ABO matched living sibling donor because of a fulminant flare-up of chronic hepatitis B virus (HBV) infection, under lamivudine coverage.^{10,11} Graft failure occurred due to portal vein thrombosis. She underwent a second emergency OLT 17 days later from a cadaveric donor (blood group A). Peri-operative plasmapheresis (one plasma volume exchange: four liters), with fresh frozen plasma replacement was performed, immediately before her operation, and four and seven days after it. Serial monitoring of the anti-A hemagglutinin titers was performed, and levels were kept below 1 in 8.⁶ For both OLTs, the immunosuppression used was prednisolone (20mg daily) and FK506 (target trough level 10-15 ng/mL),¹² with the addition of OKT3 induction (5 mg × 5 days) for the second OLT. One month after the second OLT, she was admitted to the intensive care unit with swinging fever, pancytopenia and a grossly elevated lactate dehydrogenase (LDH) level (506U/L normal: 200-360) (Figure 1). Her complete blood picture showed hemoglobin (Hb): 4.9g/L, white cell count (WCC): 5.9×10⁹/L and platelet count (Plt): 15×10⁹/L (uncorrected for red blood cell (RBC) fragments). A peripheral blood film showed severe red cell fragmentation, polychromasia, nucleated RBC and very severe thrombocytopenia. The coagulation profile was normal. Rapid clinical deterioration followed, with renal failure, sepsis and seizures. A magnetic resonance imaging (MRI) scan showed hyperintense white matter infiltrates in bilateral cerebellar hemispheres and occipital lobes, characteristic of TTP¹³ (Figure 2). Extensive screening for auto-immune antibodies, direct antiglobulin test (DAT), lupus anticoagulant and viral studies were negative, and her anti-A hemagglutinin titer was not

Correspondence: Wing Y Au, M.D., Department of Medicine, Queen Mary Hospital, Hong Kong SAR, China.
Phone: international+86-852-2854792 - Fax: international+86-852-29741165 - Email: auwing@hotmail.com

raised. A diagnosis of FK506 induced TTP was made, and the drug was stopped. Intensive daily plasmapheresis (four liters per day) with cryosupernatant replacement was started. Four days later, improvement in RBC morphology was seen, with reduced transfusion requirements and LDH level (Figure 1). There was a transient rise in the bilirubin and liver transaminase levels, and FK506 was resumed due to suspected graft rejection. This caused rapid clinical and biochemical deterioration. The immunosuppressive agent was changed to mycophenolate mofetil (MMF, 1 g twice daily). Low dose daily prostacyclin (Iloprost, PGI₂) infusion (50 µg/day over 8 hours) was added for ten days.¹⁴ There was marked improvement, and plasmapheresis was stopped after 24 days. The peripheral film showed normal RBC morphology, and the complete blood picture and LDH returned to baseline levels.

Discussion

Thrombotic thrombocytopenic purpura is diagnosed by a clinical pentad of fever, neurologic abnormality, microangiopathic hemolytic anemia, thrombocytopenia and renal impairment.¹⁵ The coagulation profile is usually normal, which helps to distinguish TTP from disseminated intravascular coagulation (DIC). Although our case had a classical fulminant presentation, there is a wide spectrum of TTP severity, and patients often present with unusual symptoms. The underlying pathology in TTP is abnormal platelet aggregations in the microcirculation, due to abnormal platelet-endothelial interactions.¹ However, distinction from other related clinical and pathological syndromes such as hemolytic-uremia syndrome (HUS) and DIC may be difficult. TTP itself is also a heterogeneous disorder.¹ Idiopathic or primary TTP may run a recurrent or familial course. An antibody against von Willebrand's factor (vWF)-cleaving metalloprotease is the major cause of primary TTP.^{2,3} Secondary TTP occurs due to infection,¹⁶ drugs,^{6,17} organ transplantation¹⁸ or auto-immune disease, notably, systemic lupus erythematosus^{19,20} and antiphospholipid syndrome.²¹ In secondary TTP, other auto-antibody mediated and non-immune mediated mechanisms of vascular damage and platelet activation may be involved.^{1,4,6,20,22} The association between TTP and cyclosporin is well described in the setting of bone marrow and solid organ transplantation.^{6,7} There are fewer reports of TTP related to FK506 in marrow and kidney recipients.^{7,8,23} In a recent review of 21 cases of FK506 related TTP, 80% occurred in renal allograft patients.⁸ This probably reflects the larger number of renal transplantation performed, and the more extensive use of FK506 in this setting. Only three cases of FK506-related TTP after OLT have been reported.^{8,24,25} Notably, in a review of 1,400 patients receiving FK506 for OLT, auto-immune hemolysis was reported in eight cases, but TTP was not observed.²⁶ It is possible that in mild cases, the diagnosis of TTP is delayed, if not missed. Evidence for FK506 involvement is also circumstantial, since episodic TTP is unrelated to trough FK506 levels, and often occurs in the setting of infection and other systemic disturbances.⁸ In our case, the improvement of

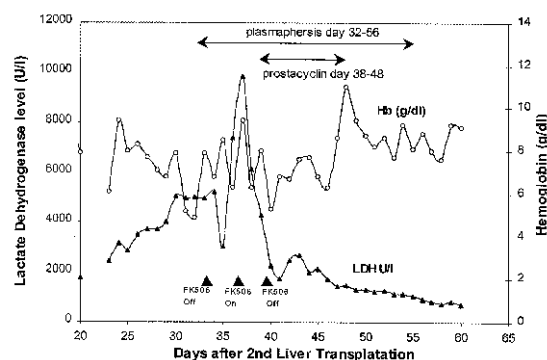


Figure 1: Clinical course of thrombotic thrombocytopenic purpura complicating tacrolimus immunosuppression after second orthotopic liver transplantation.

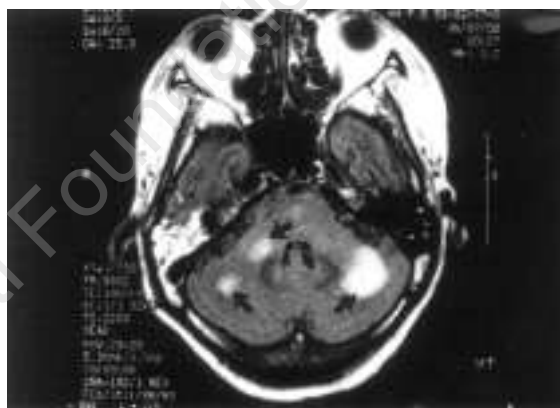


Figure 2: A T1-weighted magnetic resonance imaging (MRI) scan showing bilateral multiple subcortical cerebellar hyperintense lesions (arrows)

TTP with FK506 withdrawal, and its deterioration after FK506 re-challenge make FK506 the most likely culprit. This is most likely related to its immunomodulating effect, although an auto-antibody was not formally demonstrated. This is the also first report of TTP in ABO mismatched OLT patients, who are susceptible to DAT positive, immune-mediated hemolysis.²⁷ Crossing the ABO blood group barrier has not been implicated in any case of FK506-related TTP so far reported. An ABO mismatched OLT, sepsis and extensive major vessel thrombosis may all have been contributory in our case by causing significant endothelial injury. Since the median time to development of TTP after FK506 exposure is four months (range <1 to 23),⁸ it is not surprising that TTP was not observed at initial FK506 exposure after the first ABO matched OLT.

Like its diagnosis, the therapy of TTP is challenging. The most effective therapy is plasmapheresis, and up to a hundred sessions may be needed.²⁸ For refractory cases, splenectomy, intravenous γ -globulin, vincristine, alkylators, aspirin, or even paradoxically,

cyclosporin²⁹ have all been reported to be effective.⁶ The use of prostacyclin analogs, which inhibit endothelial reactivity and platelet aggregation, has been reported in fewer than 50 cases.^{30,31} Iloprost, a long-acting PGI₂ analog, was used because of local availability and its reported efficacy was rapid, especially in combination with plasmapheresis.³¹ Its use coincided with a rapid remission in our case. This suggests that early combination therapy may help to break the vicious cycle of endothelial damage and hasten recovery. Our case also illustrates the advantage of the availability of a wider choice of effective immunosuppressive drugs in solid organ transplantation in the face of severe side effects.³²

Contributions and Acknowledgments

WYA, AKWL and CCKL were responsible for the hematological diagnosis and management of TTP, and performed literature revision and wrote the final article. CML was chief transplant surgeon for the case, and amended the manuscript and references. STF, CLL and KY were surgeons and intensive care specialist responsible for the continuous treatment of the case, supervision of specialty care, and gave important advice on the manuscript preparation. The criteria for the order in which the names of the authors appear are based on the authors' contribution to the interpretation of the data and the management of the case.

The authors thank Dr. CS Lau from the division of rheumatology for the supply of PGI₂, and Dr. HW Liu of the Red Cross Transfusion service for the supervision of supply of plasma products.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received on 17 September 1999; accepted 14 February 2000.

References

- Porta C, Caporali R, Montecucco C. Thrombotic thrombocytopenic purpura and autoimmunity: a tale of shadows and suspects. *Haematologica* 1999;84:260-9.
- Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998; 339:1585-94.
- Furlan M, Robles R, Galbusera M, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998; 339:1578-84.
- Nagaya S, Wada H, Oka K, et al. Hemostatic abnormalities and increased vascular endothelial cell markers in patients with red cell fragmentation syndrome induced by mitomycin C. *Am J Hematol* 1995; 50:237-43.
- Porta C, Danova M, Riccardi A, Bobbio Pallavicini E, Ascari E. Cancer chemotherapy-related thrombotic thrombocytopenic purpura: biological evidence of increased nitric oxide production. *Mayo Clin Proc* 1999; 74:570-4.
- Moake JL, Byrnes JJ. Thrombotic microangiopathies associated with drugs and bone marrow transplantation. *Hematol Oncol Clin N* 1996; 10:485-97.
- Singh N, Gayowski T, Marino IR. Hemolytic uremic syndrome in solid-organ transplant recipients. *Transplant Int* 1996; 9:68-75.
- Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation* 1999; 67:539-44.
- George JN, Gilcher RO, Smith JW, Chandler L, Duvall D, Ellis C. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: diagnosis and management. *J Clin Apheresis* 1998;13:120-5.
- Lo CM, Fan ST, Lai CL, et al. Lamivudine prophylaxis in liver transplantation for hepatitis B in Asians. *Transplant Proc* 1999; 31:535-6.
- Lo CM, Fan ST, Liu CL, et al. Applicability of living donor liver transplantation to high-urgency patients. *Transplantation* 1999; 67:73-7.
- Lo CM, Fan ST, Liu CL, et al. Use of FK506 as primary or rescue therapy after liver transplantation in Hong Kong. *Transplant Proc* 1998; 30:3587-8.
- Bakshi R, Shaikh ZA, Bates VE, Kinkel PR. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. *Neurology* 1999; 52:1285-8.
- Mok MY, Tse HF, Lau CS. Pulmonary hypertension secondary to systemic lupus erythematosus: prolonged survival following treatment with intermittent low dose iloprost. *Lupus* 1999; 8:328-31.
- Ruggenti P, Remuzzi G. Pathophysiology and management of thrombotic microangiopathies. *J Nephrol* 1998; 11:300-10.
- Sutor GC, Schmidt RE, Albrecht H. Thrombotic microangiopathies and HIV infection: report of two typical cases, features of HUS and TTP, and review of the literature. *Infection* 1999; 27:12-5.
- Muszkat M, Shapira MY, Svir S, Linton DM, Caraco Y. Ticlopidine-induced thrombotic thrombocytopenic purpura. *Pharmacotherapy* 1998; 18:1352-5.
- Paquette RL, Tran L, Landaw EM. Thrombotic microangiopathy following allogeneic bone marrow transplantation is associated with intensive graft-versus-host disease prophylaxis. *Bone Marrow Transplant* 1998; 22:351-7.
- Porta C, Bobbio-Pallavicini E, Centurioni R, Caporali R, Montecucco CM. Thrombotic thrombocytopenic purpura in systemic lupus erythematosus. Italian Cooperative Group for TTP. *J Rheumatol* 1993; 20:1625-6.
- Musio F, Bohlen EM, Yuan CM, Welch PG. Review of thrombotic thrombocytopenic purpura in the setting of systemic lupus erythematosus. *Semin Arthritis Rheum* 1998; 28:1-19.
- Asherson RA. The catastrophic antiphospholipid syndrome, 1998. A review of the clinical features, possible pathogenesis and treatment. *Lupus* 1998; 7(Suppl 2):S55-62.
- Kobayashi M, Wada H, Wakita Y, et al. Decreased plasma tissue factor pathway inhibitor levels in patients with thrombotic thrombocytopenic purpura. *Thromb Haemost* 1995; 73:10-4.
- Tezcan H, Zimmer W, Fenstermaker R, Herzig GP, Schriber J. Severe cerebellar swelling and thrombotic thrombocytopenic purpura associated with FK506. *Bone Marrow Transplant* 1998; 21:105-9.
- Holman MJ, Gonwa TA, Cooper B, et al. FK506-associated thrombotic thrombocytopenic purpura. *Transplantation* 1993; 55:205-6.
- Mach-Pascual S, Samii K, Beris P. Microangiopathic hemolytic anemia complicating FK506 (tacrolimus) therapy. *Am J Hematol* 1996; 52:310-2.
- Abu Elmagd KM, Bronsther O, Kobayashi M, et al. Acute hemolytic anemia in liver and bone marrow

- transplant patients under FK 506 therapy. *Transplant Proc* 1991; 23:3190-2.
27. Angstadt J, Jarrell B, Maddrey W, et al. Hemolysis in ABO-incompatible liver transplantation. *Transplant Proc* 1987; 19:4595-7.
 28. Bandarenko N, Brecher ME. United States Thrombotic Thrombocytopenic Purpura Apheresis Study Group (US TTP ASG): multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. *J Clin Apheresis* 1998; 13:133-41.
 29. Hand JP, Lawlor ER, Yong CK, Davis JH. Successful use of cyclosporine A in the treatment of refractory thrombotic thrombocytopenic purpura. *Br J Haematol* 1998; 100:597-9.
 30. Bobbio-Pallavicini E, Porta C, Tacconi F, et al. Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura. Four case reports and review of the literature. Italian Cooperative Group for Thrombotic Thrombocytopenic Purpura. *Haematologica* 1994; 79:429-37.
 31. Sagripanti A, Carpi A, Rosaia B, et al. Iloprost in the treatment of thrombotic microangiopathy: report of thirteen cases. *Biomed Pharmacother* 1996; 50:350-6.
 32. Klupp J, Bechstein WO, Platz KP, et al. Mycophenolate mofetil added to immunosuppression after liver transplantation--first results. *Transpl Int* 1997; 10:223-8.

©Ferrata Storti Foundation