Case Report

Mycophenolate mofetil causing deep venous thrombosis in a renal transplant patient with factor V Leiden

David Z. I. Cherney¹ and Jeffrey S. Zaltzman²

¹Faculty of Medicine, University of Toronto, Toronto, Ontario and ²Nephrology Division, St Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada

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Mycophenolate mofetil (MMF) is a drug that is commonly used as a post-transplant immunosuppressive agent. The mechanism of action of MMF is via non-competitive, reversible inhibition of inosine monophosphate dehydrogenase (IMPDH). IMPDH is required for purine synthesis during lymphocyte activation [1]. Although effective for treating allograft rejection [2–5], MMF has well known side effects including gastrointestinal upset, lymphopenia, and the risk of opportunistic infections [6–7]. Hepatotoxicity and nephrotoxicity are not common [8].

The factor V Leiden mutation involves a single adenine-for-guanine mutation at position 506, first described in 1993 [9–10]. Mutated factor V is resistant to degradation by activated protein C, predisposing patients to thrombosis [9].

In this paper, we describe a case of proven deep venous thrombosis (DVT) in a 62-year-old cadaveric renal transplant recipient several days after starting MMF. The MMF was administered on two separate occasions, several months apart, and 4 years post-transplant because of episodes of chronic allograft nephropathy (CAN). The patient developed a DVT soon after receiving the MMF on both occasions. A haematological investigation revealed that the patient (P.F.) was heterozygous for factor V Leiden.

The timing and reproducible relationship between the administration of MMF and the development of DVT strongly suggest a causal relationship between the drug and the occurrence of thrombosis. In this paper we describe what we think is a rare case of DVT as a complication of MMF.

Case

P.F. is a 62 year-old woman who was diagnosed with primary membranous glomerulonephritis in 1992. Her renal function declined and by March 1995 she required peritoneal dialysis.

On 25 July 1995 the patient underwent a right-sided cadaveric renal transplant. An ultrasound performed prior to discharge revealed a normal transplant kidney. Her creatinine decreased from a pre-operative level of 586 µmol/l to 78 µmol/l by the time of discharge. Her discharge medications included cyclosporine A micro-immunisation 100 mg PO bid, azathioprine, and a tapering dose of prednisone.

The patient’s post-operative course was uneventful except for a nasal abscess, and the development of type 2 diabetes mellitus secondary to her immunosuppressive medications. Her creatinine stabilized at 130–135 µmol/l until April 1999, when her creatinine was noted to be 160 µmol/l, and continued to increase slowly, reaching 236 µmol/l by the beginning of June 1999.

A renal biopsy that was performed 7 June 1999 demonstrated CAN, Grade III, with features of chronic transplant glomerulopathy and severe interstitial fibrosis. There was no evidence of membranous nephropathy in the transplanted kidney. One gram of MMF PO bid was substituted for azathioprine, starting on 14 June 1999. One day later the patient began to experience bilateral aching pains in her feet. The following day she developed oedema involving both feet, which slowly progressed proximally up both legs. Four days after starting MMF, P.F. experienced fevers, chills, a sore throat and loose, non-bloody stools. She was seen by her family doctor who prescribed trimethoprim–sulphamethoxazole for presumed bacterial pharyngitis.

The patient presented to the emergency department on 24 June 1999, 10 days after starting MMF, and was admitted to the ward after it was discovered that her creatinine had risen to 376 µmol/l. She had minimal proteinuria (0.3 g/day) and her serum albumin was normal. On admission, her physical examination was...

Correspondence and offprint requests to: Jeffrey S. Zaltzman, Nephrology Division, St Michael’s Hospital, Toronto, Ontario, Canada.

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normal except for mild bilateral oedema of both legs. The MMF was held on the suspicion that it may have been related to the patient’s illness and she was discharged once she had defervesced, the investigations having proven negative, and her creatinine decreased. Upon discharge, however, the oedema of the left leg increased in severity and a Doppler examination of the lower extremities revealed a left leg deep venous thrombosis extending from the popliteal veins to the external iliac vein. She was placed on doxaparin and warfarin, and then maintained on warfarin alone with a therapeutic international normalized ratio (INR) between two and three.

The patient’s creatinine had reduced to 170 μmol/l by mid-July and stayed at that level until 29 September, when it was noted to be 199 μmol/l. On 9 October 1999, MMF was re instituted in the hope of alleviating the CAN.

On 10 October 1999, P.F. was feeling well and went dancing with her husband. The following day she woke up with a painful and oedematous left foot. She presented to the emergency department the next day. On examination, her temperature was 36.7°C, pulse 84 bpm, respiratory rate 20 breaths/min and blood pressure 160/70 mmHg. She had a diffusely tender and oedematous left leg and a positive Homan’s sign. Her creatinine was 198 μmol/l and her INR was therapeutic at 2.5. She still had minimal proteinuria and normal serum albumin. Abdominal ultrasound revealed a right-sided 12 cm renal graft. Duplex ultrasound with Doppler revealed a new left femoral-popliteal DVT that was in the same location as the first one.

The patient was started on subcutaneous low molecular weight heparin for 1 week and maintained on warfarin. The MMF was discontinued and azathioprine substituted in its place. Her symptoms resolved by the third day of admission and she was discharged on cyclosporine A, prednisone, azathioprine, warfarin, and low molecular weight heparin.

Subsequent haematological investigations revealed that P.F. was heterozygous for factor V Leiden. Tests for haemostasis activation (i.e. lupus anticoagulant, antiphospholipid antibody and prothrombin gene mutations) and abnormal fibrinolysis were negative. She has remained on warfarin and has been in good health since.

Discussion

DVT is a relatively common occurrence after renal transplantation. In a retrospective study of 480 renal transplant patients over a 10-year period, 8.3% of patients experienced a venous thromboembolic event [11]. In this cohort, the incidence of DVT was highest in the first 4 months after transplant. The authors suggested that this might have been due to the concurrent rise in haemoglobin that occurred in this group of patients [11]. Pulmonary embolism was found to be the fourth leading cause of death during the study period.

Another study by Humar et al. examined a much larger group of kidney (1833 patients) and simultaneous kidney–pancreas transplant patients (276 patients) [12]. They found a 6.2% incidence of DVT and pulmonary embolism. As opposed to the previous study, this group of investigators discovered that the most common time for a post-transplant patient to suffer a DVT was within the first post-operative month. Pulmonary embolism occurred in 2.1% of patients and was fatal in 30% of these (13 patients in total).

Deep thrombophlebitis is listed as a possible complication in 1% of patients taking 1 g bid of MMF (n = 501) and in 1.2% of patients taking 1.5 g bid of MMF (n = 490), compared with 0% of patients taking placebo (personal communication courtesy of Hoffman-LaRoche). These numbers pertain to patients taking MMF to prevent acute rejection. The MMF monograph reports the incidence of thrombosis, as an adverse effect of MMF in renal transplant patients, as ≥3% and <10% [12].

A literature search using Medline, Embase, RoScopes, Biosis and Current Contents revealed no reports of DVT as a complication of MMF. In an unpublished case series, courtesy of Hoffman-LaRoche Canada, MMF has been suspected to have a relationship with DVT and thrombotic thrombocytopenic purpura [12]. However, in these cases other thrombogenic agents were being used at the same time (including allopurinol, azathioprine cyclosporine and tacrolimus). In addition, none of these other cases had such a close time correlation between the use of MMF and the development of DVT [12]. Even though the patient in this case was exposed to the above potentially thrombogenic agents, she had no thrombotic complications until she was exposed to MMF, suggesting, if not causal role of MMF leading to DVT. In other unpublished cases where MMF has been associated with DVT, there were other confounding issues such as the post-surgical risk of DVT and the risk of DVT in the acutely ill who are immobilized [12].

In contrast, however, this case involved a patient who had lived for 62 years free of thrombosis and had no post-transplant DVT when one might have expected the risk of such an event to be at its highest. This suggests that although her heterozygous factor V Leiden genotype may have predisposed her to hyper-coagulability, something new occurred both in June and October of 1999 to cause thrombosis. Although thromboembolic complications are common in this patient population, most of these complications occur within the first few months after renal transplantation, not many years later.

The factor V Leiden mutation leads to activated protein C resistance. Factor V is usually degraded by activated protein C, but when a mutation at position 506 occurs in the gene that codes for factor V, guanine replaces arginine and factor V becomes resistant to degradation by protein C [9]. Patients with a factor V
Leiden mutation had an odds ratio of 6.6 (confidence interval (CI): 3.6–12.0) for DVT in the Leiden Thrombophilia Study, which was a population-based case-control study of 301 individuals <70 years of age, who had their first DVT unrelated to malignancy [13]. In the Physician’s Health Study, patients with DVT had a relative risk of 2.7 (CI: 1.3–5.6) of having factor V Leiden [11]. The relative risk of having factor V Leiden was higher in patients >60 years of age who presented with DVT. The fact that the patient in this case report was heterozygous for factor V Leiden may have contributed to the development of her first DVT; however, new evidence suggests that having factor V Leiden is not a risk factor for recurrent venous thromboembolism [14]. This further supports the theory that a mechanism other than the presence of factor V Leiden was responsible for the development of DVT.

A possible aetiology for P.F.’s procoagulant state was the addition of MMF to her pharmacological regimen. Perhaps the most convincing evidence to suggest that MMF may be related to thrombosis is that the commencement of MMF was coincident with thrombosis on two separate occasions. In addition, on the second occasion, the patient was therapeutically anticoagulated with warfarin, which substantially reduces the chance of developing a DVT. This suggests that another factor, such as the addition of MMF, enhanced her procoagulant state. In addition, mechanical factors, such as venous compression in the pelvis, were unlikely due to the fact that the renal graft and the DVT were contralateral. Other haematological causes of thrombosis such as nephrotic syndrome, haemostasis activation and impaired fibrinolysis were ruled out.

Nothing in the literature relates MMF with factor V Leiden. The mechanistic relationship between the two may involve MMF as a cofactor in the coagulation cascade, perhaps altering the non-Leiden factor V such that the patient effectively becomes homozygous factor V Leiden. MMF undergoes rapid and complete absorption (Tmax = 0.9 h) after oral administration [15], and could cause a DVT through a therapeutic-dose related mechanism or via an idiosyncratic reaction independent of plasma levels. Other possibilities include the alteration of membrane proteins, platelets or blood vessel walls such that the patient becomes predisposed to thrombosis. In other words, the presence of a heterozygous factor V Leiden may be entirely coincidental.

The clinical relevance of our study is that patients with a history of DVT or pulmonary embolism or a known genetic predisposition to DVT may be at risk by using immunosuppressive agents such as MMF. Before such a recommendation is made, however, a more definitive study would be needed in order to establish the true relationship between DVT and MMF.

References

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