Case Report

Successful living donor kidney transplantation in a patient with prothrombin gene mutation: Case report and literature review

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Abstract

We present a patient with known prothrombin gene mutation and a history of prior vascular events, who underwent living donor kidney transplantation. Given the presumed elevated risk of complication from known prothrombin mutation, clinical management was directed towards optimizing living donor allograft function.

Key words: Factor V Leiden, kidney transplantation, prothrombin gene mutation, thrombophilia

Introduction

Among the many causes of inherited thrombophilia, the prothrombin G20210A gene mutation remains one of the more recent findings. Poort *et al*. discovered a novel G->A single nucleotide polymorphism at position 20210 of the prothrombin gene, which was associated with increased venous thrombosis as well as increased levels of circulating prothrombin.[1] After Factor V Leiden, this mutation is the 2nd most common inherited thrombophilic disorder found in 0.7% and 4% of the general population.[2] It increases the risk for deep venous thrombosis by a factor of 2.7-3.8[3] Prothrombin gene mutation has been implicated as a source of vascular complications after kidney transplantation leading to graft perfusion defects, venous thromboembolic complications and acute graft loss.[4-7]

Case Report

A 69-year-old female with a history of prothrombin gene mutation was scheduled for living donor kidney transplantation. After developing spontaneous left subclavian and brachial artery thrombosis 17 years ago, patient underwent therapeutic anticoagulation and maintenance on warfarin for 1 year. With therapy, her thrombosis was found to have completely resolved; however, 8 years later following an arthroscopic procedure on her right knee, she developed venous thrombosis of her right lower extremity. She was subsequently found to have a heterozygous form of the prothrombin gene 20210 mutation and hence was maintained on chronic anticoagulation with warfarin . Over the past 2 years, patient developed end-stage renal disease in the setting of diabetes and hypertension.

After careful discussion and institutional approval, patient and her son elected to undergo living donor kidney transplantation. Patient underwent general endotracheal anesthesia with smooth intravenous induction. She had a tunneled internal jugular double-lumen central venous catheter placed preoperatively and radial arterial line placed after induction. Access is sometimes difficult in renal transplant recipients and more so in our patient due to history of spontaneous subclavian and brachial artery thrombosis. As a routine practice in our institution, we place tunneled catheters preoperatively with interventional radiology for our scheduled kidney transplant recipients. There was no evidence of clots or thrombi in the internal jugular vein or vessels prior to placement of the line with ultrasound examination. A peripheral intravenous cannula was placed intra-operatively for additional access.

She received methylprednisolone and thymoglobulin for immunosuppression. In view of the patient's history of

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prothrombin gene mutation and history of prior thrombosis, she was maintained on a heparin infusion with a aim of maintaining the partial thromboplastin time (PTT) in the range of 70-75. To achieve this target PTT we gave a 2000 units bolus of heparin followed by an infusion of 1000 units/h. She remained stable throughout, maintaining a mean arterial pressure goal of > 80-85 mmHg after reperfusion. Trachea was extubated in the operating room and she was transported stable to the surgical intensive care unit. She received 2 l of albumin, 4.5 l of normal saline and 2 units of packed red blood cells during the case.

On the 3rd day post-operative, due to continued anticoagulation with heparin, patient developed retroperitoneal hematoma requiring re-exploration and washout. However, her allograft demonstrated good function and her creatinine remained stable post-operatively. She was transitioned to warfarin for anticoagulation and discharged home. Her continued immunosuppressive regimens include prednisone, tacrolimus and mycophenolate. Patient subsequently developed ureteral calculus, hydronephrosis and acute renal failure requiring nephrostomy tube placement. She has since had the nephrostomy tube removed and to date, her allograft continues to function well fifteen months later.

Discussion

There is currently no consensus on optimal management for kidney transplantation in the setting of prothrombin gene mutation. In a recent review on thrombophilia and renal transplantation, Kujovich recommends the screening of high-risk patients as well as prophylactic perioperative anticoagulation for patients with thrombophilia and a documented history of thrombosis.[8] Despite this recommendation, it is recognized that the current evidence is limited and more prospective studies are needed.

The literature regarding prothrombin gene mutation and kidney transplantation consists of several case reports and case series. Oh *et al.* presented two patients who after early renal allograft thrombosis were subsequently found to have mutations in the prothrombin 20210 gene. In both cases patients presented with medical histories suggesting an underlying disorder of the coagulation system.[4] Quintana *et al*. reported a case of renal cortical necrosis in a patient who also was revealed to have prothrombin gene mutation after subsequent screening.[7] Stier *et al.* described a case of a patient undergoing transplantation who had recurrent dialysis fistula thrombosis. Five months after initial renal transplantation, steroid resistant interstitial rejection required reinstitution of hemodialysis and she again developed thrombosis of the fistula. Screening revealed the prothrombin gene mutation. Subsequently, she underwent a 2nd renal transplantation with heparin anticoagulation and developed bleeding on the 7th day post-operative. She had stable kidney function and was discharged on daily subcutaneous low-molecular-weight heparin.[9] John *et al*. described successful renal transplantation in a patient with known factor V Leiden mutation, heterozygous prothrombin gene mutation and history of Heparin induced thrombocytopenia(HIT). Due to history of HIT II, they used recombinant hirudin as an anticoagulant throughout the procedure and reported successful transplantation of a cadaveric graft.[10]

Several case series document an increased risk of graft complications associated with prothrombin gene mutation. Fischereder *et al*. considered renal transplant outcomes in 270 consecutive white patients and found a prevalence of prothrombin gene mutation of 3.7%. The mutation carriers had a significantly reduced median graft survival of 65.9 months compared with 149 months in the patients of normal genotype.[5] In a prospective study, Heidenreich *et al*., screened 165 patients for inherited thrombophilia's. The incidence of prothrombin gene mutation was 6 out of the 165 (3.6%). The prothrombin G20210A mutation was found to be an independent risk factor for graft loss. In this study, the prothrombin gene was more prone to early graft loss than Factor V Leiden. Anticoagulation was not used in the study.[11]

In a prospective study, Pagano *et al*. screened at risk recipients with past medical history of deep vein thrombosis, past vascular thrombosis or prior early graft loss for inherited thrombophilia's and compared them to patients without thrombophilia. Patients with thrombophilia were anticoagulated for 1 year with warfarin and transitioned to heparin perioperatively. In this study, one patient out of 112 patients (0.8%) was found to have the prothrombin gene mutation. There was no increase in rejection or graft loss in the recipients with thrombophilia treated with anticoagulation. However, a significant increased risk of bleeding and an increased incidence of delayed graft function was noted.[12]

Other studies have called into question the association between inherited thrombophilia and allograft survival. Chiurchiu *et al*. retrospectively analyzed 82 patients for factor V Leiden and prothrombin gene mutation. A total of three patients (3.6%) were found to the have prothrombin gene mutation. There was a trend toward higher rejection rate, without statistical significance.[13] Meyer *et al*. examined 1327 transplant and retransplant patients for factor V Leiden, prothrombin G20210A and MTHFR C677T gene polymorphisms. They did not find an association between single nucleotide

polymorphisms factor V Leiden or MTHFR C677T with renal allograft survival. Prothrombin G20210 did result in a significant association; however, this was not sustained after Bonferroni correction.[14]

Since our patient had the prothrombin gene mutation with a prior documented history of both arterial and venous thrombosis, chronic anticoagulation and a living donor graft, management was directed toward optimizing allograft function. Intraoperative anticoagulation was established using the intravenous heparin at a therapeutic goal PTT of 70-75, which was maintained perioperatively. We recognized the increased risk of perioperative bleeding, but we felt aggressive therapeutic anticoagulation was the prudent course of action. Once allograft thrombosis occurs, reversal of this thrombosis is extremely rare. We chose unfractionated heparin due to the ability to rapidly titrate its effects and easy reversibility. Intraoperative monitoring options of the adequacy of heparin anticoagulation included activated clotting time and PTT. Alternatives to unfractionated heparin include argatroban, which has been used in the setting of heparin induced thrombocytopenia. Another available alternative includes low molecular weight heparin, which has the advantage of decreased dosing frequency and need for less stringent laboratory monitoring. The disadvantage in the immediate post-operative setting is the duration of action and difficulty in reversing in case of life-threatening bleeding. Warfarin is usually considered in long-term anticoagulation in these patients due to ease of administration.

Our patient unfortunately did develop retroperitoneal hematoma with a subsequent drop in hematocrit, necessitating re-exploration. We believe this to be an acceptable risk, given the desire to minimize thrombotic events. Our patient has continued chronic anticoagulation and has had good allograft function to date.

In patients with a known hypercoagulable history, we recommend screening for thromboembolic risk factors, including the prothrombin gene mutation. In addition a thorough screening for presence of preexisting clots is recommended. Prior to placement of invasive lines for access, it is very important to rule out the presence of clots. Perioperative anticoagulation should be carefully considered. Our case confirms that anticoagulation with heparin is safe in the setting of prothrombin gene mutation and living donor kidney transplantation, but it is not without risk. Further studies are needed to elucidate ideal treatment strategies for an uncommon, but important clinical scenario. A multidisciplinary approach involving the transplant surgeon, anesthesiologist and hematology is vital to successful management of these high-risk patients.

References

1. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698-703.
2. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, *et al*. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 1998;79:706-8.
3. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, *et al*. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 1999;341:801-6.
4. Oh J, Schaefer F, Veldmann A, Nowak G, Nowak-Göttl U, Tönshoff B, *et al*. Heterozygous prothrombin gene mutation: A new risk factor for early renal allograft thrombosis. Transplantation 1999;68:575-8.
5. Fischereder M, Schneeberger H, Lohse P, Krämer BK, Schlöndorff D, Land W. Increased rate of renal transplant failure in patients with the G20210A mutation of the prothrombin gene. Am J Kidney Dis 2001;38:1061-4.
6. Irish A. Hypercoagulability in renal transplant recipients. Identifying patients at risk of renal allograft thrombosis and evaluating strategies for prevention. Am J Cardiovasc Drugs 2004;4:109-49.
7. Quintana LF, Cofan F, Reverté JC, Oppenheimer F, Campistol JM. Renal cortical necrosis after kidney transplantation associated with the prothrombin 20210A mutation. Nephrol Dial Transplant 2006;21:1125-6.
8. 141413Kujovich JL. Thrombophilia and thrombotic problems in renal transplant patients. Transplantation 2004;77:959-64.
9. Stier C, Pötzsch B, Müller-Berghaus G, Soergel M, Klaus G. Severe thrombophilia in a paediatric patient with end-stage renal disease: Detection of the prothrombin gene G20210A mutation. Nephrol Dial Transplant 1998;10:2100-2.
10. John U, Kentouche K, Nowak G, Schubert J, Misselwitz J. Successful renal transplantation in a patient with heterozygous prothrombin gene, factor V Leiden mutation and heparin-induced thrombocytopenia using r-hirudin as anticoagulant. Pediatr Transplant 2006;10:84-8.
11. Heidenreich S, Junker R, Wolters H, Lang D, Hessing S, Nitsche G, *et al*. Outcome of kidney transplantation in patients with inherited thrombophilia: Data of a prospective study. J Am Soc Nephrol 2003;11:234-9.
12. Pagano CR, Dawson L, Dick A, Lerner SM, Valenia T, Braun J, *et al*. No increase in rejection or graft loss in kidney transplant recipients with thrombophilia treated with anticoagulation and triple immunosuppression. Transplant Proc 2005;37:1902-4.
13. Chiurchiu C, de Alvarellos T, Sanchez A, Cortiñas D, Douthat W, de la Fuente J, *et al*. Thrombophilic mutations: No association with thrombotic events in renal transplant recipients. Transplant Proc 2010;42:282-3.
14. Meyer M, Laux G, Scherer S, Tran TH, Opelz G, Mytilineos J. No association of factor V Leiden, prothrombin G20210A, and MTHFR C677T gene polymorphisms with kidney allograft survival: A multicenter study. Transplantation 2007;83:1055-8.

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