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Uncommon Site for Deep Vein Thrombosis in a Kidney Transplant Recipient After Switching Tacrolimus to Sirolimus: A Case Report

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Abbreviations:

CNI: Calcineurin Inhibitor; DVT: Deep vein thrombosis; DJ: Double J; FDA: Food and Drug Administration; IS: Immunosuppression; INR: International Normalized Ratio; mTOR: Mammalian Target of Rapamycin; NODAT: New onset Diabetes after transplantation; RAI: Radioactive Iodine; RCT: Randomized Controlled Trial; RCA: Right coronary artery; PE: Pulmonary embolism; US: United States; VTE: Venous Thromboembolism

1. Abstract

1.1. Background: Thromboembolic events can lead to significant morbidity and mortality. A thrombotic event can occur in Kidney transplant recipients due to several reasons, one of them is the use of sirolimus which has been shown to have thrombogenic potential.

1.2. Clinical Case Report: We report a 67-year-old male patient who underwent a living related kidney transplantation from his daughter. He developed New-onset Diabetes after Transplantation (NODAT). Sirolimus was introduced and Tacrolimus was stopped to avoid recurrence of a previously treated thyroid cancer. Three weeks later, the patient suddenly developed swelling of right upper limb and was diagnosed to have deep vein thrombosis. Sirolimus was discontinued and tacrolimus was restarted along with two months of anticoagulation therapy.

1.3. Conclusion: We are reporting sirolimus-related thrombotic event in a kidney transplant recipient, with paucity of similar reports from the Middle Eastern region. A causal association is suggested given the temporality and the unusual site for the DVT following the use of sirolimus. Thus, any patient post kidney transplant presenting with signs and symptoms of acute thrombotic event, Sirolimus may be considered as a cause.

2. Introduction

Deep vein thrombosis (DVT) along with Pulmonary embolism (PE) are a cause of significant morbidity and mortality [1, 2]. Several mechanisms for development of DVT had been described. Virchow's triad includes three important mechanisms that lead to thrombosis, these include Venous stasis, Hypercoagulable state and Endothelial dysfunction [3]. Each of them, in turn, has several underlying causes which predispose a patient to thrombosis.

Patients with chronic Kidney disease are at high risk for thrombosis and hemorrhage [4-6]. Renal transplantation has a significant impact on the quality of life, particularly in patients eligible for this modality of renal replacement therapy [7]. However, due to several reasons organ transplant recipients continue to be at risk for thrombotic events [8-10]. In the immediate post-transplant period, it is the immobility and general anesthesia along with the presence of catheters that lead to the development of thrombosis [11]. Early sepsis due to bacterial infections imparts additional risk for DVT [12].

Immunosuppressive (IS) medications are a cornerstone for the transplant management to prevent allograft rejection, but unfortunately, each of these drugs has its own side effects [13]. Various IS regimens are available and the therapy has to be individualized based on multiple factors [14]. Of these IS medications, sirolimus has been linked to thrombosis in previous studies.

Sirolimus, aka Rapamycin, is a macrolide that is produced by the bacterium *Streptomyces hygroscopicus*. It was first used as an antifungal agent in 1972 but was abandoned due to its immunosuppressive and antiproliferative effects [15]. Later on, due to its anti-proliferative effect it was used as an anticancer agent. In 1999, sirolimus was approved by the Food and Drug Administration (FDA) for transplant recipients due to its inhibitory effects on mTOR [16, 17]. Initially, thought to replace calcineurin inhibitors (CnI) due to their nephrotoxic and diabetogenic potential but then was found to have several side effects, and be weaker immunosuppressive compared to CnI [18]. Currently it is use is limited to transplant recipients with concerns for progressive worsening graft function, related to CnI toxicity, the potential risk of tumor occurrence or progression with the administration of CnI [19].

Several animal models demonstrated thrombogenic effects of Sirolimus [20-22]. It has been associated with regulation of endothelial cytoskeleton, which in turn, causes membrane remodeling and promoting platelet adhesion [22].

Previously thrombosis has been reported in cardiac and lung transplant recipient on sirolimus. In this case we report a kidney transplant recipient who developed DVT within weeks of sirolimus use. Although, Sirolimus related thrombosis has been reported in kidney transplant patients there is paucity of reports from the Middle Eastern population and our case also gives a good insight into our rationale of use of Sirolimus, the temporal relationship with Sirolimus in what transpired as a case of DVT.

3. Case Report

3.1. Patient information and clinical finding:

A-67-year-old Saudi male patient. In 1997, he was diagnosed with nephrotic syndrome (4 grams proteinuria and serum creatinine of 140 umol/l) his kidney biopsy revealed chronic glomerulonephritis. Seven years later, he was started on Hemodialysis through right internal jugular tunneled cuffed hemodialysis catheter, and he required multiple exchanges due to access dysfunction, however, he never developed any thrombotic events. His past medical history is significant for long-standing hypertension, dilated cardiomyopathy - mild disease of right coronary artery (RCA), follicular thyroid carcinoma, and hyperparathyroidism. His past surgical history was significant for inguinal hernia repair with right hydrocelectomy, total thyroidectomy/radioactive iodine ablation with partial parathyroidectomy for thyroid cancer and hyperparathyroidism. He underwent living related kidney transplantation (from his daughter), 2 years after cancer treatment. His post-operative course was uneventful, and he was discharged home in a week time with normal graft function. He received an induction therapy with basiliximab and a maintenance therapy with standard immunosuppression regimen of Tacrolimus, Mycophenolate mofetil, and steroids. He developed NODAT and his blood sugar was very difficult to control. Five months later, the management plan was to switch tacrolimus to sirolimus, to minimize his risk of cancer recurrence. At the time of switch, the creatinine clearance was 54 ml/min and urine tests show no abnormal proteinuria. Three weeks after starting sirolimus, he presented to the clinic with sudden onset of right arm pain associated with swelling, hotness and redness. Systemic review was unremarkable. On examination, blood pressure is 120/90 mmHg, heart rate 102bpm, temperature 36.7 Celsius and respiratory rate 20 per minute. General examination revealed no pallor, jaundice or cyanosis. The right arm shows significant swelling from the wrist till right side of the neck with diffuse redness noted predominantly over the dorsal aspect of the upper arm. Peripheral pulses were intact and neurological exam was unremarkable.

3.2. Diagnostic Assessment:

Laboratory investigations are shown in table 1. The diagnosis of deep vein thrombosis at the level of the proximal basilic vein was confirmed with an urgent Doppler ultrasound (Table 1).

Table 1

Hematology		
Test	**Result**	**Normal Values**
Hb	13.6	130–170 g/L
HCT	Men	0.42–0.52
Platelets count	237	150–400 x 10^9/L
WBC	13.6	4.5–10.5 x 10^9/L
Coagulation profile		
Test	**Result**	**Normal Values**
APTT	30	30–40 sec
INR	1	0.8–1.2
Prothrombin time	12	10–13 sec
Basic Screen		
Test	**Result**	**Normal Values**
Sodium	140	134–146 mmol/L
Potassium	3.9	3.5–5.1 mmol/L
Chloride	106	97–108 mmol/L
Bicarbonate	20	21–28 mmol/L
Urea	5.3	2.75–7.4 mmol/L
Creatinine	83	44–115 µmol/L
Glucose, fasting	3.6	3.5–6.5 mmol/L

3.3. Therapeutic intervention and outcome:

Anticoagulation therapy with Enoxaparin (Low Molecular Weight Heparin) 1mg/kg subcutaneous twice daily along with oral warfarin were initiated immediately, targeting an INR 2-2.5.

Sirolimus was stopped and tacrolimus was restarted, targeting a level between 4 and 6 ng/ml. The swelling resolved over few weeks and Six months later, warfarin was discontinued.

He was last seen in our clinic in September 2020, with no symptoms or sign of thrombosis. He has normal renal function, adequately controlled blood sugar and no recurrence of his thyroid cancer. List of events are outlined in Table 2.

Table 1 –Timeline

May 2010	Living related Kidney Transplantation
May-June 2010	NODAT
June 2010	DJ stent removal
July 2010	Right Internal Jugular vein Permcath removal
October 2010	Sirolimus started, Tacrolimus stopped
November 2010	DVT diagnosed, Anticoagulation initiated
March 2011	Sirolimus stopped, Tacrolimus restarted
June 2011	Warfarin stopped

4. Discussion

We report a case of living related kidney transplantation who had a history of multiple hemodialysis catheter dysfunctions while on hemodialysis, without a reported thrombosis, but unfortunately, had an episode of deep vein thrombosis of the right arm after commencing sirolimus, with complete resolution of the DVT after anticoagulation and discontinuation of sirolimus with no recurrence for the last ten years.

Sirolimus is used as an immunosuppressive agent for transplant recipients. It has the advantage of less nephrotoxicity as compared to CNIs, less diabetogenic effect and has anticancer effects. Sirolimus has been successfully used in transplant recipients who develop skin cancer and Kaposi sarcoma, with successful remission. However, several side effects had been reported including nephrotoxicity, delayed wound healing, dyslipidemia, hypertension, development of lymphoceles, pneumonitis and thrombotic microangiopathy. Thrombotic events related to Sirolimus had also been reported. On a cohort of 913 Kidney transplant recipients followed up over 11 years, 68 patients were reported to have various thromboembolic events, mostly occurring in the first year post-transplant with the presence of sirolimus as one of the risk factors for the development of thrombosis [23]. Another publication revealed a statistically significant difference in the diagnosis of DVT in a kidney transplant recipients treated with sirolimus compared to CNIs [24]. In April 2002, the United States Food and Drug Administration issued a warning of an increased incidence of hepatic artery thrombosis among liver-transplant recipients treated with sirolimus in combination with either CsA or tacrolimus immunosuppression. Several risk factors had been reported from the US FDA for the development of DVT in transplant population, which includes: male gender, age above 60, concomitant use of steroids/CNIs and particularly during the first 2 years post transplantation and in lung transplant recipients (FDA report, 2017).

Sirolimus is used more in Lung, Liver and Cardiac transplant recipients. Reviewing data from non-Renal transplant recipients; significantly higher occurrence of venous thromboembolism is noted in Sirolimus compared with azathioprine based immunosuppression [25]. Another comprehensive retrospective study demonstrated a statistically significant association between VTE and use of mTOR inhibitors (Sirolimus and Everolimus) [26]. In contrary, there are reports supporting the fact that Sirolimus does not induce thrombosis. In a retrospective review on 205 post-liver transplant recipients on Sirolimus, there were only 2 cases of hepatic artery thrombosis [27]. Another study on the incidence of postoperative thromboembolic event in Kidney transplant recipients, revealed that Sirolimus does not increase the risk of thrombosis compare to CNI [28].

Most of the information considering the mechanisms and pathogenesis of sirolimus induced thrombogenicity are coming from animal models and research done on Sirolimus based drug-eluting stents used during Percutaneous coronary interventions. The formation of microvilli on the rapamycin-treated endothelium in rats is one of the mechanisms [22]. Enhancing the activity of tissue factor which is a trigger of the coagulation cascade, causing arterial thrombosis, is another mechanism [21]. Rapamycin-induced inhibition of tissue plasminogen activator and promotion of plasminogen activator inhibitor 1 is a reported mechanism to induce thrombosis in rapamycin-eluting stents [29]. In some case sirolimus treatment may be complicated by severe proteinuria and a state of nephrotic syndrome promoting thrombosis due to loss of anticoagulant factors in urine leading to an imbalance between procoagulant and anticoagulants [3,30]. In addition to all above postulated mechanisms related to sirolimus itself; transplantation is considered a state of chronic hypercoagulability predisposing to thromboembolic events and this seems to be related to several factors other than sirolimus; including post-transplant erythrocytosis, concomitant use of multiple immunosuppressive agents, diabetes mellitus, post-transplant pregnancy, recurrence of primary disease with proteinuria, development of post-transplant cancer, pretransplant dialysis modality and CMV infections [31].

Sirolimus, although have some advantages over other immunosuppressive agents, it has also a number of side effects which can be graft and life-threatening. Its potential for being less diabetogenic and having anti-cancer activity makes it an attractive option. The use of Sirolimus in Kidney transplantation has declined and has been replaced mainly by tacrolimus, however, sirolimus remains an option for nonrenal transplant recipients due to less nephrotoxicity.

Our patient had several interventions over the same arm while being on hemodialysis, new onset diabetes, prior history of thyroid cancer, older age, and male gender – these factors in addition to Sirolimus lead to the development of thrombosis. In patients who have similar risk factors and are switched to Sirolimus one should remain very vigilant in detecting thromboembolic events.

Despite the presence of several contradicting reports with and against the association between sirolimus use and the development of thromboembolic events, our patient had multiple risk factors for the development of a thromboembolic event and this makes it challenging to identify a particular cause with certainty. Definitely, a larger study and preferably an RCT can answer this question more precisely. Understanding the mechanism which leads to Siro-

limus related thrombosis can potentially help in decreasing thrombogenicity or develop treatments which can minimize such events related to this compound. We cannot also rule out with confidence that patient had a partial thrombus from before. However, temporal relation of the start of Sirolimus and development of DVT as well as absence of significant other provoking event and lack of recurrence over 10 years post sirolimus discontinuation are all substantial factors that made us postulate the association.

5. Conclusion

In conclusion, this is an interesting case report of a kidney transplant recipient who developed thromboembolic event after initiation of Sirolimus. The DVT was successfully treated with anticoagulation and Sirolimus was discontinued. Sirolimus has innate thrombogenic effects with reports of thromboembolic events in kidney transplant recipients. In transplant recipients who present with signs and symptoms of acute thrombotic event, sirolimus discontinuation should be addressed.

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