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(CASE REPORT)

A 39-year-old male who received living kidney from his 62-year-old father, blood group matched and CDC cross match all negative, having acute cell mediated rejection 5 hours after transplant due to low Tacrolimus Trough level: A case report

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Abstract

A young renal transplant recipient received living kidney from his father; the Complement Dependent Cytotoxicity (CDC) cross match was all negative. He had oliguria 5 hours after transplant with fever and neutrophil leukocytosis. Doppler ultrasonogram revealed increased cortical echo with increased Resistive Index suggesting acute rejection or acute tubular necrosis. Renal transplant biopsy revealed acute T cell mediated rejection (acute TCMR) Grade IIA. Trough level of Tacrolimus blood level done on Day 5 was very low; therefore, Tacrolimus dose was increased. Therapeutic level achieved after giving 6 mg twice a day with addition of erythromycin. Escalating antibiotics, increasing steroids and Tacrolimus dose saved the transplant kidney.

Keywords: Renal Transplant Recipient; Living Kidney; Resistive Index; Cell Mediated Rejection

1. Introduction

Acute transplantation rejection occurs days to weeks after transplantation. The immune system can see the grafted organ as foreign body and attacks it; destroying it and leading to rejection. It is an immunological response leading to inflammation with specific pathological changes in the allograft. There are four different mechanisms postulated depending on the type of rejection: hyperacute rejection, acute T cell-mediated rejection (acute TCMR), ABMR (Antibody-mediated rejection- ABMR), and chronic rejection.

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Hyperacute rejection is related to preexisting circulating antibodies in the recipient's blood against the donor antigen (usually ABO blood group or HLA antigen), which is present at the time of transplantation. These antibodies attack and destroy the transplanted organ as soon as or within a few hours after allograft is revascularized.

In acute T cell-mediated rejection (acute TCMR), the recipient's lymphocytes become activated by recognition of foreign (non-self) donor antigens in the transplanted organ by antigen-presenting cells (APC) through direct, semi-direct, or indirect pathways, which leads to activation and infiltration of the T cells and damage to the allograft.

ABMR (Antibody-mediated rejection- ABMR) is related to antibodies against foreign (non-self) donor antigens, mainly HLA antigen, which leads to damage to the allograft through activation of the complement-dependent pathway as well as independent mechanisms recruiting natural killer cells (NK) cells, polymorphonuclear cells, platelets, and macrophages to attack the allograft. These antibodies can be either preexisting at a low level before the transplant or synthesized de novo post-transplant.

Chronic rejection is related to both immune and nonimmune mediated factors. The primary risk factor for chronic rejection is non-compliance with immunosuppressive medication. It can be either chronic antibody-mediated rejection, which is mainly related to the presence of donor HLA-antigens donor-specific antibody (DSA), or chronic cellular rejection, which is uncommon.

Combination of anti-rejection agents, steroids, Tacrolimus and mycophenolate mofetil, has decreased acute allograft rejection as well as graft survival. Acute transplantation rejection occurs days to weeks after transplantation. Several factors involve in rejection:

- Prior sensitization - high panel reactive antibodies
- Type of transplant: Deceased donor has a higher rejection than a living transplant
- Advanced age of the donor
- Prolonged cold ischemia time
- HLA mismatch
- Positive B cell crossmatch
- ABO incompatibility
- Recipient's age: Younger recipients have more rejection than older ones
- Recipient's race: Black race more rejects than White race
- Delayed graft function
- Therapy non-compliance
- Previous episodes of rejections
- Inadequate immunosuppression

Acute T-cell–mediated rejection (acute TCMR) presents in the transplant recipient with acute kidney injury and decreased urine output; proteinuria and tenderness in transplant kidney. It can develop at any time, as early as a week or as late as years after transplantation. With current immunosuppressive therapy, acute rejection develops in about 10% of transplant patients. Pure TCMR responds well to increased immunosuppressive therapy.

Therapeutic drug monitoring of tacrolimus is routinely done by monitoring the C0 (Tacrolimus trough level concentration). Tacrolimus has large intrapatient variation (IPV) due to many factors affecting the pharmacokinetics of Tacrolimus such as food intake, liver function, renal function, time after transplantation, co-medication, etc. Both high Tacrolimus intrapatient variability and low Tacrolimus time in therapeutic range (TTR) have been associated with risk of de novo donor–specific antibodies (dn DSA). Therefore, some studies point out that therapeutic drug monitoring of Tacrolimus by C0 is not enough for achieving better graft outcomes as well as reducing the adverse effects of Tacrolimus and then time in therapeutic range (TTR) of Tacrolimus may become more role in therapeutic drug monitoring of TAC. Time in therapeutic range (TTR) is defined as the percentage of time the patient's Tacrolimus C0 was within the target range.

2. Case presentation

The patient was 39-year-old police officer having end stage renal disease due to presumed chronic glomerulonephritis. He had been on maintenance hemodialysis for 18 months; he did not receive blood transfusion. He was neither diabetic nor hypertensive. His residual urine output was 300 cc/24 hour. He had two attacks of symptomatic urinary tract

infection in the past 3 months; it was treated according to urine culture and sensitivity results. Then, two serial urine cultures done two weeks apart were sterile. There was no history of urinary catheterization or urolithiasis.

The donor is his father; he is 62 years old. He did not have diabetes mellitus or hypertension. His peripheral pulses were normal. CDC cross match was all negative; though, HLA matching was not done to preserve money. Blood grouping was matched. Body weight of patient was 68 Kg (BMI 24.3 kg/m2); and, that of his father was 54.43 Kg.

The removal of donor kidney as well as implantation of transplanted kidney was uneventful

- First warm ischemic time was 3 minutes
- Cold ischemic time was 24 minutes
- Second warm time was 34 minutes; and, total time was 61 minutes. There were some atheromatous plaques in donor renal artery. Renal vein was connected to external iliac vein by end to side; and, renal artery to internal iliac artery.

The date of transplant was Feb 28, 2022. The immediate post operation period was excellent; stable vital signs with the urine output of 600 cc/ hour for the first 4 hours. Then, it gradually dropped; 100 cc/ hour at 11 hours and 35 cc/hour at 18 hours post-transplant surgery. Therefore, augmentation of fluid infusion together with frusemide was tried without benefits i.e., only 50 cc/ hour at 20-24 hour. Albumin infusion was done to improve oncotic pressure. His fluid balance over 24 hours was positive 4,500 cc; total intake 10,000 cc with the output 5,500 cc. He had been on crystalloid fluid infusion; ringer lactate alternating with normal saline with potassium replacement depending on 6 hourly electrolytes results.

The possibilities of gradual reduction in urine output in first 24 hour in case of post-transplant were as follows

- Acute rejection
- Hyper acute rejection which usually happens at the time of vascular anastomosis of renal artery
- Accelerated acute rejection
- Acute tubular necrosis
- Mechanical causes like vascular thrombosis
- Fluid collection around the transplanted kidney. Therefore, Doppler USG was requested; it revealed an increase in cortical shadows with intact cortico-medullary junction with normal color flow up to the cortex. The Resistive Index was 0.7; upper normal limit (normal range of Resistive Index was 0.5-0.7). As USG Doppler excluded mechanical cause, the possibilities were accelerated acute rejection and acute tubular necrosis. Thus, methylprednisolone was extended up to 5 days; the guideline being 3 days. Risks and benefits of transplant kidney biopsy were discussed.

USG was repeated on Day 2; the Resistive Index became 0.8 with further increased in cortical echo. Cortical medullary junction was still intact i.e., worsening of Resistive Index, supporting previous differential diagnosis - accelerated acute rejection and acute tubular necrosis.

His fluid balance became more positive; intake 1,500 cc with the urine output of 900 cc/24 hour. His weight was increasing; he gained 6 Kg (previous dry weight 68 kg rosed to 74 Kg). Thus, renal functioned was maintained with hemodialysis on Day 3; UF 4,000 cc removed during HD.

His temperature rose on first 24 hour (101ºF); lung fields were clear and there was no evidence of thrombophlebitis. Two possibilities were COVID-19 infection though he had booster vaccine, and recurrence of urinary tract infection. The full blood count revealed neutrophil leukocytosis; Total WBC was 11.6 x 109 /l (Neutrophils 92.1%, Lymphocytes 5.2%) with normochromic normocytic anemia (hemoglobin 9 gm %) indicating acute bacterial infection with likely source being operating theater.

Both rapid test and PCR from nasopharyngeal swab for COVID-19 were negative; his absolute lymphocyte count was very low (0.4). Blood for malaria parasites and Dengue serology were negative. Blood culture and urine culture were repeated. At the same time, Levofloxacin was added to Meropenem. Both urine and blood cultures were sterile.

The renal biopsy was done on Day 8; it was compatible with acute TCMR Grade IIA (Banff Classification- 2019) (g 0; t 1; i 3; v 1). Histological examination revealed inflammation in tubular, interstitial and vascular compartments. They were shown in figure (1) to (4). Overall findings were consistent with Acute TCMR (Banff Classification 2019 - Grade IIA).

Immunohistochemistry was consistent with negative C4d staining pattern in glomerular and peritubular capillaries (C4d0). Negative staining pattern for IgG, IgA, IgM, C3, C1q, Fibrin, Kappa and Lambda in Immunofluorescence examination.

From Day 8 onwards, the urine output was 1,500 cc/24 hour; it may be due to combined effect of methyl prednisolone and antibiotics).

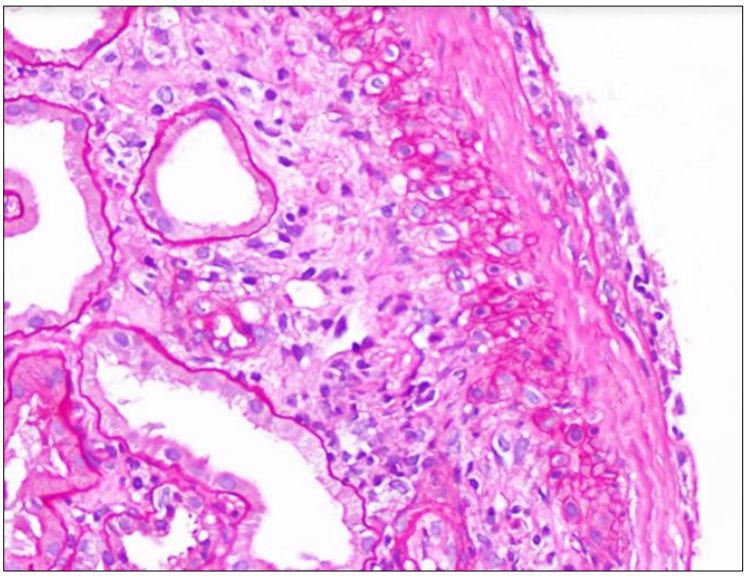

Figure 1 PAS stain. (Black circle indicates intimal arteritis)

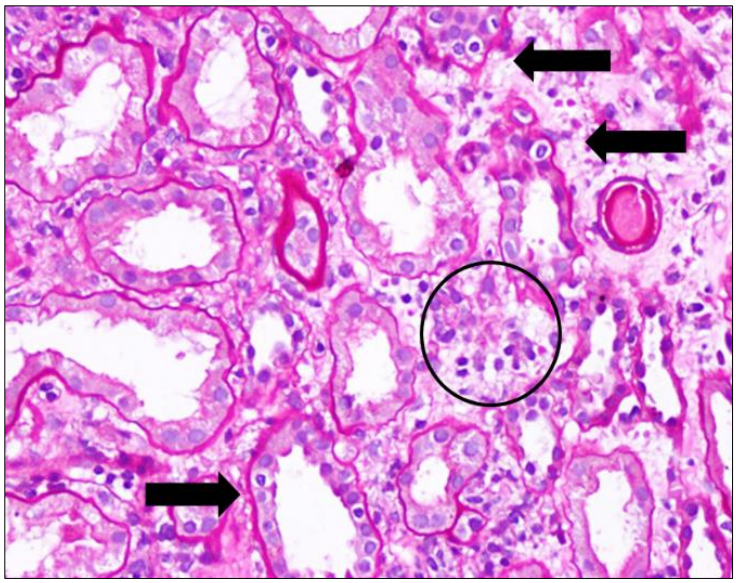

Figure 2 PAS stain (Arrows indicate intratubular lymphocytes (t1) and black circle indicates interstitial inflammation)

Trough Tacrolimus level was done on Day 5; it was 2.33 ng/ml (normal 7-10 ng/ml in first 3 months). As the body weight of the patient was 68 Kg, the initial dose of Tacrolimus was 6 mg per day; it was calculated with 0.1 mg/Kg/day in combined regimen with mycophenolate mofetil. Thus, previous dose 3 mg BD was increased to 4 mg BD. Repeat Trough Tacrolimus level on Day 11 was still low; 3.756 ng/ml. Therefore, Erythromycin 250 mg BD was added on Day 13. Tacrolimus Trough level done on Day 15 became acceptable (7.03 ng/ml). So, the patient had acute rejection due to low Tacrolimus level.

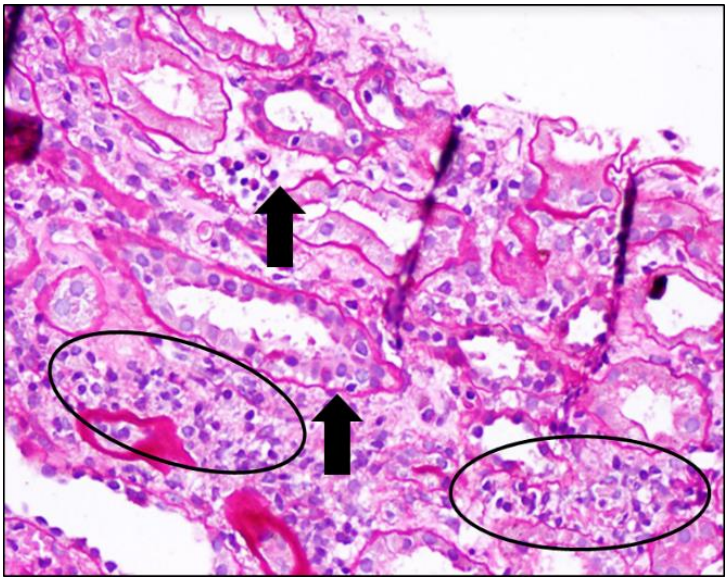

Figure 3 PAS stain. (Arrows indicate intratubular lymphocytes (t1) and black circles indicate interstitial inflammation)

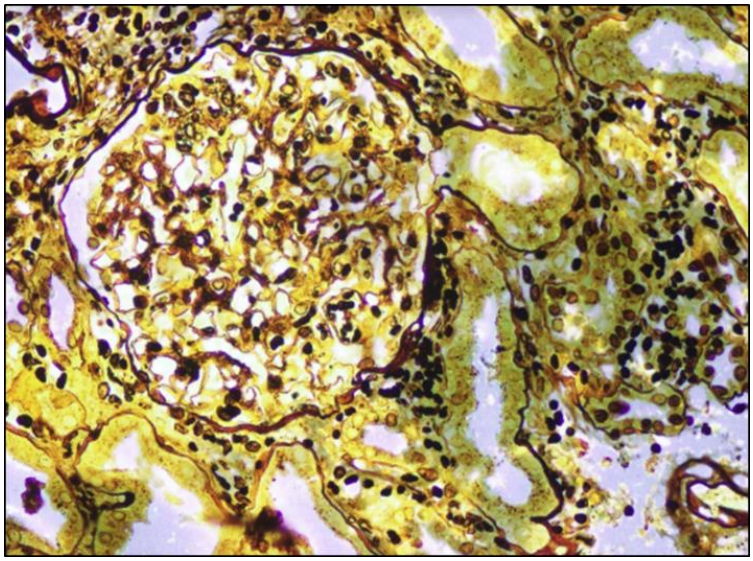

Figure 4 Silver stain. (Normal glomerulus and tubular basement membranes)

Now, the patient is Day 30 after transplant; he is well. He has been on Mycophenolate sodium 720 mg BD. His current medications are prednisolone 27.5 mg/day, Tacrolimus 4 mg twice a day, Mycophenolate sodium 720 mg twice a day, Erythromycin 250 mg twice a day and Carvedilol 6.25 mg twice a day. His average urine output is 5.0l/24 hour. Serum creatinine is 1.7 mg/dl; it has been stable for 2 weeks.

3. Discussion

The patient is middle age man; he had blood group matched and CDC cross matched negative kidney from his father. He had acute TCMR in 5 hours after transplant as evidenced by gradually falling urine output which were not correctable with fluids and frusemide, not falling serum creatinine, and fever.

Several factors involve in rejection: (1) prior sensitization - high panel reactive antibodies; (2) type of transplant: Deceased donor has a higher rejection than a living transplant; (3) Advanced age of the donor;(4) Recipient's age: Younger recipients have more rejection than older ones (5) prolonged cold ischemia time; (6) HLA mismatch; (7) Positive B cell crossmatch; (8) ABO incompatibility; (9) Recipient's age: Younger recipients have more rejection than older ones; (10) Recipient's race: Black race greater than White race; (11) Delayed graft function; (12) Therapy non-

compliance; (13) Previous episodes of rejections; and, (14) Inadequate immunosuppression. The patient did not have previous transfusion; no prior sensitization. The age of the donor seemed to be the risk factor for acute rejection as his father was 62 years old; same ABO blood group, negative CDC cross match, same cold ischemic time as other renal transplant in our center. Having the low blood trough level of Tacrolimus level up till two weeks led to acute rejection because the trough level of mycophenolate mofetil was normal.

Patients with acute rejection episodes were usually asymptomatic; they had abnormal allograft dysfunction seen only in routine blood monitoring. Allograft rejection was diagnosed if there was one or more features of the followings: (1) a sudden rise of serum creatinine to more than 25% of the baseline value; (2) the trend of serum creatinine was not falling as expected; (3) proteinuria (new-onset or worsening); (4) hypertension (new-onset or worsening); (5) fever, pain at the graft site, hematuria & dysuria; (6) fluid retention; and, (7) decreased urine output. The patient had falling urine output gradually at 5 hours after transplant; his serum creatinine was not dropped as expected on Day 2. Moreover, he had fever which might be one of the signs of rejection.

Once the hourly urine output dropped, the prerenal causes of acute injury were excluded as he had normal vital signs, blood pressure, and volume status. And, post-renal causes mainly obstructive uropathy eliminated by bladder scan, renal ultrasound. In complete blood count, there was no anemia and thrombocytopenia; thus, thrombotic microangiopathy was unlikely. Urine culture as well as blood culture was sterile, excluding infection as a cause of acute kidney injury. Transplant renal ultrasound with doppler for renal arterial and venous indices was done; RI was increasing which pointed either acute rejection or acute tubular necrosis (post-ischemic) interstitial nephritis.

Because transplant biopsy showed acute TCMR. Methyl prednisone IV (250 to 1000 mg daily) targeting T cells, B cells, and macrophages was given for 3 to 5 days. Optimize the dose and the level of the maintenance immunosuppressive drugs was done; escalation of Tacrolimus dosage gradually with addition of Erythromycin.

The differential diagnosis of renal allograft dysfunction in immediate post-transplant (less than one week) were as follows: (1) postischemic acute tubular necrosis or ischemia-reperfusion injury; (2) volume depletion leading to pre-renal AKI; (3) surgical complications like fluid collection (urinoma, perinephric hematoma, or lymphocele); (4) vascular thrombosis of arterial or venous; (5) multiple renal arteries from the donor's kidney - infarction of the part of the allograft or necrosis of the ureter leading to urinary obstruction or urinary leak; (6) aeroembolism; (7) calcium oxalate crystals deposits in renal allograft.

Tacrolimus level was done on Day 5; it was 2.33 ng/ml (normal 7-10 ng/ml in first 3 months). As the body weight of the patient was 68 Kg, the initial dose of Tacrolimus was 6 mg per day; it was calculated with 0.1 mg/Kg/day in combined regimen with mycophenolate mofetil. Thus, previous dose 3 mg BD was increased to 4mg BD. Repeat Tacrolimus level on Day 11 was still low; 3.756 ng/ml. Therefore, Erythromycin 250 mg BD was added on Day 13. Tacrolimus level done on Day 15 became acceptable (7.03 ng/ml). So, the patient had acute cell mediated rejection due to low Tacrolimus level which improved with increasing dose of Tacrolimus and adding macrolide – Erythromycin.

All the studies have shown that combination therapy of steroids, Tacrolimus and mycophenolate mofetil had better graft survival than others. Although a few reports mentioned the importance of monitoring of mycophenolate mofetil blood level; the patient had normal therapeutic range. Its Trough level done on Day 7 was 2.947 µg/ml (normal 1.0-3.5 µg/ml) and AUC 0-12 was 40.47 mg x h/L (normal 30 - 60 mg x h/L); both were acceptable.

Though Tacrolimus is very good anti-rejection effect, it has variable pharmacokinetics and pharmacodynamics. Yet there remains no consensus on how best to monitor Tacrolimus therapy. Both high Tacrolimus intrapatient variability (IPV) and low Tacrolimus time in therapeutic range (TTR) have been associated with risk of de novo donor–specific antibodies (dnDSA). Therapeutic drug monitoring of tacrolimus is routinely done by monitoring the C0 (Tacrolimus trough level concentration). Some reports suggested that higher therapeutic dose was positively with graft survival. According to study from the University of Colorado, mean Tacrolimus levels <8 ng/ml throughout the first year increased the risk of dnDSA development; and levels of 4–6 versus >8 ng/ml were associated with a 2.3-fold higher risk of acute rejection. Moreover, Tacrolimus trough levels >8 ng/ml was found to be the most effective in decreasing immunological adverse events and acute rejection (Syu et al., 2019). Furthermore, personalized approach in the timing and practice of Tacrolimus dose reduction was suggested depending on the individual's risk factors (Israni et al., 2013). In addition, the Tacrolimus trough level maintained between 5.35 and 7.15 ng/mL at the first post-transplant month was found to prevent acute rejection without increasing the increasing the incidence of infection within the first year after living kidney transplantation among Chinese patients (Yin et al., 2019). They also recommended that Tacrolimus levels < 4.0 ng/ml should be avoided during the first 12 months post-transplant when Tacrolimus was used in combination with fixed-dose mycophenolate with or without corticosteroids and induction therapy (Yin et al., 2019).

However, there was no clear relationship between Tacrolimus trough level and dnDSA incidence for kidney transplant recipients whose Tacrolimus trough levels were kept within the narrow range of 4– 6 ng/mL during the immunosuppression maintenance period. (Unagami et al., 2021)

Tacrolimus has large intrapatient variation (IPV) due to many factors affecting the pharmacokinetics of Tac such as food intake, liver function, renal function, time after transplantation, co-medication,etc. It was reported as poor sign; high intrapatient variability in Tacrolimus concentrations was strongly associated with an increased frequency of deviation from the suggested therapeutic range and an increased number of infection (E. Kim et al., 2020). Patients with high Tac IPV had an increased risk of dnDSA development and rejection episodes > year 1 posttransplant even in patients with low immunological risk profile. Therefore, in patients with high Tac IPV, potential causes should be addressed, and if not resolved, changes in immunosuppressive therapy should be considered (Baghai Arassi et al., 2022).

Nevertheless, some studies pointed out that therapeutic drug monitoring of Tacrolimus by C0 is not enough for achieving better graft outcomes as well as reducing the adverse effects of Tacrolimus; and, time in therapeutic range (TTR) of Tacrolimus may become more role in therapeutic drug monitoring of Tacrolimus. Time in therapeutic range (TTR) is defined as the percentage of time the patient's Tac C0 was within the target range. Moreover, its therapeutic effect was founded to be depended on genetics. A generalized estimating equation model analysis showed that alopecia and hyperlipidemia were associated with dose-adjusted level of Tacrolimus; Genotype of CYP3A5variants along with significant clinical covariates may be useful in individualizing tacrolimus therapy in kidney transplantation patients (I.-W. Kim et al., 2012). There were several drugs which increased blood level of Tacrolimus like macrolide group of antibiotics, coadministration of aluminum or magnesium hydroxide antacids. The intracellular action of Tacrolimus depended on its intracellular concentration rather than plasma concentration. Korean study reported that there was liner relationship between intracellular and whole blood concentrations of Tacrolimus in stable kidney recipients (Han et al., 2016). However, the correlation between blood level of Tacrolimus and intracellular level of Tacrolimus was poor; both of them did not relate with clinical outcomes (Francke et al., 2021)

Both high Tacrolimus intrapatient variability and low Tacrolimus time in therapeutic range was associated with risk of de novo donor–specific antibodies (dnDSA) and rejection. The immunologic risk associated with high Tacrolimus intrapatient variability was due to time outside of therapeutic range rather than variability in and of itself when evaluating absolute non–dose-corrected TAC levels irrespective of reason or indication (Davis et al., 2018).

An optimal therapeutic dose should be adjusted by Tacrolimus time in therapeutic range to prevent dnDSAs (Davis et al., 2018). In this case, very low Tacrolimus Trough level was the main reason for reduced graft survival; Tacrolimus time in therapeutic range would be better solution for him. Cell mediated rejection was over at present; and, Tacrolimus Trough level was normal too.

Appendix

Table 1 Serial blood parameters

	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**	**15**
HB	10.9	9.4	8.5	8.9	9.0	8.4	8.3	8.6	8.2	8.6		
WBC	8	9.7	10.7	11.6	11	6.8	6.4	6.1	6.9	5.7		
PLT	234	198	182	171	203	206	219	184	175	234		
Urea	44.7	44.2	63.6	105/58	82	140	207/88	128	171	177		
Cr	6.8	5.4	5.6	6.3/3.6	4.6	6.3	7.2/3.2	5.7	7.2	7.4		
K	3.8	3.3	4.24	4.07/3.3	3.7	3.8	3.5/3.2	3.18	2.85	3.27		
Tac						2.33					3.756	7.03

	10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Hb										

WBC										
PLT										
Urea	156	113	81	63	46	44.8	41.8	40.8	42	35.5
Cr	6.1	4.3	3.6	3.1	2.7	2.3	2.3	1.8	2.0	1.5
K										
Tac										

Table 2 Intake, output and fluid balance status

	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Intake	6343	5192	1650	890	1000	1500	1500	1500	2500	3000
Output	5110	1143	895	4510 (UF 4000)	450	480	2240 (UF 2000)	450	1500	2100
+/-	+1133	+4000	+758	-3620	+550	+1020	+1055	+1055	+1000	+900

4. Conclusion

Renal transplant rejections are not common with the advance of newer immunosuppressants. Early clinical awareness is important to get early diagnosis and, timely intervention to save graft kidney. Transplant biopsy, histopathology (including immunohistochemistry and immunofluorescence studies), is still the key for diagnosis, although donor-derived free DNA detection test is emerging as a noninvasive tool for diagnosing rejections. Treatment of rejection depends on the type of rejection, and managed with more immunosuppression and optimizing baseline immunosuppressive regimen post rejection. Tacrolimus is the most important agent for maintenance immunosuppression and prevention of immunologic injury to the renal allograft, yet there remains no consensus on how best to monitor drug therapy.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Statement of informed consent

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1,000 Bedded) Mingaladon, Myanmar. Informed consent was also taken from the patient.

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