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Tacrolimus-Induced Thrombotic Microangiopathy in a Kidney Transplant Recipient After Treatment for Acute Allograft Rejection

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 48-year-old
Final Diagnosis: Tacrolimus-induced thrombotic microangiopathy
Symptoms: Acute kidney injury • diarrhea • hematuria • nausea • numbness of extremities • thrombocytopaenia and anaemia
Clinical Procedure: —
Specialty: Nephrology • Pharmacology and Pharmacy • Transplantology

Objective: Unusual clinical course

Background: Tacrolimus is widely used in solid-organ transplantation but has been associated with thrombotic microangiopathy (TMA), a rare yet potentially life-threatening complication that can result in graft dysfunction or loss. The reported incidence ranges from 1% to 4.7% in transplant recipients. Diagnosis is challenging because clinical manifestations overlap with rejection, infection, and other secondary causes, making timely recognition critical.

Case Report: A 48-year-old kidney transplant recipient developed anemia, thrombocytopenia, and acute kidney injury 23 days after initiating tacrolimus for acute T-cell-mediated rejection. The patient also experienced neurologic and gastrointestinal symptoms. Microangiopathic hemolytic anemia was confirmed by the presence of schistocytes on peripheral smear, elevated lactate dehydrogenase, and low haptoglobin; gastrointestinal bleeding was excluded. Comprehensive diagnostic evaluation—including a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) activity, complement studies, coagulation testing, and infectious screening—excluded alternative etiologies of TMA. Although tacrolimus trough concentrations remained within the therapeutic range, the temporal association supported tacrolimus-induced TMA. Tacrolimus was promptly discontinued, resulting in complete hematologic and renal recovery within 10 days. During follow-up, tacrolimus reintroduction for refractory rejection led to recurrence of hemolytic anemia and thrombocytopenia, which again resolved after drug withdrawal. This dechallenge-rechallenge pattern yielded a Naranjo score of 9, indicating a definite adverse drug reaction.

Conclusions: This case highlights the importance of early recognition and systematic exclusion of competing etiologies when evaluating suspected drug-induced TMA. Distinguishing tacrolimus toxicity from rejection-related graft dysfunction is essential—prompt discontinuation of the offending agent can prevent irreversible kidney injury and graft loss.

Keywords: Kidney Transplantation • Tacrolimus • Thrombotic Microangiopathies
Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/953247

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Introduction

Thrombotic microangiopathy (TMA) is a pathologic process characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic organ injury due to microvascular thrombosis. Although TMA often manifests as a systemic disease, kidney-limited forms are increasingly recognized and may delay diagnosis and treatment, particularly in transplant recipients [1]. The kidney is particularly vulnerable; untreated cases can result in allograft dysfunction or loss. Drug-induced TMA represents approximately 10% to 13% of all TMA cases, with more than 70 implicated agents, including calcineurin inhibitors such as cyclosporine and tacrolimus [2,3]. Distinguishing drug-induced TMA from antibody-mediated rejection, infection, or recurrent primary disease remains clinically challenging in transplant populations [1,2]. Tacrolimus, a cornerstone immunosuppressant in kidney transplantation, has been increasingly associated with TMA (estimated incidence: 1%-4.7%) [1,3]. Clinical manifestations may be subtle or kidney-limited, contributing to underrecognition. Although a consistent dose-response relationship has not been established, symptom resolution after tacrolimus withdrawal has been reported [4,5]. Awareness of tacrolimus-induced TMA is essential because early recognition and prompt drug discontinuation are critical to prevent graft loss and mortality. This case highlights the diagnostic challenges of tacrolimus-induced TMA in a kidney transplant recipient and demonstrates definitive causality via systematic exclusion of alternative etiologies and recurrence after re-exposure.

Case Report

A 48-year-old woman with a history of kidney transplantation performed 2 decades earlier for end-stage kidney disease secondary to membranous glomerulonephritis was admitted for evaluation and management of acute kidney injury. Subsequent kidney biopsy demonstrated borderline acute T-cell-mediated rejection. There was no evidence of medication nonadherence based on patient report and clinical assessment. Her past medical history was notable for deep vein thrombosis, breast cancer status after partial mastectomy, and hyperlipidemia. Prior to admission, allograft function had remained stable while she was maintained on prednisolone 2.5 mg once daily, cyclosporine 50 mg twice daily, and everolimus 0.25 mg twice daily, along with prophylactic trimethoprim-sulfamethoxazole. Management of acute rejection included intravenous methylprednisolone pulse therapy (10 mg/kg/day) and modification of her immunosuppressive regimen to tacrolimus, which was initiated at 2 mg twice daily and subsequently titrated to 5.5 mg twice daily to achieve therapeutic levels, along with mycophenolate mofetil 500 mg twice daily. By day 23 of therapy, the patient developed anemia and thrombocytopenia, accompanied by hematuria, bilateral hand numbness, nausea, vomiting, and diarrhea. Steroid-related gastrointestinal hemorrhage was initially suspected but excluded by upper gastrointestinal endoscopy. Liver function tests, prothrombin time, and activated partial thromboplastin time were within normal limits. Due to progression of hematologic abnormalities, a comprehensive diagnostic evaluation was performed. Peripheral blood smear revealed numerous schistocytes, with elevated lactate dehydrogenase (252 U/L) and undetectable haptoglobin (<7.06 mg/dL), consistent with microangiopathic hemolytic anemia. Concurrently, serum creatinine increased from 2.46 to 3.15 mg/dL. A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) activity was within the normal range (72%), effectively excluding thrombotic thrombocytopenic purpura. Further investigations were performed to exclude secondary causes of TMA, including infectious etiologies (Shiga-toxin-producing bacteria, influenza A/B, coronavirus disease 2019 [COVID-19], cytomegalovirus, and BK virus), autoimmune disorders (antinuclear antibodies and anti-double-stranded DNA antibodies), metabolic deficiencies (vitamin B12, methylmalonic acid, and homocysteine), and complement-mediated disease (C3 and C4 levels). All results were unremarkable, supporting a diagnosis of drug-induced TMA. Tacrolimus was considered the most likely culprit given its recent initiation; the trough concentration was 13.4 ng/mL at the time of presentation. A summary of biochemical testing is provided in **Table 1**. Given the strong suspicion of tacrolimus-induced TMA, tacrolimus was discontinued and replaced with cyclosporine 75 mg twice daily. Supportive care was provided; the patient achieved complete clinical and hematologic recovery within 10 days, and she was discharged in stable condition.

The patient transitioned outpatient care to another institution. During follow-up contact several months later, she reported that tacrolimus had been reintroduced as a last therapeutic option for refractory allograft rejection. After re-exposure, hemolytic anemia and thrombocytopenia recurred, accompanied by new-onset purpura of the lower extremities. Tacrolimus was again discontinued, leading to subsequent hematologic improvement. This dechallenge-rechallenge pattern strongly supported a definite causal relationship between tacrolimus and TMA. The Naranjo Adverse Drug Reaction Probability Scale score was 9 (**Table 2**).

Discussion

Tacrolimus is a calcineurin inhibitor that serves as a cornerstone of immunosuppression in kidney transplantation; it plays an important role in the prevention and management of acute rejection. By inhibiting calcineurin-dependent activation of nuclear factor of activated T cells (NFAT), tacrolimus suppresses T cell activation and cytokine production. In patients with acute

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Table 1. Comprehensive biochemical evaluation undertaken to exclude alternative or secondary causes of thrombotic microangiopathy and microangiopathic hemolytic anemia.

Hemogram			Blood biochemistry			Serology		
Hemoglobin	6.1	g/dL	BUN	43.7	mg/dL	C3	80.6	mg/dL
Hematocrit	32.4	%	Creatinine	2.85	mg/dL	C4	22.9	mg/dL
Platelets	46	×10³/µL	AST	15	U/L	D-COOMBS	Negative	
Reticulocyte	0.8	%RBC	ALT	15	U/L	Haptoglobin	<7.06	mg/dL
Fibrinogen	284	mg/dL	D. Bilirubin	0.2	mg/dL	CH50 Assay	40.6	U/mL
FDP	<5	µg/mL	LDH	252	U/L	ADAMTS13	72	%
D-dimer	1652	FEU ng/mL	Amylase	50	U/L	**Autoimmunity**		
PT	11.6	sec	Lipase	46	U/L	Anti-Scl-70	5 (-)	AU/ml
INR	1.1		Sodium	137	mEq/L	Anti-Jo-1	4 (-)	AU/ml
APTT	27.3	sec	Potassium	3.7	mEq/L	Phospholipid IgM	<6.25	MPL units
Blood smear	Schistocytes (+2)		Calcium	8.5	mg/dL	Phospholipid IgG	7.86	GPL units
Infection			Inorganic phosphorus	2.9	mg/dL	Anti-B2-GP1 IgM	<1.1	CU
CMV-DNA Q-PCR	<34.5	IU/mL	Uric acid	5.3	mg/dL	Cardiolipin IgG	3	CU
BKV DNA Q-PCR	Negative		CRP	8.59	mg/L	Cardiolipin IgM	2.4	CU
Salmonella and Shigella	Negative		Homocysteine	19.9	µmol/L	ANA (IFA)	Negative	
Influenza A+B Ag	Negative		Vitamin B12	338	pg/mL	A-DSDNA	14.3	
SARS-CoV-2 Ag	Negative					LA screening	49.8	sec
						LA Normal ratio	1.4	

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; A-DSDNA, anti-dsDNA antibody; ALT, alanine transaminase; ANA (IFA), antinuclear antibody (immunofluorescence assay); Anti-B2-GP1 IgM, anti-B2-glycoprotein-IgM; Anti-Scl-70, anti-topoisomerase I antibody; Anti-Jo-1, anti-histidyl tRNA synthetase antibody; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BKV DNA Q-PCR, BK polyomavirus-DNA quantitative amplification test; BUN, blood urea nitrogen; C3, complement 3; C4, complement 4; Cardiolipin-IgM, anti-cardiolipin-IgM; Cardiolipin-IgG, anti-cardiolipin-IgG; CH50 Assay, complement activity total test; CMV-DNA Q-PCR, cytomegalovirus-DNA quantitative amplification test; CRP, C-reactive protein; D. Bilirubin, direct bilirubin; D-COOMBS, direct Coombs test; FDP, fibrin degradation products; INR, international normalized ratio; LA Normal ratio, lupus anticoagulant normalized ratio; LA screening, lupus anticoagulant screening; LDH, lactate dehydrogenase; Phospholipid IgG, anti-phospholipid antibody IgG; Phospholipid IgM, anti-phospholipid antibody IgM; PT, prothrombin time.

T-cell-mediated rejection, tacrolimus is often initiated or intensified after corticosteroid pulse therapy, particularly when rejection occurs under alternative regimens. Because tacrolimus has a narrow therapeutic index, careful dose titration and therapeutic drug monitoring are essential. Tacrolimus trough concentrations are commonly targeted at 8 to 12 ng/mL during the early post-transplant period, with lower targets (approximately 5-8 ng/mL) often used during stable long-term maintenance therapy [6].

Both cyclosporine and tacrolimus have been implicated in TMA among transplant recipients. Cyclosporine-associated TMA has long been recognized, and tacrolimus-related cases have been reported, without clear evidence that either agent confers a lower risk than the other. Clinical outcomes after switching between calcineurin inhibitors are variable, with both recurrence and resolution reported, suggesting a shared but incompletely understood mechanism of endothelial injury. In our patient, TMA resolved after switching from tacrolimus to cyclosporine,

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Table 2. Application of the Naranjo Adverse Drug Reaction Probability Scale to the present case. The total score was 9, consistent with a definite causal relationship between tacrolimus exposure and thrombotic microangiopathy.

Naranjo Adverse Drug Reaction Probability Scale	Total score: 9
1. Are there previous conclusive reports on this reaction?	+1 (yes)
2. Did the adverse event appear after the suspected drug was administered?	+2 (yes)
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1 (yes)
4. Did the adverse reaction reappear when the drug was readministered?	+1 (yes)
5. Are there alternative causes (other than the drug) that could independently have caused the reaction?	+2 (no)
6. Did the reaction reappear when a placebo was given?	0 (do not know)
7. Was the drug detected in the blood (or other fluids) at concentrations known to be toxic?	0 (no)
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1 (yes)
9. Did the patient have a similar reaction to the same or similar drugs during any previous exposure?	0 (do not know)
10. Was the adverse event confirmed by any objective evidence?	+1 (yes)

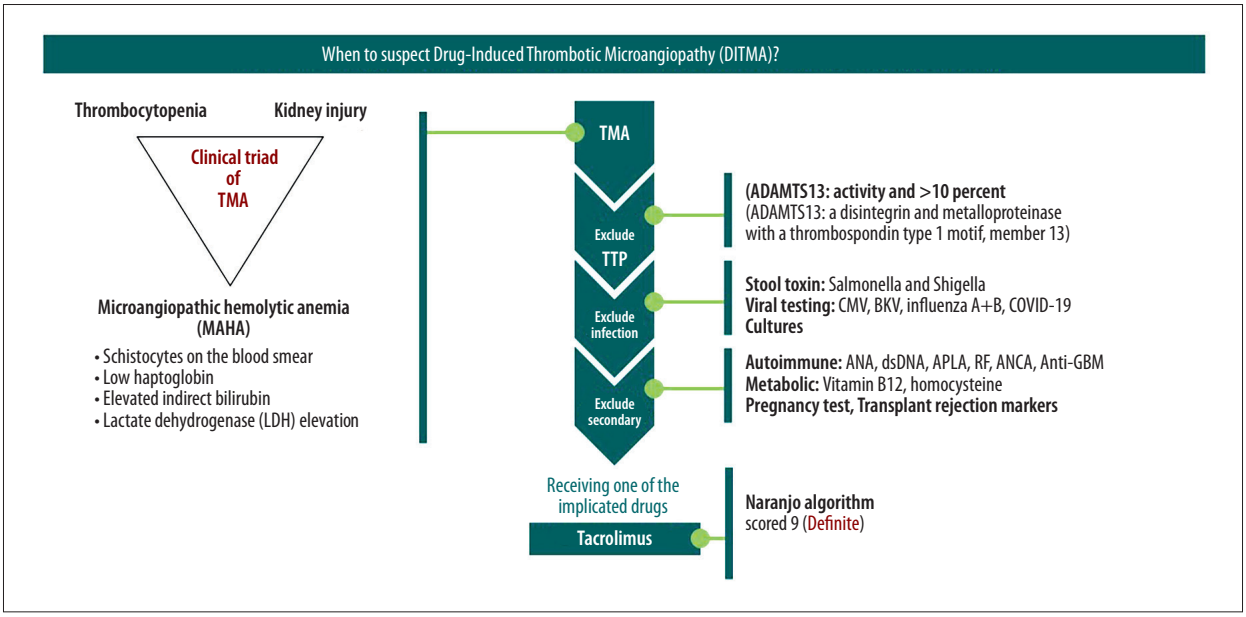

Figure 1. Diagnostic algorithm for suspected drug-induced thrombotic microangiopathy, including confirmation of microangiopathic hemolytic anemia and stepwise exclusion of secondary causes before implicating tacrolimus.
Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APLA, antiphospholipid antibodies; BKV, BK virus; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; dsDNA, double-stranded DNA; GBM, glomerular basement membrane; RF, rheumatoid factor; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

further illustrating the variability in clinical response following calcineurin inhibitor modification [4].

Tacrolimus-associated TMA is a recognized form of drug-induced TMA, particularly among transplant recipients, for whom diagnosis is often complicated by overlapping etiologies such as rejection and infection [1]. The pathogenesis centers on endothelial injury, which may arise from both dose-dependent toxicity and immune-mediated mechanisms. At the molecular level, tacrolimus induces oxidative stress, complement activation, inflammatory cytokine release, and endothelial apoptosis, collectively disrupting vascular integrity and promoting

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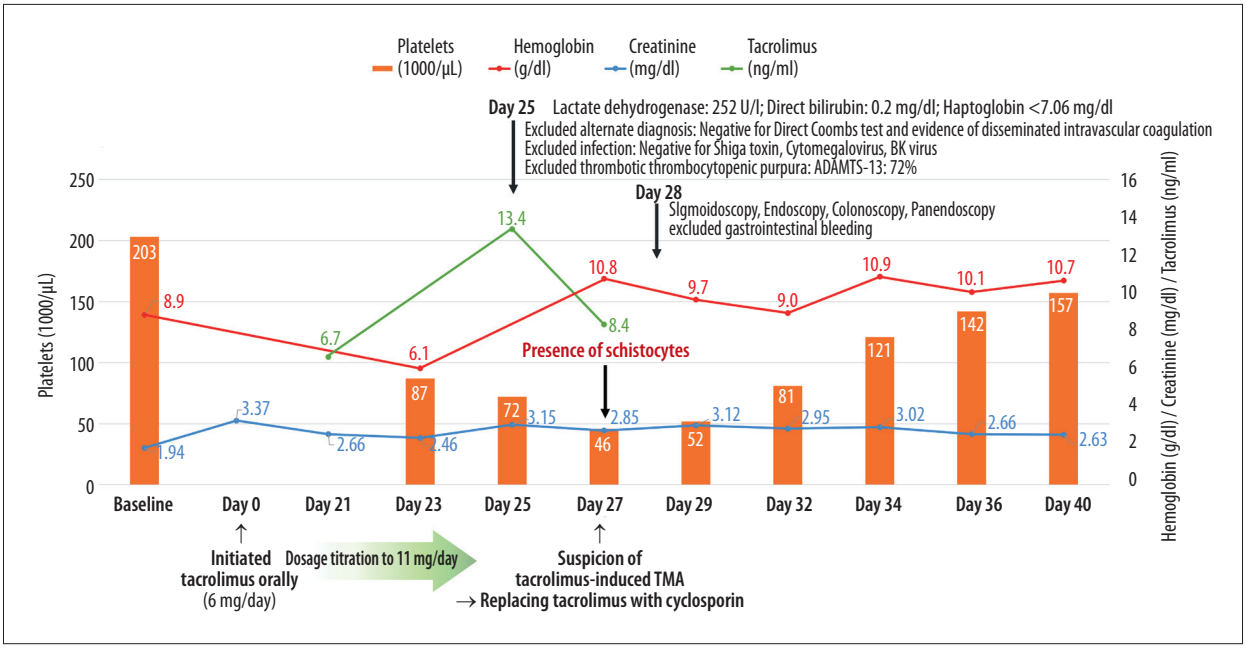

Figure 2. Temporal relationship between tacrolimus exposure and the development of microangiopathic hemolytic anemia. The figure illustrates the time course of tacrolimus administration, corresponding trough concentrations (green line), platelet count (orange bars), hemoglobin level (red line), and serum creatinine (blue line). Abbreviation: TMA, thrombotic microangiopathy.

a prothrombotic phenotype. In parallel, dysregulation of vasoactive mediators—characterized by increased thromboxane A2 and reduced prostacyclin—along with elevated von Willebrand factor levels enhances platelet aggregation and microvascular thrombosis. Complement activation may further amplify endothelial injury, suggesting overlap with complement-mediated TMA, whereas perturbations in ADAMTS13 activity may contribute to impaired regulation of von Willebrand factor multimers. Such processes culminate in platelet-fibrin thrombus formation, microvascular occlusion, and subsequent organ dysfunction, particularly in the renal allograft. Importantly, these mechanisms are often potentiated by transplant-specific factors such as ischemia-reperfusion injury, alloimmune responses, infections, and concomitant immunosuppressive agents, creating a "second-hit" environment that perpetuates endothelial damage and graft injury [1,7,8]. Most affected patients exhibit normal ADAMTS13 activity, distinguishing tacrolimus-induced TMA from thrombotic thrombocytopenic purpura and supporting an endothelial complement-mediated mechanism [7]. Given that no definitive diagnostic test exists, diagnosis relies on the presence of microangiopathic hemolytic anemia with schistocytes and systematic exclusion of alternative etiologies (**Figure 1**).

Published case reports demonstrate that the onset of tacrolimus-associated TMA is highly variable, ranging from early post-transplant presentation to late-onset disease years after transplantation [4,5,9,10]. Saito et al described TMA development in the early stage after kidney transplantation, temporally associated with high tacrolimus trough concentrations (15-20 ng/mL), suggesting an exposure-related contribution [4]. In contrast, Ozaki et al reported de novo TMA occurring 2 years after kidney transplantation, which emphasizes that tacrolimus-associated TMA can emerge after prolonged treatment and may be diagnostically delayed [5]. Although most reports involve kidney transplantation, tacrolimus-associated TMA has also been described after other solid-organ transplants. Gill and Meghrajani reported tacrolimus-associated TMA following orthotopic heart transplantation, with clinical improvement after tacrolimus discontinuation and supportive management [9]. Similarly, Choi et al described transplant-associated TMA in a lung transplant recipient occurring 4 months after transplantation during receipt of tacrolimus, accompanied by substantially elevated trough concentrations (>30 ng/mL); despite tacrolimus withdrawal and plasma exchange, the clinical course was fatal due to severe complications [10]. Collectively, these cases show that tacrolimus-associated TMA can occur across diverse transplant settings, with variable onset and severity; prompt recognition with tacrolimus discontinuation or dose reduction remains the cornerstone of management.

Although tacrolimus trough levels were not uniformly reported, pronounced elevation in selected cases supports a possible exposure-related mechanism and underscores the importance of therapeutic drug monitoring when TMA is suspected. In our patient, TMA developed approximately 3 weeks after tacrolimus initiation, with trough concentrations of 13.4 ng/mL; rapid clinical recovery after tacrolimus discontinuation further supports tacrolimus as the likely precipitating factor. The present case also suggests that tacrolimus-associated TMA can occur

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even at concentrations within or near conventional therapeutic ranges (**Figure 2**).

Conclusions

This report describes tacrolimus-associated TMA in a kidney transplant recipient, supported by a comprehensive diagnostic evaluation with systematic exclusion of alternative etiologies. Our case emphasizes that early recognition and prompt drug withdrawal are essential to prevent irreversible graft injury. Importantly, among transplant recipients, distinguishing drug-induced TMA from rejection-related graft dysfunction is critical because delayed identification of the offending agent may lead to inappropriate escalation of immunosuppression and adverse graft outcomes. Notably, tacrolimus-induced TMA can occur even at therapeutic drug levels, underscoring the need for a high index of suspicion regardless of measured concentrations.

Department and Institution Where Work Was Done

Department of Pharmacy, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Patient Consent

Written informed consent for publication of this case report, including all accompanying images and data, was obtained from the patient.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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