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Management of Tacrolimus-induced thrombotic microangiopathy in a heart transplant recipient: Utilizing novel immunosuppression strategies

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Thrombotic microangiopathy (TMA) represents a heterogeneous group of disorders characterized by endothelial injury, complement activation, and platelet aggregation, and may occur in association with systemic diseases, infections, or drug exposure. In solid organ transplant recipients, TMA is most commonly linked to immunosuppressive therapy, particularly calcineurin inhibitors and mammalian target of rapamycin inhibitors, with increased risk during combined use. Drug-induced TMA is rare but potentially life-threatening, and management relies primarily on prompt withdrawal of the offending agent and modification of immunosuppression. We report the successful use of belatacept-based immunosuppression in a heart transplant recipient with tacrolimus-associated TMA. Belatacept, a selective T-cell costimulation blocker, represents a promising alternative immunosuppressive strategy in this setting, particularly in patients with drug-related vascular toxicity.
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Thrombotic microangiopathy (TMA) is a clinical–pathological syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ dysfunction resulting from endothelial injury and microvascular thrombosis.[1] In solid organ transplantation, de novo TMA is a recognized complication, most frequently associated with immunosuppressive therapy, particularly calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine.[2] Management is challenging, as withdrawal of the offending agent must be balanced against the need for adequate immunosuppression, especially early after transplantation. Belatacept, a selective T-cell costimulation blocker, has emerged as a renal-sparing alternative to CNIs and is increasingly explored in heart transplantation.[3,4] We report a case of tacrolimus-induced TMA following orthotopic heart transplantation (OHT), successfully managed with belatacept-based immunosuppression.

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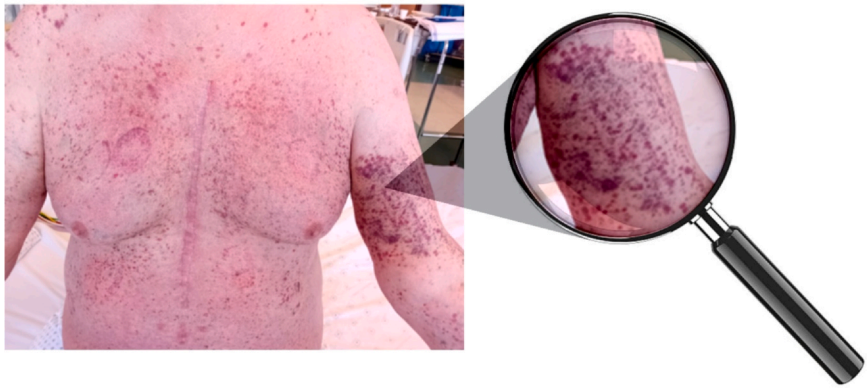

Figure 1 Diffuse petechiae at admission: small (1-2 mm), non-blanching, red to violaceous macules. They are typically flat, non-palpable, and may darken over time and can coalesce into larger purpuric areas as seen in the image

Case report

A 57-year-old male underwent OHT for non-ischemic dilated cardiomyopathy. The early postoperative course was complicated by antibody-mediated rejection, treated with plasmapheresis, intravenous immunoglobulins, and methylprednisolone pulses. After stabilization on tacrolimus, mycophenolate mofetil (MMF), and methylprednisolone, the patient was discharged with normal graft function.

Four months after transplantation, the patient presented with purpura (Figure 1), dizziness, paresthesia, and bilateral leg edema. Transthoracic echocardiography showed mildly impaired right ventricular function and preserved left ventricular function. Tacrolimus trough levels were supratherapeutic (16 ng/ml). Laboratory testing (Figure 2) revealed pancytopenia (hemoglobin 90 g/L, leukocytes 2.39 × 10^9/L, platelets 86 × 10^9/L), markedly elevated lactate dehydrogenase (15.45 μkat/L), undetectable haptoglobin, and normal creatinine and transaminases. Peripheral blood smear demonstrated 4.7% schistocytes. Donor-derived cell-free DNA and donor-specific antibodies were low, making clinically relevant rejection recurrence unlikely.

Based on hemolytic anemia, thrombocytopenia, purpura, and elevated LDH, tacrolimus-induced TMA was suspected. Alternative etiologies, including thrombotic thrombocytopenic purpura (preserved ADAMTS13 activity), complement-mediated TMA (normal complement panel workup: C3, C4, C5b-9, CH50, AH50, lectin pathway activity, factor H, factor I, factor B, factor B cleavage product Bb, anti-factor H antibodies, anti-C1q antibodies, C3 nephritic factor and urinary C5b-9), infection-related TMA (negative blood cultures, normal inflammatory biomarkers, negative stool shiga toxin), and other drug-induced causes, were excluded.[1,2] Tacrolimus was discontinued, and after a washout period, everolimus was introduced. Although transient improvement followed tacrolimus withdrawal, clinical and laboratory deterioration occurred after achieving therapeutic everolimus levels, including worsening pancytopenia, rising LDH, renal dysfunction, proteinuria, and

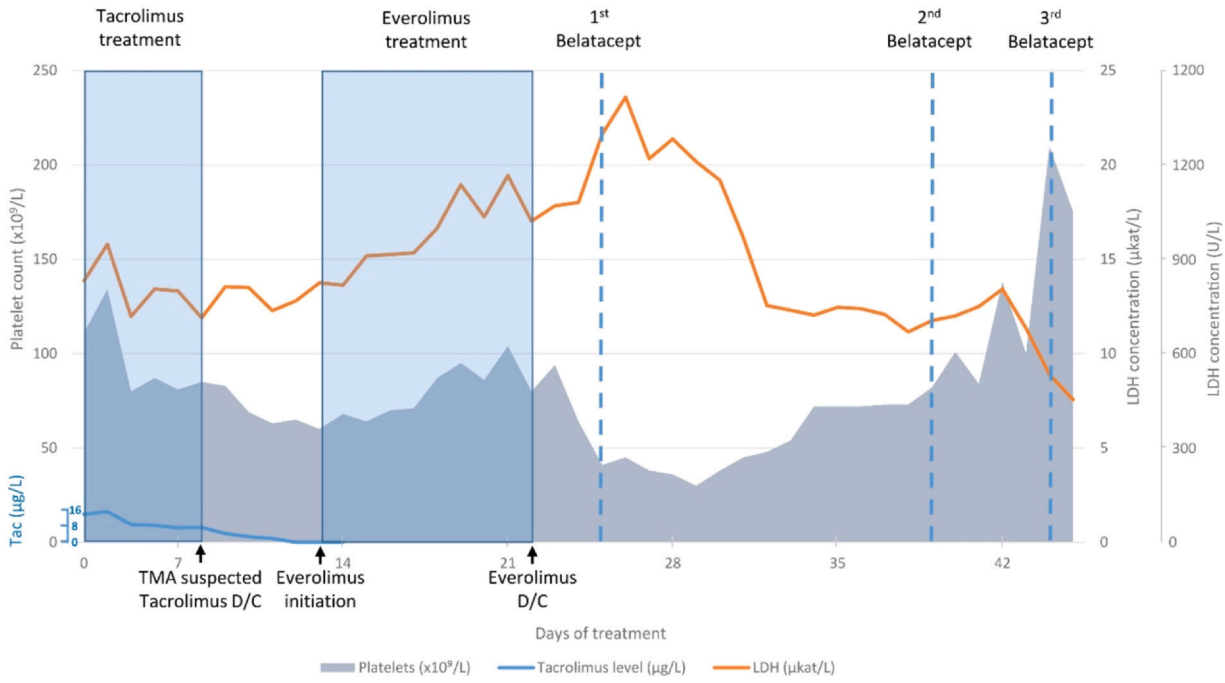

Figure 2 Biochemical changes after medical interventions

Table 1 Summary of Experience with Belatacept Use in Kidney Transplantation

Study / Author	Patient profile (age/ transplant type)	Suspected trigger	Treatment approach	Clinical outcome / graft status
Ashman et al. (2009)[7]	26 F; Living related kidney	Serial sensitivity to Ciclosporin, Tacrolimus, and Sirolimus	Withdrawal of all triggers; Belatacept maintenance (5 mg/kg monthly), Prednisolone, and Azathioprine.	Excellent; resolution of hemolytic parameters. SCr 1.4 mg/dL and **no proteinuria** at day 260.
Koppula et al. (2013)[8] - **Case 1**	56 M; Deceased donor en bloc pediatric kidney	Tacrolimus	Tacrolimus withdrawal; 3 sessions of plasmapheresis; Belatacept conversion (10 mg/kg induction, then monthly).	Platelet normalization by Day 10. SCr improved from peak 8.6 mg/dL to 1.4 mg/dL by Day 50.
Koppula et al. (2013)[8] - **Case 2**	47 F; Simultaneous kidney-pancreas	Tacrolimus; exacerbated by CMV viremia and Banff 1B/2A rejection	Thymoglobulin, steroids, IVIG, plasmapheresis (for rejection context); Belatacept (10 mg/kg) with slow Tacrolimus taper.	Resolution of TMA. Stable graft function (SCr 1.6 mg/dL) at 21 months post-transplant.
Acharya et al. (2024)[9]	17 M; Deceased donor kidney (Prune Belly Syndrome)	Tacrolimus	Tacrolimus withdrawal; 2 doses of Eculizumab (**pediatric dose: 600 mg**); Belatacept conversion (10 mg/kg induction, then monthly).	Recovery from peak SCr 9.5 mg/dL to stable eGFR 76 mL/min/1.73 m² at one year. Switched to Sirolimus at 12 months.
Leong et al. (2024)[3]	41 F; Spousal kidney	Everolimus (following MMF-to-mTORi switch for CMV)	Everolimus permanent withdrawal; 8 cycles of TPE; IV Methylprednisolone; **brief Tacrolimus withholding (restarted as maintenance)**.	Recovery of hemolytic markers; SCr 90 µmol/L at follow-up. Stable function maintained at one year.
Merola et al. (2016)[10]	Adult; Kidney	CNI-induced	5 doses of Eculizumab and monthly Belatacept maintenance.	Stable renal function documented 2 years post-KT.

hypogammaglobulinemia (Figure 2), consistent with mTOR inhibitor-associated exacerbation of TMA.[2] Everolimus was discontinued and supportive therapy was initiated.

Given inadequate immunosuppression with MMF and steroids alone, belatacept was introduced (10 mg/kg every 2 weeks for 2 months, followed by 6 mg/kg monthly). Clinical and laboratory parameters rapidly normalized (Figure 2), with only transient mild elevation of liver enzymes. At 6-month follow-up, graft function and renal, hepatic, and hematologic parameters remained normal, with no recurrence of TMA.

Discussion

TMA comprises a heterogeneous group of disorders characterized by Coombs-negative hemolytic anemia, thrombocytopenia, and ischemic organ injury due to microvascular thrombosis.[1] In transplant recipients, CNIs are the most commonly implicated agents, with an incidence of 1% to 4.7%.[2] Proposed mechanisms include direct endothelial toxicity, dysregulation of thromboxane A_2–prostacyclin balance, and immune-mediated vascular injury.[5] Although mTOR inhibitors are frequently used in CNI-associated TMA, they may aggravate endothelial injury by suppressing vascular endothelial growth factor-mediated repair.[2]

Belatacept, a fusion protein targeting CD80/CD86-mediated T-cell costimulation, has demonstrated comparable rejection rates with improved renal outcomes compared with cyclosporine in cases of TMA in kidney transplant recipients (Table 1). Emerging experience in heart transplantation supports its use as a CNI-free strategy in selected patients, although infectious risk requires careful monitoring.[4,6]

This case highlights the importance of early recognition of drug-induced TMA and demonstrates belatacept as an effective and safe immunosuppressive alternative when both CNIs and mTOR inhibitors must be avoided.

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Informed consent

Written informed consent was obtained from the patient for publication of this case report.

Declaration of Competing Interest

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financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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