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Thrombotic Microangiopathy After Kidney Pancreas Transplant Managed With Eculizumab and a Calcineurin Inhibitor-free Basiliximab/ Belatacept Maintenance Regimen: Between a Rock and a Hard Place

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Thrombotic microangiopathy (TMA) is a rare but significant complication after kidney transplant, resulting in graft loss in more than one-third of cases with systemic manifestations.[1-4] TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury resulting from endothelial damage and microthrombi formation in small vessels.[5] In the context of kidney transplantation, TMA can manifest as either a systemic condition with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure or as a localized form leading to progressive renal dysfunction, proteinuria, or hypertension. Clinically, systemic TMA presents with increased serum lactate dehydrogenase (LDH), fragmented erythrocytes on peripheral smear, and thrombocytopenia. TMA in the early postoperative period has been closely associated with calcineurin inhibitors (CNIs),[2,6-8] but may also occur in the setting of antibody-mediated rejection.[2]

Development of TMA posttransplantation poses significant diagnostic and therapeutic challenges. Early recognition and appropriate and immediate intervention are crucial for allograft salvage and to improve both allograft and patient outcomes if rescue is successful. Traditional therapeutic approaches include reduction or discontinuation of CNIs, transitioning from CNIs to mammalian target of rapamycin inhibitors (mTORi), and the use of plasmapheresis.[6-11] More recently, the complement inhibitor eculizumab, a long-acting humanized monoclonal antibody against complement C5, which is typically used to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS), has demonstrated efficacy in treating various forms of TMA, including those associated with kidney transplantation.[12-15] This report describes a case of TMA in a simultaneous pancreas and kidney (SPK) recipient successfully treated with plasmapheresis, cessation of all CNIs and mTORi, and eculizumab with maintenance immunosuppression of mycophenolic acid and alternating biweekly belatacept/basiliximab.

CASE DESCRIPTION

A 33-y-old woman with type 1 diabetes mellitus underwent SPK transplant. Eighteen months prior, she presented with hypertensive crisis, acute onset nephrotic syndrome, acute kidney injury, and transient vision loss. Native kidney biopsy was consistent with diabetic nephropathy and peritoneal dialysis was initiated. She also developed hemolytic anemia and underwent evaluation, including bone marrow biopsy, which was negative. Complement C3, C4, ADAMTS 13, LDH, and haptoglobin are listed in Table 1. Her haptoglobin eventually rose and hemoglobin stabilized with darbepoetin. The donor was a 32-y-old man with trauma-related brain death, body mass index 24 kg/m^2, KDPI 17, and terminal serum creatinine 1.11. Crossmatch was negative. Cold ischemia time was 13 h. The pancreas transplant was performed with systemic venous and enteric exocrine drainage and with ipsilateral placement of the pancreas and the kidney.[16] The operation was uneventful, with

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TABLE 1.

Test results for thrombotic microangiopathy

	Results, 8 mo pretransplant	Result at time of TMA	Reference range
Complement C3, mg/dL	117	159	87–200
Complement C4, mg/dL	43	67	19–52
ADAMTS 13 activity, %	90	91	≥61
Haptoglobin	<6	7	30–200 mg/dL
LDH	464	424	140–271 u/L
Factor H, mg/dL	ND	33.8	15.8–37.5
Factor I, mg/dL	ND	3	1.6–3.7
Genetic testing for aHUS	ND	Negative	

aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; ND, not done; TMA, thrombotic microangiopathy.

normal perfusion of both allografts on contrast-enhanced Doppler ultrasound.[17,18] Immunosuppression included rabbit antithymocyte globulin induction (total 5 mg/kg) with corticosteroid premedication and maintenance tacrolimus (goal trough 7–9 μg/mL) and sirolimus (goal trough 3–5 μg/mL). The patient was discharged on postoperative day 5 with excellent kidney and pancreas allograft function. She required 3 overnight readmissions for symptomatic orthostatic hypotension, which responded to intravenous fluids and initiation of midodrine, fludrocortisone, and droxidopa.[19] On postoperative day 25, she was readmitted for a rise in creatinine to 1.8 mg/dL. Kidney allograft biopsy showed 3 foci of TMA with fibrin thrombi in glomerular capillary lumens, Banff borderline rejection, and negative C4D immunohistochemistry. Significant elevation in LDH (424 units/L) and decreased haptoglobin (7 mg/dL) were consistent with TMA. ADAMTS 13, C3 and C4, Factor H and I, and aHUS genetic testing are presented in Table 1. The patient received methylprednisolone bolus and taper to off over 20 d for rejection. For treatment of TMA, she underwent 7 plasma exchanges and started eculizumab 900 mg IV every week × 4 induction (supplement dose of 600 mg after each plasma exchange) followed by maintenance 1200 mg IV q14 days. Sirolimus was initially discontinued, the goal tacrolimus trough level was decreased to 5–6 μg/mL, and mycophenolic acid 720 mg BID was added. Four days later, tacrolimus was switched to sirolimus, and the patient received a single dose of intravenous basiliximab 40 mg.[20] A repeat kidney allograft biopsy was performed when creatinine rose to 7.46 mg/dL, persistent LDH elevation (550 units/L), and low haptoglobin (<6 mg/dL) showed severe active TMA with capillary loop thrombi in 9 of 18 glomeruli and luminal thrombi in 8 arterioles. There was also acute tubular injury with foci of acute tubular necrosis and rare calcium oxalate crystals, no evidence of acute cellular rejection, and C4D immunohistochemistry remained negative (Figures 1 and 2). Eculizumab was continued, and, with the rapid deterioration of her renal function, we decided to discontinue both tacrolimus and sirolimus, as we were uncertain which was the inciting medication, and belatacept 5 mg/kg IV q2 weeks × 5 doses, and then 5 mg/kg IV q4 weeks was started. She was discharged with a regimen of mycophenolic acid, belatacept, and eculizumab. Creatinine at discharge was 6.5 mg/dL and she required intermittent hemodialysis for 3 wk. Serum creatinine remained elevated and Banff 2B acute cellular rejection was diagnosed on subsequent kidney allograft biopsy. She received rabbit antithymocyte globulin (7 mg/kg), methylprednisolone bolus, and

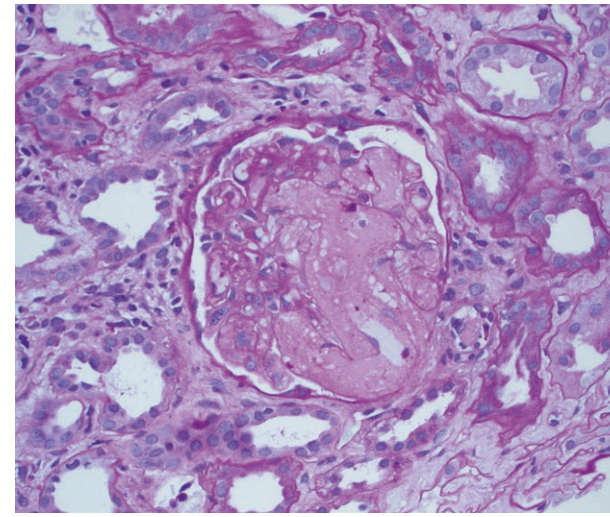

FIGURE 1. There is massive glomerular capillary loop expansion by luminal thrombi with an arteriolar thrombus (PAS stain, ×40). PAS, Periodic acid–Schiff.

taper to off over 3 wk. Monthly basiliximab infusions of 20 mg IV were added so that the belatacept and the basiliximab were alternating every 2 wk. The TMA has resolved, and she has had no further rejection episodes. The patient developed *Clostridium difficile* colitis, which resolved with oral vancomycin and BK viremia, which responded to the reduction of mycophenolic acid dose to 360 mg daily and human IVIG. On resolution, the mycophenolic acid dose was increased back to 360 mg BID. Please see Figure 3 for a timeline of all of these events.

At 12 mo posttransplant, the maintenance immunosuppression regimen remains belatacept 5 mg/kg IV q4 weeks and basiliximab 20 mg IV q4 weeks (alternating each agent every 2 wk), and mycophenolic acid 360 mg BID with creatinine of 2.10 mg/dL. Pancreas allograft function has persistently remained excellent. She has had no signs of pancreas rejection, and at 1 y, hemoglobin A1c was 5.2%. Eculizumab 1200 mg IV q2 weeks has been continued for TMA treatment. As the patient has now been receiving eculizumab therapy for >1 y, a slow weaning schedule has been initiated with plans to discontinue.

DISCUSSION

TMA is a rare but severe complication of kidney transplant, significantly impacting both allograft and patient survival.

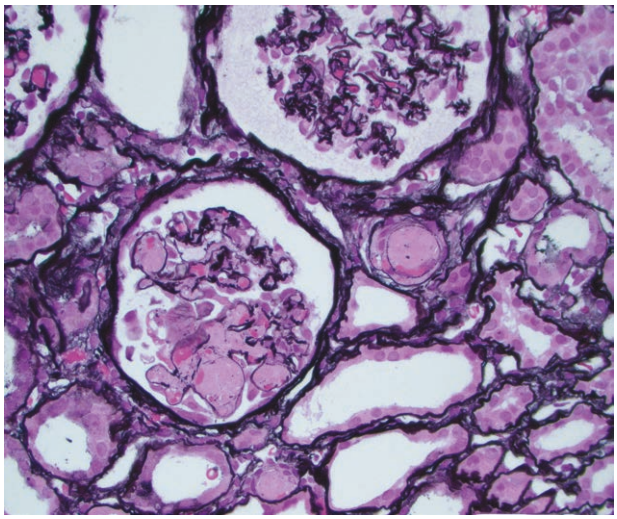

FIGURE 2. The glomerulus (left) contains capillary loop thrombi with an adjacent occlusive arteriolar thrombus. Background portions of all glomeruli show ischemic corrugation of the capillary basement membranes. (Jones Silver Stain, ×40).

Early recognition and appropriate intervention are critical. The most common causes of de novo TMA are antibody-mediated rejection and CNI induced, but cases have also been reported with mTORi.[21] The management of TMA in kidney transplant recipients involves a combination of supportive care, immunosuppressive adjustments, and specific therapies aimed at addressing the root cause of endothelial injury and thrombosis. Plasma exchange is a cornerstone of treatment.[22,23] In cases where CNI-induced TMA is suspected, discontinuing CNIs is an immediately indicated first step to minimize further damage. Switching to mTORi or using a steroid-based therapy has been reported.[2,24,25] When TMA is caused by mTORi, switching to an alternative immunosuppression regimen such as CNI or belatacept may lead to resolution.[21] The prognosis improves with a reduction in CNI or mTORi levels and the introduction of alternative immunosuppressants, but renal recovery may still be limited, especially when TMA has caused significant irreversible damage to the kidney vasculature.

Belatacept has been approved by the Federal Drug Administration for use in kidney transplant but not in pancreas transplant. Several case reports in kidney transplant recipients have demonstrated that switching from CNIs to belatacept can lead to the resolution of TMA.[21,26,27] There are no reported cases of belatacept used specifically in SPK recipients with TMA. Belatacept is commonly used in kidney transplant recipients and may be beneficial in some patients with TMA, but it may not provide the same level of protection against acute rejection of the pancreas allograft. For example, a phase 2 multicenter randomized trial in SPK recipients was halted early because belatacept did not provide sufficient immunosuppression to reliably prevent pancreas rejection in SPK recipients undergoing tacrolimus withdrawal and those who remained on belatacept with low-dose tacrolimus experienced higher rates of opportunistic infections.[28] Subsequent reports of small case series suggest that the best use of belatacept is with low-dose CNI to prevent pancreas rejection, although CNIs was not an option in this case.[29-31] As an alternative approach to CNI sparing, our group has recently published results of long-term basiliximab maintenance immunosuppression in combination with reduced dosage or discontinuation of CNIs in pancreas transplant recipients.[20] This case is the first report of the combination of belatacept and basiliximab applied together as maintenance immunosuppression instead of primary CNI or mTORi immunosuppression.

Eculizumab has become a key treatment in managing TMA.[32] Long-term use requires monitoring for infectious complications, particularly meningococcal infections, which necessitate prophylactic vaccinations before starting therapy.[33] None of the cases described earlier where belatacept was used to eliminate CNIs in kidney transplant recipients with TMA used eculizumab as part of the approach. However, Merola et al[34] reported a case of CNI-associated TMA after kidney transplant successfully treated with eculizumab and a switch from CNI to belatacept. For SPK recipients, eculizumab has demonstrated promising early results in several case reports of TMA secondary to CNI toxicity[12] or aHUS.[14,15]

This case highlights the complex management of TMA in an SPK recipient, with a focus on plasma exchange, CNI/mTORi withdrawal, and the use of eculizumab. The evolving strategy of CNI/mTORi withdrawal, the use of alternative immunosuppressants such as belatacept and basiliximab, and concerns related to balancing rejection and infection were key aspects of her management. However, the need for close outpatient monitoring was evident, as this patient struggled with both rejection and infectious complications. The combination

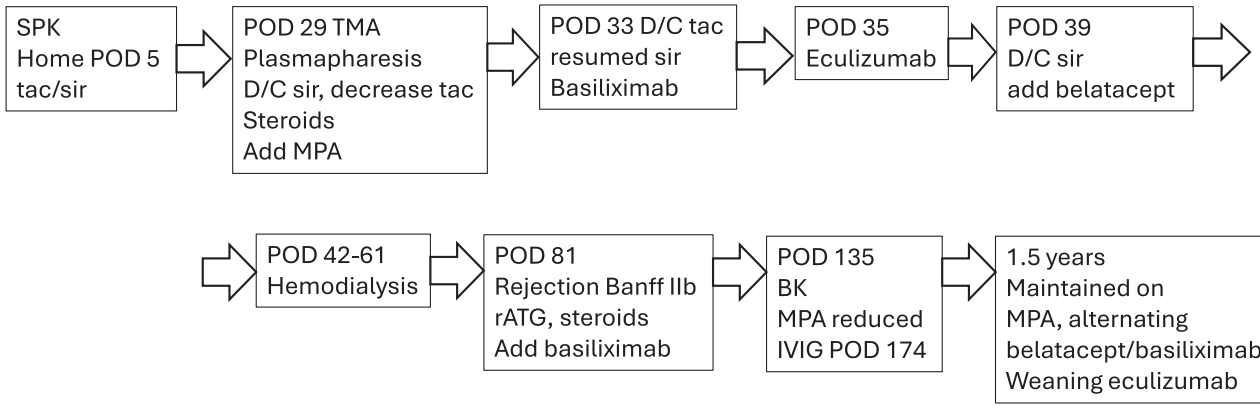

FIGURE 3. Timeline of events following simultaneous pancreas and kidney transplantation. D/C, discontinued; MPA, mycophenolic acid; POD, postoperative day; SPK, simultaneous pancreas and kidney transplant; TMA, thrombotic microangiopathy.

of alternating belatacept/basiliximab has been effective at preventing further rejection episodes.

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