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Case Report

A Rare and Complex Case of Multifactorial Thrombotic Microangiopathy in A Kidney Transplant Recipient: Interplay Between Antibody Mediated Rejection, Tacrolimus Toxicity, Cytomegalovirus Disease and BNT162b2mRNA Vaccine

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Abstract

Thrombotic microangiopathy (TMA) in kidney transplant recipients is uncommon and difficult to manage, often with poor graft outcomes [1]. This is a complex and interesting case of an older, highly sensitised kidney transplant recipient who presented with *de novo* post-transplant TMA in the setting of antibody mediated rejection (ABMR), with other drivers being tacrolimus toxicity, cytomegalovirus (CMV) infection and anti-SARS-CoV-2 BNT162b2 mRNA vaccination. This led to rapid, irrecoverable graft loss. 76-year-old female presenting three years post deceased donor renal transplant with ABMR. Her three-year course post-transplant was complicated with further opportunities for sensitisation. Firstly, with two discrete episodes of CMV disease requiring alteration in immunosuppression regimen. Secondly, she

had a biopsy-confirmed episode of cell mediated rejection after switching from tacrolimus to everolimus due to tacrolimus toxicity. Finally, her admission with fulminant rejection was preceded by almost 6 months of sub-therapeutic tacrolimus levels. 4 weeks prior to this admission, the patient also had her second dose of BNT162b2 mRNA vaccine. Her graft function deteriorated rapidly, with final transplant biopsy showing severe TMA with graft infarct. This case illustrates a complex case of a highly sensitised patient with a difficult post-transplant course who unfortunately suffered a very severe episode of ABMR-associated TMA after further sensitisation during her post-transplant course, with other drivers including CNI toxicity and CMV disease as well as potential further immune stimulation from BNT162b2 mRNA vaccine.

Keywords
Thrombotic microangiopathy; thromboembolic complications; SARS-CoV-2; kidney transplant; antibody mediated rejection; vaccination; sensitisation; rejection

1. Introduction

De novo post-kidney transplant thrombotic microangiopathy (TMA) is an important clinical phenomenon with an incidence rate ranging from 0.8% to 14% [1]. It can be precipitated by a range of triggers causing injury to the vascular endothelium, with the most common being antibody mediated rejection (ABMR), calcineurin inhibitor (CNI) toxicity and infections [1]. It has a heterogenous spectrum of presentation, though up to 40% of cases are renal-limited disease found on biopsy [2]. It is clinically challenging to manage and treatment is usually focused on the precipitant [1]. Unfortunately, graft outcomes are usually poor with literature suggesting graft loss in up to 40% of cases, particularly when associated with ABMR [1, 3, 4].

We review a challenging, clinically complex case of a patient presenting three years post renal transplant with graft failure due to TMA of multi-factorial aetiology, including ABMR, CNI toxicity, cytomegalovirus (CMV) disease and BNT162b2 mRNA vaccine.

2. Case Presentation

This case is of a 76-year-old Indigenous-identifying female with polycystic kidney disease. Her other significant past medical history included splenectomy for idiopathic thrombocytopaenic purpura and hypothyroidism.

She received donation after brain death (DBD) renal transplant with 4/6 human leukocyte antigen (HLA) mismatch. She had class I (A24) and II (DQ7) donor-specific antibodies (DSA) and so underwent anti-thymocyte globulin (ATG) induction therapy in addition to standard immunosuppression regimen of tacrolimus, mycophenolate, and prednisolone. Though it was a DBD donation, there was an eleven-hour cold ischaemia time. The post-transplant course was complicated by delayed graft function. Day 1 post-transplant mercaptoacetyltriglycine (MAG3) scan showed adequate perfusion but no excretion of radiotracer, consistent with acute tubular necrosis (ATN). A MAG3 scan was repeated on day 3 post-transplant and showed the same. Ultrasound imaging was also done at this time and showed no structural issues or hydronephrosis. She required

two sessions of haemodialysis post-transplant, which were ceased day 4 post-transplant as she started to make urine. Early day five graft biopsy showed ATN without features of rejection.

The post-transplant course was further complicated with an episode of urinary sepsis from extended spectrum beta-lactamase Escherichia coli two weeks post-transplant. This was managed with antibiotics and early removal of the urinary stent. Her creatinine at this time was 373 mmol/L.

She had repeat transplant biopsies at day thirteen and twenty-seven post-transplant which again showed no changes suggestive of rejection, but consistent with recovering ATN. Her creatinine settled at 125 mmol/L with an estimated glomerular filtration rate (eGFR) of 37 mL/min at four weeks post-transplant.

Three months post-transplant, she developed CMV viraemia with peak viral load of 198577 copies/mL. This was managed with four weeks of intravenous ganciclovir followed by two weeks of treatment dose valganciclovir along with dose reduction of mycophenolate. CMV resistance nucleic acid detection test was done, showing no mutations associated with resistance to ganciclovir, cidofovir or foscarnet. The viral load was undetectable after six weeks of treatment and she returned to valganciclovir prophylaxis.

Concurrently with this episode of CMV disease, her creatinine rose to 198 mmol/L. A transplant biopsy was done, showing mild tubular degenerative changes in keeping with ATN and isometric vacuolation consistent with calcineurin inhibitor toxicity. There was no evidence of rejection or viral inclusion bodies. In addition, immunohistochemistry was negative for SV40 and immunofluorescence negative for C4d deposition. Tacrolimus was converted to everolimus.

Her creatinine settled for a short period of time to baseline before rising again, prompting another biopsy. This time, there was evidence of intimal arteritis, interstitial inflammation and tubulitis. Minimal fibrosis was seen. There was no C4d deposition and SV40 was still negative. These changes were thought to be most consistent with acute T cell mediated rejection. She was given three doses of pulsed methylprednisolone, and tacrolimus was recommenced with discontinuation of everolimus.

A repeat biopsy was done six weeks later to review response to treatment. This showed ongoing interstitial inflammation and tubulitis consistent with cell mediated rejection, though improved. No changes were made to management from an immunosuppression perspective at this stage. Her creatinine settled at 150 mmol/L.

Unfortunately, she had another episode of graft impairment with a creatinine rise to 200 mmol/L about 5 months later. A biopsy was again done, this time showing changes of arterial intimal fibrosis with mononuclear cell infiltrate suggestive chronic T cell mediated rejection. Mesangial interposition was noted suggestive of developing transplant glomerulopathy. Immunofluorescence was negative for C4d. New DSA were noted at this time (DQ B1, DQA1 05:05, DQA1 05:03).

The patient developed CMV colitis twelve months after initial CMV viraemia treatment. This was confirmed on histopathology from endoscopy biopsies. Peak serum viral load was 1,212,015 copies/mL. The patient was started on intravenous ganciclovir and completed an eight-week course before returning to valganciclovir prophylaxis indefinitely. CMV resistance testing was completed again and was negative. Mycophenolate was ceased and everolimus re-commenced in adjunct to tacrolimus.

Almost three years post-transplant, her creatinine rose from 130 mmol/L to 180 mmol/L, leading to her eighth biopsy post-transplant. This demonstrated mild intimal arteritis, mild glomerulitis and peritubular capillaritis as well as some peritubular capillary C4d staining on immunofluorescence.

This was thought to be most consistent with acute ABMR, with no histopathological features suggestive of chronic ABMR. There were also no features of TMA. The diagnosis of acute ABMR was confirmed by new class II DSA in serum.

The patient's tacrolimus levels had been variable in the six months prior to this point ranging from undetectable to 3 μ/L. Her everolimus levels had been adequate during this time and she had been adherent with her prednisolone also. The patient had been travelling interstate to rural areas and stated difficulty obtaining tacrolimus as part of the issue. It is unclear whether there were other contributing factors to this. She was still adherent to attendance to clinic during this time. She returned to her treating facility one month prior to diagnosis of ABMR, during which time both tacrolimus and everolimus levels were in the target range.

She was admitted for management of ABMR. At the time of admission, her medications were as per Table 1. Of note, she had also received her second dose of BNT162b2 mRNA vaccine (Pfizer) four weeks prior to this admission.

Table 1 Medications Prior to Admission of Interest.

Medication use	Medication	Ceased on Admission
Immunosuppression regimen	Tacrolimus 1 mg twice daily Everolimus 0.5 mg twice daily Prednisolone 10 mg daily	
Cardiovascular risk modification	Atorvastatin 40 mg daily	
Infection prophylaxis	Roxithromycin 150 mg daily (post-splenectomy prophylaxis) Trimethoprim-sulfamethoxazole 800 mg/160 mg three times a week Valganciclovir 450 mg daily	Valganciclovir 450 mg daily
Hypertension management	Irbesartan 300 mg daily Frusemide 40 mg daily Prazosin 1 mg three times a day Metoprolol 50 mg twice daily	Irbesartan 300 mg daily Frusemide 40 mg daily Prazosin 1 mg TDS Metoprolol 50 mg BD
Hypothyroidism	Thyroxine 100 microg daily	
Gastroesophageal reflux disease and vitamin D deficiency	Pantoprazole 40 mg daily Cholecalciferol 25 microg daily	
Analgesia	Paracetamol 665 mg-1330 mg TDS as required	

An ultrasound of the graft done on admission showed new hydroureteronephrosis. A cystoscopy with stenting was done in case this was contributing to graft impairment, though there were no findings consistent with ureteric stricture. Her urine microscopy and culture were negative for urinary tract infection.

She received pulsed methylprednisolone and commenced on a two-week course of intravenous

immunoglobulin (IVIG) and seven cycles of plasma exchange. Despite this, her creatinine continued to rise, peaking at 649 mmol/L five days post admission with concurrent anaemia and thrombocytopaenia. Haemoglobin and platelet nadir were 59 g/L and 23×10^9/L respectively. Other serological features of haemolysis included a peak lactate dehydrogenase level of 815 U/L and schistocytes on blood film.

A repeat biopsy was done which showed florid changes of acute TMA with arterial fibrinoid necrosis and thrombi in glomeruli, arterioles, and arteries as well as infarction of glomeruli and tubules (Figures 1 A-F). These changes, with accompanying mild glomerulitis and immunofluorescence positivity for C4D staining (Figure 1 G), in the context of new DSA, were again suggestive of an ABMR process. There were no viral inclusion bodies and SV40 was negative.

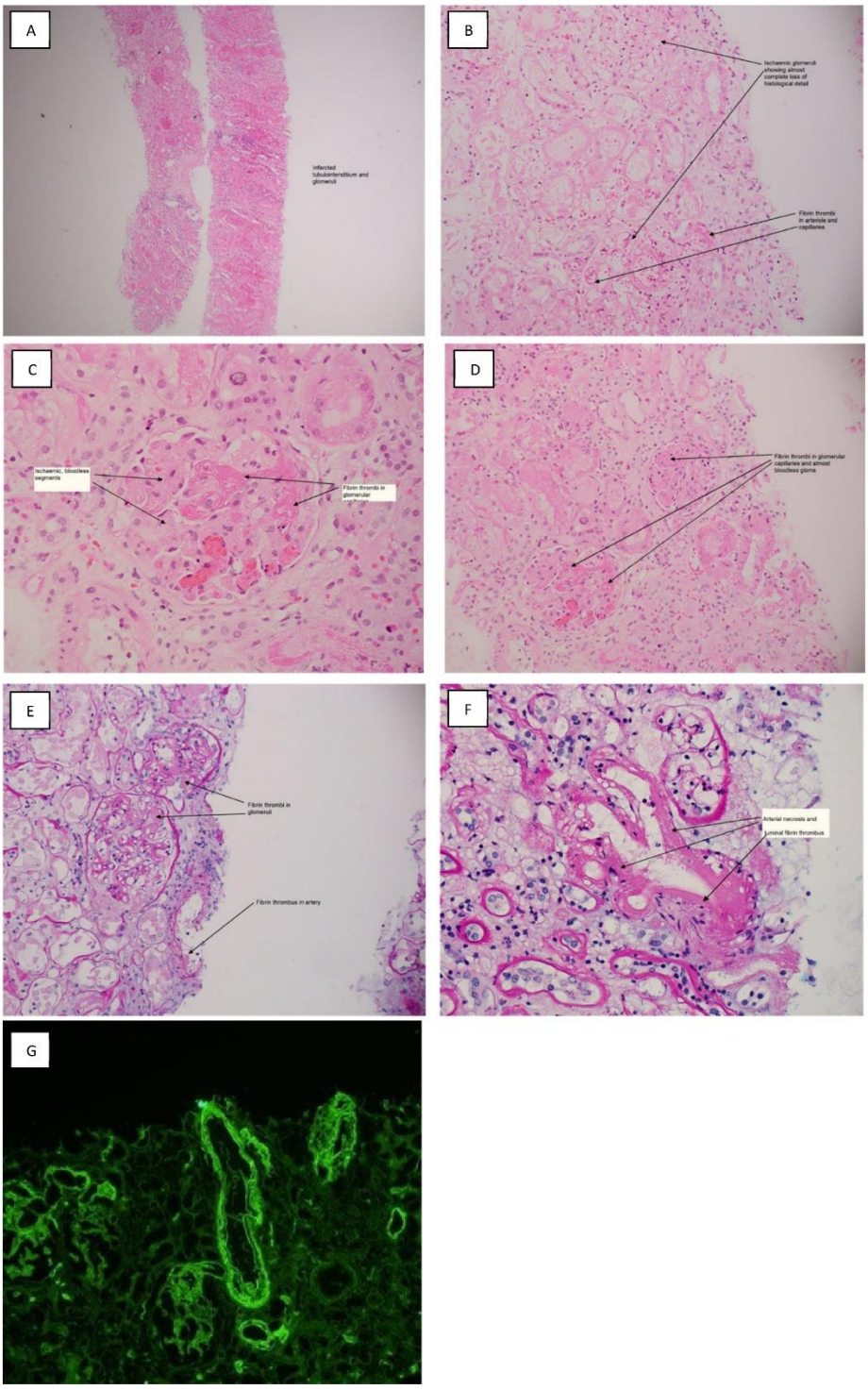

Figure 1 (A) Low power view of tissue cores showing infarcted glomeruli, tubules and interstitial parenchyma. (B) Ischaemic glomeruli. Fibrin thrombi in adjacent arteriole. Fibrin thrombi in glomerular capillary loops. (C) Fibrin thrombi in glomerular capillary loops. (D) Ischaemic glomerulus with fibrin thrombi in capillary loops. (E) Fibrin thrombi in glomerular capillary loops and adjacent artery shown using Periodic acid Schiff stain. (F) Areas of arterial necrosis and further arterial luminal fibrin thrombus shown using Periodic acid Schiff stain. (G) Positive C4d staining in tubules on immunofluorescence. Images including descriptions courtesy of Dr Yung Tran (renal pathologist), Queen Elizabeth Hospital, South Australia, Australia.

Potential TMA precipitants were evaluated. Anti-cardiolipin, heparin-platelet factor 4 antibody and SARS-CoV-2 nucleic acid testing were negative. The patient had also not had previous SARS-COV-2 infection. ADAMTS13 activity was 48% (ruling out thrombotic thrombocytopaenic purpura or TTP). There were also no other clinical features suggestive of TTP. Tacrolimus was ceased, though levels had been mostly within target range (5-7.5 μ/L) at 4.8-8.6 μ/L in the month prior to and during admission. CMV viral load was done which demonstrated CMV reactivation with >300 000 copies/mL. CMV prophylaxis had been ceased on admission as a potential nephrotoxic. Intravenous ganciclovir was commenced.

Unfortunately, the severe TMA with renal infarction led to complete loss of graft function and haemodialysis commencement six days after anti-rejection therapy was started. Ethics approval was granted by the Human Research Ethics Committee of Northern Territory Health and Menzies School of Health Research. Approval was granted on 18th November 2021 under reference number HREC 2021-4213.

3. Case Discussion

Thrombotic microangiopathy post-transplant can present as a new phenomenon or recurrence of pre-existing disease process post-transplant [5, 6]. The incidence of *de novo* post-transplant TMA is estimated at 0.8-14% and is more common than TMA recurrence (90% vs 10%) [2, 5, 6]. It typically manifests early in the post-transplant period, though there have been reports of it occurring years after transplantation [3, 5, 6]. In a large retrospective study done by Broecker et al [6], median time to all-cause TMA post-transplant was 30 days, with three quarters of cases occurring within the first year.

There are multiple processes predispose to TMA through endothelial cell injury and subsequent microthrombi formation in vasculature. Most commonly post-transplant these include infection, medications, and rejection [6-8].

ABMR-associated TMA occurs as a result of alternative complement pathway stimulation and concomitant activation of the coagulation cascade [9]. There is a complex interplay between the two systems, which can be precipitated by donor-specific HLA antibody stimulation of endothelial cells [10]. The disease course is rapid, leading very quickly to graft failure [10]. Patients with ABMR-related TMA have worse prognosis and higher rate of graft failure [1, 10, 11]. A retrospective cohort study by Teixeira et al [1] showed 41% graft survival in ABMR associated TMA compared to 70% in TMA without ABMR. Those who present much later post-transplant tend to have less severe disease manifestation and are less likely to proceed to graft failure, though this was not seen in this case [12]. Our patient was also at higher risk of ABMR given known baseline DSA with further DSA development in the context of varying immunosuppression regimens and levels, an episode of rejection and changes concerning for transplant glomerulopathy [13, 14]. Female sex has also been identified as a risk factor for worse graft outcomes when compared to males. This has been attributed to sensitisation from pregnancy, but also increased immune activation from sex hormones as well as predominance in maternal versus paternal X chromosome gene expression [15]. Of relevance to our patient, class II DSA have also been associated with chronic transplant glomerulopathy. Transplant glomerulopathy may also represent a chronic form of TMA [3, 16].

The other two most common causes of *de novo* TMA include viral infections, including CMV infection, and CNI toxicity [1, 3, 5, 6, 8]. CMV is a herpes virus that usually remains latent after initial

infection in immunocompetent patients [5]. In an immunocompromised host, reactivation manifests as CMV disease. This can either be tissue invasive disease (colitis, hepatitis, retinitis, nephritis, pneumonitis, encephalitis, oesophagitis, pancreatitis, myocarditis), or viraemia with fever and leukopaenia [5, 17]. Like other causes of post-transplant TMA, CMV can cause damage to endothelial cells and therefore stimulate platelet activation [5]. In case reports where TMA has been linked to CMV disease, often adequate treatment of the CMV led to resolution of TMA [5]. In our patient, recurrent CMV was a complication throughout her post-transplant course requiring careful balance of adequate immunosuppression, given known rejection risk, versus reducing ongoing infectious risk. A further risk factor for her was the initial ATG induction [17]. After the episode of CMV colitis, our patient had remained on valganciclovir prophylaxis. This was ceased before her final admission as a potential contributor to graft impairment. Prompt commencement of CMV treatment on recognition of increased viral load did not result in cessation of the TMA process, suggesting ABMR as the primary driver in this case. This former is supported by the fact that none of the patient's transplant biopsies showed viral cytopathic inclusion bodies or SV40 positivity, though other case reports suggest that this does not rule CMV out as a causative factor [5]. CMV can also have long term effects on the graft, from interstitial nephritis and renal artery stenosis to ureteric strictures, though again this did not seem to be a factor in our patient [17].

CNI toxicity can also lead to TMA through either direct vascular endothelial damage or mediation of prostacyclin, thromboxane A2 and plasminogen activator inhibitor with a net effect of increased platelet aggregation [5]. Usually there is a gradual increase in creatinine with these patients, compared to an acute graft impairment seen in ABMR-related TMA, again making the latter more likely in this case [11]. CNI-related TMA often occurs without supra-therapeutic CNI levels, with one TMA case series showing findings of CNI toxicity on biopsy only [11, 18]. The concomitant use of CNI with mammalian target of rapamycin inhibitors increases risk of *de novo* TMA and could have been a further risk factor here [2].

A potential final trigger in this patient's case is anti-SARS-CoV-2 mRNA vaccination. There is a longstanding suggestion that influenza vaccination is associated to reactivation of memory B cells with propensity for anti-HLA antibody production, though at a low rate [19, 20]. There are also studies that show development of *de novo* DSA post influenza vaccination in up to 1.85% of transplanted patients, though without clinically significant events [19]. This could be more of an issue with SARS-CoV-2 vaccination as the mRNA component is able to more strongly stimulate Toll-like receptors on B cells, and so reactivation of memory B cells primed for DSA production particularly in sensitised transplant recipients [21].

There is a case report of rejection post anti-SARS-CoV-2 mRNA vaccination published in 2021 [22]. This occurred in a 23-year-old renal transplant patient approximately eighteen months post-transplant with acute cell mediated rejection eight days post the second dose of BNT162b2 mRNA vaccine (Pfizer). She had renal recovery after pulsed steroid therapy [22]. This case differs to ours as this patient was not highly sensitised, had no other precipitating factors and had rapid recovery of graft function [22].

There are also two case reports which show development of *de novo* DSA – the first by Abu-Khader et al [19] which showed development of *de novo* DSA following two doses of BNT162b2 vaccination in a patient waitlisted for kidney transplant with no evidence of HLA antibodies on previous crossmatch and the second by Abuzeineh et al [23] which demonstrated development of new DSA in a SARS-CoV-2 positive patient and subsequent diagnosis of chronic ABMR. However, a

cohort study by Russo et al [20] of 82 kidney transplant recipients receiving SARS-CoV-2 vaccination did not show development of *de novo* DSA, increased intensity in pre-existing DSA or rejection events. SARS-CoV-2 vaccination is also an important measure in immunocompromised patients, given increased morbidity and mortality from SARS-CoV-2 infection in the setting of immunosuppression [20].

Another consideration regarding SARS-COV-2 infection and vaccination is its role in first presentation and recurrence of atypical haemolytic uraemic syndrome (aHUS). SARS-COV-19 causes complement activation as demonstrated by increased serum levels of membrane attack complex seen in infected patients [24]. aHUS is a form of complement mediated TMA where up to 80% of patients have complement gene variant predisposing to complement dysregulation. A further trigger, such as from infection or vaccination, can then lead to disease [24, 25]. In a cohort study by Aigner et al [24] of 27 aHUS patients in clinical remission, the incidence of TMA post-SARS-COV-2 infection was 6 cases per 100 patient years versus 1.5 per 100 patient years for SARS-COV-2 vaccination. Out of thirteen episodes of SARS-COV-2 infection three kidney transplant patients developed TMA post compared to one out of 70 SARS-COV-2 vaccination episodes (odds ratio 0.04, 95% CI 0.003 – 0.37, p=0.01) [24]. Two vaccinations were administered post-relapse episode with no further recurrence of disease [24, 25]. A retrospective case series review by Bouwmeester et al of 73 SARS-COV-2 vaccination episodes in 29 aHUS patients showed no aHUS relapse in this cohort. Overall, this suggests SARS-COV-2 vaccination precipitating complement-mediated TMA is rare, even in this cohort at seemingly at greater risk [24, 25]. In our case, genetic testing was not performed for complement gene defects, though genetic research indicates a significant proportion of patients who develop de-novo TMA have underlying mutations in complement regulating genes [5, 6, 8].

Though ABMR was found in one case series to be the most common cause of TMA in 55% of cases, a larger case series found that majority of cases (63%) did not have a clear primary cause and over half (56%) had multiple potential causative factors [3, 6]. Though ABMR seems to be the primary cause in this case, the other potential triggers may have contributed to the severity and rapidity of TMA seen.

The clinical presentation of TMA is a spectrum from renal-limited to systemic disease [9]. Serum findings are consistent with microangiopathic haemolytic anaemia, including anaemia, thrombocytopaenia, elevated lactate dehydrogenase, reduced haptoglobin and blood film evidence of red cell fragments [2, 3]. Findings on histopathology include thrombi in graft vasculature and glomeruli, basement membrane thickening and necrosis of glomeruli [10]. The extent of vascular injury is concordant with graft outcomes, with increased intimal arteritis being associated with worse graft outcomes [14]. C4d positivity in addition to presence of DSA make ABMR-related TMA more likely [6]. This group of patients are also more likely to have serological abnormalities [3]. C4d staining is also associated with poorer graft outcomes [8]. However, regardless of the initial precipitant, histopathological features are consistent between aetiologies [6].

The most common presentation is decline in renal graft function without extra-renal manifestations and requires renal biopsy for confirmation [5, 6, 9]. Satoskar et al [3], in single centre case series, found only a quarter of patients (15/59) had three of the five listed serological abnormalities.

Management is difficult and requires balance of competing risks, as treatment is targeted at the most likely precipitant [3]. However, given that in many cases the cause is multifactorial, all potential

triggers should be treated [26].

Interventions are translated from TMA management in native kidney disease with no standardized protocol targeted at the renal transplant cohort [12]. The prognosis is generally poor with almost 50% graft failure rate [3, 7, 12]. In a retrospective single centre study by Caires et al [4], 47% of patients required dialysis at time of diagnosis and 75% of patients remained on dialysis. This is potentially compounded by withdrawal of CNI [3, 7, 12]. The evidence for CNI withdrawal on impact of graft loss is contradictory and often leads to poorer outcomes if used in isolation [12, 18]. As a result, this is often done in conjunction with plasma exchange. This has been extrapolated from positive results in management of native kidney TMA and has been shown in a small number of case series to improve graft outcomes in renal transplant TMA [7, 12]. ABMR-TMA is managed with methylprednisolone, intravenous immunoglobulin, and plasmapheresis [10, 12]. Immunotherapies, such as eculizumab, are an emerging management option, though the evidence base is limited to case reports [7, 9]. This was considered in our patient's case, though decided against due to concurrent CMV viraemia and significant necrosis suggesting imminent graft loss on final biopsy.

4. Conclusion

This is a complex case of a 76-year-old sensitised kidney transplant recipient with a complex post-transplant course with further episodes of sensitising events in the context of immunosuppression titration balanced against ongoing infective complications. She unfortunately developed florid TMA in the setting of ABMR after a period of sub-therapeutic tacrolimus levels, with other risk factors for TMA including recurrence of CMV and tacrolimus toxicity. A further and novel precipitant included SARS-CoV-2 mRNA vaccination which occurred 4 weeks prior to the TMA episode and could have further enhanced immune system activation and ABMR in this patient, though there is inconsistent evidence in this space.

List of Abbreviations

Abbreviation	Definition
TMA	Thrombotic microangiopathy
ABMR	Antibody mediated rejection
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor toxicity
mRNA	Messenger ribonucleic acid
ATG	Anti-thymocyte globulin
DBD	Donation after brain death
HLA	Human leukocyte antigen
DSA	Donor-specific antibodies
ATN	Acute tubular necrosis
MAG3	Mercaptoacetyltriglycine
eGFR	Estimated glomerular filtration rate
IVIG	Intravenous immunoglobulin
TTP	thrombotic thrombocytopaenic purpura

Author Contributions

Dr Paayal Naidu completed ethics application, data collection from medical records, manuscript writing and editing, submission for publication and manuscript revisions. Dr Manohar Mogulla supervised ethics application, edited the original manuscript, contributed to manuscript revisions and approved the final manuscript. Professor Toby Coates and William Majoni reviewed manuscript revisions and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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