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De Novo Infection-Associated Complement-Mediated Hemolytic Uremic Syndrome in a Renal Transplant Recipient: A Complex Diagnostic Journey

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Abstract

A 71-year-old renal transplant recipient presented with progressive malaise, gastrointestinal symptoms, fever, anemia, and acute graft dysfunction following recent travel abroad. Initial investigations revealed Micro-Angiopathic Hemolytic Anemia (MAHA), thrombocytosis evolving into relative thrombocytopenia, elevated inflammatory markers, and declining renal function. The diagnostic process was complicated by overlapping possibilities including infection, viral reactivation, drug toxicity, rejection, and Thrombotic Micro-Angiopathy (TMA). Subsequent findings of Cytomegalovirus (CMV) viraemia, Escherichia coli urinary tract infection, and biopsy-proven TMA ultimately supported a diagnosis of de novo infection-associated, complement-mediated Hemolytic Uremic Syndrome (HUS). The patient improved with targeted antimicrobial therapy, immunosuppression adjustment, and supportive care, though renal recovery remained incomplete. This case highlights the diagnostic complexity of TMA in transplant recipients and the importance of maintaining broad clinical suspicion when multiple triggers coexist. The patient received valganciclovir for CMV, intravenous co-amoxiclav for E. coli pyelonephritis, fluid resuscitation, and temporary reduction of immunosuppression. Plasma exchange and complement-targeted therapy were considered but deferred due to clinical improvement. Hematological parameters normalized, and renal function partially recovered, stabilizing at an eGFR of 38-42 mL/min/1.73 m^2.

Keywords: Iga Nephropathy; End-Stage Renal Failure; Cytomegalovirus; Renal Allograft; *Escherichia Coli*; Kidney Transplantation; *De Novo* Hemolytic Uremic Syndrome; Thrombotic Microangiopathy; Acute Diverticulitis; Pyelonephritis; Infection-Triggered HUS; Complement-Mediated Injury; Allograft Dysfunction; Microangiopathic Hemolytic Anemia; Tacrolimus Immunosuppression; Transplant Complications

Introduction

Thrombotic Micro-Angiopathy (TMA) after kidney transplantation is an uncommon but serious complication, arising from causes such as calcineurin inhibitor toxicity, antibody-mediated rejection, viral infections, bacterial sepsis, and complement dysregulation [1-15]. Distinguishing between these aetiologies is challenging because clinical and laboratory features often overlap, and renal biopsy alone cannot reliably determine the underlying trigger [4]. Infection-associated, complement-mediated Haemolytic Uraemic Syndrome (HUS) is particularly difficult to diagnose in immunosuppressed patients, where symptoms may be subtle, multifactorial, or masked by concurrent conditions [5].

Differentiating HUS from other causes of acute graft dysfunction—such as sepsis-related acute kidney injury, rejection, or drug toxicity - requires careful integration of clinical, biochemical, microbiological, and histological data [6, 7]. HUS in transplant recipients may be recurrent (in those with underlying complement mutations) or *de novo*, the latter often triggered by infections, endothelial injury, or complement-amplifying events [8, 9].

We report a case of de novo infection-associated, complement-mediated HUS in an adult

kidney transplant recipient precipitated by a dual infectious insult: acute diverticulitis and allograft pyelonephritis. The episode resulted in a marked decline in renal function, with the estimated Glomerular Filtration Rate (eGFR) falling from 69 to 38 mL/min/1.73 m².

To our knowledge, this case adds unique value to the literature by demonstrating how multiple infectious triggers can converge to activate the complement pathway and produce TMA in a previously stable transplant recipient [10-12]. It further illustrates how timely antimicrobial therapy and immunosuppression adjustment can stabilise graft function even without complement blockade, an outcome that contrasts with many published cohorts [13-15]. This case is therefore of relevance to clinicians in nephrology, transplantation, infectious diseases, and internal medicine, and contributes meaningfully to the understanding of post-transplant TMA.

Case Presentation

Patient History

A 71-year-old man with end-stage renal disease secondary to IgA nephropathy received a cadaveric renal transplant in March 2022 after nine months of automated peritoneal dialysis during the COVID-19 pandemic. His post-transplant course was stable, with baseline eGFR~69 mL/min/1.73 m² and no prior rejection or TMA. Maintenance immunosuppression consisted of tacrolimus 0.5 mg twice daily and mycophenolate 360 mg twice daily.

He travelled to India in November 2023 for a three-month stay and remained well until January 2024, when he underwent full-mouth dental rehabilitation under co-amoxiclav cover without complications.

Symptom Onset

In February 2024, routine blood tests showed Tacrolimus trough level: 2 ng/Ml, CRP: 61 mg/L, Hemoglobin: 95 g/L (previously 145 g/L), eGFR: 38 mL/min/1.73 m².

Simultaneously, he developed malaise, anorexia, nausea, vomiting, diarrhea, sweating, rigors, left lower quadrant and suprapubic pain, dysuria and foul-smelling urine and 10 kg unintentional weight loss. He returned urgently to the UK seeking medical care.

Investigations

Initial laboratory findings showed rising creatinine from baseline (~90 μmol/L) to >150 μmol/L, normocytic anemia, initial thrombocytosis, later relative thrombocytopenia, elevated LDH, reduced haptoglobin and peripheral smear: schistocytes These findings raised concern for MAHA.

Virology and Microbiology

CMV PCR was positive with rising viral load. Stool microscopy: no C. difficile (sample insufficient for culture), Urine culture: E. coli, sensitive to co-amoxiclav, pivmecillinam, nitrofurantoin, trimethoprim

Complement and TMA Workup demonstrated C3: low, C4: normal, ADAMTS13: not severely reduced (TTP unlikely), Tacrolimus levels: within therapeutic range.

Imaging

Contrast CT chest/abdomen/pelvis (performed after infection treatment) showed no evidence of tuberculosis, resolved diverticulitis without perforation and inflammatory changes around the transplanted kidney consistent with ascending pyelonephritis.

Table 1. Timeline of Clinical Events and Key Findings

Date / Period	Clinical Events	Laboratory / Imaging Findings	Management
Mar 2022	Cadaveric renal transplant	Stable graft function (eGFR ~69)	Tacrolimus + Mycophenolate
Nov 2023 – Feb 2024	Travel to India	Well initially	—
Jan 2024	Full-mouth dental rehabilitation	No complications	Co-amoxiclav prophylaxis
Feb 2024	Onset of malaise, fever, GI symptoms, dysuria	Hb 95 (↓ from 145), CRP 61, eGFR 38, tacrolimus 2	Outpatient blood tests
Late Feb 2024	Progressive symptoms	MAHA features: ↑LDH, ↓haptoglobin, schistocytes	Iron infusions
Early Mar 2024	CMV PCR positive	Rising inflammatory markers	Valganciclovir started
Mid Mar 2024	Persistent fever, hypotension	Urine culture: E. coli	Oral then IV co-amoxiclav
Late Mar 2024	Hospital admission	AKI, MAHA, low C3, normal C4	IV antibiotics, IS adjustment
Apr 2024	CT CAP	Resolving diverticulitis; pyelonephritis of graft	Supportive care
Apr 2024	Renal biopsy	TMA without rejection	Supportive, no PLEX
May–Jun 2024	Recovery phase	Hb, platelets normalizing; eGFR 38–42	Maintenance IS

Table 1: Timeline of clinical events and key findings March-2022 to July-2024.

Renal Allograft Biopsy

Biopsy demonstrated features of thrombotic microangiopathy, no evidence of acute rejection, and no recurrence of IgA nephropathy.

Differential Diagnosis

The clinical picture prompted consideration of acute antibody-mediated rejection, calcineurin inhibitor toxicity, CMV-associated TMA, bacterial sepsis-associated TMA, tuberculosis, lymphoproliferative disorder, complement-mediated HUS and thrombotic thrombocytopenic purpura (excluded by ADAMTS13).

The coexistence of CMV viraemia and *E. coli* urinary infection complicated interpretation.

Management

Antiviral Therapy

Valganciclovir 450 mg twice daily was initiated for six weeks for CMV viraemia. Initial improvement in inflammatory markers was followed by clinical and laboratory deterioration.

Iron Deficiency Management

Severe iron deficiency (serum iron 4 μg/dL) prompted intravenous iron therapy. During the second infusion, the patient was noted to be febrile and hypotensive, prompting further microbiological evaluation.

Antibacterial Therapy

Following confirmation of *E. coli* infection and worsening

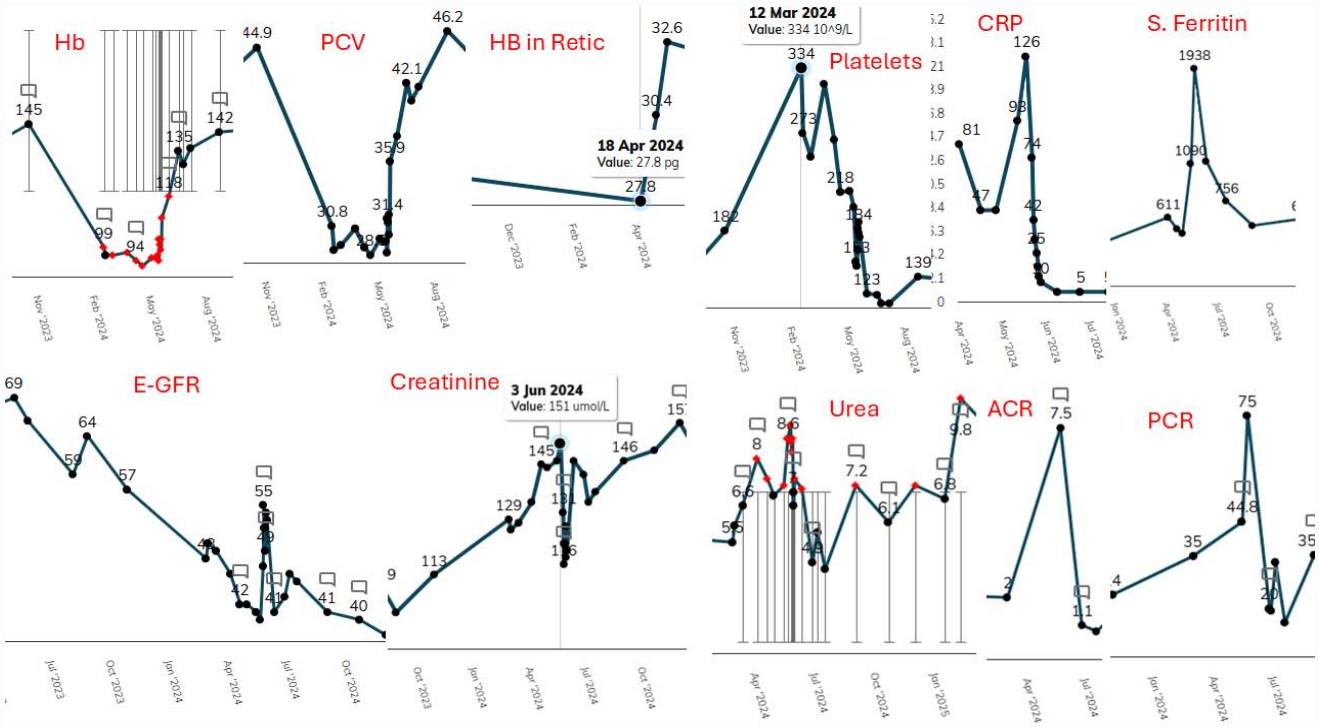


Figure 1: Laboratory investigations - Top panel showing hemoglobin, pack cell volume, hemoglobin in the reticulocytes, platelets, CRP and ferritin and Bottom panel indicating renal functions-e-GFR, creatinine, urea, ACR and PCR-Jan 2024-July 2024.

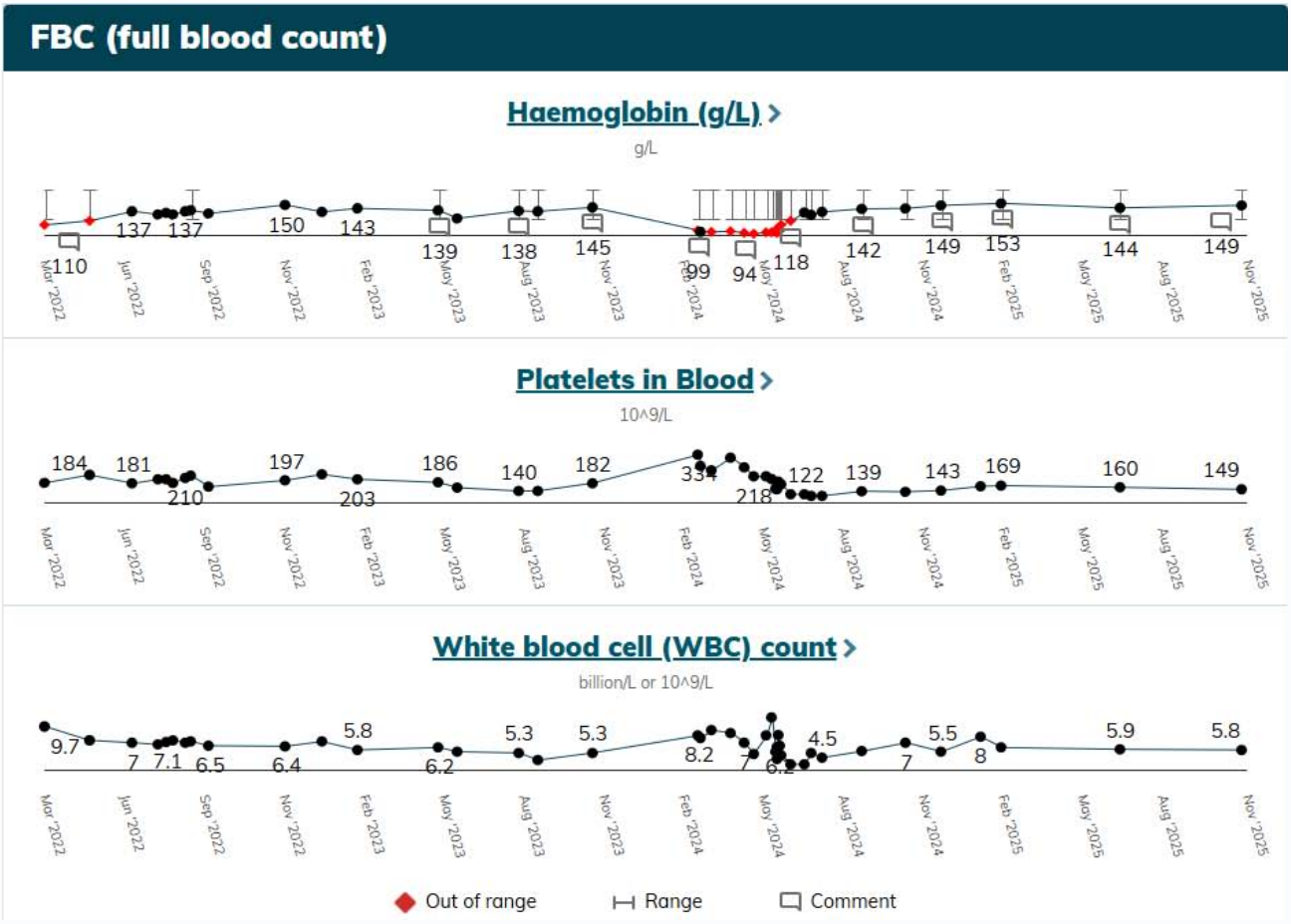


Figure 2: Decline in Hemoglobin and Platelet Count. Serial hematological parameters showing progressive anemia and relative thrombocytopenia.

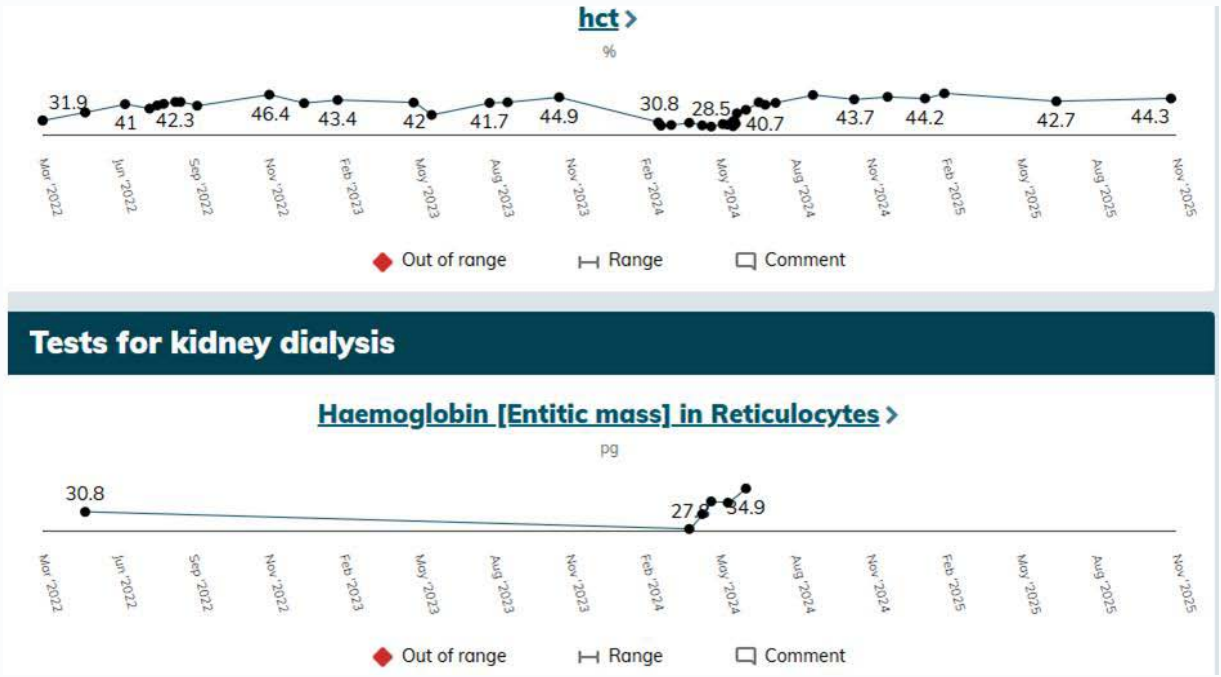


Figure 3: Hematocrit and hemoglobin in the red blood cells.

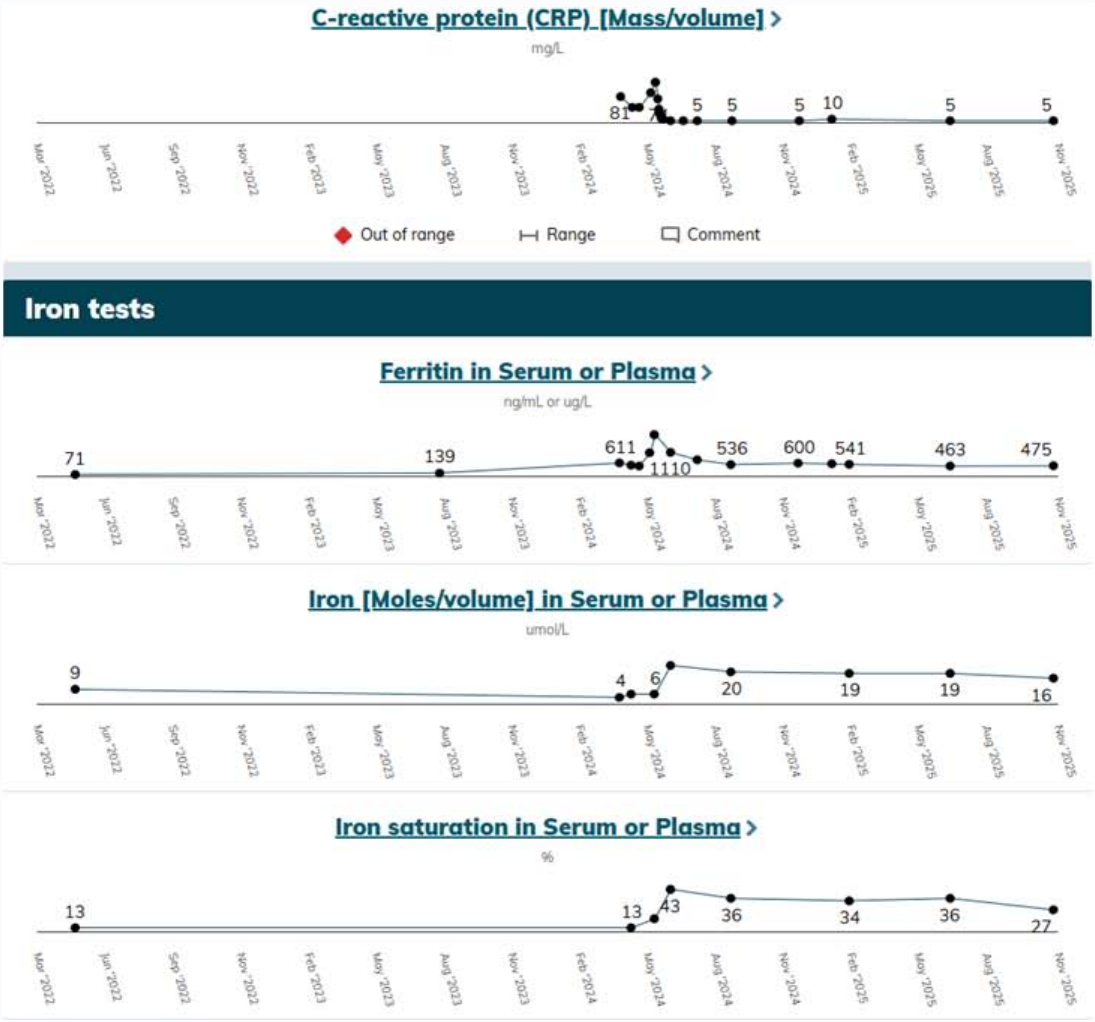


Figure 4: CRP, Ferritin, Iron and Iron saturation levels.

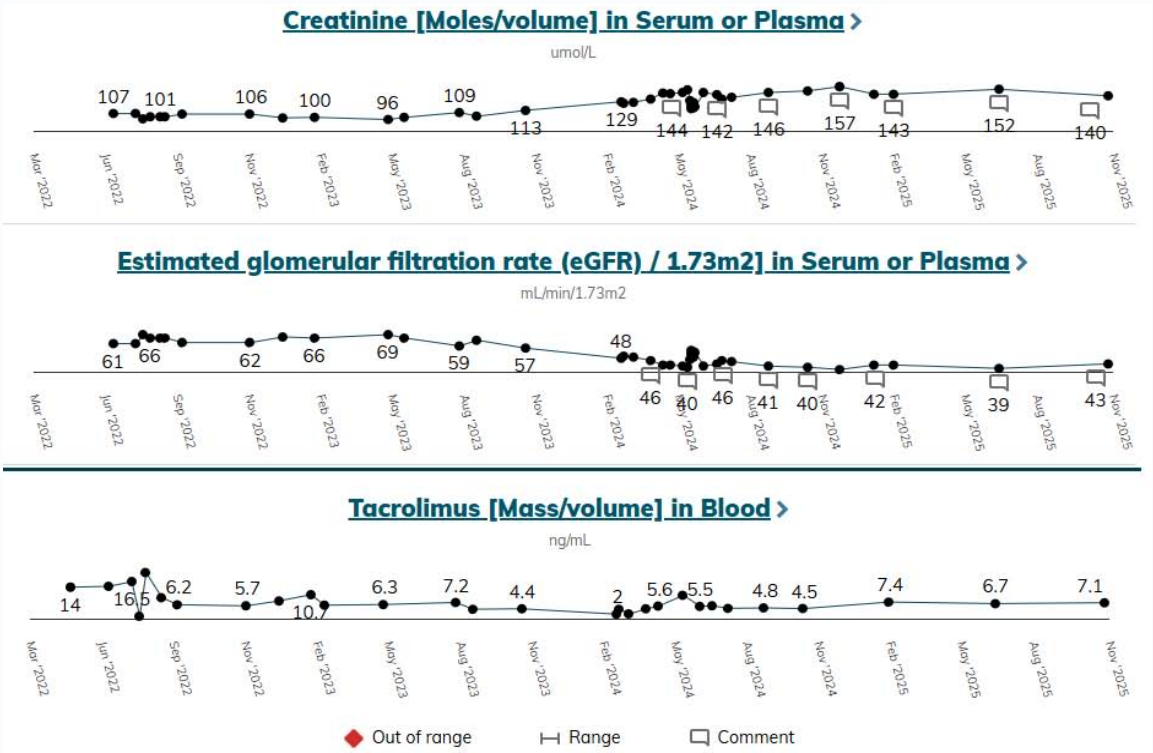


Figure 5: Renal functions- Creatinine, e-GFR and Tacrolimus levels.

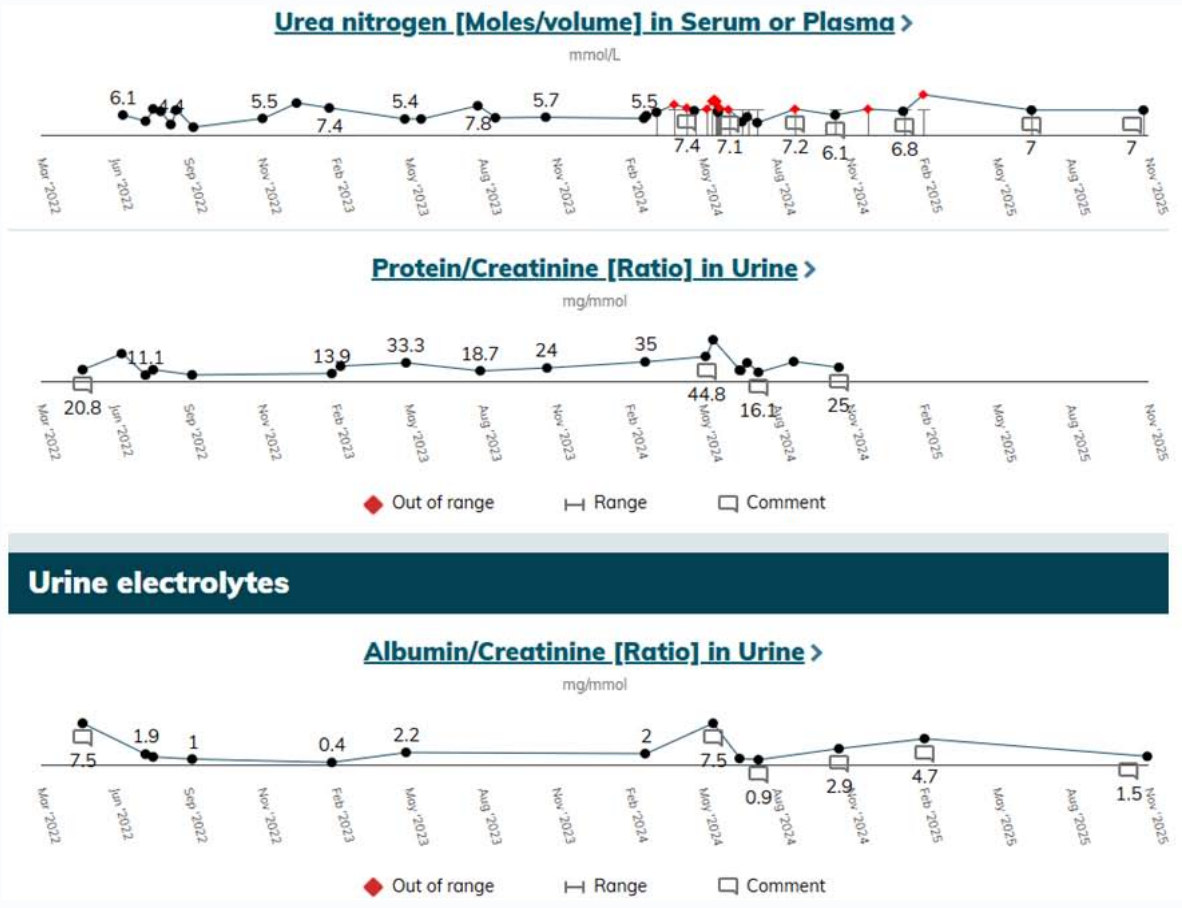


Figure 6: Renal functions-Urea Nitrogen, PCR and ACR results.

symptoms, he was admitted to hospital. Management included intravenous co-amoxiclav 1.2 g every 8 hours for 7 days followed by 5 days oral treatment, careful fluid resuscitation and treatment for suspected diverticulitis and pyelonephritis.

Immunosuppression Adjustment

Tacrolimus and mycophenolate doses were temporarily reduced during acute illness.

TMA-Directed Considerations

Plasma exchange: considered but not initiated due to improving hematological parameters. Complement-targeted therapy: discussed but deferred based on clinical trajectory and multidisciplinary consensus.

Outcome

Over subsequent weeks, the hemoglobin and platelet count gradually normalized. LDH and haptoglobin returned toward baseline. Renal function partially recovered but did not return to pre-illness baseline. His eGFR stabilized at 38-42 mL/min/1.73 m^2, representing a significant the permanent parenchymal damage often associated with allograft pyelonephritis and TMA but non-progressive decline in graft function. He remained clinically stable on adjusted immunosuppression.

Discussion

Thrombotic Micro-Angiopathy (TMA) in kidney transplant recipients is an uncommon but clinically significant complication, with reported incidence ranging from 0.8% to 14% depending on diagnostic criteria and population studied [1, 3]. Contemporary literature distinguishes between recurrent TMA, de novo TMA, and secondary TMA, each with distinct etiological patterns [4, 11]. De novo TMA is more frequently associated with calcineurin inhibitor toxicity, antibody-mediated rejection, and infections [9, 15].

Infection-Associated TMA in Transplant Recipients

Infections are increasingly recognised as potent triggers of complement activation and endothelial injury. Viral infections such as CMV, BK virus, and parvovirus B19 have been implicated in post-transplant TMA [5, 7]. Several case series describe CMV-associated endothelial dysfunction leading to MAHA and AKI, often improving with antiviral therapy and immunosuppression adjustment [5].

Gram-negative bacterial infections, particularly *E. coli*, can also precipitate complement-mediated TMA, even in the absence of shiga toxin. Reviews emphasise that systemic inflammation, endotoxin exposure, and cytokine-driven endothelial injury can activate the alternative complement pathway, resulting in HUS-like presentations in immunocompromised hosts [8, 12].

Complement Dysregulation and Low C3 Levels

Low C3 with normal C4, as seen in this patient, suggests activation of the alternative complement pathway. Studies in transplant cohorts show that complement-mediated TMA may occur even without identifiable genetic mutations, particularly when triggered by infection or ischaemic injury [6, 14]. Biopsy findings of endothelial swelling, fibrin thrombi, and arteriolar involvement are consistent with complement-mediated injury [2, 6].

Diagnostic Challenges

This case underscores several diagnostic complexities:

- Overlapping triggers: CMV viraemia and *E. coli* pyelonephritis are both capable of inducing TMA.
- Masked haematological patterns: Initial thrombocytosis due to acute-phase reaction may obscure early TMA.
- Delayed imaging and inpatient access: Real-world barriers that prolong diagnostic uncertainty.
- Sequential rather than parallel investigations: A frequent challenge in outpatient transplant care.

Current guidelines emphasise the importance of early recognition of MAHA, prompt evaluation for infectious triggers, and timely renal biopsy to differentiate TMA from rejection or drug toxicity [11, 13].

Management Considerations

Supportive therapy, infection control, and immunosuppression adjustment remain the cornerstone of treatment for infection-associated TMA [3, 11]. Plasma exchange is generally reserved for TTP or severe complement-mediated disease, while complement inhibitors such as eculizumab are considered in refractory or genetically confirmed cases [2, 4]. In this patient, improvement with antimicrobial therapy and supportive care supported an infection-triggered mechanism, and complement-targeted therapy was not required.

Prognosis and Graft Outcomes

Long-term graft outcomes in infection-associated TMA vary. Literature suggests that early diagnosis and treatment correlate with better renal recovery, though many patients experience incomplete return to baseline function [3, 15]. The patient's stabilised eGFR of 38-42 mL/min/1.73 m^2 aligns with reported outcomes in similar cases.

This case illustrates the diagnostic complexity of TMA in renal transplant recipients, particularly when multiple potential triggers coexist. Infection-associated complement-mediated HUS is rare but recognised in the post-transplant setting [8, 12]. Both CMV viraemia and Gram-negative bacterial infections are known precipitants of complement activation and endothelial injury [5, 7].

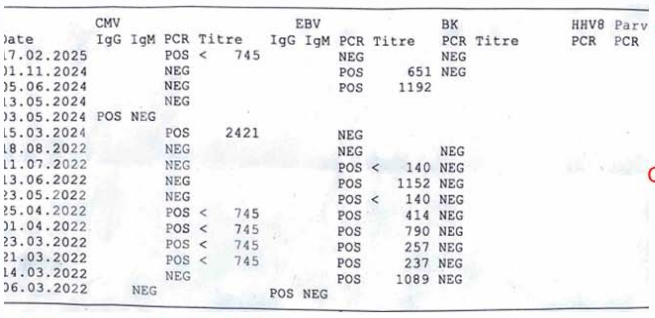
Key challenges included overlapping symptoms of infection, drug toxicity, and rejection; delayed access to imaging and inpatient care; sequential rather than parallel investigation; and an evolving haematological picture in which initial thrombocytosis masked early TMA.

The renal biopsy ultimately provided diagnostic clarity, confirming TMA in the absence of rejection or recurrent IgA nephropathy. The patient's improvement with infection control and supportive care supports an infection-triggered, complement-mediated mechanism rather than primary TTP or drug-induced TMA.

Summary of Case Significance

This manuscript describes a 71-year-old male renal transplant recipient who developed de novo HUS following acute diverticulitis and allograft pyelonephritis, resulting in a marked decline in graft function from an eGFR of 69 mL/min/1.73 m^2 to 38 mL/min/1.73 m^2. Infection-associated de novo HUS in renal allografts is rare but clinically important. In this case, dual infectious triggers likely precipitated complement activation, leading to TMA in the transplanted kidney.

We believe this case offers valuable clinical insights for transplant physicians, nephrologists, and general clinicians. It underscores



Date	CMV IgG	CMV IgM	CMV PCR	CMV Titre	EBV IgG	EBV IgM	EBV PCR	EBV Titre	BK PCR	BK Titre	HHV8 PCR	Parv PCR
17.02.2025			POS	< 745			NEG		NEG			
01.11.2024			NEG				POS	651	NEG			
05.06.2024			NEG				POS	1192				
13.05.2024			NEG									
03.05.2024	POS	NEG										
15.03.2024			POS	2421			NEG					
18.08.2022			NEG				NEG		NEG			
11.07.2022			NEG				POS	< 140	NEG			
13.06.2022			NEG				POS	1152	NEG			
23.05.2022			NEG				POS	< 140	NEG			
25.04.2022			POS	< 745			POS	414	NEG			
01.04.2022			POS	< 745			POS	790	NEG			
23.03.2022			POS	< 745			POS	257	NEG			
21.03.2022			POS	< 745			POS	237	NEG			
14.03.2022			NEG				POS	1089	NEG			
06.03.2022	NEG				POS	NEG						

A. Virology IgG, IgM, PCR titres

B. Sample MU166603B (TYPE UNSPECIFIED) Collected 28 May 2024 12:15 Received 28 May 2024 16:23
Urine culture
Urine culture
Specimen Type : Urine for Bacteriology
Urine culture
>10^5 Organisms/ml of Coliform - KESC group.
Sensitive : co-amoxiclav,pivmecillinam,nitrofurantoin,trimethoprim.

C. 10/6/24-Contrast CT-TAP-Thorax normal, Native kidneys small atrophied with small cysts. Transplant kidney in right iliac fossa appeared bulky more in the lower pole with ill-defined hypoattenuating zone mild paranephric fat stranding and fluid suggesting pyelonephritis. Several colonic diverticula with resolving infection.

D. 27/8/24-Transplant Kidney Biopsy-No transplant rejection, glomerulitis or tubulitis. No recurrence of IgA nephropathy. Moderate tubular atrophy and interstitial fibrosis (40%). Tubules with cellular debris suggesting ascending pyelonephritis. The abnormality on electron microscopy was that of notable swelling of the endothelial cells with loss of fenestrations in places. The glomeruli not bloodless, no fibrin thrombi or features of red blood cell fragmentation and no thickening of the glomerular basement membranes or multi layering of the peritubular capillary basement membranes. The vascular structures show no specific pathological abnormalities on light microscopy.

E.
urrent diagnoses
- Advanced CKD plan for PD
- Essential Hypertension
- IgA nephropathy - histologically proven
- IGA NEPHROPATHY - HISTOLOGICALLY PROVEN
- Renal biopsy CV & IFTA (moderate)

Figure 7: Virology, Microbiology, Imaging and Transplant renal biopsy (A). CMV Viral Load Trend-CMV PCR levels before and after initiation of valganciclovir therapy (B). Urine culture showing E. Coli sensitive to co-amoxiclav and other antibiotics. (C). CT Abdomen and Pelvis-Contrast-enhanced CT demonstrating inflammatory changes around the transplanted kidney consistent with ascending pyelonephritis, and resolving diverticulitis without perforation. (D). Renal Allograft Biopsy (Light and Electron Microscopy). Histological sections showing endothelial swelling, fibrin thrombi, and arteriolar changes characteristic of thrombotic microangiopathy.

the need for vigilance when transplant recipients present with systemic infection and contributes to the limited literature on infection-associated de novo HUS in renal allografts.

Discussion: Comparison with Published Cases

This case of de novo, infection-associated, complement-mediated HUS in a renal transplant recipient sits at the intersection of several patterns described in the literature: post-transplant TMA, infection-triggered HUS, and late-onset complement-mediated disease [1, 2, 11].

1. Post-transplant TMA patterns and genetic background

Large cohort studies of post-transplant TMA show that it is heterogeneous, with recurrent aHUS, de novo TMA, and secondary TMA (e.g., infection, rejection, drug toxicity) all represented [1, 3, 11]. In a recent series of 68 kidney transplant recipients with TMA, many underwent complement genetic testing, and a substantial proportion had identifiable complement pathway variants, underscoring the role of underlying susceptibility even when a clear trigger is present [6, 14].

Our patient was not genetically tested, but the presence of low C3 with normal C4 and biopsy-proven TMA in the context of infection is consistent with a "trigger on a susceptible background" model described in these cohorts [6, 14].

2. Timing and late-onset TMA

Late-onset TMA-occurring more than 12 months post-transplant - is increasingly recognised and is associated with poorer graft outcomes, even when treated with complement inhibitors [4]. In a UK multicentre experience of post-transplant TMA treated with eculizumab, patients presenting beyond 12 months had worse graft survival compared with earlier presentations [4].

Our patient developed TMA approximately two years post-transplant, placing him in this late-onset category. However, unlike many reported late-onset cases requiring eculizumab, his disease stabilised with infection control and supportive care alone - albeit with a permanent decline in Egfr - which aligns with the incomplete recovery often reported in late-onset TMA [3, 15].

3. Infection-associated HUS in transplant recipients

Shiga Toxin-producing *E. coli* (STEC)–associated HUS has been reported in adult kidney transplant recipients, presenting with MAHA, thrombocytopenia, and AKI superimposed on a transplanted kidney [8]. In those cases, STEC infection was clearly documented, and outcomes varied, with some patients experiencing significant graft dysfunction [8].

Our case differs in that there was no evidence of shiga toxin, but E. coli urinary sepsis and CMV viraemia were both present - two potent inflammatory and endothelial triggers [5, 7]. The clinical pattern - MAHA, low C3, biopsy-proven TMA, and partial renal recovery - resembles the broader category of infection-associated, complement-mediated HUS, where infection acts as the "second hit" on the complement system [2, 12].

4. Role of CMV and bacterial infection as dual triggers

Several case reports and small series describe CMV-associated TMA, often improving with antiviral therapy and reduction of calcineurin inhibitors [5]. Similarly, Gram-negative bacterial sepsis is recognised as a trigger of complement activation and endothelial

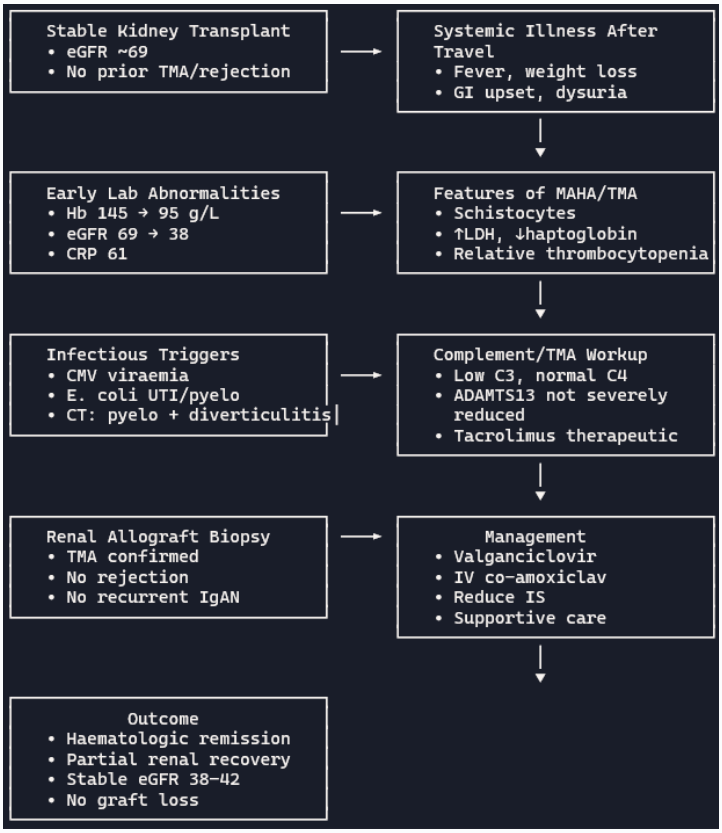


Figure 8: Clinical pathway - Diagnostic Integration Flowchart. A schematic summarizing the convergence of clinical, laboratory, microbiological, and histological findings leading to the diagnosis of infection-associated complement-mediated HUS.

injury [7, 12].

When compared with these reports, our case is notable for:

- Dual infectious triggers (CMV viraemia and E. coli pyelonephritis/diverticulitis)
- Low C3 with normal C4, suggesting alternative pathway activation
- Biopsy-proven TMA without rejection or drug toxicity

This combination fits well with the concept of secondary, infection-triggered complement-mediated HUS superimposed on a transplanted kidney, as discussed in broader TMA reviews [1, 2, 11].

5. Use (and non-use) of complement-targeted therapy

In published series of post-transplant TMA, eculizumab is often used when there is strong suspicion of complement-mediated disease, particularly in recurrent aHUS or severe de novo TMA [2, 4, 6]. Outcomes, however, are not uniformly favourable, especially in late-onset TMA, where graft survival remains poor despite complement blockade [4].

In our patient, the decision to withhold eculizumab was based on improving haematological parameters and stabilisation of renal function following infection control and immunosuppression adjustment. Compared with cohorts where eculizumab was used, his course illustrates that not all complement-mediated, infection-associated TMA mandates complement blockade, particularly when the precipitating trigger is clearly identified and effectively treated. Nevertheless, the residual graft impairment observed is consistent with published outcomes [3, 15].

6. Graft outcome compared with published series

In large TMA cohorts, graft loss rates remain substantial despite advances in diagnosis and therapy. A recent meta-analysis reported an overall graft loss rate of 33.8% in *de novo* TMA [3]. Death-censored graft survival at 12 months is significantly reduced, particularly in late-onset or genetically predisposed cases [4, 6].

Our patient's eGFR stabilised at 38-42 mL/min/1.73 m^2, representing a meaningful but non-progressive decline from baseline. This outcome aligns with partial recovery patterns described in infection-associated and late-onset TMA, where early recognition and targeted management can preserve - but not fully restore - graft function [3, 15].

Synthesis

When viewed alongside published cases and series of post-transplant TMA, STEC-HUS in transplant recipients, and complement-mediated aHUS [1-15]:

- Shared features include MAHA, AKI, endothelial injury, and incomplete renal recovery.
- Distinctive aspects of this case include dual infectious triggers (CMV and non-STEC *E. coli*), late onset post-transplant, and improvement without complement blockade.
- Clinically, it reinforces the need for early recognition of TMA, aggressive search for infectious triggers, and individualised decisions regarding complement-targeted therapy.

- This case highlights several clinically important issues:
- The complex interplay between infection, complement activation, and endothelial injury in transplant recipients [2, 5, 7].
- The difficulty of distinguishing TMA from rejection, drug toxicity, and viral reactivation, especially when symptoms evolve sequentially [9, 11].
- The importance of early recognition of MAHA and prompt investigation to prevent irreversible graft injury [11, 13].
- Real-world challenges such as delayed imaging, outpatient diagnostic pathways, and overlapping clinical priorities.
- A favourable outcome achieved without complement blockade, despite late-onset TMA - contrasting with many published cohorts [4, 6].

Long-term outcome, mortality, morbidity, and natural history of HUS/TMA in kidney allograft recipients

Incidence and overall graft impact: *De novo* TMA after kidney transplantation is uncommon but clinically important. A systematic review and meta-analysis of over 14,000 kidney allograft recipients reported an incidence of 3.2%, with both systemic and renal-limited forms described [3]. The overall graft loss rate of 33.8% underscores the significant risk of permanent allograft damage.

Our patient's course - partial recovery with a new, lower eGFR plateau - fits well within this spectrum of significant but not universal graft loss.

Natural history and patterns of disease: Post-transplant TMA can be categorised as:

- Recurrent (e.g., aHUS recurring in the graft)
- *De novo* (no prior native-kidney TMA)
- Secondary (triggered by drugs, rejection, infection, etc.) [1, 4, 11].

Recent adult series emphasise an interplay between complement genetics and multiple endothelial injuries, where infection, calcineurin inhibitors, or rejection act as triggers in genetically susceptible individuals [6, 14]. This aligns with our case: infection-associated, complement-mediated HUS superimposed on a transplanted kidney with dual triggers (CMV and *E. coli*).

The natural history typically follows:

1. Acute phase: MAHA, thrombocytopenia (or relative thrombocytopenia), AKI, systemic symptoms.

2. Subacute phase: Stabilisation with treatment of triggers, supportive care, and immunosuppression adjustment.

3. Chronic phase:

- Partial recovery with a new lower eGFR plateau (as in this case), or
- Progressive dysfunction leading to graft loss in a significant minority [3, 15].

Mortality and patient survival: Most modern series suggest that graft loss is more frequent than patient death in post-transplant TMA, particularly with current supportive care and access to complement inhibitors [3, 4]. However, systemic TMA with multiorgan involvement still carries non-trivial mortality, especially when diagnosis is delayed or when TMA occurs in the context of severe sepsis or uncontrolled rejection [11].

Our patient's survival with stable but reduced graft function represents a relatively favourable outcome compared with cohorts where one-third or more lose their graft [3].

Morbidity: beyond graft function:

Morbidity in post-transplant HUS/TMA includes:

- Chronic kidney disease progression
- Recurrent hospitalisations for infection or anaemia
- Long-term antihypertensive therapy
- Potential return to dialysis if graft fails
- burden of uncertainty regarding graft survival [3, 11].

In *de novo* TMA triggered by calcineurin inhibitors, some series report improvement after drug withdrawal, but others show persistent dysfunction and high graft-loss rates [9, 15]. In our case, tacrolimus levels were therapeutic and biopsy did not support classic CNI toxicity, suggesting morbidity was driven primarily by infection-triggered complement activation.

How our case sits within this landscape:

Compared with published data:

- Incidence: This case represents one of the ~3% of recipients who develop de novo TMA [3].
- Outcome: He avoided graft loss but sustained a permanent drop in eGFR—consistent with partial recovery patterns [3, 15].
- Triggers: Infection-driven rather than CNI toxicity or rejection, aligning with the "multiple endothelial hits" model [6, 14].
- Therapy: Managed without eculizumab, unlike many severe or recurrent aHUS cases, yet with acceptable long-term stability [2, 4].

Our patient exemplifies the intermediate outcome of de novo, infection-associated, complement-mediated TMA - survival with persistent but non-progressive graft impairment - situated between the extremes of full recovery and graft loss described in contemporary series.

Patient's Perspective

*"Looking back, this illness was one of the most frightening experiences of my life. Before this happened, I felt stable with my transplant and had been living normally. When I became unwell abroad and then again after returning home, I knew something was wrong, but I didn't expect it to become so serious. The weight loss, fever, and weakness were overwhelming, and I felt as though my body was shutting down.

What made it harder was not knowing the cause. Each new symptom added to the worry. I kept thinking, 'Is my transplant failing? Is this an infection? Why am I not getting better?' Waiting for tests, appointments, and results was emotionally exhausting. I felt

anxious, confused, and at times helpless.

When the diagnosis finally became clear, I felt relieved that there was an explanation, even though it was a serious one. The treatment was tough, but I slowly began to feel like myself again. I am grateful for the care I received and for the fact that my kidney is still functioning, even if not as well as before.

This experience has taught me to listen to my body, to speak up when something feels wrong, and to appreciate every day of stable health. I hope that sharing my story helps others understand how important it is to take symptoms seriously and to advocate for themselves during complex medical journeys."

Carer's Perspective

*"Watching him deteriorate over those weeks was incredibly distressing. At first, we thought it was just a minor infection from travelling, but as his symptoms worsened - weight loss, fever, weakness - I felt increasingly helpless. What frightened me most was how quickly he changed from being independent and active to barely able to get out of bed.

The uncertainty was the hardest part. Each new test result brought more questions than answers. I could see how anxious he was, and I tried to stay strong for him, but inside I was worried about losing the transplant he had worked so hard to protect.

When the diagnosis finally became clearer, it was a relief to know that the team understood what was happening. Seeing him slowly improve after treatment was like watching him come back to life. This experience has taught me how important it is to advocate for your loved one, to ask questions, and to push for answers when something doesn't feel right. I am grateful every day that he is still with us and that his kidney is still functioning."*

Learning Points for Clinicians

- Infection-associated complement-mediated TMA should be considered early in transplant recipients presenting with MAHA, AKI, and systemic symptoms, especially when multiple infectious triggers coexist.
- Initial thrombocytosis does not exclude TMA; acute-phase reactions may mask early hematological clues.
- Parallel, not sequential, investigation (cultures, virology, complement studies, imaging, and early biopsy) is essential to avoid diagnostic delay in complex post-transplant presentations.
- CMV viraemia and Gram-negative infections are potent endothelial triggers, capable of precipitating complement activation and TMA even in previously stable grafts.
- Renal biopsy remains the definitive tool for distinguishing TMA from rejection, drug toxicity, or recurrent disease.
- Timely antimicrobial therapy and immunosuppression adjustment can stabilize hematological parameters and preserve graft function, even without complement blockade.
- Late-onset TMA (>12 months post-transplant) carries a risk of incomplete renal recovery; early recognition may mitigate long-term graft impairment.
- Infection can be a potent trigger for *de novo* Hemolytic Uremic Syndrome (HUS) in renal allograft recipients, even in patients with previously stable graft function.
- Acute diverticulitis and pyelonephritis should raise suspicion for complement-mediated thrombotic microangiopathy when accompanied by anemia, thrombocytopenia, and rising creatinine.
- Early recognition of microangiopathic hemolytic anemia - particularly the presence of schistocytes, elevated LDH, and low haptoglobin - is essential to differentiate HUS from sepsis-related acute kidney injury, rejection, or drug toxicity.
- Timely multidisciplinary management, including infection control and immunosuppression adjustment, can stabilize hematological parameters, although residual graft impairment is common.
- Transplant clinicians should maintain a high index of suspicion for HUS in the context of systemic infection, as early intervention may help preserve long-term graft function.
- With timely management, residual graft dysfunction is common.

Conclusion

This case illustrates the diagnostic complexity of TMA in transplant recipients and highlights the importance of considering infection-associated complement-mediated HUS when MAHA, AKI, and infectious triggers coexist. Early recognition and targeted management can prevent irreversible graft injury. This manuscript describes a rare and diagnostically challenging presentation of infection-triggered, complement-mediated Thrombotic Micro-Angiopathy (TMA) in a stable renal transplant recipient, precipitated by dual infectious insults (CMV viraemia and *Escherichia coli* pyelonephritis/diverticulitis).

This case underscores the importance of vigilance for de novo HUS in renal transplant recipients presenting with infection and acute graft dysfunction. Early recognition and multidisciplinary management can stabilize hematological parameters and preserve graft function, although long-term renal impairment may persist.

This case highlights the diagnostic and clinical complexity of de novo hemolytic uremic syndrome in a renal allograft recipient with infection-related inflammatory stress. In a patient with previously stable graft function following transplantation for IgA nephropathy, the combination of acute diverticulitis and pyelonephritis acted as a significant trigger for complement-mediated thrombotic microangiopathy, resulting in abrupt hematological deterioration and a substantial decline in renal function. Early recognition of microangiopathic features, prompt investigation including allograft biopsy, and coordinated multidisciplinary management were essential in stabilizing the patient's condition. Although partial renal recovery occurred, the persistent reduction in eGFR underscores the potential for lasting graft injury even when treatment is timely. This case reinforces the need for vigilance when transplant recipients present with systemic infection, as early identification of HUS may help preserve allograft function and improve long-term outcomes.

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