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Case studies and expert opinion on the management of complement-mediated and secondary thrombotic microangiopathy in Singapore

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ABSTRACT

Complement-mediated thrombotic microangiopathy (C-TMA), previously referred to as atypical haemolytic uraemic syndrome, is a rare cause of thrombotic microangiopathy (TMA). Secondary TMAs are heterogeneous conditions associated with established triggers (e.g. drugs, infection, pregnancy), some of which may be driven by complement activation. Differentiating between C-TMA and secondary TMA can be difficult, as there may be considerable overlap between the conditions. The authors describe 3 cases of TMA potentially involving complement activation as examples of a multidisciplinary approach to diagnosis and management in Singapore. Complement component 5 (C5) inhibition is central to the treatment of C-TMA, but lack of access to therapy remains a major challenge in the region, as illustrated by Case 1 (probable C-TMA). Case 2 (gemcitabine-associated TMA) and Case 3 (lupus nephritis-associated TMA) explore the emerging role of C5 inhibitors in secondary TMAs. Short-duration C5 inhibitor treatment is feasible for some patients without pathogenic gene variants but should be undertaken only with appropriate monitoring.

Keywords: atypical haemolytic uraemic syndrome, complement-mediated thrombotic microangiopathy, complement inhibition, C5 inhibitor, microangiopathic haemolytic anaemia, secondary thrombotic microangiopathy

INTRODUCTION

Complement-mediated thrombotic microangiopathy (C-TMA)—also known as atypical haemolytic uraemic syndrome[1]—refers to the primary form of the syndrome, which arises from genetic abnormalities that result in uncontrolled complement pathway activation.[2,3] C-TMA is a rare cause of TMA and has a varied clinical presentation. The diagnosis is one of exclusion, made after ruling out other causes of TMA, particularly immune thrombotic thrombocytopenic purpura (iTTP) and Shiga toxin-producing *Escherichia coli* haemolytic-uraemic syndrome (STEC-HUS).[2] Secondary TMAs are heterogeneous conditions associated with established and clear triggers (e.g. drugs, infection, pregnancy).[1] Complement activation has been implicated in some cases of secondary TMA, with a multi-hit process resulting in TMA.[4,5]

Available guidance regards early recognition and prompt treatment of primary C-TMA with complement component 5 (C5) inhibitors as being vital to limiting adverse outcomes, such as end-stage kidney disease (ESKD).[4,6-10] C5 inhibitor therapy may also benefit cases of secondary TMA that have not responded to conventional therapy and may have an element of complement activation.[4,5]

Although international guidelines provide general recommendations for the diagnosis and management of C-TMA,[9-12] no Singapore-specific guidance exists. The challenges in Singapore include the rarity of cases, limited physician experience with the condition, restricted availability of specialised investigations, and the high cost of C5 inhibitors. These factors complicate the management of C-TMA and complement-associated secondary TMA.

This article uses illustrative case studies from Singapore to explore the recognition, diagnosis, and management of patients with probable C-TMA (Case 1), gemcitabine-associated TMA (Case 2), and lupus nephritis (LN)-associated TMA (Case 3). The aim is to equip clinicians with practical insights to support early diagnosis, guide appropriate therapy, and optimise outcomes despite practice limitations in Singapore.

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PATIENT CASE STUDIES

Case 1: Probable C-TMA

A 53-year-old woman presented with generalised tonic-clonic seizures and oliguric acute kidney injury (AKI), following an acute respiratory tract infection and fever. On admission, she had a normal coagulation screen but elevated lactate dehydrogenase (LDH), thrombocytopenia, schistocytes, and low C3 (Table 1). As her ADAMTS13 activity of 23% (i.e. not <10%) was inconsistent with iTTP,[13] a diagnosis of TMA precipitated by sepsis, or C-TMA, was considered instead. Kidney biopsy showed chronic TMA. A C-TMA genetic panel was negative for pathogenic variants.

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a]

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Age, years	53	54	16
Sex	Female	Female	Female
Medical history	Menorrhagia due to fibroids; no family history of kidney disease	Pancreatic adenocarcinoma treated with surgery and chemotherapy (capecitabine and gemcitabine); no family history of kidney disease	No significant medical history; no family history of kidney disease or SLE
Initial symptoms/presentation	Generalised tonic-clonic seizures and acute kidney failure after acute respiratory tract infection with fever and headache	TMA after receiving 6 cycles of capecitabine and gemcitabine (cumulative dose 12,400 mg/m^2), followed by mixed nephritic–nephrotic syndrome and AKI 2 months later	History of pallor for 20 days and generalised oedema for 10 days
Initial laboratory results			
Haematology	At presentation: Hb 11.8 g/dL, WBC 25.8 × 10^9/L, platelets 57 × 10^9/L, schistocytes 1+	At presentation: Hb 7.6 g/dL, WBC 13.8 × 10^9/L, platelets 264 × 10^9/L, schistocytes 5–10 per hpf After 1 month of steroids: Hb 8.3 g/dL, WBC 11.1 × 10^9/L, platelets 83 × 10^9/L, schistocytes 10–15 per hpf	Initial presentation: Hb 7.1 g/dL, WBC 4.2 × 10^9/L, platelets 128 × 10^9/L After 1 month of treatment for LN: Hb 8.2 g/dL, WBC 5.64 × 10^9/L, platelets 10 × 10^9/L, reticulocytes 1.02%; blood film suggestive of MAHA (microcytic hypochromic RBC, schistocytes 2+, crenated cells 2+)
Renal	Baseline Cr: 38 μmol/L Cr at presentation: 300 μmol/L Peak Cr: 578 μmol/L	Baseline Cr: 77 μmol/L Cr at presentation: 107 μmol/L Peak Cr: 233 μmol/L Urinalysis: RBC 76, WBC 30, granular casts 1/μL, hyaline casts 7/μL, waxy casts 6/μL Urine protein/creatinine ratio: 658 mg/mmol	Initial presentation: Cr 112 μmol/L, eGFR 52 mL/min/1.73 m^2 (Schwartz), urine protein 2+, and RBC 2+ After 1 month of treatment for LN: Cr 486 μmol/L, urine RBC >1000/hpf, urine protein: Cr ratio 1603 mg/mmol
ADAMTS13 activity	23%	86%	31%
Immunology	*ADAMTS13* Ab negative; ANA, ANCA IIF, dsDNA, anti-MPO, anti-PR3, and anti-GBM negative; C3 low (0.57 [normal 0.9–1.8 g/L]); C4 normal; anti-factor H not tested, as PLEX and rituximab had already been started (which can interfere with the result)	ANA, ANCA, and anti-dsDNA negative; direct agglutination test negative; anti-factor H antibodies not tested because (1) there was a clear cause for TMA (gemcitabine); (2) heterozygous CFHR3-CFHR1 deletion (see below) is a common CNV in the general population; (3) cost limitations	Initial presentation: ANA positive, anti-dsDNA >800 U/mL,[c] C3 0.17 g/L, C4 6 mg/dL. After 1 month of treatment for LN: ANA 1:320 (by immunofluorescence, normal <1:80),[c] anti-dsDNA 220 IU/mL,[c] C3 0.4 g/L, C4 0.15 g/L, lupus anticoagulant negative, anticardiolipin IgM and IgG negative, anti-β2-glycoprotein I IgM and IgG negative, ENA negative; direct Coombs test positive; anti-factor H antibodies not tested

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a] (Cont'd)

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Other	At presentation: LDH 5428 U/L, bilirubin and AST normal, procalcitonin 12 µg/L	At AKI diagnosis: LDH 1808 U/L; haptoglobin <0.3 g/L; PT, APTT, and fibrinogen levels normal	Initial presentation: albumin 18 g/L After 1 month of treatment for LN: haptoglobin <0.08 g/L, LDH 497 U/L, albumin 23 g/L, ESR 41 mm/hr, CRP 15.5 mg/L
Kidney biopsy	Kidney biopsy was performed 1 month after initial presentation; focal segmental and global glomerulosclerosis with features suggesting chronic TMA.	Kidney biopsy not performed	Kidney biopsy not performed
Other investigations	Lumbar puncture: unremarkable PET-CT: bilateral pleural effusions, no occult malignancy or sepsis Kidney U/S: unremarkable	PET-CT: no recurrence of pancreatic cancer; CA19-9 and CEA normal.	Initial presentation: Kidney U/S: mild swelling; no hydronephrosis or focal cortical lesions; echocardiography: bilateral pleural effusions and mild pericardial effusion
C-TMA genetic testing	Mayo Clinic C-TMA NGS panel negative (*ADAMTS13, C3, C5, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, DGKE, MMACHC, THBD*)	Invitae C-TMA NGS panel NGS panel negative (*ADAMTS13, C3, CD46, CD55, CD59, CFB, CFH, CFI, DGKE, INF2, MMACHC, PLG, THBD*) Multiplex probe identified a non-pathogenic *CFHR3-CFHR1* gene variant (University of Iowa)	Not performed
Time from initial presentation to final diagnosis	<1 month	2 months	1 month
Final diagnosis	Probable C-TMA	Gemcitabine-associated TMA (with presumed complement activation)	LN with RPGN, nephrotic syndrome, and LN-associated (secondary) TMA (with presumed complement activation)
Differential diagnoses considered	Disseminated meningococcal infection with septic acute tubular necrosis (ruled out by negative blood, urine, and CSF cultures); iTTP (ruled out as ADAMTS13 activity was not <10%); SLE with multi-organ involvement (ruled out because of negative autoimmune screen and kidney biopsy not suggestive of LN)	Malignancy-related TMA (ruled out due to no evidence of malignancy recurrence); iTTP (ruled out as ADAMTS13 activity was not <10%); C-TMA (less likely because another diagnosis was made, there was no family history of C-TMA, and no pathogenic genetic variants were found)	iTTP (ruled out because ADAMTS13 activity was not <10%); catastrophic antiphospholipid syndrome (ruled out because antiphospholipid antibody negative)
Treatment	Dialysis (1 month); PLEX, rituximab, steroids (11 months); relapsed after 11 months; eculizumab started after 13 months (given for 9 months); meningococcal vaccination 2 weeks before start of eculizumab; oral penicillin V tablets for antibiotic prophylaxis throughout the course of eculizumab	Discontinuation of gemcitabine, plus corticosteroids for 1 month (no response); eculizumab (900 mg weekly for 4 weeks, then 1200 mg every 2 weeks) for a total of 6 doses; meningococcal ACYW135, pneumococcal, and *Haemophilus influenzae* vaccinations 9 months earlier (before distal pancreatectomy and splenectomy); meningococcal serogroup B vaccination at eculizumab initiation; oral penicillin V tablets for antibiotic prophylaxis throughout the treatment duration	For LN and RPGN: intravenous pulse corticosteroids (total of 7 cycles), mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, furosemide, antihypertensives For TMA: PLEX (2 cycles of 5 sessions) with FFP as replacement fluid, eculizumab (900/1200 mg) for a total of 7 doses, FFP infusion (without PLEX) before eculizumab dose 4. Antibiotic prophylaxis (e.g. penicillin V) throughout the duration of C5 inhibition, as the patient was unlikely to respond to meningococcal vaccination due to concomitant immunosuppression for LN

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a] (Cont'd)

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Outcome	Progression to ESKD; eculizumab started after funding was secured; platelets and Hb normalised on eculizumab At 3-year follow-up after starting eculizumab, no recurrence of TMA	Within 4 weeks of starting eculizumab, TMA resolved, and there was partial recovery from AKI At 10-month follow-up, still in cancer remission; no recurrence of TMA	Slow response of LN and TMA Discharged home after 4th eculizumab dose Currently, SLE in remission, RPGN resolved, MAHA resolved
Subsequent follow-up planned	Every 6 months (full blood count, Cr, LDH, C3, C4)	Every 3 months (blood and urine evaluations)	Every 2 months
Duration of follow-up (since initial presentation)	5 years	10 months	8 months

Ab: antibody; ADAMTS13: A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13; AKI: acute kidney injury; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; anti-GBM: anti-glomerular basement membrane; APTT: activated partial thromboplastin time; AST: aspartate transaminase; CA19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; CNV: copy number variation; Cr: creatinine; CRP: C-reactive protein; CSF: cerebrospinal fluid; C-TMA: complement-mediated TMA; dsDNA: double-stranded DNA; eGFR: estimated glomerular filtration rate; ENA: extractable nuclear antigens; ESKD: end-stage kidney disease; ESR: erythrocyte sedimentation rate; FFP: fresh frozen plasma; Hb: haemoglobin; hpf: high-power field; IgG: immunoglobulin G; IgM: immunoglobulin M; IIF: indirect immunofluorescence; iTTP: immune thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; LN: lupus nephritis; MAHA: microangiopathic haemolytic anaemia; MPO: myeloperoxidase; NGS: next-generation sequencing; PET-CT: positron emission tomography-computed tomography; PLEX: plasma exchange; PR3: proteinase 3; PT: prothrombin time; RBC: red blood cells; RPGN: rapidly progressive glomerulonephritis; SLE: systemic lupus erythematosus; TMA: thrombotic microangiopathy; U/S: ultrasound; WBC: total white blood cell count

[a] The cases presented were managed at different centres in Singapore.

[b] Considerations unique to paediatric cases are included in Fig. 1.

[c] Different assays (and therefore units) were used at centres overseas and in Singapore.

Because of funding limitations for C5 inhibitors, initial treatment was plasma exchange (PLEX), pulsed methylprednisolone, rituximab, and dialysis. Anti-factor H antibodies were not tested, as PLEX and rituximab had been started (which can interfere with the result). Her initial response to PLEX was good, and she was weaned off dialysis 1 month later. Over the next 8 months, PLEX was tapered to once a week. Two months later, she had a relapse of TMA and AKI requiring reinitiation of dialysis. Despite re-intensification of PLEX, kidney function could not be salvaged.

A cost analysis indicated that 6 months of eculizumab, which would provide a 2-year relapse rate of <5%,[14] would cost less than SGD200,000 compared with annual, lifelong costs of SGD210,000–355,000 for PLEX with fresh frozen plasma (FFP) and haemodialysis for patients who developed ESKD.

Funding for eculizumab was secured, and the patient received treatment for a total of 9 months. Her platelet count normalised within a month, and her haemoglobin stabilised. She had no further recurrence of C-TMA at 3-year follow-up after starting eculizumab.

The final diagnosis was probable C-TMA despite a negative genetic panel. The initial episode was triggered by sepsis, but no clear trigger was identified at the time of relapse. The unprovoked relapse and low C3 were suggestive of underlying complement dysregulation.

Case 2: Gemcitabine-associated TMA

A 54-year-old woman presented with TMA 14 days after receiving 6 cycles of adjuvant chemotherapy (capecitabine and gemcitabine) for pancreatic adenocarcinoma. Laboratory results showed microangiopathic haemolytic anaemia (MAHA), mild thrombocytopenia, and AKI (Table 1). Chemotherapy had been administered on day 15 of cycle 6, as TMA onset was not yet recognised. The cumulative dose of gemcitabine was 12,400 mg/m^2, with TMA onset 162 days after first exposure. Following haematology consultation, gemcitabine was discontinued and the patient received a 4-week trial of corticosteroids, without significant improvement.

Two months later, she presented with mixed nephritic–nephrotic syndrome and worsening MAHA and thrombocytopenia. ADAMTS13 activity was 86%. There was no evidence of autoimmune disease or recurrence of malignancy. Genetic testing indicated a non-pathogenic heterozygous deletion of *CFHR3-CFHR1* (multiplex probe, University of Iowa). As there was a clear drug cause for TMA and this *CFHR3-CFHR1* deletion is a common copy number variation seen in the general population,[15] anti-factor H antibodies were not tested.

Gemcitabine-associated TMA was clinically suspected. As short-duration eculizumab can be appropriate in such patients,[16-20] she was treated with 6 doses of eculizumab. TMA resolved, and there was

partial recovery from AKI within 4 weeks (Supplementary Fig. S1), suggesting that complement activation was a contributing mechanism to the TMA. A later rise in creatinine, attributed to overdiuresis, gradually improved. Ten months later, she remained in cancer remission with no recurrence of TMA.

Case 3: LN-associated (secondary) TMA

A 16-year-old girl presented at a centre outside Singapore with pallor and generalised oedema, anaemia, thrombocytopenia, and AKI (Table 1). Following investigation, she was diagnosed with systemic lupus erythematosus (SLE) with LN, and received methylprednisolone, mycophenolate mofetil, and cyclophosphamide.

The patient was transferred to Singapore 1 month after initial presentation. Her creatinine level had increased further, and she had progressive thrombocytopenia associated with elevated LDH and MAHA on blood film (Table 1). Her ADAMTS13 activity level was 31%. The diagnosis was LN with rapidly progressive glomerulonephritis (RPGN) and LN-associated TMA.

Treatment for proliferative LN and RPGN continued. PLEX was started for LN-associated TMA but produced no early improvement, and the patient continued to have high transfusion requirements. Based on the literature[21-23] and local experience, the prognosis was considered poor, warranting more aggressive therapy. Given that complement is implicated in the pathogenesis of LN, and eculizumab can be beneficial in some cases of LN-associated TMA,[24-26] eculizumab was initiated.

A gradual response was observed for both LN and TMA (Supplementary Fig. S1). In total, she received 7 cycles of pulse intravenous methylprednisolone, 10 sessions of PLEX with FFP as replacement fluid, 7 doses of eculizumab, and an infusion of FFP (without PLEX) before the fourth eculizumab dose. One month after starting eculizumab, she no longer required transfusions and her condition had improved enough for her to be discharged home, suggesting that complement activation was a contributing mechanism to the TMA. Five months later, SLE was in remission, and RPGN and MAHA had resolved.

DISCUSSION

Prompt management of C-TMA and secondary TMA with presumed complement activation is important to prevent complications.[7,10,11,27] In Singapore, where such cases are rare, physicians need to be aware of the different causes of TMA and their underlying triggers, as early diagnosis and treatment are essential to prevent kidney function deterioration.

Given the heterogeneous clinical manifestations of C-TMA, the possible presence of associated conditions, and the occurrence of complement activation in some cases of secondary TMA, diagnosis and management require a multidisciplinary approach.[6] Not all tests/assays relevant to C-TMA are available in Singapore. ADAMTS13 activity testing (to rule out iTTP) is performed centrally at a reference laboratory in Singapore using fluorescence resonance energy transfer–VWF73 and enzyme-linked immunosorbent assay methodologies.[28] STEC-HUS can be ruled out based on clinical and microbiological findings. However, functional testing of complement activities and screening of pathological complement gene variants are not available in Singapore. Where genetic testing was deemed necessary in the example cases, samples were sent to laboratories in the US (Mayo Clinic in Case 1, Invitae and University of Iowa in Case 2). Heterogeneity exists between centres because of the rarity of cases and absence of a standardised pathway. The time required to obtain genetic test results, or the absence of pathogenic gene variants, should not preclude making a clinical diagnosis of C-TMA and prompt treatment initiation.

C5 inhibitors are the cornerstone of C-TMA treatment.[6-8,29,30] Eculizumab and ravulizumab are both approved for use in Singapore.[31,32] Early initiation of C5 inhibitor treatment can help prevent progression to ESKD.[7,27] In addition, without specific treatment of C-TMA, the risk of TMA recurrence is high (Case 1).[4] As C5 blockade increases the risk of infections, patients should receive meningococcal vaccination before treatment starts and prophylactic antibiotics during C5 inhibitor treatment.[4,29]

Since April 2026, eculizumab has been included in the Medication Assistance Fund in Singapore, allowing MediSave, the national medical savings scheme, to be used for payment.[31] This further reduces patients' out-of-pocket payments. Case 1 highlights that, in appropriate patients, eculizumab is cost-saving in the long run compared with a lifetime of dialysis and PLEX.

Case 1 also illustrates the clinical consequences of a funding-related treatment delay. Treatment duration for C5 inhibitors should be considered on a case-by-case basis and guided by genetic testing results if available. Although long-term eculizumab may be required in patients with pathogenic variations, it can be discontinued safely after a short duration of treatment in patients with C-TMA without pathogenic variants (Case 1), although with certain caveats.[14,33] A study assessing eculizumab discontinuation after achieving remission reported an overall relapse rate of 23% (13/55 patients), which was highest (50%) in patients carrying rare complement gene variants and lowest (4%) in those without a variant.[14] Investigators implemented structured monitoring after treatment cessation, and eculizumab was resumed within 7 days of relapse in all but 1 case. If eculizumab discontinua-

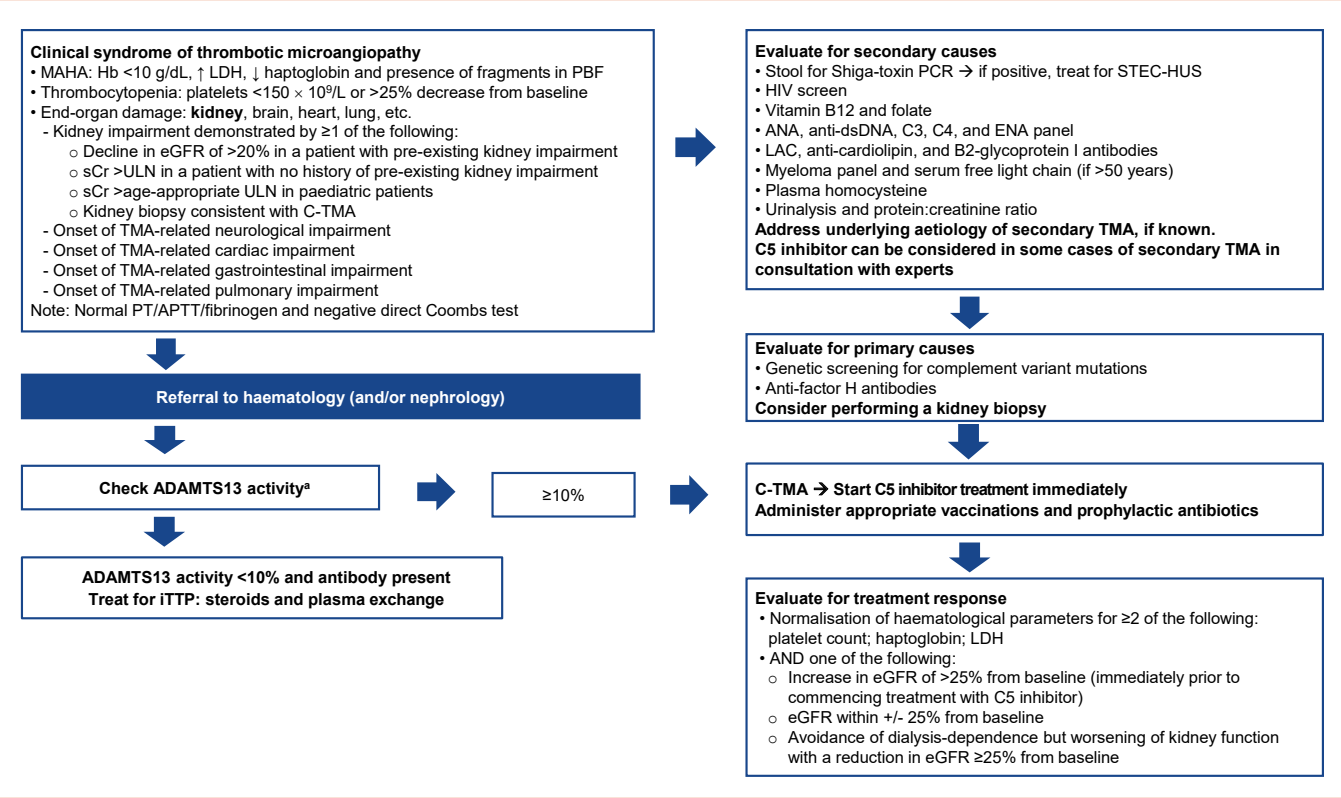
tion is considered in a routine practice setting, the patient should be monitored closely, and early restart of treatment must be guaranteed in the event of relapse. Data from France and the US indicate that prompt initiation of eculizumab and a genetics-based discontinuation strategy can reduce overall healthcare costs.[14,34]

PLEX may be used in patients with TMA until iTTP has been ruled out, in patients with factor H antibodies, or when C5 inhibitors are not available.[6,9] However, PLEX is not a preferred long-term solution and is associated with eventual renal deterioration, mortality, and other transfusion-related complications.[4] Case 1 illustrates the limitations of PLEX for achieving a durable response, and the importance of prompt C5 inhibitor therapy for salvaging kidney function.

The primary therapeutic strategy for drug-induced TMA is drug cessation.[9,12] The pathophysiology of gemcitabine-associated TMA appears to relate in part to complement activation.[20,35] Eculizumab may be beneficial in some patients.[18-20] It can be considered particularly for severe cases or cases that do not resolve after drug cessation and supportive measures (Case 2).[10,17,18,29] Short-duration eculizumab may be safe and feasible in such patients after removal of the culprit drug.[14,16,20]

Autoimmune diseases, such as SLE, can trigger TMA or occur concurrently.[21,22,25,26] Complement overactivation by both classical and alternative pathways is often found in patients with LN.[21,23] Given the increased incidence and severity of SLE in Asian populations,[36-38] physicians in Singapore should be aware of the possibility of SLE-associated TMA. The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 LN guideline recommends managing LN-associated TMA according to its underlying aetiology and lists eculizumab as a treatment to consider once iTTP and other causes have been excluded.[39] Eculizumab can provide a favourable response in such patients, including Asian patients.[24-26] Case 3 illustrates that, in appropriate patients, short-duration eculizumab induction therapy can improve thrombocytopenia and kidney function.

Fig. 1. Workflow for suspected C-TMA.



ADAMTS13: A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13; ANA: antinuclear antibodies; APTT: activated partial thromboplastin time; C3: complement component 3; C4: complement component 4; C5: complement component 5; C-TMA: complement-mediated TMA; dsDNA: double-stranded DNA; eGFR: estimated glomerular filtration rate; ENA: extractable nuclear antigens; Hb: haemoglobin; HIV: human immunodeficiency virus; iTTP: immune thrombotic thrombocytopenic purpura; LAC: lupus anticoagulant; LDH: lactate dehydrogenase; MAHA: microangiopathic haemolytic anaemia; PBF: peripheral blood film; PCR: polymerase chain reaction; PT: prothrombin time; sCr: serum creatinine; STEC-HUS: Shiga toxin-producing *Escherichia coli* haemolytic-uraemic syndrome; TMA: thrombotic microangiopathy; ULN: upper limit of normal

[a] Paediatric cases: iTTP is very rare in children. Treatment for C-TMA can start before the results of tests to rule out iTTP become available.[40]

Note: The workflow is based on expert opinion and has been adapted from existing consensus guidance[10,40] for applicability in Singapore.

Guidelines on the management of patients with C-TMA, including those with secondary TMA associated with complement activation, are available in several Asian countries, including Taiwan, Korea, and Japan,[4,9,12] as well as from international organisations.[11] The authors' recommended approach for healthcare providers in Singapore involves recognising the signs and symptoms of C-TMA, identifying secondary TMA involving complement activation, and ensuring a timely diagnosis and prompt treatment initiation (Fig. 1). The proposed workflow is based on expert opinion and adapts available consensus guidance[10,40] for applicability in Singapore.

Uncontrolled case observations cannot establish efficacy or causation and are subject to selection and reporting bias. In Cases 1 and 2, the temporal coincidence of eculizumab with recovery cannot exclude a role for concurrent immunosuppression, removal of the offending drug, or the natural history of a resolving trigger. C5 inhibitor treatment was associated with haematological recovery, but its independent contribution to renal outcomes cannot be determined from uncontrolled observations.

CONCLUSION

Physicians need to be aware of C-TMA and secondary TMA associated with complement activation as potential causes of TMA. Early recognition and treatment of TMA are essential to prevent kidney function deterioration. The authors propose a multidisciplinary diagnostic approach to guide healthcare providers in Singapore, based on expert opinion and adapted from international guidance for applicability in Singapore. C5 inhibition is central to the treatment of C-TMA, but lack of access to therapy remains a major problem in this region. There is an emerging role for C5 inhibitors in secondary TMAs postulated to be driven by complement activation. Short-duration treatment is feasible in some patients without pathogenic gene variants but should be undertaken only with appropriate monitoring.

Ethics statement

The patients have provided their informed consents for the use of their de-identified data as case examples for the purpose of this publication. These case vignettes are used to illustrate specific scenarios with regard to the management of C-TMA followed by accompanying commentary from the authors' perspectives.

Declaration

LLC, HZT, YCT, and ESY received an honorarium from AstraZeneca Singapore for participating in scientific advisory board activities. LL received an honorarium from AstraZeneca Singapore for advisory board activities and talks on complement inhibition. FY declares no conflict of interest. Content Ed Net provided writing support. AstraZeneca funded the project but has no direct involvement in the writing, data analysis, treatment of the patients, manuscript preparation, or expert opinion statements.

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