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

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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

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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.