J R Coll Physicians Edinb 2020; 50: 25–31 | doi: 10.4997/JRCPE.2020.107 REVIEW

Thrombotic microangiopathy with renal injury: an approach for the general physician

Zay Htet[1], Mahzuz Karim[2]

Abstract

Thrombotic microangiopathy with renal dysfunction is a haematological and renal emergency warranting urgent diagnosis and intervention. As the potential underlying causes may be complex, assessment and management can be challenging for treating clinicians, and a timely and collaborative approach between general physicians, haematologists and nephrologists may be extremely helpful in order to optimise clinical outcomes. This paper will aim to build an understanding of different potential presentations of thrombotic microangiopathies and provide a practical framework for diagnosis and management, using a case-based discussion format, for acute and general physicians. Some aspects of subsequent specialist management are also discussed.

Correspondence to:
Zay Htet
Department of Renal Medicine
Norfolk and Norwich University Hospital
Colney Lane
Norwich NR4 7UY
UK

Email:
zay.myohtet@nnuh.nhs.uk

Keywords: haemolytic uraemic syndrome, microangiopathic haemolytic anaemia, renal injury, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

Financial and Competing Interests: No conflict of interests declared

Introduction

Thrombotic microangiopathy (TMA) represents a diverse group of conditions that classically present with microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia together with organ dysfunction, and which can be associated with significant morbidity and mortality. Pathologically there is endothelial injury and thrombus formation in the microvasculature. This leads to platelet consumption, mechanical destruction of erythrocytes by fibrin strands and end-organ ischaemia due to vessel occlusion. Disseminated intravascular coagulation, in which there are also abnormalities in the coagulation cascade, is regarded as a separate pathological entity and is not covered in this review.

Classification and differential diagnoses of thrombotic microangiopathies

Nomenclature and classification of TMA can be confusing, particularly since they continue to be refined as understanding of the underlying pathophysiological mechanisms increases. These are summarised in Table 1, although a detailed description is outside the scope of this review.[1] Historically, TMA was classified as primary or secondary. Primary was subdivided into haemolytic uraemic syndrome (HUS) where there was predominant renal involvement, and thrombotic thrombocytopaenia purpura (TTP) where other organ dysfunction (particularly neurological) was more prominent. Secondary TMA can be associated with a wide range of systemic conditions, such as pregnancy, malignancy, infection, severe hypertension, connective tissue or other autoimmune disease, and haematopoietic or solid organ transplantation, or be due to adverse drug reactions.[2]

Historically there have been difficulties in distinguishing between HUS and TTP in clinical practice. However, more recent studies investigating the pathogenetic mechanisms behind these conditions have facilitated front-line diagnosis. Both conditions are due to an inability to break down large multimers of von Willebrand Factor; these multimers then activate platelets, leading to TMA. Von Willebrand Factor multimers are normally rapidly cleaved by circulating enzymes, with the most important being 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13', or ADAMTS13. In TTP, ADAMTS13 activity is reduced: this is either hereditary (genetic enzyme deficiency) or acquired (most commonly due to the development of an IgG autoantibody that blocks enzyme activity). In HUS, enzyme activity is normal, but endothelial injury leads to release of large quantities of von Willebrand Factor multimers that exceed the capacity of ADAMTS13 to clear. In the most common form of HUS, often referred to as 'Shiga toxin' (ST-HUS), 'classical', 'typical' or 'diarrhoea-associated' HUS, there is enteric infection with bacteria (often *Escherichia coli* of particular serotypes or *Shigella dysenteriae*) that produce Shiga toxin that damages endothelial cells.[3] More rarely, there are cases (sometimes familial) with the clinical features of HUS (including normal ADAMTS13 activity) but in the absence of Shiga toxin-producing organisms or enteric symptoms. Some of these have been shown to be due to dysregulation of the alternate complement pathway leading

[1]Specialty Registrar, Department of Renal Medicine, Norfolk and Norwich University Hospital, Norwich, UK; [2]Consultant Nephrologist, Department of Renal Medicine, Norfolk and Norwich University Hospital, Norwich, UK

Table 1 Causes of thrombotic microangiopathies

Thrombotic microangiopathy	Causes/associations
'Primary' TMA	
TTP, inherited or acquired	ADAMTS13 functional deficiency due to gene mutations or antibody-mediated inhibition
ST-HUS	Shiga toxin produced by *Escherichia coli* O157:H7 and O104:H4 and *Shigella dysenteriae*
Complement-mediated HUS/ aHUS	Dysregulation of alternate complement pathway due to mutations in CFH, CFI, CFB, C3 and MCP (CD46), or autoantibody activity against CFH and CFI[4,9]
'Secondary' TMA	
Autoimmune diseases	SLE, systemic sclerosis, antiphospholipid syndrome
Pregnancy-associated conditions	Pre-eclampsia, eclampsia, HELLP syndrome
Severe hypertension	Endothelial damage
Solid organ and bone marrow transplantation	Antibody-mediated rejection or CNI toxicity in renal/ solid organ transplant recipients, and antigraft vs host disease regimens in HCT
Drug induced	Quinine, clopidogrel, ticlopidine, CNIs, IFN, VEGF inhibitors
Infection	Bacterial endocarditis, HIV, parvovirus B19, CMV, EBV, influenza A, hepatitis viruses, malaria
Glomerular disorders	Membranous nephropathy, IgA nephropathy, FSGS, ANCA-positive vasculitis, MCGN
Metabolic	Cobalamin C deficiency due to MMACHC gene mutations
Malignancy	Systemic cancers or secondary to chemotherapy

ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS: atypical haemolytic uraemic syndrome; ANCA: antineutrophil cytoplasmic antibodies; C3: complement component 3; CFB: complement factor B; CFH: complement factor H; CFI: complement factor I; CMV: cytomegalovirus; CNI: calcineurin inhibitor; EBV: Epstein-Barr virus; FSGS: focal segmental glomerulosclerosis; HCT: haematopoietic cell transplantation; HELLP: haemolysis, elevated liver enzymes, and low platelets; HIV: human immunodeficiency virus; HUS: haemolytic uraemic syndrome; IFN: interferon; MCGN: mesangiocapillary glomerulonephritis; MCP (CD46): membrane cofactor protein; MMACHC: methylmalonic aciduria and homocystinuria type C protein; SLE: systemic lupus erythematosus; ST: Shiga toxin; TTP: thrombotic thrombocytopaenic purpura; VEGF: vascular endothelial growth factor

to complement overactivation and consequent endothelial damage. Similar to TTP, this may be genetic (e.g. mutations in various complement regulatory genes) or due to the development of autoantibodies. This group is thus variously referred to as 'atypical HUS' (aHUS), 'diarrhoea-negative' or 'complement-mediated' HUS/TMA.[1–4]

Causes of secondary TMA are summarised in Table 1. Interestingly (but complicating matters further), it is now recognised that some patients with an identified secondary trigger have one of the types of genetic mutation mentioned above that predisposed them to developing TMA.

TTP is rare, with a recorded incidence of 6 cases per million per year,[5] while that of HUS has been reported to be around 3 cases per 100,000 per year, with aHUS representing 5–10% of these.[6] Management of TMA varies according to the underlying cause and may include plasma infusion, plasma exchange, anticomplement therapy (such as eculizumab) or supportive therapy alone. Urgent recognition and diagnosis are therefore critical in order to allow optimal management. For example, if it left untreated, mortality from TTP may be as high as 95%, but may be reduced to <10% with early initiation of plasma exchange.[7,8] Similarly, without eculizumab therapy, the prognosis of aHUS is extremely poor, with 60–70% of patients progressing to end-stage kidney disease requiring permanent renal replacement therapy and a high risk of recurrence after renal transplantation.[9] Figure 1 provides an algorithm to assist in ascertaining the underlying diagnosis in patients with TMA.

Primary TMA

TTP

Case history

A 42-year-old female, generally fit and well, presented with a few days' history of headache, generalised weakness, numbness of fingers on both hands, and a petechial rash on both upper and lower extremities together with a fever of 37.8°C. She was found to have abnormal blood results: haemoglobin 108 g/l (reference range 120–150 g/l), platelets 11 × 109/l (150–410 × 109/l), serum creatinine 106 µmol/l (45–84 µmol/l). TMA was confirmed following

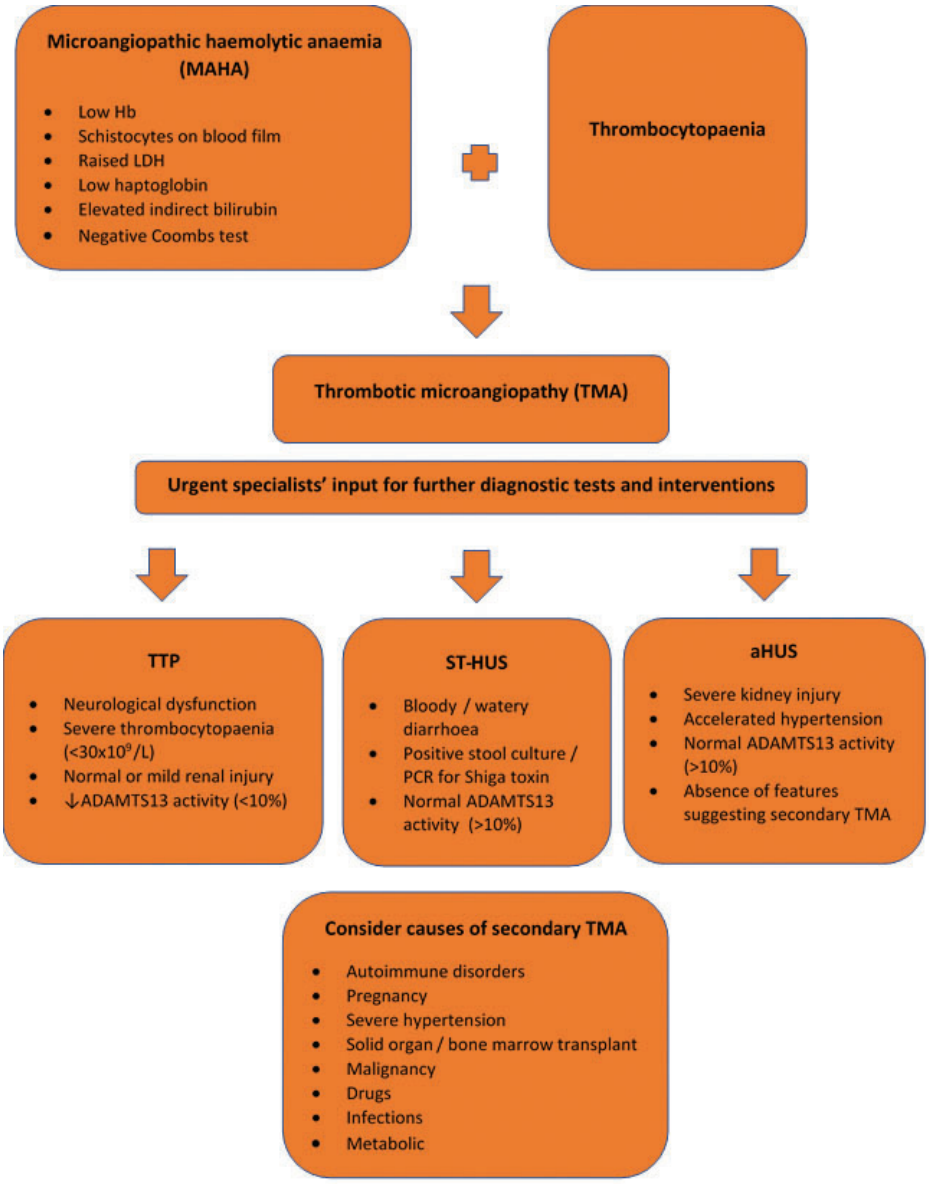

Figure 1 Diagnostic algorithm for the evaluation of a patient presenting with thrombotic microangiopathy. ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS: atypical haemolytic uraemic syndrome; Hb: haemoglobin; LDH: lactate dehydrogenase; PCR: polymerase chain reaction; ST-HUS: Shiga toxin haemolytic uraemic syndrome; TTP: thrombotic thrombocytopaenia purpura

the additional findings of schistocytes on blood film, high lactate dehydrogenase (LDH) of 1,750 U/l (125–243 U/l) and low haptoglobin of 0.2 g/l (0.7–3.2 g/l). A clinical diagnosis was made of TTP and plasma exchange therapy [using fresh frozen plasma (FFP) as the replacement fluid] was, therefore, commenced. Prior to treatment a blood sample was taken for measurement of ADAMTS13 activity. This was subsequently reported as severely reduced (<10% of normal), in keeping with the clinical diagnosis of TTP.

Diagnosis and management

TTP, like other TMA syndromes, leads to MAHA, typically in association with severe thrombocytopaenia (platelet count usually <20 × 10^9/l).[10] MAHA is characterised by fragmented erythrocytes (schistocytes) on peripheral blood film together with other features of haemolysis, such as reticulocytosis, elevated indirect bilirubin concentration, low haptoglobin and high LDH levels. There is often an associated fever, a petechial rash may occur and neurological manifestations are common. Other organ systems (such as gastrointestinal or renal) may also be involved, although the degree of renal injury is usually less marked than in other forms of TMA – in one observational study, median serum creatinine was around 123 µmol/l.[10]

Diagnosis of TTP can be difficult without a high index of suspicion, and clinicians should bear in mind that the classical diagnostic pentad of MAHA, thrombocytopaenia, renal impairment, neurological dysfunction and pyrexia is observed in <5% of TTP patients.[11] In patients with MAHA and thrombocytopaenia together with a strong clinical suspicion of TTP, an ADAMTS13 level can help to confirm the diagnosis (enzyme activity is typically <10% of normal),[12] but treatment should not be delayed while awaiting the result. TTP is considered a medical emergency associated with high risk of complications (such as stroke) and mortality. Urgent input from haematologists and (depending on local setup) nephrologists is warranted in order to make a diagnosis and institute appropriate management. The mainstay of therapy is prompt plasma exchange (predominantly to remove any potential IgG autoantibodies inhibiting ADAMTS13 activity) with FFP as the replacement fluid (providing a source of

ADAMTS13).[13] Where plasma exchange or specialist advice are not immediately available, FFP infusion should be commenced in the interim (provided that the patient is not fluid overloaded). For subsequent specialist management, in the absence of an identified underlying cause for TTP, immunosuppression is usually indicated, most commonly in the form of corticosteroids and/or rituximab.[14] More recently a clinical trial of caplacizumab (a humanised, bivalent, variable-domain-only immunoglobulin fragment that targets the A1 domain of von Willebrand Factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor) has shown promising results.[15] In patients with TTP, platelet transfusion may increase the risk of ischaemic or thrombotic complications and is, therefore, generally not recommended unless there is evidence of active haemorrhage or the patient requires invasive procedures.[16] TTP patients often show a good clinical and haematological response to initial treatment, but the risk of relapse is significant so close ongoing monitoring is required.[8]

Shiga toxin-mediated (typical) HUS

Case presentation

A 24-year-old male presented feeling generally unwell following the onset of profuse diarrhoea a few days beforehand; he had also become jaundiced. This illness had developed following consumption of undercooked meat at a local restaurant. Initial blood results revealed platelets of 52×10^9/l, haemoglobin 110 g/l, schistocytes on blood film, total bilirubin 240 µmol/l (1–17 µmol/l) and elevated LDH of 1,100 U/l. He had mild renal dysfunction with a serum creatinine of 140 µmol/l. He received supportive management with intravenous fluid and antibiotic therapy initially. A provisional clinical diagnosis was made of diarrhoea-positive HUS, and supportive management was instituted. Stool culture subsequently grew *E. coli* O157:H7, and ADAMTS13 activity was normal (>60%). Within a few days his diarrhoea resolved and his haematological parameters and renal function normalised.

Diagnosis and management

ST-HUS is more common in the paediatric population, but clinical outcomes are often poorer in adults, particularly the elderly.[17] Patients usually experience gastrointestinal symptoms (such as bloody or watery diarrhoea, vomiting, abdominal pain, fever), but in some cases these have already resolved by the time haematological and renal manifestations become apparent.[18] A clinical history should include travel to high-risk areas and exposure to contaminated or undercooked food. However, it is important to note that the possibility of ST-HUS should not be discounted in patients without a history of diarrhoea, as in one retrospective cohort of 37 patients with ST-HUS, about 5% did not have colitis.[19] Patients with evidence of TMA, even in the absence of overt gastrointestinal symptoms, should therefore undergo stool testing for Shiga toxin-related infection by culture/polymerase chain reaction. ST-HUS is usually a self-limiting illness that carries a good prognosis, with two-thirds of patients making a complete recovery. However, 10–30% may be left with significant residual renal damage (with 3% progressing to end-stage kidney disease), and the acute mortality rate has been reported to be around 1–4%.[20,21] Expectant management should be employed; this includes careful management of fluid balance, cessation of nephrotoxic agents, monitoring for haemorrhagic complications and provision of dialysis if indicated.[22] There is no evidence to support the routine use of plasma exchange or anticomplement therapy. Once the diagnosis is confirmed, prompt notification to the public health authorities is warranted as these cases may be part of an outbreak requiring intervention.

Atypical (complement-mediated) HUS

Case presentation

A 62-year-old female presented with a 3-day history of frontal-temporal headache, confusion and lower limb weakness; however, there were no gastrointestinal symptoms. She was found to have stage 3 acute kidney injury with a serum creatinine of 450 µmol/l compared to a normal baseline 6 months earlier. Her haematological parameters were also profoundly abnormal with a haemoglobin of 80 g/l, low platelets of 32×10^9/l, schistocytes on blood film and raised LDH of 1,200 U/l, consistent with MAHA. In view of a possible diagnosis of TTP, a sample was sent for ADAMTS13 and plasma exchange was initiated; she also required haemodialysis. She received a total of five sessions of plasma exchange. However, her ADAMTS13 result was subsequently reported as only mildly reduced and so was not consistent with TTP. No secondary causes of TMA were identified and atypical HUS was therefore thought to be the most likely diagnosis. She was commenced on anticomplement therapy with eculizumab, with which she showed a gradual haematological and renal recovery. Genetic studies were performed and she was found to have a mutation in the CFH gene.

Diagnosis and management

As discussed above, patients with clinical features of HUS but with no identifiable Shiga toxin-related infection have historically been labelled as having aHUS, and it has since been demonstrated that many of these patients have mutations in genes regulating the alternate complement pathway.[6,9,23,24] In addition to MAHA, thrombocytopaenia and acute kidney injury, these patients are often severely hypertensive.[4,9]

There are no universally accepted diagnostic criteria available at present, and cases require careful assessment on an individual basis. Features that may assist in this are clinical and haematological features of TMA, absence of identifiable underlying causes (e.g. Shiga toxin-producing organisms, other infections, drugs) and adequate ADAMTS13 activity.[4,9] As these patients are often initially thought to have TTP, lack of response to plasma exchange therapy may also point towards a diagnosis of aHUS. In England, diagnosis and management of aHUS is commissioned through the National Renal Complement Therapeutics Centre based in Newcastle upon Tyne (http: //www.atypicalhus.co.uk), and local specialist teams usually discuss these patients urgently with a view to consideration of therapy with eculizumab and

testing for genetic mutations. Renal biopsy is generally not advocated as patients are at high risk of post-biopsy bleeding due to their thrombocytopaenia, and it usually shows general TMA-related changes rather than any specific diagnostic features. Eculizumab (a monoclonal antibody that targets the terminal complement pathway by inhibiting C5 convertase) has become the mainstay of therapy for patients with newly diagnosed aHUS and for those who develop end-stage kidney disease and undergo renal transplantation (in order to prevent post-transplant recurrence).[4,8,25,26] It increases the risk of infection by capsulated bacteria (particularly *Meningococcus*), and patients, therefore, require vaccination and antibiotic prophylaxis.[4]

Secondary TMA

Drug-induced TMA

The diagnosis of drug-related TMA can be overlooked if a high index of suspicion is not exercised. Table 1 lists some of the agents that have been reported as causing TMA; however, clinicians also need to be aware that some of these may also be encountered in other forms, for example quinine, one of the commonest drugs causing TMA, may be present in nutritional supplements, tonic water, and other beverages.[27,28] Drugs may cause TMA in a number of ways, including via dose-dependent and immune-mediated mechanisms.[4,28,29] Presentation may vary from a sudden onset idiosyncratic reaction (with systemic manifestations within hours of exposure) to months or years after cumulative use of a causative drug.[28,29] Management is supportive, with immediate cessation of the offending agent and close monitoring of response. Plasma exchange is often initially commenced until the diagnosis of TTP has been excluded and may be beneficial in cases where there is an immune-mediated mechanism, although evidence for this is limited.[4] Drug-induced TMA usually carries a good prognosis, but delay in undertaking appropriate measures, such as rapid identification and discontinuation of offending agents, can lead to chronic kidney disease and even end-stage renal failure.[4,28,29]

Pregnancy-related TMA

A number of conditions may cause TMA during pregnancy or in the peripartum period, and it is important for clinicians to identify serious and potentially life-threatening disorders, such as preeclampsia, eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes and low platelets).[30,31] Given that these systemic conditions can mimic each other and have overlapping clinical features, reaching the correct diagnosis can be challenging and an urgent collaboration between obstetricians, haematologists and nephrologists is almost always required. Without timely recognition and institution of effective medical and obstetric interventions (in particular expediting delivery), severe maternal and foetal complications (including death) may occur. It is important to recognise that pregnancy may act as a trigger for primary TMA syndromes in patients with underlying genetic mutations such as those discussed previously;[4,31] where there is any clinical suspicion of this, appropriate investigation and discussion with a specialist centre should be undertaken without delay as specific therapy (such as plasmapheresis or eculizumab) may be indicated.

TMA associated with autoimmune conditions

Certain autoimmune diseases can be associated with TMA, of which systemic lupus erythematosus (SLE), catastrophic antiphospholipid syndrome and systemic sclerosis with scleroderma renal crisis (SRC) are the most commonly reported.[2,4] TMA is a severe renal manifestation in patients with SLE and may result in rapid deterioration of kidney function leading to permanent irreversible damage.[32] This can happen with or without associated antiphospholipid syndrome.

Prognosis in these patients is variable and largely dependent on management of the underlying disorder. Plasma exchange should be considered as an initial therapy while awaiting the effect of appropriate immunomodulatory therapy.[4] Small case series have suggested some benefit from anticomplement therapy,[33] but more robust trials are awaited.

Patients with SRC often present with accelerated hypertension and TMA together with end-organ damage, such as acute kidney injury, cardiac failure and hypertensive encephalopathy. Prompt initiation of angiotensin converting enzyme inhibitors (ACE-I) is the cornerstone of management in order to reduce mortality and optimise renal recovery.[4,34]

Malignancy-associated TMA

In patients with malignancy, TMA can occur either as a result of the malignancy itself or due to chemotherapeutic agents used for treatment.[35,36] In some patients without an existing diagnosis of cancer, TMA may be the presenting feature of a previously undiagnosed malignancy. In patients already known to have malignancy, it is important to make an inquiry about cancer stage, progression and any treatment that the patient has received to date. Renal biopsy is generally not advocated as it is unlikely to change the management strategy and potentially carries a high risk in this patient group owing to their significant comorbidity. No specific interventions (other than treating the underlying malignancy and withdrawing any causative agents) have proven to be beneficial in cancer-related TMA.[37] The prognosis is usually dictated by that of the malignancy itself and the presence of any reversible causes.[37,38]

TMA after transplantation

TMA following solid organ or bone marrow transplantation mandates urgent referral to the relevant transplant team. While a detailed discussion is outside the scope of this review (and is not necessary for the front-line acute physician), potential causes may include: recurrence of the primary disease that caused organ failure;[39–41] side effect of immunosuppressive drugs, in particular the calcineurin inhibitors ciclosporin and tacrolimus;[41] acute antibody-mediated rejection;[39,41] viral infections such as cytomegalovirus;[42] and, chemotherapy conditioning regimens prior to bone marrow transplantation and post-transplant graft vs host disease.[43] Importantly,

about one-third of patients with post-transplant TMA do not demonstrate typical extrarenal features (such as MAHA or thrombocytopaenia),[39,41] so the diagnosis should still be considered by front-line clinicians even where only some manifestations are present.

Hypertension-associated TMA

Severe hypertension can induce TMA through endothelial injury, although the exact mechanism is not entirely clear; this can lead to significant dysfunction of major organs. Treatment is essentially supportive, and recovery of haematological and renal parameters can be expected following careful control of blood pressure, although renal function may initially worsen before it improves (particularly when ACE inhibitors or angiotensin receptor blockers are used).[4] However, the challenging aspect for the clinician is in differentiating between a TMA driven by high blood pressure vs severe hypertension as part of another TMA syndrome. This is critical in making the important decision whether or not to initiate plasma exchange or anticomplement therapy or to perform genetic studies. No specific diagnostic tests are currently available for hypertension-associated TMA; one study has suggested that clues may include a prior history of poorly controlled/untreated high blood pressure, only modest thrombocytopaenia and lack of severe ADAMTS13 deficiency (activity usually >10%).[44] In some patients, the hypertension itself may be due to an underlying condition such as glomerulonephritis. Prognosis of hypertension-associated TMA is variable and patients with severe manifestations at presentation may be at higher risk of long-term consequences such as end-stage kidney disease.[45]

Conclusion

TMA can occur owing to a wide range of pathological processes and may lead to serious complications such as organ dysfunction or death. Initial manifestations may be subtle, particularly in those in whom haematological changes such as haemolysis or thrombocytopaenia are mild, but can worsen rapidly. A high index of clinical suspicion is therefore needed for prompt recognition and reaching a correct diagnosis. As investigation and management of these patients is often complex (potentially requiring genetic testing or treatments such as plasma exchange or eculizumab), early multidisciplinary and specialist advice should be sought.

References

1 George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; 371: 654–66.
2 Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; 347: 589–600.
3 Salvadori M, Bertoni E. Update on hemolytic uremic syndrome: diagnostic and therapeutic recommendations. *World J Nephrol* 2013; 2: 56–76.
4 Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. *Clin J Am Soc Nephrol* 2018; 13: 300–17.
5 Scully M, Yarranton H, Liesner R et al. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. *Br J Haematol* 2008; 142: 819–26.
6 Noris M, Remuzzi G. Hemolytic uremic syndrome. *J Am Soc Nephrol* 2005; 16: 1035–50.
7 Tsai HM. Current concepts in thrombotic thrombocytopenic purpura. *Annu Rev Med* 2006; 57: 419–36.
8 Kremer Hovinga JA, Coppo P, Lammle B et al. Thrombotic thrombocytopenic purpura. *Nat Rev Dis Primers* 2017; 3: 17020.
9 Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011; 6: 60.
10 Page EE, Kremer Hovinga JA, Terrell DR et al. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv* 2017; 1: 590–600.
11 George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood* 2010; 116: 4060–9.
12 Mannucci PM, Peyvandi F. TTP and ADAMTS13: when is testing appropriate? *Hematol Am Soc Hematol Educ Program* 2007: 121–6.
13 Fontana S, Kremer Hovinga JA, Lammle B et al. Treatment of thrombotic thrombocytopenic purpura. *Vox Sang* 2006; 90: 245–54.
14 Chen H, Fu A, Wang J et al. Rituximab as first-line treatment for acquired thrombotic thrombocytopenic purpura. *J Int Med Res* 2017; 45: 1253–60.
15 Scully M, Cataland SR, Peyvandi F et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2019; 380: 335–46.
16 Polito MG, Kirsztajn GM. Thrombotic microangiopathies: thrombotic thrombocytopenic purpura / hemolytic uremic syndrome. *J Bras Nefrol* 2010; 32: 303–15.
17 Petruzziello-Pellegrini TN, Marsden PA. Shiga toxin-associated hemolytic uremic syndrome: advances in pathogenesis and therapeutics. *Curr Opin Nephrol Hypertens* 2012; 21: 433–40.
18 Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome. *Lancet* 2005; 365: 1073–86.
19 Brandt JR, Fouser LS, Watkins SL et al. *Escherichia coli* O 157: H7-associated hemolytic-uremic syndrome after ingestion of contaminated hamburgers. *J Pediatr* 1994; 125: 519–26.
20 Loos S, Aulbert W, Hoppe B et al. intermediate follow-up of pediatric patients with hemolytic uremic syndrome during the 2011 outbreak caused by *E. coli* O104: H4. *Clin Infect Dis* 2017; 64: 1637–43.
21 Spinale JM, Ruebner RL, Copelovitch L et al. Long-term outcomes of Shiga toxin hemolytic uremic syndrome. *Pediatr Nephrol* 2013; 28: 2097–105.
22 Iijima K, Kamioka I, Nozu K. Management of diarrhea-associated hemolytic uremic syndrome in children. *Clin Exp Nephrol* 2008; 12: 16–9.
23 Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009; 361: 1676–87.
24 Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2007; 18: 2392–400.

25 Noris M, Ruggenenti P, Remuzzi G. Kidney transplantation in patients with atypical hemolytic uremic syndrome: a therapeutic dilemma (or not)? *Am J Kidney Dis* 2017; 70: 754–7.
26 Legendre CM, Licht C, Muus P et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; 368: 2169–81.
27 Page EE, Little DJ, Vesely SK et al. Quinine-Induced thrombotic microangiopathy: a report of 19 patients. *Am J Kidney Dis* 2017; 70: 686–95.
28 Zakarija A, Bennett C. Drug-induced thrombotic microangiopathy. *Semin Thromb Hemost* 2005; 31: 681–90.
29 Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol* 2001; 8: 286–93.
30 George JN, Nester CM, McIntosh JJ. Syndromes of thrombotic microangiopathy associated with pregnancy. *Hematol Am Soc Hematol Educ Program* 2015; 2015: 644–8.
31 Fakhouri F, Vercel C, Fremeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. *Clin J Am Soc Nephrol* 2012; 7: 2100–6.
32 Chen M-H, Chen M-H, Chen W-S et al. Thrombotic microangiopathy in systemic lupus erythematosus: a cohort study in North Taiwan. *Rheumatology* 2010; 50: 768–75.
33 Brocklebank V, Kavanagh D. Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea. *Clin Kidney J* 2017; 10: 600–24.
34 Woodworth TG, Suliman YA, Li W et al. Scleroderma renal crisis and renal involvement in systemic sclerosis. *Nat Rev Nephrol* 2016; 12: 678–91.
35 Scully M. Cancer and thrombotic microangiopathy. *J Oncol Pract* 2016; 12: 531–2.
36 Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. *Am J Kidney Dis* 2015; 66: 857–68.
37 Govind Babu K, Bhat GR. Cancer-associated thrombotic microangiopathy. *Ecancermedicalscience* 2016; 10: 649.
38 George JN. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. *Oncology* 2011; 25: 908–14.
39 Abbas F, El Kossi M, Kim JJ et al. Thrombotic microangiopathy after renal transplantation: Current insights in de novo and recurrent disease. *World J Transplant* 2018; 8: 122–41.
40 Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. *Am J Transplant* 2010; 10: 1517–23.
41 Garg N, Rennke HG, Pavlakis M et al. De novo thrombotic microangiopathy after kidney transplantation. *Transplant Rev* 2018; 32: 58–68.
42 Java A, Edwards A, Rossi A et al. Cytomegalovirus-induced thrombotic microangiopathy after renal transplant successfully treated with eculizumab: case report and review of the literature. *Transpl Int* 2015; 28: 1121–5.
43 Obut F, Kasinath V, Abdi R. Post-bone marrow transplant thrombotic microangiopathy. *Bone Marrow Transplant* 2016; 51: 891–7.
44 Khanal N, Dahal S, Upadhyay S et al. Differentiating malignant hypertension-induced thrombotic microangiopathy from thrombotic thrombocytopenic purpura. *Ther Adv Hematol* 2015; 6: 97–102.
45 Shavit L, Reinus C, Slotki I. Severe renal failure and microangiopathic hemolysis induced by malignant hypertension—case series and review of literature. *Clin Nephrol* 2010; 73: 147–52.