

Nephrology: thrombotic microangiopathy (haemolytic–uraemic syndrome)

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Introduction/epidemiology

The thrombotic microangiopathies (TMAs) are a group of disorders presenting with a common clinical presentation: microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. MAHA and thrombocytopenia describe the blood picture, whereas TMA is a histological term used to describe the finding of arteriolar and capillary thrombosis due to endothelial injury.

Classification/definition

Primary TMA syndromes

- > Thrombotic thrombocytopenic purpura (TTP) – classically described as a pentad of MAHA, thrombocytopenia, neurological abnormalities (coma, stroke, seizures), renal impairment and fever. There is a severe (inherited or acquired) deficiency of the matrix metalloproteinase a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) (<10% of normal activity), which cleaves von Willebrand factor (vWF) multimers. When this process is disrupted, the vWF multimers attract activated platelets and form the basis for the platelet thrombi.
- > Diarrhoea-associated/typical haemolytic–uraemic syndrome (dHUS) – MAHA with thrombocytopenia and AKI. Seen in association with bloody diarrhoea secondary to infection with a Shiga toxin-producing bacterium, usually *Escherichia coli* O157:H7 or *Shigella*. This form is commonest in children and can be sporadic or in outbreaks from contaminated food. Approximately two to three cases per 100,000 per year. Approximately 6–9% of patients with the infections develop HUS.
- > Atypical HUS (aHUS) – similar presentation to dHUS but without prodromal bloody diarrhoea (although there may be some diarrhoea – possibly a triggering infection). aHUS is caused by inherited or acquired (autoantibody-mediated) defects in the proteins that regulate complement deposition/activation on cell surfaces, particularly endothelium. It is rare – two cases per million population per year.

- > Drug-induced TMA – causative drugs include quinine, immunosuppressants (calcineurin inhibitors (CNIs) – ciclosporin and tacrolimus), chemotherapeutic agents (mitomycin C).

Secondary TMA syndromes

The following may also present consistent with TMA:

- > pregnancy – pre-eclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome
- > accelerated-phase hypertension
- > infections (subacute bacterial endocarditis (SBE), HIV)
- > malignancy (often disseminated)
- > rheumatological disorders – SLE, scleroderma.

Pathology

In HUS, abnormal activation of complement, either through the activity of bacterial toxins (dHUS) or lack of normal regulatory proteins (aHUS), leads to endothelial damage and hence platelet activation and thrombus formation. Although biopsy is not required for diagnosis, affected organs show platelet-based thrombi lodged in the microcirculation, leading to the clinical manifestations. It is not clear why the central nervous system (CNS) and kidneys are more prone to development of TMA (Fig 1).

Clinical presentation

- > AKI and MAHA with thrombocytopenia
- > hypertension – usually present and often severe
- > neurological symptoms – may be present in those with TTP
- > other – fatigue, dyspnoea, bleeding, petechiae, haematuria.

Investigations

Bloods

- > FBC and clotting – with an urgent blood film if TMA is suspected to look for characteristic abnormalities: fragments and schistocytes (fragmented red cells, also termed ‘helmet cells’)
- > haemolysis screen – bilirubin (high), lactate dehydrogenase (LDH) (high), haptoglobins (low), direct antiglobulin test (DAT) (Coombs) test (typically negative)
- > renal function and urinalysis
- > liver function
- > ADAMTS13 activity – check if clinical suspicion of TTP.

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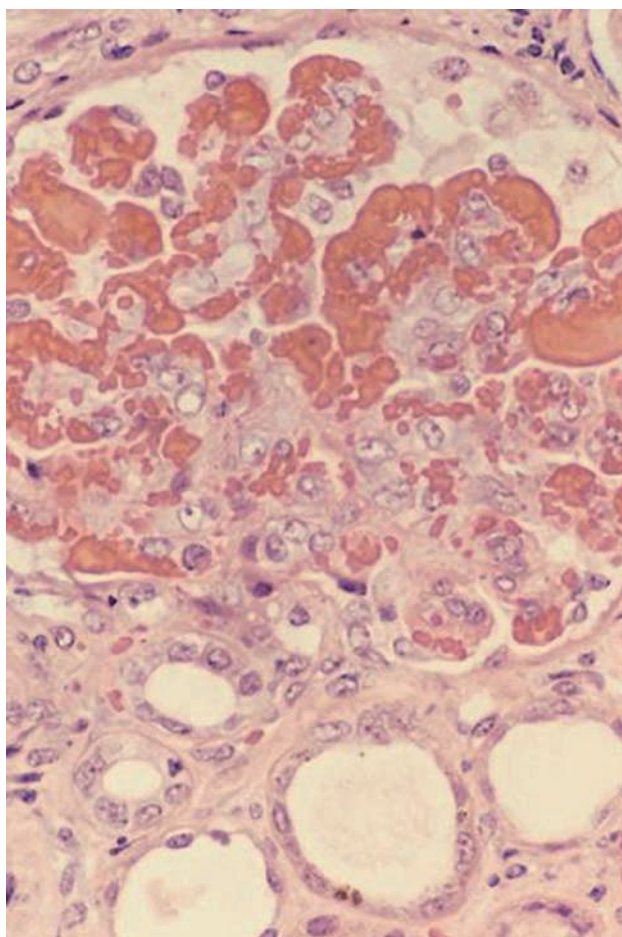


Fig 1. Haemolytic-uraemic syndrome (HUS). Typical renal histological appearance with intraglomerular thrombi (H&E; magnification $\times 300$).

Other

- > CT or MRI head – in patients presenting with abnormal neurology
- > renal biopsy – may confirm the diagnosis but is not required and is high risk for bleeding.

In all cases, urgent discussion with a local or national centre may be appropriate.

Treatment

Specific treatment depends on the presentation – current recommendations are:

Primary TMAs

- > TTP – plasma exchange and steroids
- > dHUS – best supportive care
- > aHUS – plasma exchange has been the mainstay of treatment, but is now being superseded by eculizumab.

Secondary TMAs

- > Treat the underlying cause.

Special note must be made of eculizumab (a C5 inhibitor, see Fig 2). This monoclonal antibody has recently been licensed for the treatment of paroxysmal nocturnal haemoglobinuria and aHUS. It binds to C5 and blocks its conversion to C5b, which is the final common pathway in complement activation. By thus preventing formation of the membrane attack complex (MAC), much of the endothelial damage is prevented, and hence platelet activation

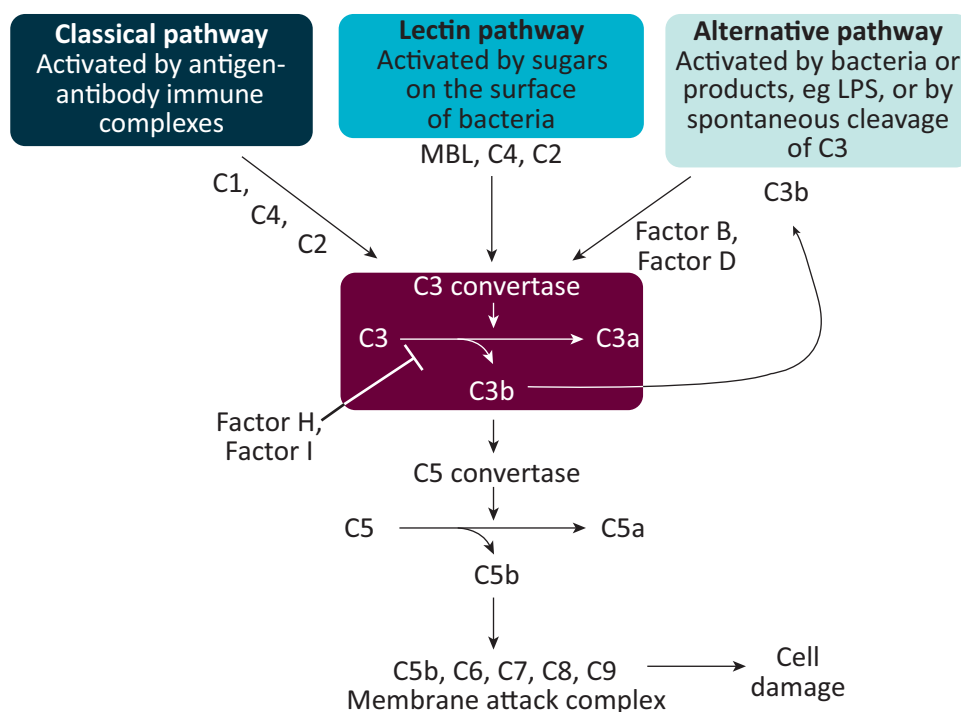


Fig 2. Simplified complement cascade, with the final common pathway shown in dark red. Defective function of factor H, factor I, factor B, C3 and thrombomodulin (not shown) have been discovered in patients with atypical haemolytic-uraemic syndrome (HUS). From the efficacy of eculizumab (C5 blockade) it appears the final common pathway is a key step in the damage associated with TTP-HUS. LPS = lipopolysaccharide; MBL = mannose-binding lectin.

and aggregation prevented. It has been shown to significantly improve outcomes in aHUS.

Prognosis

The overall mortality rate is 10%, although this may fall with the advent of eculizumab. The prognosis is worse in adults. aHUS

previously had a poor prognosis, with over 40% progressing to end-stage renal failure (ESRF) with a high recurrence rate post transplantation, but with eculizumab both risk of dialysis and risk of recurrence have been reduced. Trials are ongoing as treatment is expensive and at present continued indefinitely, but it may prove possible to stop it safely in some individuals. ■



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