REVISE NEPHROLOGY

Thrombotic microangiopathies

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Learning points

- Difference between MAHA and TMA
- D/D of conditions presenting with MAHA and thrombocytopenia
- TTP, HUS, CM-TMA(atypical HUS) **AND** differences in clinical presentation between the three
- When to suspect CM-TMA?
- Drug induced and metabolism-mediated TMA

Microangiopathic hemolytic anemia (MAHA) versus thrombotic microangiopathy (TMA)

- MAHA is hemolytic anemia due to intravascular RBC fragmentation and is characteristically Coombs-negative
- MAHA is mostly caused due to abnormalities in the arteries and capillaries when it is termed thrombotic microangiopathy (TMA) **BUT** can be due to intravascular devices such as a prosthetic heart valves
- Characteristic laboratory findings-
  - Hemolytic anemia (low haptoglobin, high reticulocytes, raised LDH and indirect bilirubin)
  - Negative Coombs test
  - Schistiocytes (fragmented RBCs) on peripheral blood film
- *Remember not all MAHA is caused by TMA, but nearly all TMAs cause MAHA and thrombocytopenia*

What is thrombotic microangiopathy (TMA)

- TMA is microvascular thrombosis due to abnormalities in the vessel walls
- Injury to the endothelial cells is the central pathophysiology
- Clinically TMA presents with
  - -MAHA (hemolytic anemia with schistocytes) AND thrombocytopenia
  - - Variable signs of organ injury due to platelet thrombosis e.g. AKI, neurological involvement etc.
- TMA is a histological diagnosis characterised by:
  - -Platelet microthrombi within small arterioles and capillaries
  - -Characteristically swollen endothelial cells and subendothelial space, along with vessel wall thickening

'Syndromes of Thrombotic Microangiopathy'; James N. George, and Carla M. Nester; August 14, 2014; N Engl J Med 2014; 371:654-666; DOI: 10.1056/NEJMra1312353

Differential diagnosis of microangiopathic haemolytic anaemia (MAHA) with thrombocytopenia

Primary thrombotic microangiopathy (TMA) syndromes

- Thrombotic thrombocytopenic Purpura (TTP)
- Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)
- Complement-mediated TMA (previously called atypical HUS)
- Drug-induced TMA (DITMA) syndromes
- Disorders of vitamin B12 metabolism mediated TMA

Secondary causes of microangioapthic haemolytic anaemia (MAHA) with thrombocytopenia

- Pregnancy-associated (severe preeclampsia, HELLP syndrome)
- Autoimmune disorders(SLE, SS, anti-phospholipid)
- Severe hypertension
- Systemic infections (bacterial endocarditis, HIV, CMV)
- DIC
- Haematopoietic stem cell transplant or organ transplantation
- Bone marrow ablation (e.g. total body radiation, high-dose chemotherapy)
- Immunosuppressive drugs (e.g. calcineurin inhibitors*)*

Thrombotic Thrombocytopenic Purpura (TTP)

- Previously healthy individual present with MAHA and severe thrombocytopenia
- Caused by severe deficiency of ADAMTS13 to typically <10%
- AKI usually **NOT severe** and anuria unlikely
- Severe thrombocytopenia **very common** (platelets usually <30,000/microL)
- Neurologic dysfunction common ranging from headache to seizures, stroke and coma
- Classic textbook pentad of thrombocytopenia, MAHA, neurological abnormalities, fever and renal dysfunction rarely seen(<5 %)
- High fatality rate without prompt treatment

Pathophysiology of TTP

- Endothelial cells synthesize and secrete the ultra large von Willebrand factor (VWF) which is involved in coagulation
- ADAMTS13's main role is as a *VWF-cleaving protease*
- Deficiency of ADAMTS13 causes VWF to accumulate which provides a nidus for platelet trapping leading to thrombocytopenia
- RBCs fragmented as make their way through these platelet rich plugs causing formation of schistiocytes
- Mostly ADAMTS13 deficiency acquired due to auto-antibody(>95%) rather than being a genetic condition

Diagnosis of TTP

- Hemolytic anemia with severe thrombocytopenia (platelets usually <30,000/microL)
- Low haptoglobin and high reticulocytes, elevated LDH, elevated indirect bilirubin, and negative Coombs testing
- Schistiocytes (usually 2 or more per high power field)
- ADAMTS13 activity<10%
- Creatinine usually <176 µmol/L
- *Remember fever, neurologic findings, or AKI are not required for diagnosis*

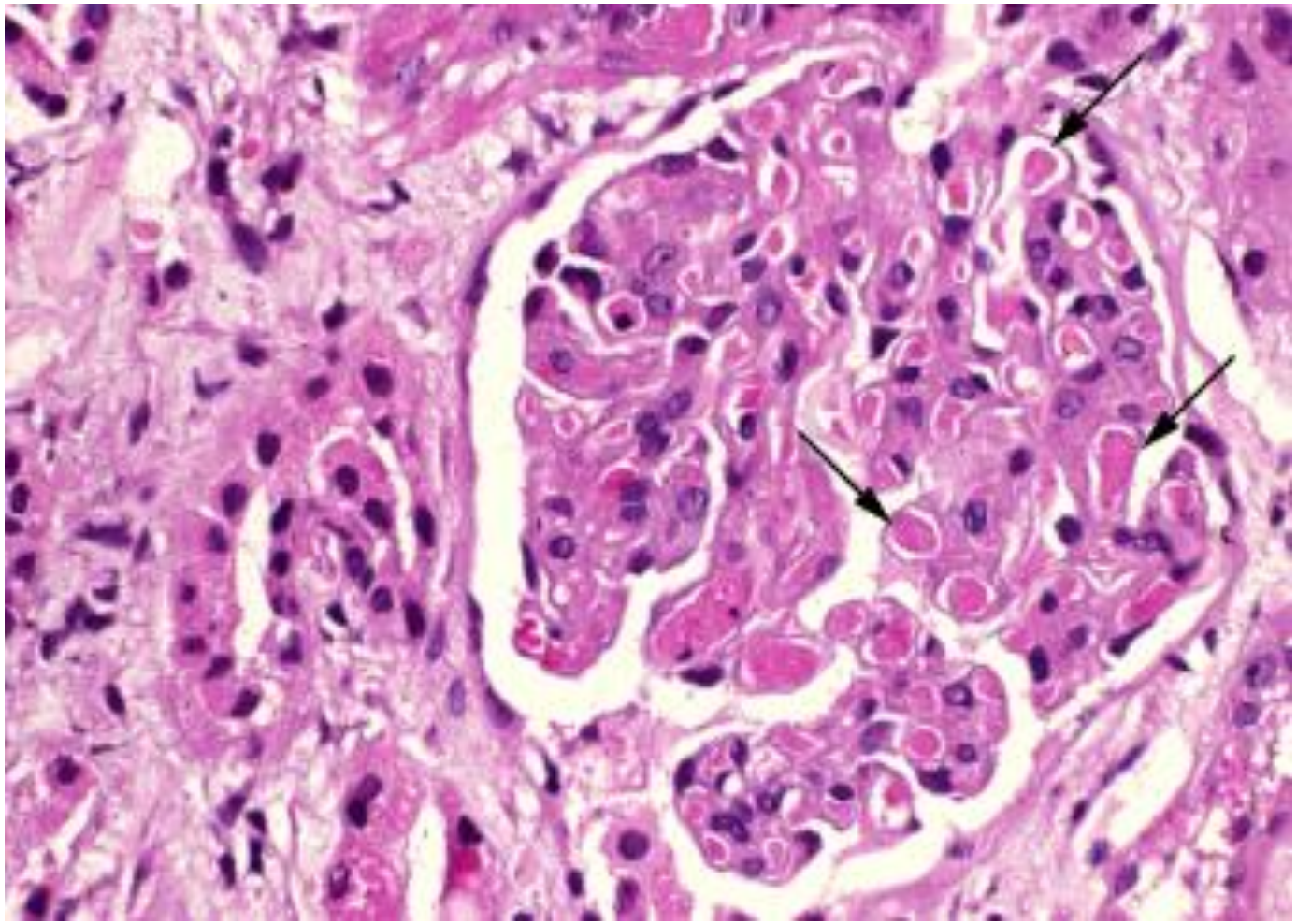
Renal biopsy

- Remember that renal biopsy in all cases of TMA show:

-Platelet microthrombi within small arterioles and capillaries

-Characteristically swollen endothelial cells and subendothelial space, along with vessel wall thickening

LM shows glomerular intracapillary thrombi typical of TMA



Should we treat for TTP while awaiting ADAMTS13 result?

- **Try and get an urgent ADAMTS13 result- CALL UP/BEG**
- If ADAMTS13 result not available and patient deteriorating, use PLASMIC score to estimate the pretest probability and diagnosis of TTP
  - Platelet count <30,000/microL
  - Hemolysis (Reticulocyte>2.5% OR undetectable haptoglobin OR high indirect bilirubin)
  - No active cancer
  - No solid organ or stem cell transplant
  - MCV <90 fL
  - INR <1.5
  - Creatinine <176 µmol/L
- PLASMIC score 5 or higher should be empirically treated for TTP with plasma exchange

Management of TTP

- Plasma exchange (PEX) with FFP: cease when platelet count is normal for at least two days (improved mortality rates from 90% to < 15%)
- Prednisolone 1mg/kg daily: hastens recovery by reducing production of the ADAMTS13 inhibitor; taper once the ADAMTS13 activity > 20 to 30%
- Rituximab: chimeric monoclonal antibody directed against CD20; reduces relapse rate from 40 to 13%
- Caplacizumab is anti-VWF antibody **used in severe cases** (neurologic findings/high troponin levels/thrombocytopenia not responding after 2 to 3 days of TPE, glucocorticoids, and rituximab):
  - Rapidly halts the formation of microthrombi BUT does not reduce production of ADAMTS13 inhibitor
- Platelet count trend most reliable measure of disease response

Shiga toxin-mediated haemolytic Uremic Syndrome (ST-HUS)

- Simultaneous occurrence of MAHA, thrombocytopenia, and AKI with history of recent diarrhoea
- Commoner in children
- Shiga toxin-producing E. coli (mostly O157:H7) haemolytic uraemic syndrome (STEC HUS) is the commonest worldwide
- Streptococcus pneumoniae associated HUS in 5-15% childhood cases
- In Australia 50 % of post-diarrhoeal HUS are due to E. coli 0111 while Shigella dysenteriae type 1-associated HUS is seen in India, Bangladesh, and southern Africa
- In E. Coli-associated HUS, undercooked meat is the most common culprit, with secondary person-to-person spread also seen

ST-HUS

- HUS complicates 6 to 9% of Shiga toxin-producing E. Coli (STEC) infections and usually begins 5 to 10 days after the onset of diarrhoea
- Sudden onset of haemolytic anaemia with fragmented RBCs on the peripheral blood film, thrombocytopenia and AKI
- **Although one-half to two-thirds of patients require dialysis during the acute phase, the overall renal prognosis is good**
- Neurological signs including stroke, seizure or coma in up to 25%
- Pancreatitis in up to 20% with occasional patients presenting with severe haemorrhagic colitis, bowel necrosis and perforation

HUS Diagnosis

- Diagnosis suspected on the basis of history and laboratory findings: prodrome of diarrhoea followed 5-10 days later by onset of MAHA, thrombocytopenia, and AKI
- Confirmation rests on the detection of offending organisms in stool or rectal swab, which may be demonstrable even several weeks after the event
- Renal histopathology (not needed for diagnosis though) show glomerular thrombotic microangiopathy

HUS treatment and prognosis

- Maintain hydration
- Supportive management for anaemia, thrombocytopenia, and hypertension
- Antibiotics and antimotility drugs not helpful
- No proven benefit of plasma therapy
- Eculizumab used for severe CNS involvement
- Indications for dialysis same as in patients with AKI due to other causes
- Most patients needing dialysis make complete or partial renal recovery and are able to come off dialysis
- While mortality rates are less than 5%, another 5% may be left with significant sequelae (e.g. stroke or ESRD)

Complement mediated thrombotic microangiopathy (CM-TMA)

- Previously called atypical HUS (aHUS) arises from excess activation of the complement system- alternative pathway Need to rule out HUS and TTP before considering diagnosis
  - **AKI usually severe in comparison to TTP**
  - **Thrombocytopenia usually not as severe as in TTP**
  - **No history of diarrhoea differentiates from HUS**
  - **Has known association with pregnancy; remember pregnancy associated HELLP or severe preeclampsia can cause MAHA with thrombocytopenia**
- Life-threatening syndrome requiring prompt initiation of therapy

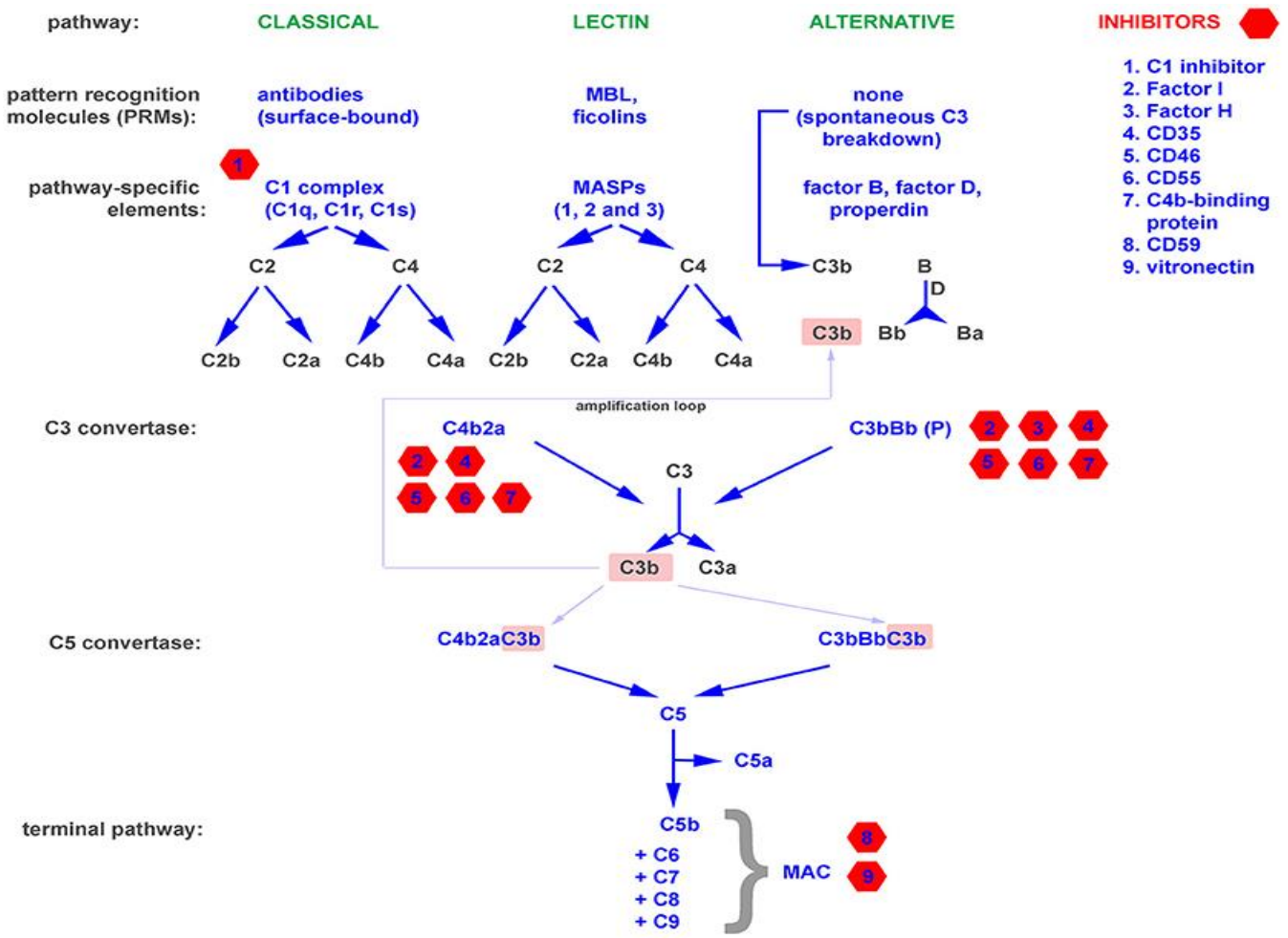
When to suspect CM-TMA?

- Known family or personal history of CM-TMA
- Presentation of significant AKI during pregnancy or postpartum
- TMA with progressive deterioration in kidney function
- No history of abdominal pain or bloody diarrhoea **ruling out** ST-HUS
- No history of exposure to one of the drugs associated with a drug-induced TMA (discussed later)
- **ADAMTS 13 not low**

Pathogenesis of CM-TMA

- Alternative pathway is constitutively active as a result of spontaneous hydrolysis of C3 to C3b; regulation needed to limit self-injury
- CM-TMA may result from either loss-of-function mutation in a regulatory gene (*CFH, CFI,* or *CD46*) or a gain-of-function mutation in an effector gene (*CFB* or *C3*); no mutation identified in up to 50%
- *Lack of regulation causes complement-induced lesions of endothelial cells*
- In adults with CM-TMA, genetic mutations causative in >90%
- Autoantibodies against complement proteins causing CM-TMA detected in 8 to 10% cases (usually against CFH) and mostly seen in children
- *Remember in contrast >95% of TTP is secondary to autoantibodies to ADAMTS13*

Inhibitors of complement pathways



Management of CM-TMA

- Treatment with either eculizumab or ravulizumab
    - Monoclonal antibodies directed against the C-5 complement component
    - Block formation of the membrane attack complex (MAC)
- Ensure meningococcal antimicrobial prophylaxis in addition to vaccination
- Plasma exchange to remove the antibodies along with corticosteroids if eculizumab is not available
- Plasma exchange and immunosuppression in confirmed complement factor H variants (has worst prognosis)
- Appropriate duration of treatment with anti-complement therapy unknown
- May consider discontinuation of therapy after kidney function has improved or stabilised especially in those whose genetic testing is negative-50% of total

Drug induced and metabolism-mediated TMA

- **Drug induced TMA** has two distinct categories:
- Immune-mediated: Quinine most common, other drugs being quetiapine, oxaliplatin and gemcitabine
- Drug dose dependent:
  - Presentation might be acute, caused by a toxic dose of an approved or illegal drug, or chronic when the patient may present after weeks to months of drug exposure
  - Seen with chemotherapeutic agents (such as gemcitabine and mitomycin), immunosuppressive agents (CNIs-cyclosporine and tacrolimus), vascular endothelial growth factor (VEGF) inhibitors (sirolimus and bevacizumab), and narcotics taken inappropriately or illegal agents (oxymorphone and cocaine)
- **Metabolism-mediated TMA** –
  - Hereditary disorders of intracellular vitamin B12 metabolism can cause TMA
  - Elevated homocysteine and low methionine levels in plasma, while urine often shows methylmalonic aciduria

TTP	Severe MAHA and thrombocytopenia **Renal failure usually not severe** **Severe thrombocytopenia** Neurologic abnormalities common Severe deficiency of ADAMTS13 (activity <10%) >95% have ADAMTS13 inhibitor (autoantibody)
ST-HUS	-Abdominal pain; diarrhoea (often bloody); possible history of outbreak or exposure to livestock or contaminated food, although most cases are sporadic -**Renal failure is prominent but often reversible** -Stool may be positive for the organism (*Escherichia coli* or *Shigella dysenteriae*) or Shiga toxin -Prognosis better than TTP or CM-TMA
Complement-mediated TMA (CM-TMA)	-**Renal failure more severe and thrombocytopenia less severe than in TTP** -Normal levels of ADAMTS13 -Usually due to loss-of-function mutation in a regulatory gene (*CFH, CFI,* or *CD46*) or a gain-of-function mutation in an effector gene (*CFB* or *C3*) ->90% due to genetic mutation in adults -Acquired disorder in 8-10% overall and commoner in children
Drug-induced TMA (DITMA) syndromes	-Immune-mediated: Quinine is most widely recognised, with other drugs implicated being quetiapine, oxaliplatin and gemcitabine -Drug dose dependent toxicity related: chemotherapeutic agents (such as gemcitabine and mitomycin), immunosuppressive agents (such as cyclosporine and tacrolimus), vascular endothelial growth factor (VEGF) inhibitors (such as sirolimus and bevacizumab), and narcotics taken inappropriately or illegal agents (such as oxymorphone and cocaine)

Do not fear to be eccentric in opinion, for every opinion now accepted was once eccentric.

-Bertrand Russell

Thank you