Thrombotic Microangiopathy (TMA) and the Kidney.

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Introduction.

- Thrombotic microangiopathy (TMA) as a pattern of injury. Severe acute only as trainee.
- Dr Helmut Rennke in Boston. Chronic TMA as a distinct pattern of injury.
- Alternative complement pathway modulation therapy has highlighted the importance of its recognition.
Thrombotic Microangiopathy.

- Thesis behind this presentation relates to role of Alternative complement pathway.
- This pathway can be triggered/activated by very many disease processes, spanning spectrum of human diseases.
- Many cytogenetic abnormalities of alternative complement pathway identified.
- TMA, however, is just a pattern of injury with perhaps many potential causes, not just alternate complement abnormalities.
The Role of Complement in aHUS
Chronic Uncontrolled Complement Activation Leads to Devastating Consequences in aHUS

Ongoing Research in the Field of Complement Inhibitors

- Most genetic mutations have been discovered in the past 20 years\(^1\)
- 30–50% of patients with aHUS have no identifiable genetic mutation\(^2\)

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Chronic Uncontrolled Complement Activation Leads to Endothelial and End Organ Damage

Uncontrolled complement activation on cells

Endothelial cells:
- Activation
- Swelling and disruption

Platelets:
- Activation
- Aggregation

Leukocytes:
- Activation

Red cells:
- Haemolysis

Clinical consequences:
- Platelet consumption
- Mechanical haemolysis
- Blood clotting
- Vessel occlusion
- Inflammation
- Ischaemia

Systemic multi-organ complications

Systemic, Complement-mediated TMA Affects Multiple Vital Organs and Tissues

Renal
More than 50% of patients progress to ESRD\(^1\)
- Elevated creatinine\(^2\)
- Proteinuria\(^3\)
- Oedema,\(^4\) malignant hypertension\(^5\)
- Decreased eGFR\(^6\)

CNS
Up to 48% of patients experience neurological symptoms\(^3\)
- Confusion\(^7\)
- Stroke\(^7\)
- Encephalopathy\(^5\)
- Seizure\(^7,8\)

Blood
- Thrombocytopenia\(^1\)
- Decreased haptoglobin\(^9\)
- Elevated LDH\(^9\)
- Decreased haemoglobin\(^9\)
- Schistocytes\(^9\)

Cardiovascular
Up to 43% of patients experience cardiovascular symptoms\(^3\)
- Myocardial infarction\(^6\)
- Hypertension\(^10\)
- Diffuse vasculopathy\(^6\)
- Peripheral gangrene\(^11\)

Gastrointestinal
Up to 30% of patients present with diarrhoea\(^12\)
- Colitis\(^7\)
- Nausea/Vomiting\(^8\)
- Pancreatitits\(^8\)
- Abdominal pain\(^7,8\)
- Gastroenteritis\(^5\)
- Liver necrosis\(^5\)

Pulmonary
- Dyspnoea\(^6\) • Pulmonary haemorrhage\(^13\) • Pulmonary oedema\(^6\)

Visual
- Ocular occlusion\(^14\)
Definition of TMA

- A pattern of injury with many potential causes
- TMA is a pathology that results in thrombosis of capillaries and arterioles due to endothelial injury. (Glomerulus is an elaborate capillary proliferation)
- It may be acute or chronic!
Recognised causes of TMA pattern of injury

- **Infection:** bacteria (toxin producing and others) and viruses (many)
- **Drugs:** calcineurin inhibitors, chemotherapy, clopidogrel / ticlopidine, BMT, OCP and penicillin
- **Tumour:** vascular, carcinomas and AML
- **Connective tissue diseases:** scleroderma, SLE, antiphospholipid antibody syndrome and RA
- **Pregnancy**
- **Severe hypertension**
- **Genetic:** complement abnormalities, including ADAMTS13 deficiency
- **Others**

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, 13; AML, acute myeloid leukemia; BMT, bone marrow transplant; OCP, oral contraceptive pill; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus
Traditional views of TMA

- Only acute forms are considered.
- Always associated clinically with HUS or TTP features.
- Uncommon.
- Precise roles of factors such as toxins, von Willebrand factors, ADAMTS 13 deficiency, complement, etc confused.

However...
Most cases with a TMA pattern of injury on renal biopsy are:

- Chronic
- Not associated with HUS or TTP clinical features
- Not associated with a clear cause at diagnosis
At the end of this presentation, I hope you will consider that:

- TMA is a common pattern of injury on kidney biopsy.
- It has many potential causes. (Or complement activation events?)
- Pathology can be very subtle, including familial cases that recur in a transplant.
- Focusing only on dramatic acute cases with HUS or TTP clinical features will mean missing many, probably most, cases and can potentially lead to patient mismanagement.
- Mild chronic cases may have implications for live related transplants.
Pathological assessment of all medical renal biopsies

- Immunofluorescence
- Light microscopy including a range of special stains, sequentially assessing:
  - Glomeruli
  - Tubules
  - Interstitium
  - Arteries
  - Arterioles
- Electron microscopy

All 3 are essential!
Pathological features of TMA: glomeruli, small arteries and arterioles

- Acute
- Organising
- Chronic
Acute glomerular lesion
H + E Stain

Fibrin thrombus

Small crescent
Acute glomerular lesion
M Tri Stain
Segmental
Acute glomerular lesion

M Tri

Thrombus

Inflammation

Organisation
Acute glomerular lesion – organising
Silver Stain

Mesangiolysis
Double contour
“tram-track”
Acute glomerular lesion – organising
Silver

Extensive double contour formation
Acute glomerular lesion – cellular crescent
PAS
Acute glomerular lesion – EM

Fibrin
Acute glomerular lesion – EM

Fibrin phagocytosis
However...

- Glomerular lesions, including cases with a strong family history, may be more subtle
Chronic glomerular lesion

Silver

Focal and segmental double contour formation
Chronic glomerular lesion
Silver
Very subtle lesion
Organising subendothelial lesion in peripheral capillary loop
M Tri

Tubulo-interstitium
M Tri

Tubulo-interstitium
Severe fibrosis

Arteriolar occlusion
Normal arteriole
Acute arteriolar thrombosis
Organising arteriolar thrombosis
Acute arteriolar thrombosis
Organising arteriolar thrombosis
“Onion skin lesion”