Thrombotic Microangiopathy, Drug Induced

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Direct endothelial injury or immune mediated
- > 60 drugs reportedly associated with TMA but often difficult to establish causative role
  - Chemotherapeutic agents
  - Anti-vascular endothelial growth factor (VEGF) therapy
    - Transmembrane communication between podocyte and endothelium via VEGF signaling disrupted by anti-VEGF therapy
  - Immunomodulators (CNi, mTORi)
  - Antiplatelet drugs of thienopyridine family
    - ADAMTS13 levels can be severely deficient (< 5%), or ADAMTS13 inhibitor detected
  - Quinine

CLINICAL ISSUES

- Proteinuria ranges from mild to nephrotic
- Mild renal insufficiency or acute renal failure
- Worsening hypertension
- Treatment
  - Withdrawal of offending drug
  - Plasma exchange helpful in some settings
  - Better prognosis if TMA limited to kidney
- Diagnosis
  - Thrombocytopenia
  - Schistocytes on peripheral smear
  - Serum lactate dehydrogenase may be elevated
  - ADAMTS13 levels may be low in TMA due to thienopyridines

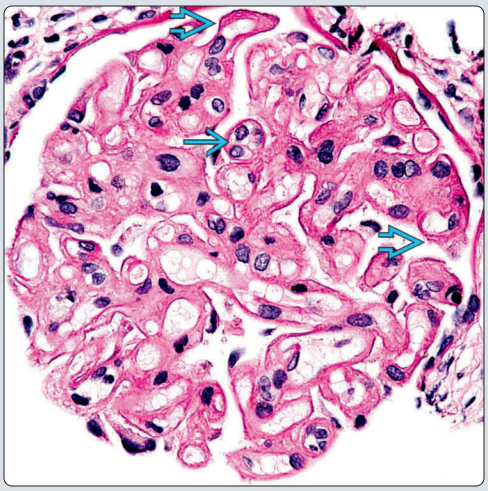
MICROSCOPIC

- Fibrin thrombi and endothelial swelling in glomeruli and arterioles
- Reduplicated GBM in chronic phase

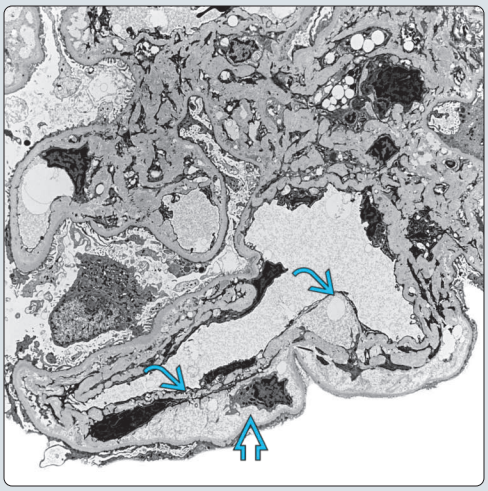
TOP DIFFERENTIAL DIAGNOSES

- TMA due to other causes
- Antibody-mediated rejection in renal allografts

Endothelial Swelling in TMA Due to Sirolimus

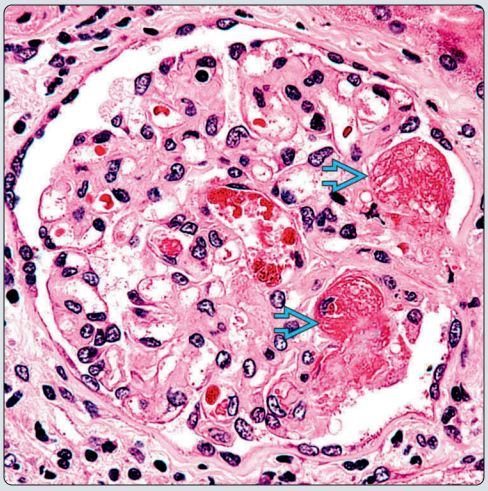


Subendothelial Expansion in TMA

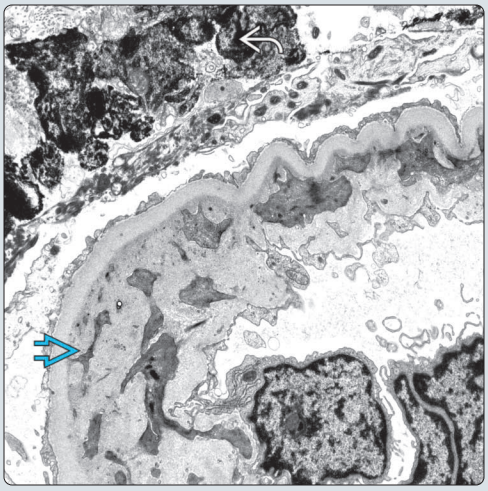


(Left) *The glomerulus demonstrates extensive duplication of basement membranes associated with endothelial swelling and mild mesangiolysis. TMA in this 13 year old with renal allografts is attributed to sirolimus.* **(Right)** *TMA is characterized by expansion of the subendothelial space as seen in this biopsy. The endothelial membrane is lifted off the GBM with subendothelial cells and flocculent material. TMA in this case is due to aflibercept, a VEGF trap.*

Fibrin Thrombi in Cyclosporine Toxicity



GBM Duplication in Anti-VEGF Therapy



(Left) *A 39-year-old woman, 3 weeks post renal transplantation, presented with acute renal failure. Fibrin thrombi are seen in the capillary lumens, and TMA is attributed to cyclosporine toxicity.* **(Right)** *GBM duplication and mesangial cell interposition is seen in a 64 year old with TMA. The patient received aflibercept (VEGF trap) for prostate carcinoma. Fibrin is also seen in the urinary space.*

TERMINOLOGY

Abbreviations

- Thrombotic microangiopathy (TMA)

Definitions

- Atypical hemolytic uremic syndrome (HUS) caused by drugs

ETIOLOGY/PATHOGENESIS

Mechanism of TMA Induction

- Direct endothelial injury due to dose-related toxicity
  - Gradual onset of renal failure over weeks or months
- Immune-mediated dose-unrelated idiosyncratic reaction
  - Sudden onset of severe systemic symptoms with anuric acute renal failure

Implicated Drugs

- > 60 drugs reportedly associated with TMA
  - Often difficult to establish causative role
- Chemotherapeutic agents
  - Mitomycin-C
    - Dose-dependent endothelial toxicity
    - Median time from last dose to development of TMA is 75 days
  - Gemcitabine
    - Endothelial damage causes TMA
    - Median time from initiation of therapy to development of TMA is 6-8 months
    - Withdrawal of drug resolves TMA in > 50%
  - Other agents include bleomycin, cisplatin, daunorubicin, vinblastine, deoxycoformycin
    - Mutation in complement gene *CD46* reported in cisplatin-induced HUS
- Anti-vascular endothelial growth factor (VEGF) therapy
  - Bevacizumab is anti-VEGF monoclonal antibody and aflibercept/VEGF trap is decoy VEGF receptor
    - TMA most common pathology, occurring in ~ 50%
      - Transmembrane communication between podocyte and endothelium via VEGF signaling disrupted by anti-VEGF therapy
      - Also disrupts endothelial cell synthesis of nitric oxide, vasodilator, resulting in endothelial injury and hypertension
      - TMA due to endothelial damage can occur 1 week to 9 months after initiation of therapy
      - Symptoms can occur after discontinuation of drug
      - Some biopsies show associated focal segmental glomerulonephritis (FSGS)
      - Mild proteinuria common with bevacizumab (21-63%)
      - Nephrotic-range proteinuria occurs only in 1-2%
    - VEGF synthesis by podocytes needed for survival of glomerular endothelial cells that express VEGF receptors
    - Other less common pathology (either alone or superimposed on TMA) includes
      - Collapsing glomerulopathy
      - Mesangioproliferative glomerulonephritis
      - Cryoglobulinemic glomerulonephritis
      - Immune-complex mediated focal proliferative glomerulonephritis
      - IgA nephropathy
  - Tyrosine kinase inhibitors that inhibit VEGF receptors (sunitinib, sorafenib, pazopanib)
    - Endothelial damage causes TMA
    - Other pathology FSGS, minimal change disease
      - Likely related arterial thrombosis-related ischemia and hypertension
- Immunomodulators
  - Calcineurin inhibitors (CNi)
    - Cyclosporine and tacrolimus associated with TMA
    - Direct endothelial toxicity due to reduced prostacyclin synthesis or reduced formation of activated protein C
    - Cyclosporine shown to reduce protein expression of clusterin, a fluid phase regulator of terminal complement complex formation
    - Toxicity often seen in first 6 months after transplantation
    - In most, cyclosporine or tacrolimus can be resumed after resolution of TMA or patients may tolerate switching of drug
  - mTORi (mammalian target of rapamycin inhibitors)
    - Sirolimus and everolimus can cause post-transplant de novo TMA and increase risk of recurrent atypical HUS
    - mTOR regulates VEGF production and affects cell cycle
    - Inhibition of VEGF results in endothelial damage
    - Toxicity exacerbated by concomitant calcineurin inhibitors
- Antiplatelet drugs of thienopyridine family
  - Ticlopidine and clopidogrel
    - TMA occurs < 1 month (or even 1 week) of exposure
    - Cause direct endothelial toxicity
    - ADAMTS13 levels can be severely deficient (< 5%), and inhibitor to ADAMTS13 has been detected
    - At risk polymorphisms in *CFH* gene reported in ticlopidine-induced TTP
- Miscellaneous drugs
  - Quinine
    - Treatment of malaria and nocturnal leg cramps
    - Found in herbal supplements and tonic water
    - Patients develop antibodies to platelet glycoprotein Ib/IX or IIb/IIIa complexes
    - TMA not dose related, can occur after years of intake, and recurs after reexposure
  - α-interferon, β-interferon,
    - Antiphospholipid antibodies or anti-ADAMTS13 antibodies can be induced
  - Cocaine
  - Simvastatin
  - Aprotinin
  - Valacyclovir
  - H2-receptor antagonists
  - NSAIDs
  - Vaccines
  - Several antibiotics
  - Hormone supplements

CLINICAL ISSUES

Presentation

- Proteinuria ranges from mild to nephrotic

- Microscopic hematuria
- Mild renal insufficiency or acute renal failure
- Worsening hypertension

Laboratory Tests

- Thrombocytopenia
- Schistocytes may be present on peripheral smear
- Serum lactic acid dehydrogenase may be elevated
- ADAMTS13 levels may be low in TMA due to thienopyridines
- Serum complement and genetic testing maybe helpful in some patients

Treatment

- Withdrawal of offending drug
- Plasma exchange helpful in some settings

Prognosis

- Variable but usually associated with high morbidity and mortality
- Better prognosis if TMA limited to kidney as can occur in renal transplantation

MICROSCOPIC

Histologic Features

- Glomeruli
  - Fibrin thrombi and endothelial swelling
  - Ischemic collapse of capillary tuft
  - Mesangiolysis
  - Duplicated GBM in chronic phase
- Tubulointerstitium
  - Acute tubular injury with degenerating epithelium
  - Tubular atrophy and interstitial fibrosis maybe related underlying chronic kidney disease
- Arterioles and interlobular arteries
  - Endothelial swelling and fibrinoid necrosis
  - No associated arterial inflammation

ANCILLARY TESTS

Immunofluorescence

- Fibrin in glomerular and arterial thrombi
- Nonspecific entrapment of C3, IgM in glomeruli and vessels
- No evidence of immune complexes

Electron Microscopy

- Glomeruli
  - Endothelial swelling and subendothelial expansion by lucent material
    - Loss of endothelial fenestrations
  - Platelets and fibrin in capillary lumens
  - No electron-dense deposits
  - Podocyte foot processes generally well preserved
    - Effacement in sunitinib toxicity associated with severe proteinuria

DIFFERENTIAL DIAGNOSIS

TMA Due to Other Causes

- Rule out: Malignant hypertension, infections, postpartum HUS, scleroderma, HUS/TTP
- Clinical history and serological evidence of autoantibodies help determine etiology

Antibody-Mediated Rejection

- C4d stain and donor-specific antibodies usually positive
- Difficult to distinguish in renal allograft biopsy
- Glomerulitis, tubulointerstitial inflammation, and peritubular capillaritis helpful if present

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Isolated kidney involvement has favorable outcome compared to systemic involvement
- Biopsy features of isolated glomerular TMA associated with favorable prognosis than when arterioles involved

Pathologic Interpretation Pearls

- Etiology cannot be determined on biopsy findings alone
- Thrombocytopenia and peripheral smear schistocytes may not be evident in mild disease

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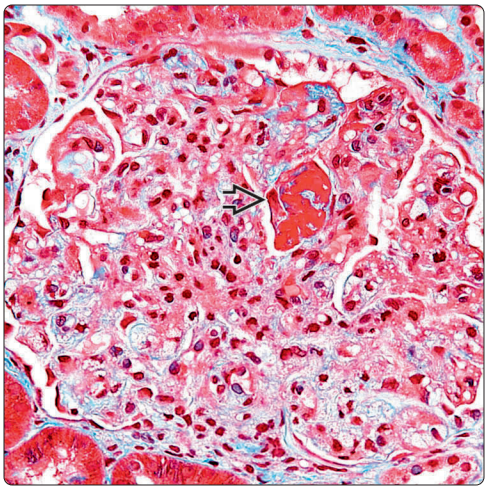
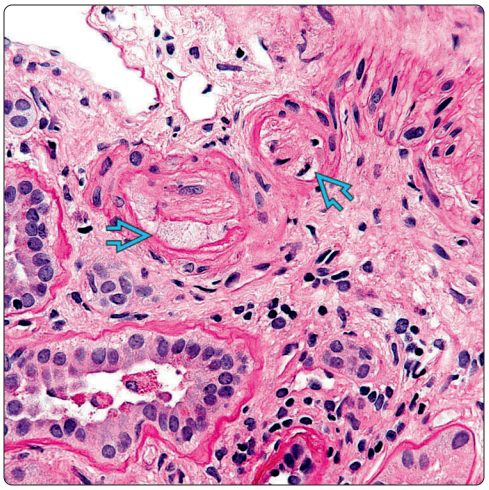
Glomerular Fibrin in Sirolimus Therapy

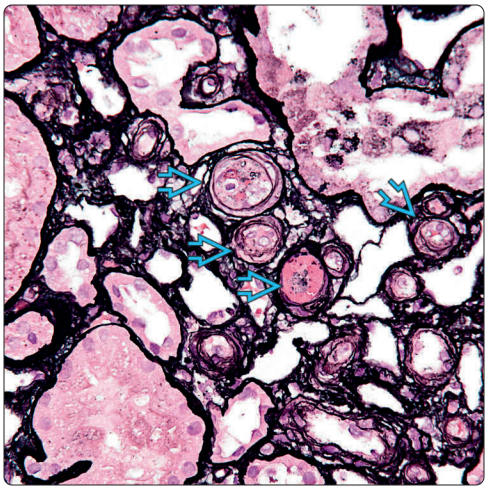


Arteriolar Endothelial Swelling

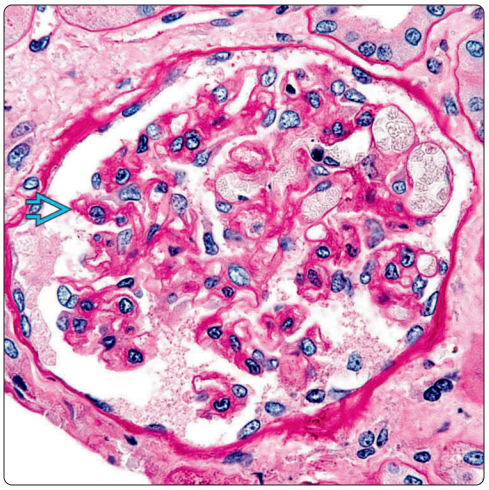


(Left) *Glomerular fibrin thrombus stains red on trichrome in this biopsy with TMA. Histological features do not help distinguish the etiology of TMA, and in this case, it is clinically attributed to sirolimus toxicity.* **(Right)** *An interlobular artery shows severe intimal edema with luminal occlusion. No inflammatory infiltrate is seen to suggest vasculitis. The arteriolar TMA changes in this post transplantation biopsy are due to sirolimus.*

Fibrinoid Necrosis in Arterioles

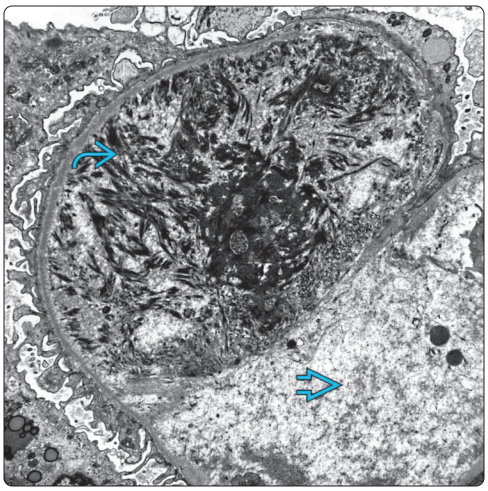


Ischemic Collapse of Glomerular Capillaries

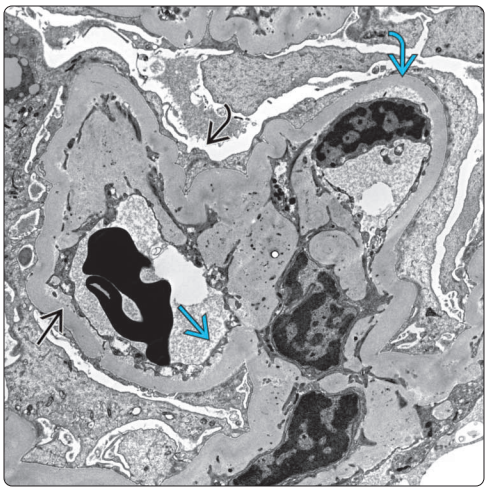


(Left) *Cross sections of arterioles show endothelial swelling with entrapped erythrocytes and apoptotic debris. These TMA changes are due to VEGF trap therapy the patient received for metastatic prostate carcinoma.* **(Right)** *The glomerulus shows collapse of the capillary tuft with wrinkling of the GBM. Characteristic features of TMA with arteriolar and glomerular fibrin thrombi are seen elsewhere in this biopsy from a patient with cyclosporine toxicity.*

Fibrin Thrombi With Bevacizumab



TMA With Proteinuria and TMA Due to Sunitinib



(Left) *A glomerular capillary is occluded with fibrin tactoids and depolymerized fibrin. The endothelium is absent. This patient on bevacizumab for neuroendocrine carcinoma presented with proteinuria and TMA.* **(Right)** *This diabetic patient developed proteinuria on sunitinib for ~ 10 months. Glomerular endothelial cells show loss of fenestrations, detachment, vacuolization, and subendothelial lucency. Extensive foot process effacement is present. The thickened GBM is due to diabetes.*