COVID-19 Nephropathies

KEY FACTS

ETIOLOGY/PATHOGENESIS

- Virus binds to angiotensin converting enzyme 2
- Expressed on alveolar cells in lung, endothelium, vascular smooth muscle, podocytes, proximal tubules, intestinal epithelium, nasopharynx
- Endothelial and epithelial cytotoxicity
- Cytokine "storm"
- Coagulopathy
- Collapsing glomerulopathy associated with *APOL1* risk alleles

CLINICAL ISSUES

- Cough, fever, dyspnea, muscle aches, fatigue, diarrhea
- AKI during infection in 3-9% of patients
- Proteinuria, may be nephrotic-range
- AKI is independent risk factor for mortality

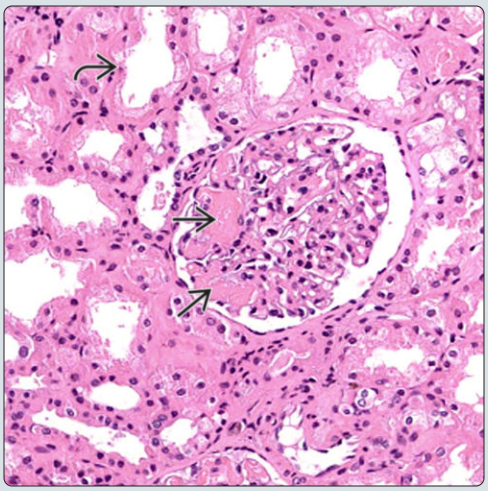
MICROSCOPIC

- Acute tubular injury
- Glomeruli
  - Endothelial swelling and vacuolization, fibrin thrombi
  - Collapsing glomerulopathy (associated with APOL1 risk alleles)
  - Variety of other patterns of glomerulopathy and glomerulonephritis have been observed
- Electron microscopy
  - Endothelial injury
  - Purported viral particles 65-136 nm in diameter with spikes; likely clathrin-coated vesicles
    - Present in podocytes and tubular epithelium

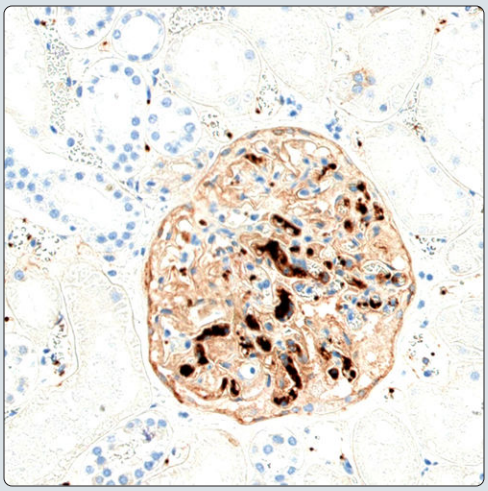
DIAGNOSTIC CHECKLIST

- Tubular epithelial and podocyte damage
- Endothelial damage contributing to thrombotic microangiopathy

Glomerular Thrombi and Acute Tubular Injury

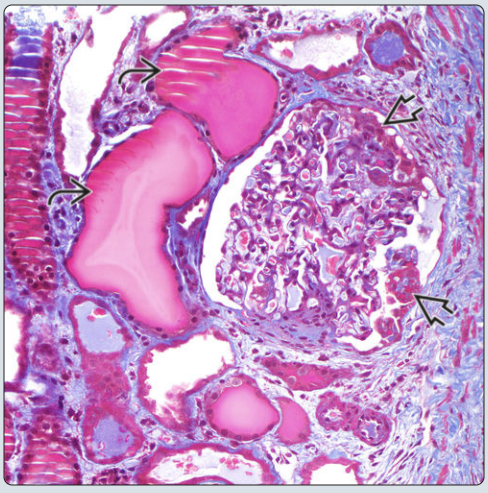


Platelet Thrombi in Glomeruli

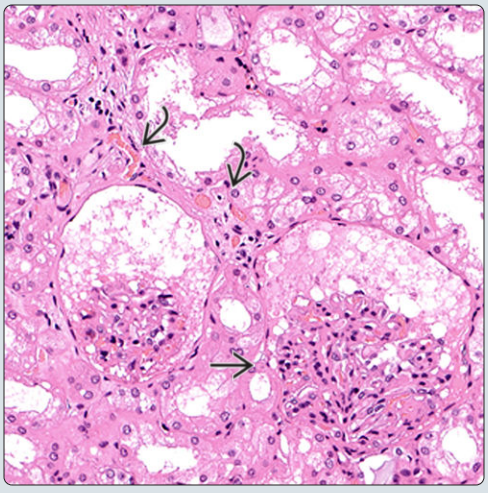


(Left) *Kidney from patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who died in Wuhan is shown. Glomerular thrombi are indications of the thrombotic microangiopathy that occurs in COVID-19. Tubules show marked loss of brush borders. (Courtesy C. Zhang, MD and H. Su, MD.)* **(Right)** *Thrombotic microangiopathy is a common and serious consequence in COVID-19 disease. Platelets can be demonstrated in glomeruli with anti-CD61, as in this autopsy case. (Courtesy J. Stone, MD, PhD.)*

Collapsing Glomerulopathy



Glomerular Ischemic Collapse and Peritubular Capillary Congestion



(Left) *A biopsy from a patient with COVID-19 infection shows a lesion of collapsing focal segmental glomerulosclerosis with podocyte proliferation and tubular microcysts.* **(Right)** *Kidney from a patient who died in Wuhan is shown. Glomerular ischemic collapse is evident as well as widespread acute tubular injury with vacuoles and congestion in peritubular capillaries. (Courtesy C. Zhang, MD and H. Su MD.)*

TERMINOLOGY

Definitions

- Kidney disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus

Caveat

- Knowledge of virus and pathology are still emerging and not fully defined

ETIOLOGY/PATHOGENESIS

Coronavirus SARS-CoV-2

- Enveloped, (+) strand RNA virus
- Believed to originate in bats then pangolins

Pathogenesis

- Possible direct viral infection: Virus binds to angiotensin converting enzyme 2 (*ACE2*), expressed on lung alveolar cells, vascular endothelium and smooth muscle, intestinal epithelium, nasopharynx, and possibly podocytes and proximal tubules
  - Serine protease *TMPRSS2* needed for cellular entry
  - Podocytes and proximal tubule cells express *ACE2* and *TMPRSS2*
  - Endothelium and pulmonary epithelium cytotoxicity
    - Acute lung injury, thrombotic microangiopathy
  - SARS-CoV-2 RNA detected in glomeruli by in situ hybridization; SARS-CoV-2 protein detected by IF in podocytes, glomerular endothelial cells, and tubular epithelial cells (Puelles 2020)
- Cytokine "storm"
- Coagulopathy
- Ischemia

Genetics

- Collapsing glomerulopathy associated with *APOL1* risk alleles

CLINICAL ISSUES

Epidemiology

- 1st known outbreak in Wuhan, China, December 2019
  - Became pandemic in January-March 2020
  - > 17 million people infected worldwide as of July 2020
- Incubation period 2-14 days
- Increased risk among Hispanic and Black patients

Presentation

- Cough, fever, dyspnea, muscle aches, fatigue, diarrhea, anosmia
- Acute respiratory distress syndrome in 33% of patients
- Acute kidney injury (AKI) during infection in 3-9% of patients
  - AKI in 28-46% of hospitalized patients
  - ~ 5% of ICU patients require dialysis
  - Higher mortality rate among patients with kidney involvement
- Proteinuria in 45-50%
  - Nephrotic-range proteinuria in 53% in one antemortem biopsy series (Kudose 2020)
- Hematuria in 11%
- Among hospitalized patients in China
  - 34-60% proteinuria, 44% microhematuria
- ≥ 25% are symptomless (asymptomatic or "presymptomatic")
- Nephrotic syndrome
  - Recent African descent (with *APOL1* risk alleles)
- Kawasaki-like syndrome in children
  - Rash, fever, cardiac symptoms

Laboratory Tests

- PCR detects virus in nasal swabs in active infection
- Cytokine storm (IL2, IL6, IL7, IL10, TNFα, IFNγ, G-CSF, CXCL10, CCL2, CCL3)
- ↑ ESR, CRP, ferritin, D-dimer, LDH, lymphopenia
- Serologic tests for past exposure (IgM/IgG)
  - IgM serologic tests lack specificity

Treatment

- Supportive
- Remdesivir
- Dexamethasone for severe lung involvement
- Many therapies/drugs under investigation
  - Transfer of convalescent immunoglobulin

Prognosis

- Fatal in ~ 15% of hospitalized patients
  - Much higher risk in patients > 70 years and those with preexisting diabetes, obesity, hypertension, lung or heart disease
- AKI is independent risk factor for mortality
- Vaccines under development

MICROSCOPIC

Histologic Features

- Kidney tissue findings
  - 2 antemortem kidney biopsy series as of July 2020, also autopsy studies of kidney pathology
  - Most common findings are acute tubular injury, collapsing glomerulopathy, thrombotic microangiopathy/endothelial cell injury
  - Less common findings
    - Glomerulonephritis, acute pyelonephritis, arterial inflammation
- Glomerular disease patterns
  - Endothelial injury
    - Endothelial swelling
    - Capillary thrombi
  - Collapsing glomerulopathy
  - Focal segmental glomerulosclerosis
  - Minimal change disease
  - Membranous glomerulonephritis
  - Diabetic glomerulosclerosis (preexisting)
    - Patients with diabetes more likely to have severe COVID-19 infection
  - Crescentic transformation of preexisting lupus nephritis
  - Anti-GBM nephritis
  - ANCA-associated pauci-immune glomerulonephritis
- Tubules
  - Acute tubular injury
    - Loss of brush borders
    - Detachment, necrosis, vacuolization

  - Cellular debris in tubular lumens
  - Pigmented casts, calcification
  - Myoglobin casts
  - Hemosiderin granules within tubular epithelium
  - Tubulitis
  - Oxalate crystals (rare)
- Interstitium
  - Edema, little infiltrate
  - Erythrocyte aggregation in peritubular capillaries
- Vessels
  - Congestion in peritubular capillaries
  - Rare arterial inflammation, attributed to pyelonephritis
- Kidney transplant pathology
  - Acute T-cell-mediated rejection (Banff type 2)
  - Cortical infarct
  - Acute tubular injury
  - Focal segmental glomerulosclerosis with collapsing features
- Pulmonary pathology
  - Acute interstitial pneumonia with diffuse alveolar damage
  - Major pulmonary thromboemboli with pulmonary infarcts
  - Microvascular fibrin deposition, microthrombi in arterioles
  - Interstitial lymphocytic pneumonitis with intraalveolar fibrin deposits
- Cardiac pathology
  - Rarely lymphocytic myocarditis
  - Cardiac vasculitis (Kawasaki syndrome) in children

ANCILLARY TESTS

Immunohistochemistry

- Viral antigen sometimes demonstrated in tubules
  - Anti-SARS-CoV nucleoprotein (Sino Biological, Beijing)
  - Inconsistently observed

Immunofluorescence

- No common findings
  - Rare cases with membranous glomerulonephritis pattern
  - 1 case with IgG immune complexes in GBM
  - 1 IgA case (presumed incidental)
  - 1 anti-GBM nephritis

Electron Microscopy

- Purported viral particles 65-136 nm in diameter with corona of spikes
  - Described in podocytes, proximal tubules, and endothelial cells
  - Distinction from multivesicular bodies/exosomes difficult
  - Likely represent
- Podocyte detachment and vacuolization
- Endothelial swelling, vacuolization, proliferation
  - Subendothelial lucency
- Tubuloreticular inclusions in endothelial cells (occasional)

NanoString Analysis

- No viral RNA in kidney in collapsing glomerulopathy biopsies
- Viral RNA detected in lung and kidney at autopsy

DIFFERENTIAL DIAGNOSIS

Acute Tubular Injury, Other Causes

- Detection of virus in kidney tissue is inconsistent

DIAGNOSTIC CHECKLIST

Clinically Relevant Pathologic Features

- Tubular epithelial and podocyte damage
- Endothelial damage contributing to thrombotic microangiopathy

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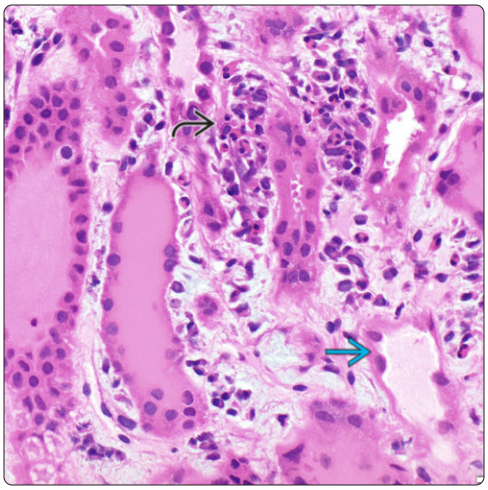
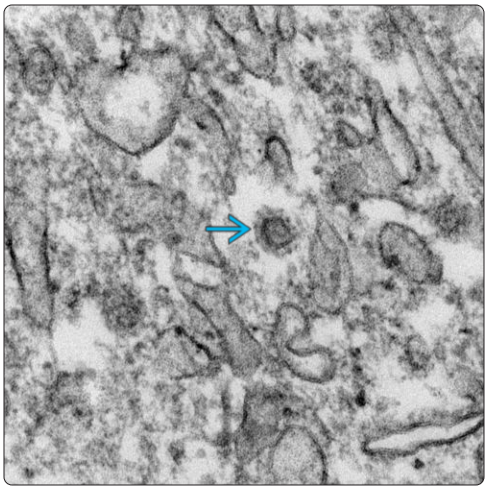
Tubular Injury and Interstitial Inflammation

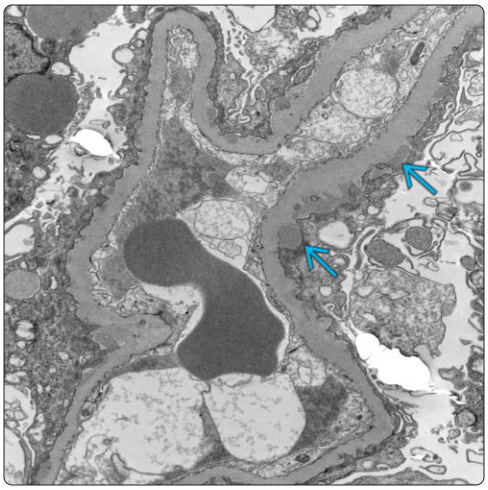


Clathrin Coated Vesicle

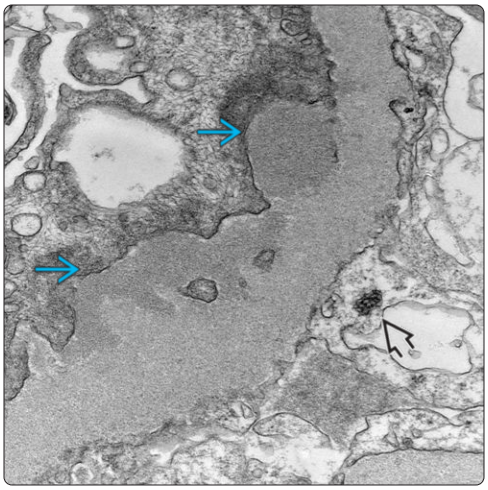


(Left) *A biopsy from a patient with COVID-19 infection and collapsing glomerulopathy also showed acute tubular injury and an interstitial nephritis with increased plasma cells, which may be related to the glomerulopathy.* **(Right)** *A probable clathrin coated vesicle is seen within the tubular epithelial cell cytoplasm in a patient with COVID-19 and acute tubular necrosis.*

Membranous Glomerulonephritis

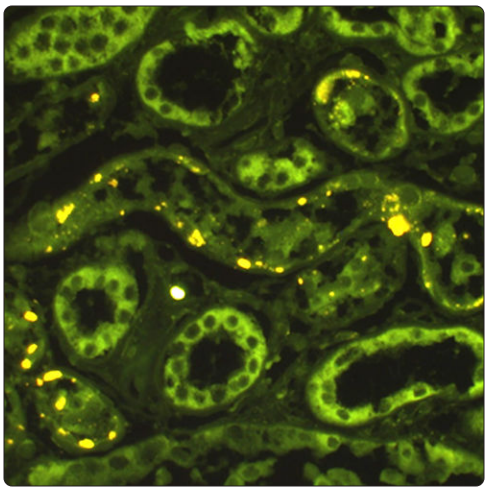


Membranous Glomerulonephritis

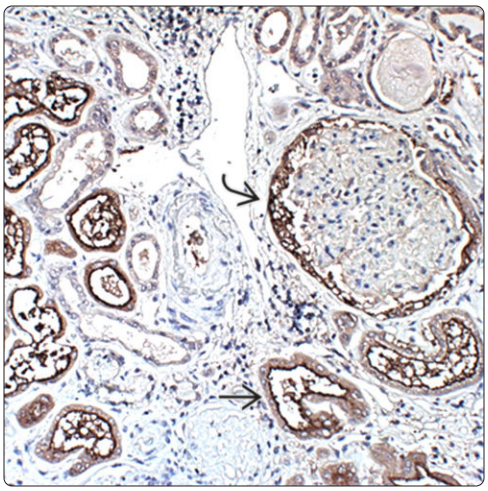


(Left) *A patient with COVID-19 had acute kidney injury and nephrotic range proteinuria. A kidney biopsy showed membranous glomerulonephritis. Subepithelial deposits are seen.* **(Right)** *A patient with COVID-19 had acute kidney injury and nephrotic range proteinuria. A kidney biopsy showed membranous glomerulonephritis. Subepithelial deposits are seen, as is a tubuloreticular inclusion in an endothelial cell.*

SARS-CoV Nucleoprotein in Proximal Tubules



ACE2 Expression in COVID-19



(Left) *Anti-SARS-CoV nucleoprotein shows antigen in proximal tubules in an autopsy sample from Wuhan. Viral particles were also detected in proximal tubules. Antibody 40143-T62, Sino Biological, Beijing. (Courtesy C. Zhang, MD and H. Su, MD.)* **(Right)** *ACE2 is increased in the proximal tubules and parietal epithelial cells in this patient who died of COVID-19 in Wuhan. The peritubular capillaries are negative. Normal kidney shows ACE2 only in proximal tubules. (Courtesy C. Zhang, MD and H. Su, MD.)*