SARS Pneumonia

KEY FACTS

TERMINOLOGY

- Infectious viral diseases belonging to human *Coronaviridae* family of enveloped, positive-sense, single-stranded RNA viruses
  - SARS: Severe acute respiratory syndrome secondary to SARS-CoV infection
  - MERS: Middle East respiratory syndrome secondary to MERS-CoV infection
  - COVID-19: "Coronavirus disease," refers specifically to 2019 novel coronavirus (SARS-CoV-2)

ETIOLOGY/PATHOGENESIS

- Acute lung injury secondary to coronavirus infection
- May involve
  - Immune system dysfunction
  - Hyperinduction of chemokines and cytokines (TNF-α, CXCL9, CXCL10, IL-6, IL-8, interferons etc.)
  - Deregulation of complement system (specifically SARS-CoV-2)
- Transmission via close contact (primary mode of transmission for MERS-CoV), droplet, and/or airborne

CLINICAL ISSUES

- Clinical pictures are highly complex ranging from asymptomatic to mild respiratory illness to acute respiratory distress syndrome (ARDS) and death
- More severe disease generally seen in elderly, immunocompromised, and those with cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, chronic kidney disease, and/or obesity
- Mortality rates range from <2% (COVID-19) to up to 35% (MERS)

IMAGING

- Predominant pattern on CT imaging is diffuse, bilateral, ill-defined ground-glass opacification with consolidation in advanced cases
- If fibrosis develops, persistent ground-glass opacities and reticular opacities may be identified

MACROSCOPIC

- Congestion and fullness of lung parenchyma

MICROSCOPIC

- DAD and/or AFOP patterns of acute lung injury
- Early stage of disease characterized by features of viral pneumonia with extensive edema, congestion, and no hyaline membranes
- Multinucleated giant cells may be scattered through lung parenchyma
- Rare intracytoplasmic inclusions may be seen
- Multiple fibrin thrombi may be present in small pulmonary arteries
- Complement-associated microvascular injury and thrombosis reported in small subset of COVID-19
- Viral involvement of numerous organs reported for SARS, MERS, and COVID-19

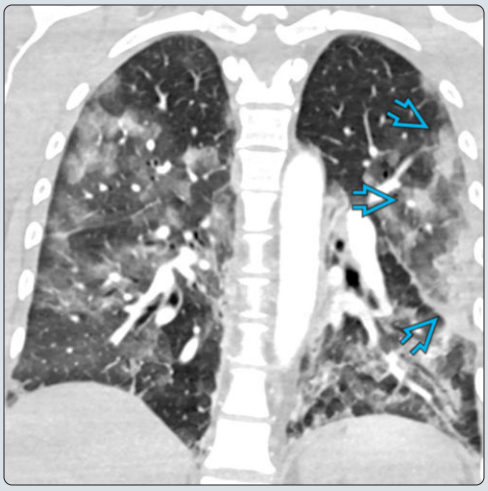
ANCILLARY TESTS

- Specific antibodies for SARS-CoV, MERS-CoV, and SARS-CoV-2 exist but are not widely available
- Antibodies (C4d, C5b-9, MASP2) for complement deposition may be helpful in identifying complement-mediated vascular injury in SARS-CoV-2
- In situ hybridization may detect viral RNA within type II pneumocytes, as well as alveolar macrophages
- Real-time reverse-transcriptase PCR assays allow for qualitative detection of viral nucleic acids in patient samples with SARS, MERS, and COVID-19
- Viral particles may be identified by electron microscopy (EM)

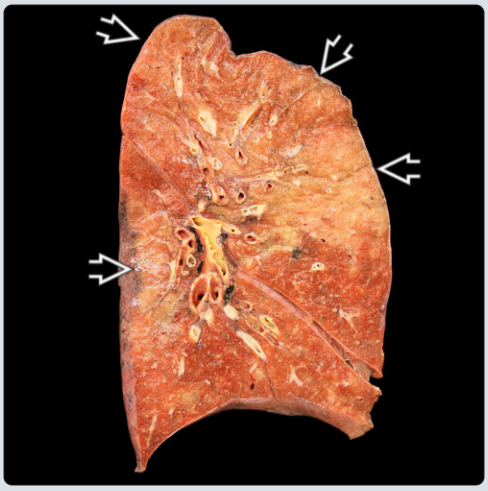
TOP DIFFERENTIAL DIAGNOSES

- Avian influenza A (H5N1)
- Diffuse alveolar disease of other etiologies

CT Scan of Advanced-Stage COVID-19



Gross Image of COVID-19 Lung



(Left) *A representative CT scan of advanced-stage COVID-19 demonstrates numerous foci of ground-glass opacity with multifocal consolidations. (Courtesy Dr. Brent Little.)* **(Right)** *A parasagittal section of the lung from a COVID-19 autopsy shows multifocal consolidations consistent with an advanced stage of the disease +/- superimposed bronchopneumonia. (Courtesy of Dr. Isaac Solomon and Robert Padera.)*

TERMINOLOGY

Abbreviations

- SARS: Severe acute respiratory syndrome
- MERS: Middle East respiratory syndrome
- COVID-19: "Coronavirus disease," refers specifically to 2019 novel coronavirus (SARS-CoV-2)

Definitions

- Infectious viral diseases belonging to human *Coronaviridae* family of enveloped, positive-sense, single-stranded RNA viruses

ETIOLOGY/PATHOGENESIS

Infectious Agents

- SARS coronavirus (**SARS-CoV**)
- MERS coronavirus (**MERS-CoV**)
- SARS coronavirus 2 (**SARS-CoV-2**)

Pathogenesis

- Highly complex, may cause disease ranging from asymptomatic to mild respiratory illness to ARDS and death
- May involve
  - Immune system dysfunction
  - Hyperinduction of chemokines and cytokines (TNF-α, CXCL9, CXCL10, IL-6, IL-8, interferons etc.)
  - Compromised cellular immune response
  - Deregulation of complement system (specifically SARS-CoV-2)
- Angiotensin-converting enzyme 2 (ACE2) receptor identified as functional receptor for SARS-CoV, as well as SARS-CoV-2
- Dipeptidyl peptidase 4 (DPP4) receptor identified as functional receptor for MERS-CoV
- Transmission
  - Close contact (primary mode of transmission for MERS-CoV)
  - Droplet transmission
  - Airborne transmission

CLINICAL ISSUES

Epidemiology

- SARS-CoV
  - Initial outbreak identified in 2002 in Guangdong province of southern China, subsequently spread to 26 countries
  - Overall incidence difficult to establish, but, at end of initial epidemic in 2003, 8,096 probable cases and 774 deaths had been reported
  - More severe disease generally seen in elderly and immunocompromised
- MERS-CoV
  - Initial outbreak identified in 2012 in Saudi Arabia, with 27 additional countries reporting cases
  - ~ 1,917 cases and 677 deaths reported to date
  - 80% of cases reported by Saudi Arabia
- SARS-CoV-2
  - Initial outbreak identified in December of 2019 in city of Wuhan, Hubei Province, China, subsequently spread to ~ 200 countries
  - As of April 28, 2020, ~ 3.6 million cases and 212,000 deaths have been reported
    - ~ 988,490 cases and 56,256 deaths in United States
  - More severe disease generally seen in elderly, immunocompromised, and those with cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, chronic kidney disease, and/or obesity
    - Male patients tend to have worse prognosis than female patients

Presentation

- Influenza-like symptoms common to all three viruses, including fever, cough, chills, malaise, shortness of breath
- Pneumonia may be present
- Gastrointestinal symptoms and diarrhea may occur
- Loss of smell and taste reported in COVID-19
- Other organ involvement, including CNS, skin, renal, cardiac, testes, muscle, and other tissues, has been reported

Treatment

- No specific treatments or vaccines currently available for SARS/MERS/COVID-19
- Mild cases may only require minimal supplemental oxygen by nasal cannula
- Severe cases require ICU admission, intubation, and ventilator support
- Efficacy of additional therapies, such as steroids, antiviral, antimalarial, and immune modulating drugs, remains controversial

Prognosis

- SARS-CoV
  - Mortality: ~ 10% of reported cases
  - Elderly patients (>60 yr of age) account for 50% of fatal cases
  - In younger patients, mortality has been estimated to be <10%
  - Mortality appears to be higher in male patients than female patients
- MERS-CoV
  - Mortality: ~ 35% of reported cases
- SARS-CoV-2
  - Mortality: ~ 1-5% of reported cases; however, true value likely lower (<2%) due to under-reported asymptomatic individuals
  - Majority of cases occur in middle aged (40s-50s) to elderly (60s-70s)
  - Mortality appears to be higher in male patients than female patients, as well as in elderly populations

IMAGING

General Features

- Predominant pattern on CT imaging is diffuse, bilateral, ill-defined ground-glass opacification with consolidation in advanced cases
- If fibrosis develops, persistent ground-glass opacities and reticular opacities may be identified

MACROSCOPIC

General Features

- Congestion and fullness of lung parenchyma

MICROSCOPIC

Histologic Features

- SARS-CoV
  - Diffuse alveolar damage (DAD) pattern of acute lung injury
    - Exudative phase shows edema, hyaline membrane formation, type II pneumocyte hyperplasia
    - Proliferative phase of DAD shows organizing pneumonia-like histology with fibroblastic plugs in alveolar spaces
    - Longstanding disease (DAD/ARDS) may lead to development of pulmonary fibrosis
  - Acute fibrinous and organizing pneumonia (AFOP) pattern of acute lung injury may be seen along with DAD pattern and may be predominant in some patients
  - Multinucleated giant cells may be scattered through lung parenchyma
  - Scattered foci of vasculitis may be present
  - Prominent intracytoplasmic inclusions are not feature of SARS-CoV although may be seen by EM
- MERS
  - Shows similar histology to SARS-CoV with DAD pattern of acute lung injury
- SARS-CoV-2
  - Shows similar histology to SARS-CoV with acute lung injury; DAD pattern is often predominant
  - Early stage of disease may only show extensive edema and congestion with features of viral pneumonia (increased cellularity of alveolar walls and perivascular inflammation)
  - Multinucleated giant cells may be scattered through lung parenchyma
  - Rare intracytoplasmic inclusions may be seen
  - Multiple fibrin thrombi may be present in small pulmonary arteries, reflecting hypercoagulable state
  - Complement-associated microvascular injury and thrombosis have been reported in small subset
- Viral involvement of numerous organs reported for SARS, MERS, and COVID-19
  - Gastrointestinal tract, hematopoietic system, CNS, skeletal muscle, cardiovascular system, thyroid, testes, and liver
- Bacterial pneumonia may be superimposed

ANCILLARY TESTS

Immunohistochemistry

- Specific antibodies for SARS-CoV, MERS-CoV, and SARS-CoV-2 exist but are not widely available
  - SARS-CoV positivity identified predominantly within type II pneumocytes, as well as alveolar macrophages
  - SARS-CoV-2 positivity identified within type II pneumocytes, as well as alveolar macrophages
- Antibodies (C4d, C5b-9, MASP2) for complement deposition may be helpful in identifying complement-mediated vascular injury in SARS-CoV-2

In Situ Hybridization

- RNA in-situ hybridization may detect viral RNA within type II pneumocytes, as well as alveolar macrophages

PCR

- Real-time reverse transcriptase PCR assays allow for qualitative detection of viral nucleic acids in patient samples with SARS, MERS, and COVID-19
  - Current SARS-CoV-2 RT-PCR assays usually contain multiple primer sets targeting viral nucleocapsid genes (N1, N2) specific to SARS-CoV-2

Serologic Testing

- ELISA available to determine prior exposure and immune status
- Cytokine/inflammatory marker testing may play role in managing "cytokine storms"

Electron Microscopy

- Identification of viral particles

DIFFERENTIAL DIAGNOSIS

Avian Influenza A (H5N1)

- Although it also shows DAD, avian influenza follows more aggressive course with marked necrosis and hemorrhage in lungs
- Multinucleated giant cells present in SARS are not present in avian influenza

DAD of Other Etiologies

- Bacterial pneumonia and/or aspiration can be cause of DAD in patients with SARS, MERS or COVID-19

DIAGNOSTIC CHECKLIST

Pathologic Interpretation Pearls

- DAD and/or AFOP patterns of acute lung injury
- Multinucleated giant cells may be scattered through lung parenchyma, but viral cytopathic changes are rare
- Large number of fibrin thromboses may reflect hypercoagulable state

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3. Zhang H et al: Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med. ePub, 2020
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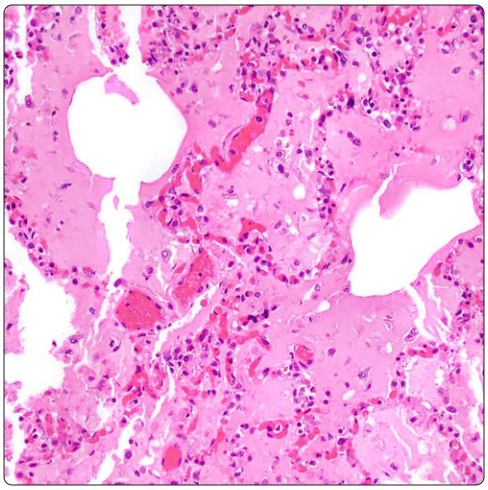
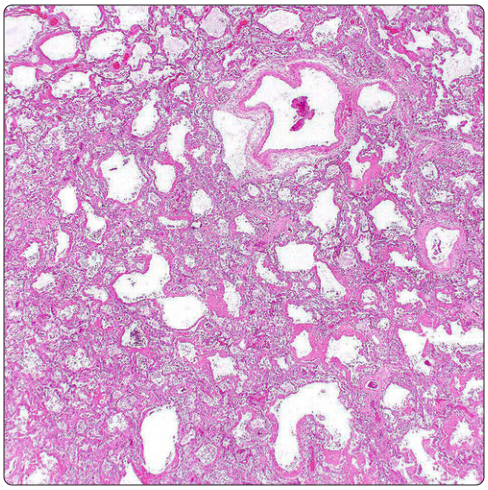
Edema and Congestion

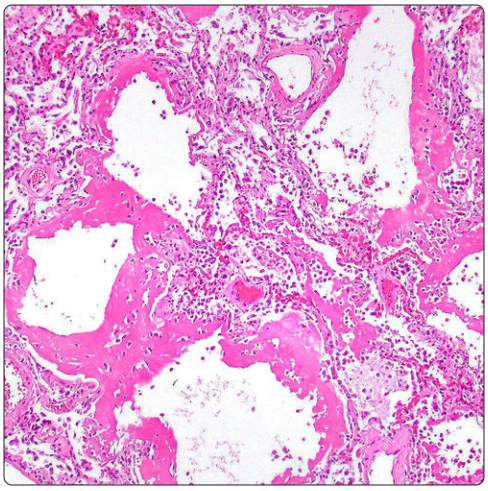


Exudative Phase of DAD

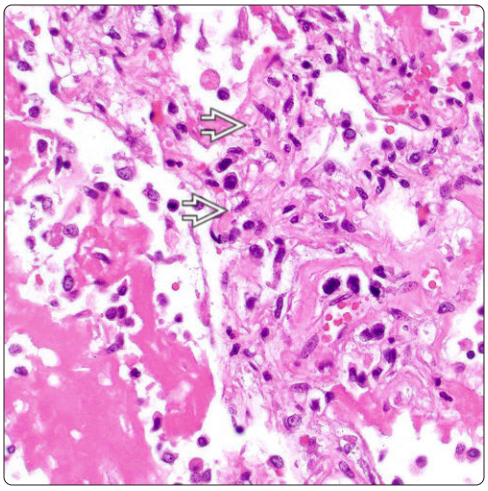


(Left) *An early-phase image of COVID-19 shows extensive areas of edema and congestion with increased cellularity of alveolar walls but no hyaline membranes (magnification 200x). Of note, inflammatory infiltrate may be limited to perivascular areas in the early phase.* **(Right)** *A representative section from a COVID-19 autopsy demonstrates the architecturally intact lung parenchyma diffusely involved by hyaline membrane formation consistent with the exudative phase of DAD (magnification 20x).*

Exudative Phase of DAD

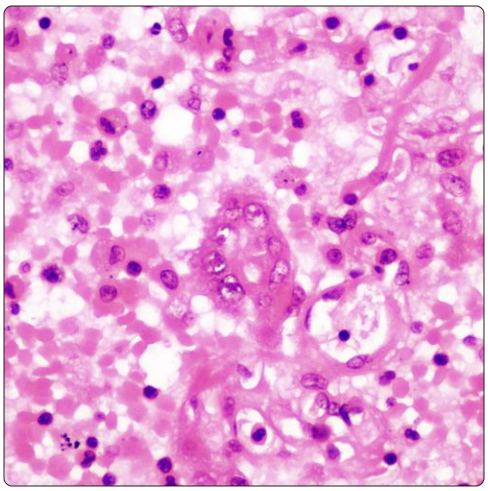


Early Organizing Phase of DAD

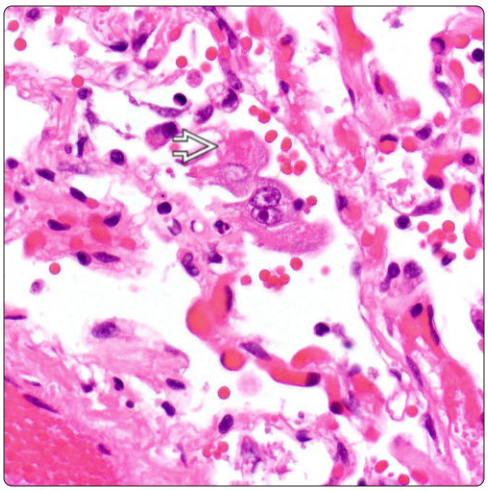


(Left) *Higher-power magnification shows multiple alveoli lined by thick hyaline membranes, a feature commonly seen in fulminant cases of SARS or COVID-19 (magnification 100x).* **(Right)** *In this autopsy from a COVID-19 patient, there are scattered foci with a spindle cell proliferation ⇨, leading to mild thickening of alveolar walls along with prominent hyaline membranes, consistent with the early organizing phase of DAD (magnification 400x).*

Multinucleated Giant Cells



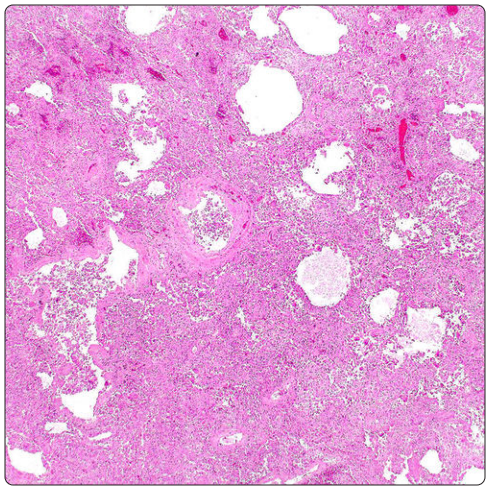
Viral Cytopathic Changes



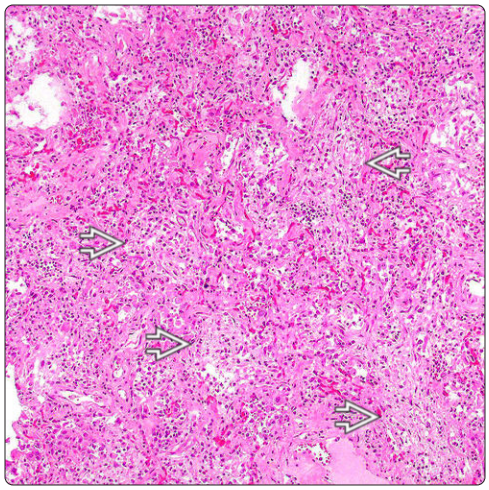
(Left) *Scattered, usually rare, multinucleated giant cells may be seen throughout the lung parenchyma in cases of SARS or COVID-19. Of note, prominent intracytoplasmic inclusions are not a feature of SARS.* **(Right)** *Viral cytopathic changes are rarely seen in COVID-19 lungs. This rare example shows an intracytoplasmic inclusion ⇨ in a detached cluster of enlarged type II pneumocytes, suggestive of viral cytopathic changes (magnification 600x).*

(Left) *The proliferative phase of DAD is characterized by marked alveolar wall thickening and collapse of alveoli, resulting in scattered large airspaces in the "consolidative"-appearing background (magnification 20x).* **(Right)** *Areas with an organizing pneumonia pattern may be seen and characterized by fibromyxoid proliferation with scattered inflammatory cells filling alveolar spaces (magnification 100x).*

Proliferative Phase of DAD

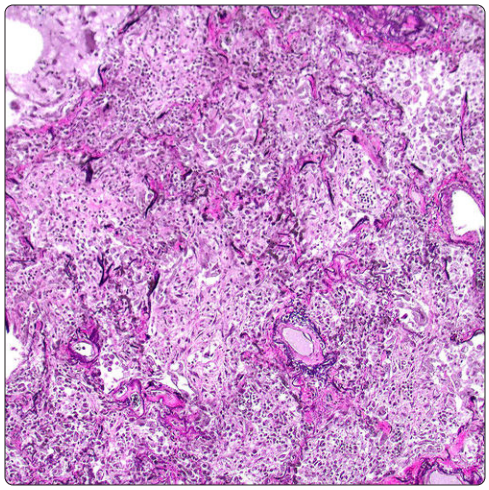


Organizing Pneumonia - Pattern of Fibrosis

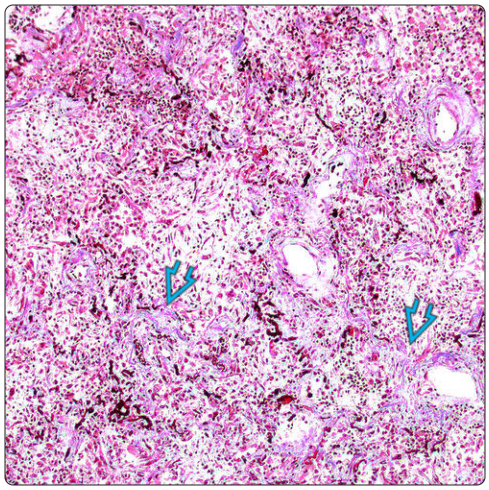


(Left) *Elastic stain highlights intact alveolar framework (black lines) in the background of the fibromyxoid proliferation filling alveolar spaces (magnification 100x).* **(Right)** *Trichrome stain reveals a lack of mature collagen in the intraalveolar fibromyxoid proliferation consistent with organizing fibrosis. Of note, alveolar walls show mild mature collagen fibrosis highlighted blue in this case (magnification 100x).*

Organizing Pneumonia - Pattern of Fibrosis

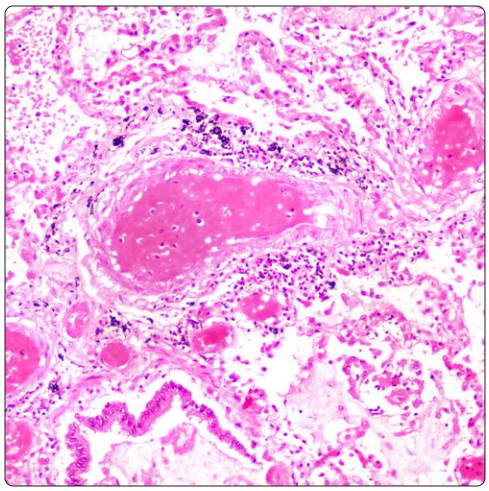


Organizing Pneumonia - Pattern of Fibrosis

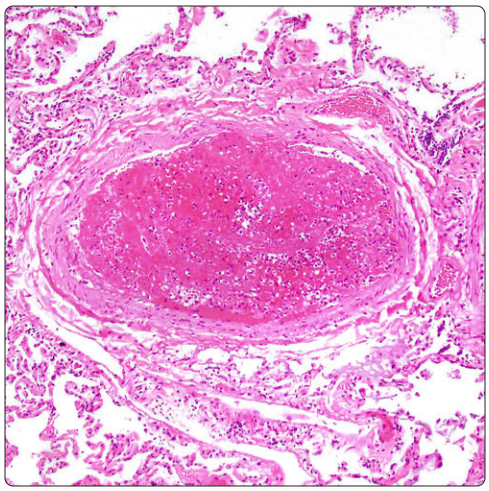


(Left) *SARS may show focal areas of vascular damage in which inflammatory infiltrates infiltrate vessel walls (magnification 200x).* **(Right)** *COVID-19 lungs may have a large number of fibrin thrombi in small pulmonary arteries, beyond the range seen in conventional DAD, reflecting a hypercoagulable state (magnification 100x).*

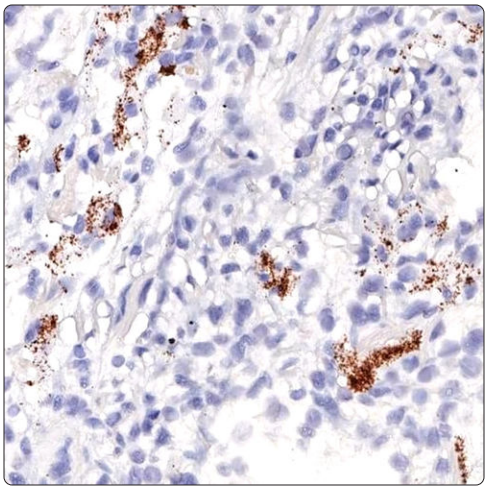
Vascular Damage



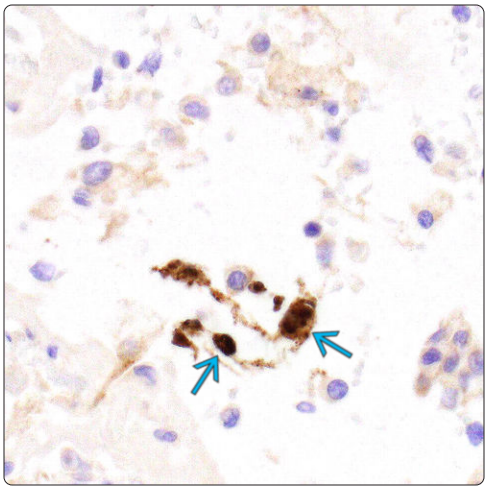
Fibrin Thrombus



RNA In Situ Hybridization for COVID-19

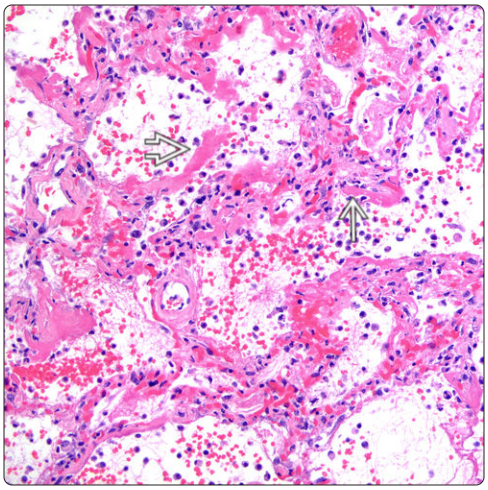


SARS Nucleocapsid Immunostain

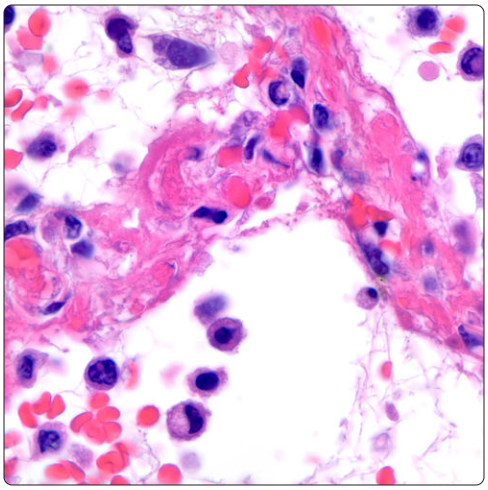


(Left) *RNA in situ hybridization for COVID-19 demonstrates high viral RNA copy number within type II pneumocytes (magnification 200x). (Courtesy Dr. Gerard Nuovo.)* **(Right)** *SARS nucleocapsid immunostain highlights type II pneumocytes in an autopsy section from a patient with COVID-19 (magnification 600x).*

Complement-Associated Microvascular Injury

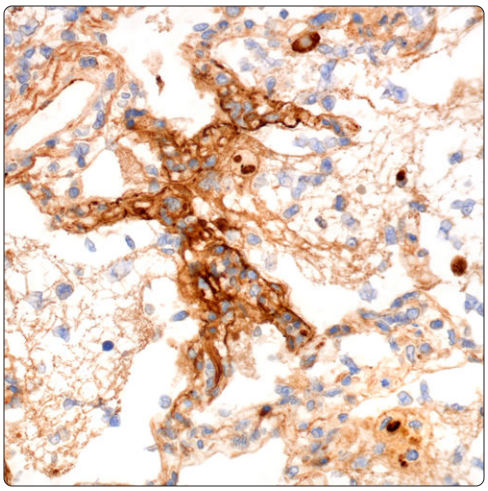


Complement-Associated Microvascular Injury

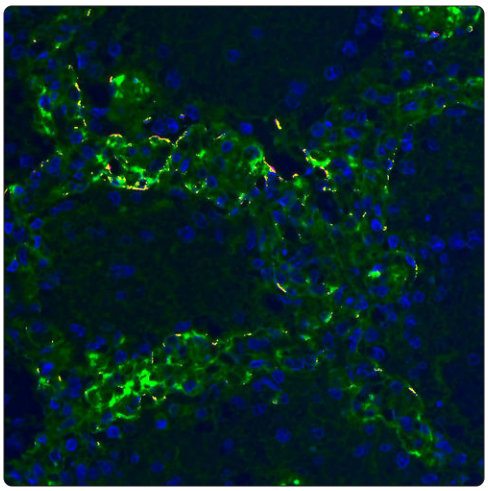


(Left) *A small subset of COVID-19 patients exhibit septal capillary injury with significant mural and luminal fibrin deposition in capillaries and permeation of the inter-alveolar septa by neutrophils. Features of classic DAD are not present (magnification 200x). (Courtesy Drs. Cynthia Magro and J. Justin Mulvey.)* **(Right)** *Septal capillary injury is characterized by capillary wall disruption accompanied by fibrin deposition and red cell extravasation (magnification 1,000x). (Courtesy Drs. Cynthia Magro and J. Justin Mulvey.)*

Complement-Associated Microvascular Injury



Colocalization of Complement Components with SARS-CoV2



(Left) *Extensive C4d deposition is seen throughout the lung parenchyma, with striking septal capillary localization (magnification 200x). (Courtesy Drs. Cynthia Magro and J. Justin Mulvey.)* **(Right)** *Merged immunofluorescence of C4d (green) and SARS-CoV2 spike glycoprotein (red) reveals a significant degree of C4d and SARS-CoV2 colocalization (yellow) within the alveolar septa, suggestive of activation of complement pathways with SARS-CoV2 spike glycoprotein. (Courtesy Drs. Cynthia Magro and J. Justin Mulvey.)*