COVID-19-Related Pathology and Pediatric Multisystem Inflammatory Syndrome

KEY FACTS

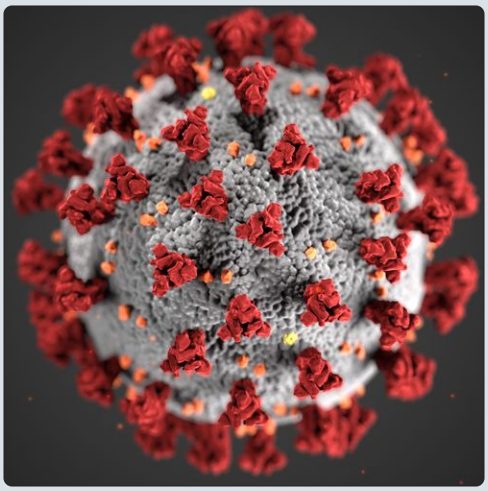
CLINICAL ISSUES

- Children comprise 5% of infections and < 1% of hospitalizations
- 90% of infected pediatric patients are asymptomatic or demonstrate mild to moderate symptoms
  - Common symptoms: Fever, cough, shortness of breath, mild gastrointestinal symptoms
- However, small proportion have been critically ill, requiring intensive care with reported fatalities
  - Children with comorbidities have increased risk of critical illness
  - Infants are at greater risk for severe disease
- **Pediatric multisystem inflammatory disorder in children (MIS-C)**
- Hypothesized to be postinflammatory response following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
- Unlike pediatric patients with severe coronavirus disease 2019 (COVID-19), most patients previously healthy
- Older than children with acute severe COVID-19, majority between 6-12 years of age
- Features resemble those of Kawasaki disease, toxic shock syndrome, and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- Treatment for MIS-C: Supportive care, intravenous immunoglobulin (IVIG), steroids
- Cardiovascular symptoms: 80%
  - Hyperinflammatory myocarditis: Tends to occur in older patients
  - Coronary artery dilatation: Tends to occur in younger patients

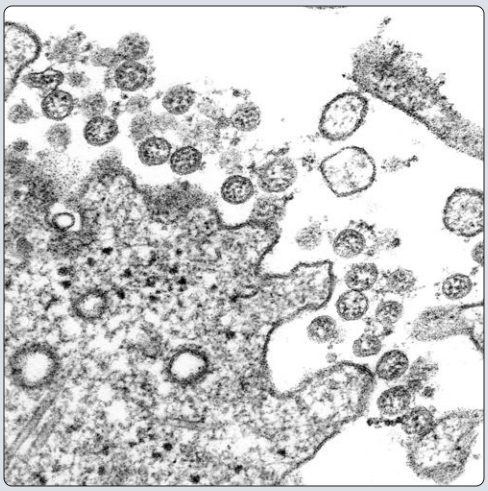
MICROSCOPIC

- Published autopsy cases in children are rare
- Placental findings reported in association maternal SARS-CoV-2 infection
  - Features of fetal vascular malperfusion and maternal vascular malperfusion

Severe Acute Respiratory Syndrome Coronavirus 2

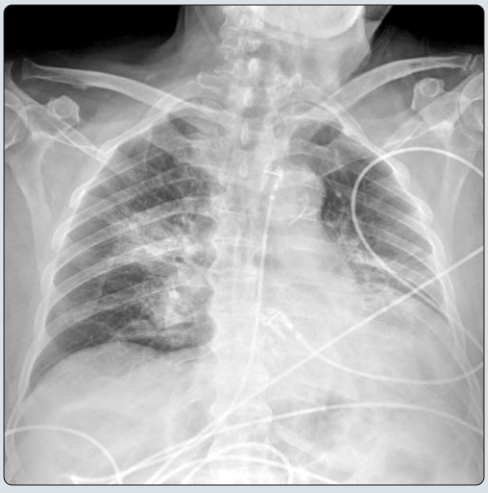


Ultrastructural Features

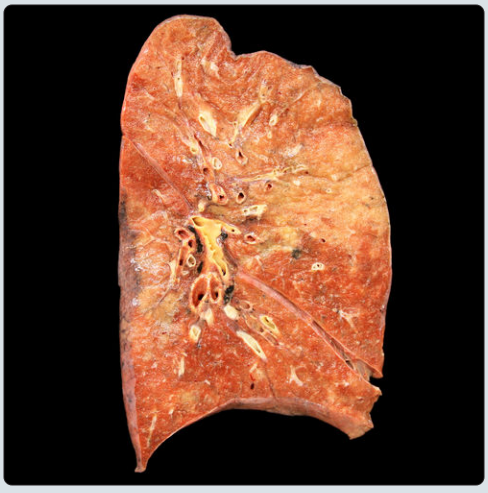


(Left) *This illustration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shows surface spikes (red), giving a halo appearance incorporated into the name "corona." (From DP: Infectious Diseases.)* **(Right)** *This transmission electron micrograph shows spherical extracellular particles with surface spikes and cross sections through the viral genome (black dots), features characteristic of SARS-CoV-2. (From DP: Infectious Diseases.)*

Chest X-Ray



Gross Features



(Left) *This portable chest X-ray shows parenchymal opacities with asymmetric distribution, consolidation in the right perihilar region, and opacity in left lung base, findings consistent with coronavirus disease 2019 (COVID-19) pneumonia. (From DP: Infectious Diseases.)* **(Right)** *This section of lung from a fatal case of COVID-19 shows areas of red congested and edematous parenchyma, consistent with diffuse alveolar damage. (From DP: Infectious Diseases.)*

TERMINOLOGY

Abbreviations

- Coronavirus disease 2019 (COVID-19)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)
- Multisystem inflammatory syndrome in children (MIS-C)

Definitions

- SARS-CoV-2
  - Enveloped positive-sense, single-stranded linear RNA virus
  - Contains 4 essential structural proteins
    - Spike (S) glycoprotein
    - Envelope (E) protein
    - Membrane (M) protein
    - Nucleocapsid (N) protein
- MIS-C
  - Hypothesized to be postinflammatory response following SARS-CoV-2 infection
  - CDC case definition
    - Individual aged < 21 years presenting with fever, laboratory evidence of inflammation **and**
    - Evidence of clinically severe illness requiring hospitalization with multisystem (≥ 2) organ system involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic) **and**
    - Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or exposure to suspected or confirmed COVID-19 case within 4 weeks prior to onset of symptoms

ETIOLOGY/PATHOGENESIS

Pathogenesis

- SARS-CoV-2 virus
  - Enters host cells mediated by S protein using angiotensin converting enzyme ACE2 as receptor
    - Virus binds ACE2 receptor with high affinity
    - ACE2 receptor possesses hypoxia inducibility
  - ACE2 receptor is expressed in following cells, which explains their involvement in COVID-19 infection
    - Types I and II pneumocytes
    - Vascular cells, including endothelial cells, pericytes, arterial smooth muscle cells
    - Cardiac myocytes
    - Neurons and microglia
    - Macrophages
    - Renal tubular cells
    - Enterocytes
- Tissue injury due in part to
  - Vascular injury
  - Coagulation abnormalities
  - Inflammation
- Neurologic presentation
  - Animal model studies show that neurologic spread begins in olfactory bulb and proceeds to invade subcortical and cortical structures
  - Hematologic spread via infected leukocytes is also suggested as portal to CNS
  - Multifactorial process may play role: Direct infection of CNS cells with secondary inflammatory responses
    - Vasculitis, intravascular coagulation, thrombotic events
- MIS-C theories of pathogenesis
  - Stage 1
    - SARS-CoV-2 infection: Asymptomatic to mildly symptomatic
  - Stage 2
    - Macrophage activation and stimulation of T-helper cells
    - Cytokine release, stimulation of macrophages, neutrophils, monocytes, B cells and plasma cells with production of antibodies
  - Stage 3
    - Hyperimmune response: Immune dysregulation with inflammatory syndrome

CLINICAL ISSUES

Epidemiology

- Children comprise 5% of infections and < 1% of hospitalizations
- Contagious period of SARS-CoV-2
  - May start 2 days prior to onset of symptoms
  - Continues for 7-10 days after onset of symptoms
- Most children contract virus via horizontal transmission from household member
- Data on ethnicity and socioeconomic status of children with COVID-19 are sparse

Presentation

- 90% of infected pediatric patients are asymptomatic or demonstrate mild to moderate symptoms
- Common symptoms: Fever, cough, shortness of breath, mild gastrointestinal symptoms
- Overall, children are less severely affected than adults
- However, small proportion have been critically ill, requiring intensive care with reported fatalities
  - Children with comorbidities have increased risk of critical illness
    - Cardiac disease is most frequent comorbidity
    - Respiratory disease and obesity are prominent comorbidities
  - Infants < 1 year of age are at greater risk for severe disease
    - ~ 10% of severe and critical cases reported to occur in infants
      - Presence of congenital heart disease or other comorbidity may seriously affect course of disease
    - 35% of children with COVID-19 requiring mechanical ventilation are infants < 1 year of age
- Respiratory symptoms
  - Shortness of breath
  - Acute respiratory distress syndrome (ARDS)
- Dermatologic findings
  - Chilblain-like lesions ("COVID-toes")
    - Children, adolescents, and young adults
    - Generally in good health

  - Most all in feet (74-100%)
  - More prevalent in colder climates
  - Clinically and histologically similar to idiopathic chilblain lesions
- Erythema multiforme
- Retiform purpura
  - Usually seen in association with more severe disease and high viral load
- Urticaria
- Vascular eruption

- Neurologic manifestations
  - Neurologic symptoms rare in pediatric population; those reported include
    - Headache
    - Encephalopathy
    - Confusion
    - Stroke or intracranial hemorrhage
    - Seizures
  - Neurologic symptoms associated with MIS-C
    - Headache, irritability, encephalopathy
  - Anosmia and ageusia have been reported in children and adolescents
- **MIS-C**
  - Exact incidence is not known
  - Unlike pediatric patients with severe COVID-19, most patients previously healthy
  - Age group
    - Older than children with acute severe COVID-19, majority between 6-12 years of age
  - Condition of higher severity than COVID-19
    - 68% of cases require intensive care support
  - Often occurs 1-6 weeks following SARS-CoV-2 infection
    - Most between 2-4 weeks
  - Features resemble those of Kawasaki disease (KD), toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis (SHLH)/macrophage activation syndrome (MAS)
  - Gastrointestinal symptoms: 92%
    - Abdominal pain, diarrhea
  - KD-like features: 40%
    - Many MIS-C patients present with fever and mucocutaneous manifestations similar to KD
    - MIS-C patients with KD features more likely to be < 5 years old, similar to KD patients
    - More frequent cardiovascular involvement than in KD
  - Cardiovascular symptoms: 80%
    - Hyperinflammatory myocarditis: Tends to occur in older patients
    - Coronary artery dilatation: Tends to occur in younger patients
  - Respiratory symptoms: 70%
    - Respiratory insufficiency or failure: 59%
  - Mucocutaneous symptoms: 74%
    - Conjunctivitis, rash
  - Hematologic symptoms: 76%
  - 3 patterns of disease among hospitalized children
    - Persistent fevers and elevated inflammatory markers but without KD, shock, or organ failure
    - Patients fulfilled criteria for KD
    - Shock and clinical, echocardiographic, and laboratory evidence of myocardial injury
  - Subgroups of MIS-C
    - Shock/multisystem organ failure: ~ 35%
    - Respiratory system involvement: ~ 30%
    - Fever, rash, mucosal involvement: ~ 35%
- **Maternal SARS-CoV-2 infection**
  - Fetal/neonatal findings
    - Studies suggest that vertical transmission of COVID-19 is at most very rare but possible
  - Placental findings
    - Varied findings have been reported in different studies
    - Findings of fetal vascular malperfusion (FVM) in some reports suggest the possibility that maternal COVID-19 infection may be associated with fetal vascular thrombosis
      - Low-grade, segmental lesions reported
    - Findings of maternal vascular malperfusion (MVM) in some reports suggests abnormal maternal circulation
    - There are also reports of no specific pathologic pattern in placentas of COVID-19-infected mothers

Laboratory Tests

- Positively correlated with severity and mortality of COVID-19
  - Decreased CD4(+) and CD8(+) T cells
  - High LDH
  - Higher percentage of peripheral blood neutrophils
- Children with MIS-C
  - Neutrophilia
  - Lymphopenia
  - Increased C-reactive protein
  - Increased procalcitonin &/or ferritin
  - Increased troponin T and proBNP (brain natriuretic peptide)
  - Elevated D-dimer, low fibrinogen
  - Most serologically positive; may be PCR(+) or (-)

Treatment

- Remdesivir: Antiviral
- Treatment for MIS-C
  - Currently no published CDC guidelines or recommendations
  - Supportive care
    - Vasopressor support for cardiac involvement
  - Antimicrobial treatment
  - Immunomodulatory therapy, including
    - Intravenous immunoglobulin (IVIG)
    - Steroids
    - Low-dose aspirin
    - Refractory treatment
      - Anakinra (recombinant IL-1β antagonist)
      - Tocilizumab
    - Interleukin-6 inhibitors

Prognosis

- COVID-19 infection
  - Vast majority of pediatric patients asymptomatic or with mild symptoms

- Small percentage of children become critically ill with fatalities reported
- MIS-C
  - Intensive care unit admission: 80%
  - Requiring mechanical ventilation: 20%
  - Deaths: 2%

IMAGING

Neuroimaging in COVID-19 Infection

- MR findings reported in adults
  - Acute and subacute infarcts
  - Leukoencephalopathy
  - Microhemorrhages
- MR findings reported in children
  - Features indicative of meningoencephalitis
  - Leptomeningeal enhancement

MIS-C Syndrome

- Echocardiogram
  - Depressed cardiac ventricular function
  - Coronary diltation
  - Coronary ectasia
  - Coronary aneurysm
  - Pericardial effusion
  - Pleural effusion

MICROSCOPIC

Histologic Features

- Published autopsy cases in children are rare; most reported findings are from adult patients
- Lung pathology (autopsy)
  - Although current autopsy studies are comprised of adult patients, it is postulated that pediatric patients with severe COVID-19 infection requiring mechanical ventilation have similar lung pathology
  - Diffuse alveolar damage
    - Exudative and early proliferative phase
    - Late proliferative and fibrotic phase
  - Acute fibrinous and organizing pneumonia (AFOP)
  - Platelet and fibrin microthrombi
  - Perivascular inflammation
- Vascular findings
  - Vascular wall thickening
  - Luminal occlusion
  - Microthrombi
  - Vascular hyperplasia
  - Focal hemorrhage
- Cardiac findings
  - Epicardial and myocardial inflammation without myonecrosis
  - Myocyte hypertrophy
- Dermatopathologic findings
  - Chilblain-like lesions
    - Histopathologically similar to idiopathic chilblain lesions
      - Superficial and deep chronic perivascular inflammation
      - Thrombi in superficial dermal vessels
    - SARS-CoV-2 spike protein present in both endothelial and eccrine cells
    - Prominent vascular damage
- Neuropathologic findings (autopsy)
  - Adult autopsy series
    - Mild to moderate acute hypoxic injury most common finding
    - Mild perivascular, parenchymal, and leptomeningeal lymphocytic inflammation without vasculitis
    - Moderate to marked microglial inflammation
    - Microhemorrhages
  - Pediatric case reports
    - Angiocentric mixed mononuclear inflammatory infiltrate in 7-year-old boy
    - Necrotizing granulomatous meningoencephalitis and vasculitis in 5-year-old girl with concurrent *Mycobacterium tuberculosis* infection
  - IHC and ISH for SARS-CoV-2 negative in majority of cases
- Hematologic findings
  - Hemophagocytosis
- Placental findings reported in association maternal SARS-CoV-2 infection (varied findings reported in different studies)
  - Features of FVM
    - Intramural fibrin deposition
    - Villous stromal-vascular karyorrhexis
    - Intramural nonocclusive thrombi
  - Features of MVM
    - Most prominently, decidual vascular hypertrophy
    - Villous infarction
  - Intervillous thrombi
  - Disorders of increased villous vascularity
    - Chorangioma
    - Chorangiosis
    - Hypervascularity
  - Chronic deciduitis with plasma cells

ANCILLARY TESTS

Immunohistochemistry

- Stains (cytoplasmic) for SARS-CoV-2 have been developed
  - Anti-Nucleocapsid protein
  - Anti-Spike protein

Electron Microscopy

- Virion particles can be identified on electron microscopy

SELECTED REFERENCES

1. Baergen RN et al: Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol. 23(3):177-80, 2020
2. Colmenero I et al: SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol. 183(4):729-37, 2020
3. De Rose DU et al: Novel coronavirus disease (COVID-19) in newborns and infants: what we know so far. Ital J Pediatr. 46(1):56, 2020
4. Dolhnikoff M et al: SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health. 4(10):790-4, 2020
5. Dufort EM et al: Multisystem inflammatory syndrome in children in New York state. N Engl J Med. 383(4):347-58, 2020
6. Freeman MC et al: Immunocompromised seroprevalence and course of illness of SARS-CoV-2 in one pediatric quaternary care center. J Pediatric Infect Dis Soc. ePub, 2020
7. Freij BJ et al: Fatal central nervous system co-infection with SARS-CoV-2 and tuberculosis in a healthy child. BMC Pediatr. 20(1):429, 2020

Syndrome Clusters According to Age Group Among Patients With Multisystem Inflammatory Syndrome in Children

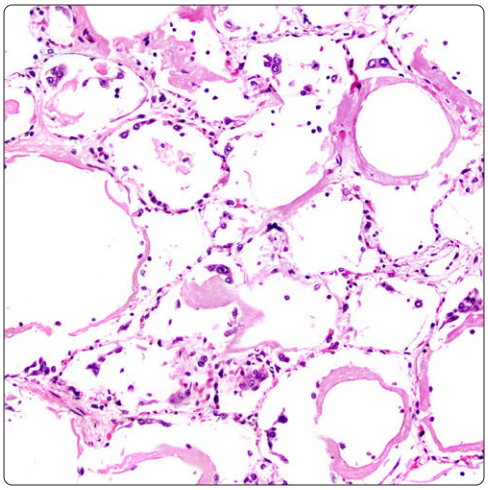
Symptom Category	0-5 Years (n=31)	6-12 Years (n=42)	13-20 Years (n=26)
Dermatologic or mucocutaneous	87.1%	78.6%	61.5%
Gastrointestinal	74.2%	83.3%	80.8%
Kawasaki disease or atypical Kawasaki disease	48.4%	42.9%	11.5%
Myocarditis	38.7%	50.0%	73.1%
Neurologic	12.9%	38.1%	38.5%

Dermatologic or mucocutaneous included the following symptoms: Rash, conjunctivitis, swollen hands or feet, and mucosal changes. Gastrointestinal included the following symptoms: Abdominal pain, nausea or vomiting, and diarrhea. Kawasaki disease or atypical Kawasaki disease was determined by discharge diagnosis or code in the International Classification of Diseases, 10th Revision (ICD-10). Myocarditis was determined by discharge diagnosis or ICD-10 code. Clinical myocarditis was defined as cardiac dysfunction on echocardiography with an elevated troponin level. If the troponin value was missing, clinical myocarditis was defined as an elevated level of pro brain natriuretic peptide or brain natriuretic peptide and cardiac dysfunction or arrhythmia on electrocardiography in the context of an inflammatory process. Neurologic included the following symptoms: Headache, altered mental status, and confusion.

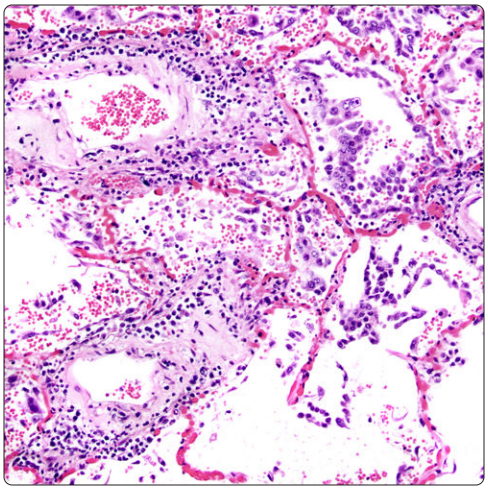
Modified from Dufort et al: Multisystem inflammatory syndrome in children in New York state, NEJM, 383;4, 2020.

8. Gutierrez Amezcua JM et al: COVID-19-induced neurovascular injury: a case series with emphasis on pathophysiological mechanisms. SN Compr Clin Med. 1-17, 2020
9. Hariri LP et al: Lung histopathology in COVID-19 as compared to SARS and H1N1 influenza: a systematic review. Chest. ePub, 2020
10. He M et al: Histopathology of third trimester placenta from SARS-CoV-2-positive women. Fetal Pediatr Pathol. 1-10, 2020
11. Magro C et al: Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 220:1-13, 2020
12. Maiese A et al: Autopsy findings in COVID-19-related deaths: a literature review. Forensic Sci Med Pathol. ePub, 2020
13. Mak Pet al. Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents. Pediatr Infect Dis J. 2020;39(8):e199-200
14. Mamishi S et al: Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in 45 children: a first report from Iran. Epidemiol Infect. 148:e196, 2020
15. Mitchell WB: Thromboinflammation in COVID-19 acute lung injury. Paediatr Respir Rev. 35:20-4, 2020
16. Nakra NA et al: Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel). 7(7), 2020
17. Prieto LM et al: Cardiovascular magnetic resonance imaging in children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 and heart dysfunction. Clin Microbiol Infect. ePub, 2020
18. Radia T et al: Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev. ePub, 2020
19. Sarzaeim M et al: Kawasaki disease and multisystem inflammatory syndrome in children with COVID-19. SN Compr Clin Med. 1-6, 2020
20. Shanes ED et al: Placental pathology in COVID-19. Am J Clin Pathol. 154(1):23-32, 2020
21. Solomon IH et al: Neuropathological features of Covid-19. N Engl J Med. 383(10):989-92, 2020
22. Torrelo A et al: Erythema multiforme-like lesions in children and COVID-19. Pediatr Dermatol. 37(3):442-6, 2020
23. Whittaker E et al: Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 324(3):259-69, 2020
24. Williams N et al: COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities. Eur J Pediatr. ePub, 2020
25. Zhou MY et al: From SARS to COVID-19: what we have learned about children infected with COVID-19. Int J Infect Dis. 96:710-4, 2020

Hyaline Membranes

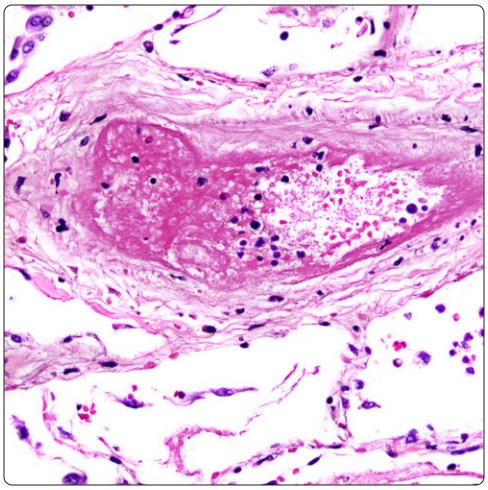


Interstitial Inflammation and Edema

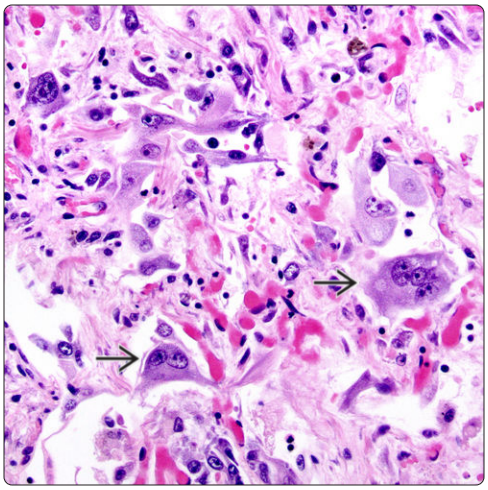


(Left) *Early histologic findings in COVID-19 pneumonia include eosinophilic hyaline membranes, consistent with exudative (acute) diffuse alveolar damage. (From DP: Infectious Diseases.)* **(Right)** *COVID-19 pneumonia includes variable amounts of interstitial and perivascular chronic inflammation and edema. (From DP: Infectious Diseases.)*

Fibrin Thrombi

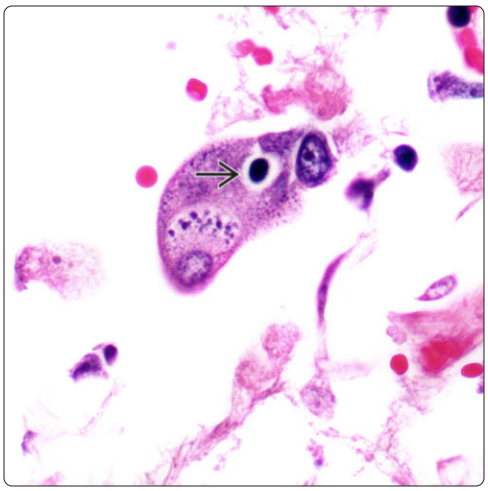


Multinucleated Giant Cells

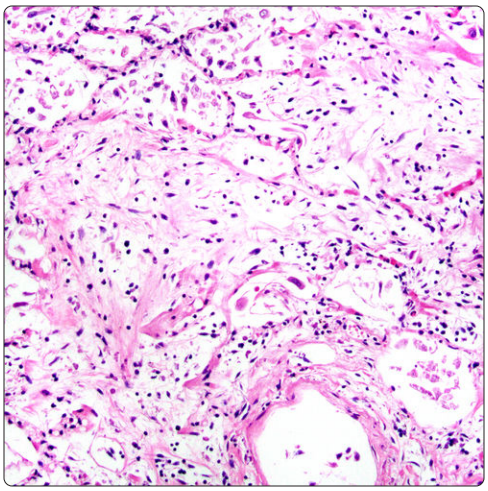


(Left) *Fibrin thrombi involving small vessels are occasionally present in COVID-19 pneumonia. (From DP: Infectious Diseases.)* **(Right)** *Multinucleated giant cells with prominent reactive-appearing nucleoli are variably present in COVID-19 pneumonia ⇨. (From DP: Infectious Diseases.)*

Lymphophagocytosis



Fibroblast Proliferation



(Left) *A reactive histiocyte is present containing an engulfed lymphocyte ⇨ that should not be confused with a viral inclusion. (From DP: Infectious Diseases.)* **(Right)** *Fibroblast proliferation and collagen production in alveolar spaces reflect organized alveolar damage. (From DP: Infectious Diseases.)*