UCDAVIS HEALTH | Department of Pathology and Laboratory Medicine

Sudden Infant Deaths with COVID-19: A Report of Three Cases

Alexander Ladenheim, M.D.
Jacob Donnelly, D.O.
Irfan Chaudry, M.D.
Jason Tovar, M.D.
Keng-Chih Su, M.D.
Sarah E. Avedschmidt, M.D.
Katherine Raven, M.D.

Outline

- Epidemiology of SARS-CoV-2 infection in children
- Case presentations
- Discussion
  - Key observations
  - Utility of postmortem nasal swab PCR for SARS-CoV-2
  - Histologic findings
  - B.1.429 variant

Epidemiology in Children

- SARS-CoV-2 severity: in general, children << adults
  - However, evolving understanding of disease in children
  - PEDSnet cohort[1]
    - 5734 children with PCR+ COVID-19 (4% of cohort)
    - 359 (7%) were hospitalized
    - 8 (0.1%) died
    - Age < 1 year was risk factor for severe disease (OR 2.96, 95% CI 1.85-4.73)
  - N3C cohort:[2] preliminary findings similar
    - 91,865 children with PCR+ COVID-19 (12.6% of cohort)
    - 5213 (6%) were hospitalized
    - 50 (1%) died

Case 1 – Clinical History

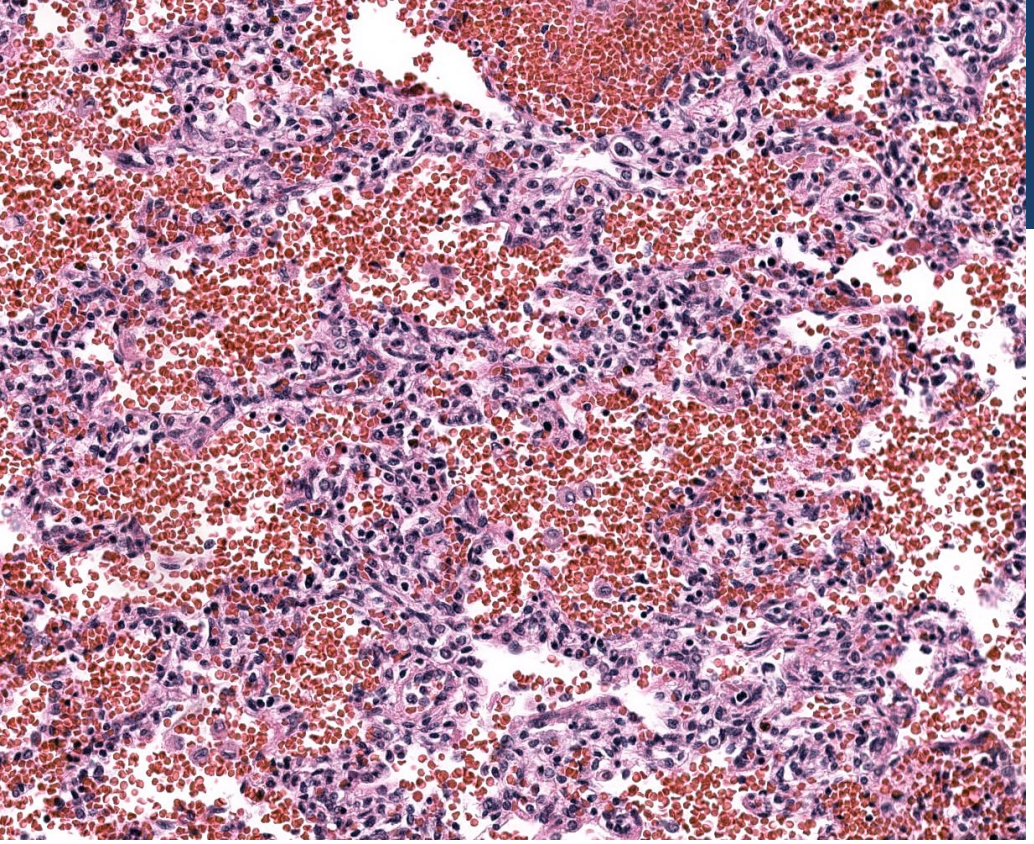
- Maternal History:
  - 32-year-old G5P4 mother
  - 1.2 ppd smoking history
  - Received prenatal care throughout pregnancy.
- Decedent History:
  - 49 days old male
  - No symptoms or health concerns prior to death
  - Term (born at 37 weeks); no health issues after delivery

Case 1 – Clinical History

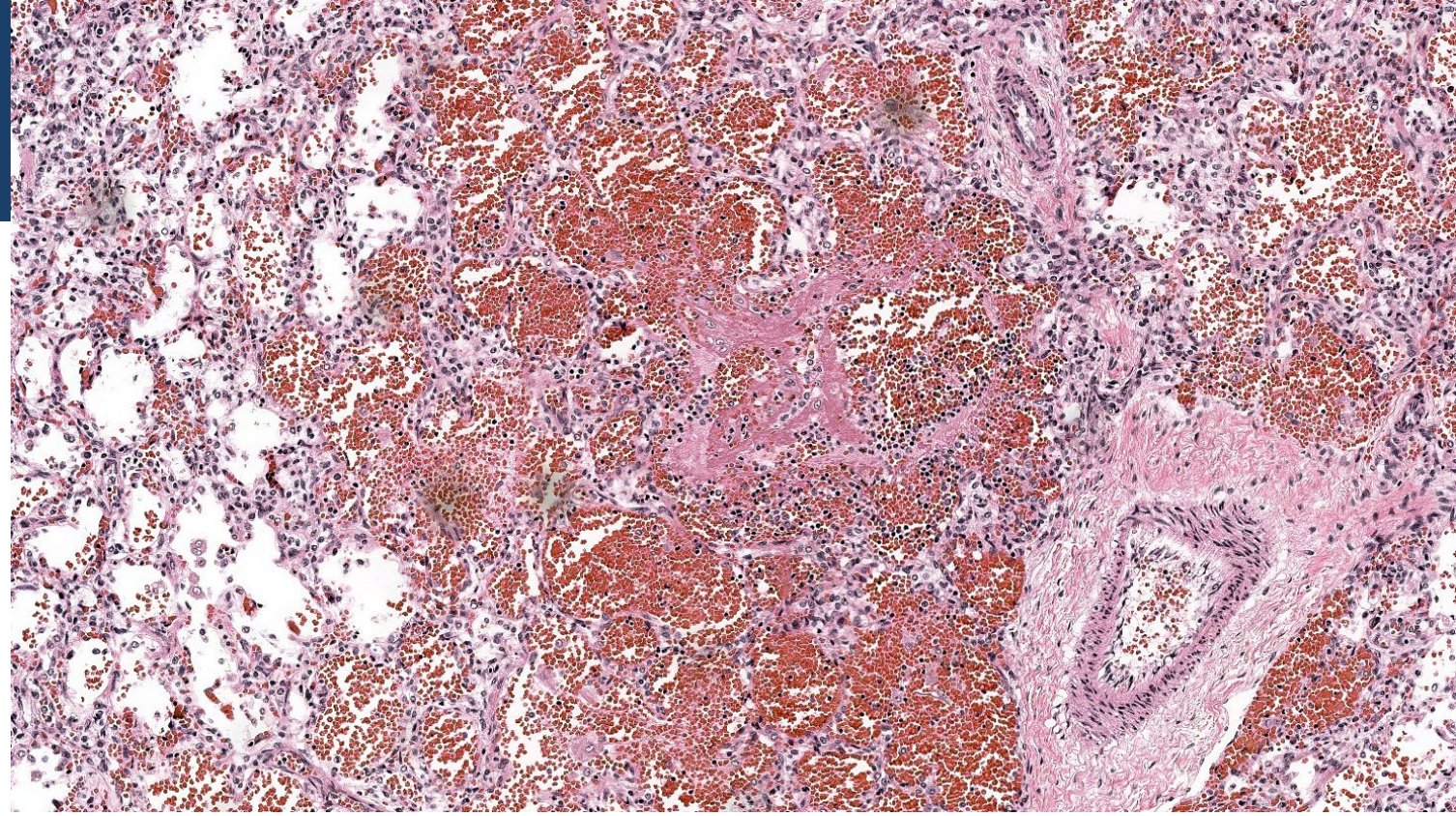
- Timeline Of Events On The Day Of Death:
  - Fed at 09:00, then mother and a 2-year-old sibling napped in mother's bed
  - Mother woke at 11:00 to find the decedent apneic and unresponsive
  - The decedent was lying in dried fluids
  - The baby was moved to a nearby crib, and EMS was contacted
  - EMS arrived and began CPR; cardiac rhythm alternated between PEA and asystole
  - Pronounced dead at ED
- Postmortem Laboratory Testing:
  - SARS-CoV-2 PCR (nasal swab): Positive
  - Genotyping: viral variant B.1.429

Case 1 – Gross Findings

- Autopsy findings:
  - Cardiovascular:
    - Heart weighed 18.8 g, with unremarkable anatomy and great vessels.
  - Respiratory:
    - Mild congestion was present in the lung parenchyma bilaterally.
    - Combined lung weight of 85.6 g.
    - These findings were consistent with viral pneumonia.



H&E, 200x: Chronic interstitial inflammation and hemorrhage



H&E, 100x: Hemorrhage and focal fibrin

Case 1 – Microscopic Findings

- Respiratory:
  - Bilateral lungs congested with diffuse hemorrhage and focal intraalveolar fibrin accumulation.
  - Interstitial lymphohistiocytic inflammatory infiltrates and thickened alveolar septae

Case 2 – Clinical History

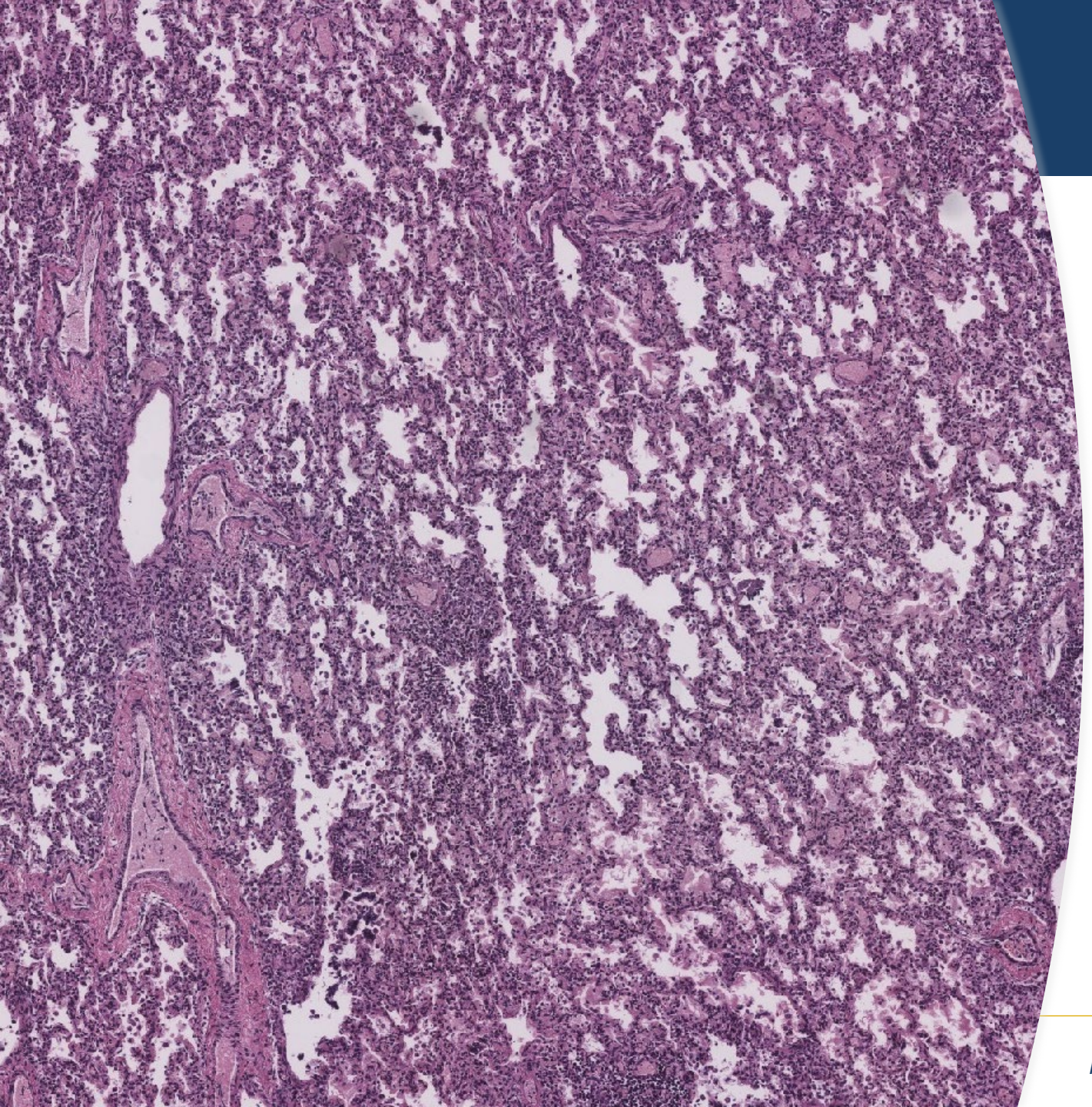
- Maternal History:
  - 21-year-old G6P3 mother
  - Received prenatal care beginning at 20 weeks
  - 22 weeks: had threatened abortion and UTI
  - 28 weeks: hospitalized for preeclampsia; received steroids and had C-section delivery
- Decedent History:
  - 4 months old male
  - Preterm (born at 31 weeks, 2 days); remained in the NICU for 5 weeks after birth
  - Healthy after discharge; slept exclusively in a crib
  - 3 months: began experiencing intermittent apneic periods and tested positive for SARS-CoV-2
  - Apparently recovered: seen three weeks later at pediatrician's office and appeared asymptomatic, received three-month vaccinations without incident

Case 2 – Clinical History

- Timeline Of Events On The Day Of Death:
  - Fed at 11:00 under supervision of father
  - At 15:30 decedent became fussy, and the father placed the decedent in the crib supine for a nap
  - At 17:30 decedent woke and was placed on in the prone position with a pacifier.
  - At 18:30 the decedent was observed to be napping and sucking on the pacifier in the prone position
  - At 19:30 the decedent was found lying prone and unresponsive
  - EMS was contacted and CPR was initiated by the mother
  - EMS found the decedent pink, warm, dry, with agonal respirations
  - Pronounced dead in ED
- Postmortem Laboratory Testing:
  - SARS-CoV-2 PCR (nasal swab): Positive
  - Genotyping: viral variant B.1.429

Case 2 – Gross Findings

- Autopsy findings:
  - Cardiovascular:
    - Heart weighed 18.4 g, with unremarkable anatomy and great vessels.
  - Respiratory:
    - Congestion in the lung parenchyma bilaterally with patchy subpleural hemorrhage bilaterally.
    - The combined lung weight was 70.6 g.



Case 2 – Microscopic Findings

- Respiratory:
  - Bilateral lungs with diffuse hemorrhage and focal intraalveolar fibrin
  - Prominent chronic interstitial inflammatory infiltrate

H&E, 40x: Prominent chronic interstitial inflammation

Case 3 – Clinical History

- Maternal History:
  - 26- year-old G6P6004 mother
  - Unknown prenatal history
  - The mother had two other children who died in early childhood and two children removed from the home by social services
- Decedent History:
  - 9 months old female
  - Term (born at 39 weeks)
  - No health issues after delivery and was discharged home
  - By report of 1 caretaker, was experiencing a cough on the day of death

Case 3 – Clinical History

- Timeline Of Events Prior to Death:
  - Placed under the care of the decedent's maternal grandfather
  - The grandfather placed the decedent on the floor sitting up with a bottle of formula and took a nap in an adjacent room
  - After an unspecified period, the grandfather woke, checked on the decedent, and found them supine and unresponsive
  - EMS was contacted; the grandfather took the decedent to a nearby hospital via his personal vehicle
  - Upon arrival to the ED, the decedent was in PEA on cardiac monitoring
  - Intubated and had return of spontaneous circulation after resuscitation efforts
  - Transferred to another facility for further treatment

Case 3 – Clinical History

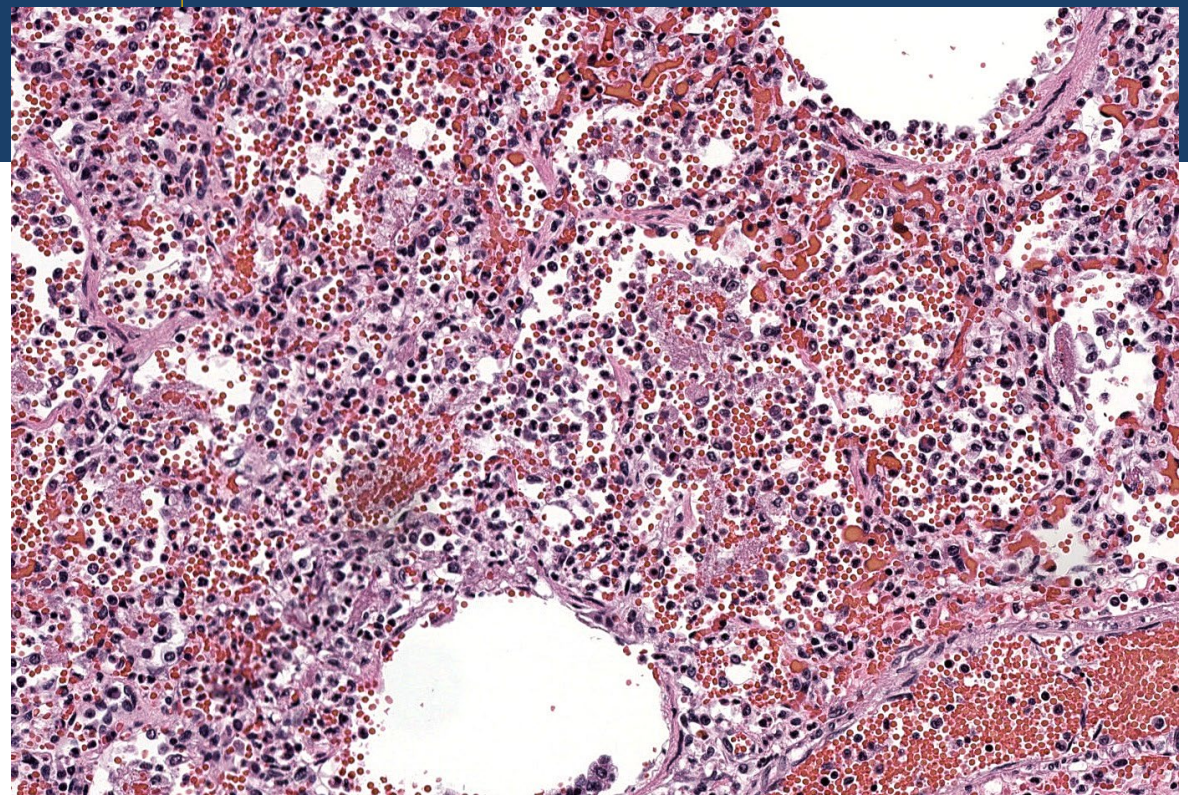
- Imaging:
  - Chest X-ray demonstrated patchy perihilar infiltrates bilaterally and consolidation of the RUL lung
- Antemortem Laboratory testing:
  - Severe metabolic acidosis, lactic acidosis, and hyperglycemia (pH 6.80, HCO3- 4.7 mmol/L, PO2 387 mmHg, PaCO2 35 mmHg, glucose 881 mg/dL, anion gap 25 mEq/L, lactate 19.0 mmol/L, and elevated troponins (0.22 ng/mL); likely related to cardiac arrest and resuscitation.
  - SARS-CoV-2 PCR (nasal swab): Negative

Expired the following day despite supportive care

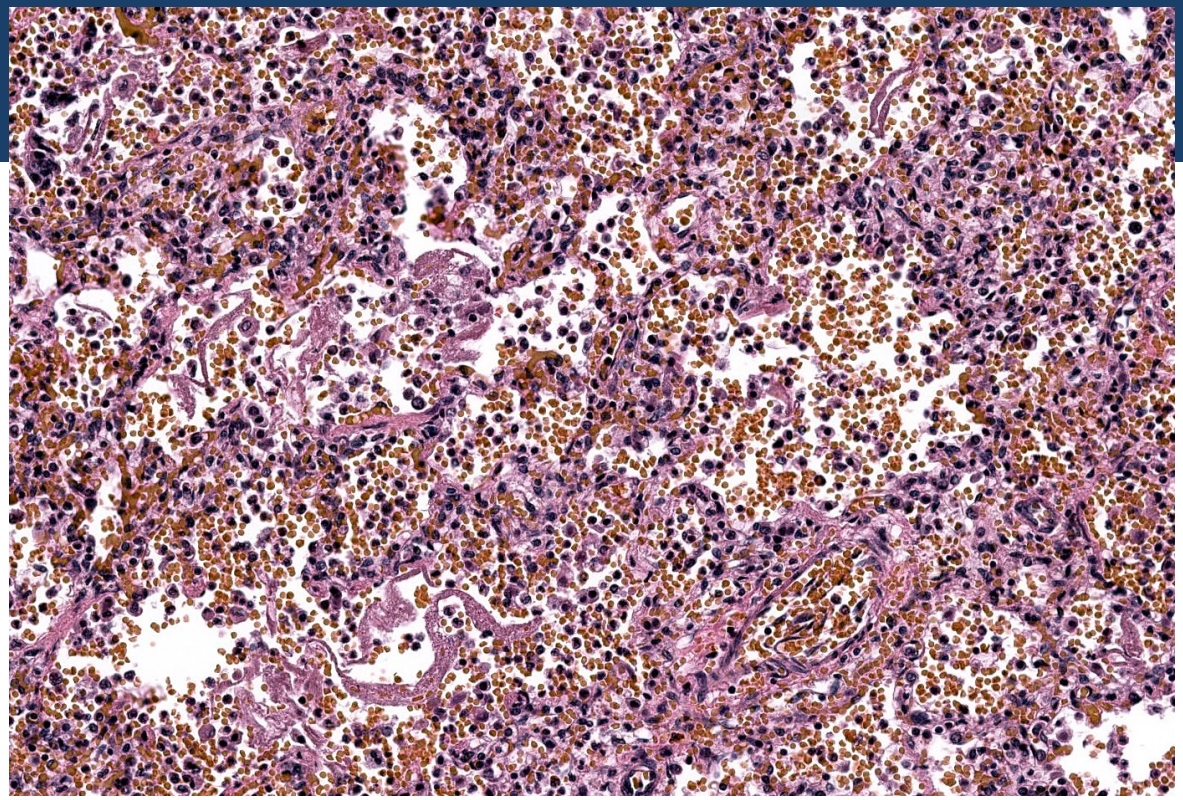
- Postmortem Laboratory Testing:
  - SARS-CoV-2 PCR (nasal swab): Positive

Case 3 – Gross Findings

- Autopsy findings:
  - Cardiovascular:
    - Heart with unremarkable anatomy and great vessels.
  - Respiratory:
    - Congestion in the lung parenchyma bilaterally and right upper lobe consolidation



H&E, 200x: Acute pneumonia and focal fibrin



H&E, 200x: Hemorrhage, chronic interstitial inflammation, and focal fibrin

Case 3 – Microscopic Findings

- Respiratory:
  - Bilateral lungs with congestion, acute pneumonia, and evidence of acute lung injury with diffuse hemorrhage and scattered intraalveolar fibrin
  - Mild interstitial chronic inflammation

Discussion – Key Observations

	Case 1	Case 2	Case 3
Age	1.5 mo	4 mo	9 mo
Risk factors	(none)	Pre-term (31 wks)	Sibling deaths in childhood
Disease course	Healthy prior to DoD	COVID infection 3 wks prior, recovered	Healthy prior to DoD
Symptoms	(none)	(none)	Possible cough
Unobserved period prior to death	Yes	Yes	Yes

Discussion – COVID Testing

	Case 1	Case 2	Case 3
Antemortem COVID PCR	(none)	Positive (3 wks prior to death)	Negative (1 day prior to death)
Postmortem COVID PCR	Positive	Positive	Positive

Discussion – COVID Testing

- Case 1: asymptomatic; positive postmortem test
- Case 2: asymptomatic; prior confirmed COVID infection
  - Viral shedding? Positive postmortem test may not represent active infection
- Case 3: possible cough; negative antemortem test (1 day prior to death)
  - False negative antemortem test?
    - Sensitivity of SARS-CoV-2 PCR testing in children as low as 58.1%[3]
    - Preanalytic factors: collection practices, difficulty obtaining patient cooperation, problems with specimen transport or storage
    - Timing of testing: tests performed closer to symptom onset more likely to be positive
- Limited data on sensitivity and specificity of postmortem PCR testing
  - One study showed a sensitivity of 96.7% and a 94.2% specificity[4]
  - Testing performed within 0-6 days of death

Discussion – Pulmonary Microscopic Findings

Pathologic Finding	Number of cases	Notes
Diffuse hemorrhage	3/3	
Intraalveolar fibrin	3/3	Most prominent: case 3
Acute pneumonia	1/3	
Interstitial chronic inflammation	3/3	Most prominent: case 2
Alveolar septal thickening	2/3	

- These findings are similar to those reported in adults with SARS-CoV-2 infection:[5-6]
  - Diffuse alveolar damage
  - Interstitial lymphohistiocytic inflammation
  - Intravascular fibrin thrombi
  - (Possibly) viral cytopathic changes

Discussion – Investigation of Sudden Death

- Integrating available data[7]
  - Reported history
  - Scene investigation
  - Antemortem clinical findings and laboratory assessment
  - Autopsy gross findings
  - Radiography
  - Postmortem laboratory assessment
  - Autopsy microscopic findings

Discussion – Investigation of Sudden Death

- Reported history
  - Unobserved periods and risk factors for asphyxia
- Autopsy findings
  - Pulmonary gross abnormalities
  - No external trauma
  - No specific or soft signs of asphyxia or airway obstruction
- Microscopic findings
  - Histologic evidence of pulmonary injury
  - No microscopic evidence supporting alternate theories
- Laboratory assessment
  - Positive postmortem SARS-CoV-2 PCR testing

SARS-CoV-2 Variant B.1.429

- Sequencing of NP swab samples detected this variant in 1 case
- Circulating in California in late 2020 to early 2021[8]
- Notable mutations:[9]
  - Viral spike proteins: L452R mutation
  - Same mutations seen in the current variants of concern
- Impact: associated with[8-10]
  - Higher viral loads
  - Increased infectivity
  - Escape from neutralizing antibodies
  - Resistance to monoclonal antibody therapies
- Emerging variants and vaccination practices: shift in vulnerable groups?

Summary

- Although less common, the pediatric population can suffer severe and fatal SARS-CoV-2 infections
- Very young children may be apparently asymptomatic, or signs may go unnoticed by caregivers
- Postmortem nasal swab PCR may play a role in surveillance for SARS-CoV-2 infection and the investigation of sudden/unexpected death
- The pulmonary histologic findings in children are similar to those reported in adults
- Emerging viral variants and vaccination practices may cause a shift in epidemiology, with an increased SARS-CoV-2 disease burden in younger populations

References

1. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States. JAMA Pediatr. 2021;175(2):176-184. doi: 10.1001/jamapediatrics.2020.5052
2. Martin B, DeWitt PE, Russell S, et al. Children with SARS-CoV-2 in the National COVID Cohort Collaborative (N3C). medRxiv [Preprint]. 2021:2021.07.19.21260767. doi: 10.1101/2021.07.19.21260767
3. Di Pietro GM, Capecchi E, Luconi E, et al. Diagnosis of SARS-CoV-2 in children: accuracy of nasopharyngeal swab compared to nasopharyngeal aspirate. Eur J Clin Microbiol Infect Dis. 2021;40(6):1155-1160. doi:10.1007/s10096-020-04131-z
4. Hall JA, Harris RJ, Emmett HE, et al. On the Sensitivity and Specificity of Postmortem Upper Respiratory Tract Testing for SARS-CoV-2. J Infect Dis. 2021;224(3):389-394. doi: 10.1093/infdis/jiab270
5. Vasquez-Bonilla WO, Orozco R, Argueta V, et al. A review of the main histopathological findings in coronavirus disease 2019. Hum Pathol. 2020;105:74-83. doi:10.1016/j.humpath.2020.07.023
6. Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020;33(11):2128-2138. doi: 10.1038/s41379-020-0603-3
7. Corey TS, Hanzlick R, Howard J, et al. A functional approach to sudden unexplained infant deaths. Am J Forensic Med Pathol. 2007;28(3):271-7. doi: 10.1097/01.paf.0000257385.25803.cf
8. McCallum M, Bassi J, De Marco A, et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. Science. 2021;373(6555):648-654. doi: 10.1126/science.abi7994
9. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and neutralization of a spike L452R SARS-CoV-2 variant. Cell. 2021 Jun 24;184(13):3426-3437.e8. doi: 10.1016/j.cell.2021.04.025
10. "SARS-CoV-2 Variant Classifications and Definitions." CDC.gov. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html. Updated August 24, 2021. Accessed August 24, 2021.