DOI: 10.1002/ppul.25881

CLINICAL CORRESPONDENCE

WILEY

Fatal SARS-CoV-2 Omicron variant in a young infant: Autopsy findings

Pierre Goussard PhD[1] | Pawel Schubert MPhil (Paed Path)[2,3] | Noor Parker FC (Paed)[1] | Chantelle Myburgh FC (Paed)[1] | Helena Rabie PhD[1] | Marieke M. van der Zalm PhD[1] | Gert U. Van Zyl PhD[3,4] | Wolfgang Preiser PhD[3,4] | Tongai G. Maponga PhD[3,4] | Janette Verster FC (Path)[5] | Andre G. Gie PhD[1] | Savvas Andronikou PhD[6,7]

[1]Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

[2]Division of Anatomical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

[3]National Health Laboratory Service, Tygerberg, Cape Town, South Africa

[4]Division of Medical Virology, Faculty of Medicine and Health Science, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

[5]Division of Forensic Medicine, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

[6]Department of Pediatric Radiology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[7]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Pierre Goussard, PhD, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, PO Box 241, Cape Town 8000, South Africa.
Email: pgouss@sun.ac.za

SARS-CoV-2 has spread rapidly worldwide since December 2019, but fewer children are diagnosed with SARS-CoV-2 and mortality remains relatively low compared to adults.[1] Even fewer neonates and infants are testing SARS-CoV-2 positive and data from the United States showed that children <1 years only represented 0.27% of all cases.[2] The majority of infants and children present with mild symptoms.

The first case of the SARS-CoV-2 Omicron variant was reported in November 2021 in South Africa and has since become the dominant strain globally.[3]

A 7-week-old male infant (weight 2.05 kg) was admitted to the Paediatric Intensive Care Unit (PICU) after intubation for apnea and respiratory failure. He was a premature baby at 29 weeks with a birth weight of 1455 g who required continuous positive airway pressure after birth, but not surfactant replacement therapy. The baby was unexposed and had a negative HIV test.

Tracheal aspirate confirmed polymerase chain reaction (PCR) SARS-CoV-2 positive, with no other concomitant viruses or bacteria identified. The blood results included white cell count 2.85×10^9/L, neutrophil count 1.60×10^9/L, lymphocyte count 0.70×10^9/L, and C-reactive protein 6 mg/L. During the course of the disease, *Candida albicans* was identified on tracheal aspirate on Day 5. *Klebsiella pneumonia* was isolated from blood cultures on Day 10. Intermittent positive-pressure ventilation was changed to High-frequency Oscillatory Ventilation due to increasing Oxygenation index (OI) and air leak syndromes which included pneumothorax and pulmonary interstitial emphysema (PIE). The chest X-rays showed progression of changes from Day 1 (Figure 1A) when there was a diffuse ground-glass appearance to both lungs, to (Figure 1B) Day 6 where bilateral pneumothoraces developed (tension pneumothorax left) and (Figure 1C) Day 8 through Day 12 (Figure 1D) to Day 14 (Figure 1E) where the pneumothoraces were treated with drains and there was progressive development of PIE and re-accumulation of the pneumothoraces. The baby was initially treated with Meropenem, ganciclovir, co-trimoxazole, and dexamethasone at 0.15 mg/kg per day.

There was no improvement in the infant's condition, and he was demised 17 days after admission.

Two tracheal aspirates were done, one on December 11, 2021, and another on December 23, 2021. Both swabs were tested Xpert® Xpress SARS-CoV-2 (Cepheid) and both had similar high respiratory

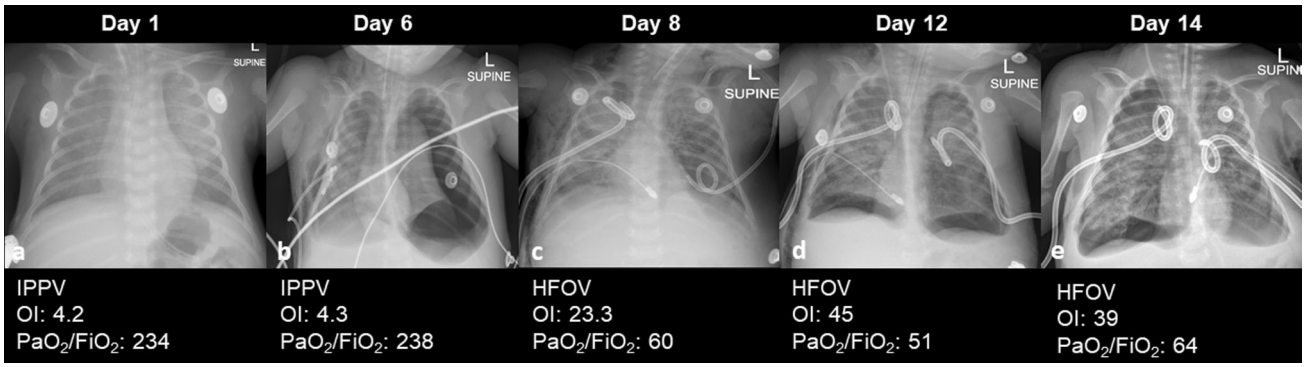

FIGURE 1 (A) Day 1: Bilateral, symmetric "ground-glass" density throughout both lungs. (B) Day 6: Tension pneumothorax on the left and a basal pneumothorax on the right. (C) Day 8: Bilateral thoracic pig-tail drains and additional basal thoracic drain with the tip overlying the cardiac shadow. PIE in the medial portion of the left lung and lower medial portions of the right lung. (D) Day 12: Re-accumulation of bilateral pneumothoraces and progression of PIE in both lungs. (E) Day 14: Reposition of left-sided pigtail drain and new left basal chest drain with improvement of the left pneumothorax, but further expansion of right pneumothorax and worsening of bilateral PIE. PIE, pulmonary interstitial emphysema

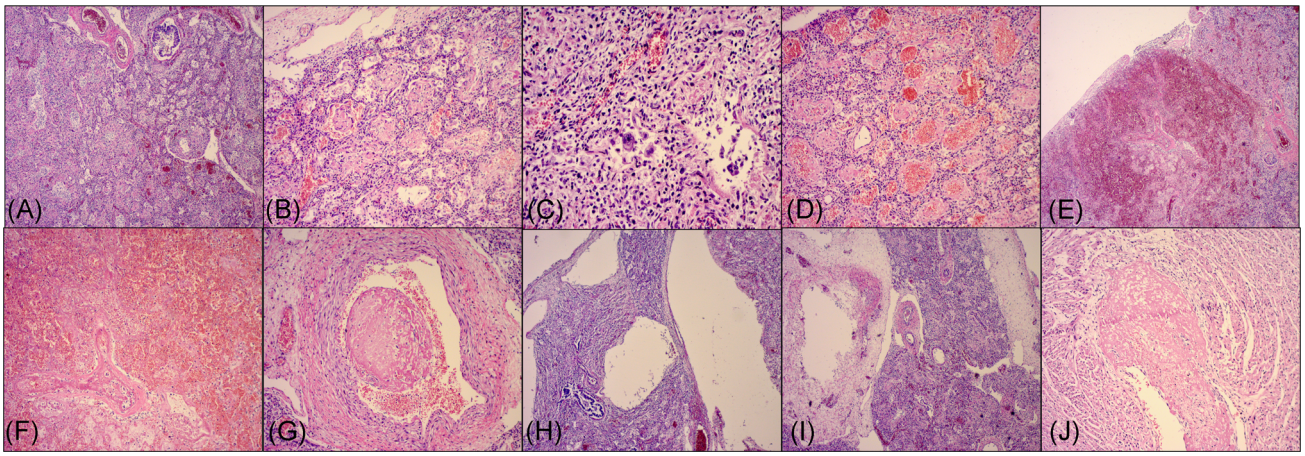

FIGURE 2 (A) Right lung showing a rather solid appearance with widespread organizing pneumonia. Hematoxylin and Eosin stain, 4×. (B) Higher magnification of organizing pneumonia with fibrin ball-like collections in the alveolar spaces that are already showing signs of organization. The interstitium is expanded with chronic inflammatory cell infiltrates. Hematoxylin and Eosin stain, 10×. (C) High power magnification of the lung, showing a very solid, diffusely fibrotic lung (fibrosing organizing pneumonia) with a few visible alveoli that contain multinucleated giant cells in the alveolar spaces. Hematoxylin and Eosin stain, 20×. (D) Low power magnification of the lung section showing some alveoli with organizing pneumonia while others still contain hyaline membranes lining the alveolar walls with the alveolar lumens still being patent and containing some inflammatory cells. The interstitium is expanded with acute and chronic inflammatory cells. Hematoxylin and Eosin stain, 10×. (E) Low magnification photograph showing the pleural space top left with a hemorrhagic, wedge-shaped pleural infarct. Hematoxylin and Eosin stain, 4×. (F) High magnification of (E), highlighting the infarcted nature of the lung parenchyma. Hematoxylin and Eosin stain, 10×. (G) Photograph of a pulmonary artery contains a large, but nonocclusive thrombus. Hematoxylin and Eosin stain, 10×. (H) Low magnification image of subpleural lung parenchyma (pleural space top left corner) showing dilated lymphatic channels (the lining of which are D2-40 positive on immunohistochemical staining), giving a "microcystic" appearance to this section of the lung parenchyma, compressing the adjacent lung lobules. Hematoxylin and Eosin stain, 4×. (I) Low magnification image with the pleural space being seen top right. The pulmonary artery and vein are seen "hanging" in clear spaces which are dilated lymphatic channels. Hematoxylin and Eosin stain, 4×. (J) Section of the right ventricle with a thrombus seen attached to the wall of the ventricle and propagating into the ventricular lumen. Hematoxylin and Eosin stain, 10× [Color figure can be viewed at wileyonlinelibrary.com]

viral loads as evident from the Ct values: E-gene 18.1; N2-gene 19.9 and E-gen 17.9 and N2-gene 19.8 on the first and second samples, respectively. Oxford Nanopore Sequencing of the second sample using the "Midnight" protocol revealed an Omicron variant (B.1.1.529), first identified in the Gauteng Province of South Africa and in Botswana and which emerged in the Western Cape province in the latter half of November 2021.[4]

Sequencing was done on the original sample and the infant was confirmed to have been infected with the Omicron variant (B.1.1.529).

The mother of the infant was not vaccinated but she tested PCR negative for SARS-CoV-2 when the child was sick. SARS-CoV-2 antibodies against N-protein from the mother were done that showed high IgM (2.67 g/L) and IgG (15.89 g/L) suggesting recent infection which likely occurred at the same time as the child's illness.

A limited autopsy restricted to the chest cavity was performed. The lungs appeared consolidated, firm, and mottled with the right being more affected than the left.

On histological examination, both lungs showed similar pathology; however, the right lung was more diffusely affected. At low magnification, the lungs appeared solid (Figure 2A) with the alveolar spaces obliterated by fibrinous balls with organization, (organizing pneumonia) with additional alveolar macrophages, lymphocytes (Figure 2B), and multinucleated giant cells (Figure 2C). Mainly a chronic inflammatory cell infiltrate is seen expanding the interstitial septae. Some alveoli still showed hyaline membranes while adjacent alveoli showed a more pronounced organizing pneumonia pattern (Figure 2D). Small foci of ongoing neutrophilic pneumonia and foci of squamous metaplasia were also noted.

Focal areas of subpleural hemorrhagic lung infarction (Figure 2E,F), as well as focal thrombosis in the pulmonary arteries, were noted (Figure 2G).

There were multiple areas of dilated lymphatic vessels in the subpleural parenchyma (Figure 2H), forming microcystic areas with compression of surrounding parenchyma, while in other regions these dilated lymphatic channels were seen surrounding the bronchovascular bundles which are seen "hanging" within clear spaces (Figure 2I). These dilated lymphatics are most likely indicative of air dissection into the lymphatic vessels (interstitial emphysema) with resultant breakthrough into the pleural cavities with pneumothorax as complications.

Additionally, a thrombus was found in the right ventricle of the heart, attached to the endocardial wall (Figure 2J).

The parents gave consent for a limited postmortem and gave consent for the publication of this case report. The study was approved by the Stellenbosch University Health Research Ethics Committee (N20/04/013_COVID-019).

Accumulating evidence shows a relatively mild clinical course of the newly discovered Omicron variant; however, this case report describes a fatal course in an infant.

There is limited postmortem information of lung pathology in young infants with SARS-CoV-2 and no current reports on lung histology findings in children, resulting from the Omicron variant. This was a young infant, with prematurity as the only identifiable comorbidity with no other respiratory pathogens except SARS-CoV-2 identified.

The histological findings, in this case, include the pronounced organizing pneumonia pattern, with some alveoli still showing hyaline membranes. Including some focal areas of subpleural hemorrhagic lung infarction as well as focal thrombosis in the pulmonary arteries and thrombus formation in the right ventricle, attached to the ventricular wall, were observed.

The hemorrhagic infarct and thrombi in the pulmonary arteries are not well described in neonates and young infants.

This patient did receive dexamethasone but was not on any anticoagulation treatment and further research is necessary to determine if young infants with SARS-CoV-2 pneumonia must be treated with anticoagulants. This case shows a potential need for the routine measurement of D-dimers in neonates and young infants with severe pneumonia.

The histopathological findings of SARS-CoV-2 infection in adults include diffuse alveolar damage with hyaline membranes, desquamation of pneumocytes, edema (interstitial with variable alveolar edema), and lymphocyte infiltration in the interstitium. Additional findings include Type 2 pneumocyte hyperplasia, multinucleated giant cells, capillary congestion, fibrin thrombi, and foci of bronchial squamous metaplasia.[5] Organizing pneumonia seems to be a late phase complication and bronchopneumonia can occur at any stage mostly as a result of superimposed infection. Most of these published series were described in adults and during the first two waves of the virus. Organizing pneumonia seems to be one of the pathways to fibrotic lung changes seen in some patients post-COVID infection.

Coagulopathy and endothelial damage caused by SARS-CoV-2 have led to routine D-dimer level monitoring and use of anticoagulant therapy in adults.

Antenatal vaccination has been shown to induce a maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy and in future prevention of cases of severe SARS-CoV-2 pneumonia in young infants.

We report a case of severe pneumonia due to SARS-CoV-2 infection with the newly discovered Omicron variant. The histological findings showed thrombotic infarctions which suggest careful assessment in infants and children presenting with severe SARS-CoV-2 pneumonia and warrant further investigations.

REFERENCES

1. van der Zalm MM, Lishman J, Verhagen LM, et al. Clinical experience with severe acute respiratory syndrome Coronavirus 2-related illness in children: hospital experience in Cape Town, South Africa. *Clin Infect Dis*. 2021;72(12):e938-e944. doi:10.1093/cid/ciaa1666
2. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children – United States, February 12-April 2, 2020. *Morb Mortal Wkly Rep*. 2020;69(14):422-426. doi:10.15585/mmwr.mm6914e4
3. Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature*. 2022. doi:10.1038/s41586-022-04411-y
4. Pembaur A, Sallard E, Weil PP, Ortelt J, Ahmad-Nejad P, Postberg J. Simplified point-of-care full SARS-CoV-2 genome sequencing using nanopore technology. *Microorganisms*. 2021;16(912):2598. doi:10.3390/microorganisms9122598
5. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77(2):198-209. doi:10.1111/his.14134

How to cite this article: Goussard P, Schubert P, Parker N, et al. Fatal SARS-CoV-2 Omicron variant in a young infant: Autopsy findings. *Pediatric Pulmonology*. 2022;57:1363-1365. doi:10.1002/ppul.25881