A Child with COVID-19 Complicated by Rapidly Progressive Severe Organizing Pneumonia: A Case Report

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https://www.doi.org/10.62547/XGJS9690

Abstract

A 2-year-old boy tested positive for SARS-CoV-2 and, after 30 days of mild-moderate respiratory symptoms, suddenly deteriorated and required extracorporeal membrane oxygenation. Lung biopsy was performed with findings consistent with organizing pneumonia. He received intensive therapy with high-dose methylprednisolone, intravenous immune globulin, rituximab, and plasmapheresis without improvement. He died after 85 days hospitalization. This case highlights unique presentations of COVID-19 and reaffirms the concept that, while rare in Hawai'i, pediatric COVID-19 is an ongoing problem and that severe, even fatal, disease can occur.

Keywords

children, complication, coronavirus, MDA-5, mortality, SARS-CoV-2

Abbreviations

COVID-19 = coronavirus disease 2019
ECMO = extracorporeal membrane oxygenation
IVIG = intravenous immune globulin
MDA-5 = melanoma differentiation-associated protein 5
MIS-C = multisystem inflammatory syndrome in children
OP = organizing pneumonia
PCR = polymerase chain reaction
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Introduction

Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initiated a global pandemic in late 2019. SARS-CoV-2 was first detected in the US in January 18, 2020, quickly spread and as of April 2024 resulted in 6 929 940 hospitalizations and 1187 994 deaths in the US.[1] One characteristic of COVID-19 is that severe cases are seen mainly among older individuals, yet children have not been spared, with 112 453 hospitalization and 1834 deaths reported in the same period.[1] The state of Hawai'i was able to contain the spread of SARS-CoV-2 initially with the first case not detected until March 6, 2020 followed then by a trickle of cases until July 2020, when more widespread circulation led to 211 850 hospitalizations and 2173 deaths by April 2024. As in the rest of the country, children in Hawai'i were affected to a lesser degree but there have still been 3042 hospitalizations and, sadly, 8 deaths among Hawai'i's children.[2] This is a report of one of those pediatric deaths. The authors present the case of a 2-year-old boy with a history of recent COVID-19 infection who was found to have organizing pneumonia (OP) that progressed to respiratory failure requiring extracorporeal membrane oxygenation (ECMO) and died despite aggressive management.

Case

A 2-year-old previously healthy boy tested positive for SARS-CoV-2 by nasal polymerase chain reaction (PCR), remained ill with mild to moderate respiratory symptoms, and after 30 days worsened with cough, fever, progressive weight loss, weakness, and elevated transaminases prompting hospitalization. Chest radiograph on admission showed slight increase in bilateral infiltrates (**Figure 1, panel A**), and computed tomography revealed multifocal, bilateral patchy infiltrates most prominent in the upper lobes (**Figure 1, panel B**). Initial evaluation was negative for infectious and inflammatory conditions including respiratory viruses, alpha-1-antitrypsin, human immunodeficiency virus, *Pneumocystis*, and tuberculosis. On hospital day 6, his respiratory condition worsened, prompting bronchoscopy. Bronchoalveolar lavage fluid was tested for infectious agents and found negative for *Mycobacterium tuberculosis* via PCR and acid-fast bacilli smear, bacterial culture, fungal culture and Gomori methenamine silver stain, viruses via respiratory viral PCR panel, *Pneumocystis jiroveci* via Direct Fluorescent Antibody and PCR, and positive only for SARS-CoV-2 by PCR.

Left lung biopsy was then obtained on hospital day 12. Evaluation of the lung biopsy tissue on hematoxylin-eosin and trichrome stains revealed an extensive and severe process with fibroblastic plugs, myxoid stroma obliterating the alveolar spaces, and reactive alveolar epithelial changes. The intervening lung parenchyma showed significant alveolar wall thickening and lymphoplasmacytic septal inflammation, with increased number of alveolar macrophages, as well as a mild acute intra alveolar component. These findings were compatible with OP (**Figure 2**). Periodic acid-Schiff stain for fungal organisms,

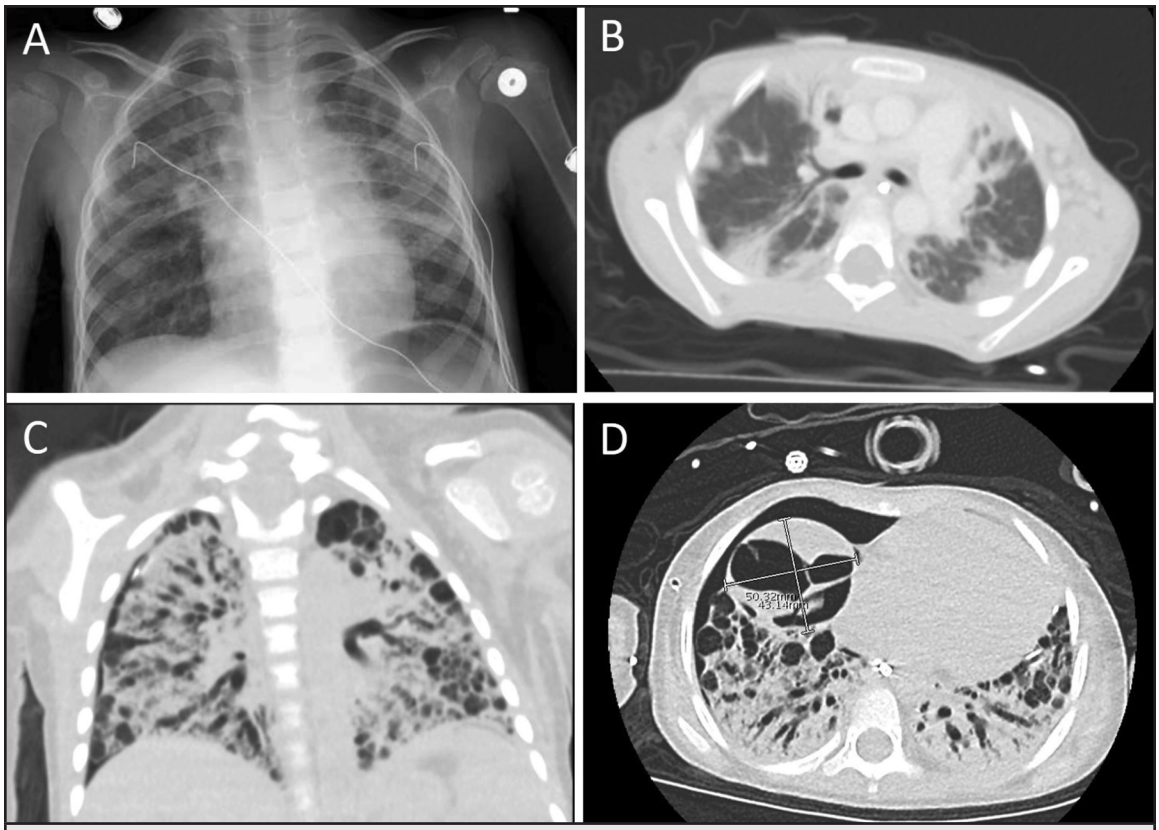

Figure 1. Progressing Radiographic Features of a Child with Organizing Pneumonia Associated with SARS-CoV-2 Infection

A: Admission chest radiograph with bilateral, mainly perihilar, infiltrates and no hilar lymphadenopathy. B: Chest computed tomography (hospital day 3) with patchy consolidate infiltrates of peripheral and upper lobes bilaterally. C: Chest computed tomography (hospital day 81) with extensive bilateral lung consolidation, marked bronchiectasis, cystic changes, and honeycombing – Coronal view. D: Axial view.

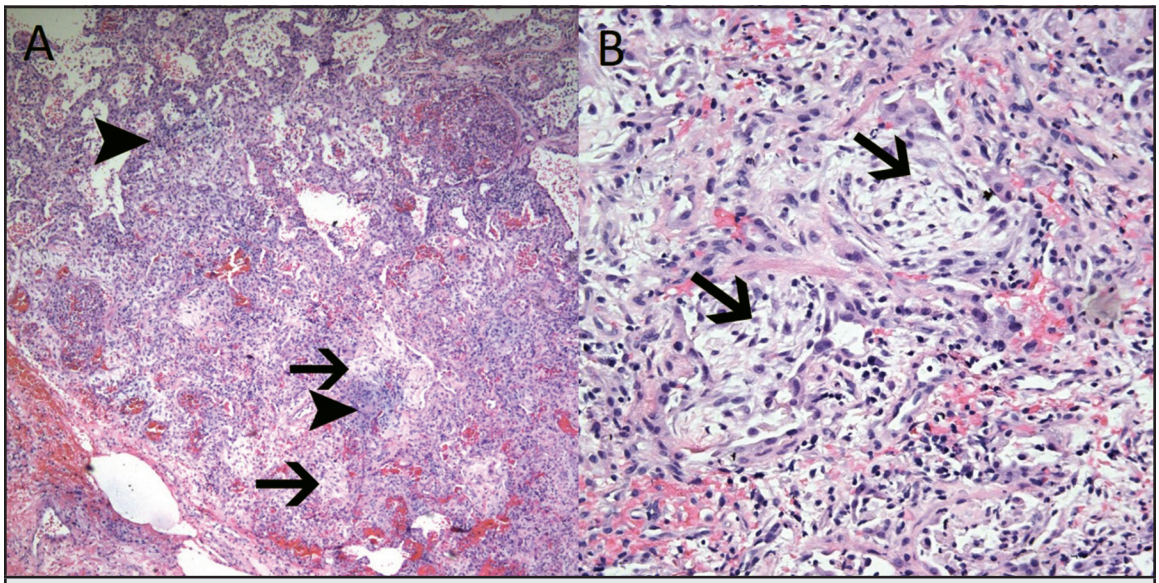

Figure 2. Histologic Features of a Child with Organizing Pneumonia Associated with SARS-CoV-2 Infection

A: Low power view of the lung biopsy reveals regions with preserved alveolar spaces (top half). In these areas, the alveolar septae are thickened. Large portions of the lung parenchyma are obliterated by a fibroblastic reaction with fibroblastic plugs filling airway spaces (arrows). A marked lymphoplasmacytic interstitial inflammatory infiltrate (arrowheads) is present throughout the biopsy (40X). B: Fibroblastic plugs with a myxoid stroma (arrows) are seen obliterating the alveolar spaces with associated reactive epithelial changes, indicative of organizing pneumonia (100X).

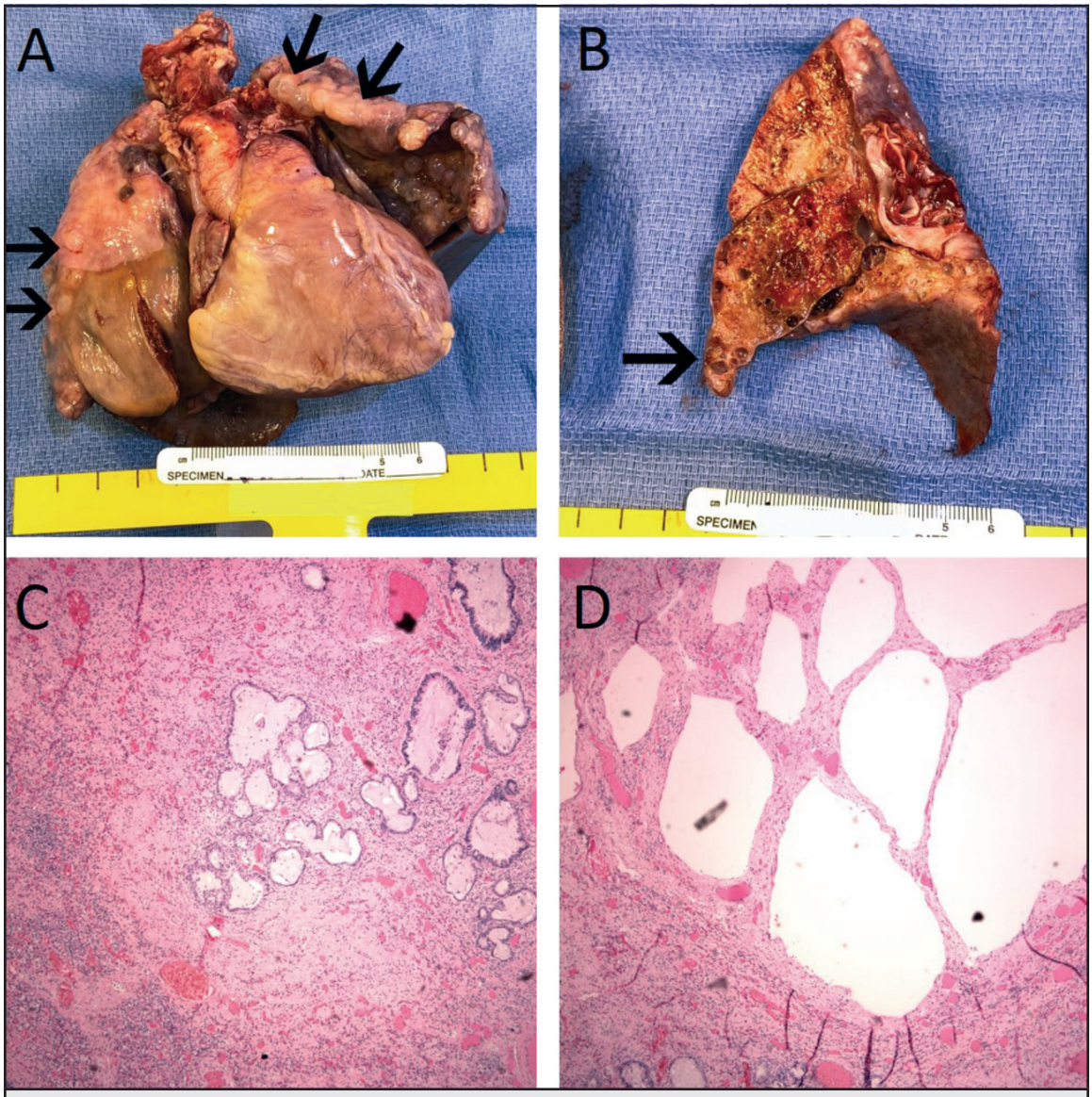

Figure 3. Autopsy Findings of a Child with Organizing Pneumonia Associated with SARS-CoV-2 Infection

A: Heart and lung block is pictured. Arrows point to subpleural nodular areas on both the right and left lung lobes that correspond to cystic spaces. B: Cut surfaces of all lung lobes reveal a dense, tan, fibrous cut surface with interspersed cystic spaces measuring between 0.2 and 2.0 cm. The left lung is pictured here. These cystic spaces are seen throughout the lung parenchyma, but are more prominent in peripheral and subpleural locations. Arrow points to a collection of subpleural cystic spaces. C: Low-power view of the right upper lobe of the lung shows dense, collagenous fibrosis obliterating the lung parenchyma. Scattered residual mucinous epithelial-lined bronchiolar structures (central) remain embedded within the fibrous stroma. Nests of atrophic alveolar structures (lower left) can be identified. D: Low-power view of a subpleural area demonstrates multicystic lung parenchyma with adjacent densely collagenous fibrous stroma obliterating the lung parenchyma. Residual bronchiolar structures are seen in the lower left.

Gomori methenamine silver stain for pneumocystis organisms, Cytomegalovirus immunohistochemical stain, and Epstein-Barr virus-encoded RNA stains were negative. Aerobic and anaerobic, acid-fast, fungal, and viral cultures performed on fresh lung tissue were negative, as was Legionella Direct Fluorescence Antibody. SARS-COV-2 in-situ hybridization stain detected rare, punctate sites of positive staining.

Following lung biopsy, the child quickly deteriorated with hypoxemia refractory to high mechanical ventilation support and inhaled nitric oxide. Veno-arterial ECMO was initiated on hospital day 14. High-dose methylprednisolone (30 mg/kg/day) was started on hospital day 13, rituximab (375 mg/m^2 BSA) and intravenous immune globulin (IVIG) (2 g/kg BW) were given on hospital day 18, both without response. He then

underwent plasmapheresis followed by a second dose of IVIG. An echocardiogram obtained on hospital day 67, showed coronary artery dilatation with all Z-scores >2, the largest (z score = 6.07) being the left anterior descending coronary artery. Despite aggressive treatment including 3 rounds of IVIG, 5 rounds of plasmapheresis, 1 round of tofacitinib (3.2 mg twice daily for 3 days, then 5 mg twice daily for 4 days), and 2 rounds of anti-interferon beta (200 mg on hospital day 64 and 76), the patient remained critical and in need of ECMO support. Chest computed tomography on hospital day 81 showed extensive bilateral lung consolidation, marked bronchiectasis, cystic changes, and honeycombing (**Figure 1, panels C and D**). Blood testing revealed antibodies against melanoma differentiation-associated protein 5 (MDA-5).

The patient died following withdrawal of cardiorespiratory support after 85 days of hospitalization and 71 days on ECMO. Autopsy findings included bilateral multicystic lungs with pleural adhesions, diffuse marked interstitial obliterative fibrosis and interstitial chronic inflammation. Patchy acute pneumonia of the left lower lobe, and large pseudocyst (6.5 cm) in the right lower lobe with organizing hemorrhage, serous pericardial effusion (14 cc) and biventricular hypertrophy were present. Other pathologic findings included hepatosplenomegaly, as well as peripancreatic, periampullary, and interstitial hemorrhage seen on the right renal pelvis and left ventricle (**Figure 3**).

Discussion

Most pediatric SARS-CoV-2 infections are mild, but severe and fatal cases have been documented.[3-5] The case here reported has many unique aspects: the patient's young age, no known co-morbidity, the subacute presentation, and rapid ultimate deterioration refractory to steroid and immunomodulatory therapy. The SARS-CoV-2 PCR positivity on bronchoalveolar lavage aspirate and positive staining on in-situ hybridization of lung tissue, but negative nasopharyngeal SARS-CoV-2 PCR suggest the persistence of the virus in the lower respiratory tract and a likely trigger of the pulmonary damage leading to OP. Given the paucity of antemortem histological lung specimens in children with COVID-19, it is possible the prevalence of OP may be underestimated.

OP is a unique pathological entity involving the lung parenchyma that can be incited by infections, drugs, environmental allergens, neoplastic, immunologic, or idiopathic processes.[6] OP has been described in association with a variety of infectious agents including *Legionella, Mycoplasma,* Influenza-B, *Mycobacterium tuberculosis*, and 2 previously known coronavirus: severe acute respiratory syndrome, and Middle East respiratory syndrome.[7-10] OP secondary to COVID-19 has been reported in adults.[11,12] To the best of the authors' knowledge, there has been only 1 case report of OP in association with severe COVID-19 in a pediatric patient, and that was after lung transplant.[13] Most cases of OP respond well to treatment with steroids but this patient, intriguingly, did not. The reason for this poor response is unknown, but the authors speculate it may be due to SARS-CoV-2 itself and the way it damages the lung parenchyma, especially when severe. Merdji et al presented an autopsy series of 22 patients with fatal COVID-19, describing that the lung histologic findings were not different between patients who had received steroids and those who had not, suggesting a lack of response to steroids among severe, fatal COVID-19.[14] Another potential explanation for the lack of response to treatment, may be the late presentation (more than a month into the illness) with advanced and possibly irreversible damage to the lung parenchyma, raising the potential value of early identification and treatment.

Two additional unique features of this case are the anti-MDA-5 positivity, and the prominent dilation of the coronary arteries. Anti-MDA-5 is an autoantibody associated with rapidly developing interstitial lung disease classically seen in patients with dermatomyositis. Only rarely has MDA-5-positive rapidly developing interstitial lung disease been reported in absence of signs of dermatomyositis.[15,16] The patient here described did not have skin findings characteristic of dermatomyositis, and the authors believe his anti-MDA-5 antibodies were possibly acquired after his SARS-CoV-2 infection, as has been proposed by others.[17] Indeed, COVID-19 has been found associated with multiple other autoimmune disease processes. [18] While more research is needed, the presence of anti-MDA-5 may represent a biomarker of severe COVID-19 disease that should prompt more aggressive treatment. Cardiac involvement in the form of coronary artery aneurysm is more frequently associated with multisystem inflammatory syndrome in children (MIS-C) than with severe acute COVID-19.[19] While there may be some overlap in the 2 entities, the clinical presentation by the patient discussed here, seems more compatible with protracted COVID-19 than MIS-C. The finding of coronary artery aneurysms would suggest that pediatric patients with severe forms of COVID-19 may benefit from a workup during their acute or post-COVID syndrome phase for evaluation of coronary vasculopathy.

Conclusion

COVID-19 represents a new and evolving pandemic that has drastically affected the world, with new manifestations still being described. Hawai'i has not been spared and, while the disease is more common and severe among adults, children have also endured severe and fatal cases. Here is presented an unfortunate, unusually severe case of COVID-19 in a child resulting in OP and a fatal outcome. With this report, the authors wish to bring awareness to the pediatric community of the entity of OP and its association with COVID-19. While it cannot be tested with a single case, it is plausible to speculate that early recognition and initiation of potentially useful therapy, including immune-targeted therapies, may prevent further progression and complications.

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Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgements

The authors are grateful to the family of the patient that, despite their loss, consented to the publication of the case in the hope to further medical knowledge and improve care for other children affected.

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