Cardiorespiratory complications in pediatric oncology patients with COVID-19 infection

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Abstract

The risk of the novel coronavirus disease 2019 (COVID-19) to pediatric oncology patients is unknown. Here, we report eight pediatric oncology patients receiving active cancer therapy that tested positive for COVID-19. Three developed severe cardiorespiratory symptoms (as defined by evidence of heart failure by echocardiogram and/or intubation secondary to respiratory failure), including one death as a result of COVID-19 infection. We identified prior anthracycline exposure and pre-COVID cardiac function as significantly associated with the development of severe cardiorespiratory complications. These data merit future and further investigation of risk factors for severe complications related to COVID-19 infections in pediatric oncology patients.

Introduction

The effect of novel coronavirus disease 2019 (COVID-19) on pediatric oncology patients is unknown. Early reports from China, Europe, and New York/New Jersey have shown minimal to no risk for morbidity or mortality in children with cancer and have been unable to find significant risk factors for severe disease in this patient population.[1,2,3,4,5] Here, we report three patients with pediatric cancer who developed severe cardiorespiratory dysfunction (as defined by evidence of heart failure by echocardiogram and/or intubation secondary to respiratory failure) following COVID-19 infections, with one resultant death. We compared clinical and host factors between these three patients with severe cardiorespiratory symptoms to five patients in active treatment at our institution who tested positive for COVID-19 but did not develop severe cardiorespiratory symptoms.

Results

Case 1: 13 year-old female, treated for Ewing Sarcoma of the left proximal femur at 2 years old per Children's Oncology Group (COG) protocol AEWS0031 (375mg/m^2 doxorubicin, no dexrazoxane) along with left above the knee amputation, presented with abdominal pain and nausea 11 weeks after testing positive for COVID-19. An echocardiogram showed severely diminished left ventricular systolic dysfunction with a 28% ejection fraction (EF) along with a large thrombus in the right atrium and right ventricle with elevated pulmonary vascular resistance and severe tricuspid regurgitation. One week prior, her annual echocardiogram revealed a 57% EF. She tested negative for acute COVID-19 infection (PCR test), but had a positive IgG for SARS-CoV-2. She was treated with milrinone, aggressive diuresis, and enalapril. A cardiac MRI showed myocarditis by MRI Lake Louise criteria, scarring characteristic of ischemia, and bilateral non-occlusive and subsegmental pulmonary embolisms in addition to the intra-cardiac thrombi. She was treated with methylprednisolone (2d) but not with IVIG, as she did not meet diagnostic criteria for multisystem inflammatory syndrome in

children (MIS-C). Unfractionated heparin and aspirin were administered for her thrombi. She was weaned off milrinone; started on digoxin, spironolactone, furosemide, and enoxaparin; and eventually discharged home. Six months later, her EF remained diminished at 35%.

Case 2: 19 year-old male, treated two years prior for low risk central nervous system (CNS) positive acute myelogenous leukemia (AML) per COG protocol AAML1031 (342mg/m^2 doxorubicin equivalents with dexrazoxane), presented with fever and cough, found to be COVID-19 positive without respiratory distress. Neutropenia and thrombocytopenia were noted. One month later, he presented with fevers and hypotension with evidence of heart failure and coagulopathy, requiring brief inotropic support. Echocardiogram revealed 24% EF, compared to 67% EF nine months earlier. He responded to IVIG (3d) and methylprednisolone (4d) treatment for MIS-C. A bone marrow biopsy for persistent neutropenia and thrombocytopenia revealed relapse of his AML. His heart failure improved 8 days later to 67% EF, but currently, he continues on lisinopril.

Case 3: 4 year-old male with a history of congenital CMV was treated for low risk CNS negative AML per COG protocol AAML1031 (342mg/m^2 doxorubicin equivalents with dexrazoxane), but relapsed three months off therapy. He underwent re-induction per COG protocol AAML1421 consisting of vyxeos (liposomal daunorubicin, 29.7 mg/m2 doxorubicin equivalents) followed by fludarabine, cytarabine, and gemtuzumab. He had a bone marrow with residual disease of 0.37% by flow cytometry prior to undergoing a matched unrelated cord transplant with anti-thymocyte globulin, busulfan, and fludarabine conditioning. He was intubated from D+18 through +37 due to complications of engraftment syndrome, eventually weaned to room air. On day +62, he was found to have 0.27% residual disease by flow cytometry after developing peripheral blasts. Immunosuppression was weaned; he received decitabine days +65 through +69 for relapse therapy. He became febrile with a blood culture positive for coagulase-negative *Staphylococcus* on day +68 and hypoxic on day +76 with a subsequent positive test for COVID-19. Multiple family members tested positive for COVID-19, and this was deemed to be hospital acquired from family members. Due to worsening respiratory status, he was intubated on D+87. An echocardiogram showed diffuse dilation of his left main and left anterior descending coronary arteries, but stable systolic function with a 30% SF compared to 28% three months prior. However, on a repeat echo three days later, his coronary arteries were normal, and he did not require IVIG treatment. He underwent treatment with remdesivir (10d), dexamethasone (3d), tocilizumab, and convalescent plasma without clinical improvement. On day +114, routine adenovirus testing was positive by PCR on blood and respiratory viral panel, after being negative 7 days prior, and he was started on cidofovir. His COVID-19 PCR remained positive until day +119 and on day +121, he succumbed to respiratory failure secondary to his prolonged COVID-19 infection with superimposed adenovirus infection.

During this time, we also cared for five pediatric oncology patients in active treatment who tested positive for COVID-19 infection, all with acute lymphoblastic leukemia (ALL) (Table 1). None of these patients developed severe cardiorespiratory complications and were thus classified as the non-severe group for this study. One patient within this group developed a cerebral sinus venous thrombosis presumed to be from a combination of his COVID-19 infection and recent pegylated aspargase treatment, but did not develop any serious sequelae or cardiorespiratory symptoms.

Comparison of potential risk factors for infectious complications of COVID-19 (including age, WBC, neutrophils, lymphocytes, platelets, or type-A blood) showed no significant differences between the severe and non-severe groups (Table 1, Fig. 1A-E). In contrast, anthracycline exposure was significantly increased in the severe group (mean 362.9+ 10.49 SEM vs 80 + 18.37 mg/m^{2}doxorubicin dose equivalents, p<0.001, t-test, Fig 1F). Baseline cardiac function (as defined by echocardiogram shortening fraction) was also significantly lower in the severe group (mean 32%+ 1.5 vs 39.8% + 2.2, p= 0.036, Mann-Whitney) (Fig 1G).

Discussion

Previous reports intimate that pediatric oncology patients with COVID-19 infection would not appear to be at increased risk for deleterious outcomes. Our report would suggest otherwise. Case 1 continues to have heart failure more than six months after initial infection with COVID-19 with MRI findings consistent with

myocardial scarring and ischemia. In contrast, Case 2 followed a more typical clinical course of heart failure in children with MIS-C with rapid improvement after immunomodulatory treatment[6,7]. Finally, COVID-19 infection largely contributed to the death of Case 3.

Prior anthracycline exposure seems to correlate with a more severe COVID-19 disease course, consistent with the increased risk for cardiotoxicity seen with anthracyclines[8] and the increased risk of morbidity and mortality seen in COVID-19 infected adults with concomitant cardiac disease.[9,10] Similar to other reports, we did not find any correlation with immune status at time of infection or type A blood with the development of severe disease.[4] We did not have sufficient data to evaluate additional risk factors such as inflammatory markers, iron overload, or post-COVID cardiac function.

This case series illustrates that pediatric oncology patients are potentially at increased risk for cardiorespiratory complications from COVID-19 infections and prior anthracycline exposure may represent a risk factor for a more severe disease course. However, given the limited sample size and lack of data of other potential risk factors, follow-up studies are merited.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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References

1. Balduzzi A, Brivio E, Rovelli A, Rizzari C, Gasperini S, Melzi ML, Conter V, Biondi A. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Estote parati. *Bone Marrow Transplant* . 2020;55(10):1900-1905.

2. Bouffet E, Challinor J, Sullivan M, Biondi A, Rodriguez-Galindo C, Pritchard-Jones K. Early advice on managing children with cancer during the COVID-19 pandemic and a call for sharing experiences. *Pediatr Blood Cancer* . 2020;67(7):e28327.

3. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, Liu ZS. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr* . 2020;16(3):251-259.

4. Madhusoodhan PP, Pierro J, Musante J, Kothari P, Gampel B, Appel B, Levy A, Tal A, Hogan L, Sharma A, Feinberg S, Kahn A, Pinchinat A, Bhatla T, Glasser CL, Satwani P, Raetz EA, Onel K, Carrol WL. Characterization of COVID-19 disease in pediatric oncology patients: The New York-New Jersey regional experience. *Pediatr Blood Cancer* . 2021;68(3):e28843.

5. Gampel B, Troullioud Lucas AG, Broglie L, Gartell-Corrado RD, Lee MT, Levine J, Orjuela-Grimm M, Satwani P, Glade-Bender J, Roberts SS. COVID-19 disease in New York City pediatric hematology and oncology patients. *Pediatr Blood Cancer* . 2020;67(9):e28420.

6. Jain S, Nolan SM, Singh AR, Lovig L, Biller R, Kamat A, Brennan MH, Erb M, Rescoe E, Tatz G, Gewitz MH. Jain S, Nolan SM, Singh AR, et al. Myocarditis in Multisystem Inflammatory Syndrome in Children Associated With Coronavirus Disease 2019 [published correction appears in Cardiol Rev. 2021 Jan/Feb;29(1):54]. *Cardiol Rev* . 2020;28(6):308-311.

7. Sharma M, Gorstein S, Aldrich ML, Hsu DT, Choueiter NF. Reversible Myocardial Injury Associated With SARS-CoV-2 in an Infant. *JACC Case Rep* . 2020;2(15):2348-2352.

8. Liesse K, Harris J, Chan M, Schmidt ML, Chiu B. Dexrazoxane Significantly Reduces Anthracycline-induced Cardiotoxicity in Pediatric Solid Tumor Patients: A Systematic Review. *J Pediatr Hematol Oncol* . 2018;40(6):417-425.

9. Sanna G, Serrau G, Bassareo PP, Neroni P, Fanos V, Marcialis MA. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. *Eur J Pediatr* . 2020;179(7):1079-1087.

10. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* . 2020;22(6):957-966.

Figure Legends

Figure 1. COVID-positive pediatric oncology patients who develop severe cardiorespiratory symptoms have significantly increased cumulative anthracycline exposure and decreased pre-COVID cardioechogram shortening fractions compared to COVID-positive counterparts who did not develop cardiorespiratory symptoms. Comparison of (A) age, (B) white blood cell count, (C) absolute lymphocyte count, (D) absolute neutrophil count, (E) platelets, (F) cumulative anthracycline exposure, and (G) pre-COVID cardiac echocardiogram shortening fraction in COVID-positive pediatric oncology patients who developed severe and mild clinical symptoms. Severe cardiorespiratory symptoms as defined by evidence of heart failure and/or intubation secondary to respiratory failure. Bars = Mean + SEM. Points represent values from individual patients. Shapiro-Wilk normality test was performed on each data set. The appropriate parametric (student t-test) or non-parametric (Mann-Whitney) test was then used. ns, non-significant. *, $p<0.05$. **, $p<0.01$. ***, $p<0.001$.

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