Received: 28 March 2021 | Accepted: 21 April 2021

DOI: 10.1002/pbc.29105

Pediatric Blood & Cancer

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

LETTER TO THE EDITOR

Transient leukopenia, thrombocytopenia, and severe neutropenia associated with acute SARS-CoV-2 infection

To the Editor:

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported to cause a myriad of manifestations and complications in both children and adults. One of the less reported phenomena relates to its effect on the bone marrow. There are several documented cases of immune thrombocytopenic purpura as well as autoimmune hemolytic anemia secondary to SARS-CoV-2 infection. However, limited evidence exists for transient severe neutropenia in the setting of diagnosed SARS-CoV-2 infection in pediatric patients.[1,2] Xu et al.[3] described the mechanism of thrombocytopenia related to COVID-19 as multifactorial including lung injury resulting in increased platelet consumption, direct infection of bone marrow stromal cells, and cytokine storm resulting in destruction of bone marrow progenitor cells. Likewise, there are documented cases of lymphopenia secondary to proposed lymphocyte apoptosis during inflammatory storms.[4] Additionally, two cases of severe neutropenia in neonates have been reported by Venturini et al.[5] in association with mild COVID-19. We present a case of a 17-year-old female diagnosed with laboratory confirmed SARS-CoV-2 infection with leukopenia, thrombocytopenia, and severe neutropenia who was cared for at our academic community-based tertiary center.

A 17-year-old female with a history of trisomy 21, aortic insufficiency, celiac disease, and obesity was admitted to our institution as a transfer from an outside emergency department with dehydration, fever, diarrhea, and a recent, known household member positive for SARS-CoV-2. Prior to admission, the patient experienced 5 days of fever, lethargy, mucopurulent nasal secretions, reduced oral intake, and decreased urine output. The patient's vital signs were normal at time of admission. Laboratory evaluation revealed leukopenia (900/μL), thrombocytopenia (98,000/μL), and severe neutropenia (0.351 $\times$ 109/L neutrophils). No morphological abnormalities were observed on the peripheral blood smear. Chest radiography revealed bilateral pneumonia visualized in the lower lung fields. The patient was placed on empiric antibiotics secondary to severe neutropenia.

Over the course of the next 24 h, the patient's nasopharyngeal swab detected SARS-CoV-2. She developed hypoxemia requiring escalation of care to our pediatric intensive care unit and high flow oxygen therapy was initiated. The patient was treated with corticosteroids and an antiviral (remdesivir) given worsening clinical status according to institutional guidelines and in consultation with pediatric infectious disease. The patient underwent further laboratory evaluation with findings of mildly elevated D-dimer level (0.87 mcg/ml) and hypoalbuminemia (2.7 mg/dl). Otherwise, no additional laboratory abnormalities were noted.

Throughout the course of her hospital stay, the patient's hematological manifestations improved with uptrend of her white blood count (1400/μL), platelet count (132,000/μL), and absolute neutrophil count (0.798 $\times$ 109/L neutrophils) without clinical complications. The patient was transferred to the general pediatrics floor on day 5 of hospitalization, weaning off oxygen support. She was subsequently discharged on day 6 of hospitalization after tolerating room air without further hypoxemia. The patient followed up with her pediatrician 1 month later and repeat laboratory evaluation revealed normal white blood count, platelet count, and absolute neutrophil count.

Previous cases of bone marrow suppression related to COVID-19 included a 33-year-old female patient who underwent extensive evaluation for myelodysplasias including bone marrow biopsy and ultimately received granulocyte colony-stimulating factor (G-CSF) for severe neutropenia 11 days following acute SARS-CoV-2 infection.[6] Additionally, a 5-month-old diagnosed with multisystem inflammatory syndrome in children in the setting of 36-h history of persistent fever, perineal cellulitis, and lip ulceration with a negative SARS-CoV-2 PCR but positive IgG and IgM was noted to have severe neutropenia treated with G-CSF. No previous clinical symptoms occurred for which acute SARS-CoV-2 infection was suspected.[7] Lastly, a 23-day-old and a 39-day-old neonate with mild COVID-19 were noted to have severe neutropenia that resolved without intervention, and thought to be related to postinfectious transient neutropenia associated with viral infections in infancy.[1] The true extent of viral-induced bone marrow failure is not completely understood, especially as it relates to SARS-CoV-2. For example, the influenza virus, hepatitis virus, enterovirus, and Ebstein–Barr virus are thought to facilitate hepatic platelet clearance, deplete hematopoietic progenitor cells, and induce anti-neutrophil antibody formation, thus causing thrombocytopenia, anemia, and neutropenia.[8–11] Bone marrow suppression by well-known viruses could explain the hematological manifestations of SARS-CoV-2. However, individuals with trisomy 21 are at increased risk of developing hematologic disturbances such as lymphoid and myeloid leukemias. In fact, 5–10% of infants with trisomy 21 develop transient myeloproliferative disease.[12] Mutations in *GATA 1* are well recognized in trisomy 21 to cause megakaryocyte and erythroid abnormalities but not myeloid.[13] Thus, the presence of leukopenia, thrombocytopenia, and severe neutropenia in our patient remain novel findings. Rapid bone marrow response occurred without

further evaluation with a bone marrow biopsy or requiring therapeutic intervention. Bone marrow biopsy may not be indicated in patients with SARS-CoV-2 infection and hematological abnormalities given the transient nature of blood cell lines even in those with trisomy 21.

ACKNOWLEDGMENTS

The authors would like to acknowledge the multidisciplinary team at Lehigh Valley Reilly Children's Hospital. We would like to acknowledge the child and her family for providing consent for the publication of this report.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Austin Schatzman
Julia Vandenheuvel
Tibisay Villalobos
Kris Rooney

Department of Pediatrics, Lehigh Valley Reilly Children's Hospital, Allentown, Pennsylvania, USA

Correspondence
Julia Vandenheuvel, Department of Pediatrics, Lehigh Valley Reilly Children's Hospital, 1200 South Cedar Crest Blvd, Allentown, PA 18103, USA.
Email: Julia.vandenheuvel@lvhn.org

ORCID

Julia Vandenheuvel https://orcid.org/0000-0001-5345-926X

REFERENCES

1. Rosenzweig JD, McThenia SS, Kaicker S. SARS-CoV-2 infection in two pediatric patients with immune cytopenias: a single institution experience during the pandemic. *Pediatr Blood Cancer*. 2020;67(9): e28503.
2. Hersby DS, Do TH, Gang AO, Nielsen TH. COVID-19-associated pancytopenia can be self-limiting and does not necessarily warrant bone marrow biopsy for the purposes of SARS-CoV-2 diagnostics. *Ann Oncol*. 2021;32(1):121-123.
3. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. 2020;99(6):1205-1208.
4. Kosmeri C, Koumpis E, Tsabouri S, Siomou E, Makis A. Hematological manifestations of SARS-CoV-2 in children. *Pediatr Blood Cancer*. 2020;67(12):e28745.
5. Venturini E, Palmas G, Montagnani C, et al. Severe neutropenia in infants with severe acute respiratory syndrome caused by the novel coronavirus 2019 infection. *J Pediatr*. 2020;222:259-261.
6. López-Pereira P, Iturrate I, de La Cámara R, Cardeñoso L, Alegre A, Aguado B. Can COVID-19 cause severe neutropenia? *Clin Case Rep*. 2020;8(12):3349-3351.
7. Bouslama B, Pierret C, Khelfaoui F, Bellanné-Chantelot C, Donadieu J, Héritier S. Post-COVID-19 severe neutropenia. *Pediatr Blood Cancer*. 2021. 68(5):e28866. https://doi.org/10.1002/pbc.28866
8. Jansen AJ, Spaan T, Low HZ, et al. Influenza-induced thrombocytopenia is dependent on the subtype and sialoglycan receptor and increases with virus pathogenicity. *Blood Adv*. 2020;4(13):2967–2978.
9. Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. *Aliment Pharmacol Ther*. 2007;26(Suppl 1):13-19.
10. Althof N, Whitton JL. Coxsackievirus B3 infects the bone marrow and diminishes the restorative capacity of erythroid and lymphoid progenitors. *J Virol*. 2013;87(5): 2823–2834.
11. Segel GB, Halterman JS. Neutropenia in pediatric practice. *Pediatr Rev*. 2008;29(1):12-24.
12. Maclean GA, Menne TF, Guo G, et al. Altered hematopoiesis in trisomy 21 as revealed through in vitro differentiation of isogenic human pluripotent cells. *Proc Natl Acad Sci U S A*. 2012;109(43): 17567-17572.
13. Mast KJ, Taub JW, Alonzo TA, et al. Pathologic features of down syndrome myelodysplastic syndrome and acute myeloid leukemia: a report from the Children's Oncology Group Protocol AAML0431. *Arch Pathol Lab Med*. 2020;144(4):466-472.