Received: 17 October 2021 | Accepted: 20 October 2021

DOI: 10.1002/pbc.29433

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

SARS-CoV-2 infection coincident with newly diagnosed severe aplastic anemia: A report of two cases

To the Editor

Severe aplastic anemia (SAA) is a rare, life-threatening condition associated with peripheral cytopenias and bone marrow hypocellularity.[1] The pathogenesis of acquired SAA is varied; in some cases, evidence supports immune dysregulation leading to T-cell-mediated destruction of hematopoietic stem cells.[2,3] Treatments include matched sibling donor hematopoietic cell transplant, when feasible, or immunosuppressive therapy (IST).[4,5] Pediatric patients who contract severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can develop a spectrum of illness including coronavirus disease-2019 (COVID-19), with symptoms ranging from minimal symptoms to severe respiratory distress or postinfectious multisystem inflammatory syndrome in children (MIS-C).[6,7] We present two patients with SARS-CoV-2 infection coincident with new SAA diagnosis.

This case report was approved by the Vanderbilt University Medical Center Institutional Review Board.

Case 1: A 12-year-old female presented with pallor, fatigue, and chest tightness. Initial laboratory analysis revealed the following: white blood cell (WBC) count 2300/μl, absolute neutrophil count (ANC) 280/μl, absolute lymphocyte count (ALC) 1900/μl, hemoglobin (Hgb) 6.3 gm/dl, reticulocyte count 34,000/μl, and platelet count 10,000/μl. On pre-admission screening, she tested positive for SARS-CoV-2 via polymerase chain reaction (PCR). She was diagnosed with SAA based on laboratory criteria, confirmed by bone marrow biopsy which revealed a hypocellular marrow with 10% cellularity and no evidence of malignancy (Figure 1A). Thorough evaluation of inherited and acquired etiologies of SAA did not reveal a cause. She experienced a mild clinical course of COVID-19 with fever but made a complete recovery. A sibling match was not identified, so she received IST with anti-thymoglobulin (ATG) and cyclosporine. She became transfusion independent 2 months following initiation of IST and cyclosporine wean was initiated.

Case 2: An 18-year-old male presented with fatigue, headache, and fever. Labs were notable for WBC 2200/μl, ANC 390/μl, ALC 1690/μl, Hgb 3.8 gm/dl, reticulocyte count 18,000/μl, and platelet count 13,000/μl. Pre-admission screening was positive for SARS-CoV-2 via PCR. Bone marrow biopsy showed 10% cellularity without evidence of malignancy (Figure 1B), confirming SAA. Extensive evaluation for inherited or acquired etiologies of SAA was unrevealing. He had no siblings and received IST with ATG and cyclosporine. While he has been transfusion independent, he was started on eltrombopag due to refractory thrombocytopenia to 20,000/μl and has had a good response.

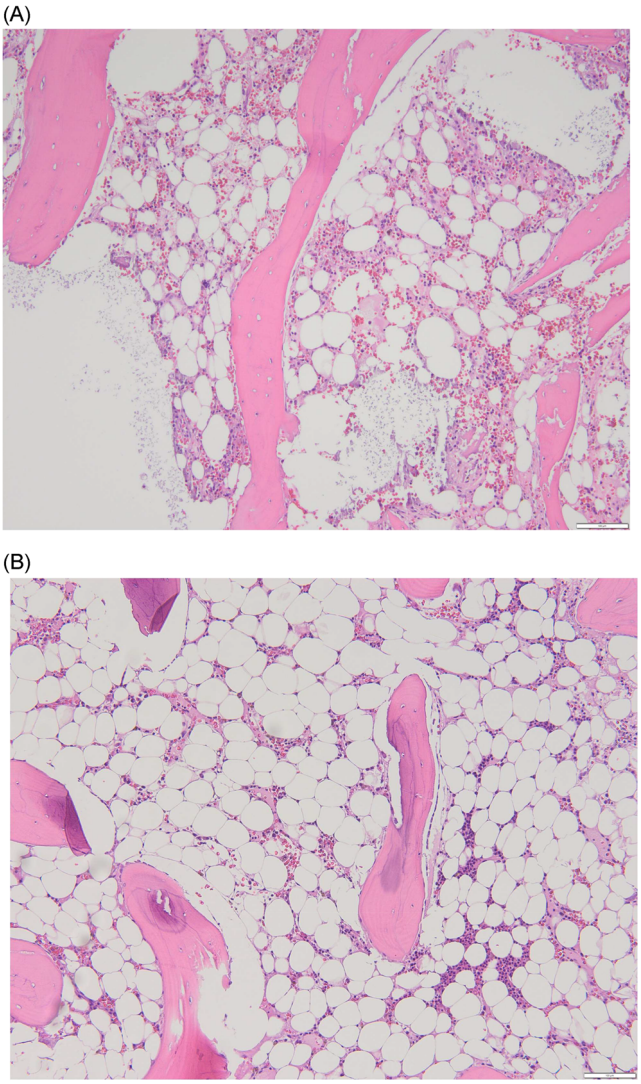

FIGURE 1 Initial bone marrow histology for Case 1 (A) and Case 2 (B). The hematoxylin and eosin-stained bone marrow sections at 100× magnification reveal markedly hypocellular marrow of 10% with decreased trilineage hematopoiesis without significant dysplasia, lymphoid aggregates, or increase in blasts

Although some cases of SAA are attributed to infections, drugs/toxins, hepatitis, or underlying bone marrow failure disorders,[3,8,9] there are a proportion that are immune mediated. In children with COVID-19 and MIS-C, studies have found elevation of various inflammatory cytokines suggesting immune dysregulation.[7,10] During an initial period of observation, our patients did not demonstrate spontaneous resolution of peripheral cytopenias and marrow hypocellularity arguing against a diagnosis of viral myelosuppression. Rather, their clinical course and response to IST has led to our hypothesis that this novel coronavirus may contribute to the typical immune-mediated pathogenesis of SAA. We acknowledge that further studies regarding this infection's effect on the immune system along with evaluation of more patients with similar presentations will be imperative to understand the mechanism of action.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Rohini Chakravarthy[1]
Meghan L. Murphy[1]
Mary Ann Thompson[2]
Heather L. McDaniel[1]
Sara Zarnegar-Lumley[1]
Scott C. Borinstein[1]

[1] *Division of Pediatric Hematology/Oncology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA*
[2] *Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA*

Correspondence
Rohini Chakravarthy, Department of Pediatrics, Vanderbilt University Medical Center, 2220 Pierce Ave., 397 Preston Research Building, Nashville, TN 37232-6310, USA.
Email: rohini.chakravarthy.2@vumc.org

ORCID

Rohini Chakravarthy https://orcid.org/0000-0002-8299-2554

REFERENCES

1. Young NS. Aplastic anemia. *N Engl J Med*. 2018;379(17):1643-1656.
2. Schoettler ML, Nathan DG. The pathophysiology of acquired aplastic anemia: current concepts revisited. *Hematol Oncol Clin North Am*. 2018;32(4):581-594.
3. Hartung HD, Olson TS, Bessler M. Acquired aplastic anemia in children. *Pediatr Clin North Am*. 2013;60(6):1311-1336.
4. Thomas ED, Storb R, Fefer A, et al. Aplastic anaemia treated by marrow transplantation. *Lancet*. 1972;1(7745):284-289.
5. Yoshida N, Kojima S. Updated guidelines for the treatment of acquired aplastic anemia in children. *Curr Oncol Rep*. 2018;20(9):67.
6. Rasmussen SA, Thompson LA. Coronavirus disease 2019 and children: what pediatric health care clinicians need to know. *JAMA Pediatr*. 2020;174(8):743-744.
7. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. *J Clin Invest*. 2020;130(11):5967-5975.
8. Shimano KA, Narla A, Rose MJ, et al. Diagnostic work-up for severe aplastic anemia in children: consensus of the North American Pediatric Aplastic Anemia Consortium. *Am J Hematol*. 2021.
9. Rauff B, Idrees M, Shah SA, et al. Hepatitis associated aplastic anemia: a review. *Virol J*. 2011;8:87.
10. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021;191(1):4-17.