COVID-19 and Hereditary Spherocytosis: A Recipe for Hemolysis

Tyler Severance[1], Mahvish Rahim[1], James French[1], Richelle Baker[1], Andrew Shriner[1], Alka Khaitan[1], and Kathleen Overholt[1]

[1]Riley Hospital for Children

May 28, 2020

Abstract

Coronavirus Disease 2019 (COVID-19) is the most devastating pandemic of this century. Little is known about the impact of COVID-19 on children, especially those with underlying conditions. We describe the case of a 4-year-old with hereditary spherocytosis who was found to be positive for COVID-19 and secondary hemolytic anemia. With supportive care and transfusions, he clinically improved, and his hemoglobin stabilized. This case reminds us to remain vigilant in evaluating high risk patients for hemolysis in the face of infection. Further studies on the clinical presentation and trajectory of patients presenting with COVID-19 and underlying disease should be encouraged.

Main Text

Introduction:

Hereditary spherocytosis (HS) is an inherited hemolytic disease which has a wide spectrum of phenotypic expression ranging from asymptomatic to chronic ongoing hemolysis[1]. Clinical findings of this disease are due to genetic mutations in plasma membrane proteins which result in an unstable red blood cell membrane-cytoskeleton interaction. This dysfunctional interaction places the red blood cells at higher risk for hemolysis triggered by various stressors including fever and hypoxia.[1-3] Splenic clearance of damaged red blood cells results in anemia , thus patients are treated with supportive transfusion and splenectomy can be utilized to decrease chronic hemolysis in severely affected patients.[4,5]

The novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19), emerged in Wuhan province in China in December 2019 and has affected over 2 million people globally as of April 2020.[6] Many studies have found that the spread of COVID-19 is very rapid due to the highly contagious nature of the disease, resulting in a global pandemic.[7-10] While information about this virus is still evolving, children have had less severe manifestations of COVID-19 with proportionately fewer pediatric cases requiring hospitalization.[11] In the US, a Center for Disease Control Morbidity and Mortality Weekly Report found that children account for 22% of the population but only 1.7% of overall COVID-19 cases.[12] There is still much to learn regarding how COVID-19 affects children with underlying chronic disorders and what important clinical presentations and labs should be followed in patients who have a chronic illness.

We describe a unique case of a pediatric patient infected with COVID-19 in the setting of a known chronic illness, HS, and the resulting presentation and medical complications. This case report is published with parental permission.

Case:

We present a 4-year-old male with a history of moderate HS and sickle cell trait without prior splenectomy who presented with two days of worsening cough, congestion, and subjective fevers. At presentation, he had

mild decrease in oral intake and mother had noted some slight yellow discoloration of his eyes. The patient's mother was sick with similar upper respiratory symptoms, but there were no known COVID-19 exposures.

He reported to the emergency room and was found to be febrile and tachycardic, but otherwise hemodynamically stable. His exam was notable for a palpable spleen tip just below the rib margin and scleral icterus without other significant findings. Additionally, a chest x-ray was within normal limits.

Lab work-up was notable for a hemoglobin of 6.5 GM/dL, an absolute reticulocyte count of 333 k/cumm, and a total bilirubin of 6 mg/dL, suggestive of an acute hemolytic process. Other cell lines were within normal limits with a reassuring differential, and his remaining metabolic profile was also within normal limits. Due to the fever, cough, and congestion, a COVID-19 nasopharyngeal polymerase chain reaction was performed in accordance with our institution's guidelines. He was admitted and given an infusion of 10ml/kg of packed red blood cells (pRBCs). The transfusion was complicated by a fever, and he only received 6ML/kg of red blood cells.

On hospital day 1, labs continued to indicate a hemolytic process and hemoglobin was relatively unchanged at 6.5 gm/dL (Table 1). His COVID-19 sample returned positive and COVID-19 specific labs showed a white blood cell count of 6.9 k/cumm, a lymphocyte percentage of 52%, a C-reactive protein of <0.5 mg/dL, and Aspartate aminotransferase (AST) and alanine transaminase (ALT) of 37 and 11 Units/L respectively. It is believed that his fever during the transfusion was due to COVID-19 and was not a transfusion reaction. With the persistently low hemoglobin, he received a second transfusion of red blood cells without complications. His hemoglobin improved to 10.7 gm/dL, and his hemolysis markers were trending to normal. Hemoglobin obtained 6 hours later was found to be stable at 10.7 gm/dL, indicating no further hemolysis. He was at his baseline behavior and resolution of scleral icterus without any respiratory distress. He was discharged home with instructions to quarantine for at least 14 days in accordance with published guidelines. At time of phone follow up 48 hours after discharge, he continued to do well with no appreciable evidence of jaundice or worsening respiratory status.

Discussion:

Hereditary spherocytosis results in an increased risk of hemolysis with cellular stress and splenic clearance. Patients can develop significant intermittent hemolysis and splenomegaly or have baseline chronic hemolysis which occasionally necessitates splenectomy for control of severe chronic anemia. Patients and care providers are educated on the importance of monitoring for hemolysis during febrile episodes to avoid an array of complications from acute anemia. While hemolysis in patients with HS and viral infection is a well-known complication of this disorder, it has only been described in the context of hydroxychloroquine toxicity in subjects with COVID-19.[13]

Our patient, with underlying HS with COVID-19 infection and hemolysis, emphasizes the necessity to follow patients at risk for hemolysis closely in the setting of COVID-19. There have been reports about patients with sickle cell disease who were infected with COVID-19, however no case report has addressed the risk of hemolysis in patients with hemolytic anemias.[14-16]

Splenectomy is often thought of as "curative" in patients with HS as the site of red cell clearance is in the spleen. However, the red cell membrane defect is not corrected with splenectomy and as such patients remain at an increased risk of hemolysis with significant cellular stress.[17] Patients who have previously had an anatomic splenectomy may have a milder course of hemolysis due to removal of the red cell clearance organ.

There are numerous hemolysis markers that can be followed during a hemolytic crisis. Bilirubin levels are an important marker of hemolysis and elevation is due to the breakdown of the protoporphyrin IX ring of heme.[18] In our patient it was reassuring to note the down trending bilirubin value prior to discharge. Ferritin is another hemolytic marker; however, it is also an acute phase reactant and has been found to rise in patients with severe COVID-19 infection who develop cytokine storm.[18,19] In the setting of recent transfusions and an acute illness, a ferritin level could be elevated and not offer insight to acute hemolysis. Lastly, we followed

lactate dehydrogenase (LDH) while hospitalized. LDH increases with hemolysis as LDH-1 and LDH-2 are isoenzymes present in red blood cells and released during a hemolytic event.[18] We noted in our patient that LDH trended down as the hemolytic event was resolving. This trend has additional utility in the setting of COVID-19 in that severe infections can progress to a cytokine storm with elevated LDH as one potential marker.

This case highlights the importance of monitoring hemoglobin and hemolytic markers in patients with hemolytic disorders who are infected with COVID-19. If widespread COVID-19 testing with nasopharyngeal swabs is initiated, children with positive results and underlying hemolytic disorders should be screened for hemolysis. HS has a varying severity of hemolysis and it is possible that the first hemolytic event could take place in the setting of a COVID-19 infection. Due to this, it is important for any provider to keep an open differential when noticing hemolysis in the setting of COVID-19.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgements: We have no additional acknowledgements to share

References:

1. Ciepiela O. Old and new insights into the diagnosis of hereditary spherocytosis. *Annals of Translational Medicine.*2018;6(17):339.
2. Bogardus HH, Maksimova YD, Forget BG, Gallagher PG. A de novo band 3 mutation in hereditary spherocytosis. *Pediatr Blood Cancer.*2012;58(6):1004.
3. Bogusławska DM, Heger E, Machnicka B, Skulski M, Kuliczkowski K, Sikorski AF. A new frameshift mutation of the β-spectrin gene associated with hereditary spherocytosis. *Ann Hematol.*2017;96(1):163-165.
4. Schrier SL. What does the spleen see? *Blood.*2012;120(2):242-243.
5. Li H, Lu L, Li X, et al. Mechanics of diseased red blood cells in human spleen and consequences for hereditary blood disorders.*Proc Natl Acad Sci U S A.* 2018;115(38):9574-9579.
6. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time [published online ahead of print, 2020 Feb 19]. *Lancet Infect Dis* . 2020;S1473-3099(20)30120-1. doi:10.1016/S1473-3099(20)30120-1
7. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg Infect Dis.* 2020;26(7).
8. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med.*2020;382(13):1199-1207.
9. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. The Novel Coronavirus, 2019-nCoV, is Highly Contagious and More Infectious Than Initially Estimated. medRxiv. 2020. doi: https://doi.org/10.1101/2020.02.07.20021154.
10. Coronavirus spreads quickly and sometimes before people have symptoms, study finds. ScienceDaily. https://www.sciencedaily.com/releases/2020/03/200316143313.htm. Published 2020. Accessed April 29, 2020.
11. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* . 2020;145(6):e20200702
12. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422–426. DOI: http://dx.doi.org/10.15585/mmwr.mm6914e4
13. Tateno Y, Suzuki R, Kitamura Y. Previously undiagnosed hereditary spherocytosis in a patient with jaundice and pyelonephritis: a case report. *J Med Case Rep.* 2016;10(1):337.
14. De Luna G, Habibi A, Deux JF, et al. Rapid and Severe Covid-19 Pneumonia with Severe Acute Chest Syndrome in a Sickle Cell Patient Successfully Treated with Tocilizumab. *Am J Hematol.* 2020.
15. Beerkens F, John M, Puliafito B, Corbett V, Edwards C, Tremblay D. COVID-19 pneumonia as a cause of acute chest syndrome in an adult sickle cell patient. *Am J Hematol.* 2020.
16. Nur E, Gaartman AE, van Tuijn CFJ, Tang MW, Biemond BJ. Vaso-occlusive crisis and acute chest syndrome in sickle cell disease due to 2019 novel coronavirus disease (COVID-19). *Am J Hematol.*

2020.
17. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations regarding splenectomy in hereditary hemolytic anemias. *Haematologica.*2017;102(8):1304-1313.
18. Barcellini W, Fattizzo B. Clinical Applications of Hemolytic Markers in the Differential Diagnosis and Management of Hemolytic Anemia.*Dis Markers.* 2015;2015:635670.
19. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.*2020;395(10229):1033-1034.

Hosted file

`Table1.docx` available at https://authorea.com/users/327186/articles/454832-covid-19-and-hereditary-spherocytosis-a-recipe-for-hemolysis