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TRANSFUSION

CASE REPORT

Hyperhemolysis in a patient with sickle cell disease and recent SARS-CoV-2 infection, with complex auto- and alloantibody work-up, successfully treated with tocilizumab

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Abstract

Background: Hyperhemolysis syndrome (HHS) is a severe delayed hemolytic transfusion reaction seen in sickle cell disease (SCD) patients, characterized by destruction of donor and recipient RBCs. It results in a drop in hemoglobin to below pretransfusion levels and frequently reticulocytopenia.

Case Report: We report a case of a man in his thirties with SCD with a recent hospitalization 2 weeks prior for COVID-19. His red cell antibody history included anti-Fy(a) and warm autoantibody. At that time, he was given 2 units of RBC and discharged with a hemoglobin of 10.2 g/dl.

He returned to the hospital approximately 1.5 weeks later with hemoglobin 6.0 g/dl and symptoms concerning for acute chest syndrome. Pretransfusion testing now showed 4+ pan-agglutinin in both gel-based and tube-based testing. Alloadsorption identified an anti-N and a strong cold agglutinin. Three least incompatible units were transfused to this patient over several days, with evidence of hemolysis. Further reference lab work revealed anti-Fy^a, anti-Fy^b, anti-Le^a, anti-Le^b, and an anti-KN system antibody. The patient's hemoglobin nadired at 4.4 g/dl. The patient was treated with a single dose of tocilizumab, his hemoglobin stabilized, and he was discharged.

Discussion: We present a case of HHS proximate to recent SARS-CoV-2 infection with multiple allo and autoantibodies identified. Information on the relationship between SARS-CoV-2 infection and HHS is limited; however, it is possible that inflammation related to COVID-19 could predispose to HHS. Tocilizumab is an approved treatment for COVID-19. Additionally, tocilizumab appears to be a promising treatment option for patients with HHS.

KEYWORDS

AIHA/drug-induced IHA, immunohematology (RBC serology, blood groups), transfusion complications—non-infectious

Abbreviations: LDH, lactate dehydrogenase; LISS, low ionic strength saline.

1 | BACKGROUND

Patients with sickle cell disease (SCD) are more likely to have a severe COVID-19 disease course and a higher case-fatality rate.[1,2] RBC transfusions are commonly given to patients with SCD and COVID-19.[2,3] Hyperhemolysis syndrome (HHS) is an infrequent severe hemolytic transfusion reaction that has primarily been described in patients with SCD.[4] HHS is characterized by rapid destruction of RBCs, both donor and recipient, resulting in severe anemia (below pretransfusion levels of hemoglobin) and commonly reticulocytopenia; HHS can progress to multi-organ failure and death. While the pathophysiology of HHS is not fully understood, several mechanisms have been proposed, including immune-mediated bystander hemolysis,[5] macrophage activation, HLA antibodies, and complement-mediated destruction.[4,6]

There are limited data to guide treatment of HHS. Avoidance of further transfusions and supportive care is the mainstay. Immunosuppressive therapy should be initiated promptly in patients with life-threatening hemolysis: glucocorticoids and intravenous immunoglobulin have been used with varying success at arresting hemolysis.[7] More recent case reports have reported good treatment outcomes with monoclonal antibodies such as rituximab, eculizumab, and tocilizumab.[6,8–11] Rituximab targets CD20 and causes B-cell apoptosis, eculizumab blocks the C5 convertase and reduces classical and alternative complement activation of the membrane attack complex, and tocilizumab blocks the interleukin-6 (IL-6) receptor and prevents macrophage response to that pro-inflammatory cytokine. Tocilizumab has been used to treat various autoimmune conditions including macrophage activation syndrome (MAS),[12] cytokine release syndrome (CRS), and most recently, patients with severe COVID-19 pneumonia.[13] The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization for the use of tocilizumab in the treatment of COVID-19 in hospitalized patients.

Here we report a case of HHS in a patient with recent symptomatic SARS-CoV-2 infection (COVID-19). The patient's HHS was complicated by the development of numerous alloantibodies and a potent cold agglutinin. The patient developed multi-organ failure and was successfully treated with a single dose of tocilizumab.

2 | CASE HISTORY

The patient is a male in his thirties with a history of sickle cell disease (HbSS) complicated by prior vaso-occlusive crises and acute chest syndrome (ACS). His probable *RHD* genotype is RHD*01 and his probable *RHCE* genotype is RHCE*ce733G/RHCE*ce733G. Antibody history includes anti-Fy^a and a warm autoantibody. RBC antigen genotyping revealed the presence of the canonical mutation in the GATA binding site of the *FY* gene, resulting in loss of Fy^b expression on RBCs. Per SCD matching policy, our Blood Bank provided this patient with RBC units negative for C, E, K, Fy^a, and HgbS. The patient had been previously transfused a total of 6 RBC units at our institution.

The patient was unvaccinated and was admitted for COVID-19 pneumonia (Day +0) and possible ACS. His symptoms included headache, myalgia, leg pain, fever (38.4 C in the ED), and shortness of breath. He had a SpO2 of 91% before being put on 2 L NC. A chest X-ray showed worsening right patchy opacities compatible with COVID pneumonia or ACS. His hemoglobin on admission was 9.5 g/dl. Antibody screen showed a pan-agglutinin in gel-based testing. This was a new finding compared to prior antibody screen from Day minus 4 (−4). In tube-based testing, the pan-agglutinin was not detectable and all RBC crossmatches were compatible in LISS. Red cell exchange was considered but deferred in favor of simple RBC transfusion to achieve hemoglobin of 10 g/dl, a frequent goal of RCE in ACS.[14] He was transfused 2 RBC units on Day +2 with pretransfusion hemoglobin of 8.4 g/dl. The patient was discharged on Day +4 with hemoglobin of 10.2 g/dl.

The patient returned on Day +14 with chest pain, fever, and back pain. A chest X-ray showed multifocal pulmonary opacities. There was no increased oxygen requirement (SpO2 97% on room air in ED). He had not received any other transfusions in the interim. The differential diagnosis included ACS versus persistent/recrudescent COVID pneumonia. His hemoglobin on re-admission was 6.0 g/dl. Antibody screen now showed a 4+ pan-agglutinin in both gel-based and tube-based testing. The patient's sample was sent to a regional immunohematology reference lab for alloadsorption. An anti-N (reacting at 37 C and AHG phase) and a strong cold agglutinin (with broad thermal amplitude, including reacting at 37 C) were reported. Four units of RBC were crossmatched in gel- and tube-based testing. One was weakly incompatible in gel and three were 2+ incompatible in gel and in tube (LISS) with pre-warm technique.

The weakly incompatible unit was issued on Day +16. The unit was negative for C, E, K, N, S, Fy^a, Fy^b, Jk^b, and HgbS (Fy^b, Jk^b, S negative status was per chance). Prior to the transfusion, the patient's hemoglobin was 5.4 g/dl. During the transfusion, the patient experienced pain in his chest, right arm, and back as well as hemoglobinuria (confirmed by urinalysis with 2+ gross blood, <3 RBC/hpf). Vitals remained stable during the transfusion and there was no fever. The Transfusion

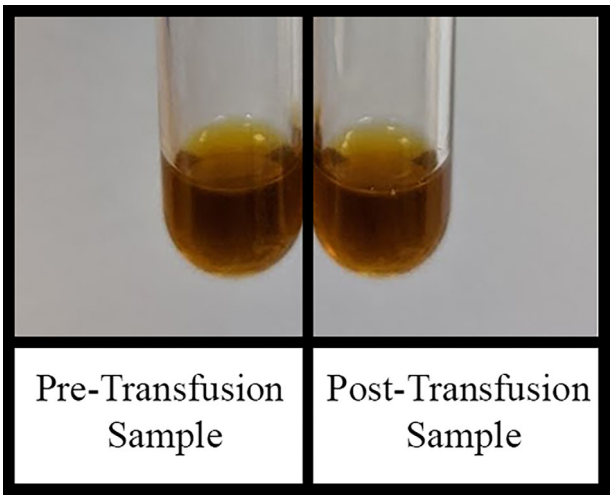

FIGURE 1 Icteric plasma from (left) pre- and (right) post-RBC #3 (Day +17) transfusion samples. Degree of icterus was unchanged. [Color figure can be viewed at wileyonlinelibrary.com]

Service was not informed of the transfusion reaction. The patient's post-transfusion hemoglobin was 5.5 g/dl. An additional RBC unit was ordered on Day +16 and one of the 2+ incompatible units was issued. The unit was C, E, K, N, S, Fy^a, Jk^b, and HgbS negative. The patient was pre-medicated with acetaminophen. The transfusion itself was uneventful, and the post-transfusion hemoglobin was 5.1 g/dl.

On the morning of Day +17, the patient had a 38.3 C degree fever and complained of shortness of breath, requiring oxygen by nasal cannula. An RBC transfusion was ordered and a 2+ incompatible unit was issued. The unit was C, E, K, N, S, Fy^a, and HgbS negative. Prior to the transfusion, the patient's hemoglobin was 5.1 g/dl. During the transfusion, the patient had nausea and the transfusion was stopped and a transfusion reaction evaluation was requested. The hemoglobin after this partial transfusion was 4.9 g/dl.

A pretransfusion sample (after the first 2 units of RBC given on the re-admission) and post-transfusion sample (after the third unit of RBC) were both equally icteric (Figure 1). Both the pre- and post-samples had a positive DAT with anti-IgG reagent (gel 1+) and anti-C3 (tube 1+). Eluate was positive in all cells. Plasma showed panreactivity which was not ameliorated by prewarming. The transfused units were re-crossmatched with the patient's pre- and post-samples. For all 3 units, the IgG crossmatch (gel) was n4+ incompatible with both pre- and post-samples.

At the ARC National Reference Lab for Blood Group Serology (NRLBGS), antibody screen was positive at all testing phases (IS, RT, 37°C-ALB, ALB-AHG, and PEG-AHG) with negative autocontrol. Phenosimilar cells (based on prior molecular genotyping) showed similar pan-reactivity for all but one cell which was nonreactive at IS, RT, and ALB-37°C phases. This nonreactive cell was Le(a-b-). With the use of Lewis Neutralization Substance (Immucor), the reactivity was reduced/removed at IS, RT, and Alb-37°C phases; this identified anti-Le^a, anti-Le^b, and anti-N at these phases. The patient's red blood cells typed Le(a-b-) serologically. The clinical significance of these antibodies was demonstrated by the prewarmed technique (IgG and 37°C settle).

The additional pan-reactivity at the AHG phases suggested there were additional alloantibody specificities. The reactivity pattern with enzyme-treated RBC with Lewis neutralized plasma demonstrated a weakly reactive antibody at the AHG phase and reacting to a dilution of 64 suggesting a high-titer low-avidity antibody (HTLA). The reactivity with phenosimilar cells was removed with 0.2 M DTT and with the use of unlicensed recombinant blood group antigens with specificity for Knops Blood Group System antigens. Therefore, a probable antibody to an antigen in the Knops system was identified. Allogeneic adsorptions of the patient's plasma with untreated R1, R2, or rr red blood cells were performed and the adsorbed plasma tested against 0.2 M DTT-treated reagent red blood cells. Presumed anti-Fy3/Fy5 was identified with this strategy.

The patient's hemoglobin reached a nadir of 4.4 g/dl on Day +18. The patient was given a single dose of tocilizumab 8 mg/kg on Day +18. His LDH subsequently decreased from a peak of 1371 U/L (Figure 2). His percentage reticulocyte count and absolute reticulocyte count continued to increase. Serum ferritin peaked at 4156 ng/ml on Day +17, subsequently decreasing to 1057 ng/ml on Day +23 (Table 1). The patient was discharged on Day +27 with hemoglobin of 6.1 g/dl. Antibody screen at that time remained pan-positive (3–4+) with gel-based testing. Hemoglobin reached 9.1 g/dl by Day +64. Antibody screen remained pan-positive (2+) with gel-based testing.

3 | DISCUSSION

We describe a patient with a profound drop in hemoglobin lower than pretransfusion level, refractoriness to repeat RBC transfusions, and evidence of hemolysis, meeting the criteria for HHS.[15] The exact contribution of COVID-19 to our patient's hyperhemolysis is unclear, but the inflammatory drive may have contributed to the development of numerous new alloantibodies and strong cold agglutinin. We hypothesize that infection with SARS-CoV-2 may increase the risk for HHS based on the marked pro-inflammatory drive and possible

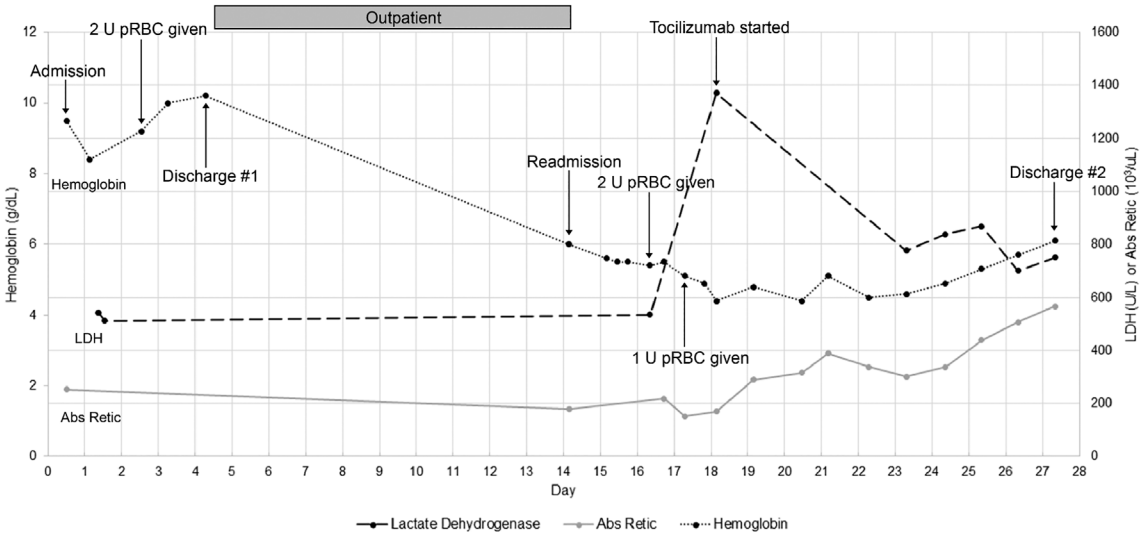

FIGURE 2 Trends of hemoglobin, lactate dehydrogenase, and absolute reticulocyte count during admissions

TABLE 1 Laboratory trends

	Haptoglobin (mg/dl)	Ferritin (ng/ml)
Initial presentation		
Day +0	139	734
Re-presentation		
Day +14		
Day +16	<20	1005
Day +17	<20	4156
Tocilizumab given (Day +18)		3326
Day +23		1057
Discharge #2 (Day +27)		
Day +38		1107
Day +45		827

complement deposition on the RBC surface.[16] In Merrill et al.,[4] 40.7% (22 of 54) of HHS episodes occurred in the setting of infection. It must be noted that Merrill et al.[4] showed that bacteremia was the most common HHS-associated infection; viral infections were 9% of lab-identified associated infections but were possibly under-reported.

In a non-SCD patient population, a small number of COVID-19 patients develop autoimmune hemolytic anemia, with increased complement deposition on RBC.[17–22] Cold agglutinins were identified in 14 of 50 COVID-19 patients with AIHA (positive in all 14 patients tested).[17] In Jacobs et al.,[17] the median (interquartile range) time frame from COVID-19 symptom onset to AIHA diagnosis was 7 days. In our patient, onset of significant hemolysis was between Day +4 and +14. While the mechanism of AIHA precipitated by infectious pathogens is not fully understood, the most widely accepted hypothesis involves molecular mimicry between microbial epitopes and epitopes on RBCs.[17] In Angileri et al.,[22] the ankyrin 1 erythrocyte membrane protein and the SARS-CoV-2 viral protein spike are compared, as they have similar structures.

In our patient, tocilizumab was chosen given the proinflammatory milieu created by recent SARS-CoV-2 infection and concern for macrophage activation (as evidenced by peak serum ferritin of 4156 ng/ml). Clinical features of HHS such as hyperferritinemia are reminiscent of subtypes of MAS/CRS.[6,11] There have been several case reports that have shown success in treating HHS with tocilizumab.[6,9,11] Our patient showed dramatic clinical improvement after initiation of tocilizumab. Additionally, he had decreased panagglutinin reactivity after starting tocilizumab, declining from +4 to +2 in the antibody screen. While there have been no clinical trials on tocilizumab's efficacy in the treatment of COVID-19 pneumonia specifically in SCD patients, there are prior case reports that suggest tocilizumab is helpful in this population.[23,24] In studies of tocilizumab as treatment for SARS-CoV-2 infection in the general population, the results have been somewhat heterogenous; patients with elevated CRP appear to show the most benefit.[25,26] A meta-analysis of six randomized controlled trials of COVID-19 patients showed that tocilizumab was associated with a statistically significant reduction in the primary composite outcome of mechanical ventilation or 28-day mortality.[27] The time-course for achieving measurable improvement after tocilizumab in COVID-19 has been reported as 5–6 days.[28,29]

Alloimmunization is a common problem when transfusing patients with SCD. Only 35.2% of HHS episodes are associated with either a new alloantibody or new autoantibody.[4] Anti-N is a rarer entity, with only one HHS patient developing an anti-N in the 26-year look-back study by Merrill et al.[4] In addition to the anti-N and a previously identified anti-Fy^a, our patient also developed cold agglutinins, anti-Le antibodies, presumed anti-Fy3/Fy5, and HTLA-like antibody with KN specificity. It should be noted that patients of African ancestry with the canonical *FY* GATA mutation can still make alloanti-Fy3/Fy5 if exposed to Fy^b antigen-positive RBC, as with our patient.[30,31] This complex auto- and alloimmunization event necessitated multiple work-ups and send-out to two different immunohematology reference labs, including our blood supplier's national reference lab.

In conclusion, the relationship between SARS-CoV-2 infection and HHS is not well understood; however, it is likely that COVID-19 can augment risk factors associated with the onset of HHS. The anti-IL-6R agent tocilizumab (which has EUA for COVID-19) also shows potential to be an effective treatment for patients with SCD that develop HHS, including patients with recent SARS-CoV-2 infection. Here we report an example of rapid recovery from HHS after a single dose of tocilizumab, in a patient with HHS with complex serologic work-up.

CONFLICT OF INTEREST

CF, VK, TCC, SS, and PM have disclosed no conflicts of interest. GDW has disclosed financial relationships with Diagnostica Stago.

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