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CASE REPORT

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Warm autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis/macrophage activation syndrome occurring after COVID19 infection and administration of Casirivimab + Imdevimab (COVID19 monoclonal antibody)

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Key Clinical Message

Warm Autoimmune Hemolytic Anemia (WAHA) is the most common form of autoimmune hemolysis and there is a growing body of evidence of an association between SARS-CoV-2 infection, WAHA and a hyperinflammatory state, including hemophagocytic lymphohistiocytosis/macrophage activation syndrome. However, there is no literature to date of WAHA or hyperinflammatory state following administration of anti-SARS-CoV-2 monoclonal antibody treatment. This report documents a case of a patient with history of WAHA who developed brisk hemolysis and a hyperinflammatory state consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome after COVID-19 infection and treatment with an anti-SARS-CoV-2 monoclonal antibody. He was successfully treated with multimodal treatment involving steroids, intravenous immunoglobulins, rituximab, anakinra, and vincristine with resolution of the hemolysis.

KEYWORDS

case report, COVID-19, hemolytic anemia, macrophage activation syndrome, monoclonal antibody

1 | INTRODUCTION

Warm autoimmune hemolytic anemia (WAHA) is characterized by premature red blood cell destruction by autoantibodies that are active at normal body temperature and is the most common form of autoimmune hemolysis. WAHA is commonly associated with lymphoproliferative disorders, drugs, autoimmune disorders, as well as certain infections.[1] Since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) pandemic, there is accumulating evidence of an association between COVID-19 and WAHA. There have also been case reports of autoimmune hemolytic anemia after administration of the SARS-CoV-2 mRNA vaccine and a growing body of evidence that COVID-19 can cause a hyperinflammatory syndrome leading to fulminant cytokines release and hemophagocytic lymphohistiocytosis/macrophage activation syndrome.[2–6] However, there has not been a documented case of WAHA or hemophagocytic lymphohistiocytosis following administration of an anti-SARS-CoV-2 monoclonal

antibody. Herein, we report a case of a patient with a known history of underlying WAHA who presented with severe hemolytic crisis and hemophagocytosis in the setting of recent COVID-19 infection and monoclonal antibody administration.

2 | CASE PRESENTATION

A 42-year-old man with a known history of WAHA, recurrent pulmonary embolism, and recent COVID-19 infection was transferred from an outside hospital with respiratory failure and a recurrence of WAHA. He was first diagnosed with WAHA at age 17 and had splenectomy soon after. He had been treated successfully with multiple steroids courses and rituximab (last received in 2013) and was in remission before his recent admission. He also carried a history of recurrent venous thromboembolisms, attributed to his chronic hemolytic process, and complicated by chronic thromboembolic pulmonary hypertension for which he was treated with riociguat and warfarin as an outpatient.

The patient developed initial symptoms of fatigue and shortness of breath 14 days prior to presentation to the tertiary care center. Five days after symptom onset, he tested positive for SARS-CoV-2. Of note, he had declined SARS-CoV-2 vaccination. Nine days after initial symptom onset, he continued to feel unwell and presented to his local community hospital where he was admitted and received COVID-19 directed monoclonal antibodies (REGEN-COV – casirivimab+imdevimab, Regeneron Pharmaceuticals, Tarrytown, NY) prior to discharge home. At that time, he did not have evidence of hemolysis. Three days later, he failed to improve and presented to another community hospital where he was given ivermectin—a drug that has been used to treat COVID-19 off label and without supporting scientific evidence. Two days later and 14 days after symptoms onset, he presented again with severe fatigue, fever, jaundice, and hyperchromic urine and was transferred to the University of Pittsburgh Medical Center, Presbyterian University Hospital for higher level of care.

On admission to the tertiary care center, the patient was in moderate distress. Vital signs were notable for temperature 37.6°C, blood pressure 114/70, heart rate 116 beats/min, oxygen saturation 94% on 2 liters of oxygen. Laboratory values were notable for hemoglobin 5.3 g/dL, MVC 99.9 fl, reticulocyte count 6.3%, haptoglobin <30 mg/dL, lactate dehydrogenase 2970 IU/L. Labs were also significant for white blood cell count of 44.9/μL with absolute neutrophil count 27.84/μL, absolute lymphocyte count 4.04/μL, ferritin >7500 ng/mL and CRP 6.0 mg/dL (additional laboratory values are shown in table 1 and lab trends during treatment course in table 2). Coomb's test was positive for IgG 4+ and anti-C3d and the eluate revealed a pan reacting autoantibody (panagglutinin). A peripheral blood smear revealed signs of brisk hemolysis with numerous reticulocytes, nucleated red blood cells, mirospherocytes as well as a surprising finding of monocytes englufing red blood cells consistent with hemophagocytosis (Figure 1).

On hospital day 1, the patient received methylprednisolone 1 mg/Kg, IV immune globulin 500 mg/Kg and rituximab 375 mg/m2. Anakinra 2 mg/Kg was added due to the concern for hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). The patient continued to hemolyze and was placed on 40 mg dexamethasone daily on hospital day 2 instead of methylprednisolone.

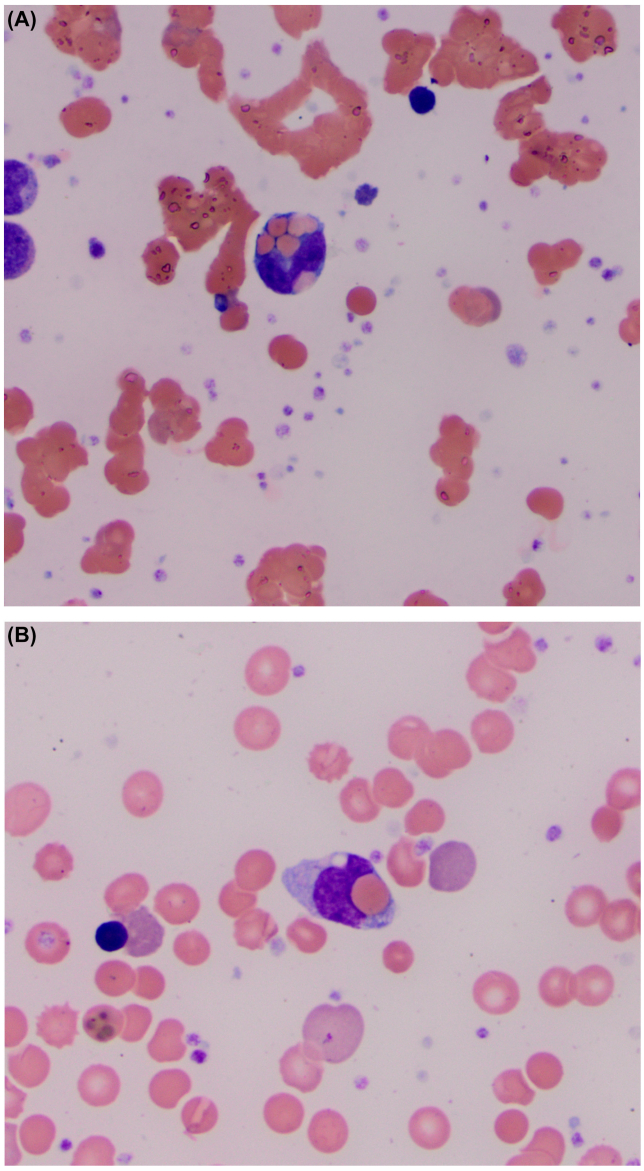

FIGURE 1 Peripheral blood smear showing hemophagocytosis.

Over the next 5 days, the patient's severe hemolysis continued and his anemia was refractory to treatment with high doses of glucocorticoids, immunoglobulin, rituximab and anakinra. Simple transfusions with packed red cells did not result in appreciable increases in hematocrit, and the Hb levels continued to decline reaching a nadir of 2.8 g/dL. We obtained the patient's consent to administer hemoglobin-based oxygen carrier-201 (HBOC-201) (Hemopure; HbO2 Therapeutics, Souderton, PA), an investigational drug that is available via expanded access (compassionate use), as an adjunctive measure until the hemolytic crisis had improved. A total of 6 units of HBOC-201 were administered within a 3 day-period. During this time, the methemoglobin level had increased to 18%; this was treated with ascorbic acid and methylene blue, and subsequently fell to 1.4%. Given his rapid hemolysis

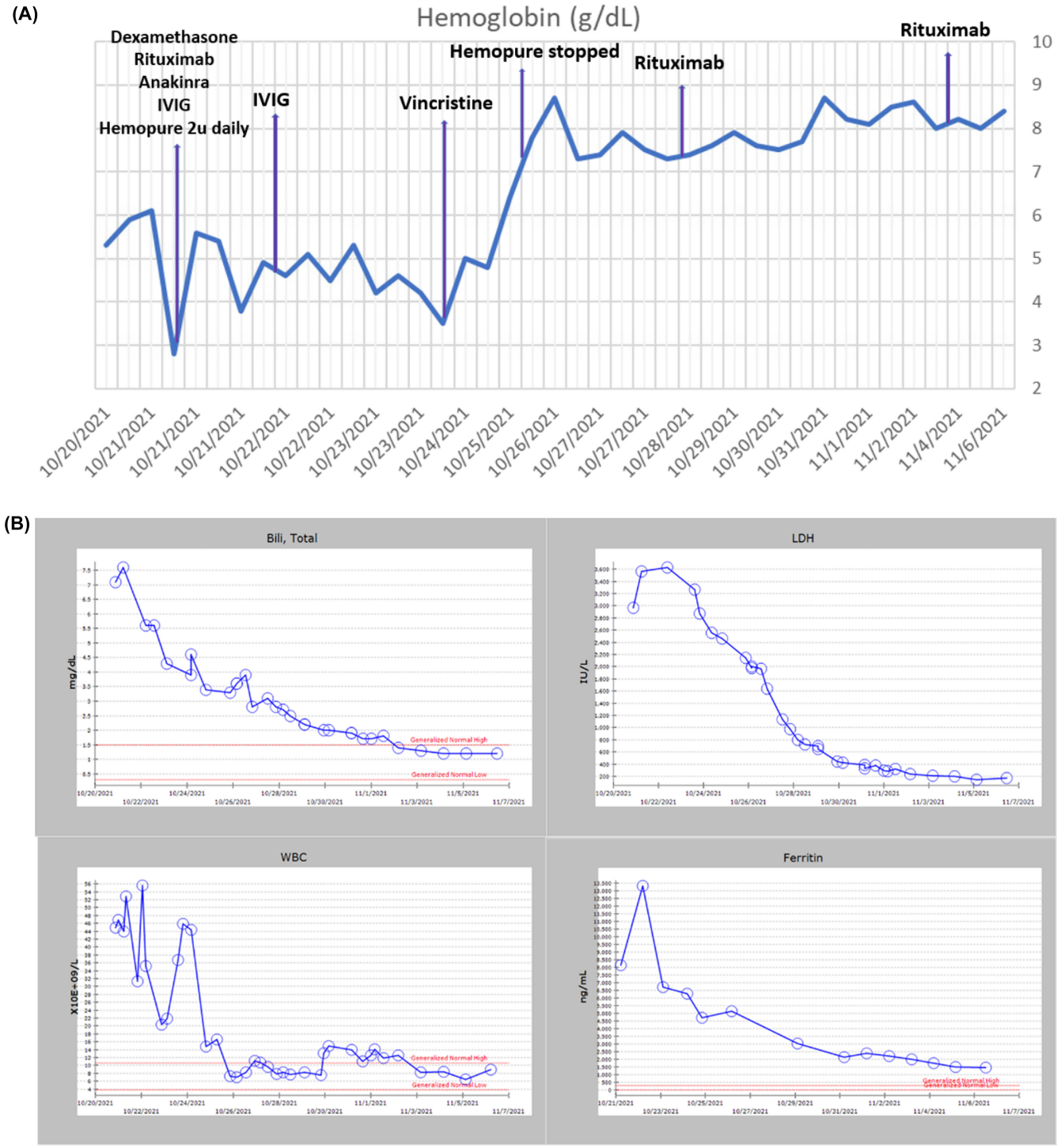

FIGURE 2 Laboratory values during treatment of warm autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis.

without improvement with the above interventions, one dose of vincristine 2 mg was administered on hospital day 5 to further blunt the immune response.

On day 6 of admission to UPMC, the patient's LDH began to fall, and his hemoglobin started to stabilize around 7 to 8 g/dL after receiving additional units of pRBC. He was given two additional weekly doses of rituximab during the hospital stay. Additional doses of vincristine were held due to clinical improvement. Anakinra was tapered and the patient was discharged to home with corticosteroid taper on hospital day 16. Lab values and treatment over the patient's hospital course are shown in Figure 2.

3 | DISCUSSION

COVID-19 has been associated with many hematological complications. A few case reports have shown an association between WAHA and cold autoimmune hemolytic anemia and COVID-19.[2–6] While these cases presented as a consequence of COVID-19, it remains unknown how COVID-19 affects patients with existing autoimmune hemolytic anemia.

Monoclonal antibodies emerged as an effective therapeutic option against COVID-19 during the pandemic and before viral mutations reduced their efficacy. REGEN-COV is a mix of two fully human neutralizing antibodies, casirivimab and imdevimab, that target the receptor binding domain on the SARS-CoV-2 spike protein, and thereby prevent viral entry into the host cell. One case reported WAHA following COVID-19 vaccination, yet it is unknown whether monoclonal antibodies can also trigger WAHA in the absence of an alternative cause.[7] Our patient had a history of WAHA that was managed with splenectomy, however he developed a severe hemolytic crisis 14 days after COVID-19 symptoms onset and 5 days after receiving the monoclonal antibodies. Additionally, clinical and laboratory findings showed a concomitant presentation of hemophagocytosis concerning for HLH/MAS.

Corticosteroids are considered as first-line therapy in WAHA.[1,8] In patients with WAHA refractory to corticosteroids, rituximab can be utilized as second-line therapy. In our patient, WAHA was refractory to both agents and required a third-line therapy with vincristine. Furthermore, anakinra, an interleukin-1 receptor antagonist, has been effective in the treatment of secondary HLH/MAS in the adult and pediatric population.[9] Our patient demonstrated similar findings that required us to include anakinra early in the management. Our patient was also supported using Hemopure via compassionate use as an adjunctive measure until hemolytic crisis had resolved, based on evidence from prior studies using bovine hemoglobin to support patients in hemolytic crisis.[10,11]

In conclusion, our patient developed a severe hemolytic crisis with hemophagocytosis 2 weeks after developing symptomatic COVID19 infection and 5 days after the administration of the monoclonal antibodies. Although the pathogenesis of HLH/MAS is poorly understood the timing of the development of both the brisk hemolytic crisis and HLH/MAS shortly after the patient was diagnosed with COVID19 and received a monoclonal antibody treatment argues in favor of COVID19 monoclonal antibody induced WAHA and HLH/MAS. Per our review of the literature, this case represents the first documented instance of severe hemolytic crisis and HLH/MAS following COVID-19 directed monoclonal antibody therapy. Additionally, this case highlights the importance of a multimodal treatment approach for successful treatment of patients with severe hemolytic crisis and HLH/MAS.

AUTHOR CONTRIBUTIONS

Andrew W. Swartz: Conceptualization; writing – original draft; writing – review and editing. **Enrico M. Novelli:** Conceptualization; formal analysis; investigation; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest related to this manuscript submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

A written and informed consent was acquired from the guardian (mother) regarding names and evidence used in this publication. And she had no objections what so ever.

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