

Letter to the Editor

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Life-threatening autoimmune hemolytic anemia following mRNA COVID-19 vaccination: don't be too prudent with the red gold<https://doi.org/10.1515/cclm-2022-0118>

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To the Editor,

Autoimmune hemolytic anemia (AIHA) is a relatively rare disorder characterized by an increased destruction of autologous red blood cells (RBCs) caused by autoantibodies [1, 2]. It can either occur primary or be secondary to underlying conditions such as viral infections, autoimmune disorders and lymphoproliferative disorders [3]. Warm AIHA (wAIHA) is its most prevalent form (60–70% of all cases) and can usually be attributed to immunoglobulin G (IgG) autoantibodies that may activate complement if IgG1 and IgG3 subclasses are prevalent or if present at high titers. In wAIHA, extracellular hemolysis through the spleen (IgG-coated RBCs are recognized by macrophage Fcγ receptors) and liver (C3b-coated RBCs are recognized by macrophage C3b-receptors) is the main driver of RBC destruction [3, 4]. Patients with wAIHA often suffer from severe anemia with a subsequent transfusion need. However management of transfusion in patients with wAIHA is not an evident task as it is frequently associated with a unique set of hurdles, such as selection of units due to

interference of panreactive autoantibodies in the classical pretransfusion hemagglutination assays [5].

Herein, we describe a case of life-threatening wAIHA that illustrates the need for a thorough understanding of compatibility testing principles among clinicians. We emphasize the necessity of good communication between transfusion medicine personnel and clinicians to review the urgency of compatibility testing and transfusion. Furthermore, this case illustrates the potential of treatment success with plasmaexchange as a last resort in extreme cases.

A 67-year-old man was admitted to the emergency department 22 days after receiving his third dose of the Pfizer-BioNTech mRNA COVID-19 vaccine. The patient reported a five-day history of fever, fatigue and general weakness, with jaundice and dark urine. Moreover, he suffered from diarrhea and clinically significant anorexia. Physical examination revealed an anemic and icteric patient without apparent other abnormalities. With the exception of a mild thrombocytopenia documented but not explained since 2019, his medical history did not include any other significant findings.

Initial laboratory analysis revealed an anemia with a hemoglobin (Hb) level at 75 g/L (ref. range 135–170 g/L) accompanied by a reticulocytopenia ($24.1 \times 10^9/L$, ref. range $30\text{--}93 \times 10^9/L$). Haptoglobin was undetectable (<0.10 g/L, ref. range 0.3–2.0 g/L) and high levels of lactate dehydrogenase (LDH, 1,100 U/L, ref. range 105–250 U/L) were noted. Further abnormalities in peripheral blood included a decreased platelet count ($106 \times 10^9/L$, ref. range $143\text{--}325 \times 10^9/L$), absolute neutrophilia ($7.5 \times 10^9/L$, ref. range $1.9\text{--}5.9 \times 10^9/L$) and high ferritin levels (4,335 µg/L, ref. range 20–280 µg/L). Total bilirubin was increased at 336.9 µmol/L (ref. range 3.4–18.8 µmol/L) with an indirect bilirubin of 309.5 µmol/L (ref. range 1.7–13.7 µmol/L). Glucose-6-phosphate dehydrogenase activity was within normal ranges.

Peripheral blood smear showed no (micro)spherocytes, nor agglutination or the presence of any findings that could raise the suspicion of other causes of anemia

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(e.g. schistocytes). ADAMTS13 activity appeared to be normal, thereby excluding a microangiopathic hemolytic anemia due to classical thrombotic thrombocytopenic purpura. COVID-19 PCR testing on a nasopharyngeal sample was negative. Fecal culture, viral serology, respiratory mucus culture, and respiratory multiplex PCR were all negative. A thoracic CT scan demonstrated an infiltrate in the left lower lobe for which broad-spectrum antibiotics were initiated. A full body PET/CT scan showed no arguments for an underlying malignant process. In addition, no anomalies were found on cytomorphological and flow cytometric assessment of a bone marrow aspirate. Flow cytometric screening for paroxysmal nocturnal hemoglobinuria and testing for cold agglutinins were negative.

However, the direct antiglobulin test appeared to be positive for polyspecific anti-human globulin (anti-IgG + anti-C3d). Differentiation by monospecific testing showed a distinctive positive reaction for anti-IgG and a weak reaction for anti-C3b/C3d. An eluate prepared from the patient's RBCs showed a strong panreactivity against all test cells. These results indicated the presence of IgG auto-antibodies without specificity and with additional complement activation. The panreactive autoantibodies also interfered with standard pretransfusion tests (i.e. the indirect antiglobulin test and crossmatching).

In need of transfusion, generally two specialized procedures are available for patients with wAIHA. First, genotyping of the RBC antigens (Rhesus, Kell, Duffy, Kidd and MNS) for extended phenotype-matched units and second, performing adsorption tests to identify alloantibodies. In general, only the latter is accessible in an emergency setting. While the transfusion laboratory adequately supplied the clinician with information about the complexity of compatibility test procedures in patients with wAIHA, the clinician preferred to transfuse with extended phenotype-matched units and decided to postpone transfusion until after the weekend (i.e. two days) due to the absence of a clinical actual transfusion need.

Putting the clinical and laboratory findings together, a diagnosis of wAIHA was made. While wAIHA has already been recognized as a potential complication of COVID-19 infection, several case reports have also suggested a potential link with COVID-19 mRNA vaccination [6, 7]. Although the exact underlying mechanism for vaccine-induced autoimmunity is not yet clear, a potential role for molecular mimicry and the development of auto-reactive T-cells has been hypothesized [6, 7]. Based on the chronology of events and the absence of other underlying causes, it could not be excluded that the COVID-19 vaccine was the trigger, and the disease episode was therefore reported as a possible, but not probable, vaccine-related side effect.

Since the cornerstone of wAIHA treatment is immunosuppression, methylprednisolone (1 mg/kg) was initiated. The next morning, the patient showed confusion and laboratory analysis revealed critically low Hb levels (35 g/L). Nevertheless, transfusion was not immediately started due to the incompatible pretransfusion test results and the order was made for an urgent allogeneic adsorption test to exclude the presence of RBC alloantibodies, but none were detected. These circumstances significantly delayed (overall 8 h) the administration of the first units of compatible packed RBCs. Consequently, the patient had to be transferred to the intensive care unit for adequate monitoring. Due to insufficient response, the dose of methylprednisolone was increased to 1 g/day on day 3. In addition, daily plasmaexchange was initiated at day 5 (until 9) and weekly rituximab infusions (1 g) were started on day 12 (for four weeks). On day 5, the LDH levels began to fall, and transfusion need started to decline. The Hb and LDH trends, and the response to the different treatment modalities can be found in Figure 1. Eventually, the patient could be discharged from the hospital at day 21, showing stable Hb levels around 70 g/L.

Patients with wAIHA may develop anemic hypoxia that cannot successfully be treated by the administration of oxygen until therapeutic actions (e.g. corticosteroids and rituximab) become effective. While various authors have encouraged clinicians to start to transfuse patients in decompensated wAIHA, independent of the compatibility test results [5, 8, 9], there are also many reports dealing with the risks that should be taken into account prior to transfusion (e.g. hemolytic transfusion reactions due to mismatched blood) [8]. With this case study, we learned that the unique caution associated with transfusion in wAIHA can sometimes result in more harmful than useful delay. This may jeopardize patients who urgently require blood and, therefore, the decision to transfuse should primarily be dependent on an assessment of the patient's individual transfusion need. wAIHA with severe anemia (Hb < 60 g/L), confusion, hypoxia, or hemodynamic instability should be considered an indication for urgent transfusion to reduce the risk of severe complications such as myocardial infarction, or even death by pulmonary edema, or arrhythmia [3]. ABO- and RhD-compatible blood should be administered promptly since the risk of a transfusion reaction due to alloantibodies is nearly negligible among people who have not been sensitized to foreign red-cell antigens (no history of transfusion or pregnancy), and remains even low (<10%) in patients with a history predisposing to red cell sensitization [3]. Yürek et al. [8] already stated that the incidence of alloimmunisation, as well as adverse hemolytic transfusion reactions

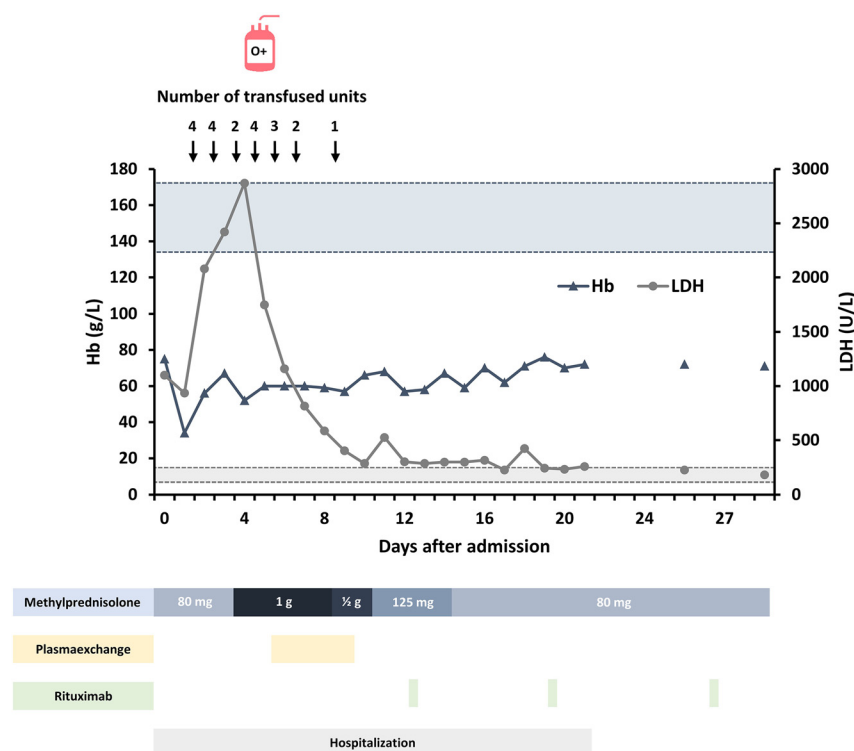


Figure 1: Evolution of hemoglobin (Hb, solid blue line with triangle markers, reference ranges with dashed blue lines) and lactate dehydrogenase (LHD, solid grey line with circular markers, reference ranges with dashed grey lines), and their response to treatment, during the course of disease. The X-axis represents the number of days following hospital admission. The Y-axes represent Hb (g/L) and LDH (U/L) concentrations. The black arrows illustrate the number of transfused red blood cell (RBC) units. Methylprednisolone (dosage scheme included), plasmaexchange and rituximab are shown in blue, orange and green, respectively. The hospitalization period is in grey.

is unnecessarily overestimated in wAIHA. Clinicians should be aware of the fact that, due to interference of panreactive autoantibodies, adequate testing for alloantibodies in a patient with wAIHA may take at least 4–6 h using warm autoadsorption or allogeneic adsorption tests, or even longer when testing is performed in a referral laboratory. Requesting the right tests at the right time can be life-saving, but in urgent situations, the lesser risk may be to transfuse rather than wait for time-consuming and specialized compatibility testing or for the availability of extended phenotype-matched units [5].

This patient was also treated rather unconventionally with plasmaexchange. Since there are limited and controversial data in literature, plasmaexchange should only be considered as a rescue therapy in case of life-threatening wAIHA and massive intravascular hemolysis [10]. In order to avoid complement activation, it is key to add albumin solutions as a replacement fluid and not plasma [11].

As a conclusion, we state that urgent transfusion should not be unequivocally delayed nor avoided in patients with life-threatening wAIHA and incompatible pre-transfusion tests, despite some dogma to the contrary. It cannot be emphasized enough that as soon as it becomes evident that a patient with wAIHA develops a transfusion need, a timely discussion between clinicians and the transfusion service should be regarded as the holy grail, and activated before this need even has the risk to become critical. A prepared clinician is worth double.

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