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LETTER TO THE EDITOR

Autoimmune hemolytic anemia in children with COVID-19

To the Editor,

Pediatric 2019 novel coronavirus disease (COVID-19) is characterized by a wide clinical spectrum, including hematological manifestations.[1] Anemia and thrombocytopenia occur mainly in severe forms of the disease and in multisystem inflammatory syndrome[2] but are rare in asymptomatic and mildly symptomatic patients. Only few reports of autoimmune hemolytic anemia (AIHA), rarely associated with immune thrombocytopenia (ITP), have been described in children with COVID-19.[3–5] Here, we present two pediatric cases of severe cold agglutinin disease and a brief review of the literature.

A 15-year-old male presented with nausea, vomiting, and asthenia. He was febrile, tachycardic, and tachypneic. Clinical examination revealed hepatosplenomegaly. Blood tests showed severe hemolytic anemia (hemoglobin 3.7 g/dl, hematocrit 7.4%, bilirubin 3.51 mg/dl, lactic dehydrogenase [LDH] 425 U/L), positive direct antiglobulin test (DAT) with high title cold agglutinins (IgG+/C3d+), and thrombocytopenia (platelets 77 $\times$ 10^9/L) with anti-platelet antibodies. A nasopharyngeal swab resulted positive for SARS-CoV2. Peripheral blood smear revealed severe anisocytosis and aggregates of red blood cells. Evans syndrome was diagnosed. The patient was promptly transfused with red blood concentrates (RBCs), and intravenous corticosteroids (prednisone 2 mg/kg) were administered, showing only a partial response. On day 7, he thus received a 3-day regimen of intravenous immunoglobulins (IVIG) (0.5 mg/kg/die). Over the next few days, hemoglobin levels rapidly improved. Prednisone was gradually tapered after day 13 and then withdrawn at day 32. The patient was discharged on day 16. Extensive immunophenotyping was performed showing normal results. Figure 1 highlights the clinical and laboratory course of this case together with therapies.

A 2-year-old male child affected by beta thalassemia major received an allogeneic hematopoietic stem cell transplantation (HSCT) at 16 months of age from matched unrelated donor. He developed steroid sensitive chronic graft versus host disease (GvHD). At 3-month follow-up, bone marrow aspirate showed complete donor chimerism. Six months after transplantation, he presented with fever, anorexia, and weakness. Nasopharyngeal swab resulted positive for SARS-CoV2. At admission, he was receiving cyclosporine (CsA) as GvHD prophylaxis. Blood samples showed severe hemolytic anemia (hemoglobin 2.3 g/dl, hematocrit 4.8%, bilirubin 2.94 mg/dl, LDH 510 UI/L) with DAT positive for cold pan-agglutinins (IgA+/IgG+/IgM+/C3c+/C3d+). Severe anisocytosis and aggregates of red blood cells were detected at peripheral blood smear. Corticosteroids (prednisone 2 mg/kg) and RBCs were rapidly initiated. Hemoglobin levels slowly normalized, requiring repeated transfusions, the last on day +23. Concurrently, his dosage of prednisone was gradually reduced from day +34 and withdrawn at day +42. The patient tested persistently positive for SARS-Cov2 on nasopharyngeal swabs until day +35.

AIHA is a rare disorder in children, often secondary to self-limited viral or bacterial infections.[6] When treatment is required, corticosteroids represent the first-line therapy. Other options include rituximab and IVIG.[7] This condition is more common in children with innate or acquired immune dysregulation (e.g., autoimmune lymphoproliferative syndrome, post-HSCT), in whom the management is frequently challenging.[8] Moreover, AIHA can be combined with thrombocytopenia (Evans syndrome).[7]

Since the beginning of the pandemic, AIHA has seldom been described in adults with COVID-19[9,10] and appears to be even rarer in children.[3–5] The five pediatric patients reported in literature so far (see Table S1) developed severe anemia during the acute phase of infection (hemoglobin range 2.3–6.3 g/dl). No child presented with symptoms of severe respiratory syndrome. They all received steroids as first-line therapy, while only one child required rituximab, because of refractory course of disease.[4] According to our clinical practice in ES, IVIG were administered as second-line treatment.[11] All patients showed a clinical response within 1 month. One child was previously affected by refractory chronic ITP.[3] Our second patient developed AIHA 6 months after allogeneic HSCT, during CsA therapy. The other three patients had no relevant comorbidities. In our first case, immunological investigations excluded underlying immune disorders.

Severe AIHA has to be considered within the spectrum of pediatric COVID-19 complications. ITP and bilinear cytopenia (Evans syndrome) can also be associated with SARS-Cov2, even if rarely reported in the pediatric population so far.[3,4,12–15] The underlying pathogenic mechanism could be related to the predominant immunological and inflammatory activation secondary to SARS-CoV-2 infection.[1,2,16] Furthermore, in adults immune-mediated cytopenia seems to be more common in the moderate-to-severe respiratory form of COVID-19.[16] On the contrary, affected children did not present any respiratory involvement. Molecular mimicry has also been proposed as potential mechanism for ITP.[16] Indeed, Angileri et al. reported the structural affinity and potential cross-reactivity between erythrocyte membrane protein Ankyrin-1 and viral protein spike.[17]

The severity of anemia appears not to be dependent on the patient's immunological status. Regardless, children with an underlying immune dysregulation may require particular attention considering a specific susceptibility to autoimmune manifestations during infections. Moreover, a protracted course of AIHA, possibly related to a delayed

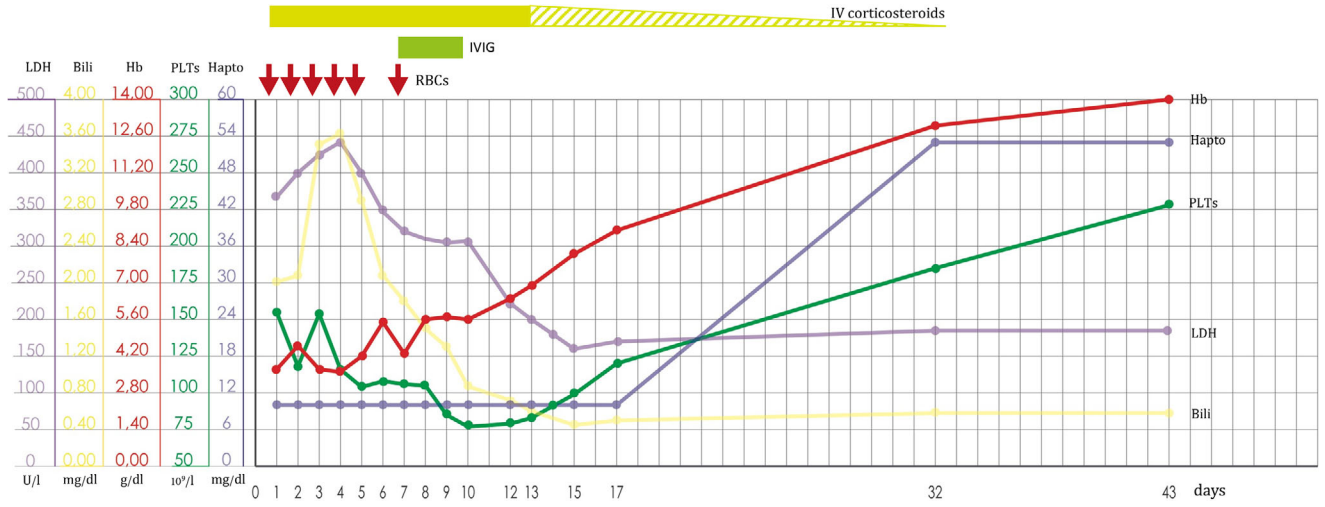

FIGURE 1 *Case 1*: The lines refer to the laboratory course (LDH, Bilirubin, Hb, PLTs, haptoglobin) for case one during hospitalization and follow-up. The yellow rectangle marks the duration of corticosteroids, while the green rectangle indicates the days in which immunoglobulins (IVIG) were administered. Red arrows show red cell concentrates (RBCs) transfusions. Hb, hemoglobin; Hapto, haptoglobulin; PLTs, platelet count; LDH, lactic dehydrogenase; Bili, bilirubin; IVIG, intravenous immunoglobulin

resolution of the infection, can occur in immunosuppressed children, as emblematically observed in our transplanted patient.

So far, the relation between COVID-19 and immune-mediated cytopenia remains unclear. Similar to other viral infections, SARS-CoV-2 can act as a trigger and has to be considered during pandemic among the viral causes of new-onset AIHA. In a pediatric setting, clinical management can be challenging, particularly in patients with an innate or acquired disorder of immune regulation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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