Cold agglutinin disease secondary to severe SARS-CoV-2 treated with eculizumab

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SUMMARY

Impaired immune response with uncontrolled inflammation and various immunological disorders have been reported during SARS-CoV-2 infection. Here, we report a case of cold agglutinin disease occurring during a severe coronavirus disease 2019 (COVID-19) in a French intensive care unit. A patient was presented with acute respiratory distress syndrome, acute renal failure and haemolytic anaemia. Direct antiglobulin test was positive with a cold agglutinin titre of 1/512. No other cause than COVID-19 explained the occurrence of cold agglutinin disease; however, causality could not be formally established. Persistent anaemia despite transfusion therapy and the short-term life-threatening, prompted the infusion of a monoclonal anti-C5 antibody (eculizumab). Eculizumab therapy quasi-fully resolved haemolysis within a few days, but ultimately the patient died from his severe COVID-19 infection. Data regarding the specific treatment of cold agglutinin disease during COVID-19 are rare. Although additional studies are warranted, eculizumab may be considered in critical situations.

BACKGROUND

Emerging from China in December 2019, COVID-19 became rapidly pandemic, causing more than 6 million deaths worldwide. Clinical manifestations vary from asymptomatic to life-threatening complications. Understanding of its pathophysiology is still incomplete but there is growing evidence that impaired immune response with uncontrolled inflammation may be responsible for the most severe cases.[1]

CASE PRESENTATION

A male patient with history of diabetes, hypertension and cutaneous T-cell lymphoma (stage B1 Sezary syndrome in remission), without any previous event of haemolytic anaemia, was presented with acute respiratory distress syndrome preceded by 2 weeks of ongoing fever, cough and fatigue. Chest CT showed bilateral pulmonary embolism and ground-glass opacities. Persistent respiratory distress on oxygen therapy, neurological disorders and respiratory acidosis prompted invasive mechanical ventilation. SARS-CoV-2 infection was diagnosed by RT-PCR testing of an endotracheal aspirate.

Clinical assessment on presentation did not reveal any skin lesion or peripheral lymph node. The patient's haemoglobin decreased from 109 g/L on day 1 to 80 g/L on day 4 along with acute renal failure. Platelet count remained normal.

INVESTIGATIONS

The haemolytic nature of anaemia was confirmed by an elevated lactate dehydrogenase (LDH) serum level up to 2072 U/L (normal value <245 U/L), a low haptoglobin rate at 17 mg/dL (normal value >56 mg/dL) and elevated reticulocyte count, up to 123.7×10^9/L (normal value $50–120\times10^9$/L). Thrombotic microangiopathy was initially considered as a differential diagnosis, given the presence of both haemolysis and renal failure, but was then ruled out in the absence of schistocytes on blood smear examination and isolated tubular necrosis on kidney biopsy.

Autoimmune haemolytic anaemia was diagnosed with a strongly positive C3d and weakly positive IgG direct antiglobulin test. Decrease of C3 (56 mg/dL, normal range 80–170 mg/dL) and C4 (8 mg/dL, normal range 12–40 mg/dL) complement fractions and of CH50 (25 U/mL, normal range 25–100 U/mL) suggested complement classical pathway activation. A blood smear revealed marked erythrocyte agglutination at room temperature (figure 1). The diagnosis of cold agglutinin disease (CAD) was confirmed with two cold agglutinin titers of 1/128 and 1/512, respectively, with anti-I specificity.

Further investigations aimed to determine the underlying aetiology of CAD.

DIFFERENTIAL DIAGNOSIS

First, there was no evidence for primary CAD. Cold-induced circulatory symptoms such as Raynaud phenomena or acute anaemia during infectious processes are found in 90% of patients with primary CAD,[2] but our patient did not have such history.

Secondary CAD can be related to haematological or infectious disease. Most cases of CAD are secondary to underlying haematological malignancies such as lymphoproliferative disorders. Postinfectious disease typically occurs after *Mycoplasma pneumoniae* infection[3] but has also been described after respiratory viral infections, such as 2009 influenza AH1N1.[4]

To rule out an underlying haematological malignancy, a blood lymphocyte immunophenotyping was performed and showed B and T lymphopaenia, without argument for lymphoproliferative disorder, specifically cutaneous T-cell lymphoma transformation. Serum electrophoresis and immune fixation did not reveal any monoclonal gammopathy. There was no lymphadenopathy or tumour on thoraco-abdominopelvic CT-scan. Bone marrow aspirate showed no malignant infiltrate.

Second, we tested for the main viruses responsible for CAD. We performed multiplex PCR assay of

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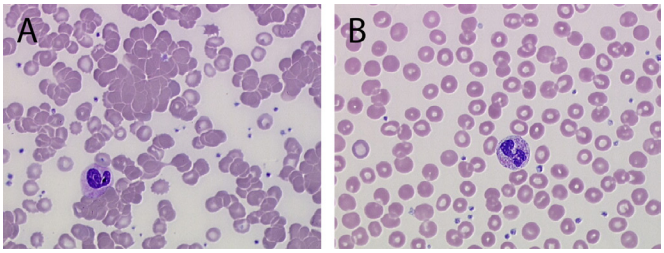

Figure 1 Blood smear examination before and after eculizumab treatment. (A) Blood smear examination before eculizumab treatment showing marked red blood cell agglutination at room temperature (May-Grünwald-Giemsa stain, original magnification ×40). (B) Blood smear examination after eculizumab treatment showing no red blood cell agglutination (May-Grünwald-Giemsa stain, original magnification ×40).

endotracheal aspirate, including detection of influenza virus and mycoplasma pneumonia, which was negative. We also performed hepatitis C virus and HIV serology, PCR testing for parvovirus B19, which were all negative. PCR testing for Epstein-Barr virus and cytomegalovirus showed limited viral replication (<3 log). No other pathogen than SARS-CoV-2 was therefore identified.

In conclusion, diagnosis of infectious cold agglutinin syndrome, as suggested by anti-I specificity, secondary to COVID-19, was retained even though causality could not be formally established.

TREATMENT

Diagnosis of CAD was made on day 8. Haemolysis in CAD is induced by low temperature, so initial treatment consisted of warming of all fluids administered to the patient, notably packed red blood (pRBC) cells transfusions. In order to support bone marrow regeneration, erythropoietin therapy was also added.

Despite initial management, haemolysis persisted with elevated LDH up to 1151 U/L and undetectable haptoglobin. The patient had required 13 pRBC without plasma infusion by day 10 of hospitalisation, and despite this, his clinical condition continued to deteriorate with severe heart and lung failure. Treatment options were discussed. Corticosteroids were not administered, since there is no strong level of recommendation in the course of CAD and for fear of the increased risk of nosocomial infections. Furthermore, this case occurred before the publication of different studies showing the benefits of corticosteroid therapy in COVID-19. This patient was managed according to the standard of care for non-COVID acute respiratory distress syndrome (ARDS).[5] Rituximab was not chosen because of its long onset of action. Finally, plasma exchange presented a haemodynamic risk and the patient was already suffering from heart failure. It was therefore decided to treat the patient with eculizumab, which had a better benefit/risk ratio and a short onset of action. Eculizumab infusions were performed on day 11 and day 13.

OUTCOME AND FOLLOW-UP

One day after infusion of eculizumab, biological markers of haemolysis abated (LDH 514 U/L, haptoglobin 223 mg/dL) with blood smear examination showing no red blood cell agglutination (figure 1). The patient required only two pRBC in the following 10 days period. After eculizumab, haemolysis abated and no recurrence was observed.

Unfortunately, the patient's condition worsened due to COVID-19-related ARDS with multiorgan failure (respiratory, liver, neurological, cardiac and renal failure). The decision of life-support withdrawal led to death on day 33.

DISCUSSION

Among various immunological disorders, a case of immune thrombocytopaenia and seven cases of autoimmune haemolytic anaemia were recently described during COVID-19 infection.[6 7]

Recently, Lazarian *et al*[7] reported three cases of CAD occurring during SARS-CoV-2 infection. In two out of three, an underlying lymphoproliferative disorder was present. One patient was treated with corticosteroids, the other one received corticosteroids and rituximab. Both were in partial response at the time of publication. In those cases, COVID-19 was not life-threatening (most patients were not hospitalised in ICU). On the opposite, in the present case the COVID-19 ARDS was short-term life-threatening. Haemolysis may have worsened both cardiac and respiratory failure. Considering the delayed action of rituximab compared with eculizumab and the fact that steroids are not effective in CAD we chose to treat haemolysis with eculizumab.

The pathophysiology of CAD mainly involves the activation of IgM antibodies. IgM antibodies are potent complement enhancers. Exposition to cold induces the fixation of the antibody on red blood cells, which triggers the activation of the classical complement pathway. The binding of C1q induces activation of C2 and C4 leading to the formation of C3b, which binds to red blood cells and generates extravascular haemolysis by opsonisation, mainly in the liver. C3b also activates C5 leading to the formation of the membrane attack complex responsible for intravascular haemolysis.[8]

Several therapeutic agents targeting earlier actors of the activation cascade, such as C3 or C1, are being studied.[9–12] This would allow targeting intravascular and extravascular haemolysis, but the evidence is not robust enough yet for clinical use.

Eculizumab is an anti-C5 antibody that inhibits intravascular haemolysis by blocking the formation of the membrane attack complex but does not interrupt extravascular haemolysis. Eculizumab has been safely used in various complement-mediated diseases for more than 10 years, including in one reported case of postinfectious CAD.[13] In addition, recent data suggest that the deterioration of respiratory function in severe COVID-19 may result from microvascular injuries mediated by activation of complement pathways.[14] Supporting this finding, a trial assessing the efficacy and safety of complement inhibition in patients with COVID-19 infections was started but then interrupted due to lack of inclusions (ClinicalTrials.gov Identifier: NCT04346797).[15 16] Another study showed a significant decrease in mortality in patients admitted to the ICU with severe COVID-19 who received eculizumab compared with standard of care but those results need to be confirmed in randomised clinical trials.[16]

Plasma exchanges could have been considered because of the urgency of our situation. However, our patient presented an acute heart failure with haemodynamic instability, therefore eculizumab seemed to have a better risk benefit ratio. Rituximab was considered, but the 2 weeks delay of action seemed too long given the patient's critical condition.[8]

Although our patient died as a result of his severe COVID-19 infection, we considered the CAD episode cured due to the absence of recurrence of haemolysis.

Two years after the emergence of COVID-19, there is still no revolutionary treatment for the most severe cases in the ICU. Corticosteroid therapy is one of the only treatments which proved to be beneficial in patients who require oxygen. Eculizumab may be a rightful option in severe COVID-19 when CAD is present, yet more research is needed to evaluate its efficacy and safety.

In conclusion, the temporal sequence and the absence of alternative aetiology of CAD (no other virus found nor argument for neoplasia) both suggest that SARS-CoV-2 was the causal agent of CAD in our case, even if it could not be formally proven. Clinicians should be cautious when facing unusual blood cell count abnormalities and foster proper investigations. Specific treatment strategies for CAD, such as eculizumab, should be evaluated in larger studies and more research is still needed to fully understand the underlying mechanisms of action.

Learning points

- SARS-CoV-2 infection may be responsible for cold agglutinin disease (CAD) along with other immune cytopenia.
- Complement pathway activation could enhance the inflammatory and prothrombotic triggers already at play during COVID-19.
- Targeted blockade using eculizumab can successfully treat haemolysis in severe CAD cases and may be of interest in broader indications during SARS-CoV-2 infection.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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