Cold agglutinin–mediated autoimmune haemolytic anaemia associated with COVID-19 infection: a case report

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Case report

In November 2020, a 70-year-old woman with diabetes mellitus, hypertension, and dyslipidaemia presented with a 3-day history of fever, cough, and rhinorrhoea. She reported no chest pain, shortness of breath, anosmia, or ageusia. Physical examination revealed that she was awake and not tachypneic. There was mild pallor present, but no jaundice. The patient's blood pressure was 118/56 mm Hg, pulse rate 62 beats per minute, and temperature 36.5°C. Respiratory rate was 16 breaths per minute and pulse oximetry revealed oxygen saturation of 98% on ambient air. Chest auscultation revealed bibasilar crackles. There were no signs of lymphadenopathy, splenomegaly, or autoimmune disease. Physical examination was otherwise unremarkable.

Haematological analysis revealed haemoglobin 8.1 g/dL, white cell count 9.6 × 10^9/L (absolute lymphocyte count 3.1 × 10^9/L) and platelet count 346 × 10^9/L. The peripheral blood film showed moderate anaemia with occasional spherocytes and marked red blood cell agglutination that dispersed when blood was heated to 37°C, indicating cold agglutinin (Fig). The absolute reticulocyte count was raised at 2.3% and direct antiglobulin test showed presence of anti-complement (C3d) antibodies but not anti-immunoglobulin G antibodies. Due to a lack of facilities at the district hospital, we were unable to conduct the following tests: serum haptoglobin, direct antiglobulin test performed with warm-washed red blood cells, cold agglutinin titre, and thermal amplitude testing. Mild hyperbilirubinaemia was present, with indirect bilirubin predominating (total bilirubin 26.2 mol/L, direct bilirubin 4.7 mol/L, indirect bilirubin 21.5 mol/L). Liver transaminases and renal profile were within the normal range.

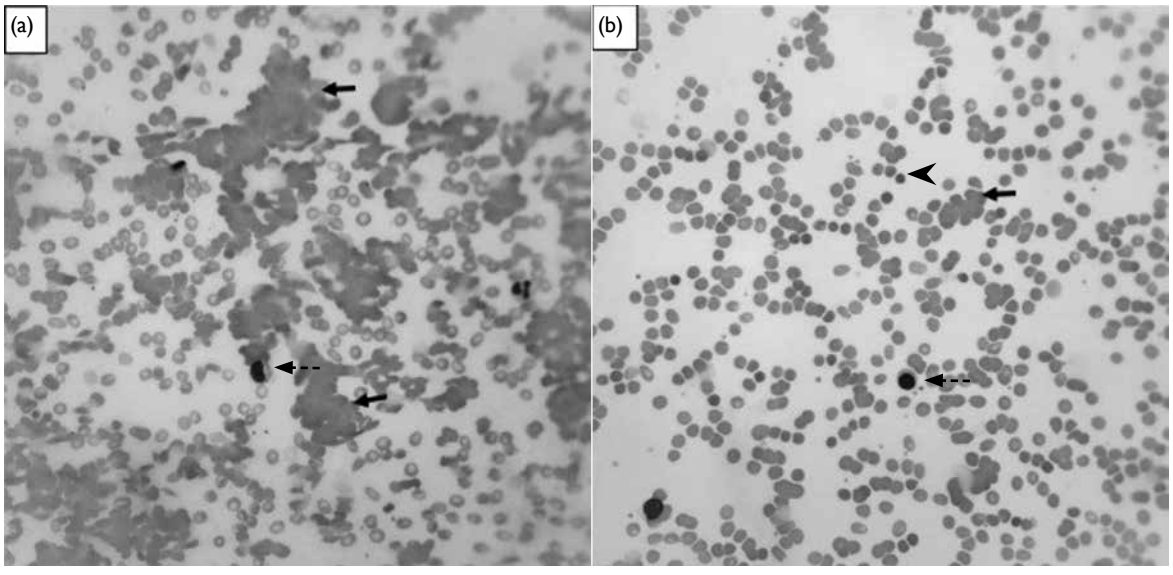

FIG. (a) Peripheral blood smear prior to 'pre-warm' method. (b) Peripheral blood smear after the application of 'pre-warm' method. The smears show a leucoerythroblastic picture (dashed arrows). There are extensive red cell agglutinations (black arrows) in (a) that dispersed on warming of blood to 37°C. Occasional spherocytes are seen in (b) [arrowhead]. No abnormal lymphoid cells are present

C-reactive protein, serum ferritin, and serum lactate dehydrogenase level was 5 mg/L, 2671 μg/L, and 321 U/L, respectively. Mycoplasma serology, blood cultures, D-dimer, and autoimmune screening were all negative, as were tests for hepatitis B, hepatitis C, and human immunodeficiency virus.

Chest radiograph showed ground-glass opacities in both lower zones. Coronavirus disease 2019 (COVID-19) infection was confirmed by reverse transcriptase-polymerase chain reaction for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in nasopharyngeal and oropharyngeal swab samples (Ct value; E gene 16.09, RdRp gene 19.23). A diagnosis of cold agglutinin–mediated autoimmune haemolytic anaemia (AIHA) due to SARS-CoV-2 was made. On the seventh day of her illness, she developed hypoxaemic respiratory failure, necessitating 3 L/min supplemental oxygen administered via nasal cannula. At the time, inflammatory markers were elevated, and a new chest radiograph revealed worsening bilateral airspace opacities. The patient was prescribed intravenous methylprednisolone 500 mg as a single dose, followed by 2 mg/kg once daily for the next 5 days. She responded well and oxygen supplementation was discontinued 7 days later. Blood inflammatory marker levels (C-reactive protein 3.1 mg/L) and chest radiograph showed improved findings. The patient was prescribed a tapering dose of dexamethasone. One unit of packed cells was transfused on the third, fifth, tenth, and fourteenth day of hospitalisation due to ongoing low-grade haemolysis. In the absence of any constitutional symptoms, and no lymphadenopathy or organomegaly on physical examination, a computed tomography scan was not performed. She was discharged home on day 21 of her illness after her symptoms had resolved and she had been transfusion-independent with stable haemoglobin level for 1 week. At 1-month follow-up examination, the patient remained well: haemoglobin was 10 g/L and new peripheral blood film examination found no cold agglutinin haemolysis.

Discussion

This pandemic has taken the world by storm, with many new undocumented symptoms and treatment strategies. An increasing number of COVID-19-related complications involving various disciplines, particularly haematology, are being reported. Coronavirus disease 2019 is associated with prominent haematopoietic system manifestations, including leukopenia, lymphopenia, thrombocytopenia, disseminated intravascular coagulation, and prothrombotic state.[1] An association between AIHA and COVID-19 infection has nonetheless been reported infrequently. The pathophysiology of this association is poorly understood with few cases reported worldwide.

Cold agglutinin disease (CAD) is a form of AIHA mediated by cold agglutinins that can agglutinate red blood cells at a temperature of 3°C to 4°C, resulting in complement-mediated haemolysis. Cold agglutinins arise from either primary (unknown) or secondary (when cold agglutinins are produced as a result of an underlying infection or haematological malignancy) conditions.[2] The pathogenesis of CAD as a result of infectious agents is unclear. It may be the result of complement system activation, and associated with an inflammatory state, including the upregulation of pro-inflammatory cytokines.

In this case, our patient fulfilled the diagnostic criteria for CAD that include haemolytic anaemia, reticulocytosis, elevated lactate dehydrogenase, hyperbilirubinaemia, positive anti-C3d antibodies, and negative anti-immunoglobulin G antibodies.[3] Other infections and autoimmune diseases were excluded, and no signs of malignancy were discovered. We concluded that the CAD in this case was caused by SARS-CoV-2 (COVID-19). Because of the ongoing haemolysis, our patient required packed cell transfusions on multiple occasions. We believe that her condition deteriorated due to the "cytokine storm" and complement cascade, necessitating oxygen supplementation and blood product transfusion.

Lazarian et al[4] reported seven cases of AIHA (four cases of warm AIHA and three cases of cold AIHA) associated with COVID-19 infection. Extensive investigations into the three cases of cold AIHA revealed the presence of underlying malignancies (marginal zone lymphoma, 2 cases; prostate cancer, 1 case). No malignancy was evident in our patient. Patil et al[5] reported a case of COVID-19 infection with AIHA and pulmonary embolism, and Maslov et al[6] reported a patient with COVID-19 infection and cold agglutinin haemolytic anaemia complicated by stroke and bilateral upper extremity venous thrombosis. Our patient showed no signs of thromboembolism. Although patients infected with COVID-19 are at increased risk of thromboembolic complications, AIHA/CAD should be considered as a possible contributory factor.

Treatment of CAD is not recommended in patients who are asymptomatic with mild anaemia or compensated haemolysis and corticosteroids should not be used to treat CAD.[7] However, in our patient, the use of methylprednisolone was indicated as treatment for severe COVID-19 pneumonia. Corticosteroid administration has been proposed to reduce the systemic inflammatory response that leads to lung injury and multiorgan failure in COVID-19. Prompt administration of methylprednisolone has been shown to significantly

reduce mortality rate and ventilator dependence.[8] The improvement of haemolysis in our patient coincided with a favourable treatment response of COVID-19 to corticosteroid. This was reflected in her need for fewer packed cell transfusions, as well as stabilisation of her haemoglobin and no need for blood transfusions for one week prior to discharge. Rituximab has also been used to treat COVID-19-associated AIHA in two reported cases following corticosteroid failure and marginal zone lymphoma, respectively.[4] More research is needed to assess the safety and efficacy of these therapies in the treatment of COVID-19-associated AIHA.

Author contributions

Concept or design: CY Chang.
Acquisition of data: CY Chang, HH Chin.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: CY Chang, HH Chin.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patient(s) provided written informed consent for all treatments and procedures and for publication of this case report.

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