Cold agglutinin-mediated autoimmune hemolytic anemia associated with COVID-19 infection

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Case Report

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Abstract

Cold agglutinin-mediated autoimmune hemolytic anemia (AIHA) is a rare disorder associated with COVID-19 infection. Here, we present a case of COVID-19 pneumonia with concomitant cold agglutinin syndrome (CAS). On admission, the patient was anemic with reticulocytosis and the direct antiglobulin test showed the presence of anti-complement (C3d) antibodies. Peripheral blood film demonstrated red cell agglutination which was dispersible on blood warming. Chest radiography showed bilateral lower zone ground glass appearance. SARS-CoV-2 was detected in the nasopharyngeal and oropharyngeal swab samples by the RT-PCR method. Additional workup for malignancy, autoimmune disease, and other infections yielded negative results. Systemic corticosteroids and oxygen therapy were administered as she developed hypoxic respiratory failure. In addition, she received packed cell transfusion in view of hemolysis. Following corticosteroid and other supportive therapy, she recovered and was discharged well.

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2 and was first reported in Wuhan, China in December 2019, and subsequently spread globally [1]. Patients may develop acute respiratory distress syndrome (ARDS) as part of the serious complications and thus leading to death in severe cases of COVID-19 [2]. In addition, COVID-19 has been associated with multiple hematological abnormalities and complications including lymphopenia, thrombocytopenia, disseminated intravascular coagulation, and thromboembolism [3].

Cold agglutinin syndrome (CAS) which is a form autoimmune hemolytic anemia (AIHA) mediated by cold agglutinins, is a rare disorder often associated with infection, autoimmune disorders, or lymphoid malignancies [4]. The presentation of CAS among patients infected with COVID-19 has been rarely reported, and till date, the exact mechanism behind this association still remain unknown. Lazarian et al. described 3 cases of cold agglutinin AIHA associated with COVID-19 infection in his case series. Extensive investigations were carried out for these cases and revealed the presence of underlying malignancies (marginal zone lymphoma, 2 cases; prostate cancer, 1 case) [5]. Zagorski et al. reported a fatal case of COVID-19 complicated with severe ARDS and acute CAS [6]. Here, we report a case of cold agglutinin-mediated AIHA in the presence of COVID-19 in Malaysia; probably the first being reported.

Case History

A 70-year-old female with a history of diabetes mellitus, hypertension and dyslipidemia presented with fever, cough, and rhinorrhea 3 days prior. She reported no chest pain, breathlessness, anosmia or ageusia.

On physical examination, she was alert and not tachypneic. There was mild pallor but no jaundice. Her blood pressure was 118/56 mmHg, pulse rate was 62 beats per minute, and temperature was 36.5°C. Her respiratory rate was 16 breaths per minute and the oxygen saturation as measured by pulse oximetry while breathing ambient air was 98%. Auscultation of the lung revealed bibasal crackles. There was no

lymphadenopathy, splenomegaly, or clinical signs of autoimmune diseases. The remainder of the physical examination was unremarkable.

The hematological analysis revealed a hemoglobin of 8.1 g/dL, white cell counts of $9.6 \times 10^3/\mu\text{L}$ (absolute lymphocyte count = $3.1 \times 10^3/\mu\text{L}$) and platelet counts of $346 \times 10^3/\mu\text{L}$. The peripheral blood film showed moderate anaemia with occasional spherocytes seen and marked red blood cell agglutination which disperse on warming the blood to 37°C suggesting cold agglutinin disease (Fig. 1). The absolute reticulocyte count was raised (2.3%) and direct antiglobulin test showed presence of anti-complement (C3d) antibodies and absent anti IgG antibodies. However, we could not proceed with further testing as follows: serum haptoglobin, characterization of the erythrocyte autoantibodies, direct antiglobulin test performed with warm-washed red blood cells, cold agglutinin titre, and thermal amplitude testing since this facility was unavailable at the district hospital. There was mild hyperbilirubinemia with predominantly indirect bilirubin (total bilirubin = 26.2 $\mu\text{mol/L}$, direct bilirubin = 4.7 $\mu\text{mol/L}$, indirect bilirubin = 21.5 $\mu\text{mol/L}$). The liver transaminases and renal profile were within normal limits. The C-reactive protein (CRP), serum ferritin and serum lactate dehydrogenase (LDH) levels were 5 mg/L, 2671 mcg/L and 321 U/L respectively. The mycoplasma serology, blood cultures, D-dimer, and autoimmune screen were negative and so were the hepatitis B, C and HIV tests.

The chest radiograph showed ground-glass opacities in the bilateral lower zones. The patient was diagnosed with COVID-19 infection after detection of SARS-CoV-2 via RT-PCR from the nasopharyngeal and oropharyngeal swab samples (Ct value; E gene = 16.09, RdRp gene = 19.23). Her condition deteriorated on day 7 of illness as she developed hypoxemic respiratory failure requiring supplemental oxygen of 3L/minute administered via nasal cannula. At that point in time, the inflammatory markers were elevated, and chest radiograph showed worsening of bilateral airspace opacities. Hence, she was started on intravenous methylprednisolone 500 mg as single dose, followed by 2 mg/kg once daily for the subsequent five days. She responded to the administrated therapy as oxygen supplementation was weaned off 7 days later, along with improvement of blood inflammatory marker levels (CRP = 3.1 mg/L) and chest radiograph findings. Subsequently, she received a tapering dose of dexamethasone. During the hospitalization, she received packed cell transfusion of one unit each on the 3rd, 5th, 10th, and 14th hospital day in view of ongoing low-grade hemolysis. She was discharged home on day 21 of illness after her symptoms had resolved and she was completely transfusion-independent with stable hemoglobin levels for one week prior to discharge. One month later, she remained well upon review at the clinic and her repeated haemoglobin was 10 g/L. She did not report of any constitutional symptoms and there was no lymphadenopathy or organomegaly on physical examination, hence computed tomography (CT) scan was not done.

Discussion

This pandemic has taken the world by storm with many new undocumented symptoms or treatment strategies. We began to see more reports of COVID-19 related illness involving various disciplines namely haematology. COVID-19 is associated with prominent manifestations from the hematopoietic system in

which leukopenia, lymphopenia, thrombocytopenia, disseminated intravascular coagulation, and prothrombotic state are among the common hematological findings [3]. However, an association between AIHA and COVID-19 infection has been rarely reported. The pathophysiology behind this association was not well studied and only several cases had been reported worldwide.

Cold agglutinin disease (CAD) is a form of AIHA mediated by cold agglutinins that are able to agglutinate red blood cells at an optimum temperature of 3–4°C, with subsequent complement-mediated haemolysis. Cold agglutinins may be seen with primary cold agglutinin disease (unknown cause), or secondary CAS (when cold agglutinins are produced secondary to an underlying infection or hematological malignancy) [4, 7]. The pathogenesis of CAS attributed to infectious causes remains undetermined. It could be resulted from activation of complement system that is associated with an inflammatory state, including the upregulation of pro-inflammatory cytokines [7].

In this present case, our patient fulfilled the diagnostic criteria for CAS which include presence of hemolytic anemia, reticulocytosis, elevated lactate dehydrogenase, hyperbilirubinemia, positive anti-C3d and negative anti-IgG antibodies [8]. The screening for other infection and autoimmune diseases was negative, and there were no suspicious findings of malignancy. Therefore, we deemed that CAS in this case was due to SARS-CoV-2 (COVID-19). Our patient required packed cell transfusion on multiple occasions in view of the ongoing hemolysis. We believed that through activation of much believed 'cytokine storm' and complement cascade, her condition deteriorated, leading to requirement of oxygen supplementation and blood product transfusion.

Treating the underlying cause; in this case, COVID-19 remains the mainstay of management of CAS. Corticosteroid usage has been proposed to mitigate the systemic inflammatory response that leads to lung injury and multiorgan failure in COVID-19. Early administration of corticosteroids such as methylprednisolone has been proven to reduce death rates significantly and decreased ventilator dependence [9]. The hemolysis seen in our patient improved following favorable treatment response of COVID-19 to the administered corticosteroid. This was reflected by the decreasing requirement for packed cell transfusion which coincided with the biochemical and radiological improvement of COVID-19, and her hemoglobin stabilized without blood transfusion for one week prior to discharge. Rituximab was also being used to treat COVID-19 associated AIHA in two reported cases, following corticosteroid failure and marginal zone lymphoma respectively [5]. Further research is needed to evaluate the safety and effectiveness of these therapies in the treatment of COVID-19 associated AIHA.

Lazarian et al. reported seven cases of AIHA (warm AIHA, four cases; cold AIHA, three cases) associated with COVID-19 infection. While the median time between the first symptoms of COVID-19 and AIHA onset in those cases was nine days, the early occurrence of AIHA on the third day of illness as presented in this case is so far unique [5]. Till date, there are two case reports describing thromboembolism in patients with COVID-19 infection and cold agglutinin disease. Patil et al. described a case of CAD with AIHA, and pulmonary embolism as a presentation of COVID-19 infection, while Maslov et al. reported a patient with COVID-19 infection and cold agglutinin hemolytic anemia complicated with stroke and venous

thrombosis of bilateral upper extremities [10, 11] However, our patient did not exhibit any features of thromboembolism. While patients with COVID-19 infection are generally at elevated risk of thromboembolic complications, AIHA/CAD should be considered as a possible contributory factor.

Conclusion

COVID-19 can predispose to numerous hematological complications. Cold agglutinin-mediated AIHA associated with COVID-19 is rare and further research is warranted to evaluate the relationship between COVID-19 and AIHA.

Declarations

Funding

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Conflicts of interest/Competing interests

The authors declare that they have no competing interests.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' contributions

CYC: Conception of the study, interpretation of data, drafting the article. **HHC, PWC:** Acquisition of data, drafting the article. **MZ:** Revise the article and provide important intellectual content. All authors read and approved the final manuscript.

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
3. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastiris E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847.
4. Berentsen S. How I manage patients with cold agglutinin disease. *Br J Haematol*. 2018;181(3):320-330.
5. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol*. 2020;190(1):29-31.
6. Zagorski E, Pawar T, Rahimian S, Forman D. Cold agglutinin autoimmune haemolytic anaemia associated with novel coronavirus (COVID-19). *Br J Haematol*. 2020;190(4):e183-e184.
7. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. *Front Immunol*. 2020;11:590.
8. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):1114-1121.
9. Salton F, Confalonieri P, Meduri GU, et al. Prolonged Low-Dose Methylprednisolone in Patients With Severe COVID-19 Pneumonia. *Open Forum Infect Dis*. 2020;7(10):ofaa421. Published 2020 Sep 12. doi:10.1093/ofid/ofaa421
10. Patil NR, Herc ES, Girgis M. Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection. *Hematol Oncol Stem Cell Ther*. 2020:S1658-3876(20)30116-3.
11. Maslov DV, Simenson V, Jain S, Badari A. COVID-19 and Cold Agglutinin Hemolytic Anemia. *TH Open*. 2020;4(3):e175-e177.

Figures

Figure 1

(A) Peripheral blood smear prior to 'pre-warm' method (B) Peripheral blood smear after the application of 'pre-warm' method. The smears show leucoerythroblastic picture (yellow arrow). There are extensive red cell agglutinations (black arrow) in (A) which disperse on warming the blood to 37°C. Occasional spherocytes are seen in (B) (blue arrow). No abnormal lymphoid cells are present.