College, Bengbu, China.
E-mail: gaoyu@bbmc.edu.cn

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References

1. Paules, CI, Marston, HD & Fauci, AS Coronavirus infections-more than just the common cold. *JAMA*. 2020;**323**(8):707.
2. 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**:497–506.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected Pneumonia in Wuhan, China. *JAMA*. 2020;**323**(11):1061.
4. Mehta, P, McAuley, DF, Brown, M, Sanchez, E, Tattersall, RS & Manson, JJ COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;**395**(10229):1033–4.
5. Younan P, Iampietro M, Nishida A, Ramanathan P, Santos RI, Dutta M, et al. Ebola virus binding to Tim-1 on T lymphocytes induces a cytokine storm. *MBio*. 2017;**8**(5): https://doi.org/10.1128/mBio.00845-17.
6. Chien JY, Hsueh PR, Cheng WC, Yu CJ, Yang PC. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. *Respirology*. 2006;**11**:715–22.
7. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;**395**:473–5.
8. Patel P, Nandwani V, Vanchiere J, Conrad SA, Scott LK. Use of therapeutic plasma exchange as a rescue therapy in 2009 pH1N1 influenza A – an associated respiratory failure and hemodynamic shock. *Pediatr Crit Care Med*. 2011;**12**:e87–89.
9. Hadem J, Hafer C, Schneider AS, Wiesner O, Beutel G, Fuehner T, et al. Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-centre study of 23 patients. *BMC Anesthesiol*. 2014;**14**:24.
10. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. *Thromb Res*. 2020;**192**:3–8.

Cold agglutinin autoimmune haemolytic anaemia associated with novel coronavirus (COVID-19)

Cold agglutinin syndrome (CAS), a rare disorder accounting for 25–30% of autoimmune haemolytic anaemias, has been associated with infection, autoimmune disorders and lymphoid malignancies.[1] *Mycoplasma pneumoniae*, Epstein–Barr virus, human immunodeficiency virus, rubella virus, *Legionella*, varicella zoster virus, and influenza viruses have been commonly associated with cold agglutination.[1] Described here is a case in which the patient develops acute CAS associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19).

The pathogenesis behind secondary infectious causes of CAS remains undetermined. It is clear, however, that complement activation is associated with inflammatory states, including the up-regulation of pro-inflammatory cytokines.[2] This may indeed create the perfect storm for haemolysis, especially in such a pro-inflammatory infection as COVID-19.

A 46-year-old female with a history of immune thrombocytopenic purpura (ITP) 27 years ago during pregnancy, status post splenectomy, iron deficiency anaemia, and asthma presented with muscle aches, lethargy, and dyspnoea. Blood work performed six months prior to admission revealed normal bilirubin levels and a haemoglobin of 117 g/l, which was at the patient's baseline. Additionally, the patient had a negative rheumatologic work-up in the last several years including antinuclear antibody, rheumatoid factor and anti-citrullinated protein antibody.

On admission, patient was febrile at 38·2°C, with a heart rate of 107 beats per minute, and a respiratory rate of 29 breaths per minute. On examination, she appeared ill with generalised jaundice and increased work of breathing but did

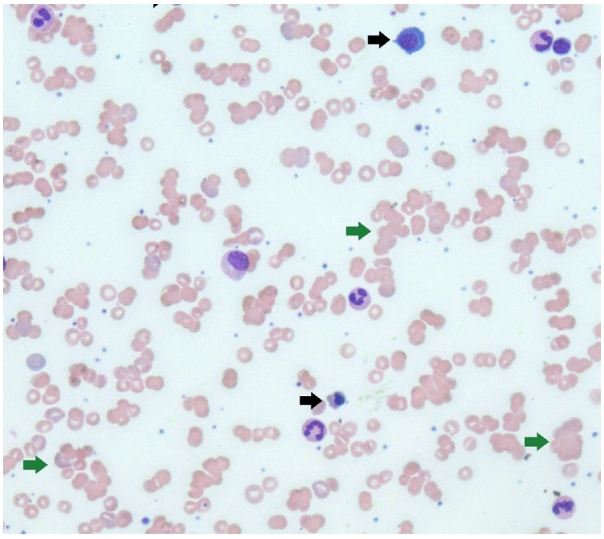

Fig 1. Black arrows represent nucleated red blood cells while green arrows represent agglutination.

not have any evidence of petechiae or rash. Contrast computed tomography imaging showed bilateral patchy lung infiltrates without evidence of pulmonary embolism and hepatomegaly with hepatic steatosis, without lymphadenopathy.

Additional laboratory testing revealed a haemoglobin level of 53 g/l, white blood cell count of 23,800 g/μl (75·2% neutrophils), 28·9% reticulocyte count, and normal platelets of 318,000 g/μl. Total bilirubin was elevated at 9·2 mg/dl (3·6 mg/dl direct) and a ferritin of 1930 ng/ml. Prothrombin time was normal at 24·1 s. Creatinine was 0·83 mg/dl with an estimated glomerular filtration rate of 75·05 ml/min/1·73 m^2. SARS-CoV-2 RNA polymerase chain reaction (PCR) was positive. A hepatitis viral panel and a respiratory pathogen panel including *Mycoplasma pneumoniae* were negative. Previous HIV 1/2 antibody testing was non-reactive.

Blood typing could not be performed due to strong cold agglutination. Direct Coombs testing with warming technique was strongly positive to immunoglobulin G (IgG) and complement. Lactate dehydrogenase was 1,316 u/l, and haptoglobin was undetectable. Urinalysis was 3+ positive for blood, but no red blood cells (RBC) were seen upon urine microscopy. a peripheral smear revealed agglutination of RBCs, marked polychromasia, and a large number of nucleated RBCs (Fig. 1). Patient was issued urgent type O blood given lack of blood typing. Unfortunately, within hours of admission, the patient became increasingly hypoxaemic despite a high-flow nasal cannula at maximum settings. Moments prior to intubation, she became bradycardic and pulseless. Despite best efforts, she passed away as a result of cardiac arrest.

An increasing amount of literature is contributing to understanding the COVID-19 process. Several other haematologic disorders have already been associated with COVID-19 including ITP and anti-phospholipid antibody syndrome.[3,4] While the pathophysiology of these associations has not yet been fully elucidated, the concern for a hypercoagulable state leading to cerebral infarction and venous thromboembolism in COVID-19 patients has been emphasised in many case reports.[4,5] While several recent reports reveal both warm and cold agglutinin autoimmune haemolytic anaemia as well as Evan's syndrome with SARS-CoV-2 infection, the rapid progression and acuity presented in this case is so far unique[6,7]

Most importantly, treatment of the underlying cause remains the mainstay of management for CAS. Finding a compatible blood transfusion via standard cross-matching can be prolonged in the presence of autoimmune haemolysis. Urgent transfusion of O-negative, non-cross-matched blood raises the risk of increased haemolysis from the underlying disease process or an alloantibody present in the serum. This risk may be acceptable in an unstable patient.[8] Treatment of the underlying cause remains the mainstay of management for CAS. Additional treatment modalities could not be considered or instituted due to rapid deterioration of our patient and her eventual demise, less than 24 h after presenting to our institution. Our observation of this accelerated onset and progression of CAS was humbling. Ongoing surveillance will be required for further potential associations of COVID-19 and CAS.

Emily Zagorski
Tushar Pawar
Shoja Rahimian
Daniel Forman
Department of Internal Medicine, Reading Hospital/ Tower Health, West Reading, Pennsylvania, USA.
E-mail: emily.zagorski@towerhealth.org

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References

1. Jager U, Barcellini W, Broome C, Gertz M, Hill A, Hill Q, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2019;**41**:100648.
2. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. *Front Immunol*. 2020;**11**:590.
3. Zulfiqar A-A, Lorenzo-Villalba N, Hassler P, Andrès E. (2020) Immune Thrombocytopenic Purpura in a Patient with Covid-19. New England Journal of Medicine, e43.
4. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with covid-19. *N Engl J Med*. 2020;**382**:e38.
5. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Res* 2020;**3848**:145–7.
6. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, et al. Autoimmune hemolytic anemia associated with COVID-19 Infection. *Br J Haematol*. 2020.
7. Li M, Nguyen C, Yeung Z, Sanchez K, Rosen D, Bushan S. Evans syndrome in a patient with covid-19. *Br J Haematol*. 2020.
8. Swiecicki P, Hegerova L, Gertz M. Cold agglutinin disease. *Blood*. 2013;**122**:1114–21.