Correspondence

Keywords: blue-green inclusions, COVID-19, lactic acid, liver injury, SARS-CoV-2

First published online 13 June 2020
doi: 10.1111/bjh.16882

References

1. Courville EL, Crisman S, Linden MA, Yohe S. Green neutrophilic inclusions are frequently associated with liver injury and may portend short-term mortality in critically ill patients. Lab Med. 2017;48:18–23.
2. Gorup T, Cohen AT, Sybenga AB, Rappaport ES. Significance of green granules in neutrophils and monocytes. Proc (Bayl Univ Med Cent). 2018;31:94–6.
3. Haberichter KL, Crisan D. Green Neutrophilic inclusions and acute hepatic failure: clinical significance and brief review of the literature. Ann Clin Lab Sci. 2017;47:58–61.
4. Harris VN, Malysz J, Smith MD. Green neutrophilic inclusions in liver disease. J Clin Pathol. 2009;62:853–4.
5. Hodgkins SR, Jones J. A Case of blue-green neutrophil inclusions. ASCLS Today, 2019:32:431.
6. Hodgson TO, Ruskova A, Shugg CJ, McCallum VI, Morison IM. Green neutrophil and monocyte inclusions - time to acknowledge and report. Br J Haematol. 2015;170:229–35.
7. Jazaerly T, Gabali AM. Green neutrophilic inclusions could be a sign of impending death!. Blood. 2014;123:614.
8. Patel N, Hoffman CM, Goldman BI, Bentley K, Burack WR, Evans AG. Green Inclusions in neutrophils and monocytes are an indicator of acute liver injury and high mortality. Acta Haematol. 2017;138:85–90.
9. Sin E, Korus AJ, Patterson A, Psevdos G. An unanticipated finding on peripheral smear: Blue-green crystals of impending death? Am J Hematol. 2019;94:733–4.
10. Soos MP, Heideman C, Shumway C, Cho M, Wooll A, Kumar C. Blue-green neutrophilic inclusion bodies in the critically ill patient. Clin Case Rep. 2019;7:1249–52.
11. Vicente-Steijn R, Tomé A, Maduell F, Xipell M, Castro P, Molina A, et al. Green inclusions in neutrophils: A critical finding that must be reported. Int J Lab Hematol. 2020;42:e101–e104.
12. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13.
13. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol. 2020;8:18–24.
14. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–81.
15. Zini G, Bellesi S, Ramundo F, d’Onofrio G. Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol. 2020.

Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19?

The British Journal of Haematology recently published two papers describing autoimmune haemolytic anaemia (AIHA) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.1,2 AIHA is characterised by the destruction of red cells by autoantibodies, but the mechanism underpinning autoimmunity in patients with coronavirus disease 2019 (COVID-19) has yet to be elucidated.

We recently postulated that molecular mimicry could be at the basis of the most severe complications observed in SARS-CoV-2-induced disease (COVID-19).3,4 For example, antibodies elicited against viral proteins could very well cross-react with vascular endothelial proteins if they shared antigenic epitopes. This would trigger extensive vasculitis followed by thrombosis and widespread intravascular coagulation with multi-organ failure.5

Here, we would like to posit the hypothesis that molecular mimicry is also a determinant factor in AIHA in patients with COVID-19, with Ankyrin 1 (ANK-1) and the viral protein Spike being the central players. ANK-1 is an erythrocyte membrane protein that is important for red cell differentiation and function, providing the primary connection between the membrane skeleton and the plasma membrane.6 It is defective in patients with hereditary spherocytosis, a common cause of haemolytic anaemia.5

We found that ANK-1 shares a putative immunogenic-antigenic epitope (amino acids LLLQY) with 100% identity with the SARS-CoV-2 surface glycoprotein named Spike protein (Table I). We established that this epitope is part of the Spike’s predicted immunogenic epitope 750-SNLQLQYGFSCTQL-763 for B cells by using the immune epitope database and analysis resource [Immune Epitope Database (IEDB), https://www.iedb.org/]. This database contains experimentally validated epitopes and tools to predict epitopes recognisable by T and B cells and is used also in the design of vaccines.7

With this Letter, we would like to call the attention of the scientific community to the structural similarity between ANK-1 and the viral protein Spike. We hope it will prompt further research aiming at determining if the potential immunological cross-reactivity between ANK-1 and Spike contributes to the pathogenesis of AIHA in patients with COVID-19. Information on this topic may open new avenues toward designing efficacious therapies.

© 2020 British Society for Haematology and John Wiley & Sons Ltd
British Journal of Haematology, 2020, 190, e57–e94
COVID-19 and ABO blood group: another viewpoint

Li et al.1 have recently published ‘Association between ABO blood groups and risk of SARS-CoV-2 pneumonia’, an observation already reported a few weeks ago as a MedRxiv preprint by Zhao et al.2 and which had a certain impact in the press.

In both studies, the ABO blood groups distribution of patients with coronavirus disease 2019 (COVID-19) were compared to that of controls from the local populations that showed that blood group A was associated with an increased risk of infection, whereas group O was associated with a decreased risk. Considering this information rather as a working hypothesis, some scientists have called for caution.3

However, as already strongly suggested by others,4 this variable susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could be linked to circulating anti-A antibodies, which could interfere or even inhibit the virus–cell adhesion process.

We had the idea to analyse these important available data series from the anti-A or -B antibodies viewpoint instead of ABO blood group antigens as the authors did.

In fact, considering the largest series of patients with COVID-19 (N = 1888) analysed by Zhao et al.,2 we compared the proportion of those possessing anti-A in their serum (i.e. those of B and O blood groups) and those who

| Protein                        | Accession number | Epitope amino acids | Identity percentage, % |
|--------------------------------|------------------|---------------------|------------------------|
| SARS-CoV-2 surface glycoprotein| NCBI ID: YP_009724390-1 | 752-LLLQY-756       | 100                    |
| Ankyrin 1                      | UniProt ID: P16157 | 323-LLLQY-327       |                        |

Table I. Shared identical epitope between Ankyrin 1 and SARS-CoV-2 surface glycoprotein

ID, identifier; NCBI, National Center for Biotechnology Information.

1We used for comparative analyses BlastP (available at: https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins) and the whole virus proteome (available at: https://www.ncbi.nlm.nih.gov/nuccore/MN908947).

References

1. Lopez C, Kim I, Pandey A, Huang T, DeLoughery TG. Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. Br J Haematol. 2020 [Epub ahead of print]. https://doi.org/10.1111/bjh.16786.
2. 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 [Epub ahead of print]. https://doi.org/10.1111/bjh.16794.
3. Cappello F. Is COVID-19 a proteiform disease inducing also molecular mimicry phenomena? Cell Stress Chaperones. 2020;25:381–2.
4. Cappello F. COVID-19 and molecular mimicry: The Columbus’ egg? J Clin Neurosci. 2020 [Epub ahead of print]. https://doi.org/10.1016/j.jocn.2020.05.015.
5. Angileri F, Legare S, Marino Gammazza A, Conway de Macario E, Macario AJ, Cappello F. Molecular mimicry may explain multi-organ damage in COVID-19. Autoimmun Rev. 2020, in press.
6. Gallagher PG, Tse WT, Scarpa AL, Lux SE, Forget BG. Structure and organization of the human ankyrin-1 gene. Basis for complexity of pre-mRNA processing. J Biol Chem. 1997;272:19220–8.
7. Vita R, Overton JA, Greenbaum JA, Ponomarenko J, Clark JD, Cantrell JR, et al. The immune epitope database (IEDB) 3.0. Nucleic Acids Res. 2015;43:D405–12.

Keywords: ankirin 1, autoantibodies, autoimmunity, COVID-19, molecular mimicry, severe acute respiratory syndrome coronavirus 2

First published online 8 June 2020
doi: 10.1111/bjh.16883

Correspondence

© 2020 British Society for Haematology and John Wiley & Sons Ltd
British Journal of Haematology, 2020, 190, e57–e94