Cold- and warm-type autoimmune hemolytic anemia associated with COVID-19 infections: What lies beneath?

Anthony Nanajian[1,2,*], Xiaolan Tang[1,2,*], Uma Iyer[2,3]

[1]University of Central Florida College of Medicine, Graduate Medical Education. Orlando, FL
[2]North Florida Regional Medical Center, Internal Medicine Residency Program. Gainesville, FL
[3]Florida Cancer Specialists and Research Institute. Gainesville, FL
[*]First co-authors

UNIVERSITY OF CENTRAL FLORIDA | NORTH FLORIDA REGIONAL MEDICAL CENTER
NORTH FLORIDA REGIONAL HEALTHCARE
UNIVERSITY OF CENTRAL FLORIDA COLLEGE OF MEDICINE / HCA HEALTHCARE GME CONSORTIUM

Introduction

While COVID-19 infections frequently result in pneumonia and respiratory failure, broader manifestations, such as autoimmune sequelae, have been increasingly recognized [1]. Autoimmune hemolytic anemia (AIHA) is one such rare complication that has been previously reported among COVID-19 patients. AIHA involves an autoantibody-mediated recognition and destruction of red blood cells in the presence or absence of an underlying condition. Infection, malignancy, immune deficiency and autoimmunity are some of the underlying factors that may contribute to secondary AIHA [1-4]. Such conditions have been found in all cases involving cold-type AIHA with concurrent COVID-19 infections [1-4]. In this paper, we report a patient who initially presented with a COVID-19 infection and was subsequently found to have concurrent warm-type AIHA in the absence of an underlying pathology typically associated with AIHA.

Cases

We report the case of a 49 year-old previously healthy woman, brought to the emergency department for acute onset of altered mental status, confusion, lethargy and slurred speech. She tested COVID-19 positive on admission. Physical exam was pertinent for mild tachycardia, mild tachypnea, lethargy, jaundice, scleral icterus, and disorientation to time. Remainder of the physical exam, including neurological exam, was otherwise normal.

Lab findings were consistent with hemolytic anemia, and a peripheral blood smear showed multiple spherocytes. Bloodwork demonstrated a positive direct Coombs' test with warm-reactive antibodies, consistent with warm AIHA. Brain MRI was concerning for acute subacute infarction in the left frontoparietal and right occipital lobes, suggesting embolic etiology. Patient was not a candidate for tPA. TTE findings were consistent with a patent foramen ovale in the atrial septum.

Her neurological symptoms were likely exacerbated by encephalopathy secondary to hemolytic anemia and metabolic derangement. She had no history of hemolytic anemia, autoimmune conditions. No history or findings of other underlying conditions predisposing to AIHA. Four units of blood were transfused and her AIHA and COVID-19 infection were treated with a steroid regimen. The COVID-19 infection was further treated with Remdesivir. The patient's anemia gradually improved with steroid therapy, and she was discharged on apixaban on Day 3.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Discussion

To date, a total of nine adult patients have been reported with COVID-19 and AIHA: Six patients with warm-type AIHA and three patients with cold-type AIHA [1-4].

Of the above nine patients with concurrent COVID-19 and AIHA, only three patients were reported to have no other underlying pathology, whether neoplastic, lymphoproliferative, autoimmune or infectious. Interestingly, we note that all three of those patients had warm-type AIHA. On the other hand, all the cold-type AIHA cases with COVID-19 infections had other underlying conditions commonly associated with AIHA.

Our findings from this study raise the question whether warm-type AIHA may be triggered by COVID-19 (possibly via molecular mimicry), while cold-type AIHA may be secondary to another underlying pathology and not directly triggered by COVID-19.

Molecular mimicry involving immunological cross-reactivity between the Ankyrin 1 [ANK-1] erythrocyte membrane protein and the COVID-19 Spike protein has been postulated as a factor contributing to the pathogenesis of AIHA in patients with COVID-19 [5]. The concept of molecular mimicry is further discussed in Figure 1 below.

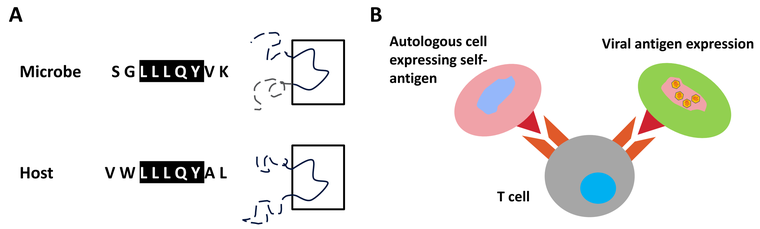

Figure 1. Concept of Molecular Mimicry. A) Molecular mimicry involves a shared linear or conformational amino acid sequence between a microbial and a host protein [6]. **B)** This epitope is initially recognized by T cells as foreign and stimulates an immune response. Such a cross-reactivity may result in a self-antigen recognition as 'foreign' and lead to autoimmunity [6].

Using the Immune Epitope Database (IEDB; https://www.iedb.org), the Spike protein's putative immunogenic-antigenic epitope 750-SN**LLLQY**GSFCTQL-763 was found to share the amino acids **LLLQY** with ANK-1 (Table 1) [5].

Table 1. Ankyrin 1 and COVID-19 Spike protein share an identical epitope (Refer to *Angileri et al.*)

Protein	Accession number	Epitope amino acids	Identity percentage, %
COVID-19 Spike protein	NCBI ID: YP_009724390.1	752-LLLQY-756	100
Ankyrin 1	UniProt ID: P16157	323-LLLQY-327	

In light of our findings, we are conducting a retrospective study to further explore whether warm-type AIHA may be triggered by COVID-19, while cold-type AIHA may be secondary to another underlying pathology. It would also be a worthwhile endeavor to further investigate the molecular mimicry postulate via T cell receptor sequencing of T cells isolated from the peripheral blood of patients with concurrent COVID-19 and warm AIHA. The goal of these studies is to determine the mechanism by which COVID-19 may trigger autoimmunity.

Conclusion

- We report a patient who initially presented with a COVID-19 infection and was subsequently found to have concurrent warm-type AIHA in the absence of an underlying pathology typically associated with AIHA.
- Our findings raise the question whether warm-type AIHA may be triggered by COVID-19, while cold-type AIHA may be secondary to another underlying pathology and not directly triggered by COVID-19.
- Molecular mimicry involving immunological cross-reactivity between the ANK-1 erythrocyte membrane protein and the COVID-19 Spike protein has been postulated as a factor contributing to the pathogenesis of AIHA in COVID-19
- This study provides a groundwork for further investigations to determine whether cross-reactivity between COVID-19 proteins and self-antigens may contribute to autoimmune manifestations.

References

1. Lazarian, G., et al., Autoimmune haemolytic anaemia associated with COVID-19 infection. British journal of haematology, 2020. 190(1): p. 29-31.
2. Sahu, K.K., A. Borogovac, and J. Cerny, COVID-19 related immune hemolysis and thrombocytopenia. Journal of medical virology, 2021. 93(2): p. 1164-1170.
3. Jacobs, J. and Q. Eichbaum, COVID-19 associated with severe autoimmune hemolytic anemia. Transfusion, 2021. 61(2): p. 635-640.
4. Lopez, C., et al., Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. British Journal of Haematology, 2020. 190(1): p. 31-32.
5. Angileri, F., et al., Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19? British Journal of Haematology, 2020. 190(2): p. e92-e93.
6. Oldstone MB. Molecular mimicry, microbial infection, and autoimmune disease: evolution of the concept. Curr Top Microbiol Immunol. 2005;296:1-17.

HCA Healthcare