Secondary Cold Agglutinin Hemolytic Anemia and Unconventional Treatment with Rituximab

Jacob Trimble, MD, Roy Dennis III OMS IV, Zachary Bondranko, DO, Mary Therese Thomas, DO, Thomas Bumbalo, MD

Introduction

- Cold autoimmune hemolytic anemias are diagnosed with a direct antiglobulin test at <37°C
- Primary cold haemolytic anemias are complement mediated, while secondary are caused by the virus Mycoplasma pneumonia or the Epstein-Barr virus (<1%)
  - Polyclonal IgM mediated against the “big I” or “little i” (<1%) antigens of the I blood group
- In this case presentation we present a patient with this rare finding of IgM antibody directed against the “little i” antigen on their RBCs from an EBV infection and treatment with an unconventional agent, Rituximab

Case Presentation

- 69-year-old female presented after 24 hours of generalized weakness, found on the bathroom floor by her husband
- Exam was normal, febrile to 104∘F
- WBC 19, Hgb 8, Plt 86, negative schistocytes on peripheral smear, fibrinogen 172 mg/dL, LDH 2021 mmol/L, ferritin 31,200 mg/mL
- Hematology noted that there was severe clumping, requiring frequent rewarming. Epstein Barr Virus antibody resulted positive
- Over the course of her hospital stay, she because extremely encephalopathic requiring intubation and acute renal failure requiring CRRT
- Her bilirubin peaked 87.9 mg/dL, with associated severe scleral icterus, jaundice, and the early signs of acrocyanosis of the most distal tips of her digits
- Supportive measures for cold agglutinin anemia such as heated transfusions, heated blankets, and increased room temperature did not result in improvement of clinical s/s
- It was decided to trial plasmapheresis and Rituximab, despite its use typically in only primary cold agglutinin disease
- On hospital day 14, she woke up, was able to be liberated from the ventilator and had resolution of her anemia
- In total, she spent 11 weeks in the hospital before being discharged home with no deficits

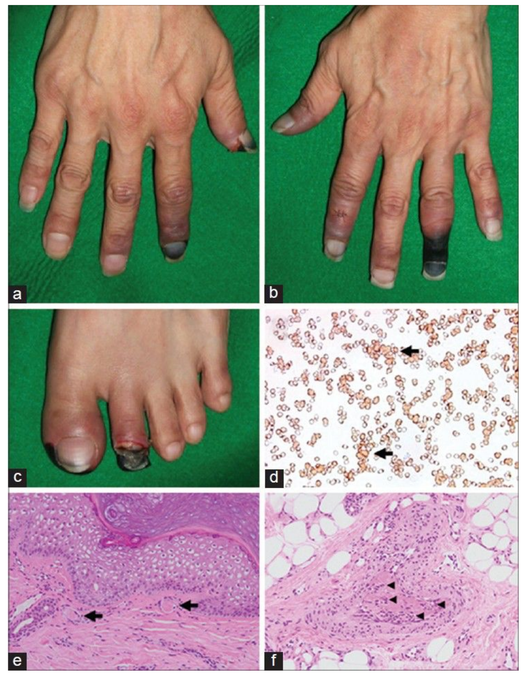

Figure 1: (a-c) Clinical features of the CAD patient. Acrocyanosis and digital gangrene rapidly appeared in the patient's hands and feet. (d) A blood smear test revealed erythrocytic coagulation. The arrow indicates a representative agglutination. Histopathological examination of the cyanotic lesion on the finger revealed thrombosis (arrow) in superficial dermal vessels (e) and endothelial proliferation (arrowhead) associated with thrombosis in subcutaneous vessels (f). (e and f: H and E, ×200)

Photo used from Koike Y, Akiyama Y, Utani A. Cold agglutinin disease-associated digital gangrene treated with plasmapheresis . Indian J Dermatol Venereol Leprol 2014;80:575-576

Rituximab as Treatment

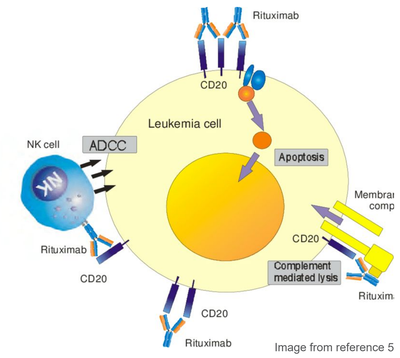

Image from reference 5

- Rituximab binds to CD20 in B cells, inducing cell death and ultimately, suppression of B-cell mediated production of antibodies, cytokines, and their antigen presenting cell function
  - Has shown effectiveness in patients with primary cold agglutinin disease
- Limited cases have used Rituximab in treatment of secondary disease, suspected reasoning being that most responsible viruses have a self-limited disease process
- Meta Analyses propose that there may be some efficacy in use of Rituximab in severe refractory disease
  - Most effective in the acute setting of two to four months or in treatment of relapsing disease as a nonsurgical alternative to splenectomy

Discussion

- In clinical practice when presented with encephalopathy and jaundice, it is important to rule out hepatic, obstructive, and infectious causes
  - Initial diagnosis was anchored on septic shock due to the initial presentation of encephalopathy, fever, hypotension, and elevated lactic acid, likely due to hepatic/gallbladder pathology
- Obtaining appropriate imaging (i.e., ultrasound, CT abdomen, MRI, or MRCP) can help rule out hepatic versus obstructive causes
- Early consultation with Hematology and a peripheral blood smear should be priority
  - The C3b complement protein marks the RBC for phagocytosis by splenic and hepatic cells, which is why there are no schistocytes seen on a smear
- While antibiotics and blood product resuscitation seemed to help with the encephalopathy of this patient, a declining respiratory status and persistent anemia indicated that alternative differential diagnoses needed exploring

Conclusion

- The overall goal for treatment of cases of secondary cold agglutinin AIHA is to prevent the progression of the disease, to avoid dry necrosis of peripheral extremities, and prevent acute hypoxic emergencies, ultimately decreasing morbidity and mortality
- Most importantly, nontraditional treatment with plasmapheresis and Rituximab in secondary cold AIHA may provide a new treatment option in severe or refractory cases

References

1. MARSH W. L. (1961). Anti-i: a cold antibody defining the Ii relationship in human red cells. British journal of haematology, 7, 200–209. https://doi.org/10.1111/j.1365-2141.1961.tb00329.x
2. JENKINS, W. J., MARSH, W. L., NOADES, J., TIPPETT, P., SANGER, R., & RACE, R. R. (1960). The I antigen and antibody. Vox sanguinis, 5, 97–121. https://doi.org/10.1111/j.1423-0410.1960.tb04667.x
3. Murakhovskaya I. Rituximab Use in Warm and Cold Autoimmune Hemolytic Anemia. Journal of Clinical Medicine. 2020;9(12):4034. doi:doi.org/10.3390/jcm9124034
4. Dierickx D, Verhoef G, Van Hoof A, et al. Rituximab in auto-immune haemolytic anaemia and immune thrombocytopenic purpura: a Belgian retrospective multicentric study. Journal of Internal Medicine. 2009;266(5):484-491. doi:10.1111/j.1365-2796.2009.02126.x
5. Huergo-Zapico, L., González-Rodríguez, A. P., Contesti, J., Fernández-Guizán, A., Huerta, A. A., López‐Soto, A., & González, S. (2012). Immune response and immunotherapy in chronic lymphocytic leukemia. In InTech eBooks. doi:10.5772/27086

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.