Clinical Medicine Insights: Case Reports

CASE REPORT

Warm Autoimmune Hemolytic Anemia with a Direct Antiglobulin Test Positive for C3 and Negative for IgG: A Case Study and Analytical Literature Review of Incidence and Severity

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Abstract: Polygenic IgG autoantibodies are implicated in majority of the cases of warm autoimmune hemolytic anemia (WAIHA). In some of these cases, complement (C3) proteins accompany the IgG antibodies. WAIHA mediated by C3 alone is relatively rare. We present an interesting case of WAIHA with a direct antiglobulin test (DAT) positive for C3 but negative for IgG in a 79-year-old woman and perform an analytical literature review of the incidence and severity of this clinical entity.

Keywords: auto immune hemolytic anemia, complement C3, Coombs test

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Introduction

Autoimmune hemolytic anemia (AIHA) is the anemia from hemolysis due to autoantibodies. Three different types of AIHA can be studied based on the behavior of the autoantibodies involved in the pathogenesis:[1] (1) Warm AIHA, which is most commonly mediated through IgG autoantiobodies (polygenic; commonly against the antigens of Rh system) that are most potent at temperatures ≥ 37 °C, (2) Cold AIHA, which is generally mediated through C3 componant of the complement that binds to and hemolyzes the red blood cells (RBCs) coated with IgM antibodies (commonly against I and also against i and Pr antigens of the RBCs) typically at temperatures much lower than body temperatures (commonly around 25 °C),[2] and (3) *Paroxysmal Cold Hemmoglobinuria (PCH),* which is mediated through IgG or Donath Landsteiner antibodies (commonly against P antigen) that fix the complement to the RBCs partially at low temperatures of ≤30 °C[3] (commonly 4 °C–18 °C as per in vitro testing)[1] and then complete the process at temperatures ≥ 37 °C. Most of the cases of AIHA have no identifiable etiology and hence are termed idiopathic or primary AIHA. The few cases where an underlying cause is identified are termed secondary AIHA and could be associated with lympho-proliferative diseases (lymphoma, Chronic Lymphocytic Lymphoma (CLL)), infections (mycoplasma[4] as in cold AIHA or syphilis[5] as in PCH and various other viral infections, such as the herpes family,[6,7] retrovirus,[8] and hepatitis[9]), drugs (penecillin and methyl dopa),[1] and other miscellaneous causes (connective tissue diseases, thyroid disease, ulcerative colitis, pernicious anemia, etc).[1] PCH occurs much more commonly in young children with infections (where a cold temperature is not involved in vivo). The temperature-dependent chronic primary PCH (usually in adults) is extremely rare. Lab abnormalities noted among all the AIHA in general include anemia, unconjugated hyperbilirubinemia, and elevated Lactate Dehydrogenase (LDH) levels.[1] Spherocytosis is often seen in WAIHA.[1] Severity of the clinical features and labs depend on the extent and rapidity of onset of the anemia and the ability of bone marrow to compensate for the anemia.[1] WAIHA with a Direct Anti-globulin Test (DAT) positive only for C3 is relatively rare.

Case presentation

A 79-year-old woman with a history of dementia was referred to our tertiary care center after she was found to have severe anemia with hemoglobin (Hgb) of 3.6, hyperbilirubinemia, and a positive Coombs test at a small hospital a day previously, where she had presented after being found unresponsive by her family. The patient was transfused 4 units at the initial hospital with appropriate rise in the hemoglobin. However, she was noted to be severely anemic with Hgb of 2.6 g/dL upon presentation to our hospital and so was admitted to the intensive care unig for blood transfusion and close monitoring of vitals and Hgb. The patient was also started on Solu-mederol 1 mg/kg intravenous (IV) and folic acid 1 mg orally once daily. Her initial LDH was 442 U/L; unconjugated bilirubin was 10 mg/dL. A peripheral blood smear showed spherocytes, polychromasia, and reticulocytosis. A DAT was repeated and was positive for C3 alone and was negative for IgG, IgA, and IgM. A cold agglutinin screen and eluate were negative. Her Hgb improved to 10.2 g/dL after Packed Red Blood Cells (PRBC) transfusion, and she was transferred to the step-down unit. She continued to require PRBC transfusions on an as needed basis for Hgb ≤ 8 g/dL. After discussion with the patient's family, the patient was admitted to the palliative care unit with discontinuation of as needed PRBC transfusions and any lab testing. She was, however, continued on 0.5 mg/kg Solumederol IV daily. The patient expired after a few days.

A written consent was obtained from the patient's daughter for the purpose of using patient information for this study.

Discussion

WAIHA commonly has a DAT positive for IgG with or without C3, IgM, and IgA. However, cases of WAIHA with a DAT positive only for C3, IgM, or IgA have been reported.

Though the exact cause of C3 only WAIHA has not definitively been proved, the following hypotheses have been proposed:[10]

a. Complement components may get bound to the RBC during adherence of antibody-antigen complexes that later dissociate, leaving the complement still attached to the RBC.

b. When natural antibodies associate with RBC damaged by the in vivo action of microbial enzymes, the complement may also be fixed to the RBC.
c. Complement activated in fluid phase by antigen-antibody complexes unrelated to the RBC may then fix to the RBC.
d. The complement may fix to the RBC by IgM that is present in serologically undetectable quantities.

In general, C3 only WAIHA is a relatively rare entity. Also since C3 alone coated RBC are not cleared efficiently by the macrophages[11] and since such complement coating of the RBC is seen in normal subjects also,[12] theoretically the hemolysis in C3 alone coated WAIHA should be mild. For the same reason, sparse IgG coating[13] of the RBC, not detectable by conventional lab testing, has been speculated as a mechanism for increased hemolysis in the rare cases of C3 alone WAIHA with severe hemolysis. However, different authors have mentioned varying incidences and clinical severity of this disease. For this reason, we sought to perform an analytical literature review of these parameters for this disease. A search of Medline NLM and Google with the terms "C3 only warm autoimmune hemolytic anemia" yielded only one pertinent article.[14] Further pertinent articles were derived through the references of the initial article and articles further down. Some references were also obtained through textbooks of Hematology.[1,11] Through this method, we obtained a total of 13 references of which 6 mentioned an incidence range for this pathology and 3 studies that commented on the presence and severity of hemolysis due to C3 only WAIHA.

Our review yielded the results presented here.

Incidence

Most of the authors reported an incidence for C3 only WAIHA as being less than 25%. Commonly it seems to have an incidence ranging between 6% and 13%.[1, 10,11,14,15,16]

Severity

The majority of the patients with DAT positive for C3 only do not seem to have any hemolysis. Among the patients who do have hemolysis, the clinical picture can range from mild asymptomatic anemia that is self-resolving or responding well to simple conservative measures such as oral steroids, to life threatening anemia requiring multiple blood transfusions and refractory to various conservative therapies including prednisone, IVIG, cyclosporine, azathioprine, and danazol and requiring splenectomy. However, in our study, we did not come across any reports of deaths due to this clinical entity.[14,16,17]

A study[17] involving 72 patients and comparing coexisting underlying diseases, severity of hemolysis, and response to therapy in patients with DAT positive for IgG versus C3 (either alone or in conjunction with IgG), mentioned that coexisting chronic diseases such as lymphatic neoplasms and connective tissue disorders were more common in patients with C3 positivity than the other groups.

The strength of the DAT has not shown a definite correlation to the occurrence or severity of hemolysis despite multiple studies over many years.[15]

Treatment of C3 only WAIHA is not well-documented given the paucity of these cases. However, in the study mentioned above,[17] the most satisfactory initial response to steroids was noted in patients with complement coating and normal cold agglutinins.

Conclusion

WAIHA with a DAT positive for C3 only is relatively rare with an incidence ranging between 6% and 13% and can have a clinical picture ranging from mild to severe anemia. In general, steroids should be used as a first-line therapy in these cases.

Author Contributions

Conceived and designed the experiments: AP. Analyzed the data: AP. Wrote the first draft of the manuscript: AP. Contributed to the writing of the manuscript: AP. Agree with manuscript results and conclusions: AP, FK, MC. Jointly developed the structure and arguments for the paper: AP, FK. Made critical revisions and approved final version: AP, FK, MC. All authors reviewed and approved of the final manuscript.

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Disclosures and Ethics

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