CASE REPORT

PAROXYSMAL COLD HEMOGLOBINURIA: TWO CASES OF A POORLY RECOGNIZED ENTITY

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Abstract

Even though paroxysmal cold hemoglobinuria (PCH) is a well-known cause of autoimmune hemolytic anemia, this syndrome is often not recognized at the time of initial presentation. PCH was originally recognized in individuals with secondary and tertiary syphilis. However, this association with syphilis is now very infrequent, and PCH is more commonly seen in children following a recent infection. In children, the term PCH is misleading. PCH generally presents as a single acute episode of intravascular hemolysis leading to hemoglobinuria in the setting of a recent infection and hence is not paroxysmal. Furthermore, PCH in children is not typically associated with cold exposure. Despite these different clinical presentations, the pathophysiology of the syndrome is the same in children as it is in the classic scenario of an adult with syphilis. We present two classic cases of acute PCH in children at a single institution that illustrate how this syndrome can often be overlooked. By keeping PCH on the differential in a child presenting with significant unexplained anemia in the setting of a recent infection, it may be possible to avoid invasive testing with its many associated costs.

Introduction

Paroxysmal cold hemoglobinuria (PCH) is a form of primary autoimmune hemolytic anemia (AIHA) and is most commonly seen in children following a viral illness. It generally causes severe intravascular hemolysis with anemia, hemoglobinemia and hemoglobinuria. The estimated annual incidence of AIHA in children is 1 in 80,000. (1) PCH, while uncommon, is estimated to account for 30 to 40 percent of these cases of AIHA. (2) PCH was first described in the early 1900's with the recognition of the association between cold exposure and the passing of red to brown urine. It was most frequently seen in patients with secondary or tertiary syphilis. An autoantibody was identified as the cause in 1904, following studies by Donath and Landsteiner. (2) PCH is now infrequently seen in association with syphilis as a result of effective antibiotic treatment and is most commonly seen in children after a viral-like illness. (3) In children, however, the term paroxysmal cold hemoglobinuria is a misnomer and might be best referred to as "Donath-Landsteiner Hemolytic Anemia." (2) This syndrome, rather than being paroxysmal, is usually associated with a single acute episode of hemolysis and is not usually associated with cold exposure. We present two classic cases of acute PCH in children at our institute.

Case 1: A 19 month old male was admitted for severe anemia. One week prior to admission, he developed eye drainage, cough and fever lasting several days. In the emergency department, he was diagnosed with pneumonia by chest x-ray and treated with amoxicillin-clavulanate. Two days later, he developed sudden jaundice and dark red urine and was admitted to a local hospital. He was found to have a hemoglobin of 2 gm/dl and was transferred to our hospital for further management. On examination, he had jaundice, coarse breath sounds, and pallor. Investigations revealed a white count of 15,700 cells/cumm, hemoglobin of 2.6 gm/dl, total bilirubin of 2.6 mg/dl, AST of 112 IU/L and a lactate dehydrogenase (LDH) of 2407 U/L. Urinalysis was positive for large quantities of blood. An extensive infectious disease workup was undertaken and included antibodies to Ebstein Barr virus (EBV), cytomegalovirus (CMV) and mycoplasma, a full respiratory virus panel and studies for hepatitis viruses. The only positive finding was for respiratory syncytial virus (RSV) by PCR. A direct anti-globulin test (DAT) on peripheral blood was positive for C3d but negative for IgG. Donath-Landsteiner auto-antibody test was positive, supporting the diagnosis of PCH. He was transfused with 380cc of washed red blood cells (RBC) in two aliquots, which elevated his hemoglobin to 8.5 gm/dL. His admission length totaled two days.

Case 2: A two year old female presented with new onset fatigue, confusion and pallor. Within the past two weeks, she had had an upper respiratory tract infection of five days duration. At an outside hospital, investigations revealed a white count of 40,000 cells/cumm, hemoglobin of 3.8 gm/dL, and platelet count of 631000 cells/cumm. The severe anemia and the elevated white count raised a concern for leukemia, and she was transferred to our hospital for further management. On examination, she was found to be tachycardic (heart rate of 180/min) with pallor and listlessness. Additional investigations revealed a total bilirubin of 1.8 mg/dL and LDH of 1154 U/L. Bone marrow biopsy was normal. Flow cytometry on the corresponding aspirate revealed a 0.3% myeloid blast population of undetermined significance. Moderate quantities of blood were found on urinalysis. An extensive infectious disease workup to include respiratory viral panel, enterovirus PCR, blood culture, and antibodies to Bartonella henselae, EBV and Leptospira was negative. She received multiple aliquots of RBC's and her hemoglobin only marginally increased to 5.3 g/dL. A DAT was done on admission blood, which was positive for C3d and negative for IgG. Donath-Landsteiner autoantibody test was positive and the diagnosis of PCH was made. The patient was treated with IV methylprednisolone in attempt to improve response to transfusion. Multiple additional aliquots of packed red cells were administered using blood warmers. In total, she received 954 cc of red blood cells (RBC) in eleven aliquots. Upon discharge, her hemoglobin had increased to 8.4 gm/dL. Her admission length totaled nine days.

Discussion

The two cases of PCH described in this report demonstrate that the diagnosis of PCH is often not included in the differential diagnosis of children with severe anemia. In a report by Heddle, it was noted that at one hospital no cases of PCH were recognized over a

6 year period. However, once a single case of PCH was diagnosed, 4 more cases were recognized in the next 9 months. (4) It is therefore important for PCH to be considered in the differential in children presenting with AIHA, particularly following an infectious process. There are three commonly recognized categories of primary AIHA in children: Warm-reactive AIHA, PCH and Cold Agglutinin Disease (CAD). (1) These three entities can generally be differentiated by the characteristics of the autoantibodies as well as the clinical presentation. (1) PCH is unique among these types of autoimmune hemolytic anemia in that a "cold-reacting" IgG antibody (the Donath-Landsteiner antibody) sensitizes RBCs and precipitates complement-mediated intravascular hemolysis. The Donath-Landsteiner antibody that forms in PCH is an unusual "cold-reacting" IgG antibody directed against the P antigen on the surface of the red blood cell. As blood circulates to peripheral, cooler parts of the body, it cools, and the Donath-Landsteiner antibody is able to fix to the red blood cell along with the first two components of the complement system. As the blood returns to warmer parts of the body, the complement cascade is completed, resulting in intravascular hemolysis. (5)

If a DAT is positive for C3 on the surface of the red cells but negative for IgG, the autoantibody is most likely cold reactive. The differential diagnosis is then CAD and PCH. (4) A Donath-Landsteiner assay should be ordered if the clinical scenario is fitting with PCH. The test requires the patient's serum is maintained at 37 degrees Celsius. (2)

The acute episode of PCH usually resolves within a few weeks. (2) Transfusion should be undertaken if the child displays symptomatic anemia (usually hemoglobin <5 gm/dL). Steroids have been used in many children with PCH. It is difficult to assess whether or not this tactic is effective, as most children have entered the recovery phase of the episode by the time treatment is initiated. (4) Blood warmers can be utilized during transfusion, but again there is little evidence as to the efficacy. (2) Our first patient responded very well to transfusion. It is likely that he was in the resolving phase of PCH with very low to absent titers of autoantibody. The second patient did not have a satisfactory increase in hemoglobin with initial transfusion. She was likely in the active phase of the syndrome, with elevated titers of autoantibody. Steroids were then administered and a blood warmer was utilized. It is hard to say whether the success of the subsequent transfusions was due to these modalities or in fact due to the passage of time with a decrease in autoantibody titer or a combination of both.

Conclusion

A key to the management of children with PCH is prompt and early recognition, and the initiative to request a very specific assay. This can result in a conservative approach and ideally an avoidance of invasive and unnecessary testing.

Authors Contribution

KH and MS drafted the initial manuscript and approved the final manuscript. JS contributed clinically to both cases, coordinated the report, critically reviewed the manuscript, and approved the final manuscript.

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References :

1. Ware RE. Autoimmune hemolytic anemia in children and adolescents. Available at URL: http://www.uptodate.com/contents/autoimmune-hemolytic-anemia-in-children-classification-clinical-features-and-diagnosis. Accessed on September 1, 2015
2. Eder AF. Review: Acute Donath-Landsteiner hemolytic anemia. Immunohematology 2005; 21: 56-62.
3. Gottsche B, Salama A, Mueller-Eckhardt C. Donath-Landsteiner Hemolytic Anemia in Children. Vox Sang. 1990; 58:281-286.
4. Heddle NM. Acute Paroxysmal Cold Hemoglobinuria. Transfusion Medicine Reviews. 1989; 3: 219-229.
5. Paroxysmal Cold Hemoglobinuria. Available at URL: http://www.uptodate.com/contents/paroxysmal-cold-hemoglobinuria. Accessed on October 28, 2015.

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