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Donath- Landsteiner Hemolytic Anemia – Cold Induced Dark Urine!

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Abstract

Donath- Landsteiner hemolytic anemia is a rare cause of anemia, presents with hemoglobinuria, hemoglobinemia, jaundice together with symptoms of anemia. After the development of Donath Landsteiner test, the diagnosis was well established, hence now it is quite common cause of young childhood hemolytic anemia (1,2)

Key Words: Donath Landsteiner; Autoimmune hemolytic anemia; paroxysmal cold hemoglobinuria

Introduction

The body produce Donath Landsteiner autoantibody in response to infections or neoplasms. These antibodies bind RBC surface proteins leading to complement mediated hemolysis. The antigen- antibody complex will trigger complement mediated intravascular hemolysis.
We present a 3 ½ year old previously healthy boy who presented with symptoms of anemia, jaundice and dark colored urine. The final diagnosis is DL anemia.

Case Presentation

A 3 ½ year old adequately grown, previously healthy boy presented with one day history of high degree fever with chills and rigors. History didn't point to a specific infection. He had dark colored urine towards the end of the day.
His examination revealed, jaundice and pallor. He was hemodynamically stable with good hydration status. There was no hepatosplenomegaly.
The initial investigations revealed a Hb of 10.5g/dl with normal white cell and platelet count.

Gradually Hb dropped up to 4.3 g/dl with normal red cell indices. His blood picture showed normocytic normochromic blood cells with minor population of spherocytes.
The reticulocyte count initially was 1% and increased to 9%. Total bilirubin was 5.71mg/dl with the direct fraction of 0.29mg/dl. Urine examination revealed no red blood cells in the full report, urine for urobilinogen was in the normal range but urine for hemoglobin was positive. Renal functions were normal. Therefore, we investigated for intravascular hemolysis.
His direct agglutination test (DAT) was positive, and further immune-hematological investigations showed DAT (poly specific: +3), (IgG specific: 0), (C3d specific: +3).
His cold agglutinin titer was negative for adult, cord and patient cells. His DL antibodies was positive.
Antibody testing for mycoplasma and Epstein- Barr virus was negative but testing for other viral infections were not performed.
He was transfused with warm packed red cells 10ml/kg as a slow transfusion, since he had symptomatic anemia.
Prednisolone 2mg/kg/day was started then slowly tailed off.
Supportive therapy with keeping the peripheries warm with socks and blankets and

avoiding cold exposure was done.
Patient had an uneventful recovery, with improvement of Hb with time.

Discussion

Donath Landsteiner anemia is a form of autoimmune hemolytic anemia (1,2,3,5). It was also called as paroxysmal cold hemoglobinuria, but as the name implies the children with the disease didn't usually had paroxysms of hemolysis directly related to cold exposure (2). Therefore, it is better described as DL hemolytic anemia (2)
In the past, classical syphilitic DL anemia leading to chronic hemolytic anemia was described (2,3,4). But now it is exceedingly rare. Usually, it is a single brief acute transient viral illness which predisposes and after 1-2 weeks later the hemolysis develops (2,1,4). Rarely it is accompanied with neoplasms and collagen vascular diseases (6). It is an intravascular hemolysis, with hemoglobinemia, hemoglobinuria (dark urine) with jaundice (1,2, 3,4).

Patient will present with sudden onset of back and abdominal pain, headache, leg cramps and fever with chills and rigors (1)
Patient may develop renal failure and hepatosplenomegaly either due to an underlying neoplasm ex- lymphoreticular malignancy (6) or in 25 % of cases as reactive (2).

Urticaria is also a described entity.
Due to molecular mimicry, IgG type DL antibodies cross react with antigen on the RBC surface, binding in the cold peripheries and initiating the complement cascade. Once RBCs reach warmer central circulation the IgG dissociate but complement reaction will continue leading to continued intravascular hemolysis and biphasic nature of the disease (1). The degree and duration of the hypothermia required to initiate hemolysis depends on the temperature requirement of antibody and red cell reaction and concentration availability of complements (1)
The same antigen is present in the skin fibroblasts and is the pathophysiology behind urticaria.

The lab workup is to confirm intravascular hemolysis, determine what type of antibody involved and to determine whether it is primary or secondary hemolytic anemia (1)
There will be severe progressive anemia and reticulocytopenia.
Blood picture will demonstrate few spherocytes, anisopoikilocytosis, fragmented red cells, basophilic stippling, polychromasia, autoagglutination and nucleated red cells (3)
urine for free hemoglobin will confirm intravascular hemolysis. If it is chronic hemolysis urine for hemosiderin will also be positive.
Direct coombs test is the marker of autoimmune hemolysis. Once it is positive, further evaluation is needed with anti- IgG and C3d monoclonal antisera. It will be positive due to C3d but not for IgG, confirming cold type autoimmune hemolysis. The next step is DL antibody, and if it is positive DL hemolytic anemia is confirmed (1,2,3,4,5)

Infectious work up for an etiology includes, treponema pallidum, measles, mumps, varicella, cytomegalovirus, Epstein bar virus serology and gram smear and culture for Hemophilus influenza, mycoplasma, klebsiella and smear for malaria (1)

Management is mainly supportive, keeping peripheries warm with socks, blankets and educating patient to avoid cold exposure (1,2,3)
Folic acid is needed to produce new cells after hemolytic episode. Folic acid 1 mg/daily is recommended with fresh fruits and vegetables rich in folate (1)
Monitoring cardiovascular and hydration status is needed with daily blood counts, LDH, retic counts and monitoring for hemoglobinuria (1,3).
Symptomatic anemia may need warm slow blood transfusions and may be lifesaving (1,2,3). Selection of blood includes ABO compatible, Rh & k phenotypically matched, antigen negative for clinically significant alloantibodies, leucoreduced and preferably < 14 days old blood.
Corticosteroid is not proven to be effective (4,5).
For refractory cases intensive immunotherapy with intravenous immunoglobulin, antiCD-20 monoclonal antibody ex- rituximab and complement inhibitors ex- eculizumab are used (4,5).

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