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Case Report



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Acute paroxysmal cold hemoglobinuria upon dengue fever: A case report

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ABSTRACT

Rationale: Dengue fever is capable of inciting the formation of transient polyclonal antibodies directed at red blood cell antigens, resulting in complement-mediated hemolysis, leading to intravascular hemolysis and hemoglobinuria.

Patient's concern: A 12-year-old male patient who recovered from dengue fever a week ago had red blood cell agglutination, spherocytes, and engulfment of red blood cells (erythrophagocytosis) by monocytes and neutrophils on routine hematological peripheral blood smear. The unexpected blood smear results prompted the lab physicians to investigate autoimmune hemolytic anemia, which revealed a monospecific positive direct antiglobulin test for complement (C3d, C3b) and the presence of Donath-Landsteiner antibody.

Diagnosis: Paroxysmal cold hemoglobinuria (PCH), secondary to dengue fever.

Interventions: Oxygen supplements, antibiotics, intravenous immunoglobulins, steroid therapy, and packed cell transfusions were administered.

Outcomes: The patient's condition was improved following the therapy.

Lessons: Post-dengue PCH is a rare complication that requires a thorough peripheral smear examination for erythrophagocytosis, as advanced hematology analyzers fail to detect such findings.

KEYWORDS: Paroxysmal cold hemoglobinuria; Dengue; Erythrophagocytosis; Donath-Landsteiner test; Treatment

1. Introduction

Paroxysmal cold hemoglobinuria (PCH) also known as Donath-Landsteiner (DL) hemolytic anemia, is an uncommon form of autoimmune hemolytic anemia (AIHA) that primarily affects children and young adults and is usually caused by a viral infection. In patients with PCH, the red blood cells (RBCs) are specifically targeted by an autoantibody called the DL antibody, which has the unusual ability to bind P antigen on RBCs at a lower temperature (possibly, 4°C). The phenomenon of engulfment of RBCs by monocytes and neutrophils is rarely described in cold agglutinin diseases[1], hematological malignancies[2], and spider bites[3]. However, when the temperature is raised to 37°C, complement-mediated lysis of the RBCs occurs, leading to intravascular hemolysis and hemoglobinuria[4]. Dengue fever, the most common arthropod-borne viral infection, is capable of inciting the formation of transient polyclonal antibodies directed at RBC antigens, resulting in complement-mediated hemolysis.

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2. Case report

A 12-year-old male patient was brought to the emergency department of our hospital by his parents with a history of fever associated with chills and rigors and yellowish discoloration of the eyes for three days. He was passing red-brown colored urine and was suffering from a loss of appetite, generalized weakness, giddiness, and three episodes of vomiting for the past two days. The patient was pale and febrile (38.67°C), and had jaundice, tachycardia (125 beats/min) (normal: 60-100 beats/min) and tachypnea (34 breaths/min) (normal: 12-18 breaths/min), hypotension (86/56 mmHg) (normal: 120/80 mmHg), and a room air oxygen saturation of 94% during the clinical examination. The systemic examination was unremarkable except for hepatosplenomegaly (a liver span of 10 cm and grade I enlarged spleen).

The initial hematological investigations revealed severe anemia of hemoglobin 2.40 g/dL (normal: 13-16 g/dL), a total leucocyte count of 30 560 cells/mm³ (normal: 5000-13 000 cells/mm³), and a normal platelet count of 360 000/mm³ (normal: 150 000-450 000/mm³). His RBCs' mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were 80.2 fL (normal: 83-101 fL), 27.9 pg (normal: 27-32 pg), and 34.8 g% (normal: 31g%-34 g%), respectively. Peripheral blood smears showed RBCs agglutination (Figure 1A) with polychromasia, spherocytes (Figure 1B), and three nucleated RBCs for every 100 white blood cells. Phagocytosis of erythrocytes by neutrophils (Figure 1B) and monocytes (Figure 1C) was also seen.

The white blood cell morphology revealed a few immature myeloid cells. A bone marrow aspiration smear showed stressed hematopoiesis with erythrophagocytosis (Figure 1D). The reticulocyte count was high at 15% (normal: 0.5%-2.0%). The direct (monospecific C3d, C3b) and indirect antiglobulin tests were positive. There was panagglutination in the screen cell panel with uniform strength of reactivity. The DL antibody test revealed the presence of DL antibody. The autoantibody titers, when performed at a cold temperature were found to be high (>256) (normal: 1:64). The blood conventional coagulation studies were normal. The patient's serum was non-reactive for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, and a rapid plasma regain test for syphilis was negative. A routine urine examination revealed proteinuria 2+ and elevated urobilinogen (2+) with normal microscopic findings. A manual test for hemoglobinuria in urine revealed positive results.

In the emergency department, oxygen was administered at a rate of 2 L/min through nasal prongs followed by 5 L/min through the mask. Intravenous fluids, antiemetics, and vital signs were monitored as parts of supportive care. The blood arterial gas study demonstrated CO₂ washout and hypoxia (pH: 7.3, pCO₂: 33, pO₂: 21, HCO₃: 19, and lactate: 7) (normal: pH: 7.35-7.45, pCO₂: 35-45 mmHg, pO₂: 83-

108, HCO₃: 22-26 mEq/L, and lactate: <2 mmol/L). The patient was uneventfully transfused with 3 units of packed RBCs at the pediatric intensive care unit. He was given 500 mg of azithromycin daily and injections of piperacillin and tazobactam (100 mg/kg/dose) three times a day. Methylprednisolone 10 mg/kg/day was administered for two days, along with 1g/kg of intravenous immunoglobulin. The patient was advised to stay warm. After two to three days of medication, his oxygen saturation returned to normal in room air. During treatment, there was an improvement in hemoglobin levels which was revealed by a complete blood picture. Peripheral smear examination did not show any evidence of erythrophagocytosis. The patient was discharged against medical advice (due to financial constraints). At the time of discharge, a significant improvement in his hemoglobin (7.8 g/dL) (normal: 13-16 g/dL) and liver function tests were noted.

3. Discussion

PCH was among the first to be recognized as an autoimmune illness. PCH accounts for 2%-10% of AIHA. The DL autoantibody is a specific and unique serological antibody seen in PCH. It was first described in 1904 by Drs. Donath and Landsteiner. Most cases have been documented in young boys with a boy-to-girl ratio of 2:1[5]. It might manifest as an acute non-recurring postinfectious incident in children or chronic relapsing episodes in adults. PCH has been associated with chickenpox[6], measles, mumps, respiratory tract infections, and Haemophilus influenza[7]. Pediatric patients commonly suffer from sudden onsets of hemolytic anemia, fever, tiredness, pallor, jaundice, and hemoglobinuria after being exposed to cold temperatures and viral-like diseases. The postulated etiology for red-brown urine is the release of hemoglobin as a result of intravascular hemolysis, which binds to haptoglobin. However, haptoglobin's binding capacity is exceeded, resulting in free hemoglobin in plasma, which is filtered by the kidneys and reabsorbed in the proximal convoluted tubule. When the reabsorption capacity is surpassed, urine turns cola-colored. In our case, a 12-year-old male patient was recently treated and recovered outside for dengue classical fever following a positive NS1 antigen test. After a week, symptoms were fever, jaundice, vomiting, and passing red-brown urine[8].

A laboratory diagnosis of PCH is characterized by decreased hemoglobin, increased reticulocytes, bilirubin, and lactate dehydrogenase. There are also pieces of evidence of erythrophagocytosis and erythrocyte neutrophil rosetting along with polychromasia and nucleated RBCs in the peripheral smear. Erythrophagocytosis by neutrophils is a distinguishing feature of PCH, exhibiting the severity of the rapid-onset hemolytic process. In addition to PCH, neutrophil erythrophagocytosis has

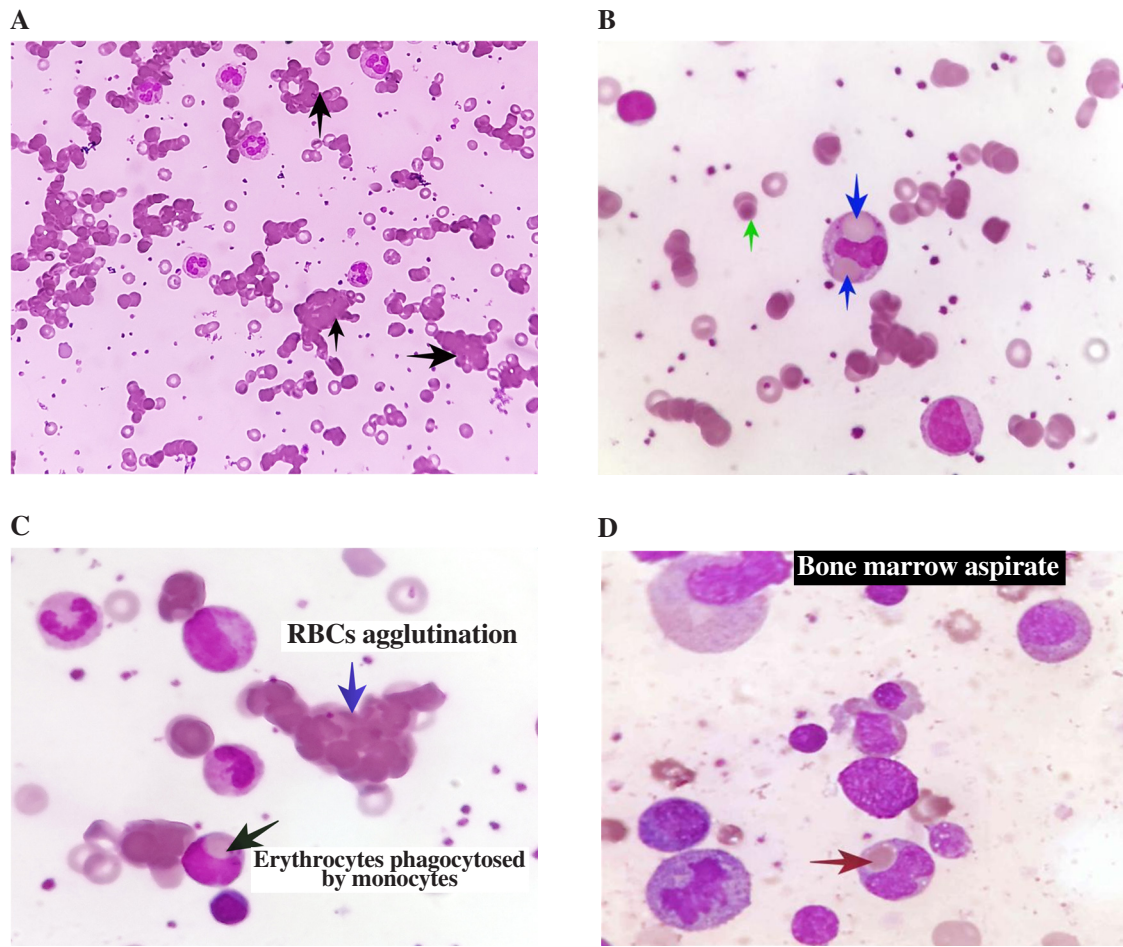


Figure 1. The peripheral blood smears and bone marrow aspiration smear of a 2-year-old male patient showing RBC agglutination (black arrows) (A), erythrophagocytosis of neutrophils (blue arrows) and spherocytes (green arrow) (B), monocyte-mediated erythrophagocytosis (black arrow) (C), and erythrophagocytosis of neutrophils (red arrow) in bone marrow aspirate (D).

been reported in cases of potassium chlorate poisoning, sickle cell disease, and incompatible transfusions. Erythrophagocytosis by monocytes or macrophages is occasionally seen in hematologic cancers, autoimmune hemolytic anemia, and hemophagocytic lymphohistiocytosis[9]. The mechanism underlying neutrophil erythrophagocytosis is unknown, however, its presence in peripheral smears leads the pathologist to diagnose AIHA, namely PCH. In our case, hemolysis and erythrophagocytosis in peripheral smears prompted the laboratory physician to look for PCH.

During the DL test, a biphasic hemolysin is detected, which is a complement-binding immunoglobulin (IgG) autoantibody that adheres to RBCs when cooled. Hemolysin often shows anti-P blood group specificity. The complement factor hemolyzes hemolysin-sensitized RBCs when the blood temperature rises to 37°C. As a result, the DL test is regarded as the determining test for detecting this kind of hemoglobinuria. These antibodies typically emerge within a week of the commencement of hemolysis and can last up to three months[10]. Other diagnostic confirmations include anti-P specific IgG autoantibodies and the presence of hemoglobin in urine.

Mycoplasma or the Epstein-Barr virus are the primary causes of acute cold AIHA and are considered the primary differential diagnosis for PCH. Cold agglutinin syndrome is defined by significant RBC agglutination on peripheral smears and unusually high RBC indices (mean corpuscular volume and mean corpuscular hemoglobin)[5]. Atypical lymphocyte cells, which are found in Epstein-Barr virus infection, were not present in our case. Additionally, there was a positive DL test. Moreover, the abrupt onset of severe anemia accompanied by erythrophagocytosis in the peripheral smear, reticulocytosis, and a positive DL test, confirmed the diagnosis.

The children who suffered from acute PCH and experienced self-limiting hemolysis, require supportive treatment and monitoring. In severe cases, packed red cell transfusions, corticosteroids, intravenous immunoglobulin, plasmapheresis, and rituximab are suggested. During transfusions, it is recommended that one should avoid cold temperatures and use blood warmers. In cases of severe and long hemolysis, P-negative blood transfusions may be useful. It is also critical to monitor hemograms, reticulocyte counts, and

renal function until full recovery. However, if severe anemia remains untreated, children can suffer acute renal impairment and other complications.

Although dengue is one of the most common viral (arboviral) illnesses transmitted by arthropods in humans, it can induce post-infection complications such as PCH and is relatively rare. The laboratory physicians should pay attention to suspects PCH by examining the peripheral smear for erythrophagocytosis by neutrophils and monocytes and perform a DL test for confirmation. A comprehensive examination of the peripheral smear is required because, despite advances in hematology analyzers, erythrophagocytosis can only be detected through analysis of the peripheral blood smear.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

All presented data are available in the tables and figures. For more details, please contact the corresponding author.

Authors' contributions

MMAB, SAA, and RDSR: conception, design of the work, data collection, review, and editing of the manuscript. MMAB, SAA, and AA: data collection, interpretation of data, original draft preparation, and writing.

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