A Rare Case of Parvovirus B19 Infection Induced Paroxysmal Cold Hemoglobinuria in an Adult Female

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Abstract

Paroxysmal cold hemoglobinuria (PCH) is a rare form of autoimmune hemolytic anemia (AIHA). PCH occurs in acute and chronic forms. The main risk factors for PCH include viral infections, vaccination, and syphilis. PCH presentations are common in the pediatric population. The occurrence of PCH following parvovirus B19 infection in adults is rare. We report a case of a 23-year-old female who presented with giddiness, fatigue, greying of vision, and presyncope for four days, on subsequent evaluation was found to have evidence of hemolysis and bone marrow suppression. Parvoviral intranuclear inclusions were detected in bone marrow biopsy and parvoviral B19 IgM antibody was detected. Donath Landsteiner antibody test was also positive. Hence a diagnosis of PCH secondary to parvovirus B19 infection was made. She was started on pulse dose steroids and intravenous immunoglobulin (IVIG) and showed significant improvement.

Introduction

Paroxysmal cold hemoglobinuria (PCH) is a rare form of autoimmune hemolytic anemia (AIHA), characterized by biphasic, polyclonal IgG autoantibody that binds specifically to the P antigen of RBCs [1]. This binding occurs at a lower temperature leading to complement system activation and red cell lysis at 37°C. The IgG autoantibody involved is Donath-Landsteiner (DL) antibody [2]. PCH is more common in the pediatric population [3]. PCH can occur in both acute and chronic forms. The important risk factors for acute PCH include viral infections (mumps, measles, chickenpox, Epstein-Barr virus, cytomegalovirus, influenza, parvovirus B19, coxsackievirus A9, and adenovirus) and vaccination (measles) [4,5]. The occurrence of parvovirus B19 infection predisposing to acute PCH in adults is rare. Here we report such a rare case of parvovirus B19 induced acute PCH.

Case Presentation

A 23-year-old Indian female, with no significant past medical history and family history, presented to our hospital with giddiness, fatigue, greying of vision, and presyncope for four days. There was no history of fever, chest pain, palpitation, shortness of breath, pedal edema, abdominal pain, vomiting, hematemesis, haematuria or malena. She denied any history of alcohol intake or substance abuse. Her menstrual cycles were regular with no history of menorrhagia or polymenorrhea. The patient was on a non-vegetarian diet. On examination, she was conscious and oriented, with a temperature of 37°C, pulse rate of 114/min, blood pressure of 110/60 mm Hg, respiratory rate of 18/min, and SpO2 of 96% in room air. Physical examination showed the presence of pallor in the conjunctiva, nailbed, and palms. Systemic examination was unremarkable except for a systolic flow murmur. Labs at presentation were significant for bicytopenia (Table 1).
| Variable                     | Measurement | Reference Values |
|------------------------------|-------------|------------------|
| Hemoglobin (g/dL)            | 6.7         | 12-16            |
| Total leucocyte count (/mm³) | 2400        | 4000-11,000      |
| Neutrophils (%)              | 36          | 50-70            |
| Lymphocytes (%)              | 46          | 30-45            |
| Platelet count (/mm³)        | 2,05,000    | 1,50,000-4,50,000|
| ESR (mm/h)                   | 148         | 0-20             |
| MCV (microm³)                | 99          | 80-98            |
| MCHC (g/dL)                  | 34          | 33-36            |
| MCH (pg/cell)                | 34          | 28-32            |
| Urea (mg/dL)                 | 16          | 8-20             |
| Creatinine (mg/dL)           | 0.5         | 0.5-1.1          |
| Total bilirubin (mg/dL)      | 1.3         | 0.3-1.0          |
| Direct bilirubin (mg/dL)     | 0.3         | 0.1-0.3          |
| ALT (units/L)                | 36          | 10-40            |
| AST (units/L)                | 28          | 10-40            |
| ALP (units/L)                | 66          | 30-120           |

**TABLE 1: Labs at presentation**

MCV: mean corpuscular volume; ESR: erythrocyte sedimentation rate; MCHC: mean cell hemoglobin concentration; MCH: mean cell hemoglobin; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase

ECG and chest X-ray were normal. Ultrasound of abdomen showed no hepatosplenomegaly. On the second day of hospital stay, she collapsed suddenly. On examination, she was tachycardic and hypotensive with a pulse rate of 112/min and blood pressure of 80/60 mm Hg. Labs showed a rapid decline in hemoglobin and evidence of hemolysis (Table 2). She was transferred to the ICU, transfused with two units of packed red cells, and was started on pulse dosage steroids with intravenous methylprednisolone 1000 mg once daily. There was no history of cold shower or swimming that led to a rapid change in body temperature.
| Variable                  | Measurement | Reference values |
|--------------------------|-------------|------------------|
| Hemoglobin (g/dl)        | 2.7         | 12-16            |
| Total leucocyte count    | 3700        | 4000-11,000      |
| Neutrophils (%)          | 63          | 50-70            |
| Lymphocyte (%)           | 28          | 30-45            |
| Platelet count           | 2,24,000    | 1,50,000-4,50,000|
| Total bilirubin (mg/dL)  | 2.4         | 0.3-1.0          |
| Direct bilirubin (mg/dL) | 0.4         | 0.1-0.3          |
| Reticulocyte count (%)   | 0.1         | 0.5-1.5          |
| LDH (units/L)            | 696         | 80-225           |
| TSH (micro Units/mL)     | 0.9         | 0.5-4.0          |
| Serum vitamin B12 (pg/mL)| 400         | 200-800          |
| Serum folate (ng/mL)     | 12          | 1.8-9.0          |
| Serum iron (microg/dL)   | 80          | 50-150           |
| TIBC (microg/dL)         | 300         | 250-310          |
| Transferrin saturation (%)| 30        | 20-50            |
| Serum ferritin (ng/mL)   | 100         | 11-307           |
| ANA-IF                   | Negative    |                  |

**TABLE 2: Labs on Day 2 showed rapid decline in hemoglobin level, evidence of hemolysis and low reticulocyte count**

TB: total bilirubin; DB: direct bilirubin; DCT: direct Coombs test; LDH: lactate dehydrogenase; TSH: thyroid stimulating hormone; TIBC: total iron binding capacity; ANA-IF: antinuclear antibody immunofluorescence

Peripheral smear showed normocytic normochromic anemia and leucopenia with a neutrophilic predominance. In view of severe bicytopenia and low reticulocyte count, bone marrow biopsy was done and revealed evidence of proerythroblasts with parvoviral intranuclear inclusions (Figure 1). Parvovirus B19 IgM was found to be positive. Hence she was initiated on intravenous immunoglobulin (IVIG) and continued for five days.
A hemolytic anemia workup was done to confirm the type of autoimmune hemolytic anemia. Direct Coombs test (DCT) for monospecific and polyspecific IgG-C3d was positive. The thermal amplitude of the antibody was found to be 4+ at 4°C, 2+ at 22°C, and reactive at 37°C, with evidence of hemolysis. Cold agglutination titer performed in normal saline plain gel card was found to be negative. DL test was done (Figure 2) and showed a positive result (Figure 3). Hence a diagnosis of PCH secondary to parvoviral B19 was made.
She was continued on IVIG and steroids. Her general condition improved over the next one week. The total duration of hospital stay was four weeks. She was discharged on a tapering dose of steroids with oral prednisolone 50 mg once daily.

Discussion

PCH is an AIHA characterized by DL antibody causing red cell lysis [6]. The occurrence of PCH is rare, accounting for less than 1% of all autoimmune hemolytic anemias [7]. PCH causes complement fixation at low temperatures, subsequently leading to intravascular hemolysis on rewarming. PCH can present in both acute and chronic forms. When PCH was first identified, it was described as a chronic condition in adults with tertiary syphilis [5]. With the advent of effective treatment for syphilis, the chronic relapsing form of PCH became rare [8]. Nowadays, the common presentation of PCH is an acute transient non-recurring illness.

Acute PCH predominantly occurs in the pediatric population with a recent history of viral illnesses or following immunization [9]. The incidence in pediatric groups is 0.001/100000 per year in boys and 0.0005/100000 per year in girls [10,11]. The mean age of onset is 3.8 years [8]. Certain viruses have been implicated in precipitating episodes of PCH in children, including measles, mumps, varicella, cytomegalovirus, Epstein - Barr virus, influenza virus, parvovirus B19, coxsackie, and adenovirus [12]. The mechanism of how an infectious agent induces PCH is poorly understood. One proposed theory suggests that viruses alter the glycoproteins on the erythrocyte membrane which further stimulates autoantibody formation [4]. Another theory points that molecular mimicry between self-antigens and foreign antigens leads to the production of cross-reactive antibodies [4].

Typical clinical features include fever, chills, abdominal pain, and hemoglobinuria on exposure to cold. Hemoglobinuria can persist for several months despite the resolution of intravascular hemolysis. Physical examination may show fever, pallor, icterus, and abdominal tenderness [13]. Laboratory findings include features of red blood cell lysis like indirect hyperbilirubinemia, low haptoglobin, decreased complement, elevated LDH, reticulocytosis, and hemoglobinuria. Hemosiderinuria is also characteristic but usually develops three to four days after the onset of hemolysis. The pathognomonic finding is erythrophagocytosis by neutrophils in peripheral blood smear [5]. The diagnosis of PCH is confirmed by the presence of
Disclosures

Additional Information

References

1. Levine P, Celano M, J, Falkowski F: The specificity of the antibody in paroxysmal cold hemoglobinuria (P.C.H.). Ann N Y Acad Sci. 1965, 124:456-461. 10.1111/j.1749-6632.1965.tb18978.x
2. Sokol RJ, Booker DJ, Stamps R: Paroxysmal cold hemoglobinuria and the elusive Donath-Landsteiner antibody. Immunohematology. 1998, 14:109-112.
3. Barcellini W: New insights in the pathogenesis of autoimmune hemolytic anemia. Transfus Med Hemonog. 2015, 42:287-293. 10.1119/201500539002
4. Leibrandt R, Angelino K, Vizel-Schwartz M, Shapira I: Paroxysmal cold hemoglobinuria in an adult with respiratory syncytial virus. Case Rep Hematol. 2018, 2018: 10.1155/2018/7586719
5. Bunch C, Schwartz FC, Bird GW: Paroxysmal cold haemoglobinuria following measles immunization. Arch Dis Child. 1972, 47:299-300. 10.1136/adc.47.2.299
6. Fukuoka M, Furuha H, Notou K, Takagi C, Suyama Y, Ishikura H, Kato Y: Adult type of idiopathic paroxysmal cold hemoglobinuria. [Article in Japanese]. J Clin Hematol. 1991, 32:1498-1502.
7. Barcellini W: Immune hemolysis: diagnosis and treatment recommendations. Semin Hematol. 2015, 52:504-512. 10.1055/s-0035-1505310
8. Heddie NM: Acute paroxysmal cold hemoglobinuria. Transfus Med Rev. 1989, 3:219-229. 10.1016/0887-7965(89)70082-1
9. Gunawardena D, Velu M, Senuvratne SN: Case report on a child with paroxysmal cold haemoglobinuria. Indian J Hematol Blood Transfus. 2012, 28:112-115. 10.1007/s12288-011-0094-y
10. Papalia MA, Schwarer AP: Paroxysmal cold haemoglobinuria in an adult with chicken pox. Br J Haematol. 2000, 109:528-529. 10.1046/j.1566-2141.2000.02010.x
11. Sokol RJ, Hewitt S, Stamps BK: Haemolysis associated with donath-landsteiner antibodies. Acta Haematol. 1982, 68:268-277. 10.1111/j.1749-6632.1982.tb00692
12. Sanford KW, Rosell SD: Detection and significance of Donath-Landsteiner antibodies in a 5-year-old female presenting with hemolytic anemia. Lab Med. 2010, 41:209-212. 10.3141/09-LM19252Z3EPA
13. Shemp SN, Davisom SM, Slateyen JS, Gikalo DA, Wusman DA: Two case studies and a review of paroxysmal cold hemoglobinuria. Lab Med. 2014, 45:253-258. 10.1309/LMWD51B2KIF8BLL
14. Bhatt R, Calvo L, Raju G, Podrumar A: Case of Donath-Landsteiner haemolytic anaemia in an adult female. BMJ Case Rep. 2018, 2018: 10.1136/bcr-2018-226475
15. Jaime-Pérez JC, Rodríguez-Martínez M, Gómez-de-León A, Tarín-Arzaga L, Gómez-Almaguer D: Current approaches for the treatment of autoimmune hemolytic anemia. Arch Immunol Ther Exp. 2013, 61:385-395. 10.1007/s00005-013-0232-3

16. Barros MMO, Blajchman MA, Bordin JO: Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transfus Med Rev. 2010, 24:195-210. 10.1016/j.tmrv.2010.03.002

17. Koppel A, Lim S, Osby M, Garratty G, Goldfinger D: Rituximab as successful therapy in a patient with refractory paroxysmal cold hemoglobinuria. Transfusion. 2007, 47:1902-1904. 10.1111/j.1537-2995.2007.01414.x

18. Andersen E, Skov F, Hippe E: A case of cold haemoglobinuria with later sarcoidosis. Treatment with plasmapheresis and immunosuppressiva. Scand J Haematol. 1980, 24:47-50. 10.1111/j.1600-0609.1980.tb01316.x