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Paroxysmal cold hemoglobinuria in an elderly patient: A rare case with poor prognosis

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ABSTRACT

Introduction: Paroxysmal cold hemoglobinuria (PCH) is a very rare type of cold-mediated autoimmune hemolytic anemia causing direct intravascular hemolysis and hemoglobinuria, typically after exposure to cold. The reaction is caused by an IgG antibody known as Donath-Landsteiner (D-L), which binds specifically to the P antigen of red blood cells at low temperatures, leading to complement activation and red cell lysis. Case Report: We report a case of rare occurrence of acute syphilitic paroxysmal cold hemoglobinuria in an elderly female with evidence of intravascular hemolysis complicated with peripheral gangrene and multiple organ dysfunctions. Conclusion: The prognosis of PCH associated with syphilis is usually considered excellent and benign. However, we encountered a syphilitic PCH in an elderly female with a grave prognosis who passed away within five months after her first episode. Based on our case experience, we recommend that acute episodes of PCH in an elderly patient should be treated in a closely monitored setting with high dose of steroids and warm blankets.

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INTRODUCTION

Paroxysmal cold hemoglobinuria (PCH) is a very rare type of cold-mediated autoimmune hemolytic anemia causing direct intravascular hemolysis and hemoglobinuria, typically after exposure to cold. The reaction is caused by an IgG antibody known as Donath-Landsteiner (D-L), which binds specifically to the P antigen of red blood cells at low temperatures, leading to complement activation and red cell lysis [1]. The PCH is the least common form of autoimmune hemolytic anemia (AIHA), affecting 2–5% of all patients with AIHA [2]. The two known types of PCH are syphilitic and non-syphilitic. The syphilitic type is caused by cold-warm hemolysin unique to syphilis patients occurring in both adults (late-syphilis) and children (congenital syphilis), while the non-syphilitic type is accompanied by unusually high titers of cold hemagglutinins [2, 3]. In the early 1900s, more than 90% of patients with chronic PCH had a positive test for syphilis and approximately 30% showed clinical evidence of disease. The incidence of chronic PCH has decreased

drastically due to effective treatment of syphilis. PCH is now most frequently encountered as an acute transient syndrome in young children with a recent history of viral illness [4]. Here, we report a case of rare occurrence of acute syphilitic paroxysmal cold hemoglobinuria in an elderly female with evidence of intravascular hemolysis complicated with peripheral gangrene and multiple organ dysfunctions.

CASE REPORT

A 91-year-old woman with a medical history of hypertension, peripheral vascular disease and dementia presented to the emergency department in January (winter time) with complaints of progressively worsening abdominal pain and vomiting for three days. Recently, admitted to another hospital with similar complaints and pink colored urination, where she received multiple blood transfusions and underwent amputation of five gangrenous left toes, which was believed to be due to PVD. During this admission, she was found to have abdominal tenderness, dry mucus membrane, pallor and icterus. Laboratory studies revealed anemia with severe hemolysis, elevated LDH level and indirect hyperbilirubinemia. Direct antiglobulin test was positive. After reviewing labs, as given in Table 1, a provisional diagnosis of autoimmune hemolytic anemia was made.

The patient was transfused with two units of packed red blood cells. On daily monitoring, patient was noted to have morning hemoglobinuria. Type and cross demonstrated cold antibodies, RBC coated with IgG and complement. Later, the patient was noted to have peripheral cyanosis at the fingertips (Figure 1) and toes with ongoing hemoglobinuria. Rheumatological workup for other causes of secondary Raynaud's phenomena was found to be negative, including cryoglobulin, complements, hepatitis C, lupus anticoagulant, cardiolipin antibody and RA factor. Embolic etiology was also ruled out. Due to worsening of peripheral cyanosis and severe peripheral infarction, patient had transmetatarsal amputation of toes. A bone marrow biopsy was performed to rule out lymphoproliferative disorders and PNH (paroxysmal nocturnal hemoglobinuria), which showed mild hypercellular marrow with maturing trilineage hematopoiesis. There was no down-regulation of CD55 and CD59 detected on selectively gated erythrocytes, granulocytes or monocytes, and no FLAER(-) cells were identified among the neutrophils or monocytes. Thus, PNH and lymphoproliferative disorders were rule out.

Peripheral smear showed normocytic normochromic RBCs with no polychromasia and neutrophils with few toxic granulations, erythrophagocytosis and 1–2 schizocytes.

Workup for cold antibody mediated hemolysis showed positive direct antiglobulin test for both IgG and complement in a cold sample, pointing diagnosis towards PCH. A sample sent to a warm water bath had no evidence of hemolysis. Blood for Donath-Landsteiner antibody tested positive in moderate titers. Diagnosis of syphilitic paroxysmal cold hemoglobinuria was confirmed. Due to the association of PCH with secondary and tertiary syphilis, syphilis serology was sent, and was found to have positive RPR (1:8) and positive fluorescent treponemal antibody. Patient was started on weekly benzathine penicillin injection for treatment of late syphilis. Patient was kept warm; no further hemolysis was noted and patient remained in a stable condition thereafter. Patient was discharged back to nursing home on oral steroids and

Table 1: Following labs were obtained on the day of admission

Sodium	143 MMOL/L	White Cell Count	5.1 K/cmm
Potassium Serum	7.4 MMOL/L	Red Cell Count	1.67 M/cmm
CO2	22 MMOL/L	Hematocrit	18 %
Creatinine	1.8 MG/DL	Mean Corp Vol	106 fL
BUN	40 MG/DL	MCH	37 pg
Glucose Random Serum	100 MG/DL	MCHC	34.6 g/dL
Anion Gap	11	Red Cell Dist. Width	15.8 %
Calc Osmolality	295 MOSM/KG	Auto Neutro	62.2 %
Calcium	9.7 MG/DL	Auto Lymph	30.5 %
Bilirubin Total	4.2 MG/DL	Abs Lymph	1.5 %
Bilirubin Direct	0.7 MG/DL	Abs Neutro	3.1 %
AST	149 U/L	Mean Platelet Vol	8.9 fL
ALT	22 U/L	Platelet Count	197 K/cmm
Albumin	4.2 G/DL	Hemoglobin	6.1 g/dL
Alkaline Phosphatase	72 U/L	TBHC B12	1424 pg/mL
Total Protein Serum	8.9 G/DL	Reticulocyte Count	2.5 %
Lactic Acid	3.8 MMOL/L	LDH	>3325 U/L
Lipase	80 U/L	DAT Anti IGG Coombs Serum	POSITIVE
DAT Complement Specific	POSITIVE	DAT Broad Spect Coombs	POSITIVE

instructions to stay warm; however, she was admitted again in two months due to worsening peripheral cyanosis and severe anemia. Despite aggressive measurements, patient succumbed to her illness after multiple organ system failure.

DISCUSSION

The PCH was first described by Donath and Landsteiner in 1904. The hemolytic antibody (D-L antibody) was first observed as a cross-reacting antibody to an antigen on *Treponema pallidum* [5]. Nowadays, PCH predominantly affects young children with an acute non-relapsing form shortly after an episode of upper respiratory infection [6]. The prognosis of PCH associated with syphilis is usually considered excellent and benign; however, we encountered a syphilitic PCH in an elderly female with a grave prognosis who passed away within five months after her first episode. Patient was never diagnosed with syphilis, neither had any clinical presentations of syphilis. Her first episode of cold related acrocyanosis was at the age of 91. Acute attacks frequently resolve spontaneously within a few days to several weeks after onset and it rarely recurs [7]. In our case with atypical history and patient's age, PCH was one of the bottom differential diagnoses. After ruling out other differentials, we sent syphilis serology, which came back positive for syphilis. Direct Coombs test, also known as direct antiglobulin test (DAT), is used to detect autoimmune hemolytic anemia. DAT detects antibodies or complements that are bound to the RBC membrane and causes their destruction. A positive Coombs test indicates that hemolysis is either autoimmune mediated (e.g., warm and cold antibody autoimmune hemolytic anemia), alloimmune mediated (e.g., hemolytic disease of newborn, hemolytic transfusion reaction), or drug-induced (e.g., methyldopa, quinidine, penicillin, etc.) There are typically three cold antibodies: autoimmune hemolytic anemia, i.e. idiopathic cold hemagglutinin syndrome (common), infectious mononucleosis and PCH (rare). In adults, cold hemagglutinin syndrome is typically caused by lymphoproliferative disease, which was ruled out in our case with bone marrow biopsy. In PCH, IgG anti-P autoantibody binds to an RBC surface antigen and causes hemolysis when exposed to cold temperatures [8]. In our test, when the patient's blood was placed in a cold temperature, hemolysis was noted in the presence of IgG and its complement.

Figure 1: Gangrenous fingers of our patient.

In this case, patient had recurrent acute episodes of PCH with deterioration of her clinical condition with each episode. Patient was started on oral steroids as it has shown improvement in some cases [9]. Based on our case experience, we recommend that acute episodes of PCH in an elderly patient should be treated in a closely monitored setting with a high dose of steroids and warm blankets. In addition to avoiding cold, long-term steroids may be beneficial in preventing subsequent attacks of PCH; however, further research is needed to investigate the role of steroids and the treatment of choice in PCH. It is crucial to restrict further episodes of PCH as consecutive attacks can be more severe and rapidly affect multiple vital organs.

CONCLUSION

The prognosis of PCH associated with syphilis is usually considered excellent and benign. Based on our case experience, we recommend that acute episodes of PCH in an elderly patient should be treated in a closely monitored setting with high dose of steroids and warm blankets.

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Author Contributions

Poras Patel – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Elizebath Guevara – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Avani Changela – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Yu Yu Thar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES

1. Chandrashekar V, Soni M. Florid erythrophagocytosis on the peripheral smear. J Lab Physicians 2012 Jan;4(1):59–61.
2. Rother RP, Bell L, Hillmen P, Gladwin MT. The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma HemoglobinA Novel Mechanism of Human Disease. JAMA 2005;293(13):1653–62.
3. Becker RM. Paroxysmal cold hemoglobinurias. Arch Intern Med (Chic) 1948 May;81(5):630–48.
4. Heddle NM. Acute paroxysmal cold hemoglobinuria. Transfus Med Rev 1989 Jul;3(3):219–29.
5. Gertz MA. Management of cold haemolytic syndrome. Br J Haematol 2007 Aug;138(4):422–9.
6. Nordhagen R, Stensvold K, Winsnes A, Skyberg D, Støren A. Paroxysmal cold haemoglobinuria. The most frequent acute autoimmune haemolytic anaemia in children? Acta Paediatr Scand 1984 Mar;73(2):258–62.
7. Petz LD. Cold antibody autoimmune hemolytic anemias. Blood Rev 2008 Jan;22(1):1–15.
8. O'Neill BJ, Marshall WC. Paroxysmal cold haemoglobinuria and measles. Arch Dis Child 1967 Apr;42(222):183–6.
9. Dacie JV. The Hemolytic Anaemias, Congenital and Acquired. Part II. The Auto-Immune Hemolytic Anaemias, 2ed. New York: Grune & Stratton; 1962.