

Haemolytic Anemia with Peripheral Gangrene a Rare Duo of Cold Agglutinin Disease

¹Dr. Nilesh Kumar, ²Dr. Amita Diwakar, ³Dr. Vijay Parashar, ⁴Dr. Pankaj kumar kannauje, ⁵Dr. Nikhil Srivastva

Assistant professor, Department of General Medicine, IMS, BHU

Junior Resident, IMS, BHU

***Corresponding author**

Nilesh Kumar

Email: nilesh19arreno@gmail.com

Abstract: Primary cold agglutinin disease is usually associated with monoclonal cold-reacting auto antibodies. Disease is chronic and occurs after the fifth decade of life, with a peak incidence in the seventh and eighth decades. Acrocyanosis and Reynaud's phenomenon usually associated with cold agglutinin syndrome where as Gangrene is a rare complication, usually associated with infections or B-cell lymph proliferative disorders. We present a case of fulminant gangrene of fingers in 50-year-old male with severe Hemolytic Anemia.

Keywords: agglutinin, Hemolytic Anemia, antibodies.

INTRODUCTION:

Primary cold agglutinin is a complex and not well known process which is characterized by an immune reaction against red blood cell (RBC) and temperature dependent, consist of warm-, cold-, or mixed-reactive antibody types [1]. The auto antibodies may be primary (idiopathic) or secondary related to an underlying condition such as infection, malignancy, or immune disease [2]. Apart from hemolysis, clinical manifestations include cold-induced circulatory symptoms; lived reticular is, Reynaud disease, acrocyanosis and, rarely, cutaneous necrosis also noted [3].

Case Report:

A previously healthy 50 year old male presented to outdoor department on a chilly winter morning with persistent painful bluish discoloration of fingers of both hands since last 10 days. The discoloration, which was initially bluish, was acute onset gradually progressive in a distal to proximal pattern and has now turned to black since last 5 days. Pain was exacerbated in cold surrounding like coming in contact with water and relieved in warmer vicinity. The discoloration was not preceded by pallor nor followed by any rubor. There is a similar history of blackish discoloration of left fourth and fifth finger two years back for which partial amputation of fourth finger was done. There was also history of on and off yellowish discoloration of urine which used to occur

during winter months and get subsided over few weeks without any medications on its own since last 5 years. There is no history of fever, breathlessness, polyarthralgia, skin rash, muscle weakness, paresthesia, cough/wheezing, cigarette smoking, hematemesis or malena. On examination, patient is conscious oriented. Severe pallor, mild icterus-present, pedal edema-present, no lymphadenopathy and JVP was raised (11cm) (Figure 1).peripheral gangrene present in 3rd and 4th bilateral fingers, along with proximal amputation of left 4th and 5th finger.(figure 2).Systemic examination was normal except for mild hepatomegaly (3 cm). A provisional diagnosis of cold agglutinin disease with severe anemia with CHF with digital acrocyanosis leading to gangrene was made. Patient was initially managed conservatively including avoidance to cold, keeping periphery warm and oxygen inhalation. No Blood transfusion was done.

Blood cell count showed severe anaemia Hb-5.1g/dL ,TLC-7400 /cmm , Platelets-2.93 lac , MCV-101 fl. Amongst liver function , unconjugated hyperbilirubinemia (TB/DB- 5.1/0.9) was observed, no A:G reversal was found. Renal function shows hyperkalemia – 6.4 (<5.5mmol/l) with normal Glomerular filtration Rate. Serum LDH was 942 U/L (Normal 200- 460). A Complete blood picture showed marked anisocytosis and extensive rouleaux formation suggestive of presence of cold agglutinins in the serum. Reticulocyte count was 6% (corrected- 1.94).



Fig 1: Severe pallor, mild icterus-present, pedal edema- present



Fig 2: peripheral gangrene present in 3rd and 4th bilateral fingers, along with proximal amputation of left 4th and 5th finger

To confirm cold agglutination, two GBP slides were made (one at normal atmospheric chilly temperature and the other at 37deg Celsius with full precaution). The former showed large clumps of RBCs showing agglutination and the latter significantly less RBC agglutination (and of small sizes). Serum electrophoresis showed no M-peak. Consequent bone marrow examination showed no evidence of hematological malignancy. Connective tissue disease was ruled out. A diagnosis of cold agglutinin disease of idiopathic variety was labeled.

Sequential monitoring showed improving gangrene of hands, repeat blood count showed rising Hb level (HB- 8.4g/dL) and decreased unconjugated bilirubinemia (TB/DB- 2.4/0.2). Patient improved on conservative measures and was discharged

DISCUSSION:

Cold agglutinin disease is classified as primary (idiopathic) or secondary. Usual age of presentation is 50 to 60 years of age and in most cases it is a primary disorder. Secondary disorder of Cold antibody hemolytic anemia may also occur as an in association with a number of different underlying disorders, such as certain infectious diseases and lympho proliferative disorders [4]. Cold agglutinins occur naturally in nearly all individuals. These natural cold auto antibodies occur at low titers, less than 1:64 measured at 4°C, and have no activity at higher temperatures. Pathologic cold agglutinins occur at titers over 1:1000 and react at 28-31°C and sometimes at 37°C. Cold agglutinin disease usually results from the production of a specific IgM antibody directed against the specific antigens on red blood cells [5]. Cytogenetic studies in patients with cold agglutinin disease have revealed the presence of trisomy 3 and trisomy 12. Translocation (8; 22) has also been reported in association with cold agglutinin disease [6, 7]. A common complaint among patients with cold agglutinin disease is painful fingers and toes with purplish discoloration associated with cold exposure. In chronic cold agglutinin disease, the patient is more symptomatic during the colder months. Cold agglutinin-mediated acrocyanosis differs from Reynaud phenomenon. In Reynaud phenomena, caused by vasospasm, a triphasic color change occurs, from white to blue to red, based on vasculature response. No evidence of such a response exists in cold agglutinin disease [8]. Chemotherapeutic agents should be used under appropriate circumstances, such as for an associated malignancy. When cold agglutinin disease is chronic and idiopathic, one must weigh the need for therapy, as dictated by the severity of the symptoms, versus the potentially serious, long-term consequences of chemotherapeutic or other agents used to treat monoclonal lymphoid populations. Glucocorticoids are generally not useful in IgM-induced cold agglutinin disease but may occasionally work if an underlying warm antibody-induced hemolytic anemia exists;. In patients who are pregnant, avoid all cytotoxic therapy or immunosuppressive therapy other than glucocorticoids because of the potential teratogenic effects on the fetus and the long-term effects on the mother. The anti-CD20 monoclonal antibody rituximab depletes B-lymphocytes, thereby interfering with the production of cold agglutinin frequently used. Plasma pheresis removes IgM antibody from plasma, reducing its concentration. This procedure is valuable for emergencies and allows time for drugs to have an effect [9, 10, 11, 12, 13].

Avoid unnecessary transfusions, because cold agglutinin disease is usually self-limited. Risks of blood transfusion include transfusion reactions and transmission of infections [14].

Conclusion

This case is clinically informative as it describes a occurrence of peripheral gangrene and

hemolytic Anemia associated with primary cold immune agglutinin disease. Knowledge about this presentation will make wiser to the clinicians to think of this possible differential diagnosis when a patient presents with gangrene of extremities.

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