Cold Agglutinin Autoimmune Hemolytic Anemia (C-AIHA)

In cold agglutinin autoimmune hemolytic anemia, IgM autoantibodies bind to the surface of RBCs at cold temperatures, leading to intravascular and extravascular hemolysis. Etiologies include idiopathic, infectious (Mycoplasma pneumoniae, EBV), CLL, lymphomas, and Waldenstrom's Macroglobulinemia. Symptoms include acrocyanosis and livedo reticularis. Diagnosis is made by the Coombs test. Treatment involves avoiding cold temperatures as well as rituximab with or without fludarabine.

PLAY PICMONIC

Pathophysiology

IgM Binds to RBCs at Cold Temperatures (28-31C)

Mountain-goblin Binds to RBC at Cold-thermometer

In cold agglutinin autoimmune hemolytic anemia, IgM autoantibodies bind to RBCs at cold temperatures below normal body temperature. IgM fixes complement to the RBC surface. At body temperature, the proteins such as CD55 and CD59 on the RBC cell surface prevent the activation of the complement. However, in cold temperatures blood cannot adequately circulate to peripheral locations in the body to provide anti-complement molecules; therefore, the complement is activated in these situations.

Extravascular Hemolysis

Extravascular Hemolysing-RBC

The hemolysis in cold agglutinin disease is primary extravascular. The binding of IgM to the red blood cell surface causes complement to deposit on the cell surface, especially C3b. These complement factors are then recognized by macrophages in the spleen and other cells of the reticuloendothelial system, which then destroy the tagged red blood cells. This process is an example of extravascular hemolysis. Less commonly, intravascular hemolysis can occur as well, when the complement cascade continues and results in formation of the membrane attack co

Waldenstrom's Macroglobulinemia

Winter-storm with Mountain-goblin-anemone

Chronic lymphocytic leukemia, lymphoma, Waldenstrom's Macroglobulinemia, and other lymphoproliferative disorders are frequently associated with cold agglutinin autoimmune hemolytic anemia, as these patients' RBC surfaces are more likely to contain certain antigens to which IgM cold agglutinins bind. In addition, these lymphoproliferative disorders may induce the synthesis of IgM cold agglutinins, leading to cold agglutinin autoimmune hemolytic anemia.

Mycoplasma Pneumoniae

Mic-plasma Nude-Mona

Certain infections such as Mycoplasma pneumonia have both been associated with cold agglutinin autoimmune hemolytic anemia. Mycoplasma contains a specific antigen on its surface to which IgM autoantibodies bind, causing agglutination and hemolysis.

Infectious Mononucleosis

Monkey-nuclear

EBV is a rare cause of cold agglutinin autoimmune hemolytic anemia; autoantibodies form to the i-surface antigen.

Lymphomas and CLL

Lime-foam and CaLL me crone

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Symptoms

Acrocyanosis with Cold Exposure

Acral-acorn with Cyan-crayon

Livedo reticularis may also occur with cold agglutinin autoimmune hemolytic anemia and is described as having a purple-bluish lacy or mottled appearance.

Blue Fingers and Toes

Blue Fingers and Toes

In cold agglutinin autoimmune hemolytic anemia, agglutination and hemolysis tends to occur in peripheral locations on the body such as the fingers and toes. Skin color returns back to normal in these regions once it is warmed.

Diagnosis

Positive Coombs Test

Positive Comb

The Coombs test detects if a patient has formed autoantibodies to their RBCs. A Direct Coombs test involves mixing a patient's RBCs with test serum containing anti-IgM antibodies. If a patient has cold agglutinin autoimmune hemolytic anemia, their RBCs will be coated in primarily IgM and complement, thus anti-IgM in the test serum will agglutinate the RBCs. This reaction is referred to as a positive Coombs test.

Treatment

Avoid Cold

Avoid Cold-thermometer

Because cold agglutinin autoimmune hemolytic anemia occurs below body temperature, patients should avoid the cold.

Rituximab

Red-tux-mob

Rituximab is a monoclonal antibody against B cells, some of which produce autoantibodies.

+/- Fludarabine

Fedora-bean

Rituximab is typically used in combination with other immunosuppressants or other cytotoxic agents, such as fludarabine, a purine analog.