Cold Agglutinin Disease

Tap to explore
Instructions

This information is provided as an educational resource for healthcare providers. It is not intended to be a substitute for review of the underlying reference materials and scientific literature. Healthcare providers should make all treatment decisions based on their medical judgement and the clinical profile of the individual patient. The following document cannot be copied, modified, used or distributed without the express written consent of Bioverativ.
Cold Agglutinin Disease

- Burden of Cold Agglutinin Disease
- Clinical management
- The Immunobiologic Mechanisms
Autoimmune Hemolytic Anemia (AIHA) Consists of Warm-, Cold-, or Mixed-Reactive Antibodies
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Cold <37°C
Warm >37°C
Mixed ≤37°C

<5%
Most Cold Agglutinins Are Monoclonal IgM Antibodies

- Cold agglutinins (CA) are autoantibodies; the majority of which are monoclonal\(^1\).
- Low-affinity CA occur in healthy individuals; these are predominantly polyclonal antibodies with low thermal amplitudes and do not exist in high titers\(^2\).
- \(~90\%\) of patients with cold agglutinin disease have immunoglobulin M (IgM) type CA compared with IgG and IgA antibodies each existing in \(~3.5\%\) of patients\(^3\)
Cold Agglutinins Target Red Blood Cells

- Cold agglutinins (CA) target the I antigen on red blood cells (RBCs) at low temperatures (optimum temperature ~4°C)\(^\text{[10]}\) and dissociate at higher temperatures\(^\text{[11]}\).
- Therefore, the extremities of patients with cold agglutinin disease are most susceptible in colder weather.
- Agglutination leads to impaired microcirculation and a variety of symptoms and potential complications for the patient\(^\text{[4,7]}\).

\[\begin{align*}
\text{<38°C} & \\
\text{<37°C} & 
\end{align*}\]
The Complement Cascade

- Complement activation, driven by the formation of the cold agglutinin-red blood cell complex in cold agglutinin disease, results in an enzymatic cascade, leading to production of opsonins and anaphylatoxins to clear pathogens and initiate inflammation.

- Complement can be triggered by 1 of 3 pathways:
  - Classical
  - Lectin
  - Alternative

- These 3 pathways converge at the level of C3 cleavage and lead to a common terminal pathway.

C, complement; MBL, mannose-binding lectin.
The Complement Cascade

- The classical pathway can be activated by 1 immunoglobulin M (IgM) molecule or multiple IgG molecules.

- Activation leads to the formation of the classical C3 convertase (C2aC4b) by the activation of C2 and C4 by MASP1/MASP2, which leads to the formation of lectin C3 convertase (C2aC4b).
Cold Agglutinin Bound to the I Antigen on Red Blood Cells Binds C1 and Activates the Classical Pathway

The cold agglutinin complex activates the complement pathway, leading primarily to extravascular hemolysis.

- After C1 is activated, C1 esterase activates C4 and C2, which results in cleavage of C3 to C3a and C3b.

- As temperature increases (i.e., near the body core), IgM bound to cold agglutinin dissociates from the cell surface, allowing agglutinated red blood cells to separate from each other, while C3b remains bound.

- The ultimate effect of the association of red blood cells with activated complement proteins is lysis of the cells. This hemolysis triggers the anemia that is associated with cold agglutinin disease.
References