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Short Communication

Algid and Hindered-Cold Agglutinin Disease

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Cold agglutinin disease (CAD) is an exceptionally discerned haemolytic disorder configuring ~ 30% of autoimmune haemolytic anaemias (AIHA). Autoantibodies mediating cold agglutinin disease are designated as cold agglutinins (CA) as the molecules demonstrate an ability to agglutinate erythrocytes at temperatures beneath central body temperature.

Cold agglutinin disease is engendered due to carbohydrate antigens configured from multiple ABO moieties. Contemporary international consensus segregates primary cold agglutinin disease from cold agglutinin syndrome (CAS).

Initially scripted in 1903, the autoantibodies appear concurrent to haemolysis. Cold reacting antibodies or cold autoantibodies may be associated with infection. Although clinically insignificant, cold autoantibodies may induce cold agglutinin disease.

Naturally occurring autoantibodies inducing cold agglutinin disease are configured of IgM antibodies against I antigen wherein with an elevated thermal amplitude the antibodies may react at normal body temperature, thereby inducing acquired haemolytic anaemia.

Transient anti-i antibodies appear concurrent with infectious mononucleosis due to Epstein Barr virus infection whereas transient anti-I antibodies may concur with Mycoplasma infection.

Cold agglutinin disease manifests with clonal lymphoproliferative disorder (LPD) confined to bone marrow. The condition induces production of cold agglutinins wherein adherence of circulating cold agglutinins to cellular surface antigens engenders agglutination of erythrocytes and complement mediated haemolysis with consequent emergence of cogent clinical features. Therefore, significant pathogenesis is incurred with clonal lymphoid proliferation and complement dependent haemolysis within the bone marrow, features which are amenable to precise therapy.

Cold agglutinin disease concurs with low grade, clonal B cell lymphoproliferative disorder incriminating the bone marrow which may be constituted of lymphoplasmacytic lymphoma (LPL), marginal zone lymphoma (MZL), small lymphocytic lymphoma/chronic lymphocytic leukaemia, unclassified low grade lymphoproliferative disorder, monoclonal gammopathy or reactive lymphocytosis [1,2].

Contemporary classification by World Health Organization categorizes aforesaid distinct entities as mature B cell neoplasms. Subsequent transformation into diffuse large B cell lymphoma may ensue in ~ 3.4% instances [1,2].

Cold agglutinin associated lymphoproliferative disease demonstrates clonal rearrangement of immunoglobulin heavy or light chains. Nevertheless, a variable proportion of incriminated subjects appear devoid of clonal lymphoproliferative disease.

Mean age of disease emergence is 76 years although no age of disease occurrence is exempt. A female predominance is observed with female to male proportion of ~2:1 [1,2].

Bone marrow may optimally delineate trisomy 3 along with trisomy 12 or trisomy 18. Nevertheless, several reoccurring

genomic mutations as CAD KMT2D (~70%), CARD11 (~ 30%), IGLL5 (~60%) or CXCR4 (~28%) may be encountered. Besides, genetic mutations incriminating NF-κB pathway or chromatin modification and organization may concur. However, MYD88 L265P chromosomal mutation may be exceptionally discerned or appear absent [1,2].

Haemolysis emerges as a non seasonal component of cold agglutinin disease. Fatigue is frequently observed [1,2].

Acute exacerbation of haemolytic anaemia may ensue in febrile illness associated with cold agglutinin disease. Besides, the event may be triggered by major trauma or major surgery or may be associated with blood transfusions [1,2].

Cold induced, agglutination mediated clinical symptoms concurrent with capillary circulation may appear as acrocyanosis or Raynaud-like phenomena. Exceptionally, livedo reticularis or gangrene may ensue, necessitating distinction from cryoglobulinemia or concomitant accumulation of cold reactive IgM molecules [1,2].

Haemolytic anaemia in the absence of or associated with minimal circulatory symptoms may be discerned. Additionally, haemolytic anaemia may concur with moderate or severe circulatory symptoms or circulatory symptoms accompanied with compensated haemolysis.

Majority (88%) of subjects demonstrate haemolytic anaemia whereas compensated haemolysis may be encountered [2,3].

Upon initial disease representation, mean haemoglobin appears at ~9.3 grams/decilitre and varies from 4.5 grams/decilitre to 15.3 grams/decilitre. Anaemia may occur as mild (haemoglobin 10 grams/decilitre), moderate (haemoglobin 8 grams/decilitre to 10 grams/decilitre) or severe (haemoglobin < 8 grams/decilitre) [2,3].

Akin to various autoimmune haemolytic anaemias, cold agglutinin disease is associated with complications such as thrombosis or venous thromboembolism whereas arterial thrombosis is infrequent. Thrombotic events may or may not concur with degree of haemolysis [2,3].

Tissue samples obtained from bone marrow preponderantly exhibit miniature nodular aggregates of small lymphoid cells. Besides, sparse interstitial infiltrate or singularly disseminated clonal lymphocytes may be discerned. Mature plasma cells configure <5% of nucleated cells, appear to circumscribe nodular aggregates of small lymphoid cells and are sparsely disseminated within bone marrow parenchyma. However, infiltration of nodular lymphoid aggregates with plasma cells is absent. Foci of para-trabecular tumour evolution, mast cell infiltration or focal fibrosis is absent [2,3].

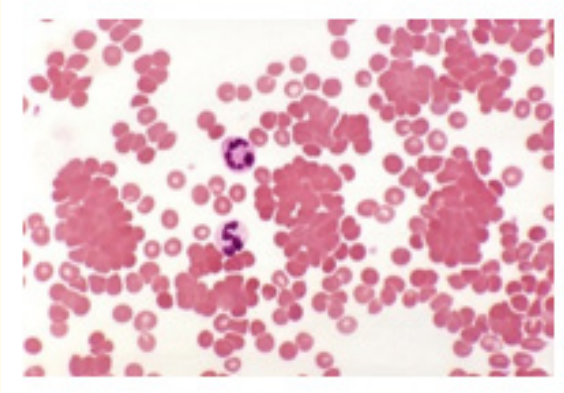

Figure 1: Cold agglutinin disease demonstrating clumping and haemolysis of red blood cells [6].

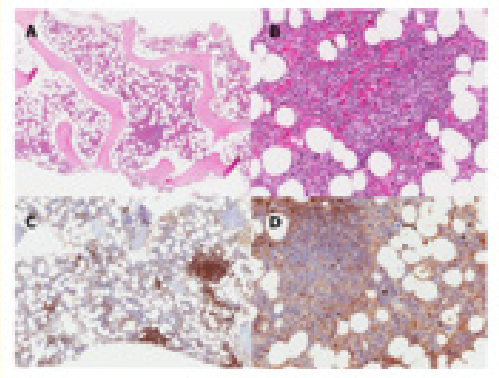

Figure 2: Cold agglutinin disease demonstrating aggregates of small lymphoid cells confined to bone marrow parenchyma. Tumour cells are immune reactive to CD20 and IgM [7].

Features	Cold agglutinin disease	Lymphoplasmacytic lymphoma
Growth pattern	Small nodules. Intra-sinusoidal growth or diffuse infiltrate absent	Nodular and/or diffuse
Location	Inter-trabecular infiltrate	Para-trabecular/inter-trabecular infiltrate
Clonal cells	Small B cells and plasma cells	Small B cells, lympho-plasmacytoid cells, plasma cells
Plasma cells	Wide parenchymal spread	Admixed in the infiltrate
Mast cells	Mast cells absent	Mast cell infiltration

Table 1: Bone marrow histology of cold agglutinin disease and lymphoplasmacytic lymphoma [1,2].

Diagnostic criterion of cold agglutinin disease is denominated as

- Essential for diagnosis
- Chronic haemolysis demonstrating low haptoglobin, high bilirubin, high lactate dehydrogenase (LDH), high absolute reticulocyte count
- Monospecific DAT with intensely reactive C3d
- Cold agglutinin titre ≥64 at 4^0C
- Absence of overt malignant conditions or relevant infection
- Confirmatory and non essential criterion
- Monoclonal IgM ǩ in plasma or serum (IgG or ƛ phenotype rare)
- Ratio between ǩ+ and ƛ+ B cells is >3.5(rarely <0.9)
- Cold agglutinin associated lymphoproliferative disorder on histology
- Absent MYD88L265P genetic mutation [1,2].

Small lymphoid cells configuring cold agglutinin disease associated lymphoproliferative disorder appear immune reactive to B cell markers as CD19, CD20, CD22, PAX5, CD79a, CD79b, IgM and monotypic light chain, frequently kappa (κ) light chains. Constituent plasma cells appear immune reactive to IgM and kappa (κ) light chains. Immune reactivity to CD5 may occur in ~40% instances.

Small lymphoid cells appear immune non reactive to BCL6, MUM1, CD23 and cyclin D1 [4,5].

Flow cytometry of bone marrow aspirate exhibits kappa (κ) and lambda (λ) B cell ratio > 3.5.

Exome sequencing of clonal B cells enunciates a minimal mutational burden.

Antibodies are commonly discerned within 4 °C and may occur at immediate spin with consequent ABO mismatch wherein pre-transfusion assessment may be challenging [4,5].

Thermal amplitude evaluates serum or plasma reaction within red blood cells at temperatures as 40°C, 220°C, 300°C and 370°C.

Reactive antibodies emerging beyond > 30°C appear clinically significant with clumping and occurrence of adverse cold agglutinins.

Direct antiglobulin test (DAT) may be beneficially adopted for screening cold agglutinin disease [4,5].

Pharmacological therapy remains superfluous in subjects with compensated haemolysis or mild anaemia with absence of fatigue and cold induced circulatory symptoms. Therapy is indicated with symptomatic anaemia, circulatory symptoms interrupting daily tasks or significant fatigue [4,5].

Corticosteroids are to be circumvented. Splenectomy remains inefficacious as extravascular haemolysis is preponderantly encountered within hepatic parenchyma [4,5].

Efficacious therapy of cold agglutinin disease appears inclusive of treating pathogenic B cell lymphoid clone or the complement system.

Pathogenic B cell lymphoid clone may be beneficially managed with rituximab monotherapy, rituximab and oral fludarabine or rituximab and bendamustine. Besides, bortezomib monotherapy may be employed.

Incriminated subjects depict grade 3 to grade 4 neutropenia, concomitant bacterial infections or suspected emergence of delayed malignancies. However, combination of rituximab with bendamustine appears innocuous with emergence of delayed malignancies.

Bruton tyrosine kinase (BTK) inhibitor therapy with ibrutinib is a contemporary modality adopted for treating cold agglutinin mediated autoimmune haemolytic anaemia or low grade lymphoma [4,5].

Cold agglutinin disease can be subjected to therapeutic complement inhibition with anti-C5 monoclonal antibody eculizumab.

Classical pathway inhibition, circumventing classical complement pathway activation and opsonization of erythrocytes with C3b humanized monoclonal IgG4 antibody or C3 inhibition with sutimlimab emerge as efficacious therapeutic manoeuvers [4,5].

Subcutaneous infusion of pegylated cyclic peptide pegcetacoplan (APL-2), a compstatin analogue which prohibits C3 and C3b, is recommended for treating paroxysmal nocturnal haemoglobinuria as it comprehensively and efficiently blocks complement system along with rapid melioration of haemolysis and anaemia [4,5].

Upstream complement blockade may be complicated with severe bacterial infection. Thus, C1s and C3 inhibition appear optimal in subjects vaccinated against encapsulated bacteria.

Hereditary deficiencies within proximal classical pathway components are associated with possible emergence of systemic lupus erythematosus (SLE) [4,5].

Supportive measures as blood transfusion, plasmapheresis, supplementation with folic Acid and erythropoietin along with thrombosis prophylaxis are recommended [4,5].

Complete remission is indicated by disappearance of histologic and flow cytometric presentiment of clonal bone marrow lymphoproliferative disorder. However, complete remission appears non indicative of regression of bone marrow lymphoproliferative disorder [4,5].

Incomplete disease remission following therapy requires circumvention of minimal ambient temperatures, adoption of warm clothing, protection of acral segments and preventing infusion of cold liquids. Concurrent bacterial infection necessitates therapeutic intervention [4,5].

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6. Image 1 Courtesy: Medbullets.com.

7. Image 2 Courtesy: MDPI.com.