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Bone marrow pathology in cold agglutinin disease and distinction from other B-cell disorders: Preliminary results of the Re-CAD study

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A previous version of this work was submitted for the 22nd Meeting of the European Association for Hematopathology. Data have been updated since. Data collection is ongoing and will be updated at the time of the meeting.

Background

Cold agglutinins (CA) are autoantibodies directed against erythrocytes, that may cause hemolytic anemia and acrocyanosis. CA, usually of the IgM isotype, are often associated with an underlying clonal B-cell disorder in the bone marrow (BM). This clone was previously categorized as various B-cell lymphomas or their precursor conditions, including lymphoplasmacytic lymphoma (LPL) and IgM monoclonal gammopathy of unknown significance (MGUS). In the 5th WHO Classification of Haematolymphoid Tumours (WHO-HAEM5), cold agglutinin disease (CAD) was recognized as a distinct entity. Its diagnosis requires several criteria, including a BM lymphoproliferative disorder (LPD) distinct from other B-cell lymphomas, called CAD-associated LPD (CAD-LPD; **Figure 1**). Aim of the Re-CAD study was to reassess the BM histopathology of a large cohort of patients with CA, using the novel WHO-HAEM5 criteria, and to assess their applicability in distinguishing CAD-LPD from other B-cell lymphomas .

Methods

All patients at Amsterdam UMC with chronic hemolysis and a direct antiglobulin test strongly positive for C3d were included, if ≥1 archival BM trephine biopsies were available. Patients with cold agglutinin syndrome (CAS) secondary to overt infection, autoimmune disease or extramedullary lymphoma were excluded. The CA titer criterium was disregarded since it is not routinely used. Archival BM biopsies were reviewed by 2 haematopathologists, clinical data were collected retrospectively.

Results

A total of 72 eligible patients were identified, of whom 38 have thus far been evaluated. Per patient, 1-6 BM biopsies were revised. In 4/38 patients (11%), there was no evidence of a clonal B-cell disorder in electrophoresis, flow cytometry, and/or histopathology. In the remaining 34 patients, pathology revision revealed B-cell malignancies other than CAD-LPD in 6/34 (18%), classifying them as CAS (**Figure 2**). Two of these were MYD88-mutated LPL. In the remaining 28 cases, infiltration with mature B-cells was found in 22/28 (79%), with a median infiltration of 4% at first biopsy (range 1 to 10%). An increased plasma cell percentage was seen in 26/28 cases (93%), with monotypia in 12. CAD-LPD was confirmed in only 3/28 patients (11%) according to the WHO-HAEM5 criteria. All three had IgMκ monoclonal gammopathy and 2/2 tested lacked the MYD88 exon 5 L265P mutation. CAD-LPD criteria were not met in 25/28 (89%) due to polytypic plasma cells (n=11), absence of B-cells (n=8), paratrabecular growth (n=6), B-cell immunophenotype (n=4), location of plasma cells (n=3), no nodular aggregates (n=3), no plasma cells (n=2), lymphoplasmacytic maturation (n=2), increased mast cells (n=1), and/or fibrosis (n=1). Of these 25, 23 (92%) had a monoclonal gammopathy, and 15/15 (100%) were MYD88 wild-type.

Conclusion

The majority of CAD patients do not meet the histological criteria of CAD-LPD as described in the WHO-HAEM5, nor are they classifiable as LPL or other B-cell lymphomas. They display a highly heterogeneous BM infiltration pattern with a low infiltration rate, accompanied by a monoclonal gammopathy in the absence of a MYD88 mutation, distinguishing it from Waldenström's macroglobulinemia. These results indicate that the WHO-HAEM5 criteria might not capture the majority of CAD cases. Instead, CAD may best be understood as a monoclonal gammopathy of clinical significance.

Figure 1. Bone marrow histopathology characteristics of CAD-LPD according to WHO-HAEM5[1]

[1]Rossi D, Chen X, Berentsen S, et al. Cold agglutinin disease. In: WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2024 [cited 2024 05 16]. (WHO classification of tumours series, 5th ed.; vol. 11). Available from: https://tumourclassification.iarc.who.int/chapters/63.

Features	Cold agglutinin disease-associated lymphoproliferative disorder (CAD-LPD)
Histology	Nodular non-paratrabecular lymphoid infiltration, surrounded by mature plasma cells.
Morphology	Small lymphoid cells with round to oval nuclei, dense uniform chromatin pattern, limited clear cytoplasm.
Immunophenotype	B-cells: CD19+, CD20+, PAX5+, CD79a+, CD22+, CD79b+, monotypic light chain (usually kappa), IgM. CD5+ in 40%. BCL6-, MUM1-, CD23-, cyclin D1-. Plasma cells: IgM and monotypic light chain (usually kappa).
Absent	*Paratrabecular growth, lymphoplasmacytic morphology, mast cell infiltration, fibrosis and MYD88 p.L265P.*

Figure 2. Reclassification of underlying disease after bone marrow pathology revision

Sankey diagram depicting flow from original diagnosis (left) to new classification after revision conform WHO-HAEM5 classification criteria (right), of 34 patients meeting criteria for chronic hemolysis, strongly positive direct antiglobulin test for C3d and evidence of a clonal B-cell disorder.