haematologica
Journal of the Ferrata Storti Foundation

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Received: September 3, 2026.
Accepted: September 9, 2026.

Citation: Marta Coscia and Luca Arcaini. Autoimmune hemolytic anemia and chronic lymphocytic leukemia: crossing the borders between autoimmunity and malignancy
Haematologica. 2026 Sept 17. doi: 10.3324/haematol.2026.301716 [Epub ahead of print]

Autoimmune hemolytic anemia and chronic lymphocytic leukemia: crossing the borders between autoimmunity and malignancy

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Disclosures

LA: AstraZeneca, Novartis, Kite/Gilead, Beone, Abbvie (Speaker Bureau); Roche, Janssen-Cilag, Incyte, EUSA Pharma, Celgene/Bristol Myers Squibb, Kite/Gilead, Novartis, BMS, MSD (Participation on a Data Safety Monitoring Board or Advisory Board); Roche, Astra Zeneca (Support for attending meetings and/or travel)

MC: AbbVie, GSK, Johnson & Johnson (research support); AbbVie, AstraZeneca, BeOne, Johnson & Johnson, Roche (support for attending meetings and/or travel); AbbVie, AstraZeneca, Behring, Beone, GSK, Johnson & Johnson, Lilly, Roche (participation in speakers' bureau or Advisory Board).

Contributions

Both authors wrote the manuscript.

In this issue of Haematologica, Ya et al.(1) provide new insights into the clinical and biological landscape of autoimmune hemolytic anemia (AIHA) in chronic lymphocytic leukemia (CLL) based on the analysis of a large retrospective cohort of 1,404 Chinese patients. AIHA occurred in roughly 10% of patients, with warm-antibody AIHA (wAIHA) accounting for approximately 70% of cases. Patients with AIHA displayed a distinct clinical and biological profile characterized by male predominance, advanced disease stage, preferential use of the IGHV4-34 gene, and enrichment of DNMT3A mutations, whereas MYD88 mutations appeared to be more frequent in cold-antibody AIHA (cAIHA).

Of particular interest, although AIHA retained its well-known adverse prognostic significance in patients treated with chemoimmunotherapy, this effect was markedly attenuated in the era of targeted therapies. Interestingly, while unmutated IGHV status remained a major adverse prognostic factor in the overall CLL population, its impact largely disappeared among patients who developed AIHA (1).

Autoimmune manifestations, particularly autoimmune cytopenias (AIC), are among the best-recognized immune complications of CLL (2). AIHA is by far the most frequent form, followed by immune thrombocytopenia (ITP), whereas pure red blood cell aplasia and autoimmune granulocytopenia are considerably less common.

These complications arise from the complex interplay between leukemic cells, immune microenvironment, host genetic susceptibility, and external triggers such as drugs or infections. Although several studies have identified immunogenetic features associated with an increased risk of AIHA and ITP, including specific IGHV rearrangements and stereotyped B-cell receptor (BCR) subsets, the immunologic background specifically predisposing certain CLL patients to autoimmune complications remains largely unexplored. Beyond immunogenetics, human leukocyte antigen haplotypes, specific polymorphisms of cytokine genes, epigenetic regulators, and profound alterations involving both innate and adaptive immunity have all been implicated in the pathogenesis of CLL-associated autoimmunity (2).

The prevalence of AIHA observed by Ya et al. around 10% falls within the range previously reported in Western cohorts (3). Likewise, the clinical phenotype appears remarkably consistent across different populations, being characterized by more advanced disease stage, higher β2-microglobulin levels, hypoalbuminemia, and male predominance (4).

From a biological perspective, patients with AIHA have traditionally been considered enriched for adverse prognostic markers, including unmutated IGHV and *TP53* disruption (2). Interestingly, this pattern was not entirely reproduced in the present study, where *TP53*, *NOTCH1, SF3B1*, and *ATM* alterations were similarly distributed between patients with and without AIHA. This observation suggests that the development of AIHA may depend less on conventional molecular risk factors and more on specific pathways of immune dysregulation that remain incompletely understood.

Among the most intriguing findings is the enrichment of *DNMT3A* mutations in patients with CLL-associated AIHA. As acknowledged by the authors, the cellular origin of these mutations could not be determined, leaving unresolved whether they arise from the leukemic clone or reflect the presence of clonal hematopoiesis (CH). Recent single-cell transcriptomic studies have shown that CH is highly prevalent in CLL (5) and is associated with enhanced T-cell activation and a pro-inflammatory immune signature (6). These observations raise the intriguing hypothesis that CH, rather than directly influencing the leukemic clone, may contribute to a pro-inflammatory microenvironment that facilitates the development of autoimmune complications. Future studies based on purified cell populations and functional analyses will be required to clarify the cellular origin and biological significance of *DNMT3A* mutations in CLL-associated AIHA.

Notably, in the study by Ya et al. IGHV4-34 gene usage was observed in approximately one-fifth of evaluable AIHA cases, with a clear enrichment in cAIHA. IGHV4-34 is well recognized for its intrinsic autoreactive potential and has been associated with systemic autoimmune diseases as well as immune responses following viral and bacterial infections (7). Moreover, stereotyped IGHV4-34-expressing CLL subsets display distinctive antigen-binding sites, reminiscent of pathogenic anti-DNA antibodies (8). Although previous immunogenetic studies have identified within a series of 19,907 CLL patients, 339 IGHV4-34-expressing cases, their specific association with AIC has remained largely unexplored (9).

In our opinion, from a clinical point of view the most relevant message emerging from this study is that the adverse prognostic impact of AIHA appears substantially mitigated in patients receiving targeted therapies. This observation is consistent with growing evidence indicating that BTK inhibitors, unlike chemotherapy, rarely trigger new-onset AIC and frequently induce resolution of pre-existing AIHA and ITP while maintaining effective disease control (10). The present study further shows that achievement of a meaningful CLL response is closely associated with AIHA control, reinforcing the concept that effective suppression of the leukemic clone remains central to

long-term management of autoimmune complications. Together, these findings support the hypothesis that novel agents exert a dual benefit by controlling both tumor burden and the immune dysregulation underlying autoimmunity.

While these observations strengthen the rationale for using targeted therapies in patients with CLL-associated AIHA, they also raise unanswered therapeutic issues. In particular, comparative evidence demonstrating the superiority of one targeted approach over another — such as BTK inhibition versus BCL2-directed therapy — is still lacking. Addressing this question will require dedicated clinical trials, including large retrospective analyses and, ideally, prospective investigations specifically designed for this patient population.

Overall, the study by Ya et al. provides new insights into the biological basis and clinical significance of AIHA in CLL. Beyond identifying distinct immunogenetic and molecular features, it reinforces the concept that effective control of the leukemic clone with targeted therapies may mitigate the adverse prognostic impact of AIHA. Further studies are now needed to elucidate the immune mechanisms underlying the onset of this complication and to optimize its therapeutic management.

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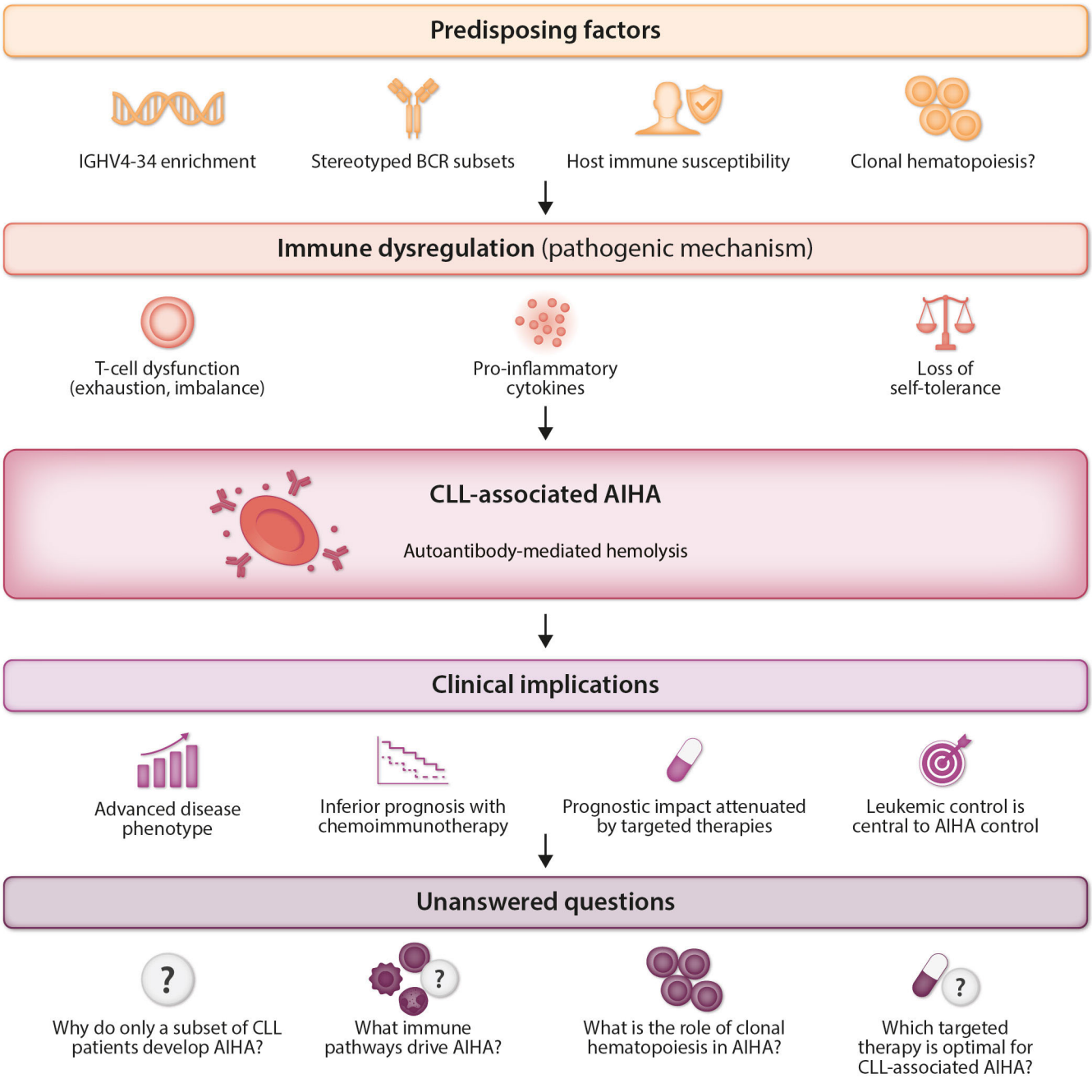
Legend to figure:

Predisposing factors, immune dysregulation and clinical implications of autoimmune hemolytic anemia associated with chronic lymphocytic leukemia


Predisposing factors
IGHV4-34 enrichment
Stereotyped BCR subsets
Host immune susceptibility
Clonal hematopoiesis?
Immune dysregulation (pathogenic mechanism)
T-cell dysfunction (exhaustion, imbalance)
Pro-inflammatory cytokines
Loss of self-tolerance
CLL-associated AIHA
Autoantibody-mediated hemolysis
Clinical implications
Advanced disease phenotype
Inferior prognosis with chemoimmunotherapy
Prognostic impact attenuated by targeted therapies
Leukemic control is central to AIHA control
Unanswered questions
Why do only a subset of CLL patients develop AIHA?
What immune pathways drive AIHA?
What is the role of clonal hematopoiesis in AIHA?
Which targeted therapy is optimal for CLL-associated AIHA?