# Autoimmune Hemolytic Anemia in Chronic Lymphocytic Leukemia

Subjects: Hematology

Contributor: Francesco Autore

Chronic lymphocytic leukemia (CLL) patients have a greater predisposition to develop autoimmune complications. The most common of them is autoimmune hemolytic anemia (AIHA) with a frequency of 7–10% of cases. Pathogenesis is multifactorial involving humoral, cellular, and innate immunity.

Keywords: CLL ; AIHA ; steroids

## 1. Introduction

### 1.1. CLL

CLL is one of the most common types of leukemia in the western world, representing approximately 20% of all hematological diagnoses [1]. The median age at diagnosis is between 67 and 72 years. CLL is a malignant lymphoid neoplasm characterized by progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. CLL has an extremely heterogeneous clinical course, ranging from years of stable disease to rapidly progressive disease [2].

### 1.2. CLL and Dysregulation

CLL patients have defects in humoral and cell-mediated immunity, represented by hypogammaglobulinemia, and functional alteration in T cell subsets, complement, neutrophils, and monocytes. CLL B-cells allow activation and propagation of immune dysregulation through immunosuppressive cytokines or by downregulation of surface molecules. Thus, defects in immunoglobulins class switching and B-cell function generate a progressive hypogammaglobulinemia that is typical for CLL patients, in particular regarding subtypes IgG3 and IgG4 generating risk of recurrent infection sustained by encapsulated organisms. Moreover, in a CLL progression setting, there is an expansion of circulating T cells that may be anergic, and with compromised proliferative potential, but able to produce cytokines [3][4]. Immune dysregulation generates a raised risk of cancers and opportunistic infections such as herpes zoster virus and cytomegalovirus and also autoimmune phenomena, in particular cytopenia, in CLL patients [4].

## 2. CLL and AIHA

Growing evidence since 1960s highlights how blood components are the main target of autoimmunity in CLL. The most frequent autoimmune cytopenias (AICs) are autoimmune hemolytic anemia (AIHA, 7–10%) and immune thrombocytopenia (ITP, 1–5%), while pure red cell aplasia (<1%) and autoimmune neutropenia (0.17%) are unusual. AIHA can present in up to a third of patients with CLL during the course of their disease, while in 10–15% cases at diagnosis [5][6][7][8].

### 2.1. Pathogenesis of AIHA

From a clinical point of view, AIHA is a heterogeneous condition, from fully compensated to life threatening. It is caused by autoantibodies directed against red blood cells (RBCs), with or without complement activation. In general, AIHA can be primary (idiopathic, 50%) or secondary to an underlying condition, such as lymphoproliferative disease (20%), infections (20%), immunodeficiency, and cancer.

The mechanisms for RBC destruction may be represented by intravascular or extravascular hemolysis. AIHA is defined according to autoantibody thermal characteristics [9][10][11]. Warm AIHAs (wAIHAs) is 70–80% of cases; involved antibodies are polyclonal IgG and direct antiglobulin test (DAT) is positive for IgG or IgG plus complement fraction 3d (C3d). This type of AIHA is called warm because antibodies act at 37 °C. Density of these RBC antigens is usually not

high enough to fix complement. Macrophages clear opsonized RBC in extravascular sites [11]. Cold AIHAs (cAIHA) are usually sustained by monoclonal IgM able to fix complement at low temperatures generating complement-mediated RBC intravascular lysis and DAT is usually positive only for C3d. A small number of patients have a mixed form of AIHA with a positive DAT for both IgG and C3d indicating presence of warm IgG autoantibodies and high titer cold agglutinine. Cold agglutinin disease (CAD) is due to clonal or oligoclonal IgM antibody binding to RBC antigens at low temperatures. Complement binding is defined by IgM structure and high antigen density on RBC, with RBC aggregation and complement activation. This may be complete causing intravascular hemolysis or incomplete with extravascular one [12][13]. AIHA pathogenesis involves humoral, cellular, and innate immunity. As regard the first, polyclonal high-affinity IgG autoantibodies produced by non-malignant B cells are fundamental. Auto-antibodies, usually IgM type, can also be produced by CLL B cells. They may interfere not only with mature B cells but also with precursor maturation. For the second type, T cells are considered essential. CLL-B cells and T cells in the context of CLL express altered patterns of surface molecules and CLL patients present an imbalanced cytokine environment. CLL B-cells have impaired apoptosis and immunoglobulins production, and they may present antigen and release inflammatory cytokines. A T-cell subsets imbalance may cause the emergence of autoreactive B-cells producing anti-RBC. T-reg expansion could reduce anti-tumor immune response and compromise immunosurveillance. A decrease in TLR2 and TLR4 and an increase in TLR9 expression are described in CLL patients. Regarding biological CLL parameters, unmutated immunoglobulin heavy-chain variable region gene (IGHV) status, stereotyped IGHV frames, and unfavorable cytogenetics represented by chromosome 17p and/or 11q deletions and nine down-regulated miRNAs are risk factors for developing AIHA in the context of CLL [3][14].

### 2.2. Diagnosis of CLL-AIHA

In the context of CLL, the diagnosis of AIHA could be difficult because blood parameters such as hemoglobin, hemolytic markers, and DAT which are relevant for AIHA may be altered by CLL progression or concomitant treatment. Regarding anemia, it could be secondary to bone marrow infiltration or failure, gastrointestinal blood loss secondary to use of corticosteroids, thrombocytopenia, mucositis or coagulopathy, hypersplenism, vitamin or iron deficiencies, renal disease, and marrow suppression secondary to chemotherapy. Regarding hemolytic signs, LDH may be elevated for CLL progression, haptoglobin for inflammatory response, bilirubin levels for treatment, and reticulocytosis could be absent or inadequate for bone marrow infiltration or suppression by cytokine and/or anti-erythroblasts antibodies and chemotherapy. Regarding the DAT, it is not enough to diagnose AIHA because it may be positive in normal subjects, also without hemolysis. Thus, around 10% of patients can present negativity of DAT but they show clear evidence of AIHA, probably due to the low-affinity or to very small autoantibodies titer [3].

## 3. Treatment

Treatment in CLL-associated AIHA is individualized and it depends on the presence of clinical symptoms (acuteness of the onset, grade of anemia, and degree of hemolysis) and their severity, disease status, and concomitant comorbidities. Anemia, if symptomatic, is primarily an indication for therapy in newly diagnosed and also persistent AIHA. [3][9][15]. Lower tolerance for anemia is typical of elderly patients who therefore more frequently require treatment, and whose adverse drug reactions, drug interactions, and therapy toxicities are more common. RBC transfusions are usually indicated in critical cases with deeper levels of hemoglobin (usually Hb < 6 g/dl) and/or symptomatic anemia, if hemodynamically unstable. To reduce the risk of alloimmunization blood transfusion should be administered only if indicated. In CLL cases, the requirement could be higher than primary cases due to BM impairment and inadequate reticulocytosis. It is also necessary to exclude the presence of alloantibodies before giving red cells. In critical cases, it is not possible to avoid or delay transfusion because of uncertainty in matching, but immediate corticosteroids treatment should be administered. In cases of CAD, warming coils to transfuse blood should be used [10][12][13][16][17]. In emergency situations, although the role of blood transfusion is crucial, immunoglobulins (0.4 g/kg for 5 days or 1 g/kg for 2 days) could be used as a bridging treatment but immunosuppressive drugs could be added. Similar to other autoimmune diseases, the administration of a bolus of intravenous methylprednisolone 500 mg may be used in fulminant and severe situations. Methylprednisolone boli is an option with or without intravenous immunoglobulins, in patients with signs of acute hemolysis and slow response to steroid treatment [18][19]. By analogy with ITP in which is possible to use thrombopoietin receptor agonists, the transient and off-label use of an erythropoiesis-stimulating agent (ESA) at a high dose may be added in patients with severe AIHA, with a high need of blood transfusions and reticulcytopenia [15][20][21][22]. Finally, management of AIHA if CLL-associated must consider the stage of the hematological malignancy: in patients with stage A CLL it is the same as AIHA, whereas in patients with active CLL, it is the treatment of the neoplastic disease.

## References


1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. CA Cancer J. Clin. 2021, 71, 7.
2. Smith, A.; Howell, D.; Patmore, R.; Jack, A.S.; Roman, E.P. Incidence of haematological malignancy by sub-type: A report from the haematological malignancy research network. Br. J. Cancer 2011, 105, 1684–1692.
3. Fattizzo, B.; Barcellini, W. Autoimmune Cytopenias in Chronic Lymphocytic Leukemia: Focus on Molecular Aspects. Front. Oncol. 2020, 9, 1435.
4. Visentin, A.; Imbergamo, S.; Gurrieri, C.; Frezzato, F.; Trimarco, V.; Martini, V.; Severin, F.; Raggi, F.; Scomazzon, E.; Facco, M.; et al. Major infections, secondary cancers and autoimmune diseases occur in different clinical subsets of chronic lymphocytic leukaemia patients. Eur. J. Cancer 2017, 72, 103–111.
5. Diehl, L.F.; Ketchum, L.H. Autoimmune disease and chronic lymphocytic leukemia: Autoimmune hemolytic anemia, pure red cell aplasia, and autoimmune thrombocytopenia. Semin. Oncol. 1998, 25, 80–97.
6. Galton, D.A. The pathogenesis of chronic lymphocytic leukemia. Can. Med. Assoc. J. 1966, 94, 1005–1010.
7. Barcellini, W.; Giannotta, J.A.; Fattizzo, B. Autoimmune Complications in HematologicNeoplasms. Cancers 2021, 13, 1532.
8. Hill, Q.A.; Hill, A.; Berentsen, S. Defining autoimmune hemolytic anemia: A systematic review of the terminology used for diagnosis and treatment Comparative Study. Blood Adv. 2019, 3, 1897–1906.
9. Michalak, S.S.; Olewicz-Gawlik, A.A.; Rupa-Matysek, J.; Wolny-Rokicka, E.; Nowakowska, E.; Gil, L. Autoimmune hemolytic anemia: Current knowledge and perspectives. Rev. Immun. Ageing 2020, 17, 38.
10. Hill, Q.A.; Stamps, R.; Massey, E.; Grainger, J.D.; Provan, D.; Hill, A. The diagnosis and management of primary autoimmune haemolytic anaemia. Br. J. Haematol. 2017, 176, 395–411.
11. Barcellini, W.; Fattizzo, B. How I treat warm autoimmune hemolytic anemia. Blood 2021, 137, 1283–1294.
12. Berentsen, S. How I manage patients with cold agglutinin disease. Br. J. Haematol. 2018, 181, 320–330.
13. Berentsen, S. How I Treat Cold Agglutinin Disease. Blood 2021, 137, 1295–1303.
14. Long, H.; Wang, X.; Chen, Y.; Wang, L.; Zhao, M.; Lu, Q. Dysregulation of microRNAs in autoimmune diseases: Pathogenesis, biomarkers and potential therapeutic targets. Cancer Lett. 2018, 428, 90–103.
15. Jäger, U.; Barcellini, W.; Broome, C.M.; Gertz, M.A.; Hill, A.; Hill, Q.A.; Jilmaf, B.; Kuter, D.J.; Michelh, M.; Montillo, M.; et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020, 41, 100648.
16. Lechner, K.; Jager, U. How I treat autoimmune hemolytic anemias in adults. Blood 2010, 116, 1831.
17. Petz, L.D. A physician’s guide to transfusion in autoimmune haemolytic anaemia. Br. J. Haematol. 2004, 124, 712–716.
18. Visco, C.; Barcellini, W.; Maura, F.; Neri, A.; Cortelezzi, A.; Rodeghiero, F. Autoimmune cytopenias inchronic lymphocytic leukemia. Am. J. Hematol. 2014, 89, 1055–1062.
19. Rogers, K.A.; Woyach, J.A. Secondary autoimmune cytopenias in chronic lymphocytic leukemia. Semin. Oncol. 2016, 43, 300–310.
20. Salama, A.; Hartnack, D.; Lindemann, H.W.; Lange, H.J.; Rummel, M.; Loew, A. The Effect of Erythropoiesis-Stimulating Agents in Patients with Therapy-Refractory Autoimmune Hemolytic Anemia. Transfus. Med. Hemother. 2014, 41, 462–468.
21. Fattizzo, B.; Michel, M.; Zaninoni, A.; Giannotta, J.A.; Guillet, S.; Frederiksen, H.; Vos, J.M.I.; Mauro, F.R.; Jilma, B.; Patriarca, A.; et al. Efficacy of recombinant erythropoietin in autoimmune hemolytic anemia: A multicenter international study. Haematologica 2021, 106, 622–625.
22. Crowther, M.; Chan, Y.L.T.; Garbett, I.K.; Lim, W.; Vickers, M.A.; Crowther, M.A. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. Blood 2011, 118, 15.