Immune-Mediated Hemolytic Anemia and Thrombocytopenia in Clonal B-Cell Disorders: A Review

Urshila Durani, MD, MPH, Ronald S. Go, MD, and Neil E. Kay, MD

The authors are affiliated with the Division of Hematology in the Department of Medicine at the Mayo Clinic in Rochester, Minnesota. Dr Durani is a fellow, Dr Go is an associate professor of medicine, and Dr Kay is a professor of medicine.

Corresponding author:
Neil E. Kay, MD
Mayo Clinic
200 First St SW
Rochester, MN 55905
Tel: (507) 284-2511
E-mail: kay.neil@mayo.edu

Keywords
Autoimmune, chronic lymphocytic leukemias, hemolytic anemia, lymphoma, multiple myeloma, thrombocytopenia

Abstract: Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia purpura (ITP) have been associated with B-cell lymphoproliferative disorders. Here, we review the epidemiology, pathogenesis, diagnosis, and treatment of these autoimmune disorders, specifically in the setting of B-cell malignancies. AIHA and ITP are classically associated with chronic lymphocytic leukemia (CLL) but have also been reported in plasmacytic and lymphoproliferative disorders. AIHA includes both warm AIHA and cold agglutinin disease, the latter of which is strongly associated with Waldenström macroglobulinemia. The pathogenesis of these cytopenias varies with the underlying disease, but malignant cells serving as antigen-presenting cells to T lymphocytes, with the generation of autoreactive lymphocytes, may be involved. The diagnosis requires the presence of hemolysis and a positive direct antiglobulin test result. In a minority of cases, the direct antiglobulin test result is negative, and more specialized testing may be required. Data on the prognostic effect of these comorbidities are conflicting, and the prognosis may vary depending on when in the B-cell malignant process the cytopenia(s) develops. The treatment of AIHA and ITP in the setting of B-cell lymphoproliferative disorders often involves treatment of the underlying disorder, although in some cases of CLL, treatment of the underlying disorder is not indicated, and management is similar to that for idiopathic AIHA or ITP.

Introduction

Autoimmune cytopenias are uncommon but well-recognized complications of clonal B-cell disorders.[1] Specifically, autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia purpura (ITP) are more frequently seen than other cytopenias. The diagnosis of these disorders is complicated, and the causal mechanism(s) of the association between the malignant disorders and the cytopenias is not completely understood, although several theories have been proposed. This review discusses the epidemiology and pathophysiol-

ogy of these comorbidities, their prognostic significance, and current options for diagnosis and treatment.

Epidemiology

Although autoimmune cytopenias have been appreciated in every type of B-cell clonal disorder, they are classically and commonly associated with B-chronic lymphocytic leukemia (CLL).[2-4] AIHA has been observed in anywhere from 4% to 25% of CLL cohorts in various studies.[2,3,5-7] However, Zent and colleagues[8] point out that many of the studies describing the cumulative risk for AIHA in CLL were conducted in tertiary care centers, with relatively small cohorts and an inherent bias toward advanced malignant disease. Newer studies, which have included larger, population-based cohorts and used more accurate diagnostic methods, consistently demonstrate a risk of 3% to 10%.[5,9] ITP occurs less commonly, in fewer than 5% of cases. Interestingly, the prevalence of a positive direct antiglobulin test (DAT) result seems to increase in patients with later-stage disease; however, clinical AIHA develops in only a subset of these patients.[9] A universal and uniform characterization of the epidemiology of AIHA and ITP in CLL is difficult because these disorders have been attributed to both the underlying disease and certain treatments, such as purine nucleoside analogues.[10]

Autoimmune hematologic complications occur less commonly in malignant hematologic disorders other than CLL. AIHA has been described in 1% to 6% of patients with lymphoma in retrospective studies, whereas ITP is seen in fewer than 1%.[11] A single-institution retrospective analysis of 637 patients with lymphoproliferative disease, published in 1987, found that 15 patients (2.4%) either presented with or acquired AIHA during the course of their disease.[12] Evans syndrome was diagnosed in 2 of these patients, and lupus with AIHA developed in 1 patient. ITP developed in 4 additional patients (0.6%). AIHA was the most commonly seen autoimmune entity in this series. A more recent study, published in 2002, found only 1 case of AIHA in the records of 421 patients with non-Hodgkin lymphoma (NHL) that spanned 20 years.[13] This variability in prevalence of AIHA is likely due to differences in the histologic subtype and biology of the lymphomas studied by each institution. The cumulative incidence of AIHA was higher in marginal zone lymphoma, a low-grade lymphoproliferative disorder (10% in one study)[14] and in T-cell lymphomas, especially angioimmunoblastic T-cell lymphoma (8%-15%), than in other lymphomas.[11,15-18] Large granular lymphocytic (LGL) leukemia is another low-grade lymphoproliferative disorder that is often preceded by a variety of autoimmune disorders, most commonly ITP. In one retrospective study, ITP preceded LGL leukemia in 59% of the patients, prompting the authors to propose, perhaps prematurely, that a diagnosis of LGL leukemia be entertained in any patient with ITP.[19] On the other hand, Hodgkin lymphoma is rarely associated with autoimmune hematologic complications. In one large retrospective study of 1029 patients with approximately 6600 person-years of follow-up, AIHA or ITP was diagnosed in only 12 patients (1.2%; 5 at presentation, 7 during follow-up).[20]

Although one prospective study conducted in India found that severe AIHA developed in 10% of patients with multiple myeloma during the course of their disease,[21] plasmacytic disorders, as opposed to lymphoproliferative disorders, generally do not have a strong association with autoimmune cytopenias. However, one retrospective study did find a high rate of monoclonal gammopathy of undetermined significance (16.5%) in patients older than 50 years with warm AIHA and no preceding lymphoplasmacytic malignancy.[22] In addition, AIHA has been reported in up to 20% of patients and cold agglutinin disease (CAD) in up to 10% of patients with Waldenström macroglobulinemia (WM) or lymphoplasmacytic lymphoma.[23] CAD is serologically characterized as a cold-reactive immunoglobulin M (IgM)–mediated process, as opposed to the usual warm IgG-associated AIHA seen in other lymphoproliferative disorders. ITP also occurs less often (<5% of patients) in WM.[23,24]

Pathophysiology

Proposed models for the development of autoimmune cytopenias in B-cell disorders differ according to the underlying malignancy. The pathogenesis of autoimmune cytopenia has been well studied in CLL. In AIHA in this disorder, polyclonal warm IgG antibodies produced by nonmalignant B cells have been found to be the culprit antibodies.[2,3] What, then, is the role of the malignant CLL B cell in the predisposition to autoimmunity? One theory is that the leukemia cell acts as an antigen-presenting cell to induce a T-cell response to red blood cell (RBC) antigens, which in turn stimulates IgG antibody production by normal B cells.[25] B-cell receptors, which serve as the point of contact between antigens and the leukemic cells, have been strongly implicated in the pathogenic process, from antigen presentation to autoimmunity. One study showed that the B-cell receptors (BCRs) found in approximately one-third of all cases of CLL are highly restricted to a handful of stereotyped configurations.[26] Subsequently, Maura and colleagues demonstrated that AIHA is more likely to develop in patients with certain preserved BCR configurations.[25] These studies suggest that a specific BCR subset in CLL may correlate with a specific array of antigen reactivity, including autoreactivity.[27-29] The BCR subsets can contribute to both disease

aggressiveness and a pattern of autoimmunity in CLL.[28,29]

Another possible clue to the pathophysiology of autoimmunity in CLL is that an adverse prognostic factor, unmutated immunoglobulin heavy chain variable region gene (*IGHV*) status, is more common in patients who have CLL with AIHA than in those without AIHA.[30] In one particular study, despite the well-established negative prognostic significance of unmutated *IGHV* status, overall survival did not differ significantly between patients with and those without AIHA (70% vs 80%; *P*>.05).[30] Unmutated *IGHV*, along with ZAP-70 positivity, has also been shown to correlate with the development of ITP and Evans syndrome.[31-37] In addition, other adverse cytogenetic predictors, such as 11q or 17p deletion, were associated with AIHA.[25] A key question arising from these observations is why unmutated *IGHV* BCR configurations would lead to an increased risk for AIHA or ITP. One possibility is that other biological features are associated with an unmutated *IGHV* gene, such as CD38 positivity, and both of these markers may reflect a CLL clone that is of pregerminal center origin, with the presence of polyreactive cell-surface receptors that can bind different types of antigens.[25,38]

The pathogenesis of AIHA in non–CLL-related B-cell malignancies (ie, lymphomas), on the other hand, has been described in a more plausible series of biological events.[39] The first event consists of the generation of autoreactive lymphocytes through immunoglobulin and T-cell receptor gene rearrangements in precursor lymphocytes. In patients with intact immune function, these cells would normally undergo apoptosis or become inactivated. However, in certain patients with immune dysregulation, the cells may lie dormant and continue to proliferate slowly. In some, the cells may even be activated by the same genetic pathway associated with lymphoma pathogenesis (ie, dysregulation of BCL-2 or c-MYC).

Deficiencies in the Fas/Fas ligand interaction—which is integral to activated lymphocyte apoptosis and immune homeostasis[40,41]—have also been hypothesized to contribute to the expansion of a malignant T-cell population that in turn stimulates B cells to produce RBC antibodies.[39] Autoimmune lymphoproliferative syndrome (ALPS), a disease characterized by lymphadenopathy, splenomegaly, and autoimmune cytopenias, is a good example of this process. ALPS is thought to be due to inherited mutations in the Fas/Fas ligand interaction, which lead to a loss of self-tolerance and the growth of autoreactive lymphocyte populations.[42] Risk for the development of lymphoma is 50-fold higher in patients with ALPS than in the general population.[43] A similar theory of an autoreactive B-cell clonal population has been proposed in multiple myeloma.[44]

CAD is an entirely different process. IgM-initiated complement-mediated erythrocyte destruction is implicated in CAD.[45] The IgM identified can be polyclonal (often postinfectious) or monoclonal.[45,46] Monoclonal IgM CAD can be associated with an underlying lymphoproliferative disease, such as WM, or can exist on its own. In one population-based study, monoclonal IgM was identified in 90% of cases, with kappa light chains in 94%.[47] Of the patients with available bone marrow histology, 76% had features of a B-cell lymphoma and 50% specifically had a lymphoplasmacytic lymphoma; in addition, a monoclonal band was identified on serum electrophoresis in 94% of the patients.[47] These findings suggest that most cases of CAD may be secondary to an underlying malignant B-cell disorder, and so the presence of CAD should raise that suspicion. In this case, the hemolysis is directly driven by malignant B cells producing IgM antibodies against certain erythrocyte antigens. Platelet-associated IgG and IgM have also been seen in cases of WM and likely are generated via a similar process.[23] In the case of warm AIHA, complement-mediated destruction is implicated as well, although to a lesser extent than in IgM-mediated CAD because IgG antibodies fix complement less efficiently than IgM antibodies do and thus work primarily through extravascular, antibody-dependent cellular cytotoxicity in the spleen and lymphoid system.[48]

One class of drugs used to treat many lymphoproliferative diseases, purine analogues, has been implicated in the pathogenesis of AIHA. Although typically associated with fludarabine, AIHA has also occurred in patients receiving cladribine for CLL or WM.[10,49] Although it can be difficult to prove that a drug, not the underlying disease, has caused AIHA, one study reviewing cases of fludarabine-associated AIHA reported to the US Food and Drug Administration found that hemolysis recurred in most patients during rechallenge with single-agent fludarabine.[50] Most cases of relapse occurred during the first 3 cycles, although the clinical presentation was later in some. These drugs are thought to cause "self-immune dysregulation" via their deleterious effect on T cells, which in turn could account for the disinhibition and subsequent emergence of an autoreactive lymphocyte population generating autoantibodies.[50]

IgA antibodies are present in 14% of patients with AIHA but usually coexist with IgG or IgM autoantibodies and rarely occur alone.[51] However, several cases of IgA-mediated hemolytic anemia with an associated lymphoma (both T- and B-cell) have been described.[52,53] Proposed mechanisms for hemolysis in the case of IgA-associated AIHA include erythrophagocytosis and splenic sequestration.[51,54] IgM-associated warm AIHA is also a rare entity that is difficult to diagnose owing to confusing DAT results. One study may provide a clue to that diagnosis—of 49 patients who had warm IgM-associated AIHA,

two-thirds presented with a DAT result that was positive for C3, and 24% presented with a DAT result that was positive for both C3 and IgG.[55] Importantly, this specific type of AIHA seems to confer a poor prognosis, given that IgM-mediated intravascular hemolysis is a far more efficient form of hemolysis than primarily extravascular IgG-mediated hemolysis and can cause death if the pathologic process is initiated at normal body temperature.[55-57]

Diagnosis

The diagnosis of AIHA is the same regardless of the underlying etiology (Table) and requires the fulfillment of 2 criteria: clinical evidence of hemolysis and the presence of an antibody directed against RBCs.[58] Evidence of hemolysis includes anemia in the setting of a low haptoglobin level, elevated indirect bilirubin, and/or elevated lactate dehydrogenase; other helpful laboratory signs include erythrocyte agglutination or spherocytosis on the peripheral smear. The presence of an anti-RBC antibody is classically demonstrated by a positive DAT result. A polyspecific antibody reagent mixed with the patient's erythrocytes is usually used for the DAT.[59] If the result is positive, monospecific anti-IgG and anti-C3 agents can be used to determine the specific culprit antibody. However, a small number of AIHA cases are DAT-negative.[60] Many of these negative results are actually false, and positive results are obtained when the specimens are sent to specialized reference laboratories. In addition, the amount of erythrocyte-bound antibody may be under the threshold for detection, or the antibody may have a low affinity for the erythrocytes when conventional serologic methods are used.[61] To enhance the detection of erythrocyte-bound antibody, washing at 4°C or column agglutination can be performed to prevent the inadvertent loss of low-affinity antibodies.[61] Alternative tests that can detect small amounts of erythrocyte-bound antibody falling below the threshold of the standard DAT include enzyme-linked immunoassay, flow cytometry, polybrene testing, and mitogen-stimulated DAT.[57,61] IgA- and IgM-specific antisera can be used to detect IgA-associated hemolysis and warm IgM, respectively.[57,61,62]

ITP, on the other hand, owing to the absence of a sensitive and specific test, remains a diagnosis of exclusion. In the studies discussed in this review, ITP has usually been defined as decreased platelet numbers along with the absence of decreased megakaryocytes in the bone marrow, in addition to lack of another likely explanation for the thrombocytopenia.

When AIHA is believed to be idiopathic, further evaluation for an underlying B-cell disorder (computed tomography of the chest/abdomen/pelvis and/or bone marrow biopsy) should be strongly considered.[61] In one retrospective study, 14 of 52 subjects (27%) with warm AIHA had an underlying B-cell clonal disorder.[63] In another study, of both warm and cold AIHA, a hematologic malignancy developed in 19 of 107 patients (18%; median time to development, 26.5 months).[64] In both of these studies, evaluation for malignancy was not universally performed, so the rate of underlying B-cell malignancy was likely underestimated.

Prognosis

The prognostic significance of AIHA and ITP in lymphoproliferative disorders remains unclear. Although anemia and thrombocytopenia are strongly negative prognostic indicators in CLL and often serve as triggers to initiate therapy,[65,66] early predictive models did not account for the etiology of the cytopenia (ie, marrow failure, splenomegaly, or hemolysis). As discussed previously, in the case of CLL, AIHA and ITP have been repeatedly associated with negative prognostic indicators, such as ZAP-70 and unmutated *IGHV* status.[25,30-35] Interestingly, the patients with AIHA in these studies did not have a worse overall survival, despite the association with adverse risk factors.[30] Patients with ITP, on the other hand, did seem to have a worse overall survival, although not after adjustment for *IGHV* status.[32] One study looking specifically at Evans syndrome found that on univariate analysis, a diagnosis of Evans syndrome was predictive of excess mortality.[36] In addition, a concurrent diagnosis of Evans syndrome and CLL conferred a significantly worse prognosis than did a diagnosis of Evans syndrome later in the disease course. However, the prognostic significance of Evans syndrome was lost after adjustment for the other confounders discussed earlier, such as *IGHV* status.

In NHL, the patients who have AIHA (either at presentation or later) may be more responsive to lymphoma-specific chemotherapy (81% response rate) than to therapy directed at AIHA alone (61%).[11] However, an accurate comparison of response rates is difficult because of the overlap of certain therapies, such as corticosteroids, rituximab (Rituxan, Genentech/Biogen), and splenectomy, for lymphoma and AIHA/ITP. This study suggested that AIHA secondary to NHL was responsive to treatment of the underlying malignancy. However, another retrospective cohort study showed a dramatic difference between the overall survival of patients who had NHL with a diagnosis of AIHA and the survival of those who did not (22.5 months vs >32 months; $P<.0001$); nevertheless, only 16 patients (3%) in the cohort were affected by AIHA.[39] Given the rarity of autoimmune hematologic sequelae in multiple myeloma, more work is needed to determine the effect of these entities on overall prognosis. In WM, on the other hand, CAD is prevalent but often

Table. Characteristics and Initial Treatment of Warm Autoimmune Hemolytic Anemia,[61] Cold Agglutinin Disease,[61] and Immune Thrombocytopenia Purpura[70,74]

	Warm AIHA	CAD	ITP
Associated malignancies	CLL NHL MM MGUS	WM NHL MGUS	CLL NHL
Clinical features	Jaundice Low haptoglobin High LDH High indirect bilirubin Reticulocytosis	Jaundice Cold-induced livedo reticularis Acrocyanosis Low haptoglobin High LDH High indirect bilirubin Reticulocytosis	Platelet count <100,000/μL Bleeding Petechiae
DAT results	Positive for anti-IgG and/or anti-C3	Positive for anti-C3 Negative for anti-IgG	Negative
First-line treatments	Corticosteroids IVIG	Temperature control Rituximab	Corticosteroids IVIG
Second-line treatments	Rituximab Splenectomy Immunosuppression (azathioprine, cyclosporine, cyclophosphamide, mycophenolate) Danazol	Rituximab + fludarabine (non-CLL) Rituximab + prednisone Cyclophosphamide Chlorambucil Bendamustine + rituximab	Rituximab Romiplostim Eltrombopag Splenectomy Fostamatinib Immunosuppression (azathioprine, cyclosporine, cyclophosphamide, mycophenolate) Danazol

AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; DAT, direct antiglobulin test; Ig, immunoglobulin; ITP, immune thrombocytopenia purpura; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; WM, Waldenström macroglobulinemia.

precedes the diagnosis of WM, in which its effect on prognosis has not been well characterized.

Treatment

When AIHA or ITP is diagnosed in the setting of a B-cell malignant disorder, treatment of the underlying disease is often more beneficial than standard regimens for idiopathic AIHA or ITP. The administration of purine nucleoside analogues (eg, cladribine or fludarabine) as single agents should be avoided if possible because they can contribute to AIHA.

Treatment for AIHA (Table) is usually initiated in the acute setting if patients are showing signs or symptoms of anemia, such as shortness of breath, confusion, and weakness, or if the hemoglobin level falls below 10 g/dL.[44] If no underlying malignancy is found, corticosteroids are a common first-line option in warm AIHA.[61] The initial dose (usually 1 mg of prednisone per kilogram daily) is maintained for at least 2 to 3 weeks or until the hemoglobin level rises to above 12 g/dL, then slowly tapered over several weeks. Rituximab weekly for 4 doses, splenectomy, or both are alternatives if corticosteroids are contraindicated. On the other hand, in CAD, rituximab-containing regimens are considered first-line therapy and corticosteroids are not thought to be helpful.[67] RBC products are transfused judiciously in AIHA, although the risk for adverse reactions and worsened hemolysis is likely overestimated.[50,58] Thus, for transfusion in the setting of AIHA, as in other anemias, indications such as symptoms or a hemoglobin level below 7 g/dL will apply.[68]

The first-line treatment for ITP also involves corticosteroids (Table) and is usually initiated if a patient has signs or symptoms of bleeding or a platelet count of less than 30×10^9/L.[49,69] Alternatively, intravenous immunoglobulin can be used to increase the platelet count more rapidly. Second-line options include thrombopoietin agonists, rituximab, and splenectomy. Platelets are transfused in symptomatic patients. This conservative approach to transfusion in ITP is based on the fact that patients with ITP are better able than those with other thrombocytopenic conditions to tolerate relatively low platelet counts.[70]

Patients with platelet counts above 30 × 10^9/L can often be observed and do not require systemic treatment.[70] However, these guidelines are adjusted according to the personal bleeding threshold of the individual patient.

Treatment for ITP/AIHA often overlaps treatment for the underlying malignancy. For example, rituximab, an anti-CD20 monoclonal antibody, is part of the treatment of many B-cell lymphoproliferative disorders and can thus be a component of the treatment for concomitant autoimmune disease. Corticosteroids also are often used in the treatment of lymphomas. However, depending on the underlying lymphoproliferative disease, certain treatments may be more helpful than others. In the case of splenic marginal zone lymphoma, splenectomy may be especially helpful.[71] CAD is generally resistant to glucocorticoids; the combination of chemotherapy and immunotherapy with rituximab is often used in this case.[45] Possible provoking agents, such as single-agent purine nucleoside analogues, should be discontinued immediately. In a patient with CLL, treatment for the underlying leukemia is not always indicated. The patient should meet the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for "active disease."[72,73] If treatment is indicated, then nonpurine nucleoside analogues should be considered. The AIHA often decreases with disease resolution.[61] For additional information, recent work published by Go and colleagues and by Cuker and Neunert provides a more detailed and comprehensive review of approaches to the treatment of AIHA and ITP.[61,74]

Conclusion

B-cell lymphoproliferative diseases are often complicated by autoimmune diseases, including AIHA and ITP. The pathogenesis of these diseases is not completely known and requires further elucidation, but immune dysregulation and/or the clonal production of autoantibodies is often involved. The prognostic and predictive implications of autoimmune diseases in patients with associated diseases, such as B-cell clonal disorders, are not well defined and require further study. However, treatment of the immune cytopenias associated with hematologic malignancies is often similar to that of idiopathic AIHA/ITP.

Disclosures

The authors have no financial disclosures.

References

1. Polliack A, Lugassy G. Autoimmunity and auto-immune syndromes associated with and preceding the development of lymphoproliferative disorders. *Leukemia*. 1992;6(suppl 4):152-154.
2. Hamblin TJ, Oscier DG, Young BJ. Autoimmunity in chronic lymphocytic leukaemia. *J Clin Pathol*. 1986;39(7):713-716.
3. Mauro FR, Foa R, Cerretti R, et al. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: clinical, therapeutic, and prognostic features. *Blood*. 2000;95(9):2786-2792.
4. Rogers KA, Woyach JA. Secondary autoimmune cytopenias in chronic lymphocytic leukemia. *Semin Oncol*. 2016;43(2):300-310.
5. Zent CS, Ding W, Schwager SM, et al. The prognostic significance of cytopenia in chronic lymphocytic leukaemia/small lymphocytic lymphoma. *Br J Haematol*. 2008;141(5):615-621.
6. Barcellini W, Capalbo S, Agostinelli RM, et al; GIMEMA Chronic Lymphocytic Leukemia Group. Relationship between autoimmune phenomena and disease stage and therapy in B-cell chronic lymphocytic leukemia. *Haematologica*. 2006;91(12):1689-1692.
7. Diehl LF, Ketchum LH. Autoimmune disease and chronic lymphocytic leukemia: autoimmune hemolytic anemia, pure red cell aplasia, and autoimmune thrombocytopenia. *Semin Oncol*. 1998;25(1):80-97.
8. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). *Best Pract Res Clin Haematol*. 2010;23(1):47-59.
9. Kyasa MJ, Parrish RS, Schichman SA, Zent CS. Autoimmune cytopenia does not predict poor prognosis in chronic lymphocytic leukemia/small lymphocytic lymphoma. *Am J Hematol*. 2003;74(1):1-8.
10. Aslan DL, Peterson BA, Long-Tsai M, Eastlund T. Early-onset autoimmune hemolytic anemia after cladribine therapy for Waldenström's macroglobulinemia. *Transfusion*. 2006;46(1):90-94.
11. Hauswirth AW, Skrabs C, Schützinger C, Gaiger A, Lechner K, Jäger U. Autoimmune hemolytic anemias, Evans' syndromes, and pure red cell aplasia in non-Hodgkin lymphomas. *Leuk Lymphoma*. 2007;48(6):1139-1149.
12. Dührsen U, Augener W, Zwingers T, Brittinger G. Spectrum and frequency of autoimmune derangements in lymphoproliferative disorders: analysis of 637 cases and comparison with myeloproliferative diseases. *Br J Haematol*. 1987;67(2):235-239.
13. Váróczy L, Gergely L, Zeher M, Szegedi G, Illés A. Malignant lymphoma-associated autoimmune diseases—a descriptive epidemiological study. *Rheumatol Int*. 2002;22(6):233-237.
14. Berger F, Felman P, Thieblemont C, et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. *Blood*. 2000;95(6):1950-1956.
15. Coiffier B, Berger F, Bryon PA, Magaud JP. T-cell lymphomas: immunologic, histologic, clinical, and therapeutic analysis of 63 cases. *J Clin Oncol*. 1988;6(10):1584-1589.
16. Pangalis GA, Moran EM, Rappaport H. Blood and bone marrow findings in angioimmunoblastic lymphadenopathy. *Blood*. 1978;51(1):71-83.
17. Wu B, Wang W, Li F, Cheng Y. Angioimmunoblastic T-cell lymphomas presenting as autoimmune hemolytic anemias: clinical manifestations and circulating cytokine features. *Ann Hematol*. 2015;94(8):1437-1439.
18. Mourad N, Mounier N, Brière J, et al; Groupe d'Etude des Lymphomes de l'Adulte. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. *Blood*. 2008;111(9):4463-4470.
19. Bockorny B, Codreanu I, Dasanu CA. Prevalence of autoimmune hematologic and non-hematologic conditions in large granular lymphocytic leukemia: exploratory analysis of a series of consecutive patients. *Leuk Lymphoma*. 2014;55(6):1399-1401.
20. Dimou M, Angelopoulou MK, Pangalis GA, et al. Autoimmune hemolytic anemia and autoimmune thrombocytopenia at diagnosis and during follow-up of Hodgkin lymphoma. *Leuk Lymphoma*. 2012;53(8):1481-1487.
21. Kashyap R, Singh A, Kumar P. Prevalence of autoimmune hemolytic anemia in multiple myeloma: A prospective study. *Asia Pac J Clin Oncol*. 2016;12(2):e319-e322.
22. Ravindran A, Sankaran J, Jacob EK, et al. High prevalence of monoclonal gammopathy among patients with warm autoimmune hemolytic anemia. *Am J Hematol*. 2017;92(8):E164-E166.
23. Bockorny B, Atienza JA, Dasanu CA. Autoimmune manifestations in patients with Waldenström macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2014;14(6):456-459.
24. Owen RG, Lubenko A, Savage J, Parapia LA, Jack AS, Morgan GJ. Autoimmune thrombocytopenia in Waldenström's macroglobulinemia. *Am J Hematol*. 2001;66(2):116-119.
25. Maura F, Visco C, Falisi E, et al. B-cell receptor configuration and adverse cytogenetics are associated with autoimmune hemolytic anemia in chronic lymphocytic leukemia. *Am J Hematol*. 2013;88(1):32-36.
26. Agathangelidis A, Darzentas N, Hadzidimitriou A, et al. Stereotyped B-cell

receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. *Blood*. 2012;119(19):4467-4475.
27. Darzentas N, Stamatopoulos K. The significance of stereotyped B-cell receptors in chronic lymphocytic leukemia. *Hematol Oncol Clin North Am*. 2013;27(2): 237-250.
28. Agathangelidis A, Vardi A, Baliakas P, Stamatopoulos K. Stereotyped B-cell receptors in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2014;55(10): 2252-2261.
29. Messmer BT, Albesiano E, Efremov DG, et al. Multiple distinct sets of stereotyped antigen receptors indicate a role for antigen in promoting chronic lymphocytic leukemia. *J Exp Med*. 2004;200(4):519-525.
30. Visco C, Novella E, Peotta E, Paolini R, Giaretta I, Rodeghiero F. Autoimmune hemolytic anemia in patients with chronic lymphocytic leukemia is associated with IgVH status. *Haematologica*. 2010;95(7):1230-1232.
31. Visco C, Giaretta I, Ruggeri M, Madeo D, Tosetto A, Rodeghiero F. Unmutated IgVH in chronic lymphocytic leukemia is associated with a higher risk of immune thrombocytopenia. *Leukemia*. 2007;21(5):1092-1093.
32. Visco C, Ruggeri M, Laura Evangelista M, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. *Blood*. 2008;111(3):1110-1116.
33. Gribben JG. Molecular profiling in CLL. *Hematology Am Soc Hematol Educ Program*. 2008:444-449.
34. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. 1999;94(6):1848-1854.
35. Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med*. 2004;351(9):893-901.
36. Carli G, Visco C, Falisi E, et al. Evans syndrome secondary to chronic lymphocytic leukaemia: presentation, treatment, and outcome. *Ann Hematol*. 2016;95(6):863-870.
37. Visco C, Maura F, Tuana G, et al. Immune thrombocytopenia in patients with chronic lymphocytic leukemia is associated with stereotyped B-cell receptors. *Clin Cancer Res.* 2012;18(7):1870-1878.
38. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*. 1999;94(6):1840-1847.
39. Sallah S, Sigounas G, Vos P, Wan JY, Nguyen NP. Autoimmune hemolytic anemia in patients with non-Hodgkin's lymphoma: characteristics and significance. *Ann Oncol*. 2000;11(12):1571-1577.
40. Akiyama K, Chen C, Wang D, et al. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/FAS-mediated T cell apoptosis. *Cell Stem Cell*. 2012;10(5):544-555.
41. Mazar J, Thomas M, Bezrukov L, et al. Cytotoxicity mediated by the Fas ligand (FasL)-activated apoptotic pathway in stem cells. *J Biol Chem*. 2009; 284(33):22022-22028.
42. Price S, Shaw PA, Seitz A, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. *Blood*. 2014;123(13): 1989-1999.
43. Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. *Blood*. 2011;118(22):5741-5751.
44. Shimanovsky A, Alvarez Argote J, Murali S, Dasanu CA. Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. *BBA Clin*. 2016;6:12-18.
45. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):1114-1121.
46. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. *Blood Rev*. 2012;26(3):107-115.
47. Berentsen S, Ulvestad E, Langholm R, et al. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. *Haematologica*. 2006;91(4):460-466.
48. Barcellini W. New insights in the pathogenesis of autoimmune hemolytic anemia. *Transfus Med Hemother*. 2015;42(5):287-293.
49. Robak T, Błasińska-Morawiec M, Krykowski E, Hellmann A, Konopka L. Autoimmune haemolytic anaemia in patients with chronic lymphocytic leukaemia treated with 2-chlorodeoxyadenosine (cladribine). *Eur J Haematol*. 1997; 58(2):109-113.
50. Weiss RB, Freiman J, Kweder SL, Diehl LF, Byrd JC. Hemolytic anemia after fludarabine therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 1998;16(5):1885-1889.
51. Chadebech P, Michel M, Janvier D, et al. IgA-mediated human autoimmune hemolytic anemia as a result of hemagglutination in the spleen, but independent of complement activation and FcαRI. *Blood*. 2010;116(20):4141-4147.
52. Salama A, Janvier D, Mayer B, et al. Lethal autoimmune hemagglutination due to an immunoglobulin A autoagglutinin with Band 3 specificity. *Transfusion*. 2014;54(8):1988-1995.
53. Tsujimoto M, Shimizu E, Nakamine H, Takenaka T, Maeda J. [A case of T-cell lymphoma with IgA type autoimmune hemolytic anemia]. *Rinsho Ketsueki*. 1986;27(4):624-629.
54. Clark DA, Dessypris EN, Jenkins DE Jr, Krantz SB. Acquired immune hemolytic anemia associated with IgA erythrocyte coating: investigation of hemolytic mechanisms. *Blood*. 1984;64(5):1000-1005.
55. Arndt PA, Leger RM, Garratty G. Serologic findings in autoimmune hemolytic anemia associated with immunoglobulin M warm autoantibodies. *Transfusion*. 2009;49(2):235-242.
56. McCann EL, Shirey RS, Kickler TS, Ness PM. IgM autoagglutinins in warm autoimmune hemolytic anemia: a poor prognostic feature. *Acta Haematol*. 1992;88(2-3):120-125.
57. Barcellini W. Immune hemolysis: diagnosis and treatment recommendations. *Semin Hematol*. 2015;52(4):304-312.
58. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. *Am J Hematol*. 2002;69(4):258-271.
59. Wheeler CA, Calhoun L, Blackall DP. Warm reactive autoantibodies: clinical and serologic correlations. *Am J Clin Pathol*. 2004;122(5):680-685.
60. Kamesaki T, Oyamada T, Omine M, Ozawa K, Kajii E. Cut-off value of red-blood-cell-bound IgG for the diagnosis of Coombs-negative autoimmune hemolytic anemia. *Am J Hematol*. 2009;84(2):98-101.
61. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. *Blood*. 2017;129(22):2971-2979.
62. Bartolmäs T, Salama A. A dual antiglobulin test for the detection of weak or nonagglutinating immunoglobulin M warm autoantibodies. *Transfusion*. 2010;50(5):1131-1134.
63. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: new insights based on a single-center experience with 60 patients. *Am J Hematol*. 2014;89(9):E150-E155.
64. Sallah S, Wan JY, Hanrahan LR. Future development of lymphoproliferative disorders in patients with autoimmune hemolytic anemia. *Clin Cancer Res.* 2001;7(4):791-794.
65. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 1981;48(1):198-206.
66. Rai KRSA, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-234. *Blood*. 2016;128(17):2109.
67. Berentsen S. Cold agglutinin disease. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):226-231.
68. Chaplin H Jr. Clinical usefulness of specific antiglobulin reagents in autoimmune hemolytic anemias. *Prog Hematol*. 1973;8:25-49.
69. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207.
70. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood*. 2005;106(7):2244-2251.
71. Franco V, Florena AM, Iannitto E. Splenic marginal zone lymphoma. *Blood*. 2003;101(7):2464-2472.
72. Stilgenbauer S, Furman RR, Zent CS. Management of chronic lymphocytic leukemia. *Am Soc Clin Oncol Educ Book.* 2015:164-175.
73. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. *Blood*. 2018.
74. Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. *Blood*. 2016;128(12):1547-1554.