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Secondary autoimmune cytopenias in chronic lymphocytic leukemia

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ABSTRACT

Secondary autoimmune cytopenias in chronic lymphocytic leukemia are distinct clinical entities that require specific management. These autoimmune disorders have a complex pathogenesis that involves both the leukemic cells and the immune environment in which they exist. The mechanism is not the same in all cases, and to varying degrees involves the chronic lymphocytic leukemia (CLL) cells in antibody production, antigen presentation, and stimulation of T cells and bystander polyclonal B cells. Diagnosis of autoimmune cytopenias can be challenging as it is difficult to differentiate between autoimmunity and bone marrow failure due to disease progression. There is a need to distinguish these causes, as prognosis and treatment are not the same. Evidence regarding treatment of secondary autoimmune cytopenias is limited, but many effective options exist and treatment can be selected with severity of disease and patient factors in mind. With new agents to treat CLL coming into widespread clinical use, it will be important to understand how these will change the natural history and treatment of autoimmune cytopenias.

1. Background and clinical experience

The course of chronic lymphocytic leukemia (CLL) is frequently complicated by concomitant autoimmune cytopenias (AIC). The most common of these secondary AIC is autoimmune hemolytic anemia (AIHA), which is an antibody-mediated destruction of autologous red blood cells (RBCs). Second most common is immune thrombocytopenia (ITP), which shares some features with AIHA and has a similar mechanism targeting platelets. These two syndromes may occur in isolation, sequentially in the same patient, or present in combination as Evan's syndrome. Pure red cell aplasia (PRCA) and autoimmune granulocytopenia (AIG) are comparatively rare and can occur alone or in combination with other AIC. PRCA can present with anemia as in AIHA, but involves a virtual absence of red cell precursors due to immune destruction of erythrocyte progenitor cells and no hemolysis. AIG has a similar mechanism to PRCA in which myeloid precursors are destroyed and patients develop infections.

1.1. Incidence

While other autoimmune disorders have been reported in CLL, AIC are by far the most frequent immune complication [1,2]. Figures regarding the percentage of patients affected by secondary AIC vary. Exact numbers are difficult to ascertain as AIC can present at any time in the CLL disease course, including predating CLL diagnosis. Further complicating the issue, the rate in any given cohort will vary based on the cohort composition as AIC are associated with higher Rai stage, prior cytotoxic treatment, and more aggressive disease characteristics [3,4]. For example, heavily pretreated cohorts will have a higher incidence of AIC compared to populations enriched with asymptomatic, treatment-naïve patients. The retrospective nature of studies reporting incidence also limits their accuracy as not all patients underwent rigorous diagnostic testing for cytopenia diagnosis and some may have had cytopenias from alternate causes such as bone marrow infiltration with leukemia.

Despite these challenges, a reasonable estimate is that AIC occur in 4%–10% of CLL patients with the highest reported rates coming from analysis of therapeutic clinical trials and lower estimates coming from large institutional studies [1,3–8]. This is a significant number of patients, as CLL is the most common adult leukemia with an incidence rate of 3.83 cases per 100,000 person-years. It is even more prevalent due to the long survival of CLL patients, making complicating AIC an important matter [9,10].

Relative frequency of the types of AIC is similar in nearly all reported cohorts with AIHA being the most common at 55%–70% of patients with AIC, ITP the second most common at 18%–47%, and PCRA and AIG being decidedly less common at 12% and 4%, respectively [1,3–8]. Patients prone to AIC may also develop more

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Table 1
Types of autoimmune cytopenias in CLL.

Type	Clinical findings	Incidence*	Mechanism	Common treatments
Autoimmune hemolytic anemia (AIHA)	Anemia, + DAT, laboratory markers of hemolysis†	10%–15%	Antibody-mediated	Corticosteroids, IVIG, rituximab, rituximab w/ chemotherapy, cyclosporine
Immune thrombocytopenia (ITP)	Unexplained low platelet count, increased megakaryocytes in bone marrow	2%–15%	Antibody-mediated	Corticosteroids, IVIG, rituximab, TPO receptor agonists, rituximab w/ chemotherapy
Pure red cell aplasia (PRCA)	Anemia, low reticulocyte count, absent red cell precursors in bone marrow, no alternate cause	< 1%	Antibody-mediated, T-cell–mediated	Cyclosporine, alemtuzumab
Autoimmune granulocytopenia (AIG)	Neutropenia, maturation arrest or absent neutrophil precursors in bone marrow	< 1%	Antibody-mediated, T-cell–mediated	Granulocyte colony-stimulating factor, cyclosporine

* In CLL patients.
† Increased reticulocyte count, LDH, and direct bilirubin. Decreased haptoglobin.

than one, and it is not uncommon for patients to have AIHA and ITP occurring either together as Evan's syndrome, or sequentially separated by years [1,3,8]. There are also many CLL patients who have a positive direct anti-globulin test (DAT) but no clinical evidence of hemolysis. This finding may predict risk of later developing AIHA but this does not occur in all cases [7,11]. Types and characteristics of AIC are found in Table 1.

1.2. Impact on clinical outcomes

The effect of AIC on outcomes for CLL patients is a subject of debate. While patients with cytopenias due to autoimmunity clearly do better than those whose cytopenias are caused by bone marrow failure, it appears that the presence of AIC confers some negative impact with shortened survival and time to treatment [5,7]. In addition, patients with AIC may experience morbidity from anemia, bleeding, transfusion complications, and infection related to immunosuppressive treatment.

CLL staging is useful for prognosis but is not straightforward in AIC patients. The widely used Rai and Binet clinical staging systems use presence of anemia and thrombocytopenia to increase stage and predict a poorer prognosis with decreased overall survival [12,13]. These staging systems do not distinguish between causes of anemia or thrombocytopenia and patients with autoimmune cytopenias receive the same stage as those with bone marrow infiltration and no evidence of autoimmune disease. Prognosis and treatment decisions should not be the same in these groups and staging was revisited in the most recent report from the International Workshop on Chronic Lymphocytic Leukemia. Cytopenias due to autoimmune causes are now not considered when assigning clinical stage to patients [3,8,14–16].

Retrospective series have examined the differences between patients with Binet stage C disease due to autoimmunity (stage C "immune") and bone marrow failure due to leukemia infiltration (stage C "infiltrative"). In these series the overall survival for patients presenting with stage C "immune" was improved compared to those with stage C "infiltrative" or there was a trend towards improved survival [3,15,16]. However, when these patients were down-staged to Binet A after AIC directed therapy their survival was consistently worse than stage A patients without AIC and more closely approximated Binet stage B patients, suggesting that the presence of AIC does indicate a more aggressive phenotype [3,15,16].

Worse outcomes for AIC patients may be related to the association with poor prognostic features in the underlying CLL and it has been proposed that AIC are a potential marker for disease aggressiveness [15]. Both AIHA and ITP have been associated with advanced age, advanced stage, shorter lymphocyte doubling time, poor-risk cytogenetics (deletion 17p and deletion 11q), high Zap-70 expression, and unmutated IGVH status [2,17]. These are all markers for worse survival from CLL and the association of AIC with these adverse disease features may account for some of the decreased survival seen in this group of patients [6,8,17–20].

The AIC themselves can decrease survival as patients with anemia and thrombocytopenia may experience end-organ ischemia or bleeding, which can be especially morbid in the older CLL population. In a series of secondary ITP patients, those with severe bleeding symptoms or refractory ITP had reduced overall survival compared to those who did not [8]. Infectious complications are also a major concern as risk for infection is already high in CLL patients. Morbidity due to infection has been documented in AIC patients treated with corticosteroids [6]. There are not enough patients with PRCA or AIG to determine associations with disease features or impact on survival. These patients, like those with AIHA and ITP, are at risk for morbidity from low cell counts and immunosuppressive treatments. This would logically impact their outcomes.

2. AIHA

2.1. Mechanism and pathogenesis of AIHA

The mechanism of AIHA in CLL patients is not completely understood, but key clinical findings, in vitro experiments, and associations with CLL disease features give insight into pathogenesis. The CLL cells themselves have been implicated in several facets of autoimmunity including antibody production, antigen presentation, and inducing changes in T cells that favor the development of AIHA. The involvement of CLL cells in different aspects of AIHA pathogenesis is shown in Fig. 1. These mechanisms contribute more or less to the development of AIHA in different patients, accounting for variability in presentation and response to treatment.

In autoimmune hemolytic anemia antibodies are produced targeting RBCs, which are then destroyed resulting in hemolysis. Most commonly the RBC targeting antibody is IgG, which coats RBCs. The IgG-coated cells are then cleared through the reticuloendothelial system in the liver and spleen. Some IgM antibodies lyse RBCs intravascularly resulting in massive acute hemolysis. As CLL cells are malignant B cells capable of producing antibody, the most concise explanation for AIHA is the malignant clone simply produces the anti-RBC antibodies directly. CLL cells do produce low amounts of polyreactive IgM and in select cases it has been demonstrated that the antibodies adherent to RBCs in circulation are of the same isotype found on the surface of the CLL cells [21–24]. However, this is a minority of cases and pathogenic antibody is usually a high-affinity, polyclonal IgG that is produced by stimulation and expansion of bystander B cells [21,22,25].