Chronic lymphocytic leukemia and autoimmunity: a systematic review

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ABSTRACT

Chronic lymphocytic leukemia is frequently associated with immune disturbances. The relationship between chronic lymphocytic leukemia and autoimmune cytopenias, particularly autoimmune hemolytic anemia and immune thrombocytopenia, is well established. The responsible mechanisms, particularly the role of leukemic cells in orchestrating the production of polyclonal autoantibodies, are increasingly well understood. Recent studies show that autoimmune cytopenia is not necessarily associated with poor prognosis. On the contrary, patients with anemia or thrombocytopenia due to immune mechanisms have a better outcome than those in whom these features are due to bone marrow infiltration by the disease. Moreover, fears about the risk of autoimmune hemolysis following single agent fludarabine may no longer be appropriate in the age of chemo-immunotherapy regimens. However, treatment of patients with active hemolysis may pose important problems needing an individualized and clinically sound approach. The concept that autoimmune cytopenia may precede the leukemia should be revisited in the light of recent data showing that autoimmune cytopenia may be observed in monoclonal B-cell lymphocytosis, a condition that can only be detected by using sensitive flow cytometry techniques. On the other hand, there is no evidence of an increased risk of non-hemic autoimmune disorders in chronic lymphocytic leukemia. Likewise, there is no epidemiological proof of an increased risk of chronic lymphocytic leukemia in patients with non-hemic autoimmunity. Finally, since immune disorders are an important part of chronic lymphocytic leukemia, studies aimed at revealing the mechanisms linking the neoplastic and the immune components of the disease should help our understanding of this form of leukemia.

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Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of monoclonal lymphocytes with a distinctive immunophenotype (i.e. $CD5^+$, $CD19^+$, $CD20^{dim}$, $CD23^+$, $SmIg^{dim}$) in peripheral blood, bone marrow, and lymphoid tissues.[1,2] Patients with CLL frequently present with immune disturbances, which constitute a notable feature of the disease compared to other chronic lymphoproliferative disorders.[3-8] In this paper, we will review autoimmune disorders in CLL, their incidence, pathophysiological mechanisms, prognostic impact, and management.

Design and Methods

To identify studies that examined the epidemiological evidence for an association between CLL and autoimmune disease, as well as case reports and series regarding CLL and autoimmune phenomena, we searched PUBMED using the keywords that are specified in the *Online Supplementary Appendix*. The abstracts and papers linked to the PUBMED searches were scanned to identify any reports not included in this computerized search. For CLL-associated immune cytopenia, we focused on prevalence, outcome and association with prognostic variables, and therapy. For non-hemic autoimmunity, we included all original case reports and series published in English which discussed the presentation of autoimmune phenomena in patients with CLL. The evidence of any causal association between the CLL and non-hemic autoimmune disease was independently assessed by KH and CM for each case report. The process we used to identify and report this literature was modeled on the PRISMA consensus, adapted to recognize the observational nature of the data and the year of publication of many of the case reports.[9]

Epidemiology

The association of CLL and autoimmune cytopenia was recognized in the late 1960s.[3,4,10,11] A positive direct antiglobu-

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lin test (DAT) with or without frank AIHA is strongly associated with CLL,[12-15] as are immune thrombocytopenia (ITP)[16-18] and pure red cell aplasia (PRCA).[19] The occurrence of immune cytopenia has been reported to range from less than 5% to 38%.[14,20] In the most recent studies, the proportion of patients presenting with autoimmune cytopenia at some point during the course of their disease ranges from 4.3% to 9.7%.[12,13,15,21,22] The most common complication is AIHA (about 7%) whereas the incidence of ITP, and particularly autoimmune neutropenia and PRCA, is lower in most studies (<1-2%). There are no case reports or epidemiological studies suggesting a link between CLL and autoimmune diseases affecting the blood coagulation system, such as acquired hemophilia or acquired von Willebrand disease.

Regarding non-hemic autoimmunity, several early studies described an increased incidence of autoimmune phenomena other than autoimmune cytopenia in CLL. In line with this, in studies published in the 1980s, autoimmune disease (AID) was reported to be more common in relatives of patients with CLL than in controls.[23] Also, autoimmunity was shown to be much more common in patients with lymphoproliferative disorders, including CLL, than in patients with myeloproliferative conditions (8% *vs*. 1.7%).[16]

In more recent studies (Table 1), clinically apparent autoimmune disorders have been reported in 2% to 12% of patients whereas positive serum markers for a variety of autoimmune conditions ("serological autoimmunity") have been found in 8% to 41% of patients.[17,25,27] However, case-control studies do not suggest an increase in AID in patients with CLL.[5]

These observations have been followed up by larger studies, examining AID as a risk factor for the development of CLL and as a complication of CLL. Regarding the possibility that autoimmune conditions predispose to CLL, a Nordic case-control study looked at the risk of developing CLL in the context of personal or family history of AID. The risk of CLL was much higher in individuals with a personal history of AIHA (odds ratio, OR 104), and somewhat raised in those with pernicious anemia (PA; OR 1.94).[28] Likewise, in another large study, individuals who developed CLL had a much higher incidence of prior AIHA compared to those who did not, meaning that AIHA carried a 3.86-fold increased risk of developing CLL. No link to other autoimmune diseases, including pernicious anemia, was observed.[29] The association between AIHA and risk of developing CLL is difficult to interpret because, as discussed later, many of these cases might harbor a CLL clone which is not easily detectable by conventional diagnostic methods.

In a large patient-control study, a positive OR (6.7) for AIHA was observed, with a trend to increased risk for ITP.[30] No increased risk of other AID was observed. In another large study looking at patients with ulcerative colitis, though an increased incidence of non-Hodgkin's lymphoma was observed, there was no increase in CLL.[31] In a recent review of the risk of lymphoid malignancy in patients with AID, there was elevated risk of organ specific lymphoma, e.g. celiac disease and enteropathy associated

Table 1. Case series of autoimmune cytopenias in chronic lymphocytic leukemia.

Author, Date	Population	Number of patients, time interval	Outcome	Clinical/biological correlates
Hamblin 1986[5]	195 patients from a single institution	19 of 195 (9.7%), 1972-1985 15 AIHA 4 ITP	Not reported	Not reported
Kyasa 2000[24]	132 patients from a single primary care system	12 of 132 (9.1%), 1989-2001 6 AIHA 5 ITP 1 PRCA	OS not different to CLL patients without autoimmune complications	Not reported
Mauro 2000[12]	1,203 patients from a single institution	52 of 1,203 (4.3%), 1986-1996	OS not different in DAT positive anemic CLL and DAT negative non-anemic CLL patients	High WCC, advanced age, male gender, active CLL
Barcellini 2006[17]	3,150 patients from the GIEMA group, 17 institutions	194 of 3,150 (6.2%), unspecified time interval 129 AIHA 35 ITP	Not reported	AIHA associated with advanced stage active CLL, old age
Duek 2006[25]	National CLL registry of 964 patients	63 of 964 (6.55%), 1971-2006 55 DAT pos at diagnosis 9 ITP or Evans	Not reported	High B2M, high CD38
Visco 2008[18]	1,278 patients from 3 institutions	64 of 1,278 (5%) ITP, 1996-2004 47 AIHA 28 DAT pos only	OS worse in CLL patients with ITP than those who never develop ITP. OS of patients with thrombocytopenia at diagnosis significantly worse than non-thrombocytopenic CLL regardless of etiology	High WCC, unmutated *IgVH* gene, high Zap70
Zent 2008, 2009[13,26]	1,750 patients from a single institution	75 of 1,750 (4.5%), 1995-2004 41 AIHA 35 ITP 9 PRCA 3 AIG	OS not different to CLL patients who never develop cytopenia. OS since cytopenia was superior in patients with immune cytopenia compared to cytopenia due to bone marrow failure	Male gender, unmutated *IgVH* gene, high Zap70, poor risk cytogenetics
Moreno 2010[15]	961 patients from a single institution	70 of 960 (7%), 1980-2008 49 AIHA 20 ITP 1 Evans	OS not different to CLL patients who never develop AID. OS of immune cytopenia at presentation superior to OS of stage C at presentation	High WCC, high LDT, high B2M, high CD38

AIHA: autoimmune hemolytic anemia; ITP: immune thrombocytopenia; PRCA: pure red cell aplasia; DAT: direct anti-globulin test; OS: overall survival; WCC: white cell count; LDT: lymphocyte doubling time; B2M: beta 2 microglobulin; IgVH: immunoglobulin heavy chain variable region.

T-cell lymphoma. However, risk of CLL was not increased.[32]

Further interest in the link between autoimmunity and CLL comes from genetic studies. Both CLL[33,34] and autoimmunity[35] are known to have a hereditary component. In the Nordic study no general increase in risk of CLL was associated with family history of AID. The lack of a link between family history of AID and CLL risk was taken to exclude an underlying genetic predisposition linking CLL and AID.[28]

Biological aspects

The biological explanation for the frequency of autoimmune cytopenia in CLL is complex and not completely understood (reviewed by Kipps and Carson,[6] Calgaris-Cappio[36] and Ghia *et al.*[37]), with neoplastic CLL cells, T cells and microenvironment cells playing a role (Figure 1).

Although it has been proposed that CLL derives from marginal zone B cells,[38,39] the normal counterpart of the $CD5^+$ B CLL cell has not been fully elucidated (reviewed in [40]). In mouse models of CLL, $CD5^+$ B cells (B1a cells) are most plentiful in the peritoneal cavity and can produce polyreactive antibodies that bind DNA and can act as rheumatoid factors, i.e. bind IgG.[41,42] However, human $CD5^+$ B cells rarely produce auto-antibodies and may not be an exact equivalent of the mouse B1 cell, at least not as the cell of origin of CLL.[37,43]

The B-cell response to antigens is mediated by the B-cell receptor (BCR). The analysis of the BCR in patients with CLL shows a stereotyped repertoire with identical or quasi-identical sequence, suggesting selection of B cells with antigen binding sites of restricted structure (reviewed in [39,44]). CLL cells, particularly those with unmutated *IGHV* gene, can present a highly polyreactive BCR which recognizes auto-antigens.[43, 45-47] Of note, the same antigens are recognized by "natural" antibodies known to be pathological in certain autoimmune diseases.[48]

However, the BCR signaling in CLL can be defective and this has been related to the low number of surface immunoglobulin molecules on CLL cells,[49] non-functional assembly of the BCR,[50,51] and mutations in accessory proteins.[52] Despite this, CLL cells can produce auto-reactive antibodies *in vitro* after stimulation.[53,54] Although in rare instances CLL cells produce auto-reactive antibodies *in vivo* in sufficient quantity to cause clinical disease (e.g. cold agglutinin disease, discussed below), the autoimmune cytopenias which are a common feature of CLL are caused by polyclonal antibodies.[20] The capacity of CLL cells to function as antigen presenting cells is nearly abrogated *in vitro*, the exception to this rule being red cell antigen Rh processing.[55] An alternative red cell antigen, B3, has also been demonstrated to be processed by CLL cells, which are then able to provoke a T-cell response.[56] It has been noted that AIHA is more common in advanced CLL, where the spleen is heavily infiltrated by leukemic cells,[12] which brings CLL cells in close proximity to damaged red blood cells.[56] In this regard, the spleen also contains CD40 ligand-expressing T cells which *in vitro* are able to induce activation of CLL cells and improve antigen presentation.[57] On the other hand, CLL cells interact with T cells to modulate the immune environment, which may be important in permitting the development of autoimmunity. Thus, CLL is characterized by acquired T-cell defects including numerical increase in T cells, inversion of the CD4:CD8 ratio, production by CLL cells of the inhibitory cytokines IL-6, IL-10, TNF and TGF-β, as well as alterations in T-cell cytoskeleton formation and vesicle transportation.[58-63] Finally, it is worth mentioning that CLL is associated with impairment of the innate immune system.[64-67]

Autoimmune cytopenia in chronic lymphocytic leukemia

Clinical and biological correlates

Several clinical and biological features of CLL have been associated with an increased risk of developing autoimmune cytopenia (Table 2). In most studies, a correlation between advanced stage and the risk of AIHA has been reported.[5,17] In line with this, AIHA has also been associated with active CLL.[12] Older patients also seem to be more

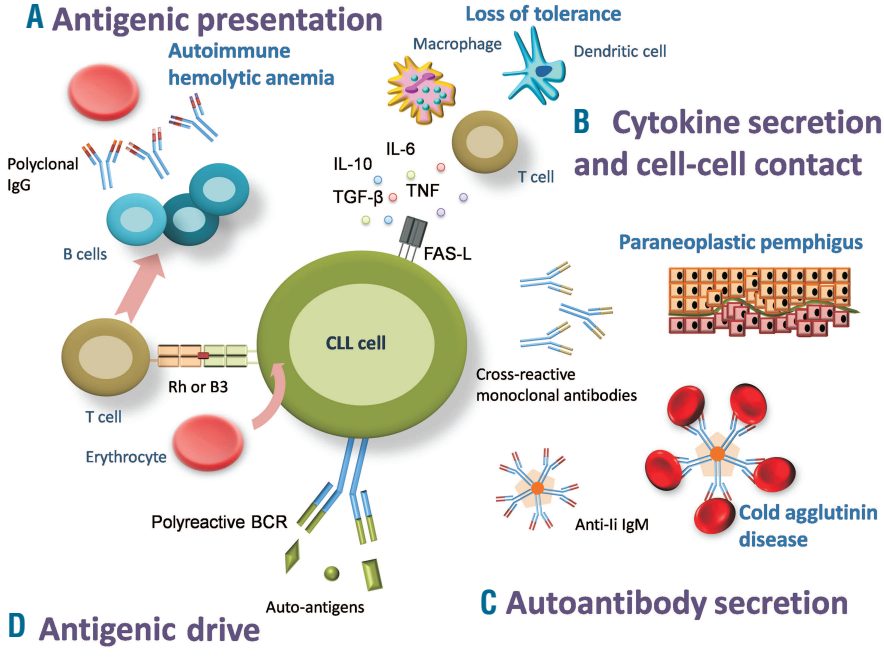

Figure 1. Mechanisms of autoimmune disease in CLL. (A) CLL cells may process red blood cell antigens and act as antigen presenting cells, inducing a T-cell response and the formation of polyclonal antibodies by normal B cells, thus indirectly provoking autoimmune hemolytic anemia. (B) CLL cells express inhibitory cytokines that alter tolerance, which may facilitate the escape of self-reactive cells. (C) Rarely CLL cells are effector cells that secrete a pathological monoclonal autoantibody. Two such diseases are paraneoplastic pemphigus, where immunoglobulins are cross-reactive with epitopes located at the dermal-epidermal junction, and cold agglutinin disease, where IgMs have anti-red cell reactivity. (D) In turn, CLL cells may be stimulated through their polyreactive BCR that recognizes auto-antigens.

prone to develop this complication, independently of CLL stage or duration.[12,17,22]

Due to the retrospective nature of most studies, the relationship between newer biological prognostic markers and autoimmune cytopenia has not been comprehensively assessed. Nevertheless, both AIHA and ITP have been associated with poor prognostic factors such as unmutated *IGHV* gene, high ZAP70 expression, and increased serum beta-2 microglobulin levels.[13,15,68] The stereotyped BCR seen in CLL may be reactive with autoantigens.[69]

Although the risk of immune cytopenia increases over the course of the disease, it can be the presenting feature of CLL and it has been classically considered that it can precede the diagnosis of CLL.[13,15,24] The association between a prior history of AIHA or ITP and the risk of presenting CLL should be interpreted with caution because peripheral blood flow cytometry is not generally performed as part of the routine diagnostic work up of AIHA. Supporting this caveat is the recent observation that the precursor condition known as monoclonal B-cell lymphocytosis (MBL) is markedly more common in patients with supposed idiopathic AIHA or ITP than in matched controls.[70] This reflects the importance of excluding CLL and other chronic lymphoproliferative diseases in patients with AIHA.[71]

The possibility that therapy could trigger autoimmune cytopenia in patients with CLL was recognized in initial descriptions of the disease.[4,11] In the early 1990s, however, there was concern that treatment with purine analogs (particularly fludarabine) could be associated with a higher frequency of autoimmune cytopenia.[72-74] This was thought to be related to prolonged suppression of $CD4^+$ T cells by fludarabine. A decrease in $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs) has been shown to lead to AID and Tregs are highly sensitive to fludarabine (reviewed in [75]).The cases reported were mainly observed in heavily pre-treated patients with active immune cytopenia who had already received purine analogs.[72,74,76] As a result of these observations, it is now agreed that purine analogs should be avoided in patients with a history of autoimmune cytopenia, particularly if related to purine-analog therapy.

Current evidence shows that the risk of developing autoimmune cytopenia after purine analog exposure is no greater than with other agents.[21,22] In the UK CLL4 trial, no differences were observed in the percentage of patients becoming DAT-positive after therapy (14% chlorambucil, 13% fludarabine, and 10% fludarabine plus cyclophosphamide). Notably, the incidence of AIHA was significantly lower in patients treated with fludarabine plus cyclophosphamide (5%) than in those allocated to receive chlorambucil (12%) or fludarabine alone (11%) ($P<0.01$).[22] This suggests that the addition of cyclophosphamide to fludarabine might have a "protective" effect on the appearance of AIHA. An earlier smaller study supports this low incidence of AIHA in patients treated with fludarabine, cyclophosphamide and rituximab.[21] In our own experience, the incidence of AIHA was slightly lower after fludarabine-based therapy (4%) than after chlorambucil treatment (5%).[15] The most recent data comes from the German CLL 8 trial of patients with CLL requiring treatment and without clinically apparent autoimmune cytopenia. When treated with fludarabine and cyclophosphamide with or without rituximab the rate of AIHA was 1%.[77] Taken together these results demonstrate that the risk of AIHA is not higher following regimes in which fludarabine and cyclophosphamide (with or without rituximab) are given together in comparison to the risk seen after older therapies for CLL. The best approach to treatment of autoimmune cytopenia in CLL is discussed below.

Prognostic significance

The effect of autoimmune cytopenia on prognosis of patients with CLL remains uncertain. There are few studies investigating this issue in large unselected series from single institutions such as would be representative of the general population with CLL.

In a series of 1,203 patients with CLL, AIHA has been associated with active disease, but without a negative impact on survival.[12] In a cohort of 1,750 patients with CLL associated cytopenia, the relative outcome was compared between cytopenia due to bone marrow failure and immune cytopenia. Patients with immune cytopenia at diagnosis had a better outcome than those in whom cytopenia was due to bone marrow failure,[13] and the later development of autoimmune cytopenia did not result in a worse prognosis than that of patients who never developed this complication.[26] Our group has investigated the impact of autoimmune cytopenia on CLL outcome in a series of 961 patients.[15] Patients who had autoimmune cytopenia at the time of diagnosis had a clearly superior survival than those who presented with cytopenia due to bone marrow failure. Similarly, development of autoimmune cytopenia at any stage in the disease did not have an impact on survival.

The UK CLL4 trial mentioned above assessed the prognostic effect of a positive DAT in 783 patients with CLL requiring treatment for the first time. A positive DAT predicted a poorer response to treatment. Both a positive DAT and AIHA were associated with a lower overall survival.[22] The authors suggest that DAT at the time of therapy may be a prognostic indicator. It is important to note, however, that this study was performed in patients requiring therapy and, hence, with poor prognosis.

A study of ITP in 1,278 patients with CLL showed that acute ITP at diagnosis or at any time in the disease was associated with an inferior outcome compared to those patients who never developed ITP, independently of other clinical prognostic variables[18] but probably related to the association of ITP with an unmutated *IGHV* gene.[68] Interestingly, the same group has demonstrated a similar association between an unmutated *IGHV* gene and AIHA, without the same negative impact on survival.[78] PRCA and

Table 2. Prognostic factors correlated with autoimmune cytopenia in CLL.

Clinical prognostic factors	References
Advanced stage	(5, 13, 17, 24)
Older age	(12, 17, 22)
Male	(12, 13)
High white cell count	(12, 15, 18)
Short lymphocyte doubling time	(15, 17)
Biological prognostic factors	
Beta 2 microglobulin	(15, 22, 25)
High CD38	(15, 25)
High ZAP 70	(13, 18)
Unmutated *IGVH* genes	(13, 18, 68)
Poor risk cytogenetics	(13)

autoimmune neutropenia are much less common, and as such, information concerning the prognostic impact of PRCA is not considered individually.

Diagnosis and management

A high degree of suspicion is required to diagnose autoimmune cytopenia in patients with CLL. Appropriate laboratory investigations include a DAT, lactate dehydrogenase (LDH), bilirubin, haptoglobins, and reticulocyte count. A bone marrow examination (aspirate and biopsy) is particularly important to differentiate between the causes of cytopenia. The multiple possible causes of cytopenia in CLL (bone marrow failure, hypersplenism, chemotherapy, sepsis, autoimmunity) and the possibility of two or more causes occurring simultaneously require careful clinical judgment in the management of these patients.

Most patients with CLL and AIHA will have an anemia with positive DAT in the context of reticulocytosis and raised bilirubin. Serum LDH is less discriminating as it may be elevated due to active CLL. Moreover, DAT negative AIHA has been seen, particularly in association with therapy.[21] Reticulocytosis may not be seen in the context of a bone marrow overwhelmed by leukemic cells or when there has been recent chemotherapy. Bone marrow examination is essential to distinguish between therapy related causes of cytopenia.[2]

ITP causes particular diagnostic difficulties. There is no sensitive and specific test to parallel the DAT in AIHA, and thrombocytopenia in CLL is more commonly due to splenomegaly and bone marrow failure secondary to infiltration by disease. Nevertheless, thrombocytopenia in a patient with CLL can be considered immune mediated when there is a sudden large fall in platelets (>50% fall to a platelet count $<100\times10^9$/L) in the absence of splenomegaly, infection or chemotherapy and with plentiful megakaryocytes in the bone marrow.[14] In advanced disease, anemia usually occurs before thrombocytopenia,[79] so isolated thrombocytopenia is more likely to be immune in origin.[80] ITP with a gradual rather than sudden decline in platelet count is seen more commonly in adults than classic acute ITP of childhood, and can present particular diagnostic difficulties. Response of thrombocytopenia to corticosteroids may be the diagnostic test.

Treatment of patients with CLL and autoimmune cytopenia is largely based on expert opinion and can be divided depending on whether the patient's CLL requires treatment at the same time.[81] In those patients with immune cytopenia in the context of quiescent CLL, the treatment is the same as idiopathic AIHA initially with corticosteroids, and then in patients who fail to respond or relapse quickly, consideration of alternative immunosuppression (e.g. ciclosporine, mycophenylate or azathioprine) or splenectomy.[71,82] There are case reports of the use of combinations of the anti-CD20 monoclonal antibody rituximab with or without immunosuppression with good effect.[83-87] The anti-CD52 monoclonal antibody alemtuzumab has also been successfully used.[88-90] Intravenous immunoglobulin can be useful where a rapid response is needed (e.g. a patient with ITP and significant bleeding) though as a single agent it will not give lasting effects. More recently, it has been found that new thrombopoietin receptor agonists may be effective in ITP associated with CLL as is the case in primary ITP.[91] Supportive care should include blood product transfusion as clinically indicated, folic acid in AIHA and local efforts to control bleeding in ITP. Failure of autoimmune cytopenia to respond to conventional treatment is considered an indication for anti-CLL therapy.

Given the concerns about therapy-triggered AIHA discussed above, there has been recent interest in the most appropriate treatment for patients with active CLL and immune cytopenia or a positive DAT (Table 3). Monotherapy with fludarabine is not appropriate, either in terms of risk of AIHA or efficacy in treatment of CLL. The studies discussed above suggest that treatment with current chemotherapy (e.g. fludarabine, cyclophosphamide) or chemo-immunotherapy (e.g. fludarabine, cyclophosphamide, rituximab) regimens do not provoke an excess of AIHA, and that patients with a previous history of AIHA or a positive DAT might be safely treated with such regimens.[21,22,77] Indeed, optimal treatment of CLL may be the most efficient way to treat associated cytopenia.[81] However, patients with active AIHA or ITP are still excluded from clinical trials, and given the ongoing concerns about using fludarabine in this setting, alternative regimens which do not feature fludarabine have also been explored (Table 3).[87,92-94] Importantly, after successful treatment, patients with stage C "immune" may be "down-staged" to Binet stage A and thus no longer fulfill the criteria for initiation of treatment for CLL. This makes a clear understanding of the origin of cytopenia in a patient with CLL even more important before a decision about treatment is made.

Chronic lymphocytic leukemia-produced auto-antigens and clinical disease

There are numerous case reports of other autoimmune diseases in patients with CLL (Table 4). Whilst the epidemiological evidence discussed above does not suggest an increased risk of AID in CLL, or CLL in AID except immune cytopenia, there are cases in which the CLL clone has been demonstrated to produce a clinically important autoantibody.[97,98,114-118] There are other cases in which, though CLL and an AID coexist in a patient, there is no evidence of a causal link (Table 4). In other situations, CLL associated with a monoclonal immunoglobulin or light chain causes organ damage, but by a mechanism which does not involve autoimmunity.[119-121]

Cold agglutinin disease

Cold agglutinin disease (CAD), where clonal IgM binds to erythrocytes in the cool peripheries, is associated with chronic lymphoproliferative disorders (CLPDs), most commonly Waldenstrom's macroglobulinemia, but also CLL.[116] In a patient with antecedent CAD who later developed CLL, *IGHV* gene mutations were invariable but associated with kappa light chain intra-clonal diversification, suggesting the CLL was derived from the CAD clone, with additional genetic evolution.[115] It has also been demonstrated that the auto-antibody may have the same BCR rearrangement as the CLL cells.[118]

Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous disease with blistering and erosion, associated with an underlying neoplasia.[122] CLL is one of the tumors most commonly associated with this disease; others include non-Hodgkin's lymphoma, Castleman's disease and Hodgkin's lymphoma.[117] There is some evidence that the antibodies that recognize multiple antigens in the epidermis and ultimately cause the disease may be produced by the tumor.[123] The antigens targeted appear to cross react

with the specific rearrangements of the *IGHV* gene. Other authors have suggested epitope spreading as the mechanism, i.e. the development of immune responses against endogenous epitopes during a chronic autoimmune or infectious response.[122] This theory is supported by the more recent recognition of PNP in association with treatment with fludarabine.[114] However, PNP does arise in untreated CLL, and has been successfully treated with fludarabine-containing regimens.[124] It has also been noted that dysregulated cytokine production, particularly IL-6, may be the mechanism by which tumors, including CLL, cause PNP.[117]

Neuropathies

As with myeloma-associated gammopathy, there are a few reports of polyneuropathy secondary to CLL with associated gammopathy. A monoclonal anti-MAG (myelin-associated glycoprotein) has been demonstrated[97,98] and anti-CLL therapy led to clinical improvement in neurological symptoms. Guillain-Barré syndrome has been reported in the context of stem cell collection, and after treatment with chlorambucil, but whether this was directly related to CLL or to viral reactivation in the context of immunosuppression is uncertain.[99]

Chronic lymphocytic leukemia complications which may be confused with autoimmune disease

Acquired angio-edema (AAE) is associated with CLPD, especially monoclonal gammopathy of uncertain significance (MGUS) and low grade NHL (splenic lymphoma with villous lymphocytes and lymphoplasmacytic lymphoma), and is due to an excess of complement 1 (C1) secondary to a low level of its inhibitor (C1-INH). This reduction in serum C1-INH can be due to an autoantibody or to consumption by the tumor. A monoclonal autoantibody has been demonstrated in MGUS and NHL, but not in CLL.[120] Earlier reports of AAE in small lymphocytic lymphoma describe a B-cell CLPD but with an immunophenotype which would not now be considered CLL (FMC7 pos, sIg strong and CD5 negative).[125] So where CLL is related to AAE, it does not appear to be by an autoimmune mechanism, but rather by direct tumor consumption of C1-INH. Similarly, a monoclonal gammopathy in CLL can cause renal disease.[119,121] However, this is not due to an autoimmune mechanism, but rather to direct damage to renal tubules caused by deposition of immunoglobulins, particularly free light chains.

Table 3. Treatment approaches for autoimmune cytopenia in CLL.

Author, Date	Population	Baseline findings	Outcome	Comments
Kaufman 2009[92]	Single institution patients with steroid-refractory immune cytopenia or immune cytopenia and active CLL treated with R-CD		Cytopenia: 21 of 21 patients responded to R-CD. CLL: not reported	No response of CLL to therapy is reported.
Bowden 2010[93]	Single institution patients with immune cytopenia and active CLL treated with R-CVP		Cytopenia: 19 of 20 patients responded to R-CVP. CLL: 17 of 20 patients responded (9 CR) with median TTT 27.7	Authors note that CLL outcome is inferior to current best therapy
D'Arena 2010[87]	Multi-center patients with steroid refractory ITP in association with inactive CLL treated with single agent rituximab		Cytopenia: of 21 patients, 12 (57%) had a CR and 6 (29%) had a PR. CLL did not require treatment in any patient	Treatment well tolerated. Patients may also have failed IVIg or vincristine.
Rossignol 2010[94]	Single institution patients with immune cytopenia and CLL, either resistant to corticosteroids or with other indication for treatment with R-CD		Cytopenia: of 48 patients, 40 (83%) had a CR and 3 (6.5%) had a PR. CLL: of 20 patients with active CLL, 7 (35%) achieved a CR, with an overall response in 19 (95%) OR	Treatment well tolerated. Relapse of autoimmune disease was strongly correlated with relapse of CLL.
Borthakur 2006[21]	FCR trial, single institution	9 of 300 had AIHA at start of therapy – one had worsening of AIHA with FCR which responded to cessation of FCR and administration of steroids	19 of 300 developed AIC 14 DAT negative AIHA 3 DAT positive AIHA 2 ITP	Incidence of AIHA not different from that in historical cohort of FC patients, though would be different if only DAT positive anemia considered
Dearden 2008[22]	UK CLL4 trial – F *vs.* FC *vs.* CLB	44 of 777 (14%) DAT positive previously untreated patients with CLL now requiring treatment (clinical AIHA excluded)	77 of 777 developed AIHA 47 (12%) chlorambucil, 21 (11%) fludarabine alone, 9 (5%) FC	DAT positivity is an independent negative predictor of outcome
Hallek 2010[77]	German CLL8 - FC *vs.* FCR		7 of 800 developed AIHA, 4 (1%) FC and 3 (<1%) FCR	

R-CVP: rituximab cyclophosphamide vincristine prednisolone; R-CD: rituximab cyclophosphamide dexamethasone; F: fludarabine; FC: fludarabine cyclophosphamide; FCR: fludarabine, cyclophosphamide rituximab; CR: complete remission; TTT: time to treatment; AIHA: autoimmune hemolytic anemia; ITP: immune thrombocytopenia; DAT: direct anti-globulin test

Table 4. Case reports of CLL and non-hemic autoimmune conditions.

AID	Author	Date	Type of report	Attempt to explain	Comment
Churg-Strauss					No reports in PUBMED
Pernicious anemia (PA)	Parker[95]	1976	2 LPD cases with PA	Descriptive only	Very brief abstract only
	Ruvidic[96]	1990	PA 23 years after diagnosis of treated CLL, develops gastric cancer	Descriptive only	Abstract only, in Serbian
Polyneuropathy	Drake[97]	1998	Acute polyneuropathy in CLL with IgG monoclonal protein and response to CLB	IgG paraprotein which responds to CLB as does neuron symptoms	Causal evidence presented
	Mitsui[98]	1999	Polyneuropathy in CLL and HTLV infection	IgM from CLL cells bound to gangliosides, but interaction with HTLV uncertain	Causal evidence presented, unsure of extent of role of HTLV
	D´Arena[99]	2004	GBS developing with cyclo prime prior to PBSC harvest	Descriptive with suggestions ?related to viral or autoimmune	No causal evidence, but may be linked
Raynaud's					No reports in PUBMED
Rheumatoid arthritis (RA)	Taylor[100]	1989	4 patients with CLL in an RA population of 1,500	Significantly increased incidence	Very small epidemiological study, no pathological examination
	Voulgari[101]	2002	Stage 0 patient who developed RA, RA patient who developed stage 0 CLL	4 per 1,000 *vs*. 0.2 per 1,000 in general population	Very small epidemiological study, no pathological examination
	Onal[102]	2005	Single case CLL patient who developed seropositive arthritis	Arthritis improved with CLL therapy	No pathological study of RhF etc.
Sjogren's syndrome	Lehner-Netsch[103]	1969	Single case report of co-diagnosis	Descriptive only	No pathological study
	Gumpel[104]	1972	Single case report of co-diagnosis	Parotid swelling reduced with CLB but still sicca syndrome	No pathological study
	Bán[105]	1984			Not available online, no abstract
Systemic lupus erythematosus (SLE)	Ho[106]	1985	Single case report of CLL in woman after 5 years of SLE		Not available online, abstract only
	Lishner[107]	1990	Single case report of CLL in woman after 5 years of SLE		Not available online, abstract only
	Lugassy[108]	1992	2 CLL pts develop SLE, 1 SLE pt develops CLL	Descriptive and literature review only	No causal evidence presented
Thyroiditis	Haubenstock[109]	1985	Single case report		Not available online, abstract only
	Beyan[110]	2006	CLL patient gets Hashimoto's 1 year after treatment with fludarabine	Descriptive only presented	No causal evidence
Ulcerative colitis (UC)	Crispino[111]	2007	UC patient develops stage 0 CLL (5 cases with heme-onc)	Descriptive, states causal link uncertain	No causal evidence presented
Vasculitis	Mariette[112]	1993	Vasculitis in a CLL patient	Monoclonal IgM showed anti-cardiolipin specificity, but serologically measured anti-cardiolipin Ab was IgG	Clinically relevant antibody not linked to clone, possible role for antigenic stimulation of CLL clone
	Pamuk[113]	2007	pANCA vasculitis in patient with CLL	No monoclonal spike, 141 other CLL patients did not have a pos pANCA so not false positive	Autoimmune mechanism link to CLL not established, but plausible

CLB: chlorambucil; RhF: rheumatoid factor; LPD: lymphoproliferative disease; GBS: Guillain-Barre syndrome; PBSC: peripheral blood stem cell; HTLV: human T-lymphotrophic virus.

Conclusions

Chronic lymphocytic leukemia is frequently associated with immune disturbances. Whereas the association of CLL with autoimmune cytopenias, particularly autoimmune hemolytic anemia and immune thrombocytopenia, is well established, there is no proof of an increased risk of non-hemic autoimmune disorders in CLL. The predilection in CLL for autoimmune disease attacking the formed elements of the blood is only partially understood and may be related to the ability of CLL cells to process and present antigens derived from blood cells, in contrast to their poor general performance as antigen presenting cells. The mechanisms leading to autoimmune cytopenia in CLL are complex and involve interactions between the malignant B-CLL cells, abnormally functioning T cells, the microenvironment, and the immune system.

While there has been important debate regarding the prognostic significance of immune cytopenias in patients

with CLL, recent studies show that this complication is not necessarily associated with impaired prognosis, with some of the conflicting results being likely due to differences in the patient cohorts studied. Importantly, patients with advanced disease due to an immune mechanism (Binet C "immune") have a better outcome than those in whom advanced stage reflects a high tumor burden with massive bone marrow infiltration (Binet C "infiltrative"). This highlights the importance of determining the origin of the cytopenia in patients with CLL for both prognostic and therapeutic purposes.

Given the clear link between autoimmune cytopenia and CLL, there has been sustained interest in the possibility of a relationship between CLL and other forms of autoimmunity. In most cases, however, there is not a causal link between non-hemic autoimmunity and CLL. However, in a few cases, including paraneoplastic pemphigus and cold agglutinin disease, there is evidence that the CLL clone produces the pathological antibody.

Finally, further research on mechanisms connecting the neoplastic and the immune component of CLL is clearly needed to improve our understanding about this form of leukemia and eventually improve its clinical management.

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