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-hemolytic autoimmune disorders in chronic lymphocytic leukemia. Likewise, there is no epidemiological proof of an increased risk of chronic lymphocytic leukemia in patients with non-hemolytic 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+, CD23-, SmIg−) in peripheral blood, bone marrow, and lymphoid tissues.1-3 Patients with CLL frequently present with immune disturbances, which constitute a notable feature of the disease compared to other chronic lymphoproliferative disorders.4 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-hemolytic 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-hemolytic 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.5

Epidemiology

The association of CLL and autoimmune cytopenia was recognized in the late 1960s.6,7,10 A positive direct antiglobu-
lin test (DAT) with or without frank AIHA is strongly associated with CLL, as are immune thrombocytopenia (ITP) and pure red cell aplasia (PRCA). The occurrence of immune cytopenia has been reported to range from less than 5% to 55%. 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%. 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. 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%). 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. However, case-control studies do not suggest an increase in AID in patients with CLL.

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). 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. 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. 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. 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 with...
T-cell lymphoma. However, risk of CLL was not increased.\(^3\) Further interest in the link between autoimmunity and CLL comes from genetic studies. Both CLL\(^{34}\) and autoimmunity\(^2\) 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.\(^2\)

**Biological aspects**

The biological explanation for the frequency of autoimmune cytopenia in CLL is complex and not completely understood (reviewed by Kipps and Carson,\(^2\) Calgaris-Cappio\(^1\) and Ghia \(^{66}\)), 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,\(^{\text{a,b}}\) the normal counterpart of the CD5\(^-\) B CLL cell has not been fully elucidated (reviewed in \(^46\)). In mouse models of CLL, CD5\(^+\) B cells (B1a cells) are most plentiful in the peritoneal cavity and can produce polyclonal antibodies that bind DNA and can act as rheumatoid factors, i.e. bind IgG.\(^{61,62}\) 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.\(^{63,64}\)

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 \(^64,66\)). CLL cells, particularly those with unmutated IGHV gene, can present a highly polyclonal BCR which recognizes auto-antigens.\(^{45,64,66}\) Of note, the same antigens are recognized by "natural" antibodies known to be pathological in certain autoimmune diseases.\(^{68}\)

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,\(^{69}\) non-function-
al assembly of the BCR,\(^{60,61}\) and mutations in accessory proteins.\(^{62}\) Despite this, CLL cells can produce auto-reactive antibodies in \textit{vivo} after stimulation.\(^{63,64}\) Although in rare instances CLL cells produce auto-reactive antibodies in \textit{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.\(^{65}\) The capacity of CLL cells to function as antigen presenting cells is nearly abrogated in \textit{vivo}, the exception to this rule being red cell antigen Rh processing.\(^{66}\) 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.\(^{67}\) It has been noted that AIHA is more common in advanced CLL, where the spleen is heavily infiltrated by leukemic cells,\(^{68}\) which brings CLL cells in close proximity to damaged red blood cells.\(^{69}\) In this regard, the spleen also contains CD40 ligand-expressing T cells which in \textit{vivo} are able to induce activation of CLL cells and improve antigen presentation.\(^{70}\) 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-\(\beta\), as well as alterations in T-cell cytoskeleton formation and vesicle transportation.\(^{65,63}\) 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.\(^{71}\) In line with this, AIHA has also been associated with active CLL.\(^{12}\) Older patients also seem to be more
prone to develop this complication, independently of CLL stage or duration.\textsuperscript{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.\textsuperscript{13,14,16} The stereotyped BCR seen in CLL may be reactive with autoantigens.\textsuperscript{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.\textsuperscript{15,12,24} 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.\textsuperscript{62} This reflects the importance of excluding CLL and other chronic lymphoproliferative diseases in patients with AIHA.\textsuperscript{71}

The possibility that therapy could trigger autoimmune cytopenia in patients with CLL was recognized in initial descriptions of the disease.\textsuperscript{41} In the early 1990s, however, there was concern that treatment with purge analogs (particularly fludarabine) could be associated with a higher frequency of autoimmune cytopenia.\textsuperscript{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\textsuperscript{75}). The cases reported were mainly observed in heavily pre-treated patients with active immune cytopenia who had already received purge analogs.\textsuperscript{72,74,76} As a result of these observations, it is now agreed that purge analogs should be avoided in patients with a history of autoimmune cytopenia, particularly if related to purge-analog therapy.

Current evidence shows that the risk of developing autoimmune cytopenia after purge analog exposure is no greater than with other agents.\textsuperscript{21,24} 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).\textsuperscript{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.\textsuperscript{5} In our own experience, the incidence of AIHA was slightly lower after fludarabine-based therapy (4%) than after chlorambucil treatment (5%).\textsuperscript{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%.\textsuperscript{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 unsellected series from single institutions such as would be representative of the general population with CLL.

In a series of 1,208 patients with CLL, AIHA has been associated with active disease, but without a negative impact on survival.\textsuperscript{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,\textsuperscript{13} and the later development of autoimmune cytopenia did not result in a worse prognosis than that of patients who never developed this complication.\textsuperscript{29} Our group has investigated the impact of autoimmune cytopenia on CLL outcome in a series of 961 patients.\textsuperscript{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.\textsuperscript{21} 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\textsuperscript{25} but probably related to the association of ITP with an unmutated IGHV gene.\textsuperscript{46} Interestingly, the same group has demonstrated a similar association between an unmutated IGHV gene and AIHA, without the same negative impact on survival.\textsuperscript{22} 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 CD8                          | (15, 25)       |
| High ZAP 70                       | (13, 18)       |
| Unmutated IGHV 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 cytophenia in patients with CLL. Appropriate 
laboratory investigations include a DAT, lactate dehydroge-
nase (LDH), bilirubin, haptoglobins, and reticulocyte count.
A bone marrow examination (aspirate and biopsy) is particu-
larly important to differentiate between the causes of 
cytophenia. The multiple possible causes of cytophenia in CLL 
(bone marrow failure, hypersplenism, chemotherapy, seg-
psis, autoimmune) and the possibility of two or more caus-
es occurring simultaneously require careful clinical judg-
ment 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 thera-
py. 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 exami-
nation is essential to distinguish between therapy related 
causes of cytophenia.

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 infil-
tration by disease. Nevertheless, thrombocytopenia in a 
patient with CLL can be considered immune mediated 
when there is a sudden fall in platelets (>50% fall to a 
platelet count <100x10^9/L) in the absence of splenomegaly, 
infection or chemotherapy and with plentiful megakaryo-
cytes in the bone marrow. In advanced disease, anemia 
usually occurs before thrombocytopenia, so isolated 
thrombocytopenia is more likely to be immune in origin. 
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 cytope-
nia is largely based on expert opinion and can be divided 
depending on whether the patient’s CLL requires treatment 
at the same time. In those patients with immune cytope-
nia 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, con-
sideration of alternative immunosuppression (e.g. 
cyclosporine, mycophenolate or azathioprine) or splenecto-
my. There are case reports of the use of combinations of 
the anti-CD20 monoclonal antibody rituximab with or 
without immunosuppression with good effect. The anti-
CD52 monoclonal antibody alemtuzumab has also been 
successfully used. 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 effec-
tive in ITP associated with CLL as is the case in primary 
ITP.

Supportive care should include blood product transfu-
sion as clinically indicated, folic acid in AIHA and local 
efforts to control bleeding in ITP. Failure of autoimmune 
cytophenia to respond to conventional treatment is consid-
ered an indication for anti-CLL therapy.

Given the concerns about therapy-triggered AIHA dis-
cussed above, there has been recent interest in the most 
appropriate treatment for patients with active CLL and 
immune cytophenia 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, cyclophos-
phamide, 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 regi-
mens. Indeed, optimal treatment of CLL may be the 
most efficient way to treat associated cytophenia. 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). 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 cytophenia in a patient with CLL even more impor-
tant 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 epidemi-
ological evidence discussed above does not suggest an 
extended risk of AID in CLL, or CLL in AID except immune 
cytophenia, there are cases in which the CLL clone has been 
demonstrated to produce a clinically important autoanti-
body. 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.

**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 com-
monly Waldenstrom’s macroglobulinemia, but also CLL. In 
a patient with antecedent CAD who later developed 
CLL, IGHV gene mutations were invariant but associated 
with kappa light chain intra-clonal diversification, suggest-
ing the CLL was derived from the CAD clone, with addi-
tional genetic evolution. It has also been demonstrated 
that the auto-antibody may have the same BCR rearrange-
ment as the CLL cells.

**Paraneoplastic pemphigus**

Paraneoplastic pemphigus (PNP) is an autoimmune 
muco-cutaneous disease with blistering and erosion, associ-
ated with an underlying neoplasia. 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. There is some evidence that 
the antibodies that recognize multiple antigens in the epi-
dermis and ultimately cause the disease may be produced 
by the tumor. 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.\textsuperscript{123} This theory is supported by the more recent recognition of PNP in association with treatment with fludarabine.\textsuperscript{14} However, PNP does arise in untreated CLL, and has been successfully treated with fludarabine-containing regimens.\textsuperscript{123} It has also been noted that dysregulated cytokine production, particularly IL-6, may be the mechanism by which tumors, including CLL, cause PNP.\textsuperscript{117}

Neuropathies

As with myeloma-associated gammopathy, there are a few reports of polymyositis secondary to CLL with associated gammopathy. A monoclonal anti-MAG (myelin-associated glycoprotein) has been demonstrated\textsuperscript{20,21} 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.\textsuperscript{9}

### 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.\textsuperscript{123} 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).\textsuperscript{127} 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 gammapathy in CLL can cause renal disease.\textsuperscript{115,121} 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.

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

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

<table>
<thead>
<tr>
<th>AID</th>
<th>Author (Ref.)</th>
<th>Date</th>
<th>Type of report</th>
<th>Attempt to explain</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churg-Strauss</td>
<td>Parker &amp; Ruzicic</td>
<td>1976</td>
<td>2 LPD cases with PA</td>
<td>Descriptive only</td>
<td>No reports in PUBMED</td>
</tr>
<tr>
<td>Pernicious anemia (PA)</td>
<td>Drake &amp; Mitsui</td>
<td>1998</td>
<td>Acute polyneuropathy in CLL with IgG monoclonal protein and response to CLB</td>
<td>IgG paraprotein which responds to CLB as does neuron symptoms</td>
<td>Causal evidence presented</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>D’Arena &amp; Taylor</td>
<td>2004</td>
<td>GBS developing with cyclo prime prior to PBSC harvest</td>
<td>Descriptive with suggestions related to viral or autoimmune</td>
<td>No causal evidence, but may be linked</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>Voulgaris &amp; Ong</td>
<td>2002</td>
<td>Stage 0 patient who developed RA, RA patient who developed stage 0 CLL</td>
<td>4 per 1,000 vs. 0.2 per 1,000 in general population</td>
<td>Very small epidemiological study, no pathological examination</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Lehner-Netsch</td>
<td>1986</td>
<td>Single case report of co-diagnosis</td>
<td>Descriptive only</td>
<td>No pathological study</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Bann</td>
<td>1984</td>
<td>Single case report of CLL in woman after 5 years of SLE</td>
<td>Not available online, abstract only</td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Lishner &amp; Lugassy</td>
<td>1990</td>
<td>Single case report of CLL in woman after 5 years of SLE</td>
<td>Not available online, abstract only</td>
<td></td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Haubenstock</td>
<td>1985</td>
<td>Single case report of CLL in woman after 5 years of SLE</td>
<td>Not available online, abstract only</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis (UC)</td>
<td>Crispino &amp; Mariette</td>
<td>1993</td>
<td>UC patient develops stage 0 CLL (5 cases with hemo-onc)</td>
<td>Descriptive, states causal link uncertain</td>
<td>No causal evidence presented</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Pamuk</td>
<td>2007</td>
<td>pANCA vasculitis in patient with CLL</td>
<td>No monoclonal spike, 141 other CLL patients did not have a pos pANCA so not false positive</td>
<td>Autoimmune mechanism link to CLL not established, but plausible</td>
</tr>
</tbody>
</table>

**CLB:** chlonambacul; **RHF:** rheumatoid factor; **LPD:** lymphoproliferative disease; **GBS:** Guillain-Barre syndrome; **PBSC:** peripheral blood stem cell; **HTLV:** human Tymphatotropic 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, 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-hemocytopenic 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.

Authorship and Disclosures

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Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.
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