

# Diagnosis and Management of Autoimmune Complications of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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**Abstract:** Autoimmune cytopenia is an important but poorly understood clinical complication of chronic lymphocytic leukemia/small lymphocytic lymphoma. We review the pathogenesis, clinical presentation, and management of autoimmune hemolytic anemia, immune thrombocytopenia, and pure red blood cell aplasia in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma.

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is the most prevalent lymphoid malignancy in the United States with a estimated incidence of approximately 15,000 new diagnoses per year.<sup>1</sup> Autoimmune cytopenias are an important cause of morbidity in patients with CLL and occur in approximately 5–10% of patients during the course of their disease.<sup>2</sup> In contrast, the risk of non-hematologic autoimmune disease in CLL patients is less well defined, with some data suggesting an increased prevalence of C1 esterase deficiency, autoimmune blistering skin diseases,<sup>3</sup> and pernicious anemia.<sup>4,5</sup> Autoimmune hemolytic anemia (AIHA) is the most common autoimmune complication in CLL,<sup>6-11</sup> affecting approximately 5% of patients, followed by immune thrombocytopenia (ITP) (1–3%)<sup>9-11</sup> and pure red blood cell aplasia (PRBCA; 1%); rarely, autoimmune granulocytopenia (AIG) may occur.<sup>9,12,13</sup> This review discusses the pathogenesis, diagnosis, and management of autoimmune cytopenias in CLL.

## Pathogenesis

Although CLL cells are known to produce monoclonal autoantibodies, these rarely cause autoimmune cytopenia. Autoimmunity is usually caused by loss of self-tolerance resulting in a pathologic immune response to autologous blood cells. Most cases of AIHA and ITP are caused by high-affinity polyclonal IgG directed against red blood cells (RBCs) or platelet antigens. In PRBCA, the mechanism is less well defined but is believed to be humorally mediated in at least some of the patients.

## Keywords

Chronic lymphocytic leukemia, autoimmune hemolytic anemia, immune thrombocytopenia, pure red blood cell aplasia.

There are few data on the mechanism of autoimmunity in patients with AIG.

Autoantibodies specific for RBCs are detectable by the direct antiglobulin test in up to 20% of patients with advanced CLL but cause AIHA in only a minority of these patients.<sup>14,15</sup> A few cases have been described in which RBC-specific autoantibodies were produced by the malignant CLL clone.<sup>16,17</sup> However, in the majority of patients, the study of the light chains, isotypes, and specificities of the autoreactive antibodies have demonstrated that they are distinct from the monoclonal antibodies secreted by the CLL cells.<sup>18,19</sup>

The etiology of anti-RBC antibodies in CLL is poorly understood. Several mechanisms have been proposed. Aberrant T-cell function is likely involved in this process. Murine and human AIHA studies have shown that autoreactive T helper (T<sub>H</sub>) cells are critical for the induction of AIHA.<sup>20-22</sup> Autoreactive T<sub>H</sub> cells specific for Rh epitopes, one of the dominant RBC antigens in AIHA, have been demonstrated in CLL patients with AIHA.<sup>15,21</sup> These autoreactive T<sub>H</sub> cells could be induced by pathologic autoantigen presented by CLL cells. Although CLL cells are usually considered to be inefficient antigen-presenting cells, they are able to present Rh antigens to T cells in vitro.<sup>15</sup> Therefore, CLL cells could function as autoantigen-presenting cells to trigger the T<sub>H</sub> cell-mediated autoantibodies production by normal B lymphocytes. Loss of function of regulatory T cells (Treg), a subset of CD4+ and CD25+ T cells with a role in maintaining peripheral tolerance,<sup>23</sup> could have significant impact in the etiology of autoimmune cytopenias in CLL. This mechanism was also suggested to be important in patients developing autoimmune cytopenias after treatment with purine analogs and alemtuzumab (Campath, Genzyme/Berlex), drugs highly toxic to T cells.<sup>24</sup> Additional research on the mechanism of autoimmune cytopenias in CLL is essential for decreasing the risk of these complications and developing more rational therapies.

### **Therapy-related Autoimmune Cytopenia**

Potentially fatal autoimmune cytopenias can complicate treatment of CLL with purine analogs and alemtuzumab.<sup>13,25-31</sup> CLL patients treated with fludarabine (Fludara, Berlex) monotherapy for the first time have an approximately 2% risk of developing AIHA, with a higher risk reported for patients receiving repeated fludarabine therapy.<sup>2</sup> This risk of autoimmune cytopenia appears to be lower with the use of fludarabine in combination regimens including cyclophosphamide and/or rituximab (Rituxan, Genentech/Biogen Idec).<sup>32,33</sup> The risk of relapse or exacerbation of preexisting autoimmune cytopenia in CLL patients treated with purine analogs or alemtuzumab is unknown. Although the etiology of treatment-induced

autoimmune cytopenia in CLL patients is not understood, fludarabine is toxic to Treg, implying that loss of Treg could have a role in loss of self-tolerance.<sup>24</sup> A better understanding of the mechanism of loss of self-tolerance could enable clinicians to better treat these patients for both their cytopenias and CLL.

### **Clinical Presentation**

The diagnosis of autoimmune cytopenia in patients with CLL can be difficult, especially in advanced disease. However, the distinction between cytopenia due to autoimmune complications and bone marrow failure could affect treatment decisions and prognosis.<sup>34</sup> The clinical classifications described by Rai<sup>35</sup> and Binet<sup>36</sup> classify all patients with anemia and thrombocytopenia as having advanced-stage disease, although there are data to suggest that patients with autoimmune cytopenia have a better prognosis than patients with Rai III-IV or Binet C stage due to bone marrow failure.<sup>11,37</sup> Correct diagnosis of the cause of cytopenia in CLL patients thus has important clinical applications.

The time of presentation of autoimmune cytopenia in CLL patients is highly variable. Autoimmune cytopenia can occur at any time in the course of CLL. In an appreciable minority of patients, the diagnosis of autoimmune cytopenia precedes (12%) or is concomitant with (15%) the diagnosis of CLL.<sup>38</sup> A lymphoid malignancy should thus be in the differential diagnosis for all patients with a newly diagnosed autoimmune cytopenia.

AIHA complicating CLL usually causes symptomatic anemia. Recognizing the autoimmune mechanism of this anemia is usually not difficult if this etiology is considered in the differential diagnosis of the anemia. However, distinguishing between bone marrow failure and AIHA can be challenging in patients with high disease burden and those who have recently received purine-analog therapy. We suggest that AIHA be considered in the differential diagnosis of all CLL patients with anemia (Table 1).

In contrast to AIHA, patients with CLL and thrombocytopenia due to ITP are usually asymptomatic at diagnosis.<sup>38</sup> Patients with CLL and progressive bone marrow failure usually develop symptoms of anemia before they have marked thrombocytopenia. Thus, ITP should be considered in the differential diagnosis of thrombocytopenia in patients with CLL, especially those patients who are not anemic or symptomatic. The diagnosis of ITP requires evidence of adequate platelet production, which is best obtained by performing a bone marrow study to evaluate megakaryocyte function (Table 1).

PRBCA is a less common but important diagnosis in patients with CLL and anemia. Failure to produce RBCs because of PRBCA can be difficult to distinguish

**Table 1.** Recommendations for Diagnosis of Autoimmune Complications of CLL

<p><b>Autoimmune Hemolytic Anemia</b></p> <ol style="list-style-type: none"> <li>1. At least one marker of hemolysis             <ol style="list-style-type: none"> <li>a. Increased indirect bilirubin not due to liver disease</li> <li>b. Increased lactate dehydrogenase without alternative etiology</li> <li>c. Increased absolute reticulocyte count or increased bone marrow erythropoiesis in the absence of bleeding <i>and</i></li> </ol> </li> <li>2. Direct or indirect evidence of an autoimmune mechanism             <ol style="list-style-type: none"> <li>a. Positive direct antiglobulin for either IgG or C3d</li> <li>b. Cold agglutinins</li> <li>c. At least 2 markers of hemolysis in absence of evidence of bleeding or hypersplenism.</li> </ol> </li> </ol> <p><b>Immune Thrombocytopenia</b></p> <ol style="list-style-type: none"> <li>1. Platelet counts <math>\leq 100 \times 10^9/L</math> <i>and</i></li> <li>2. No evidence of hypersplenism <i>and</i></li> <li>3. No evidence of increased platelet consumption due to other causes</li> <li>4. Normal or increased megakaryocytes on bone marrow examination</li> </ol> <p><b>Pure Red Blood Cell Aplasia</b></p> <ol style="list-style-type: none"> <li>1. Hemoglobin <math>\leq 12</math> g/dL <i>and</i></li> <li>2. Reticulocytopenia <i>and</i></li> <li>3. Isolated absence of erythrocyte precursors in the bone marrow</li> <li>4. Test for parvovirus infection by blood polymerase chain reaction assay.</li> </ol> <p><b>Autoimmune Granulocytopenia</b></p> <ol style="list-style-type: none"> <li>1. Sustained neutropenia (<math>&lt;0.5 \times 10^9/L</math>) <i>and</i></li> <li>2. No recent chemotherapy (within preceding 8 weeks) <i>and</i></li> <li>3. Bone marrow showing decreased or absent granulocyte precursors</li> </ol>
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from the bone marrow failure caused by disease progression. The diagnosis of PRBCA requires a bone marrow study showing the characteristic defects in RBC precursor maturation (Table 1). Transient RBC production failure due to parvovirus B19 infection needs to be excluded by polymerase chain reaction–based blood tests for viral nucleic acid.

AIG is a very rare complication of CLL and should be considered in the differential diagnosis of prolonged neutropenia. The diagnosis is made by exclusion and requires a bone marrow study to demonstrate failure of neutrophil production and eliminate other possible causes.

Autoimmune mechanisms need to be considered as possible etiologic factors in all patients with CLL who develop cytopenia. Autoimmune cytopenias are not uncommon and this diagnosis can have an important impact on therapeutic decisions. We strongly recommend that all CLL patients who develop cytopenias undergo a full evaluation including a bone marrow study before starting CLL therapy.

**Treatment**

There are limited data on the management of autoimmune cytopenia in CLL. Most CLL patients who have autoimmune cytopenias with low tumor burden are treated with the same empiric therapy used for patients with primary autoimmune cytopenias. In patients with more advanced CLL, treatment modalities are often directed at both the CLL and autoimmune cytopenia. Due to the relative rarity of these diseases, trials to test treatment strategies have been difficult to conduct.

***Treatment of Autoimmune Complications in Patients in Whom Therapy for CLL Is Not Indicated***

**AIHA** In patients with CLL that does not require therapy, corticosteroids can be the first line of therapy for AIHA. Most patients respond rapidly to treatment with high-dose corticosteroids (oral prednisone 1 mg/kg for 10–14 days or intravenous methylprednisolone 1 g/day for 3 days), followed by a gradual prednisone taper over the next 2–3 months.<sup>39</sup> However most patients (65%) will have evidence of recurrence of hemolysis as the prednisone dose is decreased<sup>39</sup> and will require either maintenance corticosteroids or alternative therapy. Pneumocystis prophylaxis is recommended for all patients on long-term higher-dose ( $\geq 20$  mg/day) prednisone therapy. In patients requiring long-term high-dose corticosteroids, steroid-sparing agents can be used. These immunosuppressive agents can also be useful in patients with steroid-refractory disease. Cyclosporine at a dose of 5–8 mg/kg daily was reported to result in a 60% remission rate at 3–11 weeks with a median duration of response of 10 months.<sup>40,41</sup> Renal toxicity was the most common side effect. The dose can be tapered to 3 mg/kg daily after initial response and patients can often be maintained at a target blood cyclosporine level of 100 ng/mL.

Intravenous immunoglobulin (IVIg; 0.4 g/kg daily for 3–5 days) can induce a rapid but usually short-duration response in patients with CLL and AIHA that is most useful in patients with severe or poorly tolerated hemolysis. In IVIg-responsive patients, retreatment is usually effective.

Rituximab can be a highly effective treatment for AIHA in CLL.<sup>42-44</sup> The mechanism of its action on CLL

remains uncertain. Although rituximab is highly effective against the normal B cells responsible for synthesis of anti-RBC antibodies, this does not explain the rapid responses to therapy that have been observed. Rituximab is usually used in our institution at the standard dose (375 mg/m<sup>2</sup> weekly for 4 weeks) together with prednisone. Once the hemolysis has begun to decrease, as measured by an increase in hemoglobin level and decrease in absolute reticulocyte count, lactate dehydrogenase, and bilirubin, the prednisone dose is decreased rapidly and stopped within 4 weeks of the last dose of rituximab, if possible. Patients are then monitored monthly and retreated with rituximab when there is evidence of recurrent hemolysis.

Transfusion of packed RBCs can be required for the management of acute hemolysis and can be done safely in most patients. Use of a blood-heating coil is advised if there is a cold reactive autoantibody. Accelerated hemolysis of the transfused RBCs is common and, if excessive, can be responsive to IVIG.

Refractory AIHA can be difficult to manage, with no consistently effective treatment options. Splenectomy can decrease hemolysis but is less effective than in management of ITP. An alternative therapeutic approach is chemoimmunotherapy with regimens such as rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), which combine drugs with single-agent efficacy in the management of AIHA. Despite a lack of published trials, our experience suggests that this therapy is frequently effective.

**ITP** Treatment options for ITP are similar to those for AIHA. Therapy can be initiated with corticosteroids and IVIG or anti-IgD (in nonsplenectomized patients) for short-term control of thrombocytopenia. In patients with refractory disease, oral high-dose dexamethasone (40 mg/day for 4 days) can be effective. Steroid-sparing agents can be used for patients requiring long term high-dose steroid therapy in a manner similar to AIHA. There are also case reports and small case series suggesting that rituximab is effective therapy for ITP in CLL.<sup>42,45,46</sup> Splenectomy is more effective in the management of ITP than AIHA in CLL. In our experience, patients with refractory ITP can be treated with R-CVP with some good results.

**PRBCA** The low incidence of PRBCA makes study of treatment response more difficult than for AIHA or ITP in CLL patients. Corticosteroids are effective but require prolonged high-dose therapy.<sup>9</sup> Use of steroid-sparing agents such as cyclosporine is therefore often required. Response should be monitored by measuring the absolute reticulocyte count, which usually increases within 2–3 weeks of initiation of therapy. Increases in hemoglobin level can take up to 1 month to be detected.

The duration of therapy needs to be individualized for each patient and immunosuppression can be decreased slowly over a period of months, although low-level maintenance therapy is usually required. There are reports of successful treatment of patients with CLL and PRBCA with rituximab<sup>47-49</sup>; however, the perceived success rate is less than that for AIHA or ITP, most likely because only about 50% of patients have a humorally mediated autoimmune process.

**AIG** There is very limited experience with management of this complication. Immune suppression has been successful in a few patients.

#### *Treatment of Autoimmune Complications in Patients in Whom Therapy for CLL Is Indicated*

There is no standard therapy for patients with both autoimmune cytopenia and progressive CLL. Although monotherapy with purine analogs increases the risk of autoimmune complications, this increased risk has not been observed with the use of chemoimmunotherapy regimens including purine analogs and rituximab.<sup>50-52</sup> Alternative immunochemotherapy regimens that do not include a purine analog, such as R-CVP, are also effective in our experience. Further research is required to determine the optimal treatment regimen.

Management of therapy-related autoimmune cytopenias associated with use of purine analogs presents a difficult challenge with little data to guide decisions on therapy. Re-challenge with purine analog-containing immunochemotherapy has been described but is not shown to be safe for all patients. Patients with minimal or no residual CLL can be treated for their autoimmune cytopenias with immunosuppression or rituximab. Further treatment of the CLL could use non-purine analog-based therapies. The role of alemtuzumab in these patients is also controversial.

## Conclusion

Autoimmune cytopenia can complicate all stages of CLL and can cause severe morbidity and mortality. Accurate and early diagnosis of the autoimmune cytopenia is important for optimal management. Therapy depends on the clinical severity of the cytopenia and CLL. Appropriate therapy can be highly effective but is rarely curative. All patients require careful long-term follow-up and early intervention for relapse.

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