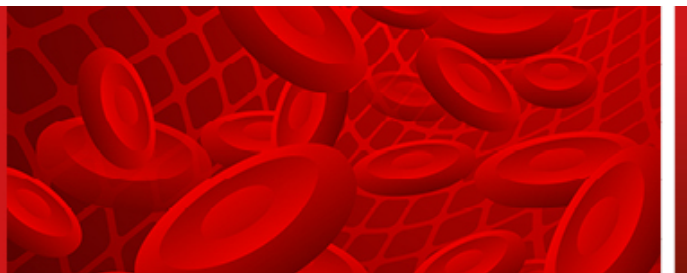


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REVIEW ARTICLE

Atypical immunophenotype of chronic lymphocytic leukemia

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Abstract

Assessment of the immunophenotype plays a crucial role in the diagnostic process of chronic lymphocytic leukemia (CLL). The expression of CD5, CD19 and CD23 antigens with a concomitant reduction or lack of surface immunoglobulin expression as well as CD22 and CD79b antigens is the basic part of CLL diagnosis. A significant diagnostic challenge is atypical CLL with cells devoid of CD5 or CD23 antigens. The assessment of additional antigens in flow cytometry, especially the CD200 glycoprotein, may facilitate the process of differential diagnosis of atypical CLL from other B-cell lymphoproliferative neoplasms. The results of current studies analyzing the influence of atypical CLL on prognosis are inconclusive. The analysis of a large group of patients with atypical CLL is difficult because of the rare occurrence of CD5(-) or CD23(-) CLL and the misdiagnosis of this disease as other B-cell lymphoproliferative neoplasms.

The following paper aims to show how important it is to include atypical CLL in the diagnostic process of this disease and to re-standardize the commonly used immunophenotypic scales for its diagnosis.

Key words: CLL, atypic CLL, CD5 antigen, CD23 antigen, CD200 antigen

Introduction

Chronic lymphocytic leukemia (CLL) is a lymphatic system neoplasm characterized by a proliferation of small, mature lymphocytes and their accumulation in peripheral blood, bone marrow and lymphatic organs [1, 2]. CLL is the most common lymphoid malignancy in Western Europe and North America. The cumulative incidence of CLL is 4.2 per 100,000 people.

The disease mainly affects the elderly, and is twice as common in males as in females. The heterogenic course of the disease encourages the search for prognostic factors which would aid the selection of the most effective individual therapy for each patient. In clinical practice, there is remarkable morphological, cytogenetic and immunophenotypic differentiation of leukemia cells in CLL patients [3–7]. Taking into consideration the phenotype of neoplastic lymphocytes in CLL, a classification has been made that differentiates the classical from the atypical form of the disease.

The typical form is characterized by both the expression of antigens CD5, CD19, CD23 and the lack of expression of immunoglobulins and antigens CD22 and CD79b [8, 9]. The atypical form however, differs from the typical one in the expression of one or fewer surface antigens and, at the same time, without any criteria met for a diagnosis of another B-cell lymphoproliferative disorder. Interestingly, a different CLL phenotype can affect the clinical course of the disease, the duration of progression-free survival, and overall survival. Furthermore, an association between CLL's immunophenotype and some specific cytogenetic disorders has been suggested, which may also affect prognosis [5, 10]. Therefore, researching new markers of the disease, or modifying the interpretation of existing ones, is crucial in clinical practice. The significance of these studies is emphasized in the light of current knowledge showing that 13% of primary diagnoses of lymphoproliferative disorders are altered during the diagnostic process.

The aim of this article was to summarize the data concerning the types of CLL with atypical immunophenotype, as well as to discuss a methodology that could be useful for differential diagnosis from other B-cell lymphoproliferative disorders.

Assessment of immunophenotype in CLL

In recent years, the Matutes Score, and its subsequent modification the Moreau Score, have been used as the basis for immunophenotypic diagnosis of CLL, as well as for differential diagnosis including CLL and other B-cell neoplasms (Table 1). The Matutes Score includes

typical CLL markers such as CD5, CD23, CD22, FMC7 and SmIg [11], while the Moreau Score additionally encompasses CD79b expression without expression of CD22 [12]. Achieving at least 4 points in both the Matutes and Moreau Scores is characteristic for the immunophenotype in typical CLL. If the score is 3 points or less, this indicates a diagnosis of a B-cell neoplasm other than CLL.

However, none of the classifications mentioned enables an appropriate differential diagnosis of the atypical form of CLL from other B-cell lymphoproliferative disorders.

Table 1. Score for a typical chronic lymphocytic leukemia (acc. to [11, 12])

Marker	Matutes Score
CD5	+
CD23	+
FMC7	–
CD22	Weak expression/–
SmIg	Weak expression
	Moreau Score
CD5	+
CD23	+
FMC7	–
CD79b	Weak expression/–
SmIg	Weak expression

CD5-negative CLL

CD5 antigen is a protein expressed on the surface of normal T lymphocytes and in a subset of B-cells known as B-1a [13]. Although the role of CD5 is unknown, the expression of this antigen has a major impact on the pathogenesis of some disorders. Population of CD5-positive (CD5+) B lymphocytes associated with the immune system overreaction has been found in some autoimmune diseases such as rheumatoid arthritis and lupus erythematosus [14, 15].

Expression of CD5 is a crucial marker in differential diagnosis of B-cell lymphoproliferative disorders, particularly CLL [14]. The presence of this antigen on the surface of neoplastic cells in flow cytometry is one of the most important elements of the diagnostic process of CLL. This protein is observed in 95% of CLL patients. CLL without expression of the CD5 antigen was first discovered in the 1990s [14]. In the light of this,

making a differential diagnosis of CD5-negative (CD5⁻) CLL and other CD5⁻ lymphoproliferative disorders such as splenic marginal zone lymphoma, lymphoplasmatic lymphoma, hairy cell leukemia, or follicular lymphoma, seems to pose a significant challenge [14].

Interestingly, the results of recent studies indicate differences between the clinical course of CD5⁻ CLL and CD5⁺ CLL. Recently, Cartron et al. presented the results of a clinical analysis of 42 patients with CD5⁻ CLL compared to a group of 79 patients with typical CD5⁺ CLL. In the CD5⁻ cohort, newly diagnosed patients presented lymphadenopathy less frequently, but splenomegaly more frequently [14]. Efsathiou et al. [15] showed that in patients with CD5-negative CLL, lymphadenopathy, splenomegaly and autoimmune hemolytic anemia were observed less frequently compared to patients with CD5⁺ CLL. Moreover, the disease was less advanced among patients with newly diagnosed CD5⁻ CLL, and their median survival was significantly longer (97.2 vs. 84 months) [15].

However, a correlation between the occurrence of an atypical immunophenotype and a better prognosis has not been confirmed in other studies. Romano et al. analyzed a cohort of 400 CLL patients including 13 patients with a CD5⁻ phenotype. In this study, no significant differences in clinical course and survival were observed, regardless of the immunophenotype of CLL cells [16]. Furthermore, Kurec et al. [17] showed that newly diagnosed patients with CD5⁻ CLL had a lower level of hemoglobin, a higher disease stage in Rai's classification, and a worse prognosis (five-year survival rate among CD5⁻ and CD5⁺ patients: 55% and >90%, respectively). Only autoimmune complications were observed less frequently in the CD5⁻ CLL cohort [17]. However, the authors noted that the increased rate of these complications in the group of patients with typical CLL might be associated with a higher percentage of patients with a more advanced stage of the disease in their cohort [17].

A crucial aspect of the diagnostic process in CLL is to set an unambiguous definition, determining the exact percentage of neoplastic CD5⁺ cells that would allow for a diagnosis of an atypical CLL. So far, in most publications, authors have assumed that the presence of less than 5% of leukemic cells with CD5 antigen allows for a diagnosis of CD5⁻ CLL [14, 15, 17].

However, Friedman et al. [18] analyzed the correlation between mean fluorescence intensity of the CD5 antigen in a population of leukemic cells and a clinical course of the disease in a group of 423 patients suffering from CLL. It was shown that high MFI rate correlates with longer progression-free survival.

Therefore, it appears worth considering not only the **expression** of CD5 protein in CLL, but also its **intensity**.

CD23-negative CLL

The CD23 antigen is a surface glycoprotein and one of the most valuable markers used in the identification of neoplastic CLL cells. It is the low-affinity receptor for IgE, and is found on resting mature B cells as well as some activated ones. CD23 takes part in the process of activation and proliferation of normal B lymphocytes [19]. Moreover, it plays an important role in the pathogenesis of B-CLL. It has been proven that higher expression of its isotypes, CD23a and CD23b, results in having a protective and proliferation stimulating effect on neoplastic B-cells, respectively [20]. Co-expression of CD23, CD5 and CD19 forms a basis of classical CLL diagnosis. The presence of CD5 and CD19, combined with the absence of CD23 however, is characteristic for MCL [21].

Keeping in mind the existence of atypical immunophenotype in both disorders (CD23⁻ in CLL and CD23⁺ in MCL), Barna et al. [22] undertook to establish a threshold of CD23 expression and MFI in differential diagnosis of the aforementioned diseases. In their study, they observed a correlation between high levels of CD23 expression (>92.5%) and/or high MFI (>44.5) and a diagnosis of CLL. At the same time, a lower expression and lower MFI were found to correlate with a more frequent MCL diagnosis. Expression oscillating between 30% and 92.5% and MFI <44.5 were observed in both CLL and MCL. The authors themselves pointed out that in these cases it is essential to include cytogenetic evaluation so that the final diagnosis can be made [22].

The potential connection between the levels of CD23 expression and the prognosis for, as well as the survival rate of, patients suffering from CLL, is drawing increasing attention. Yet so far, the results are ambiguous [10, 19, 23, 24].

Juriscic et al.'s study [19] can serve as an example. They analyzed a group of 77 patients newly diagnosed with CLL. Their analysis focused on finding a possible correlation between the level of expression of CD23 antigen and the clinical course of the disease. A correlation between a lower level of CD23 expression and the amount of peripheral blood lymphocytes was observed. Nevertheless, this correlation was found only in patients whose lymphocytosis exceeded $100 \times 10^9/l$. Furthermore, the group of patients whose CD23 expression was over 40% achieved a longer overall survival compared to those whose CD23 expression was below 40% (92.8 months vs. 35.3 months). Moreover, patients suffering from

CLL with a higher CD23 expression also achieved longer progression-free survival, which is an important prognostic factor [19].

Furthermore, Kriston et al. [10] found that coexistence of low CD23 expression and high CD20 and CD38 expression correlated significantly with the presence of trisomy 12, which is a crucial poor prognosis factor. As the authors suggest, the reduction of CD23 isotypes expression, along with trisomy 12, can even be regarded as a first step to Richter's transformation [10].

Despite the growing interest in this subject, there remains insufficient data to enable a detailed description of the correlation between CD23 expression and CLL clinical course. The abovementioned articles unequivocally depict the correlation's presence, yet it is vital to continue research into the effects of diverse CD23 expression, as well as other typical CLL antigens.

Differentiating atypical CLL forms from other B-cell neoplasms on basis of immunophenotype

Due to diagnostic problems in the process of differentiating atypical CLL forms from other lymphoproliferative disorders such as MCL or HCL, the necessity to include new antigens in immunophenotyping has been strongly emphasized in recent years.

The surface glycoprotein CD200 is a critically important antigen in differentiating atypical forms of CLL (especially CD23- CLL) and MCL. In El Din Fouad et al.'s study [26], all patients suffering from CLL with an atypical immunophenotype tested positive for CD200 expression. Moreover, some authors consider the lack of CD200 expression in mature B-cell neoplasms, together with a CD5 presence, as being sufficient to exclude CLL from differential diagnosis [25]. The confirmation of CD200 antigen's significance in differential diagnosis, including atypical CLL, can be seen in the results of studies in which 840 patients in total were observed. In all CLL cases, CD200 expression was confirmed. Conversely, only 10% of patients diagnosed with mantle cell lymphoma (MCL) presented CD200 expression [26]. Likewise, in Lesesve et al.'s study [26], among 69 patients diagnosed with CLL, 83% had CD200+ expression. Moreover, the authors also analyzed CD160 antigen expression as a helpful tool in differential diagnosis of neoplasms deriving from B-cell lymphocytes.

Li et al. in turn described the role of CD43 and CD180 antigens in the process of differentiating atypical CLL from other lymphoproliferative disorders deriving from mature B-cells. CD5- and CD23- CLL forms were given particular attention. Through modification

of the Moreau Score (excluding CD5 and CD23 and including CD43 and CCD180 at the same time), the researchers managed to achieve greater sensitivity in detecting CD5–/CD23– CLL of up to 79.4%, compared to 41.2% of cases detected using the classical Moreau Score [12].

Romano et al. [16] analyzed the immunophenotype of patients suffering from CD5– CLL. The results showed expression of surface glycoproteins, such as CD95, CD69, CD23, CD25, CD80 and CD20, distinct from a typical one, which might be applicable, while differentiating between CD5– CLL and other lymphoproliferative disorders devoid of the CD5 antigen [16]. Figure 1 and Table 2 illustrate an example of the diagnostic pattern in the process of differential diagnosis of CD5– and CD23– CLL from other lymphoproliferative B-cell neoplasms.

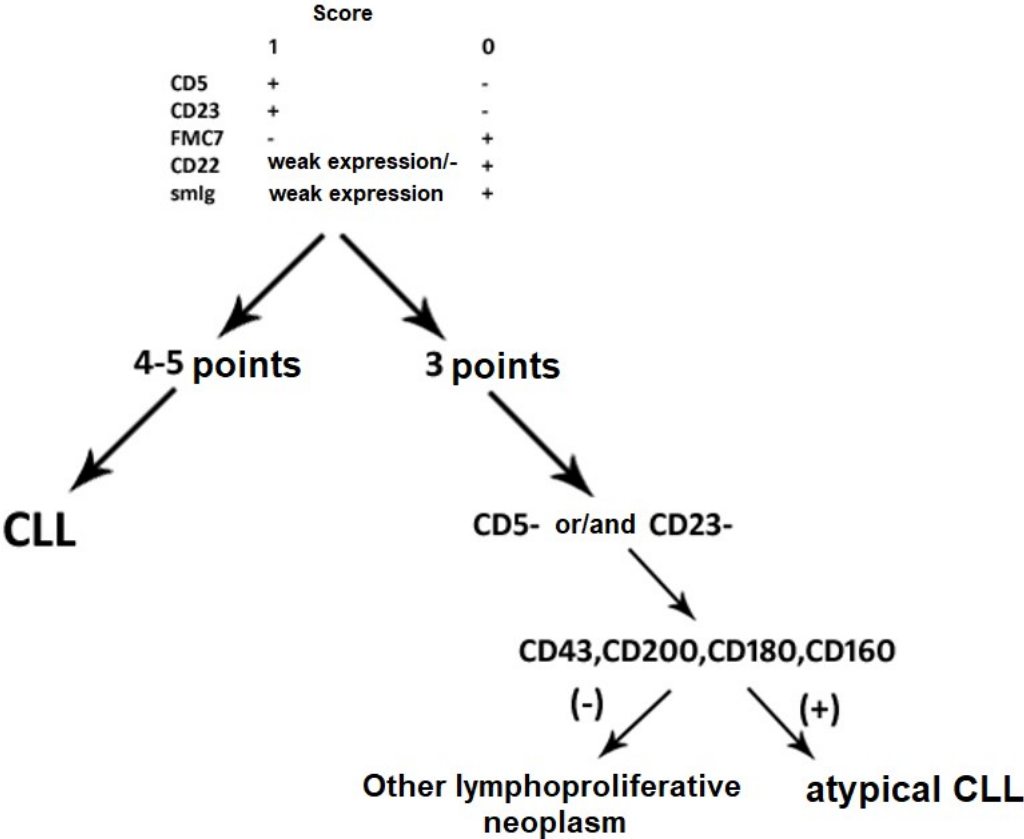


Figure 1. Possible diagnostic pattern in patients with atypical chronic lymphocytic leukemia (CLL) suspicion (based on Matutes Score [11], Table 1)

Table 2. Differential diagnosis of atypical CD5– and CD23– chronic lymphocytic leukemia (CLL) from other B-cell lymphatic system neoplasms

Lymphatic B-cell neoplasm	Antigens					
	CD19 CD20 CD22	CD23	CD5	CD10	CD11c	CD43
CLL	+	+	+	–	–/+	+
CD5– CLL	+	+	–	–	–/+	+
CD23– CLL	+	–	+	–	–/+	+
LPL	+	–	–	–	–/+	+/-
MCL	+	–	+	–/+	–	+
FL	+	–	–	+/-	–	–
SMZL	+	–	–	–	+/-	+/-
HCL	+	–	–	–	+	–
DLBCL	+	–	–/+	–/+	–	–

LPL — lymphoplasmacytic lymphoma; MCL — mantle cell lymphoma; FL — follicular lymphoma); SMZL — splenic B-cell marginal zone lymphoma; HCL — hairy cell leukemia; DLBCL — diffuse large B-cell lymphoma

Summary

Immunophenotyping is an indispensable element of the CLL diagnostic process. So far, no pathognomonic factor enabling us to determine a diagnosis has been found. In addition, attempts are still being made to establish an international agreement as to the markers essential to determine a diagnosis of CLL.

In the light of the studies pertaining to diagnostic difficulties in lymphoproliferative disorders, including CLL, it seems crucial to verify the existing scales and definitions in regards to the immunophenotype. Finding a correlation between these aspects and the clinical course of the neoplasm is also of paramount importance.

Authors' contributions

All authors participated equally in creating, editing and accepting this article.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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