**Advances in the Diagnosis of Chronic Lymphoid Neoplasms in Côte d'Ivoire: Toward Improvement**

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| **ABSTRACT**  This study aims to provide a comprehensive overview of Chronic Lymphoproliferative Disorders (CLPDs) in Côte d'Ivoire, focusing on recent advancements in diagnostic techniques to improve patient management. The study characterizes CLPDs in Côte d'Ivoire, highlighting advancements in diagnostic methods that may enhance patient care. A cross-sectional study was conducted, including 51 patients with lymphocytosis >5000/mm³. Cytological and immunophenotypic analyses were performed using flow cytometry to identify and classify CLPDs. The results showed that among the 51 cases of CLNs identified, B-cell proliferations accounted for 82%, while T-cell proliferations constituted 18%. Chronic lymphocytic leukaemia (CLL) was predominant. Immunophenotyping revealed distinct marker profiles, enabling subtype differentiation. While cytology remains relevant, emphasis was placed on integrating immunophenotyping and molecular techniques for accurate diagnosis. The combination of flow cytometry with other molecular biology techniques has been recognized as a significant advancement in the field. Further integration of cytogenetics and molecular biology aims to refine diagnostic accuracy and treatment strategies.  **Keywords**: Chronic lymphoid neoplasms, immunophenotyping, flow cytometry, haematology, Côte d'Ivoire. |

1. INTRODUCTION

Chronic Lymphoproliferative Disorders (CLPDs) are a heterogeneous group of disorders characterized by the uncontrolled proliferation of mature lymphocytes at various stages of differentiation (Justiz et al., 2023). These conditions are identified by their clinical, immunophenotypic, and molecular profiles, making precise diagnosis and classification essential for the optimal management of patients. Initially, the diagnosis of CLPDs relied on histological analysis; however, this approach has evolved significantly with the integration of immunological data from flow cytometry, as well as conventional and molecular cytogenetics, including fluorescence in situ hybridization (FISH). Advances in modern molecular biology, particularly next-generation sequencing (NGS), have enhanced our understanding of the lymphomagenesis mechanisms, offering new perspectives for patient care (Rodríguez-Vicente et al., 2017).

In Côte d'Ivoire, the primary diagnostic modality for CLPDs remains cytology, which provides critical insights into cellular morphology. However, its limitations in terms of specificity hinder the ability to differentiate between various lymphoproliferative disorders (Sawadogo et al., 2014). On the other hand, immunophenotyping, a precise diagnostic tool that identifies specific markers, enables more accurate characterization of lymphocytosis. Despite its potential, the integration of immunophenotyping into routine practice in Côte d'Ivoire faces financial, technical, and logistical challenges. This study aims to characterize various CLPDs using flow cytometry.

2. material and methods

**Study Design and Setting**

This descriptive cross-sectional study was conducted in collaboration with Longchamps, CeDReS, and Cerba laboratories from January 2023 to October 2024.

**Study Population**

A total of 51 patients with lymphocytosis exceeding 5000/mm³, which had persisted for a period of more than three months were included in the study. We obtained their informed consent after explaining the aims and requirements of the study.

**Inclusion Criteria**

All patients with lymphocytosis greater than 5000/mm³ who had also undergone immunophenotyping were included.

**Exclusion criteria**

All patients with hyperlymphocytosis greater than 5000/mm3 without immunophenotyping results.

**Sample Collection and Analysis**

Four to five milliliters of peripheral blood was collected in EDTA tubes according to standard laboratory protocols to maintain cellular integrity for cytological analyses and lymphocyte typing.

**Haematological Analysis**

Complete blood counts were conducted using a Sysmex XN 550® haematology analyzer (Sysmex, Japan) to quantify blood components and assess the leukocyte differential. Lymphocytosis was verified through a subsequent complete blood count.

**Cytological Examination**

Cytological analyses were performed on blood smears stained using May-Grünwald-Giemsa (MGG) or RAL 555 techniques. RAL 555 constitutes an alternative to the May-Grünwald-Giemsa (MGG) dye. It is employed on account of its reproducibility, simplicity and speed. The colouring time is 15 seconds. Morphological characteristics of CLPDs, including cell size, shape, cytoplasmic and nuclear features (such as nuclear shape, chromatin density, and the presence of nucleoli), were analyzed using an optical microscope with bright-field illumination.

**Flow Cytometry Immunophenotyping**

Lymphocyte immunophenotyping was conducted using a FACS Lyric® cytometer (Becton Dickinson, USA). A panel of monoclonal antibodies targeting differentiation antigens (CD markers) and conjugated with fluorochromes such as Allo-Phyco-Cyanine (APC), Peridinin-Chlorophyll-Protein Complex (PerCP), Fluorescein Isothiocyanate (FITC), and Phycoerythrin (PE) was employed to characterize the proliferative cell lineages. Clonality was assessed using CD19/Kappa and CD19/Lambda markers for B-cell proliferations and TCRαβ/TCRγδ markers for T-cell proliferations. Identification of proliferative lineages was facilitated by the use of specific markers, including CD19, CD5, CD22, CD20, CD23, CD79b, CD38, FMC7, CD11c, and CD10 for B cells, as well as CD5, CD3, CD7, CD25, CD4, CD8, CD56, and CD57 for T cells.

**Matutes Scoring**

The Matutes score is an evaluation system used in analyzing chronic B-cell neoplasms. It assigns assigns one point for the presence of CD5, CD23, weak surface immunoglobulin expression (IgS: kappa or lambda), and absent or weak FMC7 expression.

**Statistical Analysis**

Data were collected using structured survey forms and analyzed in Excel. Quantitative variables were expressed as means ± standard deviations, while qualitative variables were presented as percentages. The findings were interpreted according to the World Health Organization (WHO) diagnostic criteria for CLNs.

3. results and discussion

In this study, 51 cases of chronic lymphoid neoplasms were identified, demonstrating a male predominance with a sex ratio (M/F) of 1.4. The mean age of the patients was 57.02 years, with a range of 25 to 84 years. The most common clinical manifestations were lymphadenopathy and splenomegaly, observed in 43% and 25% of patients, respectively.

From a haematological perspective, complete blood count analysis revealed lymphocytosis, with an average lymphocyte count of 90,746/mm³ (reference range: 5,205–494,190/mm³). Notably, 53% of patients exhibited lymphocyte counts exceeding 50,000/mm³, while 52% had counts surpassing 100,000/mm³. Cytological examination revealed a monomorphic population of lymphocytes in blood smears, characterized by mature lymphocytes with variable features. Predominantly, these cells were small to medium in size, with a thin basophilic cytoplasmic rim, large nuclei containing dense chromatin, and nuclear shadows (Gumprecht shadows). Additionally, atypical lymphocytes were identified, including monocytoid cells, prolymphocytes (which featured prominent nucleoli), cloverleaf-shaped nuclei, and vacuolated cytoplasm.

Immunophenotyping by flow cytometry identified a population of mature cells characterized by strong CD45 fluorescence. The mean CD45+ cell count was 87,000/mm³ (± 70,086). B-cell monoclonality was predominant, with kappa light chain clonality detected in 63% (26 out of 42) of cases. Regarding T-cell proliferations, all cases expressed CD3+ and CD4+ markers and were of the TCRαβ subtype. All these data are summarized in Table 1. Overall, 82% (42 cases) were classified as B-cell proliferations, while 18% (9 cases) were identified as T-cell proliferations.

**Table 1:** Summary of marker expression and statistical parameters

| **Population of cells expressing the marker/mm3** | **Mean** | **Standard Deviation** | **Minimum** | **Maximum** | **Count** |
| --- | --- | --- | --- | --- | --- |
| CD45 | 85 414.91 | 70 086.78 | 312.3 | 479 364.3 | 51 |
| CD19+ Light Chains Kappa | 73 979.57 | 78 108.21 | 0 | 404 928.00 | 26 |
| CD19+ Light Chains Lambda | 12 289.05 | 18 930.31 | 0 | 187 138.22 | 9 |
| Absence of Light Chains | - | - | - | - | 7 |
| CD3 TCR αβ | 25 560.75 | 17 259.42 | 0 | 83 015.8 | 9 |
| CD3 TCR δγ | 208.26 | 194.04 | 0 | 928.74 | 0 |

B proliferations were dominated by chronic lymphocytic leukaemia, as shown in the following.

fig .1 Pie chart showing the different types of chonic lymphoid neoplasia

CLL: chronic lymphocytic leukaemia; MZL: marginal zone lymphoma/MZL/LLP: marginal zone lymphoma or lymphoplasmacytic lymphoma; SMZL –Splenic Marginal Zone Lymphoma/ML: mantle cell lymphoma.

As shown in Table 2, most CLPDs were diagnosed as chronic lymphocytic leukaemia (CLL), characterized CD19+, CD5+, CD23+, CD79b-, FMC7-, and low surface immunoglobulin. Notably, four CLL cases lacked CD5 expression, and another four cases exhibited a lack of surface immunoglobulin expression.

**Table 2:** Marker expression by chronic lymphoid neoplasm type

| **Marker** | **CD19+** | **CD5+** | **CD23+** | **CD79b-** | **FMC7-** | **Light chains +/-** | **CD200+** | **CD180+** | **CD43+** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Positive Expression | 20 | 16 | 20 | 18 | 18 | 16 | 20 | 20 | 20 |
| Negative Expression | 0 | 4 | 0 | 2 | 2 | 4 | 0 | 0 | 0 |

Additionally, marginal zone lymphomas or lymphoplasmacytic lymphomas were identified by the absence of CD5, CD23, CD11c, and FMC7 markers. T-cell proliferations consisted of three distinct syndromes: three of Sezary cell type, one case of adult T-cell leukaemia-lymphoma (ATL) type, one case of large granular lymphocytic leukaemia, and three cases of undetermined T proliferation. CD3 T lymphocyte proliferation was also noted with the following markers: CD45, CD3-, TdT-, CD4+/-, CD8-, CD2+, CD5+, CD7+, CD56-, CD57-, CD25-. The summary of cytological and phenotypic criteria is presented in Table 3 below:

**Table 3:** Cytological and immunophenotypic characteristics of Chronic Lymphoproliferative Disorders (CLPDs)

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| --- | --- | --- | --- | --- | --- |
|  | | **Cytological Characteristics** | **Immunophenotypic Markers** | | |
| **Subtypes of B-Cell Chronic Lymphoid Neoplasms (B-CLNs)** | | | | | |
| **Chronic Lymphocytic Leukemia (CLL)** | | Small-to-medium mature lymphocytes with a thin basophilic cytoplasmic rim. | CD5+, CD23+, FMC7-, CD79b-, CD10-, CD20+, CD180+, CD200+, CD43+, CD11c+/-, CD22- | | |
| Large nuclei with dense, occasionally cracked chromatin and nuclear shadows (Gumprecht shadows).  Lymphocytes occasionally grouped in clusters of 4–6 cells | CD5-, CD23+, FMC7-, CD79b-, CD10-, CD20+, CD180+, CD200+, CD43+, CD11c+/-, CD22-. | | |
| **Marginal Zone Lymphoma (MZL)** | | Atypical lymphocytes (monocytoid type) of medium size, with variable cytoplasmic characteristics.  Fine cytoplasmic villosities, sometimes polarized.  Medium-sized nuclei with irregular contours and dense chromatin. | CD5-, CD23-, FMC7+, CD79b+, CD10-, CD20+, CD180+, CD200-, CD43-, CD11c+, CD22+. | | |
| **Marginal Zone Lymphoma/Lymphoplasmacytic Lymphoma (MZL/LPL)** | | CD5-, CD23-, FMC7+, CD79b+, CD10-, CD20+, CD180+, CD200+/-, CD43-, CD11c+, CD22+. | | |
| **Splenic Marginal Zone Lymphoma (SMZL)** | | CD5-, CD23-, FMC7+, CD79b+/-, CD10-, CD20+, CD180+, CD200-, CD43-, CD11c+, CD22-, CD103+. | | |
| **Mantle Cell Lymphoma (MCL)** | | Atypical lymphocytes with irregular shapes, monomorphic "blastic" variants | CD5+, CD23-, FMC7+, CD79b+, CD10-, CD20+, CD180-, CD200-, CD43-, CD11c-, CD22-. | | |
| **Subtypes of T-Cell Chronic Lymphoid Neoplasms (T-CLNs)** | | | | | |
| **Sézary Syndrome** | Atypical medium-sized lymphocytes with moderately abundant cytoplasm  Cerebriform nuclei resembling Sézary cells with mottled chromatin. | | | CD3+, CD4+, CD5+, CD2+, CD8-, CD7-, CD10-. |
| **Adult T-Cell Leukemia/Lymphoma (ATL)** | Polymorphic lymphocyte population of varying sizes with moderately abundant basophilic cytoplasm.  Highly irregular, multilobed, or "flower-shaped" nuclei with dense chromatin. | | | CD3+, CD4+, CD5+, CD2+, CD8-, CD7-, CD10-, CD25+, CD16-, CD56-, CD57-. |
| **Large Granular Lymphocyte Leukemia (LGL)** | Atypical medium-sized lymphocytes with moderately abundant basophilic cytoplasm, sometimes with vacuoles.  Medium-sized nuclei with dense chromatin. | | | CD3+, CD4+, CD5+, CD2+, CD8-/-, CD7-, CD10-, CD16+, CD57+, CD56+. |

The ability to distinguish between different types of haematological malignancies has always been fundamental to effective diagnosis and therapeutic decision-making. Initially based on morphological examination, the classification of lymphoid neoplasia has gradually expanded to include new immunological, cytogenetic, and molecular criteria. While cytology does not provide an absolute determination of the type of lymphoid neoplasm, it serves as an essential diagnostic orientation tool. Consequently, immunophenotyping has become a critical component in the diagnosis and follow-up of chronic lymphocytic leukemia (CLL). This approach enhances morphological criteria with antigenic expression criteria (Safra et al, 2013) and has facilitated significant advancements in the field. The use of multiparametric panels in conjunction with immunophenotyping via flow cytometry has become an indispensable part of the diagnostic and follow-up process for CLPDs (Mayeur-Rousse et al., 2013). The immunological profiles of CLN have been thoroughly delineated by various expert groups, aided by the classifications developed by the World Health Organization (WHO) and documented in international recommendations. In the absence of a marker that is both sufficient and specific to characterize a particular entity, the literature proposes several multiparametric diagnostic panels. The phenotypic characteristics and abnormalities observed have been extensively documented across numerous haematological malignancies. In combination with cytology, these characteristics can also be used to differentiate certain Chronic Lymphoproliferative Disorders (CLPDs). In this study, 51 cases of chronic lymphoid neoplasia were identified. The mean age of the patients was estimated at 57 ± 11 years, which is lower than the ages reported by Gokaba (63 years) (Gokaba et al., 2020), Meryeme (62 years) (Meryeme et al., 2020), Stevenson (71 years) (Stevenson et al., 2017), and Imane (70.5 years) (Imane et al., 2023), and is comparable to that of El Borgi (57 years) (El Borgi et al., 2024).

This variation may be attributed to the duration of the studies and the sample size. Furthermore, sub-Saharan African populations are characterized by low life expectancies. The male predominance (sex ratio = 1.4) aligns with findings reported in the existing literature (Troussard et al., 2013; Gokaba et al., 2020).

The study revealed significant hyperlymphocytosis, with an average of 90,746 lymphocytes/mm³ and 52% of participants exhibiting lymphocytosis greater than 100,000 lymphocytes/mm³. The current findings were superior to those documented by Imane (Imane et al., 2023) and Biovert (Biovert et al., 2017), which reported mean lymphocyte levels of 62,260/mm³ (Algeria) and 20,900/mm³ (France), respectively.

Lymphocyte immunophenotyping using flow cytometry (FPC) is an essential tool for confirming the monoclonality of B lymphocytes and differentiating chronic lymphocytic leukemia (CLL) from other B lymphoproliferative disorders (Zimmer et al., 2020).

Clonality: Kappa clonality predominated, accounting for 63% (26 out of 42) of cases. The detection of either kappa or lambda light chains confirms monotypy, with a decrease in expression indicating a reduction in the antigenic density of the B cell antigen receptor (BCR) compared to that of normal B cells. This characteristic is associated with chronic lymphoid neoplasia (Cavailles et al., 2017). Once the malignant nature of the proliferation has been confirmed, a combination of several markers is necessary to distinguish the various types of chronic lymphocytic leukaemia (CLL).

In the present study, the predominance of the following markers in defining chronic lymphocytic leukemias (CLLs) was observed: CD19, CD5, CD23, CD43, CD200, and low expression of CD79b, FMC7, CD20, and surface immunoglobulins. These results align with those previously reported by Rawstron (Rawstron et al., 2018) and Mayeur-Rousse (Mayeur-Rousse et al., 2023), who found that CLLs were characterized by the same markers across various studies. CD5 expression has been observed in all CLL cases (Sales et al., 2017). CD200 and CD23 have been identified as effective discriminators between CLL and MCL (Canton et al., 2014). The distinction between lymphocytic malignancies (LM) and CLL is predicated on the presence of CD5 expression, a feature that is nearly constant in both conditions. However, the presence of CD23 and CD200 negativity, coupled with a Matutes score of less than three, serves to differentiate between these two conditions (Gao et al., 2009; Cavailles et al., 2017). Further distinguishing features include strong expression of FMC7, CD20, and CD79b.

CD200, a surface glycoprotein that promotes immune tolerance, is expressed in CLL but is absent in lymphoma (LM), making it a valuable diagnostic marker in flow cytometry. Its application has broadened for the differential diagnosis of other lymphoproliferative disorders, although its expression can be variable (Cavailles et al., 2017). Both CLL and LM express the markers CD19, CD5, and CD43. The CD5 molecule, typically found on the surface of T lymphocytes and a minority of B lymphocytes in a normal state, is nearly always present on CLL lymphocytes. However, four cases of CLL did not express CD5. In one study, Doukoure et al. reported three cases of CLL with a lack of CD5 expression (Doukouré et al., 2023). Some authors have noted that the absence of CD5 is rare and may indicate a more aggressive form of the disease (Demir et al., 2020). MZL and LLP accounted for nearly all non-CLL NLC-Bs. These were characterized by the following markers: CD19+, FMC7+, CD79b+, CD11c+, CD10-, CD5-, and CD23-. SMZL has been observed to disseminate into the bloodstream, with cells exhibiting the potential to express CD11c and CD103, while being CD5-/CD23- (Meryeme et al., 2020; Le Garff-Tavernier et al., 2013).

This study's findings differ from previous observations. For example, 5% of LSLV cases lacked CD103 expression. Some MZL were indistinguishable from LPL due to marker specificity issues. Plasmacytic differentiation or villeous lymphocytes exclude CLL; CD43 negativity differentiates them from LM. The Matutes score in this study was ≤2. Diagnosing chronic T-cell lymphoid neoplasia requires identifying immunophenotypic and clonal abnormalities. The EuroFlow group validated TRBC1, integrating it into the LST protocol to assess clonality in NHL (Blomme et al., 2023). TRBC1 targets the β chain's constant 1 region of the human TCR (Maciocia et al., 2017; Horna et al., 2021), confirming monotypy in all patients (9 cases) in this study.

Sezary syndrome showed loss of CD7 and CD8, while expressing CD2, CD3, CD4, and CD5, consistent with earlier research (Jevremovic &al., 2019). Large granular lymphocyte leukemia expressed CD3, CD4, CD5, CD2, CD16, and CD57, repressing CD8, CD7, and CD10 (Jevremovic et al., 2019; Sandberg & al., 2006). However, the integration of multiple markers and cytological analysis did not precisely identify five B-cell proliferations and four T-cell proliferations.

**Conclusion**

While cytological analysis remains essential for diagnosing chronic lymphoid neoplasia, immunophenotyping by flow cytometry is crucial for identifying specific phenotypic profiles. However, this technique has limitations, especially with atypical phenotypes, overlapping pathologies, or low abnormal cell counts.

Flow cytometry cannot detect genetic or molecular anomalies vital for certain diagnoses, prognoses, or therapeutic decisions. Here, cytogenetics and molecular biology are complementary, identifying chromosomal abnormalities like 17p deletion or TP53 mutations and clonal rearrangements of B or T lymphocyte receptors. This integrated approach enhances the accuracy of diagnosing and managing chronic lymphoid neoplasia.

**Ethical Approval:**

Ethical approval for the study was obtained from the Ethics Committee of the Centre hospitalier universitaire (CHU) de Cocody/ Abidjan/ Côte d'Ivoire.

**Consent:**

We obtained their written informed consent after explaining the aims and requirements of the study.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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