



## Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: [www.bioscmed.com](http://www.bioscmed.com)

# Unmasking Occult Malignancy: The Pivotal Role of the Peripheral Blood Smear in the Initial Diagnosis of Chronic Lymphocytic Leukemia

Agustinus Sigit Pamungkas<sup>1\*</sup>, Enny<sup>2</sup>

<sup>1</sup>General Practitioner, Dr. Agoesdjam Regional General Hospital, Ketapang Regency, Indonesia

<sup>2</sup>Department of Clinical Pathology, Dr. Agoesdjam Regional General Hospital, Ketapang Regency, Indonesia

### ARTICLE INFO

#### Keywords:

Chronic lymphocytic leukemia  
Lymphocytosis  
Peripheral blood smear  
Resource-limited setting  
Smudge cells

#### \*Corresponding author:

Agustinus Sigit Pamungkas

#### E-mail address:

[a.s.pamungkas.as@gmail.com](mailto:a.s.pamungkas.as@gmail.com)

All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/bsm.v9i8.1363>

### ABSTRACT

**Background:** Chronic lymphocytic leukemia (CLL) is a common hematologic malignancy in adults, frequently discovered incidentally through routine blood tests due to its often nonspecific clinical presentation. In resource-limited settings, fundamental laboratory investigations are crucial for initiating the diagnostic pathway. This report illustrates the critical diagnostic value of the complete blood count and peripheral blood smear in identifying CLL in a patient presenting with vague constitutional symptoms. **Case presentation:** A 43-year-old female with a history of type 2 diabetes mellitus presented to a rural hospital with a one-month history of debilitating fatigue, intermittent fever, and loss of appetite. Physical and radiological examinations were unremarkable. However, initial hematological analysis revealed marked leukocytosis (77,910/ $\mu$ L), mild anemia, and thrombocytopenia (54,000/ $\mu$ L). A peripheral blood smear was pivotal, showing an absolute lymphocytosis of 90% with mature-appearing lymphocytes, pleomorphism, and characteristic smudge cells. Following referral, definitive diagnosis was established through flow cytometry, which confirmed a clonal B-cell population (CD19+, CD5+, CD23+, dim CD20+). Bone marrow examination showed extensive infiltration, and molecular studies revealed an unmutated IGHV gene status, placing the patient in a high-risk prognostic category. **Conclusion:** This case underscores that even in the absence of advanced diagnostic facilities, a meticulous evaluation of the peripheral blood smear is a powerful and essential tool for unmasking serious underlying hematologic malignancies like CLL. It enables early suspicion, appropriate patient referral, and timely initiation of management, thereby significantly impacting patient outcomes.

### 1. Introduction

Chronic lymphocytic leukemia (CLL) represents the most prevalent form of leukemia in Western adult populations, constituting approximately 37% of all newly diagnosed leukemia cases in countries like the United States.<sup>1</sup> It is a malignancy defined by the progressive accumulation of functionally incompetent, mature-appearing monoclonal B-lymphocytes. These neoplastic cells, which characteristically co-express the CD5 antigen, proliferate and accumulate in the peripheral blood, bone marrow, spleen, and lymph nodes. The underlying pathophysiology involves

complex genetic and epigenetic alterations in lymphoid progenitor cells, leading to a disruption of normal apoptosis pathways and a subsequent clonal expansion of these aberrant B-cells.<sup>2</sup> This gradual infiltration into the bone marrow disrupts normal hematopoiesis, often culminating in cytopenias such as anemia, thrombocytopenia, and neutropenia, which define the more advanced stages of the disease. Furthermore, the dysfunctional nature of these B-cells and the associated hypogammaglobulinemia lead to significant immune dysregulation and an increased susceptibility to infections.<sup>3</sup>

The clinical course of CLL is notoriously heterogeneous. A significant portion of patients remain asymptomatic for years, and the diagnosis is often made incidentally during routine laboratory examinations performed for unrelated reasons. When symptoms do arise, they are frequently nonspecific constitutional "B-symptoms," including fatigue, unintentional weight loss, fever, and night sweats.<sup>4</sup> This vague clinical picture presents a considerable diagnostic challenge, as these symptoms overlap with a wide array of infectious, inflammatory, and other neoplastic conditions, potentially delaying diagnosis and management.<sup>5</sup> Given this clinical ambiguity, laboratory evaluation serves as the cornerstone of diagnosis. The initial diagnostic criterion, first established by the National Cancer Institute (NCI)-sponsored working group in 1988 and still a fundamental screening threshold, is a sustained absolute lymphocyte count (ALC) in the peripheral blood of greater than 5,000 cells per microliter ( $\mu\text{L}$ ).<sup>6</sup>

Over the past two decades, the diagnostic and prognostic framework for CLL has evolved significantly. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) updated its guidelines in 2018, emphasizing a multi-parameter approach that integrates hematologic findings with cellular morphology and, crucially, immunophenotyping by flow cytometry.<sup>7</sup> The demonstration of a clonal B-cell population expressing characteristic surface markers—including CD19, CD5, and CD23, with dim expression of CD20 and surface immunoglobulin—is required for a definitive diagnosis. In cases where the diagnosis remains ambiguous, or for prognostic purposes, a bone marrow aspiration and biopsy are recommended by major guideline bodies like the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO).<sup>8</sup> Furthermore, modern risk stratification now relies heavily on cytogenetic and molecular markers. Fluorescence in situ hybridization (FISH) to detect chromosomal abnormalities such as  $\text{del}(17\text{p})$  or  $\text{del}(11\text{q})$ , and sequencing to determine the mutation status of the immunoglobulin heavy-chain variable

region (IGHV) gene and the TP53 gene, are critical for predicting disease course and guiding therapeutic decisions.<sup>9</sup>

Despite these advances, access to sophisticated diagnostic modalities like flow cytometry and molecular genetics remains limited in many parts of the world, including rural regions of Indonesia. In such resource-constrained settings, healthcare providers must rely on fundamental clinical skills and basic, yet powerful, laboratory investigations. A complete blood count (CBC) and a meticulously prepared and expertly interpreted peripheral blood smear become the most critical tools in the diagnostic arsenal. The classic morphological findings of a profound absolute lymphocytosis dominated by small, mature-appearing lymphocytes with scant cytoplasm, clumped chromatin, and the presence of fragile "smudge cells" are highly suggestive of CLL and can effectively initiate the diagnostic process.<sup>10</sup>

The aim of this report is to present a case of a middle-aged woman from a rural hospital in Ketapang, Indonesia, whose nonspecific presentation of fatigue and fever led to a presumptive diagnosis of CLL based almost exclusively on the findings of her peripheral blood smear. The novelty of this case report lies in its detailed illustration of the diagnostic journey, beginning in a setting with minimal technological resources and culminating in a definitive, risk-stratified diagnosis at a tertiary referral center. It serves as a powerful reminder to clinicians in all settings, particularly in primary care and at peripheral hospitals, of the indispensable value of fundamental hematological analysis in unmasking occult malignancy and facilitating timely and appropriate patient care.

## 2. Case Presentation

In June 2024, a 43-year-old female presented to the Emergency Department of Dr. Agoesdjam Regional General Hospital in Ketapang, a rural facility in West Kalimantan, Indonesia. Her chief complaint was a profound and persistent sense of fatigue that had been progressively worsening over the preceding month.

She described the fatigue as a debilitating exhaustion that was present upon waking and was exacerbated by minimal physical or mental effort, significantly impairing her ability to perform daily activities. In addition to the fatigue, she reported experiencing intermittent, low-grade fevers, typically occurring in the evenings, which were not associated with chills or rigors. She also noted a significant loss of appetite over the same period, resulting in an unintentional weight loss of approximately 4-5 kilograms. She had previously sought consultation at a local community health center for these symptoms, but her condition had not improved with symptomatic treatment.

Her past medical history was notable for a diagnosis of type 2 diabetes mellitus, which had been managed for the past three years with oral metformin at a dose of 500 mg twice daily. She reported fair adherence to her medication. There was no personal or family history of hematologic disorders, cancer, or significant autoimmune diseases. She denied any history of recent travel, exposure to tuberculosis, or

high-risk behaviors for infectious diseases. She did not report any bleeding tendencies, such as easy bruising, petechiae, or prolonged bleeding from minor cuts.

Upon initial evaluation in the emergency department, the patient was fully conscious, alert, and well-oriented. Her vital signs were stable: blood pressure was 120/78 mmHg, pulse rate was 84 beats per minute with a regular rhythm and adequate volume, respiratory rate was 18 breaths per minute, and her body temperature was 37.2°C. Her oxygen saturation was 97% on ambient air. A comprehensive physical examination was performed and was largely unremarkable. A posterior-anterior chest X-ray was performed on the day of admission and showed no evidence of consolidation, effusion, masses, or mediastinal widening; the cardiac silhouette and pulmonary vasculature were normal (Figure 1). The key clinical and laboratory findings upon initial presentation are summarized in Table 1.

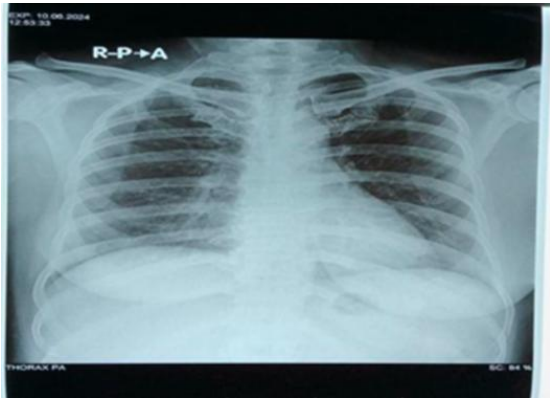


Figure 1. The initial chest X-ray showed no abnormalities.

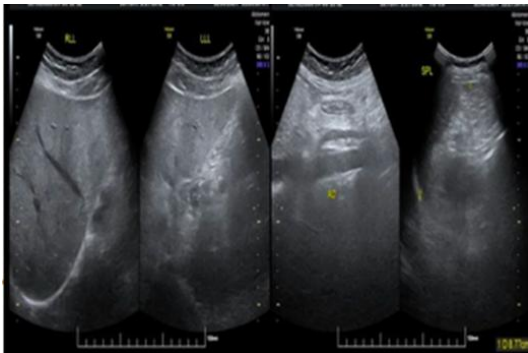


Figure 2. Whole abdomen ultrasound image showing fatty liver without evidence of organomegaly.

Table 1. Summary of patient's clinical and laboratory findings at initial presentation.

Parameter	Finding
<b>Demographics</b>	43-year-old female
<b>Presenting complaints</b>	Debilitating fatigue for 1 month
	Intermittent, low-grade fevers
	Significant loss of appetite and weight loss (~4-5 kg)
<b>Past medical history</b>	Type 2 Diabetes Mellitus, managed with Metformin 500 mg BID
<b>Vital signs</b>	BP: 120/78 mmHg; HR: 84 bpm; RR: 18/min; Temp: 37.2°C; SpO <sub>2</sub> : 97%
<b>Key physical exam</b>	No pallor, icterus, or petechiae
	No palpable lymphadenopathy (cervical, supraclavicular, axillary, inguinal)
	No palpable hepatosplenomegaly
<b>Initial radiology</b>	Chest X-Ray: No acute cardiopulmonary abnormalities (Figure 1)
	Abdominal Ultrasound: Hepatic steatosis; no organomegaly (Figure 2)
<b>Initial hematology</b>	Hemoglobin: 11.1 g/dL (Mild Anemia)
	WBC Count: 77,910/ $\mu$ L (Marked Leukocytosis)
	Platelet Count: 54,000/ $\mu$ L (Moderate Thrombocytopenia)
	Peripheral Smear (Figure 3)
<b>Initial chemistry</b>	Random Blood Glucose: 284 mg/dL
	SGOT/SGPT: Within normal limits

Due to the striking leukocytosis, a peripheral blood smear was prepared and examined. The morphological findings were pivotal, showing a profound absolute lymphocytosis of 90%. The absolute lymphocyte count (ALC) was approximately 70,119/ $\mu$ L, far exceeding the diagnostic threshold for CLL. The smear was dominated by a monotonous population of small, mature-appearing lymphocytes with scant cytoplasm, round nuclei with densely clumped chromatin, and

frequent smudge cells (Figure 3). Based on these findings, a presumptive diagnosis of a lymphoproliferative disorder, highly suspicious for CLL, was made. The patient was admitted, her blood glucose was managed, and after six days of stabilization, she was referred to Soedarso General Hospital in Pontianak for definitive workup and management.

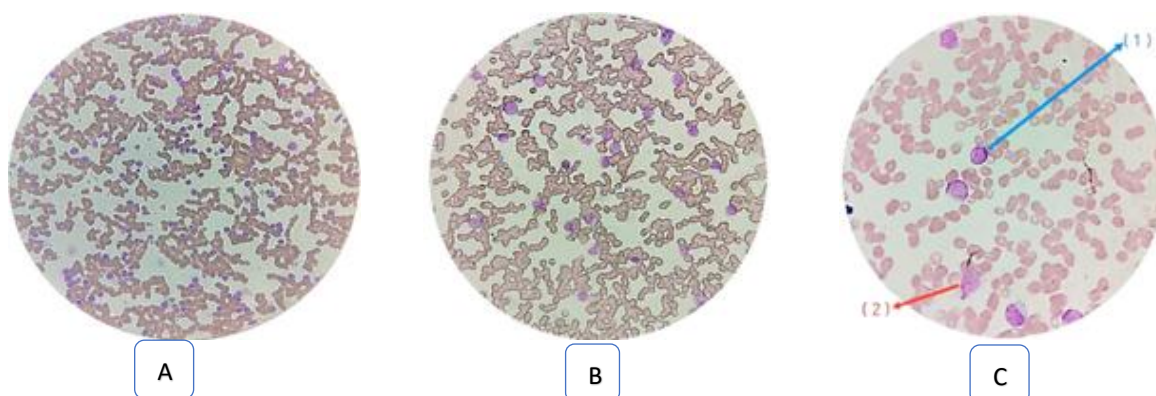


Figure 3. Peripheral blood smear evaluation. (A) Leukocytosis with a predominance of lymphoid cells (absolute lymphocytosis of 90%), 10x magnification; (B) Lymphocytosis with variable cell sizes, 40x magnification; (C) Blue arrow (1) shows nucleated lymphocytes indicating lymphocytosis, and red arrow (2) shows presence of smudge cells (+1), 100x magnification.

At the referral center, the diagnosis of CLL was confirmed. Flow cytometry of the peripheral blood revealed a monoclonal B-cell population expressing CD19, CD5, CD23, and dim CD20 with kappa light chain restriction. Bone marrow aspiration and biopsy showed a hypercellular marrow with 75% infiltration by mature lymphocytes, confirming marrow effacement as the cause of her bicytopenia. Molecular analysis was critical for prognostication, revealing an

unmutated IGHV gene status and a deletion of chromosome 13q (del(13q)) by FISH, with no evidence of del(17p) or del(11q). The patient was staged as Rai Stage IV and Binet Stage C. Given her high-risk clinical stage and adverse molecular features, a decision was made to initiate front-line therapy with a targeted regimen. The treatment plan and follow-up schedule are detailed in Table 2.

Table 2. Treatment protocol and follow-up schedule.

Phase	Details
<b>Treatment regimen</b>	<b>Acalabrutinib-based Targeted Therapy</b>
	Acalabrutinib (BTK inhibitor): 100 mg orally, twice daily.
	Obinutuzumab (Anti-CD20 antibody): Intravenous infusion.
	Cycle 1: 100 mg on Day 1, 900 mg on Day 2, then 1000 mg on Days 8 and 15.
	Cycles 2-6: 1000 mg on Day 1 of each 28-day cycle.
	Prophylaxis: Allopurinol for tumor lysis syndrome, antiviral (Acyclovir) and PCP (Trimethoprim-Sulfamethoxazole) prophylaxis initiated.
<b>Initial follow-up</b>	<b>Weeks 1-4 (Cycle 1):</b> Weekly clinical evaluation and CBC to monitor for cytopenias and treatment-related lymphocytosis. Close monitoring for infusion reactions during Obinutuzumab administration.
	<b>Month 2-6 (Cycles 2-6):</b> Clinical evaluation and CBC prior to each 28-day cycle. Monitor blood pressure, for signs of bleeding, or infection.
<b>Response assessment</b>	<b>End of Treatment (After 6 cycles of Obinutuzumab; Acalabrutinib ongoing):</b>
	Physical examination to assess for lymphadenopathy/organomegaly.
	Repeat CBC and peripheral blood smear.
	Repeat bone marrow aspiration and biopsy to assess for minimal residual disease (MRD).
<b>Long-term follow-up</b>	<b>Post-Induction:</b> Continued Acalabrutinib monotherapy indefinitely until disease progression or unacceptable toxicity.
	Clinical and laboratory follow-up every 3-6 months.
	Annual screening for secondary malignancies.

### 3. Discussion

The comprehensive evaluation of this patient provides a paradigmatic example of the diagnostic and therapeutic journey in modern hematology, a journey initiated by the most fundamental of laboratory tests. The case of this 43-year-old woman, whose vague constitutional complaints masked a life-threatening malignancy, highlights the irreplaceable value of clinical suspicion coupled with basic morphological

analysis. The subsequent confirmation and molecular dissection of her disease at a tertiary center underscore the profound shift in our understanding and management of chronic lymphocytic leukemia (CLL).<sup>9</sup> This discussion will delve deeply into the pathophysiology underlying her clinical presentation, the morphological and immunophenotypic features that defined her diagnosis, the intricate molecular landscape that dictates prognosis, and the rationale

behind the targeted therapeutic strategy ultimately employed.<sup>10</sup>

The patient's initial presentation with fatigue, fever, and loss of appetite is a textbook example of the "B-symptoms" that characterize many lymphoid malignancies. However, to the primary care physician or emergency doctor, these symptoms form a diagnostic quagmire. The pathophysiology of these constitutional symptoms in CLL is multifactorial and rooted in the complex interplay between the neoplastic B-cells and the host immune system. The malignant clone is not an inert, accumulating mass; it is an active participant in the systemic inflammatory milieu. These cells, and the reactive T-cells that surround them, produce a variety of pro-inflammatory cytokines, including Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-6 (IL-6), and interferons. TNF- $\alpha$ , in particular, is a potent pyrogen and a key mediator of cancer-associated cachexia, which directly explains this patient's fever and loss of appetite with resultant weight loss. The profound fatigue she experienced, a symptom so common it is reported by over 90% of CLL patients at some point, is more complex. It arises not only from the systemic effects of chronic inflammation and the hypermetabolic state induced by the leukemia but also directly from the developing anemia, which limits oxygen-carrying capacity. The fatigue in CLL is often described as a "central" fatigue, a sense of overwhelming lassitude that is not relieved by rest, likely mediated by the direct effects of circulating cytokines on the central nervous system.<sup>11</sup> The patient's age of 43 is notably younger than the median age of CLL diagnosis, which is approximately 70-72 years. While CLL can occur in younger adults, it is less common, and some evidence suggests that younger patients may have a distinct disease biology, sometimes associated with more aggressive features and a higher likelihood of requiring treatment sooner than their older counterparts. Her presentation with advanced-stage, symptomatic disease aligns with this observation.

In the context of this diagnostic uncertainty, the peripheral blood smear served as the "Rosetta Stone,"

translating a confusing clinical picture into a clear hematological narrative.<sup>11</sup> Its findings were not merely suggestive; they were powerfully indicative of the correct diagnosis. The three cardinal features observed were the profound absolute lymphocytosis, the specific morphology of the lymphocytes, and the presence of smudge cells.

First, the sheer number of lymphocytes was staggering. Her absolute lymphocyte count of over 70,000/ $\mu$ L is a dramatic finding. The pathogenesis of this accumulation is not primarily due to rapid proliferation, as CLL cells have a relatively low mitotic rate. Instead, the central defect is a profound failure of programmed cell death, or apoptosis.<sup>12</sup> This is most commonly driven by the massive overexpression of B-cell lymphoma 2 (BCL-2), an anti-apoptotic protein. In healthy B-cells, BCL-2 levels are tightly regulated to ensure that aging or dysfunctional cells are eliminated. In CLL, genetic and epigenetic mechanisms lead to constitutive BCL-2 overexpression, rendering the cells effectively immortal. They accumulate relentlessly in the blood, marrow, and lymphoid tissues, leading to the astronomical counts seen in this patient.

Second, the morphology was classic. The smear was dominated by a monotonous population of small lymphocytes that appeared deceptively mature. These cells are characterized by a very high nuclear-to-cytoplasmic ratio, with only a thin rim of agranular, pale blue cytoplasm visible. The nuclear chromatin is a key feature: it is not fine and dispersed like that of a lymphoblast, but rather coarsely clumped and condensed, often described as a "soccer-ball" or "checkerboard" pattern.<sup>12</sup> This appearance reflects a quiescent, non-proliferating state. While this is the typical morphology, the report of some pleomorphism and occasional larger cells with visible nucleoli is also important. These larger, more active-appearing cells are known as prolymphocytes. In CLL, the percentage of prolymphocytes is typically less than 15%. A higher percentage might suggest a transformation to a more aggressive state or a different diagnosis altogether, such as B-cell prolymphocytic leukemia (B-PLL), a

related but more aggressive disorder.

Third, the presence of smudge cells (Gumprecht shadows) provided a crucial clue. These are not intact cells but rather the naked, spread-out nuclei of lymphocytes that have ruptured during the mechanical process of creating the blood smear. For many years, they were considered simple artifacts. However, it is now understood that their presence reflects an intrinsic fragility of the CLL cell's cytoskeleton, specifically linked to lower levels of the structural protein vimentin. Their abundance is so characteristic of CLL that their absence might lead one to reconsider the diagnosis.<sup>12</sup> Interestingly, while intuitively one might think fragile cells imply worse disease, some studies have paradoxically linked a higher percentage of smudge cells to a better prognosis, possibly indicating that these clones are less robust. The notation of "+1" in this patient's report indicates they were readily identified but not overwhelmingly numerous, a typical finding.

The patient's bicytopenia—the combination of anemia (hemoglobin 11.1 g/dL) and thrombocytopenia (Platelets 54,000/ $\mu$ L)—was the direct reason for her high-risk clinical stage (Rai IV / Binet C). Understanding the mechanisms behind cytopenias in CLL is critical. In this patient, the bone marrow biopsy provided a clear answer: extensive infiltration and effacement of normal hematopoietic tissue. The marrow was hypercellular, but this cellularity was composed of malignant lymphocytes, which had physically crowded out the normal red blood cell precursors (erythroid islands) and megakaryocytes (platelet precursors).<sup>13</sup> This is a straightforward, mechanical cause of marrow failure and is the defining feature of advanced-stage CLL.

However, it is crucial for the clinician to recognize that this is not the only cause of cytopenias in CLL. The disease is also characterized by profound immune dysregulation, which can lead to autoimmune phenomena. Autoimmune Hemolytic Anemia (AIHA) and Immune Thrombocytopenic Purpura (ITP) are common complications. In AIHA, the dysfunctional immune system produces autoantibodies that target

and destroy the patient's own red blood cells, leading to anemia that can be rapid and severe. In ITP, autoantibodies target platelets, leading to their clearance by the spleen. It is possible for a patient to have cytopenias from both marrow infiltration and autoimmune destruction simultaneously. The distinction is critical because the management is different.<sup>13</sup> Marrow failure requires treatment directed at the underlying CLL to reduce the tumor burden. Autoimmune cytopenias, on the other hand, are typically treated first with immunosuppressants like corticosteroids, which may not require immediate treatment of the CLL itself. Although this patient's cytopenias were attributed to marrow infiltration, a full workup would typically include a Direct Antiglobulin Test (DAT or Coombs' test) to rule out a concomitant autoimmune hemolytic process. While the smear was highly suggestive, a definitive diagnosis of CLL in the modern era requires immunophenotyping by multiparameter flow cytometry. This technology uses fluorescently-labeled antibodies to identify specific protein markers (CD, or "cluster of differentiation" antigens) on the surface of cells. The pattern of these markers provides a unique "fingerprint" for different types of hematopoietic cells. The results from the referral center confirmed the classic immunophenotypic signature of CLL.

The finding of a clonal B-cell population positive for CD19 established the B-cell lineage. The co-expression of CD5 was the most critical finding. CD5 is typically a T-cell marker, and its aberrant expression on a clonal B-cell population is the hallmark of CLL.<sup>14</sup> Its presence is essential to differentiate CLL from most other B-cell lymphomas. The expression of CD23 is another key marker; its presence is characteristic of CLL and helps distinguish it from Mantle Cell Lymphoma (MCL), another CD5-positive B-cell malignancy that is typically CD23-negative and carries a much more aggressive clinical course. The report of "dim" expression of CD20 and dim surface immunoglobulin is also characteristic. Compared to normal B-cells, CLL cells have a lower density of these molecules on their surface, another

subtle but important clue. Finally, the demonstration of kappa light chain restriction confirmed the clonality of the population. Normal B-cells produce a mix of kappa and lambda light chains. In a malignancy, all cells arise from a single original clone and therefore all produce the exact same light chain—in this case, kappa. This skewed ratio is the definitive proof of a monoclonal, and therefore neoplastic, process.

Establishing the diagnosis is only the first step; determining the patient's prognosis is equally important, as it dictates the timing and intensity of therapy. The evaluation of this patient perfectly illustrates the tiered approach to prognostication in CLL, moving from simple clinical staging to complex molecular analysis.<sup>14</sup> The Rai and Binet staging systems, developed decades ago, remain remarkably robust and clinically useful. They are based on the simple principle that CLL progresses in an orderly fashion: starting with just lymphocytosis (low risk), progressing to enlarged lymph nodes and/or spleen/liver (intermediate risk), and finally culminating in bone marrow failure leading to anemia or thrombocytopenia (high risk). This patient's presentation with both anemia and thrombocytopenia immediately placed her in the highest risk categories: Rai Stage IV and Binet Stage C. This staging alone indicates a median survival of only a few years without effective therapy and is a clear indication to begin treatment.

However, these staging systems only capture the tumor burden. They do not capture the underlying tumor biology. Two patients can be at the same clinical stage but have vastly different outcomes based on the genetic features of their leukemia cells. This is where FISH and gene sequencing become indispensable. The FISH panel looks for large chromosomal deletions. The finding of del(13q) as the sole abnormality is the most common finding in CLL and is generally associated with a good prognosis and a long time to first treatment.<sup>15</sup> However, in this patient, this "favorable" marker was overridden by other, more powerful, adverse factors. The absence of the high-risk deletions, del(17p) and del(11q), was welcome news.

Deletion of 17p removes the master tumor suppressor gene, TP53, leading to a very aggressive disease that is resistant to conventional chemotherapy. Deletion of 11q removes the ATM gene, another key DNA damage repair gene, and is also associated with a poor prognosis.

The most critical prognostic finding in this patient was her IGHV gene mutation status. This is arguably one of the most powerful prognostic markers in CLL. It divides CLL into two fundamentally different biological subtypes. During their normal development, B-cells undergo a process called somatic hypermutation in their immunoglobulin heavy-chain variable region (IGHV) genes to generate high-affinity antibodies.<sup>16</sup> If the cell of origin for CLL has gone through this process, the leukemia is termed "IGHV-mutated" CLL. These patients typically have a more indolent, slowly progressing disease. If the cell of origin is a more primitive B-cell that has not undergone this maturation step, the leukemia is termed "IGHV-unmutated" CLL. This patient's unmutated status is a major adverse prognostic factor. IGHV-unmutated CLL is associated with a more aggressive clinical course, a shorter time from diagnosis to first treatment, and poorer overall survival. It is now understood that this is because the B-cell receptor (BCR) on the surface of unmutated CLL cells is more responsive to stimulation, leading to signals that promote cell survival and proliferation. This biological difference is the key reason why IGHV status is now a primary determinant of treatment choice. The combination of high-risk clinical stage (Binet C) and high-risk biological features (IGHV-unmutated) painted a clear picture of a patient with aggressive disease who required immediate and effective therapy.

The selection of a treatment regimen for this patient, Acalabrutinib plus Obinutuzumab, reflects the revolutionary changes in CLL therapy over the last decade. Historically, the standard of care for a young, fit patient was aggressive chemoimmunotherapy, such as the FCR regimen (fludarabine, cyclophosphamide, rituximab). While effective for IGHV-mutated patients,



FCR is significantly less effective and provides less durable remissions for patients with high-risk IGHV-unmutated disease.<sup>17</sup> Moreover, it is associated with significant short-term and long-term toxicity, including myelosuppression and an increased risk of secondary cancers.

The modern era is defined by targeted agents that interfere with specific signaling pathways essential for the survival of CLL cells. The two main classes are BTK inhibitors and BCL-2 inhibitors. Acalabrutinib is a second-generation Bruton's Tyrosine Kinase (BTK) inhibitor. BTK is a critical enzyme in the B-cell receptor (BCR) signaling pathway. As discussed, this pathway is chronically active in IGHV-unmutated CLL, providing constant survival signals to the cells. By irreversibly binding to and inhibiting BTK, acalabrutinib effectively shuts down this survival pathway.<sup>18</sup> This not only leads to apoptosis of CLL cells but also inhibits their ability to adhere and traffic to the supportive microenvironments of the lymph nodes and bone marrow. This latter effect often leads to a transient, paradoxical increase in the peripheral lymphocyte count as cells are mobilized from the tissues into the blood before they die off. Acalabrutinib was chosen over the first-generation BTK inhibitor, ibrutinib, due to its greater specificity for BTK, which translates to a more favorable side-effect profile with lower rates of atrial fibrillation, hypertension, and bleeding.<sup>19</sup>

Obinutuzumab is a next-generation, glycoengineered anti-CD20 monoclonal antibody. Like its predecessor, rituximab, it binds to the CD20 protein on the surface of B-cells and flags them for destruction by the immune system through mechanisms like antibody-dependent cell-mediated cytotoxicity (ADCC). Obinutuzumab is engineered to have enhanced ADCC activity, making it more potent than rituximab. Combining a BTK inhibitor with an anti-CD20 antibody provides a two-pronged attack, and clinical trials have shown that this combination leads to deeper and more durable responses than either agent alone. This fixed-duration combination therapy (with obinutuzumab given for 6 months and

acalabrutinib continued thereafter) is now a standard of care for front-line treatment of high-risk CLL, offering a highly effective, chemotherapy-free option.<sup>20</sup> The treatment plan outlined in Table 2, including prophylaxis for tumor lysis syndrome and infections, represents the current best practice for initiating therapy in such a patient.

#### 4. Conclusion

This case report powerfully illustrates the journey of unmasking a hidden malignancy based on fundamental diagnostic principles. A 43-year-old female presented to a rural hospital with nonspecific constitutional symptoms of fatigue and fever, a clinical picture that could suggest numerous conditions. However, the pivotal investigation was the peripheral blood smear, which revealed the classic hallmarks of chronic lymphocytic leukemia (CLL): a profound lymphocytosis and the presence of characteristic smudge cells. This single, inexpensive test served as an indispensable tool, allowing for a strong presumptive diagnosis in a resource-limited setting. It underscores that while advanced diagnostics like immunophenotyping are required for confirmation, the cornerstone of initial detection remains a meticulous morphological examination. This case serves as a compelling testament to how basic laboratory skills can bridge the gap in diagnostic capabilities, ensuring patients are appropriately referred for specialized care, which is critical for improving clinical outcomes.

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