



## Case Report

# Chronic lymphocytic leukemia / Small lymphocytic leukemia with synchronous hairy cell leukemia- A rare case report

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### ABSTRACT

Chronic lymphocytic leukemia and hairy cell leukemia are distinct entities, each characterized by specific clinical and morphological features. The coexistence of both together, known as synchronous presentation, is an exceedingly rare occurrence. Differential diagnosis, molecular testing, and appropriate immunophenotyping are crucial for accurate diagnosis. This case underscores the importance of considering concurrent hematologic malignancies in patients presenting with atypical clinical features or discordant laboratory findings. Additionally, it highlights the need for further research to elucidate the pathogenic mechanisms underlying synchronous presentation of these two rare leukemias.

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### INTRODUCTION

Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia, with a median age of 70 at diagnosis, with a slight male predominance (1.9:1) across all ethnicities.<sup>1</sup> It is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen.<sup>2</sup> CLL is often initiated by the loss or addition of large chromosomes, including deletion 13q, deletion 11q, and trisomy 12, which is followed later by additional

mutations leading to its further progression.<sup>3</sup> In most cases, the diagnosis of CLL is established by blood counts, differential counts, a blood smear, and immunophenotyping. Hairy cell leukemia (HCL) is also part of a heterogeneous group of mature B-cell lymphoid disorders, with a lower incidence, accounting for only 2% of all lymphoid leukemias.<sup>4</sup> It is characterized by the identification of hairy cells morphologically and has a specific genetic profile, a different clinical course, and a different therapeutic regimen as compared to CLL.<sup>5</sup> Here, we report a case of CLL with a synchronous minor clone of HCL cells in peripheral blood and bone marrow in a patient presenting with pancytopenia with no significant other clinical findings. Such presentation with co-expression is quite rare and only a few cases have been reported.

## CASE REPORT

A 70-year male presented with complaints of cough with scanty sputum along with mild shortness of breath for the past two months. He had a history of hydropneumothorax twenty-eight years ago, for which he was treated successfully. He also had anti-tuberculosis treatment (ATT) for six months twenty years ago. No other significant history was found. His family history was insignificant. On examination, there was no lymphadenopathy or hepatosplenomegaly. Complete blood count (CBC) analysis revealed pancytopenia (hemoglobin, 8.8 g/dL; total leukocyte count,  $2.7 \times 10^9/L$ ; and platelet count,  $106 \times 10^9/L$ ). The peripheral blood smear showed predominantly normocytic normochromic cells with few macrocytes, DLC

revealed N -52%, L-45%, E-1%, M-02%. No blasts or immature cells were seen on peripheral blood examination. His serum Iron profile, serum B12, and folic acids were within normal limits. The particulate, microcellular to partly hypercellular marrow shows megaloblastoid erythropoiesis, and myelopoiesis along with megakaryopoiesis within normal limits. Lymphoid cells increased in number, comprising 35% of all nucleated cells, and showed atypia (fig.1a). Flow cytometric immunophenotyping of the bone marrow aspirate revealed two populations of bright CD19-positive cells. The larger population (approximately 68.7%) was positive for CD5 and CD200 with dim and heterogeneous CD20 expression. These cells were negative for CD10, CD79b, and CD43 and showed no surface light chains and were negative for CD38, consistent with a phenotype of CLL. The other population was CD5 negative, bright CD20 and CD200 positive, and showed positivity for CD103, CD11c, CD123, and CD25. These cells also showed restricted lambda expression, indicative of a phenotype of HCL (Fig 2.1, 2.2,2.3). The trephine biopsy revealed focal interstitial ill-defined nodules of small lymphocytes, which were predominantly CD5 and PAX5 positive (fig. 1b,1c). Correlating peripheral blood smear findings, bone marrow findings, immunohistochemistry, and flow cytometry, a diagnosis of CLL/SLL with a small clone of HCL was made. Next generation sequencing, Leukemia panel for this patient showed Missense BRAF pVal 640 Glu mutation at VAF of 1.01% and MYD88 P1252P mutation at a VAF of 21.79%.

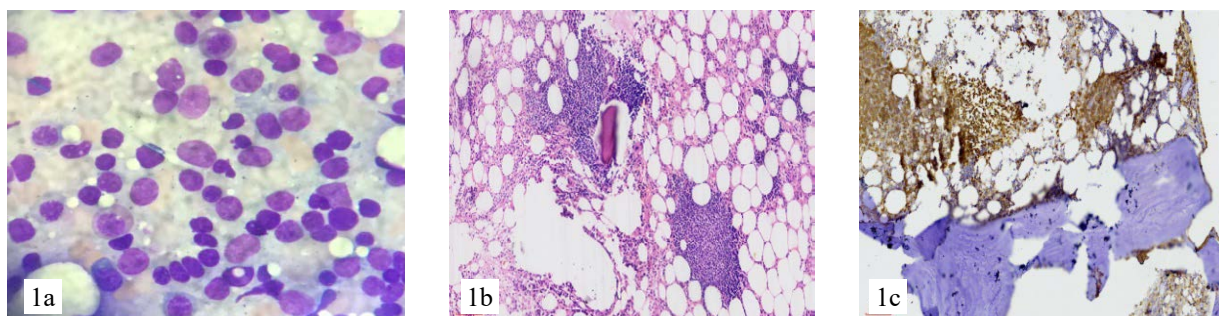


*Figure 1a: Bone marrow aspirate smears showing small lymphoid cells with coarse chromatin and inconspicuous nucleoli along with few larger lymphoid cells (MGG,X100) Figure 1b: Bone marrow biopsy showing focal interstitial ill-defined nodules of small lymphocytes (HE stain, X 400) Figure 1c: These cells were positive for CD5 on IHC*

## DISCUSSION

CLL/SLL is a slow-growing malignancy marked by the accumulation of mature yet dysfunctional B lymphocytes.<sup>1</sup> It primarily affects the peripheral blood, spleen, lymph nodes, and bone marrow. While genetic factors are the most common cause of CLL, environmental exposures such as chemicals, radiation, and tobacco use have been linked to increased risk.<sup>2</sup> CLL is most commonly diagnosed in adults around the age of 70, though it can affect those as young as 30. Men are more frequently affected than women, but women tend to experience more aggressive disease progression.<sup>2,3</sup> The pathophysiology of CLL involves two key steps: first, the maturation of monoclonal B cells due to genetic alterations and antigenic stimulation; and second, further genetic defects

or changes in the bone marrow microenvironment that drive CLL/SLL progression. This leads to lymphocytosis, splenomegaly, and hypercellular bone marrow, contributing to symptoms like anemia, thrombocytopenia, and increased susceptibility to autoimmune conditions.<sup>3,4</sup> CLL also causes systemic symptoms such as fatigue, fever, night sweats, weight loss, and early satiety, along with an increased risk of infections due to hypogammaglobulinemia.<sup>4</sup> Diagnosing CLL requires the presence of  $\geq 5000$  B-lymphocytes/ $\mu L$  in peripheral blood for at least three months. Blood smear analysis reveals small, mature lymphocytes with specific characteristics such as clumped chromatin and scant cytoplasm. CLL cells express CD5, CD19, CD20, and CD23 antigens, with low surface immunoglobulin levels compared to normal B cells. Other lymphoid cancers, such as mantle

cell lymphoma, can also express CD5, making differential diagnosis essential.<sup>5</sup> HCL is a rare, indolent B-cell neoplasm that represents 2% of all lymphoid leukemias.

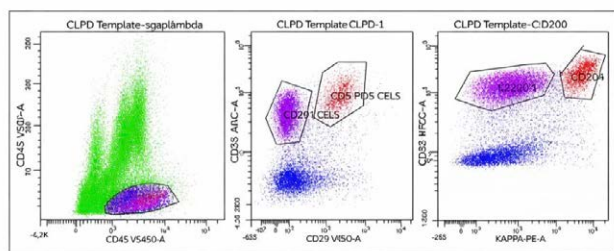


**Fig 2.1.** Both CD5 positive and CD5 negative B cells are positive for CD200 (brighter in CD5 nega cells)

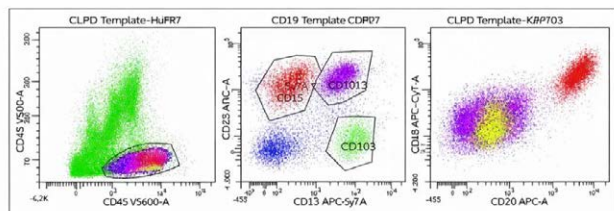


**Fig 2.2.** CD5 negative B cells (9%) are positive for CD11c, CD25, and CD103

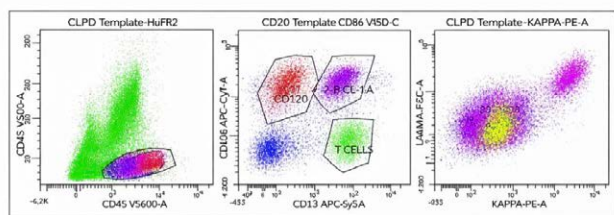


**Fig 2.3.** CD123 positive B cells are lambda restricted; CD123 negative B cells have no expression of surface light chains

It typically presents in adults around 55 years of age, with a male-to-female ratio of 4:1. Patients commonly exhibit splenomegaly, pancytopenia, and monocytopenia. The distinctive “hairy” appearance of HCL cells is due to overexpression of cytoskeleton components. HCL pathogenesis is not fully understood, but exposure to ionizing radiation, pesticides, and farming has been proposed as potential triggers. The BRAFV600E mutation is found in 80-90% of HCL cases.<sup>6</sup> HCL and CLL both stem from post-germinal center memory B cells, though it remains unclear which disease arises first. The two conditions may facilitate the development of one another due to compromised immune surveillance. HCL cells are characterized by restricted immunoglobulin light chains and overexpression of CD11c, CD25, CD103, CD123, as well as pan-B cell antigens like CD19, CD20, and CD22.<sup>6,7</sup> Most of the reported cases presented with lymphadenopathy, mild to moderate splenomegaly, and cytopenias like the present case. However, unlike our case, bone marrow biopsies of four out of seven cases showed a predominant population of hairy cells. The clonal origin was not established in all cases; it was not possible to say definitely whether the same or different clones gave rise to the two neoplastic cell lineages. It is, however, proposed that if two separate clones contributed to the two neoplasms, persistence of the clone less susceptible to chemotherapy was seen post-chemotherapy.<sup>8,9</sup> If a single clone of cells was seen, it can only be conjectured as to which came first, HCL or CLL.<sup>9</sup> It has been previously observed that the presence of the

same immunoglobulin gene rearrangements in two distinct clonal populations (HCL and CLL) may indicate a shared precursor origin.<sup>10</sup> However, other reported cases presented with two different immunoglobulin rearrangements, suggesting a different clonal origin.<sup>9,10</sup> Patients with CLL/SLL have impaired immune surveillance that makes them prone to develop second neoplasms. It has been previously observed that the presence of the same immunoglobulin gene rearrangements in two distinct clonal populations (HCL and CLL) may indicate a shared precursor origin.<sup>11</sup> However, other reported cases presented with two different immunoglobulin rearrangements, suggesting a different clonal origin.<sup>12</sup> BRAF mutations are well documented in HCL, which was seen in this case, though at a low VAF. MYD88 mutations, highly associated with LPL and DLBCL, have been reported in 16.7% cases of CLL in a study by Shekhar et al.<sup>13</sup> To the best of our knowledge, only seven cases of synchronous HCL with CLL/SLL have been reported. In the majority of cases, there was a predominant component of HCL, with SLL/CLL being the minor component. This case represents one of the rare events of CLL as a major and HCL as the existence of a minor component. Since concurrent or metachronous CLL and HCL are uncommon, they can pose a diagnostic dilemma for pathologists and management predicaments for clinicians. Treatment can be difficult because patients who initially have two clones may respond differently to chemotherapy, making the more sensitive clone invisible while the less susceptible clone eventually multiplies and gains dominance.<sup>14</sup>

## CONCLUSION

This case represents an uncommon association between the two B-cell lymphoid neoplasms found in marrow infiltrates. This case adds to the limited pool of synchronous CLL and HCL cases that already exist, emphasizing the reliability of flow cytometry in their diagnosis and the significance of identifying unidentified pathways in the pathobiology of lymphoid neoplasms. HCL and CLL recurrence may indicate an underlying link, and these two cancers may be clonal diseases at distinct stages of lymphocyte maturation. Our experience points to a diverse presentation, a variable chronology, and a stringent requirement for a precise and thorough diagnosis that results in appropriate management.

**Conflict of Interest:** None

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