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Case Report

Pathology Section

# Co-existence of Untreated Chronic Lymphocytic Leukaemia and Acute Myeloid Leukaemia: A Rare Case of Synchronous Dual Haematological Malignancy

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## ABSTRACT

The occurrence of Acute Myeloid Leukaemia (AML) or Myelodysplastic Syndrome (MDS) in patients with Chronic Lymphocytic Leukaemia (CLL) is rare. In most of the reported cases, AML occurs after treatment of CLL with cytotoxic drugs suggesting that AML may be a secondary leukaemia (therapy-related AML). AML or MDS occurring in untreated CLL patients is extremely rare with isolated case reports. Herein, we report the case of a 74-year-old male patient who was diagnosed four months back to have chronic B cell lymphoproliferative disorder, from an outside centre. The patient did not receive any treatment. Because of intermittent fever and increased fatigability, he came to our centre. Peripheral blood smear and bone marrow studies showed a dual population of atypical cells-one population of large immature cells with opened-up chromatin, prominent nucleoli, and another population of small atypical lymphocytes with clumped chromatin. Around 10% of immature cells showed Myeloperoxidase (MPO) positivity. Flow cytometric analysis also showed two separate populations of cells. The immunophenotype of one population was compatible with AML, with monocytic differentiation, and the second population showed features of CLL. A diagnosis of co-existent CLL and AML was given. The awareness of the co-existence of dual haematological malignancy, thorough morphological evaluation, and flow cytometric immunophenotyping will lead to accurate diagnosis of these combined malignancies.


**Keywords:** Acute myeloid leukaemia, Flow cytometry, Immunophenotype

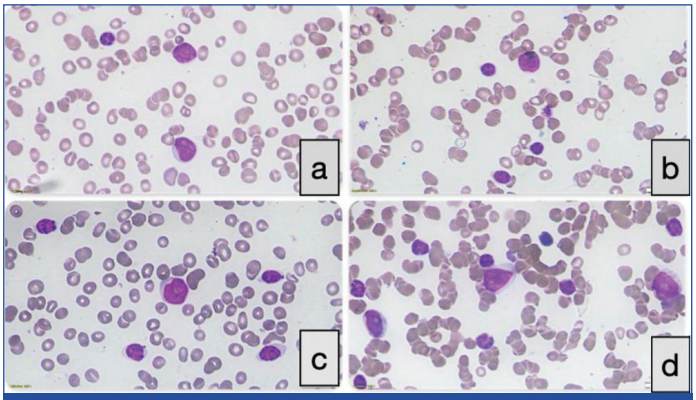
## CASE REPORT

A 74-year-old male patient presented with a history of intermittent fever, weight loss, and fatigability of 6-month duration. He was previously healthy and had not received any medication. There was no history of any metabolic diseases.

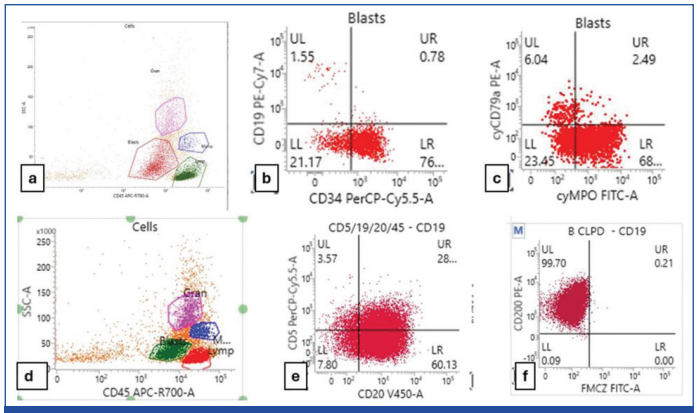
He gave a history of blood investigations from an outside hospital four months back for similar complaints. At that time his haemoglobin was 9 gm% (13.5-16 gm%), total count 34000/cmm (3600-10000/cmm) and platelet count 9800/cmm (150000-450000/cmm). Peripheral smear showed absolute lymphocytosis with atypical lymphoid cells and smudge cells, and severe thrombocytopenia. Bone marrow study showed 35% atypical small lymphoid cells which were CD20 positive on immunohistochemical examination of bone marrow biopsy. Diagnosis of B cell chronic lymphoproliferative disorder was given. The patient defaulted and he did not receive any treatment.

Since the symptoms were persisting, he came to our centre. On examination he had pallor. There was no organomegaly or lymphadenopathy. His haemoglobin was 7.1 gm% (13.5-16 gm%), total count 17400/cmm (3600-10000/cmm) and platelet count 14,000/cmm (150000-450000/cmm). The peripheral blood smear showed two distinct cell populations- one population (28%) of large immature cells with enlarged irregular nuclei, fine chromatin, and prominent nucleoli, and a second population (64%) of small lymphocytes with scant cytoplasm and condensed chromatin. Around 10% of the large immature cells showed myeloperoxidase positivity by cytochemistry. Bone marrow aspirate smears also showed two separate populations of atypical cells [Table/Fig-1].

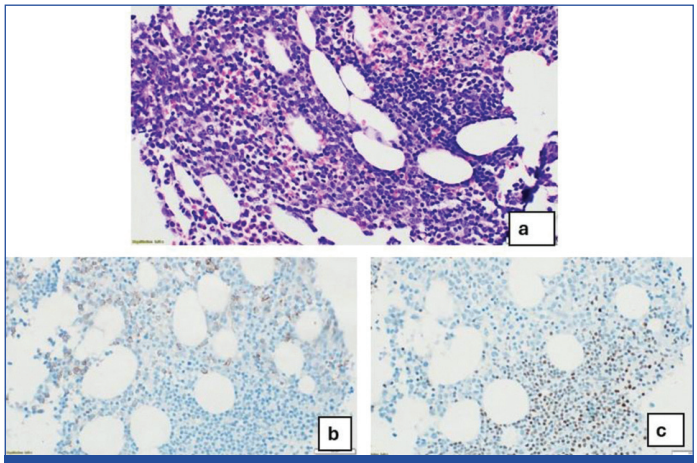
Flow cytometric analysis of bone marrow aspirate was performed. Gating was done on CD45 versus the side scatter plot [Table/Fig-2]. The gating plot revealed two different populations-First population of cells was CD45 dim to moderate positive with moderate side scatter and the second population of cells were CD45 bright positive with low side scatter. The first population (30%) of cells with dim to moderate CD45 positivity and moderate side scatter were positive for CD34, CD13, CD15, CD33, MPO, CD64 and CD11c. The second population of cells (44%) showed bright CD45 positivity and showed co-expression of CD20 and CD5. The cells were also positive for CD19, CD200, and CD23. Flowcytometric immunophenotyping confirmed the coexistence of AML with monocytic differentiation (first population) and CLL (second population). Two separate populations of cells were evident in bone marrow biopsy also [Table/Fig-3]. The small atypical lymphoid cells showed positivity for CD20, CD5, and LEF1. The large immature cells showed positivity for CD34 and CD33. Diagnosis of co-existent CLL and AML was given. The patient was planned for chemotherapy with palliative intent with Azacitidine and venetoclax. However, due to logistic reasons, the patient opted for hydroxyurea and supportive care.




**[Table/Fig-1]:** a) Peripheral smear showing immature cells with open chromatin, prominent nucleoli and atypical cells with condensed chromatin (Giemsa, X1000); b) Immature cell showing myeloperoxidase positivity (X1000); c) Bone marrow showing two separate population (Giemsa, X1000); d) Immature cell showing myeloperoxidase positivity (X1000).




**[Table/Fig-2]:** a) Flow cytometric analysis- atypical cells with dim to moderate CD45 positivity and moderate side scatter; b) showing positivity for CD34; c) MPO; d) atypical cells with bright CD45 positivity and low side scatter; e) showing positivity for CD20, CD5 and f) CD200.



**[Table/Fig-3]:** a) Bone marrow biopsy showing two separate populations (Haematoxylin and Eosin [H&E], 400X); b) Immature cells with CD34 positivity (Immunohistochemistry [IHC], 400X); c) small, atypical cells with LEF1 positivity (IHC, 400X).

## DISCUSSION

AML and CLL have rarely been diagnosed simultaneously in treatment-naive patients [1-4]. The exact cause of the co-occurrence of two different and unrelated malignancies is unclear.

Patients with CLL may have decreased immune surveillance of emerging neoplastic clones leading to increased incidence of second malignancies. The most common second neoplasms in CLL patients are lung carcinoma, colon carcinoma, and sarcomas [3]. Deregulation of normal B cell function in CLL also may lead to an increased incidence of infection and autoimmune cytopenias in many patients.

The co-occurrence of multiple haematological neoplasms is quite rare. The review by Kotchetkov R et al., revealed 41 cases of Synchronous Dual Haematological Malignancy (SDHM) among 3,036 cases [5]. The authors divided SDHM cases in three groups based on the type of combination. The myeloid/lymphoid group revealed Monoclonal Gammopathy of Unknown Significance (MGUS) as the most common haematological malignancy occurring with myeloid neoplasms. This study did not find a combination of CLL with AML [5].

The tranformation of CLL/Small Lymphocytic Lymphoma (SLL) to clinically aggressive lymphoma, mainly transformation to diffuse large B cell lymphoma, can occur. Rarely CLL/SLL patients can develop other lymphoid neoplasms such as Hodgkin Lymphoma (HL), plasmablastic lymphoma or B-lymphoblastic leukaemia/lymphoma. Transformation to acute lymphoblastic leukaemia is rare and is described in less than 1% cases [6]. The first substantiation of acute lymphoblastic transformation of CLL by flow cytometry was reported by Frenkel EP et al., in 1981 [7]. It is reported that there is 10 time increased risk of multiple myeloma in patients with CLL, with some cases hypothesised to arise from the same B-cell clone.

Transformation of chronic lymphoid neoplasms to myeloid malignancies is scarce and has only recently been reported. Carulli G et al., have reported a case of simultaneous occurrence of AML (showing monoblastic features) with CLL in a 62-year-old male patient [2]. Gottardi M et al., reported a similar case of AML with maturation and CLL [4]. They performed IgH gene rearrangement studies on CD34+/CD19- and CD34-/CD19+ immunomagnetically sorted cell populations. The genomic DNA from the CD19+/CD34- cell fraction revealed the presence of the IgH gene rearrangement whereas the CD19-/CD 34+population did not demonstrate IgH gene rearrangement. Based on the results, the authors conclude that the concomitant association of CLL and AML likely represent two different clones [4].

Al Mussaed E et al., reported the simultaneous existence of AML and CLL in a 77-year-old male patient [8]. Based on morphology, cytometric analysis and molecular studies they also supported the idea that this rare concurrence of AML and untreated CLL may represent two separate disease processes. Lai R et al., reported five cases of untreated CLL with AML and MDS [3]. In their series of five patients, all were male patients, ages ranging from 57 to 87 years. In three cases, AML (1 case each of AML M0, AML M1, and AML M5) developed in patients with untreated CLL. One case showed concurrent CLL and AML M5. Another case was the simultaneous presentation of CLL and MDS.

Ito et al., reported the case of a 65-year-old man who developed AML with aberrant CD7 expression and monoallelic CEBPA mutation in a patient with untreated CLL [1]. The authors retrospectively reviewed published cases of 27 patients who developed AML with untreated CLL. The median age at diagnosis of AML was 68 years, and the median duration between the diagnoses of AML and CLL was 4.2 years. Diagnosis of AML and CLL was made simultaneously in 16 patients. Their results demonstrated that the development of AML in patients with untreated CLL was associated with a poor response to chemotherapy and an extremely poor prognosis [1].

There are multiple theories regarding the development of simultaneous malignancies in CLL patients. The co-occurrence may be due to immunosuppression in CLL patients. Some authors hypothesise that the simultaneous occurrence of AML and CLL may be due to a common stem cell defect or leukemogenic factors or possibly a genetic susceptibility in some patients [8,9].

The occurrence of CLL and AML may represent divergent differentiation of the same stem cell clone or it may represent two separate disease processes [3,9-11]. The hypothesis of concurrent development of two separate clonal disorders is supported by the identification of two morphologically and immunologically distinct cell populations. The presence of different cytogenetic and biomolecular alterations has been demonstrated in some cases showing that they are separate neoplastic events [12].

Haematopoietic Stem Cells (HSCs) with multiple genetic abnormalities might have caused the development of several myeloid and lymphoid progenitors that consequently turned into leukaemic stem cells. Recently, it was reported that CLL cells did not originate from differentiated mature lymphocytes but rather from primitive HSC [13]. Aberrant Wnt signaling is observed in both CLL and AML patients and might play a role in transforming pre-leukaemic stem cells into leukaemic stem cells [14].

Dong Q et al., described CLL dedifferentiation to clonally related myeloid cells. These authors observed that co-activation of NF-kB and notch signaling in committed B cells primes them to convert to myeloid lineage by dedifferentiation [15].

## CONCLUSION(S)

The present report highlights the rare possibility of the development of a myeloid malignancy in a patient with lymphoid malignancy. Knowledge of this rare association is the key to timely and accurate

diagnosis. This case scenario emphasises that a high index of suspicion, careful morphological examination, and flow cytometric immunophenotyping are essential to diagnose these rare co-occurrences.

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