*Case report*

Sequential Development of Chronic Lymphocytic Leukemia Eleven Years after Chronic Myeloid Leukemia in a Caucasian Male: A Case Report

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ABSTRACT

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| **Aims:** The coexistence of myeloproliferative and lymphoproliferative neoplasms in a single patient is extremely rare. We report a case of chronic lymphocytic leukemia (CLL) developing 11 years after successful treatment of chronic myeloid leukemia (CML), to highlight this unusual sequence and discuss its clinical implications.  **Presentation of Case:** A 52-year-old Caucasian male initially presented with nosebleeds, fatigue, fever, and ascites. Investigations, including complete blood count, bone marrow aspiration, and fluorescence in situ hybridization confirmed chronic-phase CML with Philadelphia chromosome positivity. He was treated with imatinib 400 mg daily, achieving major molecular response (MMR) within 12 months, and remained in remission for 11 years. Subsequently, CBC showed persistent leukocytosis, prompting escalation of imatinib to 600 mg and bone marrow trephine biopsy. Biopsy revealed absolute lymphocytosis, and flow cytometry demonstrated a CD19+, CD20+, CD22+, CD5+, CD23+, CD200+ B-cell clone consistent with CLL. The patient was started on chlorambucil 4 mg with improvement.  **Discussion:** Although secondary malignancies in CML patients are rare, long-term follow-up may reveal additional hematological neoplasms, including lymphoid lineage disorders such as CLL. Potential mechanisms include clonal evolution, genetic instability, or treatment-related effects on hematopoiesis.  **Conclusion:** Physicians should consider the possibility of secondary lymphoid neoplasms such as CLL in patients with long-standing CML, particularly when unexpected leukocytosis or lymphadenopathy develops during follow-up. Vigilant monitoring and prompt diagnostic workup are essential for timely recognition and management of these rare but important events. |

*Keywords: Coexisting CLL/CML, chronic lymphocytic leukemia, chronic myeloid leukemia, Secondary neoplasms, Clonal hematopoiesis.*

1. INTRODUCTION

The occurrence of multiple clonal hematologic neoplasms in a single patient, particularly two distinct types such as a myeloproliferative neoplasm (MPN) and a lymphoproliferative neoplasm (LPN), is exceedingly rare. Whether these neoplasms are pathogenetically linked or arise as independent disorders remains an area of ongoing investigation.

MPNs are clonal hematological malignancies characterized by uncontrolled proliferation of one or more myeloid cell lineages in the bone marrow, leading to excessive production of mature red blood cells, white blood cells, or platelets [1]. In contrast, lymphoproliferative neoplasms are caused by uncontrolled proliferation of lymphocytes, resulting in lymphocytosis, lymphadenopathy, and infiltration of both bone marrow and solid organs [2].

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in Western populations, while chronic myeloid leukemia (CML) is the most prevalent myeloproliferative neoplasm. CML is driven by a reciprocal translocation between chromosomes 9 and 22, forming the BCR::ABL1 fusion gene, which activates constitutive tyrosine kinase signaling and promotes myeloid proliferation [1].

There is evidence that patients diagnosed with MPNs have an increased risk of developing secondary neoplasms, which can negatively affect survival and complicate treatment strategies [3,4]. In the literature, most cases of coexisting CLL and CML involve patients with simultaneous diagnoses [5,6] or patients diagnosed with CML after treatment for CLL [7–11]. However, the development of CLL several years after CML remission is rarely described, with only a handful of cases reported to date [12–14].

Understanding the pathophysiology and clinical presentation of such rare dual hematologic malignancies is crucial for ensuring timely recognition, appropriate monitoring, and tailored therapeutic approaches. In this report, we describe an additional case of CLL developing several years after achieving deep remission of CML with tyrosine kinase inhibitor therapy, further contributing to the scarce literature on this phenomenon.

2. CASE PRESENTATION

A 52-year-old Caucasian male initially presented in January 2004 with complaints of spontaneous nosebleeds, fatigue, fever, and abdominal distension consistent with ascites. Clinical evaluation revealed an ECOG performance status of 1. On examination, there was massive splenomegaly measuring 243 × 120 mm on ultrasound, with no lymphadenopathy. Laboratory investigations showed a hemoglobin level of 8.3 g/dL, a markedly elevated leukocyte count of 275 × 10^9/L, left shift and a platelet count of 111 × 10^9/L.

Bone marrow aspiration revealed findings consistent with chronic-phase chronic myeloid leukemia (CML). Cytogenetic analysis confirmed the presence of the Philadelphia chromosome with BCR: ABL1 positivity in 100% of metaphases. The patient was classified as intermediate-risk CML according to the Sokal scoring system.

Initially, he was treated with hydroxyurea 2000 mg daily to reduce the markedly elevated WBC and platelet counts. Once hematologic parameters stabilized, he was commenced on imatinib at a dose of 400 mg daily. The patient achieved complete cytogenetic remission within 7 months and major molecular response (MMR) by 12 months, and he continued follow-up with regular BCR:ABL1 monitoring, which remained negative through 2015.

In March 2014, the patient was admitted for severe respiratory infection, with complete blood count (CBC) showing hemoglobin 12.7 g/dL, leukocytes 19.8 × 10^9/L, and platelets 459 × 10^9/L, but no loss of MMR. Following resolution of the infection, counts normalized. In April 2015, CBC showed WBC of 11.77 × 10^9/L, but values continued to rise dynamically, prompting escalation of imatinib to 600 mg. Two months later, marked lymphocytosis (70%) was observed, with normal spleen size. A summary of the complete blood count and differential leukocyte count (DLC) findings during the 2014 infection episode and 2015 follow-up is presented in Table 1.

**Table 1. Differential Leukocyte Count and Complete Blood Count Summary for 2014 and 2015**

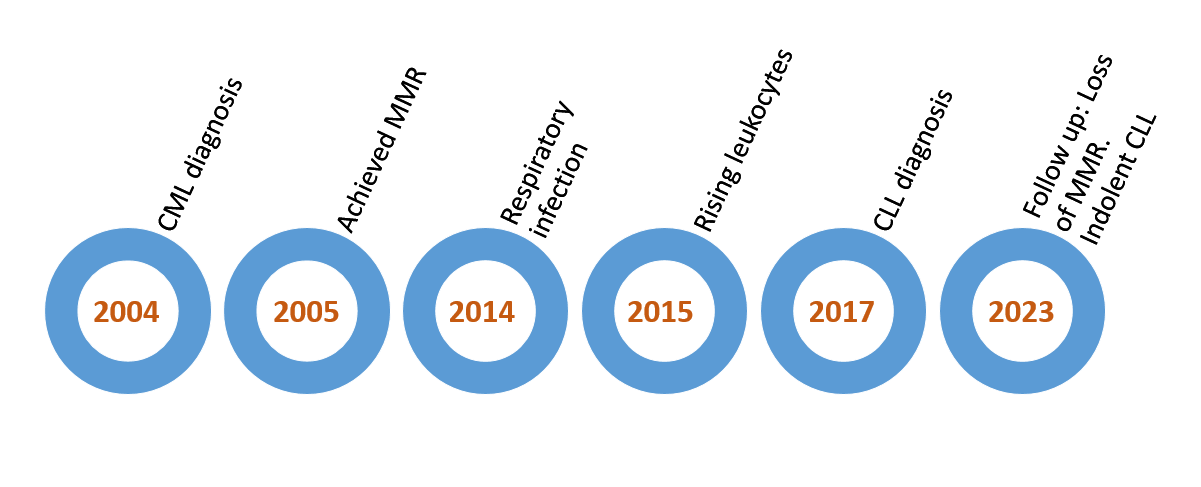
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| **Parameter (peripheral blood smear)** | **March 2014** | **April 2014** |
| Hemoglobin (HGB) | 12.7 g/dL | 11.9 g/dL |
| Leukocytes (WBC) | 19.8 × 10⁹/L | 11.77 × 10⁹/L |
| Myeloblasts | 1% | - |
| Metamyelocytes | 1% | - |
| Myelocytes | 4 % | 1 % |
| Band neutrophils | 3 % | 2 % |
| Segmented neutrophils | 77 % | 66 % |
| Lymphocytes | 9 % | 27 % |
| Monocytes | 2 % | 1 % |
| Eosinophils | 1 % | 1 % |
| Basophils | 2 % | 2 % |
| Platelets (PLT) | 459 × 10⁹/L | 433 × 10⁹/L |
| MMR Status | Maintained | Maintained |

**MMR: major molecular response.**

Given persistent lymphocytosis, a comprehensive re-evaluation was performed in 2017. Bone marrow biopsy showed 85% lymphocytes (myelocytes 0.4%, metamyelocytes 0.2%, band forms 3.2%, segmented neutrophils 7.6%, lymphocytes 85%). Flow cytometry revealed a clonal B-cell population expressing CD19+, CD20+, CD22+, CD5+, CD23+, CD200+, and negative for CD10, CD56, FMC7, CD11c, and CD103, consistent with CLL immunophenotype. CT imaging showed no significant lymphadenopathy exceeding 3 cm, although small cervical nodes and a 15 × 10 mm nodular lesion in the right iliac bone were noted, along with inflammatory changes in the left maxillary sinus.

The patient was diagnosed with chronic lymphocytic leukemia and started on chlorambucil 4 mg daily, leading to stabilization of hematologic parameters. As of his most recent follow-up, he remains in morphologic and cytogenetic remission of CML but has lost MMR (PCR IS 11.2%) while continuing imatinib at 400 mg daily. His CLL remains in an indolent phase and is monitored conservatively. A summary of the patient's clinical course, key interventions, and disease progression is illustrated in Figure 1.

**Figure 1: Timeline of Clinical Events in a Patient with Sequential CML and CLL**



3. discussion

CLL is the most frequent leukemia in adults in Western populations, while CML is the most common myeloproliferative neoplasm [12]. Both diseases are more commonly seen in older males, and their coexistence raises intriguing questions about underlying pathogenesis [12]. In patients with CLL, the risk of secondary malignancies is elevated due to prolonged immunosuppression, clonal instability, or the effects of cytotoxic therapies [13].

In contrast, second hematologic neoplasms are rarely associated with CML, particularly in the setting of long-term remission [4,14]. Most secondary neoplasms reported in CLL patients are non-hematologic solid tumors, developing years after initial diagnosis and treatment [14]. The observation of a lymphoid neoplasm emerging after myeloid disease therefore warrants close attention.

Several mechanisms could potentially explain this rare coexistence. One hypothesis suggests that BCR::ABL1–positive cells may secrete growth-promoting cytokines such as interleukin-3, which supports the proliferation of CD34+CD38– lymphoid progenitors and might contribute to secondary lymphoid neoplasms [15]. Alternatively, the prolonged use of tyrosine kinase inhibitors, while generally safe, could theoretically modify the marrow microenvironment, facilitating secondary clonal expansions through genomic instability or selective immune modulation [16,17].

Laurenti et al. [10] classified these rare CLL–CML associations into three patterns: CML preceding CLL, CLL preceding CML, and concurrent diagnoses. To date, only four well-documented cases of CLL arising after CML have been described in the literature [12–14]. Our case represents an additional report of this pattern, highlighting the importance of vigilance for unexplained lymphocytosis or lymphadenopathy even many years after successful CML treatment.

This case underscores the need for lifelong hematologic follow-up in CML patients, incorporating not only molecular monitoring of the BCR::ABL1 transcript but also broader surveillance for secondary hematologic malignancies. Prompt investigation of persistent lymphocytosis with immunophenotyping and bone marrow evaluation is critical to ensure timely recognition and tailored treatment of these rare but clinically relevant disease progressions.

4. Conclusion

Although progression from CML to CLL is exceptionally rare, this case demonstrates that such sequential occurrences can happen even after prolonged molecular remission with targeted therapy. Physicians managing CML survivors should maintain a high index of suspicion for secondary hematologic malignancies, including CLL, especially when unexplained lymphocytosis, lymphadenopathy, or atypical organomegaly is observed during follow-up.

Routine monitoring should therefore not only include molecular surveillance for BCR::ABL1 but also periodic evaluation of differential counts, peripheral blood immunophenotyping, and clinical examination for lymphoproliferative features. The presence of molecular-cytogenetic alterations in CML survivors may reflect broader genomic instability and a predisposition to develop multiple clonal neoplasms.

In conclusion, this case highlights the importance of lifelong vigilance in patients successfully treated for CML and emphasizes a tailored, patient-centered approach to identify and manage secondary hematologic neoplasms as early as possible.

Consent (where ever applicable)

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval (where ever applicable)

This case report describes a retrospective observation of a single patient and did not require prior approval from an institutional ethics committee, in accordance with local regulations. The authors confirm this case report was conducted in accordance with the Declaration of Helsinki.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors 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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Definitions, Acronyms, Abbreviations

**CML:** Chronic Myeloid Leukemia

**CLL:** Chronic Lymphocytic Leukemia

**MMR:** Major Molecular Response.