A case of CLL that was successfully treated resulted in the immediate development of AML from a coexistent myeloid line that had been suppressed

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Funding Information
No funding was provided. The first author paid for it on his own.

Received: 11 April 2014; Revised: 30 September 2014; Accepted: 25 October 2014

Clinical Case Reports 2015; 3(3): 165–169
doi: 10.1002/ccr3.184

Key Clinical Message
An 83-year-old Caucasian male presented to the emergency room with confusion and lethargy. A complete blood count revealed lymphocytosis, anemia, and thrombocytopenia. A bone marrow examination revealed chronic lymphocytic leukemia (CLL), along with a small population of abnormal immature myeloid cells. Chemotherapy for CLL was started. After one cycle, repeat bone marrow examination revealed normalization of the lymphocyte count and a proliferation of the previously noted myeloid population, consistent with acute myeloid leukemia (AML). This report presents the microscopic, immunophenotypic, and cytogenetic evidence to document the development of AML after one cycle of chemotherapy for CLL.

Keywords
Acute myeloid leukemia, chronic lymphocytic leukemia, cytogenetics, FISH, flow cytometry, peripheral smear, bone marrow examination.

Introduction
Chronic lymphocytic leukemia (CLL) is a slowly progressive disorder of abnormal and malignant neoplastic proliferation of B lymphocytes. Acute myeloid leukemia (AML) is a rapidly progressive disorder of abnormal and malignant neoplastic proliferation of myeloid cells and their precursors.

In the United States, there are approximately 10,000 new cases of CLL every year [1]. A small subset, comprising of less than 1% of these cases, will eventually develop AML [2, 3]. The majority will develop it within 2–10 years and can be attributed to chemotherapy for CLL [2]. However, there is a small number of AML cases that occur immediately after treatment for CLL [2,4–7]. The development of AML under these circumstances cannot be associated with therapy since it develops so acutely. Therefore other possible explanations are required to explain its occurrence. In this report, we present a case of CLL, which coexisted with a small population of abnormal immature myeloid cells. This aberrant myeloid cell line immediately progressed to AML after the CLL was successfully treated with one cycle of chemotherapy.

Clinical History
An 83-year-old Caucasian male presented to the emergency room of Hospital A with confusion and lethargy. Fatigue and easy bruising were present. There was a fifty pound weight loss over the past year. Conjunctival pallor was noted. There was no lymphadenopathy or splenomegaly. A CBC revealed a WBC count of $111.9 \times 10^3/\mu L$, of which 75% were lymphocytes, a hemoglobin level of 7.8 g/dL, and a platelet count of $48 \times 10^3/\mu L$. A diagnosis of CLL was made. Confirmatory flow cytometry on peripheral blood revealed lymphoid cells positive for CD5 (partial, dim), CD19, CD20 (bright), CD52, FMC7, and kappa immunoglobulin light chain expression. They were negative for CD10, CD23 and CD25 expression. Abnormal immature myeloid cells positive for CD34 expression, with abundant cytoplasm and relatively high side scatter were found. FISH/cytogenetics results revealed trisomy 12 and lack of t(11;14).
A bone marrow biopsy revealed numerous B lymphocytes with mature chromosomes and round to cleaved nuclei. Immature myeloid cells, with round nuclei, occasional prominent nuclei, abundant cytoplasm, and cytoplasmic granules were found. Chlorambucil and prednisone were started. At this time there was no evidence of AML.

The patient was referred to Auerbach Hematology-Oncology Associates in Baltimore, MD, because he wanted his further treatment and follow ups closer to home. Two weeks later the WBC count was $93.2 \times 10^3/\mu L$, of which 67.6% were lymphocytes. Prednisone and chlorambucil were discontinued and bendamustine and rituximab were started.

Fourteen days later a peripheral smear, done at Hospital B, revealed normalization of the lymphocyte count. WBCs consisting of immature myeloid cells (myeloblasts, promyelocytes and myelocytes), with atypical features were noted. Immature blast-like nuclei, abundant cytoplasm, and an increase in primary granulation were observed. There were no Auer rods. Bone marrow biopsy revealed sheets of immature myeloid cells, positive for CD34 expression, consisting of myeloblasts, promyelocytes, and myelocytes. The blast cells comprised of 90% of the bone marrow’s total cell count. No mature granulocytes were seen. FISH/cytogenetics did not reveal t(15;17). A diagnosis of AML was confirmed, however
further studies such as cytochemical stains and flow cytometry were not conducted because the patient decided to discontinue treatment due to his poor condition and prognosis. He requested comfort measures only. The patient passed away soon after.

Discussion

The development of AML following chemotherapy for CLL is rare, but documented [2,4]. The occurrence of AML as a result of CLL therapy may relate both to the specific agent, as well as to the schedule of administration [8]. Reports indicate that those exposed to either alkylating agents (chlorambucil, melphalan) or nitrosoureas (carmustine, lomustine), developed AML within 5–10 years [2]. Those exposed to both types of topoisomerase II interactive drugs, the topoisomerase II inhibitors (etoposide, teniposide) and intercalating topoisomerase II inhibitors (antracyclines, mitoxantrone), developed AML within 2–5 years [2].

In this report there are three unique findings. Firstly, the AML developed immediately after only one cycle of successful treatment for CLL. Secondly, the bone marrow examination at the time of the CLL diagnosis revealed a small population of abnormal immature myeloid cells. Thirdly, there was positive expression for FMC7 and

Figure 5. Peripheral blood smear. Immature myeloid cells with blast-like nuclei, abundant amounts of cytoplasm, and heavy primary granulation.

Figure 6. Bone marrow biopsy. Immature myeloid cells showing blast features.

Figure 7. Bone marrow biopsy. Immature myeloid cells showing blast features.

Figure 8. Bone marrow biopsy. Marrow replaced by sheets of immature myeloid cells, consisting of myeloblasts, promyelocytes, and myelocytes.
negative expression for CD23, which is an atypical feature for CLL [9]. These findings suggest it is highly unlikely that chemotherapy contributed to the development of the second neoplasm supporting the contention of another mechanism [4,7].

Stomach, skin, colon, breast, and kidney cancers are associated with a higher incidence in people with CLL compared to the general population [4–6]. It is well recognized that immunodeficient people have a higher incidence of neoplasia compared to immunocompetent people [6]. Published evidence reports low immunoglobulin levels are linked to an increased risk of developing secondary neoplasms [4,6,10]. Studies indicate the risk of secondary neoplasms in those with CLL is similar to subjects who underwent renal transplant [2]. Similar findings have been reported after bone marrow transplantation [2]. In CLL and other conditions with immunosuppression, the suppressive effect is usually only on normal cells, which is evidenced by the increased occurrence of infections and development of secondary neoplasms [5]. Our case is unique in that the second neoplasm appeared to be suppressed by the first. It is reasonable to posit this neoplastic myeloid cell line was uniquely susceptible to suppression by normally produced cytokines from the CLL. Alternatively the CLL could have been producing unique cytokines capable of suppressing the AML cells. After effective treatment for CLL, this postulated suppression was disrupted allowing AML to develop [4,5].

Previous reports with similar findings are published [2,4–7]. A 72 year-old man’s bone marrow biopsy displayed CLL, plus a small population of myeloid blasts. Following therapy with cyclophosphamide, vincristine, and prednisone, a reduction in the lymphocyte count was achieved, and the myeloid clone developed into AML [4]. Two additional reports describe subjects developing AML within 2 weeks of chlorambucil therapy for CLL [5,7]. A third report describes a 64 year-old woman who developed reticulohistiocyticblastic leukemia 3 months after a diagnosis of CLL following chlorambucil therapy [6]. Finally Meloni et al. described a 54 year old man with CLL treated with fludarabine, etoposide, and melphalan. After sixteen months, there was minimal residual CLL followed by the emergence of AML and lung cancer [2].

The pathogenesis of AML and CLL in these cases is unclear. It is not an unreasonable conjecture that an initial leukemogenic event affected separate cell lines resulting in different neoplastic conditions [4,5,7]. Evidence supporting this hypothesis is the occurrence of multiple myeloma where two distinct cell lines are involved [7]. An alternate explanation would be that the diseases evolved from a pluripotent stem cell line capable of differentiating into the observed phenotypes [4–7]. This is supported by the occurrence of ALL and CLL with monoclonal immunoglobulin heavy and light chains on the surface of both types of lymphocytes [4–6,10]. Another explanation is the CLL induced immunosuppression caused the AML [4,6]. Evidence supporting this hypothesis is the observed link between low immunoglobulin levels and increased risk of developing secondary neoplasms [4–6,10]. It is well recognized that immunodeficient people have a higher incidence of neoplasia compared to immunocompetent people [6]. A report of a 70 year-old man with 5 years of untreated CLL subsequently developing AML lends credence to this relationship [5]. Another possible explanation is the development of multiple neoplasms due to genetic susceptibility, as it occurs in multiple endocrine neoplasia and Von Hippel-Lindau disease, but no supporting evidence has been found yet [7]. Lastly the CLL and AML could be coincidental [7].

Conclusion

The initial bone marrow examination in this case report revealed CLL and a small population of aberrant myeloid cells, without conclusive evidence of a second malignancy. After one cycle of chemotherapy an essential remission in the CLL was observed. AML appeared immediately thereafter. Other cases with similar features have been documented. The acute onset of AML and presence of an aberrant myeloid clone in the initial bone marrow examination, suggest that the CLL was suppressing the AML. The pathogenesis of disease has been hypothesized to either be an initial leukemogenic event affecting two cell lines, a pluripotent stem cell line differentiating into
different diseases, or CLL induced immunosuppression causing AML. Further investigation is required to definitively determine the mechanism of suppression and the pathogenesis of these entities.

**Conflict of Interest**

None declared.

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