case report

Allogeneic stem cell transplantation for acute myeloid leukemia with del(7q) following untreated chronic lymphocytic leukemia

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The development of hematologic malignancy in the presence of chronic lymphocytic leukemia (CLL) is rare. We present a case of acute myeloid leukemia (AML) with del(7q) occurring in a patient with a 4-year history of untreated CLL. Application of flow cytometry and immunohistochemistry allowed for characterization of two distinct coexisting malignant cell populations. After undergoing induction and consolidation chemotherapy, the patient achieved complete remission of AML with the persistence of CLL. Allogeneic transplantation was pursued given his unfavorable cytogenetics. Subsequent matched unrelated donor allogeneic stem cell transplantation resulted in full engraftment and complete remission, with no evidence of AML or CLL. Due to a scarcity of reported cases, insight into treatment and prognosis in cases of concurrent AML and CLL is limited. However, prognosis seems dependent on the chemosensitivity of AML. CLL did not have a detrimental effect on treatment or transplant outcome in our case. This is the first reported case of concomitant de novo AML and CLL to undergo allogeneic transplantation. The patient remained in complete hematologic and cytogenetic remission of both malignancies over a year after transplantation.

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults. Although CLL has classically been associated with second primary solid malignancies, such as lung and skin cancer, association with hematologic malignancies is less common.[1] Most cases of concurrent AML and CLL are treatment related. Specifically, alkylating agents such as chlorambucil and purine analogs such as fludarabine have been implicated.[2,3] Given the long natural course of CLL and the use of chemotherapy agents with established leukemogenic potential, increased acute leukemia would be expected.[4] Nevertheless, patients with CLL do not have an increased incidence of acute leukemia, with the incidence rate of therapy-related AML following CLL treatment being <1%.[5,6] Robertson et al reported only 7 cases AML or myelodysplastic syndrome (MDS) in 1374 cases of CLL, with nearly three-fourths of the patients having received treatment with alkylating agents.[4] Cases in the absence of prior treatment are exceedingly rare. Only a minority of reports represent de novo AML following untreated CLL or concomitant AML and CLL. Given the scarcity of reported cases, insight into treatment of such cases is limited.

We present a patient with previously untreated CLL who developed AML four years after initial diagnosis. After undergoing chemotherapy and allogeneic stem cell transplantation, he was in complete remission of both malignancies. We will review the important features of synchronous AML and CLL, discuss hypotheses behind the phenomenon, and examine the treatment modalities used in this case and previously published reports.

CASE

A 55-year-old white male with a past medical history of diverticulosis and osteoarthritis presented with asymptomatic lymphocytosis prior to total knee replacement in January 2007. Flow cytometry at that time revealed a kappa-restricted monoclonal B-cell population that was CD5+, CD10-, CD19+, CD20+, and CD23+.

He was diagnosed with Rai low risk disease CLL and treatment was deferred. He was in good health until February 2011 when he presented with a dry cough and worsening dyspnea after a presumed upper respiratory tract infection. Physical examination revealed tender cervical lymphadenopathy. Initial laboratory studies revealed a hemoglobin of 9.8 g/dL, a platelet count of 59×10^3/mL, and a white blood cell count of 188×10^9/L with 5% neutrophils, 59% lymphocytes, and 33% blasts. The peripheral smear revealed the presence of two discrete cells: large blasts with granulocytic maturation and small mature lymphocytes (**Figure 1**).

Flow cytometry confirmed the presence of two discrete abnormal cell populations: 46.5% of cells were identified as CD45dim cells consistent with blasts, which expressed immature myeloid immunophenotype of CD13+, CD33+, CD11c+, and HLADR+. Additionally, a second abnormal population of monoclonal mature B cells, accounting for 26.6% of cells, expressed CD5+, CD10-, CD19+, CD20+, CD23+, and kappa light chain restriction. Cytogenetic analysis revealed deletion 7q- in 3.8% of cells.

Based on the morphological and immunological features, the patient was diagnosed with AML French-American-British (FAB) group M2 in the setting of B-cell CLL. At the time of diagnosis, he underwent successful 7+3+3 induction chemotherapy with cytarabine, doxorubicin, and etoposide. The post-induction hospital course was complicated by *Legionella* pneumonia, successfully treated with azithromycin. Repeat bone marrow biopsy showed residual CLL but no evidence of AML. Given the presence of deletion 7q-, allogeneic transplantation was pursued. After two rounds of high-dose cytarabine (HiDAC) consolidation chemotherapy, bone marrow biopsy showed sustained remission of AML with the persistence of CLL. His ECOG performance status was 0 and his Karnofsky score was 90%. His two siblings had chronic medical conditions that precluded them as donors. Thus a matched unrelated donor (MUD) was arranged through the National Marrow Donor Program (NMDP). He underwent allogeneic transplantation in July 2011. Post-transplant evaluation revealed full donor chimerism (100% CD3, 100% CD33, and 100% CD56). Bone marrow aspirate and biopsy no longer demonstrated findings of CLL or AML. The post-transplant course was complicated by acute grade III cutaneous graft-versus-host disease, as well as World Health Organization (WHO) grade III mucositis. More than a year after transplantation, the patient remains in complete hematologic and cytogenetic remission of both malignancies. Full donor chimerism has persisted off all immunosuppression.

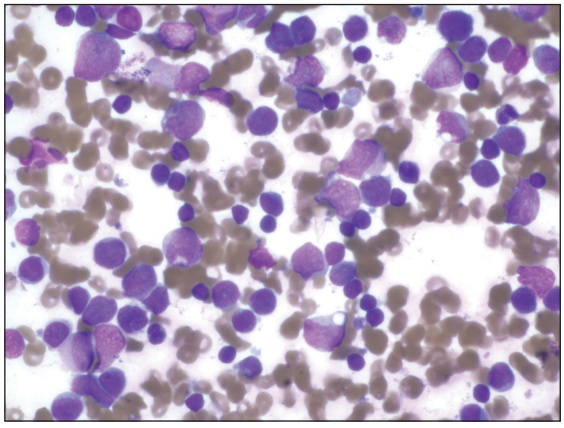

Figure 1. Bone marrow aspirate smear showing two distinct cell populations: mature lymphocytes and blasts (Wright Giemsa, ×20).

DISCUSSION

Multiple theories behind the development of simultaneous AML and CLL have been proposed. Since CLL is associated with immunoglobulin deficiencies, the risk for secondary malignancies is thought be related to immunosuppression.[7] In treatment-related cases, the development of AML is hypothesized to be the sequelae of immunosuppression combined with cytotoxicity and DNA damage induced by prior chemotherapy treatments.[8] In cases of de novo disease, leukemogenic factors and gene susceptibility may contribute to an increased risk for secondary malignancy.[7] Some have proposed that a common stem cell defect involving a pluripotential stem cell line capable of developing along two different cell lines causes the two malignancies to develop together.[9] However, others have demonstrated that the phenomenon results from separate karyotype abnormalities in the myeloid and lymphoid lines, triggering two separate neoplastic events.[1,8,10] Myeloid and lymphoid clones often have different chromosomal abnormalities and therefore the association between de novo AML and CLL is likely to be coincidental.

Our patient's treatment was aimed at eradicating AML. Induction chemotherapy resulted in complete remission of AML, while the CLL clone persisted. This supports the notion that these two malignancies represent two distinct clonal disorders. He subsequently underwent HiDAC consolidation chemotherapy in an attempt to sustain remission until allogeneic transplantation. A search through the NMDP identified a 10/10 high resolution matched donor with major ABO incompatibility. Our patient's indication for allogeneic transplantation was the diagnosis of AML with unfavorable cytogenetics of 7q- deletion.[11] For patients

Table 1. Treatment outcomes in previously published cases of concomitant AML and CLL.

Author, Year	Treatment of AML/CLL	Complete response achieved?	Clinical Outcome
Caballero et al, 1992[16]	Induction chemotherapy (daunorubicin, cytarabine) Consolidation chemotherapy (cytarabine and daunorubicin)	AML with induction CLL with consolidation	CR at 4 months
Tamul et al, 1994[17]	Vincristine and prednisone	No	Death at 2 months due to unrelated causes
Lima et al, 1996[9]	None (hospice)	No	Death at 5 months due to progressive AML
Gomez et al, 1997[7]	6-mercaptoprurine and prednisone	No	Death at 4 months due to progressive AML
Mateu et al, 1997[18]	Induction chemotherapy (idarubicin, etoposide, cytarabine) Salvage chemotherapy (mitoxantrone, cytarabine, etoposide) Consolidation chemotherapy (etoposide, cytarabine)	AML with salvage chemo CLL with consolidation	Death at 6 months due to AML relapse
Miller et al, 200[18]	None (septic)	No	Death within days due to sepsis
Muta et al, 2002[22]	None (hospice)	No	Death at 2 months due to brain hemorrhage
Gottardi et al, 2006[1]	Hydroxyurea and transfusions	No	Death at 9 months due to progressive AML
Lu et al, 2006[23]	Induction chemotherapy (daunorubicin and cytarabine) Consolidation chemotherapy, (cytarabine)	AML with induction CLL with consolidation	CR, time unspecified
Carruli et al, 2007[5]	Induction chemotherapy, (unspecified)	No	Death at 3 weeks due to progressive AML
Katz et al, 2010[10]	None (hospice)	No	Death days later due to progressive AML

with unfavorable cytogenetics in complete remission of AML, allotransplantation leads to improved long-term survival (35% to 42%) compared with nontransplantation therapy (less than 20%).[12-14] According to the current guidelines from the European Group for Blood and Marrow Transplantation, the indications for allotransplantion in CLL are cases that are nonresponsive or refractory to fludarabine or cases with p53 deletion/mutation (deletion 17p-).[15] Neither of these indications were met. A myeloablative conditioning regimen consisting of fludarabine, busulfan, and low-dose total body irradiation was used with transplantation. Repeat bone marrow biopsy and flow cytometry after donor engraftment no longer demonstrated evidence of AML or CLL.

To our knowledge, 14 cases of concomitant AML and untreated CLL have been reported since 1990.[1,5,7-10,16-23] **Table 1** summarizes the treatment courses in the 11 cases that reported clinical outcomes. Limited by age and comorbidities, only four patients underwent induction chemotherapy, with three achieving complete remission of both malignancies. Treatment-related AML traditionally carries a shorter median survival than de novo cases.[24] Due to the scarcity of reported cases, outcomes of concomitant de novo AML and CLL are unknown. However, prognosis in such cases seems to be dependent on the response of AML to induction chemotherapy and as thus should direct treatment.[5] In our case, the presence of CLL did not have a detrimental effect on treatment of AML. Our patient's clinical outcome reflects the high chemosensitivity of AML to the induction regimen and his good performance status, allowing a transplant procedure.

In contrast to previously published cases, another unique feature of this case was that CLL persisted through consolidation therapy. In previous reports, induction-resistant CLL was responsive to consolidation therapy. Two patients achieved complete remission

of AML with standard induction chemotherapy; salvage chemotherapy was required for induction failure in the third case.[15,16,23] Cytarabine consolidation resulted in complete remission of CLL in each of these cases. In our case, CLL was still present after two cycles of HiDAC consolidation chemotherapy and was only eradicated through transplantation. Although HiDAC does not have a conventional role in the treatment of CLL, these reports demonstrate success in inducing remission. This role should be further investigated.

In conclusion, with continued advancements in technology and the widespread use of flow cytometry, the identification of underlying indolent leukemias will rise. Cases of concurrent malignancies will be seen more often. Published reports indicate that prognosis is dependent on the chemosensitivity of AML and as thus should dictate treatment. In our case, allogeneic transplantation aimed at maintaining durable remission of AML also resulted in complete remission of CLL.

Author Contributions

ZD gathered the data and drafted the manuscript. DH helped to draft the manuscript. SF and ES contributed to the acquisition of data and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None of the authors declared any conflicts of interests.

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