

Unusual Case of B-Chronic Lymphocytic Leukemia with Coexistence of Precursor T-Acute Lymphoblastic Leukemia Status Post Transplant

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Keywords: Chronic Lymphocytic Leukemia, T-Acute Lymphoblastic Leukemia, Composite Lymphoma

ABSTRACT

Background: Coexistence of Chronic lymphocytic lymphoma (CLL) to Acute lymphoblastic leukemia is extremely rare with only a few reported cases [1-5]. Chronic lymphocytic leukemia is a neoplasm of small monomorphic round to irregularly shaped lymphocytes of B-cell lineage. Adverse prognostic factors in CLL include flow cytometric expression of ZAP-70 and CD38 which are surrogate markers for the mutational status of IVIg. T-cell acute lymphoblastic leukemia (T-ALL) is a neoplasm of lymphoblasts that are of T-cell lineage and are small to medium-sized cells.

Case Report: We present a case of a 62-year-old man, diagnosed with B-Chronic Lymphocytic Leukemia who was treated successfully twice. A year following an allogeneic stem cell transplantation (SCT), the CLL returned for a third time along with a secondary diagnosis of T-cell acute lymphoblastic leukemia. Our review of literature explores the potential pathophysiologic mechanisms of the coexistence of these two diagnoses. Conclusion: Chronic lymphocytic leukemia has been known to evolve into various lymphoid transformations, including diffuse large b-cell lymphoma, and prolymphocytic leukemia, however the coexistence and transformation of CLL to T-cell acute lymphoblastic lymphoma is extremely rare. Potential mechanisms of this phenomenon may include a common genetic predisposition, a malignant transformation of a common progenitor cell, immune deregulation, chronic stimulation of T-cells by the B-CLL cells, adverse effects of chemotherapy exposure, increased T-cell resistance to apoptosis, or to the slight occurrence of pure chance. Numerous hypotheses exist, however the precise relation of the two entities coexisting is unknown due to limited research and only a few known cases.

INTRODUCTION

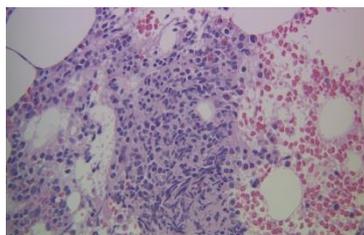
Chronic lymphocytic leukemia is the most common type of leukemia of adults in the Western World with an incidence of 4 cases per 100,000 annually. CLL may take on a variety of clinical courses and has a survival range from months to several years. CLL is known to undergo transformation (Richter's transformation) in 3% of CLL patients [6]. These malignancies have included primarily B-cell lineage lymphomas such as B-Prolymphocytic leukemia (PLL), Diffuse large b-cell lymphoma (DLBCL), Hodgkin's disease, and multiple myeloma [6]. A Richter's variant, transformation of CLL into T-cell lineage lymphomas are extremely rare, however there are increasing case reports in the literature. The phenomenon of simultaneous malignancies of two different cell lineages, also known as a composite lymphoma, has an incidence of only 1 - 4.7% [7]. Similar to the transformation of CLL to PLL and

DLBCL, there are no obvious or known causes of the potential link/progression of CLL to T-cell lineage lymphomas, or more specifically to T-ALL as in our case. The pathophysiology of two or more simultaneous hematologic malignancies occurring is not well understood, and thus there have been multiple suggested theories.

CASE REPORT

We present an exceedingly rare case of a patient with recurrent CLL and a secondary diagnosis of T-ALL. The patient is a 62-year-old man, who was diagnosed with B-Chronic Lymphocytic Leukemia in 2004 with the adverse risk factor of ZAP-70 expression. The patient was started with fludarabine, cyclophosphamide and rituximab in 2007. After 6 cycles of therapy, he went into remission for five years. In 2011 he had a recurrence of disease with cutaneous and systemic involvement (Figure 1).

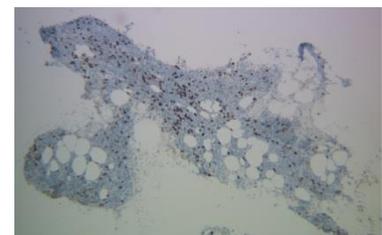
Figure 1. Bone marrow biopsy (CLL recurrence)



H&E



CD20



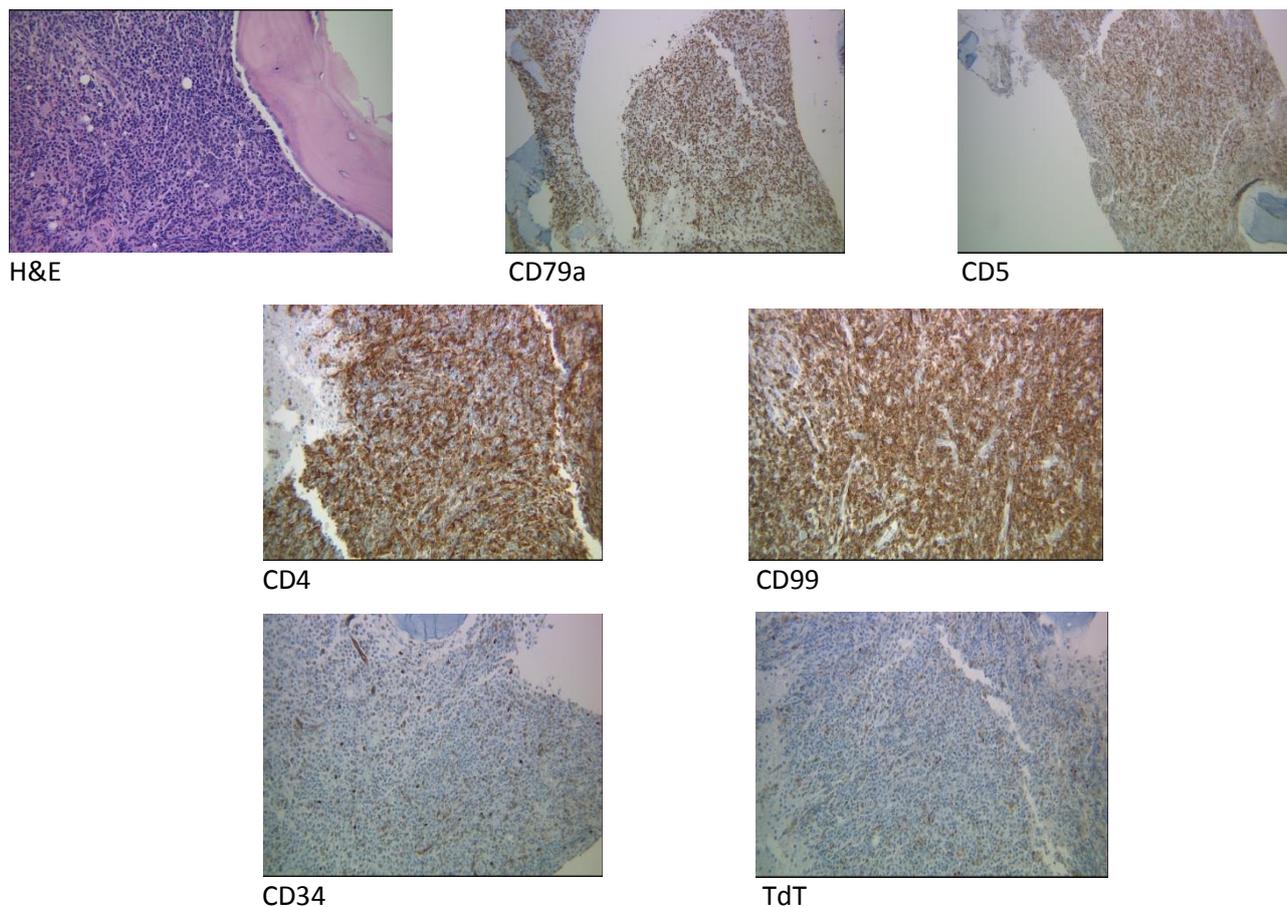
CD3

Following additional treatment for cutaneous CLL, the patient underwent allogeneic stem cell transplantation (SCT) in 2012 from an HLA matched (9 of 10) ABO incompatible male donor. The patient developed Graft-versus-host-disease in the gastrointestinal tract and a profuse body rash, which was treated with additional steroids. Three months after SCT, a bone marrow biopsy was performed, which revealed a variably hypo-cellular marrow without evidence of CLL by morphology or by flow cytometry. Chimerism, however, showed 0% donor CD34 positive cells indicative of graft failure. In July 2013, the patient had CT scans of the chest, abdomen and pelvis, revealing increasing pathologic lymphadenopathy within the neck, axillae, and pelvis.

Bone marrow biopsy was performed which showed complete replacement of the bone marrow by CLL and newly diagnosed Precursor T-

cell lymphoblastic leukemia (Figure 2). Histologically, the bone marrow showed 100% cellularity, with diffuse infiltration by small atypical lymphoid cells. Approximately 30-40% of the neoplastic cells were positive for PAX-5, CD79a, and CD5 by immunohistochemistry staining. In addition, the majority (approximately 60%) of the bone marrow was replaced by cells positive for CD3, CD4, CD99 with partial expression of CD34 (10-15%). This is consistent with Precursor T lymphoblastic leukemia. The cells were negative for TdT and no residual normal hematopoietic tissue was identified. With the diagnosis of Precursor T lymphoblastic leukemia, the patient underwent remission-induction therapy with Hyper-CVAD regimen. The patient is now in the process of undergoing second allogeneic transplantation for the treatment of Precursor T lymphoblastic leukemia.

Figure 2. July, 2013 bone marrow biopsy (CLL with secondary diagnosis of T-ALL)



DISCUSSION

There have been numerous cases in the literature reporting a composite T and B-cell lymphoma simultaneously occurring in one patient, with the highest percentage owing to the coexistence of Peripheral T-cell lymphoma (PTCL) and CLL [8]. However, to our knowledge, there are only a few cases reported of T-ALL and CLL occurring within one patient [8]. There are multiple proposed mechanisms that may link the existence of dual lineage malignancies in composite lymphomas, including our exceptionally rare case of simultaneous CLL and T-ALL. Some of the hypothesis includes a common genetic predisposition, a malignant transformation of a common progenitor cell, immune deregulation, chronic stimulation of T-cells by the B-CLL cells, adverse effects of chemotherapy exposure, increased T-cell resistance to apoptosis, or to the slight occurrence of pure chance.

A common progenitor cell giving rise to a malignant transformation has potential to result in

multiple neoplasias of different cell lineages [8]. Tadeusz et al states that some of the CLL and the Richter transformation cells have proven to originate from the same clone [6]. However, in patients' with aggressive lymphomas, there were no shared features with the CLL cells [6]. In an earlier study, Preudhomme et al claims that six cases revealed similar immunoglobulin chain isotypes in Acute Lymphoblastic Lymphoma cells as seen in the CLL cells [4]. Identical cytogenetic abnormalities were present in both ALL and CLL in one patient [4]. Development from a primary clone is a reasonable explanation however, even in any one given study, this does not hold true for all cases. There may also be a familial or acquired common genetic predisposition giving rise to two or more malignancies developing independently [8]. If this is the case for some patients, we would expect to see an increase of these related tumors within a family line. It may be difficult to confirm the presence of a common progenitor cell or a genetic predisposition when the two malignancies are located in overlapping areas of growth.

Identification of gene rearrangements of morphologically distinct malignancies are only molecularly achievable to prove if the two components have occurred in separate locations [8].

Chronic activation of T-cells by the neoplastic B-CLL represents a well-documented phenomena in the literature [7]. This may essentially stimulate a clonal expansion of malignant T-cells and result in a secondary lymphoma [8]. Martinez A. et al screened 100 peripheral blood samples from newly diagnosed CLL patients for the presence of clonal T cell populations. Evidence of clonal T-cell expansion was seen in 8 patients and an increased number of lymphocytes with large granular morphology in 7 of the 8 cases [9]. This is a significant percentage of CLL cases exhibiting T-cell stimulation by the B-CLL cells. It has also been discovered that T-cells in CLL patients tend to display a greater resistance to apoptosis when compared to T-cells of disease free individuals. As a result to these disease related modifications, potentially abnormal T-cells are under excessive activation and are more resilient to regulation thereby having a greater tendency to form secondary malignancies [7, 10].

Immune dysregulation or decreased immune-surveillance may allow for the proliferation of multiple malignant clones by creating a sustainable, non-regulated environment [8]. This theory is supported by the increased likelihood of developing lymphomas in known cases of autoimmune disorders, such as chronic

lymphocytic thyroiditis or Sjogren's syndrome [8]. Additionally, exposure to a toxic agent, such as chemotherapy for treatment of one malignancy may induce a secondary malignant process [6, 8]. Tedeusz et al illustrates how alkylating agents or purine nucleoside analogs may be associated with an increased incidence of second malignancies in patients with CLL [6].

Secondary malignancies are frequent complications in patients with chronic lymphocytic leukemia CLL. The precise mechanism of the transformation and simultaneous coexistence of these cases are still under investigation with numerous proposed hypotheses. Many attempts have been made to draw a correlation of CLL to the various Richter's transformations and all of its variants; however any particular finding cannot be applied to all cases. These coexisting processes are most likely multifactorial and are in need of further investigation and monitoring to accurately understand potential associated factors and the underlying pathophysiology.

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CONFLICT OF INTEREST

The authors certify that there is no actual or potential conflict of interest in relation to this article.

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