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Case Report
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Acute Monocytic Leukemia Secondary to Angioimmunoblastic T-Cell Lymphoma: A Case Report and Literature Review

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Abstract

Background: Angioimmunoblastic T-Cell Lymphoma (AITL) is an aggressive lymphoma with multi faced clinical features. However, it's rare to see secondary Acute Myeloid Leukemia (AML) during the AITL progression. We reported an AITL case proceeding to AML during the initial treatment and summarized the AML cases secondary to AITL from the literature.

Case Report: A 77-year-old woman presented with lymphadenopathies for one year; the lymph nodal biopsy and immunohistochemistry staining confirmed the AITL diagnosis without RHOAG17V and IDH2R172 mutations and excluded bone marrow infiltrated. After four courses of CHOP regimen treatment, the patient achieved a partial response. However, the bone marrow was observed the remarked increase of monoblasts, exceeding 70% of total monocytic linage, making the acute monocytic leukemia diagnosis. From the initial diagnosis of AITL to the diagnosis of AML was seven months, and the overall survival time was seven months.

Conclusion: We presented a rare AITL case, indicating that secondary AML could occur not only after but also during the treatment of AITL. Besides, as the alkylating agents and topoisomerase II inhibitors are the main drugs to treatment-related AML, exploring the new treatment regimen to avoid the therapy-related AML in AITL is warranted. Furthermore, high-throughput sequencing technology should be considered in this rare situation to better investigate the relationship between AITL and AML in the future.

Keywords: Angioimmunoblastic T-cell lymphoma; Secondary acute monocytic leukemia; Treatment; Acute myeloid leukemia; Therapy-related acute myeloid leukemia

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Introduction

Angioimmunoblastic T-cell Lymphoma (AITL) is an aggressive lymphoma; generally, most patients had symptoms with fever, lymphadenopathies, anemia, rashes, and some cases with polyserous effusions and hemophagocytic lymphohistiocytosis, which leading to a poor prognosis with a 5-year OS rate of 30% under the anthracyclines-based treatment [1,2]. As the AITL is derived from Follicular T Helper (TFH) cell in the germinal center, the dysregulated function of malignant TFH affects the Tumor Microenvironment (TME), leading to the aberrance of differentiation and function of B cell in follicle [3]. In rare cases, we could see the malignant transformation of B cells in TME under the different disease stage of AITL, like diffuse large B cell lymphoma [4,5]. However, it's rare to see secondary Acute Myeloid Leukemia (AML) during the AITL progression. Here, we reported an AITL case proceeding to AML during the initial treatment and summarized the AML cases secondary to AITL from the literature.

Case Presentation

A 77-year-old woman presented with bilateral cervical enlarged lymph nodes, without any other symptom for one year. As the growth of the lymph node, the patient appeared fatigued, anorexia and dyspnea, and peripheral blood test found the decrease of the platelet. To definite diagnosis, a left cervical lymph node excision biopsy revealed diffuse hyperplasia of medium-sized atypical lymphocytes and increased small blood vessels with branches and swelling endothelium. Atypical lymphocytes were positive for CD3, CD5, CD4, Bcl-6, CXCL-13, PD-1, CD30, and Ki-67 index 60%, negative for CD20, CD8, and CD10. Polymerase Chain Reaction (PCR) and genes can found TCRG

Table 1: Summary cases of AML secondary to AITL in literature.

Authors	No.	Age (y), sex	Treatment regimen for lymphoma	Gene detection in AITL	Time to diagnosis AML (type)	Gene detection in AML	Overall survival
Huang WJ [9]	1	58, F	CsA + Prednisone, EPOCH, R-DA-EPOCH, VP16+G-CSF, CBV+ASCT, MTX	Not mentioned	14 months (no mentioned)	No MLL/ELL	Not mentioned
Shang Y [10]	3	65, M	GDPT	Not mentioned	9.5 months (AML-M3)	No AML1/ETO No BCR-ABL No MLL rearrangement	20 months
		70, M	CHOP, GDPT, CTX+ Thalidomide	Not mentioned	14 months (AML-M2)	No AML1/ETO No BCR-ABL No MLL rearrangement	27 months
		64, M	EPOCH, GP + radiotherapy, CTX + CsA	Not mentioned	34 months (AML-M3)	No PML-RARα	Not mentioned
Lewis NE [6]	1	63, F	Chemotherapy, ASCT	$TET2^{C1289Y}$, $TET2^{L1899Sfs*9}$, $DNMT3A^{R771}$, No $DNMT3^{AC861Y}$ No $RUNX1^{A329Sfs*271}$, $ARID1B^{S914N}$, $DDX3X^{V526A}$, $NFE2^{T318A}$, $ROBO1^{G904R}$	32 months (AML with monocytic differentiation)	$TET2^{C1289Y}$, $TET2^{L1899Sfs*9}$, $DNMT3A^{R771}$, $DNMT3^{AC861Y}$ $RUNX1^{A329Sfs*271}$	33 months
Present case	1	77, F	CHOP	No $RHOA^{G17V}$, No $IDH2^{R172}$	7 months (AML-M5)	Not mentioned	7 months

AML: Acute Myeloid Leukemia; CsA: Cyclosporine A; CTX: Cyclophosphamide; MTX: Methotrexate; CBV: Cisplatin, Bleomycin, Vindesine; EPOCH: Etoposide, Dexamethasone, Vincristine, Cyclophosphamide, Adriamycin; R-DA-EPOCH: Rituximab, Dose-Escalated EPOCH; VP16: Etoposide; G-CSF: Granulocyte Colony Stimulating Factor; GDPT: Gemcitabine, Cisplatin, Dexamethasone, Thalidomide; CHOP: Cyclophosphamide, Adriamycin, Vincristine, Prednisone; CTX: Cyclophosphamide; GP: Gemcitabine, Cisplatin; ASCT: Auto- Hematopoietic Stem Cell Transplantation

rearrangement, indicating the AITL diagnosis.

Further, we found no RHOAG17V and IDH2R172 mutations *via* Sanger sequence. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography-Computed Tomography (PET-CT) indicated that lymph nodes from cervical, axilla and celiac were involved with the maximum SUV value 2.67. The invasion was excluded from the bone marrow detection via aspirate, biopsy, and Flow Cytometry (FCM). Several examinations were performed, including plasma Epstein-Barr virus DNA (positive, less than 50 copies/mL), serum anti-nuclear antibody (positive, 1:320), serum protein electrophoresis and immune fixation electrophoresis (without monoclonal protein). We initiated treatment with CHOP (cyclophosphamide, pirarubicin, vincristine, and prednisone) for chemotherapy and recombinant human Granulocyte Colony-Stimulating Factor (rhG-CSF) prevention for neutropenia; the patient achieved Partial Response (PR) through enhanced Computed Tomography (CT) evaluation after 2 courses. Before the fifth course of treatment, the patient was admitted to the emergence department in our hospital with gingival bleeding, epistaxis, and ecchymoses; peripheral blood detection presented: white blood cell 49.74 × 10^9/L, neutrophils 32.33 × 10^9/L, platelet 29 × 10^9/L. Considering the growth of peripheral white blood cells (71.47 × 10^9/L) and disease progression, we performed the bone marrow detection and found remarked increase of monoblast, exceeding 70% of total monocytes (AML-M5), further FCM confirmed the diagnosis of acute monocytic leukemia (Figure 1). As the disease progressed rapidly, the patient died five days after diagnosis. The cumulative dose of cyclophosphamide and Adriamycin liposomes was 3300 mg and 130 mg. From the initial diagnosis of AITL to the diagnosis of acute monocytic leukemia was seven months.

Discussion

AITL has multifaced clinical manifestations, probably due to its complex TME. Our case presented another face in AITL development and progression. To better understand the relationship between AITL and AML, we searched the literature, found 5 AML cases secondary to AITL. For the 5 cases and the one we presented here, the median year was 64.5-years-old, the ratio of male to female 1:1, AML occurred during, after the initial treatment, in disease relapse and after ASCT (Table 1). Two patients detected the gene alternation in AITL samples, found $TET2^{C1289Y}$, $TET2^{L1899Sfs*9}$, $DNMT3A^{R771}$, $RUNX1^{A329Sfs*271}$, $ARID1B^{S914N}$, $DDX3X^{V526A}$, $NFE2^{T318A}$, $ROBO1^{G904R}$ with more than 20% Variant Allele Frequency (VAF). It found no gene rearrangement related to acute myeloid leukemia in 4 patients, of which 1 patient had the same mutated gene as in AITL. The overall survival time after AML was diagnosed was very short, not exceeding 13 months.

Recently, Lewis et al. reported [6] that TET2, DNMT3A mutations in Clonal Hematopoiesis (CH) is prevalent in AITL that may give rise to both AITL and AML. In their follow-up, 1 AITL patient developed with AML, suggesting that TET2, DNMT3A mutation in Hematopoietic Stem Cells (HST), and further chemotherapy may associate with secondary AML in some AITL cases. In our case, we found no $RHOA^{G17V}$ and $IDH2^{R172}$ mutations in AITL tumor cells, and did not detect the TET2 and DNMT3A mutations in both AITL and AML cells.

AML can arise from patients with hematological disorders (mainly NHL) or as a consequence of prior therapy [7]. Xu et al. reported [8] that 10-year cumulative incidence of AML secondary to Non-Hodgkin Lymphoma (NHL) was 0.7%, most of which were aggressive B-NHL. Those who aged ≥ 45-years-old (HR 3.77, 95% CI, 1.395-10.191, p=0.009) or received more than eight cycles of chemotherapy (HR 3.76, 95% CI, 1.472-9.557, p=0.006) had increased risk of leukemia. Additionally, it has been reported that alkylating agents and topoisomerase II inhibitors are the main drugs to therapy-related AML, the average latency period was 5-10 years (alkylating agents) or 1 to 5 years (topoisomerase II inhibitors) [7]. Our patient presented with AML during the initial chemotherapy course. The

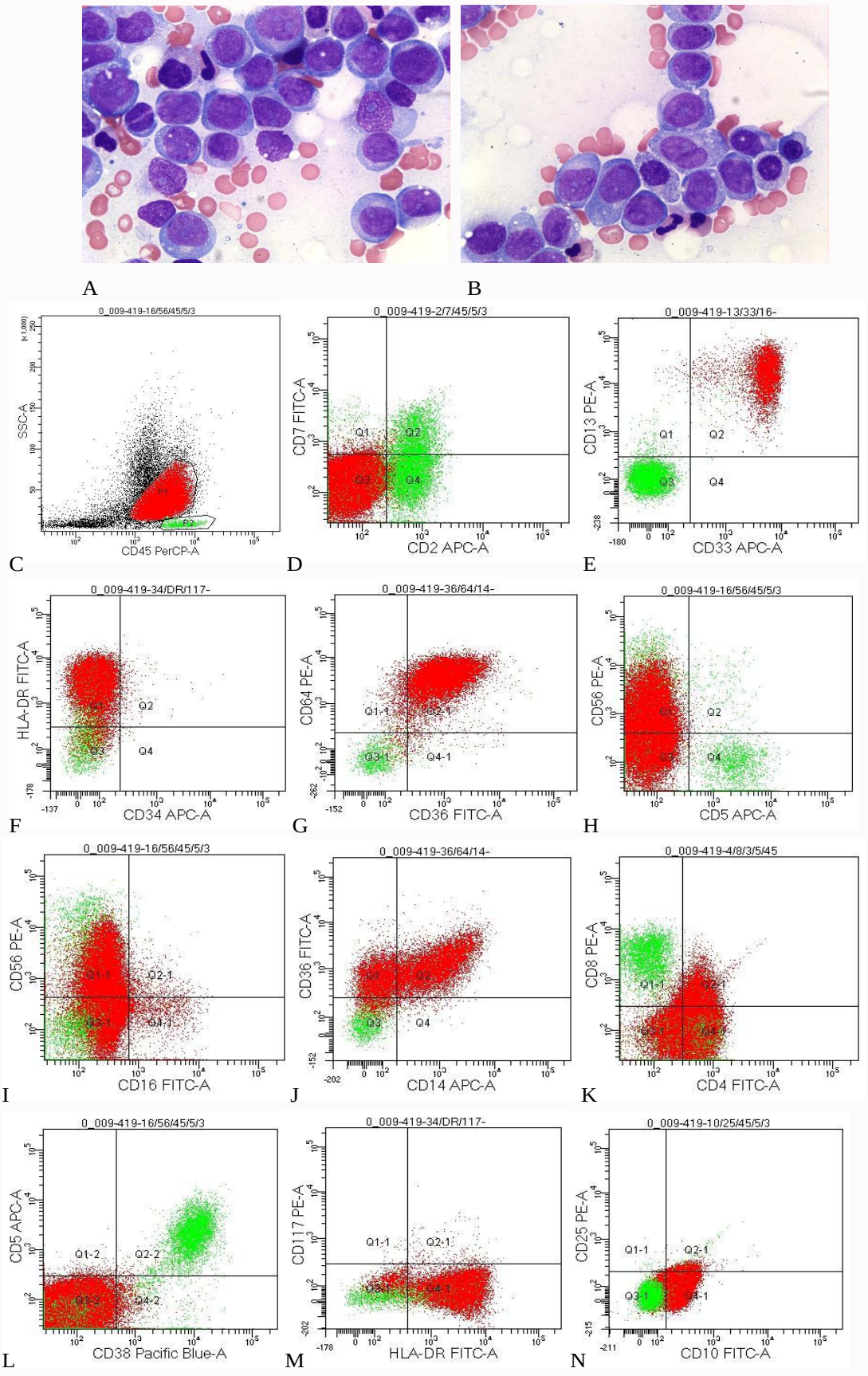

Figure 1: AITL patient presented with AML. A, B: The bone marrow aspirate showed increased monoblasts. C-N: The FCM analysis of leukemia cells in bone marrow, showed the monoblasts positive for HLA-DR, CD4, CD10, CD13, CD14 (partial), CD33, CD36, CD64 and CD56 (partial), CD16 (minority); negative for CD34, CD117, CD3, CD5, CD7 and CD19.

interval time was 7 months.

Conclusion

We presented a rare case of AITL, indicating that secondary AML could occur not only after but also during the treatment of AITL. The alkylating agents and topoisomerase II inhibitors are the primary drugs for treatment-related AML, exploring the new treatment regimen to avoid the treatment-related AML in AITL are warranted. Furthermore, high-throughput sequencing technology should be considered in this rare situation to better investigate the relationship between AITL and AML in the future.

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Author Contributions

Yang C and Zou L: Conception and design. Yang C: Collection and analysis of data. All authors were involved in manuscript writing, final approval of the manuscript, and accountability for work.

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