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Case Report

Isolated Intracerebral Diffuse Large B Cell Lymphoma Secondary to Chronic Lymphocytic Leukemia: Case Report and Literature Review

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Abstract

Patients with Chronic Lymphocytic Leukemia (CLL) may develop into Diffuse Large B Cell Lymphoma (DLBCL), which has been described as Richter Syndrome (RS). The prognosis of RS is dismal and the median survival ranges from 6 to 8 months. However, Isolated parenchymal DLBCL lesions in the Central Nervous System (CNS) secondary to CLL is extremely rare. Controversy exists as to whether diffuse large B cells of RS were derived from the preexisting CLL or de novo clone. Here we report a case of a 60-year-old male patient who had a 5-month history of CLL without treatment and developed into isolated parenchymal DLBCL in CNS. In this case, we demonstrated that the clone of DLBCL in CNS was originated from unrelated B cells but not from the preexisting CLL cells by Immunoglobulin Heavy chain (IgH) gene analysis.

Keywords: Secondary diffuse large B cell lymphoma; Chronic lymphocytic leukemia; Richter syndrome; Central nervous system; Immunoglobulin heavy chain gene

Introduction

Richter Syndrome (RS) is the development of an aggressive lymphoma in patients with CLL or SLL [1]. In 1928, Dr. Richter firstly reported RS as a secondary large cell immunoblastic lymphoma that developed in a 46-year-old man with Chronic Lymphocytic Leukemia (CLL) [2]. As previously reported, Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) have an increased incidence risk of second malignancy and at least 3% of them develop Diffuse Large B Cell Lymphoma (DLBCL) [3]. In fact, DLBCL secondary to CLL is not always derived from the clone of the preexisting B-CLL and Immunoglobulin heavy chain gene (IgH gene) analysis is one of the key method to differentiate the clones [4]. To our knowledge, few investigators discriminated the clones in RS patients. In this case, we reported a patient who has developed DLBCL in brain after the initial diagnosis of CLL and analyzed the clones of DLBCL.

Case Presentation

A 60-year-old man was referred to us because of leukocytosis of 28.6×10^9/L and lymphocytosis of 18.02×10^9/L in the peripheral blood in September 2016. Bone marrow smears were predominantly shown as mature lymphocytoid morphology. The flow cytometric analysis found that 28.6% monoclonal B lymphocytes, and his immunophenotype were as follows: CD5 +, CD19 +, CD20 +, CD23 +, CD22 (dim), FMC-7 (dim) and CD10-. His condition is generally good with no obvious organ enlargement. He was classified as stage CLL according to Rai classification and no therapeutic interventions were undertaken. Five months later, he was admitted to neurosurgery department because of language dysfunction and consciousness disturbance. Magnetic Resonance Imaging (MRI) showed a 2.5x2.8-cm size signal abnormality with peripheral edema in the deep left temporal region, and significant ring enhancement after gadolinium injection (Figure 1). Positron Emission Tomography-Computed Tomography (PET-CT) of whole body was normal except well-defined mass lesions with an increased fluorodeoxyglucose uptake in left temporal area (SUVmax: 10.27) (Figure 2). Tumor excision was performed in March 2017 and histological examination revealed the aggressive diffuse large B-cell lymphoma. The tumor cells expressed CD20, CD79a, PAX-5, CD5, BCL-2, BCL-6, MUM-1, c-myc and p53 but not CD23, CD10, CD2, CD3 or cyclinD1. Particularly, the Ki-67 labeling index is above 80%. Therefore, DLBCL was considered in the central nervous system from these findings.

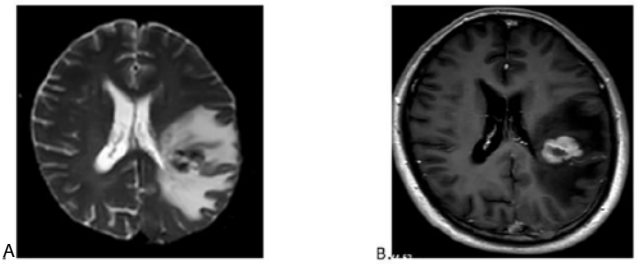

Figure 1: Magnetic Resonance Imaging (MRI) showed a 2.5×2.8 cm size signal abnormality with peripheral edema in the deep left temporal region, and the mass indicated significant ring enhancement after gadolinium injection.

The patient's laboratory tests were as follows: monoclonal B-cell lymphocytosis with the same phenotype as at the initial presentation in the bone marrow. Bone marrow biology revealed predominantly interstitial infiltration with small lymphocytes, which were positive for both CD20, CD79a, MUM1 and CD5 (lower expression). Cerebrospinal Fluid (CSF) analysis showed WBC 13×10E6 /L, RBC 210 ×10E6 /L, glucose 4.34 mmol /L, and protein 0.38 g /L. Mature

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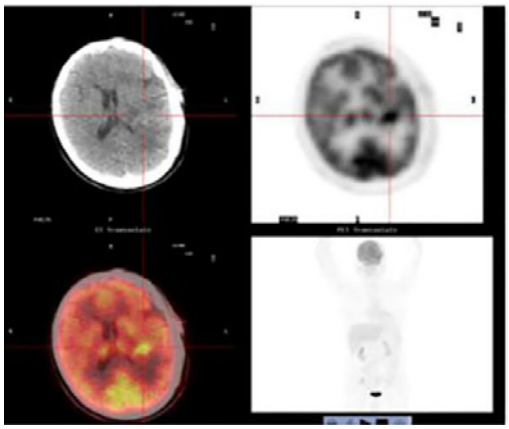

Figure 2: Positron emission tomography-computed tomography scan showing well defined mass lesions in left temporal area with an increased fluorodeoxyglucose uptake.

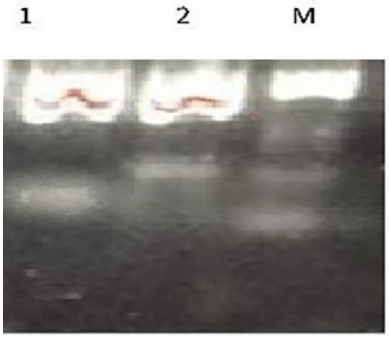

Figure 3: Polymerase Chain Reaction (PCR) amplification of immunoglobulin heavy chain genes.
1: brain sample, 2: Peripheral Blood (PB) sample, M: a molecular marker.

B-cell lymphocytes were detected by flow cytometry in the CSF. In addition, HIV sorological test, Fluorescence *in situ* Hybridization (FISH), gene mutations and Single Nucleotide Polymorphisms (SNPs) were all negative. Lactate dehydrogenase was normal. The patient diagnosed with CLL and diffuse large non Hodgkin lymphoma of the CNS.

The analysis of rearrangement of IgHs gene was performed in order to reveal the relationship of the CNS lesion and preexisting CLL as previously reported methods [5]. The IGH rearrangement pattern of different sized band from brain DLBCL and peripheral blood indicated that CLL and DLBCL cells were originated from different B-cells clones (Figure 3). Moreover, we also performed the analysis of molecular abnormalities of brain tumor and bone marrow, however gene mutations were not detected in our case.

The patient received two courses of R-MVBP regimen(rituximab 375mg/m^{2}d0, methotrexate 3g/m^{2}d1,d15, etoposide 50mg/m^{2}d2, carmustine 140mg/m^{2}d3, dexamethasone 15mg d1-4,d15-18) combined with intrathecal methotrexate 15mg and cytarabine 40mg. MRI showed a significant reduction of tumor size (Figure 4). Unfortunately, seizures and aphasia manifested as a sudden clinical deterioration of symptoms after three cycles of R-MVBP, and cerebral lesions recurred in September 2017 (Figure 4). Then, the patient was

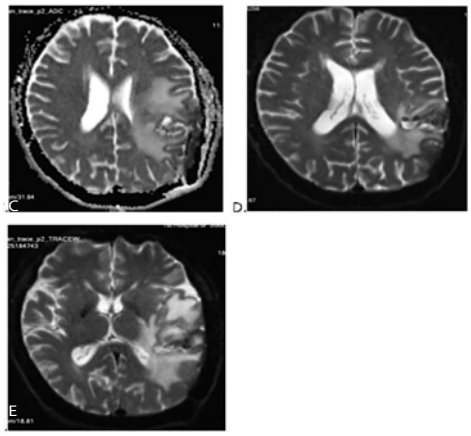

Figure 4: Left temporal tumoral lesion after surgery (3.1*2.6cm) (C), Left temporal tumoral lesion after therapy (1.8*1.2cm) (D), Reoccurrence of tumoral mass (2.3*1.7cm) (E).

started on specific chemotherapy protocol (high dose methotrexate 8g d1 with temozolomide 300mg d7-11 and ibrutinib 560mg d1-d10) for central nervous system lymphoma. In post two cycles, MRI showed the similar lesions as before. We suggested radiotherapy to the patient, and he was treated with brain irradiation (CTV 24Gy/12f, GTVnx 45Gy/22f, pGTVnx 40Gy/22f). However, the treatment was forced to stop at 14th because of his recurrent seizures. Later, the patient returned to the local hospital to perform the remained radiotherapy and MRI showed the lesions reduced. Until now, It remained a problem for him to speak frequently and to walk normally.

Discussion and Conclusions

Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) have an increased incidence risk of second malignancy [3]. Symptomatic leukemic infiltration of the brain in CLL patients occurs rarely [6]. Isolated intracerebral DLBCL secondary to chronic lymphocytic leukemia is rarely reported and it is generally believed, although incorrectly, that second DLBCL represents a transformation event for a patient with CLL (Richter syndrome). We report a patient who had CLL for 5 months without treatment and developed into isolated parenchymal DLBCL in CNS. To our knowledge, only few cases have been reported (Table 1). The patients generally presented fever in the absence of infection, night sweats, weight loss, rapid progression of lymphadenopathy [7]. In addition to these symptoms, brain invasion manifested as headache, speech dysfunction, disturbance consciousness, hemiplegia, ataxia, dementia, seizures [8]. In our case, the primary manifestation of the patient was language dysfunction and disturbance of consciousness. MRI firstly suggested the presence of a brain tumor, DLBCL was diagnosed according to histological and immunophenotypic investigations of the tumor after its surgical removal.

Richter syndrome is understood to describe the development of an aggressive lymphoma in patients with indolent lymphoma. The patient presented in this study may be described as having Richter syndrome, presenting in and confined to the brain (no additional sites of transformation were identified). Continued controversy exists as to whether diffuse large B cells of RS emerges from the preexisting CLL or represents a second de novo neoplasm [4]. It is reported

Table 1: Clinical summary previous published cases of intracerebral DLBCL secondary to CLL.

Source	Age (year)	Sex	Clinical presentation	Treatment	Outcome
Ishida F et.al, [5]	66 2	F	Fatigue, difficulty walking, disturbance consciousness, left hemiplegia	Radiation therapy, Rituximab	Recur(1year later)
Gogia A et.al, [12]	56 10	M	Fatigue, generalized lymphadenopathy and splenomegaly, headache, disorientation, left sided hempaiparesis	Chemotherapy (DeAngelis protocol) WBRT	Reduction in the size of lesions
Resende LS et.al, [13]	74 6	M	Mental confusion, bewilderment. gait disorders	Intrathecal chemotherpy radiotherapy Craniotomy	die
Bagic A et.al, [8]	58 3 y 4 m	F	Left leg paresis, seizures	Dexamethasone WBRT Rituximab	No further follow information
Bayliss KM et.al, [14]	78 concurrent	M	Disorentation, unable to follow simple commands	Craniotomy	die
O'Neill BP et.al, [15]	64 3	M	Headache, confusion, fatigue, mild dementia, aphasia, mild right hemiparesis	WBRT	Alive (3 year)
	70 10	M	Language dysfunction and right hemiparesis aphasia	Craniotomy WBRT	die
Stuplich M et.al, [11]	56 1m	M	Seizure, mild left sided hemiparesis	WBRT chemotherpy	die
	71 1	F	Vertigo, gait disturbance	WBRT chemotherpy	die
Robak T et.al, [16]	60 7	F	Left sided hemiparesis	Craniotomy Radiation therapy	–
Our case	60 5 m	M	Language dysfunction, disturbance consciousness.	Craniotomy Chemotherpy WBRT	alive

that 80% RS were derived from CLL (Identical nucleotide sequence was detected in the immunoglobulin heavy variable rearrangement between CLL and RS samples) while in the remaining cases, RS cells were clonally unrelated. In our case, different sized bands of IgH rearrangement from brain DLBCL and peripheral blood were observed, it demonstrated that CLL and DLBCL cells were derived from different B-cells clones. In our opion, we consider that only clonally related RS is a true transformation event as previously reported [7].

In addition, clonal evolution is common feature of RS at the time of disease transformation [7]. Rossi et al, reported 86 cases of RS. They noted that TP53 (10/18 cases) and c-MYC (3/4 cases) aberrations were acquired at the time of disease transformation [9]. Some investigators reported that TP53 and NOTCH1 mutations were commonly observed in RS and rarely in de novo DLBCL [10]. We also performed the analysis of molecular abnormalities of brain tumor and bone marrow, but gene mutations such as TP53 deletion, NOTCH 1 activation and MYC abnormalities were not detected in our case.

It has been established that patients with CLL/SLL have markedly increased rate of second malignant, which is the most common cause of death [3]. As previously reported, patients with isolated brain infiltration survived from 22 days to 2years [8]. However patients of RS with unrelated clone have a better survival rate. Therapeutic strategies of RS include radiation therapy, chemotherapy, targeted therapy and hematopoietic cell transplantation, but we still do not know which is optimal. Stem cell transplantation remains an important therapeutic modality for patients with RS. Unfortunately, only a minority of patients with RS is able to undergo SCT, likely due to older age in our patient. High dose methotrexate are specifically developed for CNS lymphoma with blood brain barrier-penetrating chemotherapy and results of clinical examinations in Primary Central Nervous System Lymphoma (PCNSL) patients demonstrate usefulness of HD-MTX-based chemotherapy followed by whole-brain radiotherapy [11]. This patient was refractory to R-MVBP chemotherapy, we then used methotrexate 8g followed by WBRT as salvage treatment, and unfortunately the effect was unsatisfied [12-16]. Clinical trials should be performed in the future in order to establish an optimal therapeutic strategy for patients with RS.

In summary, isolated parenchymal DLBCL lesions in the Central Nervous System (CNS) secondary to CLL is extremely rare. Relatively few cases analyzed by IgH variable sequencing have been reported. We analyse the clonal relationship to better access the prognosis of the patients. However, either clonally unrelated or clonally related RS, therapeutic strategies needs to be explored. Early recognition of symptoms, especially nervous system symptoms, and accurate histological diagnosis and immunophenotyping may lead to adopt timely CNS directed treatment and reduce mortality.

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