

Type of Treatment Can Effect on Transformation of Chronic Lymphocytic Leukaemia to Diffuse Large B-cell Lymphoma: A Rare Case with Review of Literature

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Abstract Richter transformation is defined as a diffuse large cell lymphoma, occurring by transformation of chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL) is the most common type of richter syndrome. Herein, we describe report of a 51 year-old man in western Iran that referred to Hematology Clinic with complaint of three months of weight loss and sweating with generalized abdominal lymphadenopathy and the Bulky cervical lymph node. Pathology's specimens for him demonstrated CLL in the patient (Rai system stage 4) and during seven years ago, he was treated with fludarabine and cyclophosphamide regiment for 6 courses. Cervical biopsy pathology reported a new diagnosis of diffuse large B-Cell lymphoma and also immunohistochemistry (IHC) analysis showed CD3, CD20, CD45 were positive and Bcl-2 was negative and so he was treated with new regiment of R-CHOP for 6 courses. One month after last course of chemotherapy, Cerebrospinal fluid cytology was positive with lymphomatous involvement, and also brain CT SCAN showed parenchymal involvement and therapy with high dose Methotrexate began for him. The result is that specialists should be careful that probably fludarabine therapy alone or combination it with other drug especially cyclophosphamide can effect on transformation CLL to DLBCL.

Keywords: Cyclophosphamide, Fludarabine, Lymphoma, Richter Syndrome

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1. Introduction

Richter's syndrome (RS) involves the development of an aggressive lymphoma and is a complication and disease transformation of chronic lymphocytic leukaemia (CLL) where clinical features, laboratory findings and treatment clearly differ from that of CLL [1,2] diffuse large B-cell lymphoma (DLBCL) is the most common type of RS [2]. Transformation of CLL into a large cell lymphoma has an incidence of 3-10% [3].

The RS was first described by Maurice N. Richter in 1928 as a syndrome of weight loss, abdominal discomfort, diffuse lymphadenopathy, massive organomegaly and lymphocytosis [4].

Central nervous system lymphomatous involvement in the setting of chronic lymphocytic leukemia (CLL), known as Richter transformation, is rare that in described cases involve isolated leptomeningeal or parenchymal involvement [5,6].

Herein, we report a case of a male patient with CLL who later referred to Our Clinic again with signs of DLBCL.

2. Case Report

In Apr 2014, a 51 year-old man referred to Hematology Clinic with complaint of three months of weight loss and sweating with generalized abdominal lymphadenopathy and the Bulky cervical lymph node. In future evaluation, he suffered of chronic lymphocytic leukemia (B-Cell type) (CD5, CD20 and CD23 were positive) that the pathology's specimens, shown in Figure 1A to Figure 1C, demonstrated CLL in the patient (Rai system stage 4) and during seven years ago, he was treated with fludarabine and cyclophosphamide regiment for 6 courses. In Jun 2014, cervical biopsy pathology reported a new diagnosis of diffuse large B-Cell lymphoma (Figure 1D) without lesion and it was documented with immunohistochemistry (IHC) analysis that CD3, CD20, CD45 were positive and Bcl-2 was negative. He was treated with new regiment of R-CHOP for 6 courses. At Aug 2014, final diagnosis of

diffuse large cell lymphoma of lymph node was established (Richter syndrome) and the patient became candidate for bone marrow transplantation.

One month after last course of chemotherapy, the patient referred again to our Clinic with complaint of headache and high-grade fever. Cerebrospinal fluid

cytology was positive with lymphomatous involvement, and also brain CT SCAN showed parenchymal involvement. Gradually the level of his conscious decreased, therapy with high dose Methotrexate beginning and in follow with intrathecal chemotherapy. He referred for transplantation consult.

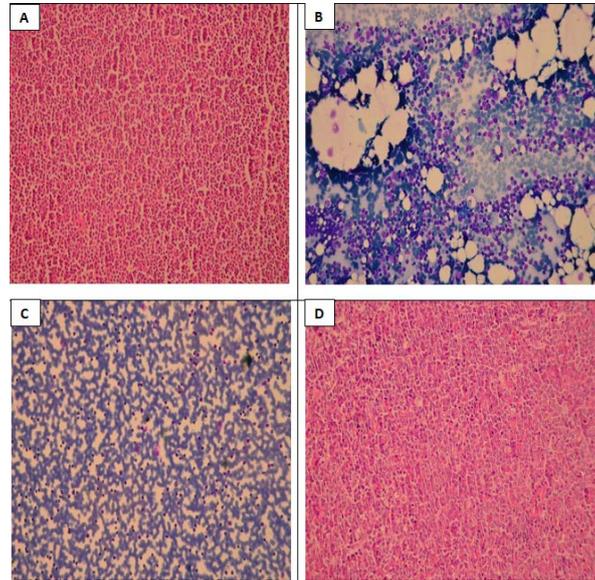


Figure 1. Pathology slide demonstrating chronic lymphocytic leukemia of A: lymph Node, B: Aspiration, C: Blood Smear and D: Pathology slide demonstrating diffuse large B-Cell lymphoma of cervical lymph node

3. Discussion

Richter transformation is defined as a diffuse large cell lymphoma, occurring by transformation of chronic lymphocytic leukemia (CLL) [5] and also Transformation of CLL into a large cell lymphoma has an incidence of 3-5% [3].

The [Table 1](#) shows case reports for patients with CLL that developed diffuse large B-Cell lymphoma between Jun 2000 and Sep 2014. The patients were almost male and Age at diagnosis of CLL was more than 50 years, except four cases. Patient complaints at the first visit were different of each other but leukocytosis, lymphadenopathy and fever were more complaints. Kind of treatment for CLL was more with fludarabine, chlorambucil, cyclophosphamid.

Table 1. Case reports for patients with chronic lymphocytic leukemia that developed diffuse large B-Cell lymphoma (Jun 2000- Sep 2014)

Reference	Sex	Age at diagnosis of CLL	Patient complaints at the first visit	Treatment of CLL
1	Male	52	Fever, neck and abdominal swelling	Chlorambucil
2	Female	66	Leukocytosis	Cyclophosphamid and Prednisone
4	Female	45	Lymphadenopathy and Leukocytosis	Chlorambucil, Prednisone, Fludarabine, Cyclophosphamide and Mitoxantrone
5	Male	59	Headache, vomiting and left occipital mass	Fludarabine
6	Male	68	Leukocytosis	Chlorambucil
7	Female	77	Anemia	Chlorambucil and Prednisone
8	Male	85	Vague chest, shortness of breath and septic with fever, tachypnea, and tachycardia	-
9	Female	52	hypertension	Fludarabine + Cyclophosphamide
10	Female	64	Nodule on nose	Doxycycline
10	Male	58	Erythematous rash on the right side of his back	-
10	Male	61	Large bruises on his right wrist and forearm and leukocytosis	Fludarabine
The present case	Male	44	Weight loss, sweating and lymphadenopathy	Fludarabine and Endoxan
11	Female	51	Chest Wall Swelling	Chlorambucil or Cyclophosphamide
12	Female	48	Leukocytosis (lymphocytosis), lymphadenopathy, and splenomegaly	Fludarabin and cyclophosphamide
12	Male	39	Lymphadenopathy, fever, and night sweats	Fludarabine, cyclophosphamide, and rituximab

The impact of initial fludarabine therapy on transformation to Richter syndrome (RS) in patients with chronic lymphocytic leukemia (CLL) is uncertain [13]. A study [3] suggested that high incidence of transformation can related to fludarabin therapy and also in our case and in a number of other cases [4,5,9,10,12], fludarabin therapy was used for treatment of CLL in the patients and it probably fludarabin can effect on transformation CLL to DLBCL. The Table 1 shows that combination of fludarabin with other drugs such as cyclophosphamide and endoxan in treatment of patients with CLL even in lower ages of 50 years can effect on transformation CLL to DLBCL. Solh M et al. [13] studied the outcomes of 521 patients with CLL who were randomized to initial fludarabine (F), chlorambucil (C) or F + C therapy that RS developed in 7%, 5% and 11% of patients, respectively. However, in future, it should consider to therapeutic options in patients of CLL. Although there is no published data on the prevalence of CNS involvement by RS, 5 (4%) had clinically identified CNS involvement. This low frequency of CNS involvement, performing of CNS staging (eg, lumbar puncture, magnetic resonance imaging of the head) only in patients with testicular, paranasal sinus, or epidural space involvement by DLBCL as well as those with 2 extranodal sites of disease, analogous to the approach in patients with de novo DLBCL.

The RS is a transformation to high-grade non-Hodgkin lymphoma in patients with CLL [7]. In our study, the patients was stage 4 in Rai system for CLL but other studies [8,12] showed that cases had stage 0 and 2, respectively. Therefore, Specialists should be careful that RS can create at each stage, and degree of CLL.

Isolated RS in the central nervous system (CNS) is very rare, a number of them with isolated leptomeningeal involvement, and rest of them with parenchymal involvement [6]. In our study, the patient had DLBCL in cervical lymph node that later cerebrospinal fluid cytology showed lymphomatous involvement, and also brain CT SCAN showed parenchymal involvement. This report shows an involvement of RS in two point of body and it is a very rare case.

4. Conclusions

Initial treatment type for CLL is important and specialists should be careful that probably fludarabin therapy alone or combination it with other drug especially cyclophosphamide can effect on transformation CLL to DLBCL even in lower ages of 50 years and at each stage, and degree of CLL. We think that one important point for

this case is CSF analysis, that must be considered in protocol of therapy that be missed in this case. This mismanagement can be cause of CNS involvement very soon as our expectation.

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