Int J Clin Exp Pathol 2017;10(8):8858-8862
www.ijcep.com /ISSN:1936-2625/IJCEP0057397

Case Report

Spinal lesion as the first manifestation of high-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements

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Received May 14, 2017; Accepted June 20, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements is a rare lymphoma which has highly aggressive clinical manifestations. The reporting case is a 72-year-old female presented with lumbago and weakness in the lower limb due to a mass at T8-10 revealed by computed tomography (CT) scan. Histological feature of the lesion shows an abundant and diffuse large lymphoid cells infiltration. Immunophenotype meets with germ center B cell (GCB) lymphoma (Hans algorithm). *C-MYC* and *BCL2* gene rearrangements are detected by fluorescence in situ hybridization (FISH). It's a rare and typical case of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements with uncommon clinical manifestation.

Keywords: Spinal, high-grade B-cell lymphoma, *MYC*, *BCL2*, gene rearrangement

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoid neoplasm, accounting for 35~40% non-Hodgkin lymphoma (NHL). High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements once termed as double hit (or triple-hit) B-cell lymphoma (DHL/THL) has the similar morphology and immunophenotype to DLBCL, but it presents more aggressive clinical behavior than latter. However, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements is rare. Only 5~10% of DLBCL can be defined as it. Making diagnosis of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (DHL/THL) is very challenging and genetic analysis should be necessary.

The known clinicopathological characteristics of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements are limited due to few cases having been studied. Herein we report an extremely rare case of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements presenting as spinal mass.

Materials and methods

Case collection

A 72-year-old Chinese woman who complained of lumbago for 2 months and weakness in the lower limb for 4 days visited West China Hospital of Sichuan University, and took an excision of a mass at T8-10.

Pathological study

Histological study

4 μm-thicken formalin fixed paraffin embedded (FFPE) tissue section series were prepared for H&E and following immunohistochemical staining.

Immunohistochemical analysis

EnVision or Elivision DAB systems were used for immunohistochemical reaction. For antigen retrieval, the slides were heated at 97°C for 25 minutes in citrate buffer at pH 6.0 or in EDTA buffer at pH 9.0. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol. CD20, CD3ε, CD5, CD10, BCL-6,

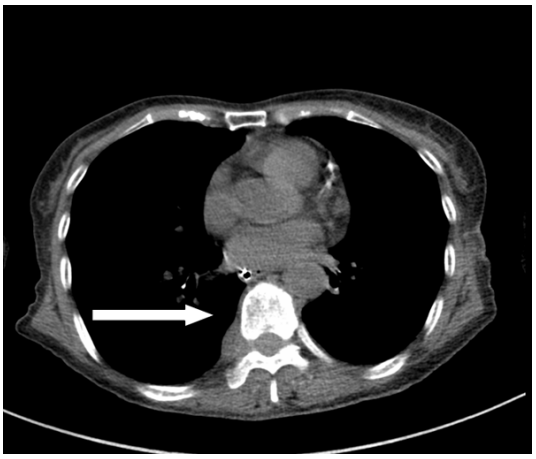

Figure 1. CT image of a mass at T8-10 with ambiguous boundaries.

MUM-1, BCL-2, C-myc, CD30, P53, NF-κB (P65) and Ki-67 (MIB1) antibodies were used. Positive and negative controls were taken in each reaction. As to Hans algorithm [1] of DLBCL-NOS, the cut-off value of CD10, BCL-6 and MUM-1 expression was designated as 30%.

In situ hybridization (ISH)

In situ hybridization was carried out with a fluorescein labeled oligonucleotide probe complementary to two Epstein-Barr virus (EBV) encoded small RNAs, EBER-1 and EBER-2 (EBER1/2) (Dako). DIG-HRP conjugated was used to combine with the probe. DAB-horseradish peroxidase is chromogenic system. EBER1/2 positive nasopharyngeal carcinoma tissue was used as positive control and replacing the probe with PBS was negative control. The dark brown hybridizing signal was located in the cell nucleus.

Two pathologists reviewed all stained slides independently without any case information.

Fluorescence in situ hybridization (FISH)

Interphase FISH in FFPE tissue sections were used to detect the rearrangement of the *MYC*, *BCL2*, *BCL6* genes regions by LSI dual-color break-apart probes (Abbott Vysis) respectively. The cut-off value of reaction was designated as 10%.

Results

Clinical manifestations

A 72-year-old Chinese women presented with lumbago for 2 months and weakness in the lower limb for 4 days. Fever, night sweat, or weight loss were denied. Laboratory findings were hydrothorax and elevated LDH. A computed tomography (CT) scan revealed a mass at T8-10 with ambiguous boundaries (**Figure 1**), and then was resected.

Histopathologic findings

Histological examination showed a diffuse infiltration of lymphoid cells. The lymphoid cells were large and centroblasts-like. The nuclei were round or oval and have rough chromatin. Neoplastic cells had visible nucleoli. Apoptosis and necrosis were easily observed (**Figure 2**).

Immunophenotype

The lymphoid cells expressed CD20 (**Figure 4**), CD79a, CD10, BCL-6, NF-κB (P65), P53 and C-myc, and were negative for CD3ε, Cyclin D1, mum-1, bcl-2, CD5 and CD30. The proliferative index, demonstrated by Ki67 stain, was more than 80% (**Figure 3**).

In situ hybridization

No EBER1/2 in situ hybridization signal was detected.

Fluorescence in situ hybridization (FISH)

Separated red and green signals were detected in more than 60% and 80% tumor cells by *MYC* (**Figure 4A**) and *BCL2* (**Figure 4B**) break apart probes respectively, demonstrating gene *MYC* and *BCL2* gene rearrangements. No *BCL6* rearrangement detected.

Follow-up

The patient was diagnosed as high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements, germ center B-cell-like (GCB) phenotype (Hans algorithm) according to World Health Organization (WHO) classification of hematopoietic and lymphoid tumors (2016 revision) [2]. The patient was evaluated as IV B stage (Ann Abor stage) and IPI 5 and then received 6 courses of EPOCH chemotherapy and got partially remission (PR) with relieving of signs and symptoms.

Discussion

Diffuse large B-cell lymphoma (DLBCL) actually has heterogeneous features implying differ-

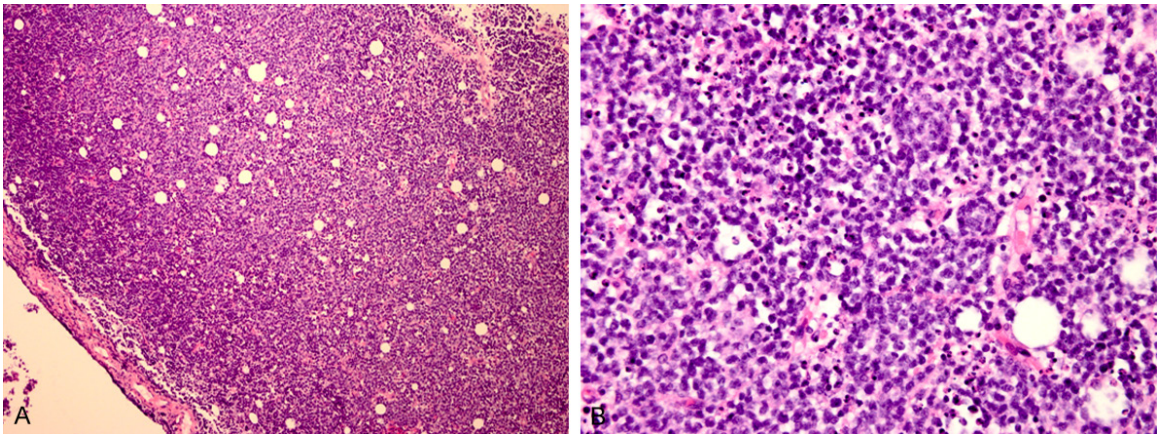

Figure 2. Hematoxylin and eosin-stained section of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. A. Diffuse lymphoid cells infiltrate (HE×100). B. An abundant and diffuse large lymphoid cells infiltrate (HE×400).

ent biological behavior. It is recognized as germinal center B-cell like (GCB) and activated B-cell-like (ABC) molecular 'subgroups' based on gene expression profile (GEP). BCL2 gene rearrangement is associated with GCB-DLBCL and has been identified as an adverse prognostic factor in DLBCL [1, 3, 4].

MYC is a powerful oncogene initially identified as the target of the t(8;14)(q24;q32) chromosome translocation in Burkitt lymphoma (BL). *MYC* gene rearrangement have been identified in many mature B-cell lymphomas that are usually associated with an aggressive clinical behavior [5]. For example, *MYC* rearrangement can be observed in approximately 10% of de novo DLBCL and correlates with a worse outcome [5, 6]. B-cell lymphoma carrying *MYC* rearrangement combination with rearrangement involving either *BCL2*, *BCL6*, or rarely other known oncogenes is regarded as double hit (or triple-hit) B-cell lymphoma (DHL/THL) [7, 8]. DHL/THL is strictly defined by the presence of rearrangement and breakpoints at the sites of both *MYC* and *BCL2* and/or *BCL6* gene mutation, low level copy number increase, or high-level amplification without a concurring breakpoint and rearrangements should not be interpreted as such. The definition is also confined de-novo DLBCL [9]. About 5-10% of DLBCLs fulfill the criteria for DHL/THL [8].

In addition to the adverse clinical impact of rearrangement of *MYC* gene combined with rearrangement involving either *BCL2* and/or *BCL6*, high stage, elevated lactate dehydrogenase (LDH), extranodal involvement (CNS involvement included), high IPI score are more common in DNL/THLs than in other lymphomas [10]. GEP studies have shown the GCB group have a better prognosis than the ABC group. Although most of *MYC/BCL2* DHLs arise within the GCB group, there is discordance between prognosis and the cell of origin (COO) subtypes [2].

DLBCL accounts for about 40% of all non-Hodgkin lymphomas. Most patients present with rapidly enlarged lymph nodes or tumor masses localized in extranodal sites. About 30% of patients present with the extranadal lesions, and 71% have extranodal involvement during the course of the disease. Common primary extranodal sites include the gastrointestinal tract and waldeyer's, but practically any organ can be involved, including bone [11]. Lymphoma is definitely less than myeloma involves spine. Since high-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements is a rare variant of DLBCL, it is a great challenge to making correct diagnose of this disease before the surgical pathology and ensure the patient receiving appropriate therapy. This rare case implies that lymphoma can involve any site and presents as any symptom or sign.

Acknowledgements

This study was supported by a grant founded by Health and Family Planning Commission of Sichuan Province (NO. 16PJ337), and a grant of Application Basic Research Project founded by Science & Technology Department of Sichuan Province (NO. 2017JY0266).

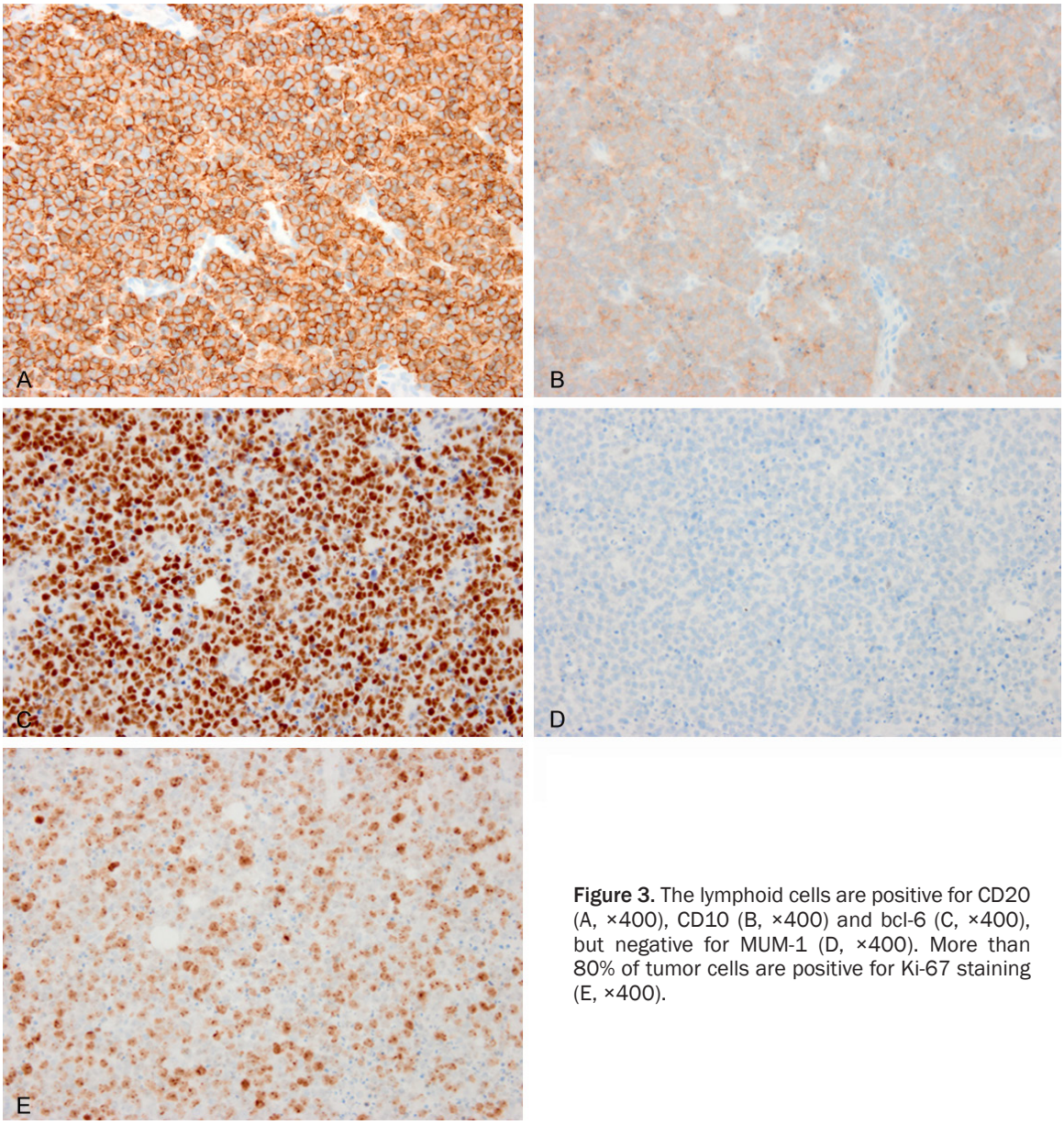

Figure 3. The lymphoid cells are positive for CD20 (A, ×400), CD10 (B, ×400) and bcl-6 (C, ×400), but negative for MUM-1 (D, ×400). More than 80% of tumor cells are positive for Ki-67 staining (E, ×400).

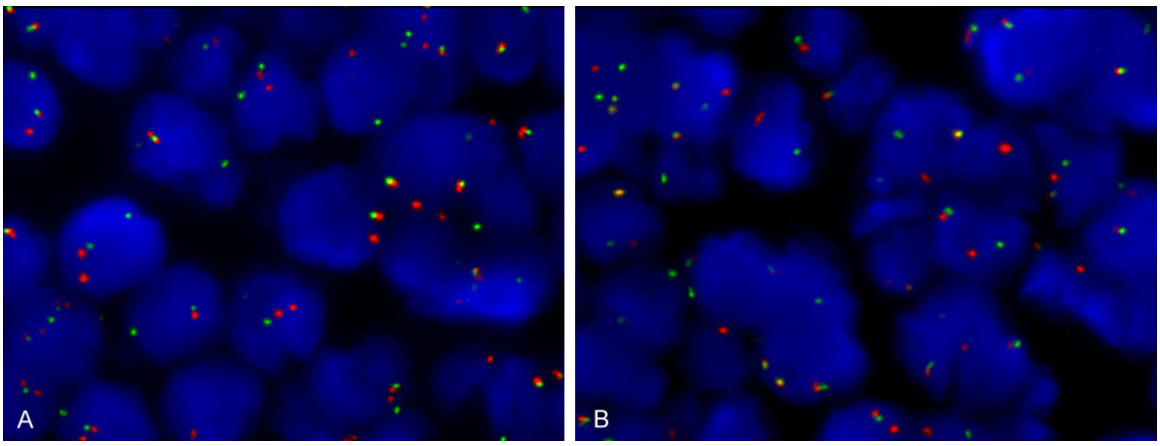

Figure 4. Detection of *MYC* and *BCL2* gene rearrangement with dual color break apart probe respectively. The *MYC* (A) and *BCL2* (B) gene rearrangement is indicated by separation of the red and green signals.

Disclosure of conflict of interest

None.

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