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【 CASE REPORT 】

Primary Chest Wall MYC/BCL6 Double-hit Lymphoma with t(3;7)(q27;p12) and t(8;14)(q24;q32) Translocations

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Abstract:

Primary chest wall lymphoma is rare and typically associated with chronic pleural inflammation. Double-hit lymphoma (DHL), which is defined as aggressive mature B-cell lymphoma with MYC and BCL2 or BCL6 rearrangements, is a highly aggressive malignancy that tends to have extranodal involvement and is resistant to standard immunochemotherapy. We herein report a 55-year-old man with no history of chronic pleural inflammation, diagnosed with primary chest wall DHL with MYC/BCL6 rearrangement, and harboring a unique BCL6 translocation, t(3;7)(q27;p12). After six courses of intensive chemotherapy, he has achieved complete remission. To our knowledge, this is the first case report of primary chest wall DHL.

Key words: chest wall lymphoma, double-hit lymphoma, t(3;7)(q27;p12), BCL6, MYC, Ikaros

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Introduction

Approximately 20-30% of malignant lymphomas either have already invaded the pleura and pleural cavity at the time of diagnosis or do so during disease progression (1); nevertheless, few lymphomas originate from the chest wall. Most pleural lymphomas are associated with chronic inflammation, which is caused by artificial pneumothorax for the treatment of pulmonary or pleural tuberculosis. These are diagnosed as pyothorax-associated lymphoma and categorized as diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation (2, 3). Primary chest wall lymphoma without any evidence of chronic pleural inflammation is rare, and its biological and clinical characteristics are still poorly understood.

Aggressive mature B-cell lymphomas harboring MYC, BCL2, and/or BCL6 rearrangements are referred to as "double-hit" lymphoma (DHL) or "triple hit" lymphoma (THL) and termed high-grade B-cell lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangements, according to the 2017 World Health Organization classification (2). Patients with DHL have very poor outcomes when treated with standard immunochemotherapy, such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (4). DHL frequently involves extranodal sites at presentation (5); however, primary chest wall DHL has not yet been reported. We herein present the first case of primary chest wall MYC/BCL6 DHL with the unique BCL6 translocation, t(3;7)(q27;p12), and no history of chronic pleural inflammation.

Case Report

A 55-year-old man presented to a local clinic with a 2-month history of right chest pain and dyspnea on exertion. Chest X-ray revealed pleural effusion around the right lung, and he was therefore referred to the department of respira-

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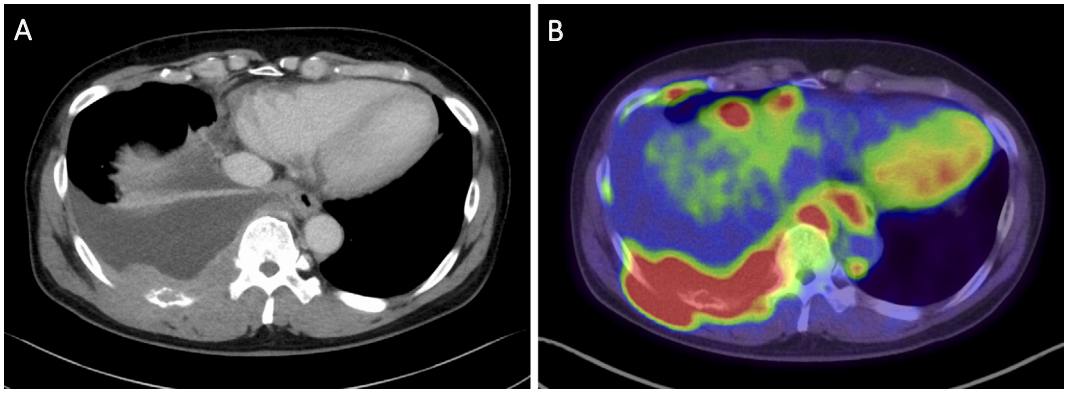

Figure 1. **Contrast-enhanced CT and PET images. (A) A contrast-enhanced CT image showing pleural thickening of the right chest wall with pleural effusion. (B) PET showing a high fluorodeoxyglucose uptake in the right pleural thickening lesions, adjacent vertebral body, and 10th rib.**

Table. **Laboratory Data on Admission (Peripheral Blood and Pleural Effusion).**

Complete blood count		Blood chemistry		Pleural effusion	
WBC	7,500 /μL	TP	6.5 g/dL	WBC	7,100 /μL
seg	90 %	ALB	3.4 g/dL	seg	1 %
lym	7 %	AST	22 U/L	lym	19 %
mono	3 %	ALT	26 U/L	abn-lym	80 %
eos	0 %	LDH	291 U/L	TP	4 g/dL
baso	0 %	ALP	269 U/L	ALB	2.5 g/dL
RBC	401×10^4 /μL	γ-GT	21 U/L	LDH	447 U/L
Hb	14.1 g/dL	T-bil	0.4 mg/dL		
PLT	14.8×10^4 /μL	BUN	16.5 mg/dL		
		Cre	0.8 mg/dL		
		sIL-2R	1,246 U/mL		

WBC: white blood cells, seg: segmented neutrophils, lym: lymphocytes, mono: monocytes, eos: eosinophils, baso: basophils, RBC: red blood cells, Hb: hemoglobin, PLT: platelets, TP: total protein, ALB: albumin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GT: gamma-glutamyl transferase, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine

tory medicine in our hospital to undergo detailed examination. Computed tomography (CT) revealed a large amount of pleural effusion and pleural thickening of the right chest wall (Fig. 1A). He had a history of cerebral infarction 2 years previously and was taking medications for hypertension, hyperlipidemia, and benign prostatic hyperplasia. No episodes of asbestos exposure or history of *Mycobacterium tuberculosis* infection were noted, and he had never smoked. His performance status [Eastern Cooperative Oncology Group (ECOG)] was 1. On physical examination, an attenuation of respiratory sounds was detected in the lower right chest. No lymphadenopathy or hepatosplenomegaly was obvious on palpation. A complete blood count and biochemistry data were normal, and tumor markers for lung cancer, including carcinoembryonic antigen, cytokeratin fragment, and pro-gastrin-releasing peptide, were within normal limits, although soluble interleukin-2 receptor was slightly elevated. The pleural effusion was exudative and contained many abnormal mononuclear cells (accounting for 80%), with elevated lactate dehydrogenase, suggesting that it was malignant (Table). No evidence of any *Mycobacterium* species was found. Positron emission tomography (PET) showed a high fluorodeoxyglucose uptake in the right pleural thickening lesions, adjacent vertebral body, 10th rib (standardized uptake value max: early=12.65, delayed=14.68) (Fig. 1B), and right axial, supraclavicular lymph nodes (standardized uptake value max: early=7.33, delayed=9.74). He was admitted to our hospital, and a CT-guided needle biopsy of the right pleural lesion was performed.

The biopsy specimens showed a diffuse invasion of large abnormal lymphocytes with a high nuclear/cytoplasmic ratio (Fig. 2A and B). Immunohistochemistry revealed the tumor cells to be diffusely positive for CD20, partially positive for BCL2 (index 50%), BCL6 (60%), MYC (40%), MIB-1 (60%), and MUM1 (40%) and negative for CD3 and CD10, as well as Epstein-Barr virus-Encoded RNA (EBER) by *in situ* hybridization (Fig. 2C-J). A flow cytometric analysis of pleural effusion showed the abnormal lymphocytes to be

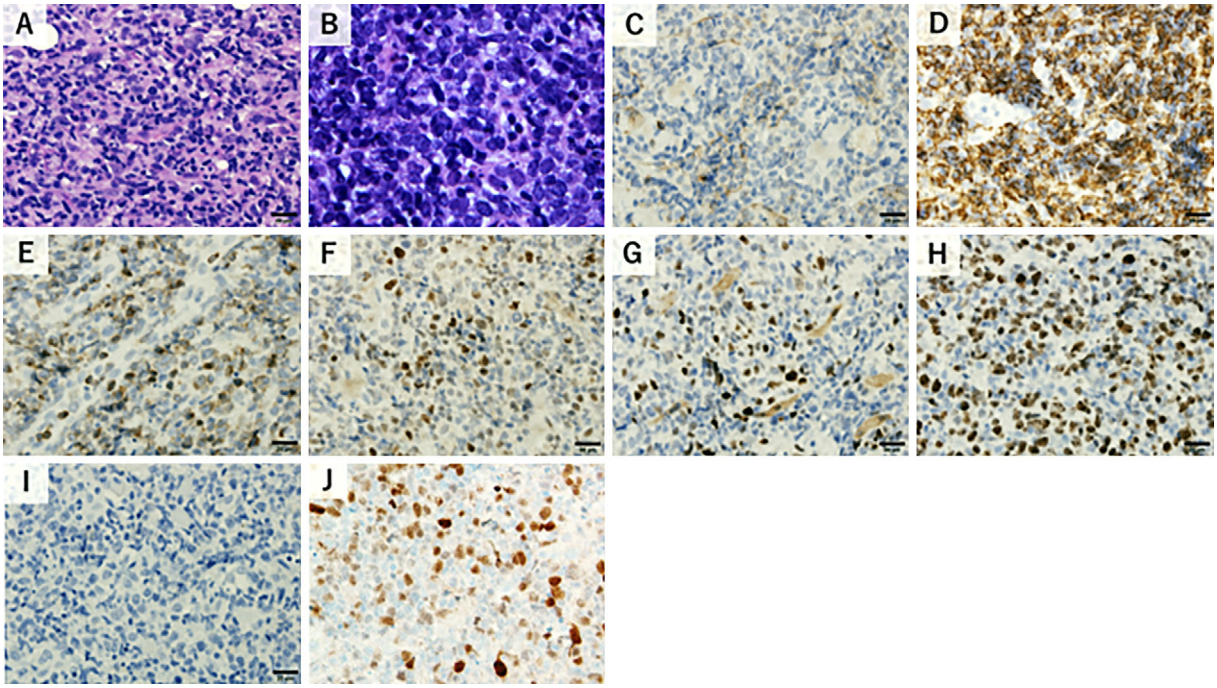

Figure 2. **Histopathological and immunohistochemical findings from the right pleural lesion sample. (A and B) Hematoxylin and Eosin staining showing the diffuse infiltration of abnormal lymphocytes with a high nuclear/cytoplasmic ratio [original magnification ×60 (A), ×400 (B)]. (C) Tumor cells were negative for CD10. (D-J) The abnormal lymphocytes exhibited a diffuse expression of CD20 (D), and focal expression of BCL2 (E), BCL6 (F), MYC (G), MIB-1 (H), and MUM1 (J). (I) EBER was negative. C-J: original magnification, ×60**

positive for CD19, CD20, and an immunoglobulin lambda chain. Bone marrow aspiration revealed no obvious invasion of these malignant cells in either smear specimens or by flow cytometry. He was diagnosed as having DLBCL of the chest wall, of which the cell-of-origin was determined to be a non-germinal center B-cell-like type according to Hans' algorithm. The clinical stage was IV, and the international prognostic index was low-intermediate risk.

R-CHOP chemotherapy was started, and a partial reduction of the pleural masses was achieved; however, the pleural effusion remained. After completing one course of R-CHOP, a chromosomal analysis of the cells in the pleural effusion obtained before starting R-CHOP revealed the karyotype 47,X,-Y,t(3;7)(q27;p12),del(6)(q?),t(8;14)(q24;q32),+19, +mar1 in 7/20 of metaphases examined (Fig. 3A). A fluorescence *in situ* hybridization (FISH) analysis revealed immunoglobulin heavy chain (*IGH*) and *MYC* fusion genes (Fig. 3B). Split *BCL6* signals were also detected (Fig. 3C). Therefore, the diagnosis of DLBCL was changed to HGBL with MYC and BCL6 rearrangements. Dose-adjusted rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone (DA-EPOCH-R) was started in place of R-CHOP, and he achieved complete remission (CR) after six courses. Complete metabolic remission was confirmed by a PET scan, and he has been doing well without recurrence for 11 months from the diagnosis.

Discussion

We herein report a rare case of primary chest wall lymphoma with no history of chronic pleural inflammation. The histopathological diagnosis was DLBCL, and G-banding of tumor cells showed t(3;7)(q27;p12) and t(8;14)(q24;q32) translocations. A subsequent FISH analysis revealed both *MYC* and *IGH* fusions and *BCL6* split signals, resulting in a final diagnosis of HGBL with MYC/BCL6 rearrangements.

Primary chest wall lymphoma with no evidence of chronic inflammation of the pleura is rare; however, several cases have been reported, mainly from Asian countries (6-12). This disease can develop in individuals aged from 17 to 84 years of age and in both sexes; however, its pathogenic and cytogenetic characteristics have yet to be clearly elucidated. In 21 reported cases in Japan, the prognosis of them may not be worse than that of patients with DLBCL in general (6). The clinical manifestations and findings of a pleural effusion analysis reveal characteristics similar to pleural tuberculosis; hence a pleural biopsy is necessary to avoid a misdiagnosis (12). Thoracic surgical resection or thoracoscopic biopsy is sometimes required when CT-guided needle biopsy (a less-invasive procedure) is unsatisfactory for a definite diagnosis of pleural lymphoma (9, 11). DLBCL is the most common type of primary chest wall lymphoma, and destructive invasion into adjacent ribs is sometimes observed, as it was in our case (6).

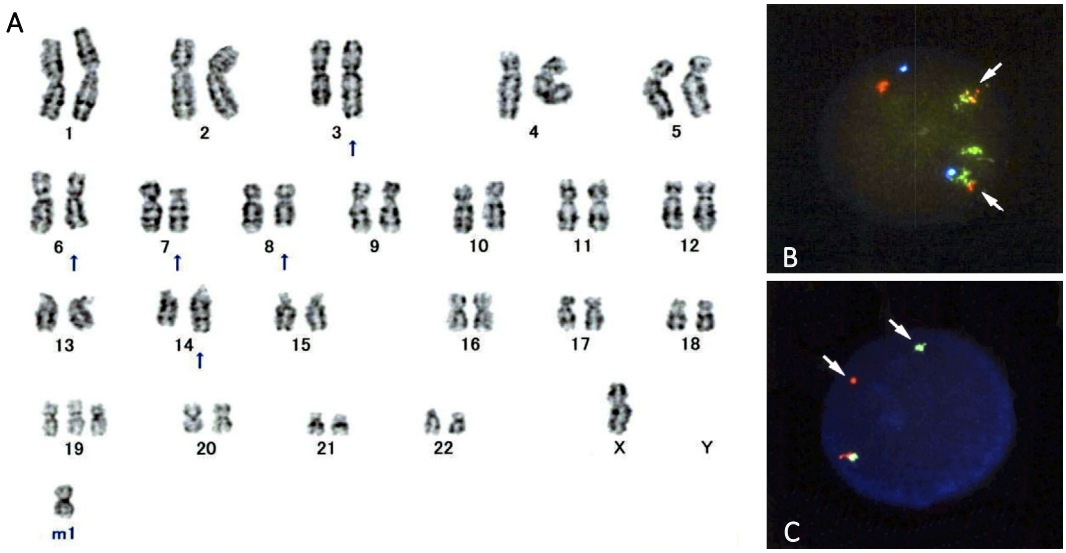

Figure 3. **Cytogenetic analysis of cells in the pleural effusion. (A) G-band karyotype showing 47,X,-Y,t(3;7)(q27;p12),del(6)(q?),t(8;14)(q24;q32),+19,+mar1. The arrows indicate abnormal chromosomes. (B) A FISH analysis showing *MYC* (red) and *IGH* (green) fusion signals (yellow, arrows). (C) FISH analysis showing *BCL6* split signals. The arrows indicate the 5' *BCL6* (red) and 3' *BCL6* (green) probe signals.**

HGBL, including DHL and THL, has a poor prognosis when treated with R-CHOP, according to DLBCL; thus more intensive chemotherapeutic regimens are preferable. In retrospective studies, DA-EPOCH-R therapy led to a superior CR, relapse-free survival (RFS), and overall survival (OS) rates than R-CHOP treatment (13-15). More recently, a prospective phase 2 study of DA-EPOCH-R in patients with MYC-rearranged aggressive B-cell lymphoma was reported. This study showed that DA-EPOCH-R induced a durable remission in patients including DHL (16). Hence, we switched the therapeutic regimen from R-CHOP to DA-EPOCH-R in the present case. There is little evidence that patients with DHL should be recommended for autologous stem cell transplantation (ASCT) as an upfront consolidation strategy after front-line therapy, although limited data are available. Landsburg et al. reported that consolidative ASCT, after achieving CR following the completion of front-line therapy, was not associated with an improved 3 year RFS or OS in patients with DHL (17). Chen et al. also reported no prognostic benefit of consolidative ASCT (18). Further prospective studies are necessary to ascertain whether ASCT is beneficial as a consolidation therapy for patients with DHL.

DHL with MYC/BCL6 rearrangements is less common, and the data describing cases with DHL are largely based on those involving MYC/BCL2. Thus, the biological and clinical features of DHL with MYC/BCL6 remain unclear. DHL with MYC/BCL6 is more likely to be classified as having a non-germinal center cell of origin, with extranodal disease, and with less cytogenetic complexity (5, 19). Some studies have reported that DHL with MYC/BCL6 has poor outcomes compared with DHL with MYC/BCL2 (5, 19-21); however, other groups reported that the former was not associated with an inferior prognosis when treated with R-CHOP therapy (22, 23). The MYC expression levels appear to affect the survival of patients with MYC/BCL6 DHL. Ye et al. speculated that MYC expression may be suppressed when BCL6 overexpression is induced by BCL6 rearrangement, as BCL6 can repress MYC (23, 24). Consistent with this hypothesis, the present patient showed a low MYC expression (40%). Further investigations are therefore needed to clarify whether a low MYC expression (<70%) in MYC/BCL6 DHL contributes to a better prognosis.

In the present case, two recurrent nonrandom translocations, t(3;7)(q27;p12) and t(8;14)(q24;q32), were detected. The translocation (3;7)(q27;p12) results in fusion of *BCL6* and Ikaros family zinc finger 1 (*IKZF1*), and a few cases of lymphoma with this translocation have been reported (25-28). *IKZF1* maps to chromosome 7p12 and encodes the transcription factor, Ikaros, an important regulator of lymphoid lineage development (29) that is frequently genetically altered in B-cell acute lymphoblastic leukemia, with poor outcomes (30, 31); however, the significance of an *IKZF1* alteration in lymphoma is unknown. Hosokawa et al. reported that *IKZF1*/*BCL6* fusions likely cause a deregulated expression of the *BCL6* gene, resulting in lymphomagenesis (26). The combination of t(3;7)(q27;p12) and t(8;14)(q24;q32) has only been reported once previously in a single case with lymphoma who relapsed immediately after six courses of R-CHOP, and that case thereafter received intensive salvage chemotherapy and high-dose chemotherapy, followed by ASCT (28).

To our knowledge, this is the first report of primary chest wall MYC/BCL6 DHL with t(3;7)(q27;p12) and t(8;14)(q24;q32). CR has been achieved after six cycles of the DA-EPOCH-R regimen, although ongoing careful observation will be needed. Further accumulation of cases is required to

clarify the biological and clinical characteristics of primary chest wall lymphoma, DHL with MYC/BCL6, and the clinical relevance of t(3;7)(q27;p12) in malignant lymphoma.

The authors state that they have no Conflict of Interest (COI).

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