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

Kazuharu Kamachi, Yasushi Kubota, Toshiaki Nagaie, Kyosuke Yamaguchi, Shinsuke Ogusu, Keisuke Kidoguchi, Kana Kusaba, Haruna Kizuka-Sano, Atsujiro Nishioka, Mariko Yoshimura, Masako Yokoo, Toshihiko Ando, Keita Kai, Kensuke Kojima, Koichi Ohshima, Eisaburo Sueoka and Shinya Kimura

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

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-

1Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Japan
2Department of Transfusion Medicine, Saga University Hospital, Japan
3Department of Pathology, Saga University Hospital, Japan and 4Department of Pathology, Kurume University School of Medicine, Japan
Received: December 15, 2018; Accepted: January 20, 2019; Advance Publication by J-STAGE: March 28, 2019
Correspondence to Dr. Yasushi Kubota, kubotay@cc.saga-u.ac.jp
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 (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 BCL6 (60%), negative for CD3 and CD10, 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 positive for CD19, CD20, and an immunoglobulin lambda

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).

| Parameter       | Value | Parameter       | Value | Parameter       | Value |
|-----------------|-------|-----------------|-------|-----------------|-------|
| WBC             | 7,500 | TP              | 6.5   | Pleural effusion| [L] 7,100 |
| seg             | 90%   | ALB             | 3.4   | WBC             | 7,100 |
| lym             | 7%    | AST             | 22    | seg             | 1%    |
| mono            | 3%    | ALT             | 26    | lym             | 19%   |
| eos             | 0%    | LDH             | 291   | ABN             | 80%   |
| baso            | 0%    | TP              | 4     | PLT             | 4 g/dL |
| RBC             | 401x10^4 | r-GT            | 21    | ALP             | 269   |
| Hb              | 14.1  | BUN             | 16.5  | ALB             | 2.5 g/dL |
| PLT             | 14.8x10^4 | Cre             | 0.8   | ALB             | 447 U/L |
| sIL-2R          | 1,246 |                |       |                |       |

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, r-GT: gamma-glutamyl transferase, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine

*, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine
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).
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/BCL6 DHL with t(3;7)(q27;p12) and t(8;14)(q24;q32) was performed (25-28). The translocation (3;7)(q27;p12) results in fusion of MYC and Ikaros family zinc finger 1 (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).

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).

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).

References

1. Das DK. Serous effusions in malignant lymphomas: a review. Diagn Cytopathol 34: 335-347, 2006.
2. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised fourth Edition 2017.
3. Aozasa K, Takakuwa T, Nakatsuka S. Pyothorax-associated lymphoma: a lymphoma developing in chronic inflammation. Adv Anat Pathol 12: 324-331, 2005.
4. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 30: 3452-3459, 2012.
5. Pillai RK, Sathanoori M, Van Oss SB, Swerdlow SH. Double-hit B-cell lymphomas with BCL6 and MYC translocations are aggressive, frequently extranodal lymphomas distinct from BCL2 double-hit B-cell lymphomas. Am J Surg Pathol 37: 323-332, 2013.
6. Iwasa Y, Okada A, Takenaka H, et al. Primary Malignant Lymphoma Originating from the Chest Wall Without Preceding Pleural Disease. Intern Med 56: 681-686, 2017.
7. Shao C, Guo Y, Xu X, et al. Non-pyothorax-associated primary pleural lymphoma without pleural effusion in an immunocompetent patient: a case report and literature review. J Thorac Dis 10: E365-E371, 2018.
8. Hirai S, Hamanaka Y, Mitsui N, Morifuji K, Sutoh M. Primary malignant lymphoma arising in the pleura without preceding long-standing pyothorax. Ann Thorac Cardiovasc Surg 10: 297-300, 2004.
9. Sun ML, Shang B, Gao JH, Jiang SJ. Rare case of primary pleural lymphoma presenting with pleural effusion. Thoracic Cancer 7: 145-150, 2016.
10. Tabatabai A, Hashemi M, Ahmadinejad M, et al. Primary chest wall lymphoma with no history of tuberculous pyothorax: diagnosis and treatment. J Thorac Cardiovasc Surg 136: 1472-1475, 2008.
11. Hsu PK, Hsu HS, Li AF, et al. Non-Hodgkin’s lymphoma presenting as a large chest wall mass. Ann Thorac Surg 81: 1214-1218, 2006.
12. Yang X, Xu X, Song B, Zhou Q, Zheng Y. Misdiagnosis of primary pleural DLBCL as tuberculosis: A case report and literature review. Mol Clin Oncol 8: 729-732, 2018.
13. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 124: 2354-2361, 2014.
14. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. Br J Haematol 166: 891-901, 2014.
15. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol 170: 504-514, 2015.
16. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol 5: e609-e617, 2018.
17. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. J Clin Oncol 35: 2260-2267, 2017.
18. Chen AI, Leonard JT, Okada CY, et al. Outcomes of DA-EPOCH-R induction plus autologous transplant consolidation for double hit lymphoma. Leuk Lymphoma 59: 1884-1889, 2018.
19. Landsburg DJ, Petrich AM, Abramson JS, et al. Impact of oncogene rearrangement patterns on outcomes in patients with double-hit non-Hodgkin lymphoma. Cancer 122: 559-564, 2016.
20. Aukema SM, Kreuz M, Kohler CW, et al. Biological characterization of adult MYC-translocation-positive mature B-cell lymphomas other than molecular Burkitt lymphoma. Haematologica 99: 726-735, 2014.
21. Turakhia SK, Hill BT, Dufresne SD, Nakashima MO, Cotta CV. Aggressive B-cell lymphomas with translocations involving BCL6 and MYC have distinct clinical-pathologic characteristics. Am J Clin Pathol 142: 339-346, 2014.
22. Copie-Bergman C, Cuilliere-Dartigues P, Baia M, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study. Blood 126: 2466-2474, 2015.
23. Ye Q, Xu-Monette ZY, Tzankov A, et al. Prognostic impact of concurrent MYC and BCL6 rearrangements and expression in de novo diffuse large B-cell lymphoma. Oncotarget 7: 2401-2416, 2016.
24. Nahar R, Ramezani-Rad P, Mosser M, et al. Pre-B cell receptor-mediated activation of BCL6 induces pre-B cell quiescence through transcriptional repression of MYC. Blood 118: 4174-4178, 2011.
25. Deweindt C, Kerkckaert JP, Tilly H, Quiel S, Nguyen VC, Bastard C. Cloning of a breakpoint cluster region at band 3q27 involved in human non-Hodgkin’s lymphoma. Genes Chromosomes Cancer 8: 149-154, 1993.
26. Hosokawa Y, Maeda Y, Ichinohasama R, Miura I, Taniwaki M, Seto M. The Ikaros gene, a central regulator of lymphoid differentiation, fuses to the BCL6 gene as a result of t(3;7)(q27;p12) translocation in a patient with diffuse large B-cell lymphoma. Blood 95: 2719-2721, 2000.
27. Ichinohasama R, Miura I, Funato T, et al. A recurrent nonrandom translocation (3;7)(q27;p12) associated with BCL-6 gene rearrangement in B-cell diffuse large cell lymphoma. Cancer Genet Cytogenet 104: 19-27, 1998.
28. Katsura Y, Ohta I, Yoshiida C, Ohtani H, Komeno T. Diffuse large B-cell lymphoma carrying both t(3;7)(q27;p12) and t(8;14)(q24;p12). Intern Med 50: 905-908, 2011.
29. Cobb BS, Smale ST. Ikaros-family proteins: in search of molecular functions during lymphocyte development. Curr Top Microbiol Immunol 290: 29-47, 2005.
30. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 360: 470-480, 2009.
31. Martinelli G, Iacobucci I, Storlazzi CT, et al. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol 27: 5202-5207, 2009.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).
