Editorial

CMJ

www.cmj.ac.kr

De Novo CD5-Positive Primary Gastric Diffuse Large B-Cell Lymphoma Coexpressing MYC and BCL6: Towards a Proper Subset of Double-Hit, Triple-Hit and, Maybe, Quadruple-Hit B-Cell Lymphomas?

Luca Roncati*

Department of Diagnostic and Clinical Medicine and of Public Health, Institute of Pathology, University of Modena and Reggio Emilia, Modena, Italy

Diffuse large B-cell lymphoma (DLBCL) is the most common histotype of non-Hodgkin lymphoma among adults,[1] with a median age at diagnosis of approximately 70 years and an annual incidence of 7-8 cases per 100'000 people in the United States of America.[2,3] The overall 5-year survival rate for older adults is about 60%, while for children ranges from 70% to 90%.[4] It can arise in any body site as a rapidly growing lymph node or mass, sometimes associated with B symptoms (fever, weight loss, night sweats) and/or serum elevation of lactate dehydrogenase.[5] Actually, DLBCL encloses a wide spectrum of aggressive, variably responding, lymphomas, different in terms of biology and clinical practice, many of which cannot be separated from one another by well-defined and widely accepted criteria.[6] In this regard, the 2016 World Health Organization (WHO) classification of lymphoid neoplasms recognizes several variants of LBCL on the basis of tumor location (central nervous system, skin, mediastinum, serous cavities, inside the vessels), cell background (T cell / histiocyte-rich, chronic inflammation) and concomitant or coexisting diseases (Epstein-Barr virus, Kaposi's sarcoma virus, Castleman disease).[7] In some circumstances, DLBCL can also share many features with Hodgkin's lymphoma, being encoded as 'B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Hodgkin's lymphoma'.[7] However, the vast majority of DLBCL cases fall into the 'not otherwise specified' (NOS) category. Current efforts are precisely intended to better characterize this still heterogeneous group by evaluating cellular morphology (centroblastic, immunoblastic, plasmablastic, anaplastic) and gene expression (germinal center B-cell-like, activated B-cell-like).[6-9] Over the years, researchers have realized that important distinctions can be quickly achieved by exploiting immuhistochemistry, and, so, the products of prognostically relevant genes, such as ALK, IRF4, CCND1, LEU1 (CD5), MYC, BCL2 and BCL6 are entered in the diagnostic procedure.[10-12] This has led to the nosological introduction of 'ALK positive large B-cell lymphoma', of 'large B-cell lymphoma with IRF4 rearrangement' and of '*de novo* CD5-positive DLBCL',[7,13] together with the widespread adoption of new terminologies, such as 'double-hit' and 'triple-hit', referring to those lymphomas characterized by a double synchronous genetic mutation, involving MYC and BCL2 or BCL6, or by a triple synchronous rearrangement of MYC, BCL2 and BCL6.[14] These subcategories have replaced the provisional entity of 'B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt's lymphoma', dating back to the 2008 WHO classification.[15] Double-hit lymphomas are often diagnosed at advanced stages, they show high recurrence rates, despite high-intensity chemotherapy, and are almost always fatal.[16] Triple-hit lymphomas are characterized by an aggressive clinical behavior, with frequent dissemination to extranodal sites (e.g. bone marrow, central nervous system), and the standard chemotherapy, used for DLBLC or Burkitt's lymphoma, results ineffective.[17] Similarly, the patients affected by *de novo* CD5-positive DLBCL usually suffer from poor performance status and extranodal involvement, like the central nervous system, and are penalized by an inferior response to rituximab-containing regimens.[13] Recently, in an 87-year-old male patient who was submitted to emergency surgery for perforated ulcer (3 cm in size) of the stomach, I diagnosed a *de novo* CD5-positive primary gastric DLBCL coexpressing Myc and Bcl6; the cytoproliferative index, evaluated by immunohistochemistry for Ki67 antigen, reached the 80% (Fig. 1). The patient died 4 months after surgery despite the administered chemotherapy (R-CHOP). Therefore, there are all the biological and clinical conditions to consider this particular subset of lymphoma a proper triple-hit

Corresponding Author:
Luca Roncati
Department of Diagnostic and Clinical Medicine and of Public Health, Institute of Pathology, University of Modena and Reggio Emilia, Policlinico Hospital, I–41124 Modena (MO), Italy
Tel: +390594224812, Fax: +390594224998, E-mail: emailmedical@gmail.com

Article History:
Received October 29, 2017
Revised November 26, 2017
Accepted December 1, 2017

https://doi.org/10.4068/cmj.2018.54.1.80

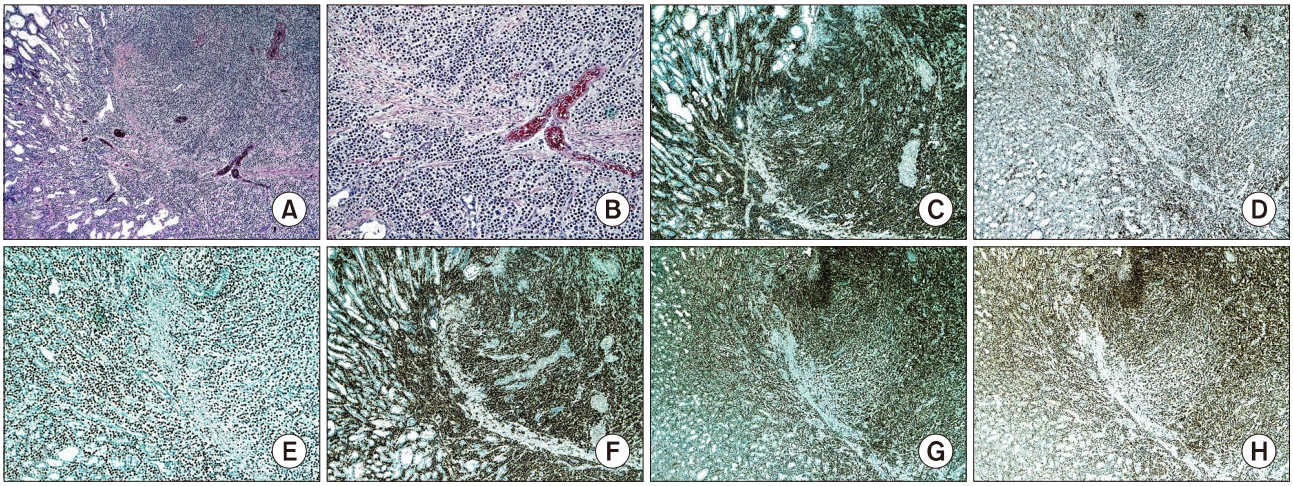

FIG. 1. The large B-cell lymphoma arises in the stomach (A, hematoxylin & eosin; 4×), it shows a diffuse pattern of growth (B, hematoxylin & eosin; 10×), it is immunoreactive for CD20 (C, clone L26, Ventana; 4×) but not for CD3 (D, clone 2GV6, Ventana; 4×), it shows a high Ki67 labeling index (E, clone 30-9, Ventana; 10×) and coexpresses CD5 (F, clone SP19, Ventana; 4×), Myc (G, clone Y69, Ventana; 4×) and Bcl6 (H, clone GI191E/A8, Ventana; 4×).

lymphoma. A final question consequently arises: does quadruple-hit lymphoma involving *de novo* CD5 (CD5 positive, Myc positive, Bcl2 positive, Bcl6 positive) exist? Just this year, Xiao and colleagues have reported the case of a *de novo* CD5-positive primary cardiac DLBCL coexpressing Myc and Bcl2.[18] Noteworthily, even in this occurrence, the lymphoma developed in an extranodal site. Previously, four lymphoma-specific genetic events (MYC, BCL2, BCL6, CCND1) have been identified in parallel in three patients affected by high grade mature B-cell lymphomas, two of whom died 6 and 9 days from diagnosis.[19,20] Hence, from a theoretical point of view, there are the assumptions for an affirmative answer.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The non-hodgkin's lymphoma classification project. Blood 1997;89:3909-18.
2. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105: 1684-92.
3. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265-76.
4. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Fermé C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-26.
5. Ueno S, Yamaguchi M, Kimura M, Odagiri H, Shiraki K, Uemoto S, Net al. Expression of CD29 on lymphoma cells and/or CD36 on microvascular endothels correlates with high serum LDH level in diffuse large B-cell lymphomas (DLBCLs) and is frequent in de novo CD5-positive DLBCLs. Int J Oncol 2005;27:1241-6.
6. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
7. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
8. Roncati L, Maiorana A. IgA plasmablastic large B-cell lymphoma. Diagnosis 2017;4:105-7.
9. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937-47.
10. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-82.
11. Choi WW, Weisenburger DD, Greiner TC, Piris MA, Banham AH, Delabie J, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009;15:5494-502.
12. Roncati L, Maiorana A. Ectopic extra-nodal in situ follicular neoplasia (ISFN). J Hematopathol 2016;9:151-3.
13. Yamaguchi M, Ohno T, Oka K, Taniguchi M, Ito M, Kita K, et al. De novo CD5-positive diffuse large B-cell lymphoma: clinical characteristics and therapeutic outcome. Br J Haematol 1999; 105:1133-9.
14. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: double hit and triple hit lymphomas and double expressing lymphoma. Blood Rev 2017;31:37-42.
15. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond:

evolving concepts and practical applications. Blood 2011;117: 5019-32.
16. Aukema SM, Siebert R, Schuuring E, van Imhoff GW, Kluin-Nelemans HC, Boerma EJ, et al. Double-hit B-cell lymphomas. Blood 2011;117:2319-31.
17. Pemmaraju N, Gill J, Gupta S, Krause JR. Triple-hit lymphoma. Proc (Bayl Univ Med Cent) 2014;27:125-7.
18. Xiao Y, Cai Y, Tang H, Xiao X. De novo CD5-positive primary cardiac diffuse large B-cell lymphoma coexpressing C-myc and BCL2 in an immunocompetent adult. Eur Heart J 2017;38:1937.
19. Bacher U, Haferlach T, Alpermann T, Kern W, Schnittger S, Haferlach C. Several lymphoma-specific genetic events in parallel can be found in mature B-cell neoplasms. Genes Chromosomes Cancer 2011;50:43-50.
20. Ittel A, Hélias C, Wissler MP, Toussaint E, Miguet L, Chenard MP, et al. Four genetic lymphoma-specific events (MYC, BCL2, BCL6 and CCND1) identified in a high grade B lymphoma case. Blood Cancer J 2015;5:e374.