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DIFFUSE LARGE B CELL LYMPHOMA

Krisna Murti

Department of Anatomic Pathology, Faculty of Medicine, University of Sriwijaya, Palembang

Email: krisna.arinafril@unsri.ac.id

ABSTRACT

Diffuse large B cell lymphoma is a neoplasm arising from B lymphocytes and having a diffuse growth pattern. The nuclei cells showed a medium or similar or larger than the sizes of normal macrophages. This entity is the most common type of non-Hodgkin lymphoma (NHL) with incidence 30-40% from all NHL types. In Indonesia DLBCL cases was 68.2%, much higher than that in western countries (37%) and slightly higher than in other Asian countries (30-60%). Another data showed that in Indonesia there was 16.125 new NHL cases in 2020. This entity has diversity of molecular pathogenesis causes DLBCL showed some heterogeneity and similarities of clinical sign and symptoms, morphology and immunopheno types with other non-Hodgkin lymphomas. Therefore, some other molecular analysis such mutation events should be performed to achieve a correct diagnosis. All clinical data, morphologic immunhistochemical foundings have to be collected and analyzed and some additional molecular examination should be also conducted such as FISH analysis, PCR-based assay to exclude differential diagnosis. Some patients can be cured with a standard regimen Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP). However, 40% of patients is refractory or relapse.

Keywords: Diffuse large B cell lymphoma, Non Hodgkin lymphoma, R-CHOP, refractory or relapse

1. INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is a neoplasm arising from B lymphocytes and having a diffuse growth pattern. The nuclei cells showed a medium or similar or larger than the sizes of normal macrophages.[1] This entity is a common type of non-Hodgkin lymphoma (NHL) with incidence 30-40% from all NHL types.[2] A study reported that in Indonesia DLBCL cases was 68.2%, much higher than western countries (37%) and slightly higher than in other Asian countries (30-60%).[3] Another data showed that in Indonesia there was 16 125 new cases of NHL in 2020.[4]

Based on the origin of cell (COO), which is identified by Hans algorithm, an immunohistochemistry technique, this lymphoma is divided into germinal center B (GCB) and non-germinal center B (non-GCB) subtypes.[5] In WHO classification, DLBCL which does not fulfill the diagnostic criteria of specific large B-cell lymphoma neoplasms was recognized as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).[6] This review was performed to enhance the knowledge of the readers about pathogenesis, clinical, and morphologic appearances of DLBCL.

2. METHOD

The method used in this writing is a literature review, which is a systematic, explicit and reproducible method for identifying, evaluating and synthesizing research works and ideas that have been produced by researchers. The library sources were obtained through international journal websites such as Pub Med, Science Direct, Cochrane Library, Google Scholar, Directory of Open Access Journal (DOAJ), and Garda Reference Digital (GARUDA). Some steps were performed namely (1) selecting the topics to be reviewed and defining the scope of the reviewed topics (2) tracking, identifying, and selecting article sources suitable/relevant, (3)

perform literature analysis and synthesis, then (4) writing and organizing the writing of literature reviews. Synthesize of this literature review using the narrative method by grouping the similar extracted resulting data according to the results measured to answer the objective. To further clarify the analysis, all articles were read and scrutinized. An analysis of the contents of the research objectives and research results/findings were conducted.

The secondary data were obtained from some sources that is books and articles which can be obtained through the search engine Pub Med, Science Direct, Cochrane Library, Google Scholar, DOAJ, and GARUDA. The keywords used for searching namely DLBCL, DLBCL, NOS, molecular pathogenesis DLBCL, therapy of DLBCL, high grade lymphoma, lymphoma, and using the Boolean operator (AND, NOT).

3. DISCUSSION

Epidemiology

Diffuse large B cell lymphoma incidence in developing nations is higher compared to those in developed nations.[7] The incidence of DLBCL is around 30-40% cases and yearly increase cases in both gender.[8,9] Generally, DLBCL found higher in elderly people with males is more affected than females.[10]

Clinical features

Almost all DLBCL patients are exhibiting one or more lymph nodes enlargement and or extranodal lump(s) that can be at a single or multiple organs. Primary extranodal involved organs is about 30% cases, including the gastrointestinal tract, Waldeyer's ring, the skin, central nervous system, mediastinum, and bone marrow.[11,12] Particularly DLBCL of breast, uterus, testis, skin and central nervous system exhibit specific clinical and biologic characteristics.[12]

Most DLBCL patients are accompanied by B symptoms including fever, night sweats, weight loss, and some are can be asymptomatic. Other patients may show specific symptoms related to the involved organ(s).[3]

Pathogenesis

Majority DLBCLs emerge de novo, however, some cases occur through transformation from underlying low-grade or indolent lymphomas namely small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma or nodular lymphocyte–predominant Hodgkin's lymphoma (NLPHL) This entity shows diversity pathogenesis and microscopic features.[13,14]

Therefore, a good knowledge of B cell development is helpful in determining a diagnosis NHL of B cells. During normal B-cell differentiation, the process of maturation majority occurs in the germinal centres (GC) of lymphatic tissues which involving somatic hypermutation (SHM), class switch recombination (CSR) of heavy-chain and activity of activation-induced cytidine deaminase (AID), thus generating long-lived T-cell-dependent plasma or memory B-cells.[14] Upon activation of B cells the formation of GC was started, initiated by proliferation of centroblasts generating dark zones (DZ) and then these cells transforming to become centrocytes and shaping light zones (LZ). These 2 types of cells have several cycles of selection to produce B cells with a high affinity B cell receptor (BCR) then leave the GC as plasma cells or as memory B-cells.[15-17]

Some transcription factors (TFs) that have important roles to GC initiation and maintenance namely B cell lymphoma 6 (BCL6) and its regulators, such as Interferon regulatory factor 4 (IRF4), Myocyte enhancer binding factor 2B (MEF2B), B lymphocyte-induced maturation protein-1 (BLIMP1), (BACH2) and (TP53). While other TFs, such as PAX5, E2A, IRF8, FOXO1, YY1, and CCND3 are vital for beginning GC

development at the proliferative DZ. In process of LZ maturation, NF-kB increases thus activate IRF4 and PRDM1 that encoding BLIMP1 in plasma cells or SPI1 which encoding PU.1, IRF8, PAX5 and BACH2 in memory B-cells along with suppression of BCL6 or MYC.[15-18]

In general, pathogenesis of B cell lymphoma is a disruption of normal mechanisms of B cell development results in arresting of development of these B cells. Therefore, the lymphoma cells express markers and transcription (TFs) factors of the stages where they arrested.[19] The complicated DLBCL molecular pathogenesis involving multi step processes, generating transformation of B cell malignant clones arising from GC or post-GC. A study showed DLBCL classification based on genetic alteration (Figure 1). Hence, each groups revealed diversity of genotypic, epigenetic, and clinical appearances. The complexity of molecular pathways of DLBCL involving BCR regulation, PI3 Kinase pathway, NF-kB activation, and BCL2 Family with their target molecules in B cell surface receptor, cytoplasm and nucleus (Figure 2).[19]

Circa 150 target protein expressed by DLBCL patients showed mutation of their coding genes or altered of their copy numbers.[20] Based on cell of origin (COO) can be assessed by gene expression profiling and genomic studies, DLBCL is classified into GCB, ABC and type 3 or unclassified or COO independent. Majority GCB and ABC large groups demonstrate TFs and pivotal molecular events correlated to GC and or post-GC differentiation in addition to abnormal molecular event occurred during lymphomagenesis.[19,21-25]

Some molecular events that can be assayed by next generation sequencing (NGS) technology has been found the heterogeneity of mutation of DLBCL pathogenesis. As a consequence, DLBCL is recently classified based on mutation-analysis. Analysis mutation demonstrated that abnormality of B-cell receptor pathway activation, epigenetic mechanisms involving EZH2 mutation, also mutations in NOTCH.[26,27]

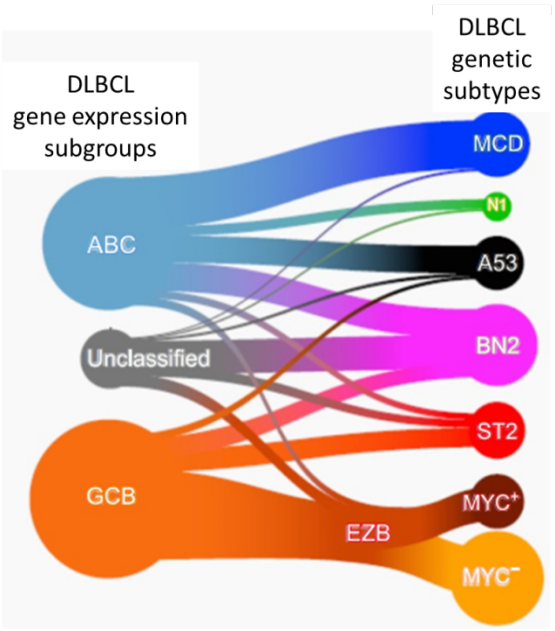

Figure 1. Diffuse large B-cell lymphoma classification. DLBCL is classified based on genetic alteration pathways of B cells.[24]

Other mechanisms of DLBCL formation are including the aberration in regulation of several miRNAs and the roles of components of tumor microenvironment (TME).[28] A study revealed TME including T cells, myeloid cells, and stromal factors share roles on pathogenesis of DLBCL.[19] Stromal factor is demonstrated a correlation with advantageous survival in DLBCL patients following immunochemotherapy.[29]

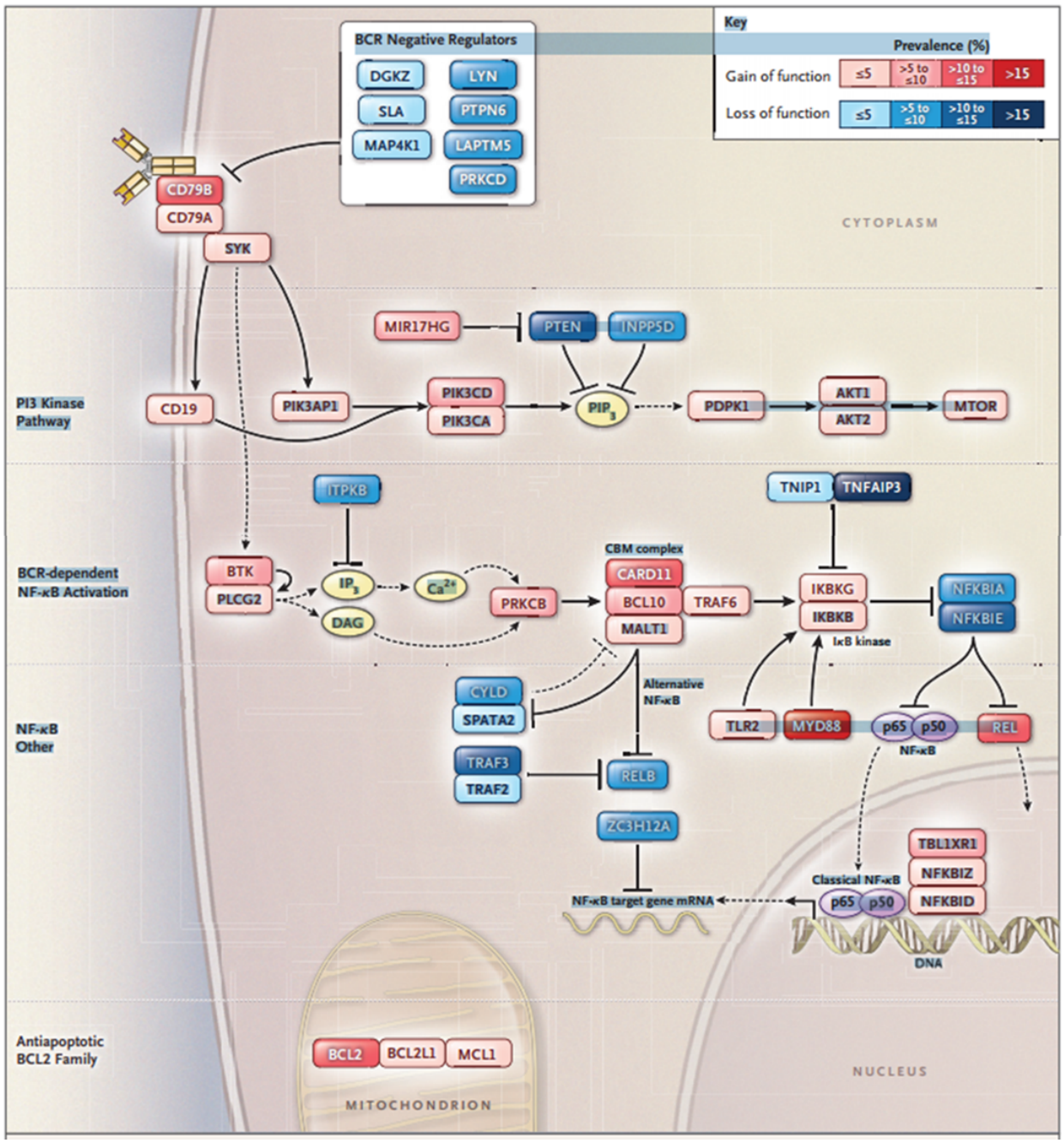

Figure 2. Molecular signaling pathways of DLBCL. Complexity of molecular pathways DLBCL involving BCR regulation, PI3 Kinase pathway, NF-kB activation, and BCL2 Family with their target molecules in B cell surface receptor, cytoplasm and nucleus.[19]

Morphologic variants

The classification of world health organization identified 3 general variants such as centroblastic, immunoblastic, anaplastic and some other rare variants.

Centroblastic

This variant is most commonly found in around 80% of DLBCL cases (Figure 3 A). The lymphoma cells are large lymphocytes with variable amount of cytoplasm, with round to oval nuclei, fine to vesicular chromatin and having few small-medium nucleoli positioned

peripherally to the nuclear membrane.[30] This variant is more often found in the GCB subtype, while immunoblastic lymphomas are frequently observed in the ABC subtype.[1]

Immunoblastic

This variant is the second percentage accounting for about 8–10% of all cases (Figure 3 B). It is usually defined by at least 90% containing immunoblasts in the cell composition of the lymphoma. This cell variant showed large lymphocytes, with moderate-to-abundant basophilic cytoplasm and a single prominent, centrally located nucleolus.[2] Immunoblastic variant was correlated with worse prognosis in comparison to other variants. This variant was characterized by recurrently translocations ofMYC to immunoglobulin heavy chains.[31]

Anaplastic

This type of variant is the rarest account for only circa 3% of all DLBCL cases (Figure 3C). It is characterized by large to very large lymphoma cells, with pleomorphic or bizarre nuclei, usually with abundant cytoplasm and frequent cohesive sheet-like growth, and partial or extensive sinusoidal involvement.[30] This variant often demonstrates CD30 expression, correlated with a favorable outcome and has frequent TP53 mutations.[32,33]

Other rare variants

Rare variants can be observed in under 1% cases of DLBCL, NOS. They showed such as a signet ring or clear cell pattern (Figure 3 D) that mimicking gastric carcinoma or spindle-cell appearance which mimicking sarcoma.[34,35]

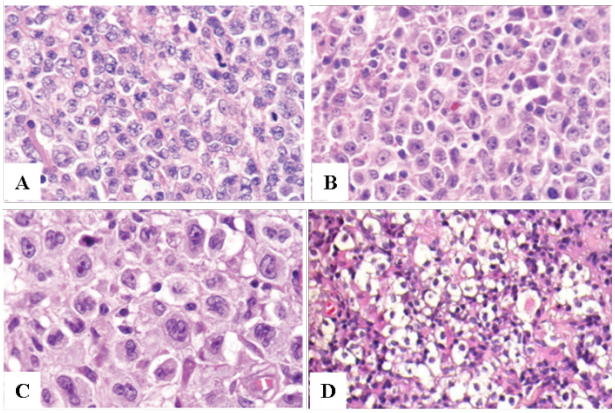

Figure 3. Microscopic appearances of DLBCL variants. A. Centroblastic variant. B. Immunoblastic variant. C. Anaplastic variant. D. Clear cell variant.[36,37]

Diagnosis

The diagnosis of DLBCL is established based on combination of clinical information, evaluation of microscopic features of histopathology, immunohistochemistry and cytogenetic or molecular examination. Based on that information the differential diagnosis can be readily excluded. Recent classification is according Blue book WHO 2017.[6] Diffuse large B-cell lymphoma is characterized by the expression of CD45 and pan B markers namely CD19, CD20, CD22, and CD79a, which can be detected by immunohistochemistry or flow cytometry. The cells majority also express surface immunoglobulin (IG).[5]

Morphologically, the features of lymph nodes or extranodal tissue is totally or partially effaced by lymphoid tumor cells with medium-to-large size. These cells can be organized as diffuse pattern or vague nodular arrangement with or without the involvement of perinodal tissues.[38] Some cases show a “starry sky” appearance due to the present of many tingible body macrophages. Thick or fine fibrosis with possible compartmentalization of small groups of lymphoma cells can also be seen and areas of geographic necrosis may be present. The tumour microenvironment of DLBCL consist

of various numbers of reactive small T-cells, histiocytes and few plasma cells.[2] Histopathologically, tissue architecture of DLBCL shows large lymphoma cells that are organized in a diffuse pattern. In some cases, vaguely nodular pattern can also be found.[38]

Treatment

The standard therapy for DLBCL to date is Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP) which are given as initial therapy. The addition of Rituximab, a monoclonal anti-CD20 antibody, to conventional CHOP chemotherapy, increased the 3-year overall survival (OS) to 93%. Although potentially curable, 40% of patients become relapsed or refractory.[39-41]

A study showed that for younger DLBCL patients with low risk clinical feature, R-CHOP × 4 is a standard of care in with early stageDLBCL.[42] While advanced stage DLBCL was given the standard treatment approach consisted dose-adjusted etoposide, doxorubicin, and vincristine with prednisone, cyclophosphamide and rituximab (DA-EPOCH-R).[39] Treatment approach for relapsed or refractory DLBCL including salvage chemotherapy followed by autologous stem cell transplantation (ASCT). However, this approach treated only few patients.[43] Those categoric patients usually have worse prognosis.[39]

4. CONCLUSION

As a heterogeneous disease DLBCL showed some similarities of clinical sign and symptoms, morphology and immunopheno types with other non-Hodgkin lymphomas. Therefore, some other molecular analysis such mutation events should be performed to achieve a correct diagnosis. Efforts in classification of DLBCL from COO-approach to mutational-based and abundance new information of DLBCL pathogenesis offers opportunities to the development potential targets of novel biomarkers of prognosis and diagnosis DLBCL. These contribute to the development of targeted and novel therapeutics for DLBCL.

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