

Epidemiology, pathogenesis, molecular characteristics, classification and prognosis of the diffuse large B-cell lymphoma

S.M. Gaidukova¹, S.V. Vidyborets¹, Yu.Yu. Popovich²

¹Shupyk National Medical Academy of Postgraduate Education, Kyiv

²Uzhgorod National University

The article presents the results of systematic review of the available literature sources (search in JAMA, Scholar, NCBI, Cochrane Library and PubMed databases, 2007–2018 has been performed) about the epidemiology, pathogenesis, molecular characteristics, classification and risk factors of the epidemiology, pathogenesis, molecular characteristics, classification and risk factors of the diffuse large B-cell lymphoma (DLBCL).

Key words: diffuse large B-cell lymphoma, epidemiology, pathogenesis, molecular characteristics, classification, risk factor.

Lymphoid neoplasms, tumors of the white blood cells, can be divided into non-Hodgkins lymphomas, Hodgkins lymphomas, lymphocytic leukemias, plasma cell dyscrasias and other related disorders. The lymphoid neoplasms are a group with a wide variation amongst their clinical presentations and behavior and based on these, divided into two main subtypes; Leukemias and Lymphomas. Lymphomas are divided further into two types; non-Hodgkins lymphomas (NHLs) and Hodgkins lymphomas. Of these two subtypes, It is through the many steps of B-cell differentiation that lymphomas occur, creating several different types of NHL, where the most frequent is DLBCL. In diffuse large B-cell lymphoma (DLBCL), the distinction of the germinal center B-cell-like (GCB) DLBCL and activated B-cell-like (ABC) DLBCL subtypes is beginning to translate into the clinic, as these diagnostic categories have significantly different survival rates after standard treatment. Similarly, the molecular distinction using gene expression profiling of DLBCL and Burkitt's lymphoma (BL) is of major clinical importance, as BL requires more intensive treatment strategies. These examples evidence that the routine application of gene expression profiling will eventually lead to the establishment of a molecular classification of malignant lymphoma.

B-cell lymphomas arise during different steps of B-lymphocyte development and represent their malignant counterpart. B-cell development encompasses different stages and is initiated in the primary lymphoid organs with subsequent differentiation in secondary lymphoid tissues such as lymph nodes, spleen, or tonsils. During these stages of development, several DNA modifications occur that are essential for a normal immune response. However, these modifications might predispose to genetic abnormalities leading to lymphoma evolution.

The development of B cells in the bone marrow is initiated by random recombination of genes that encode the variable regions of the heavy and light antibody chains to form the B-cell receptor (BCR). This process is referred as V(D)J recombination and involves double-stranded DNA breaks by recombination activating gene 1 (*RAG1*) and recombination activating gene 2 (*RAG2*), which are resolved by non homologous end-joining repair processes [15]. The immunoglobulin heavy chain genes (IgH) are assembled from various V (variable), D (diversity) and J (joining) elements, whereas the light chain is recombined from V and J elements [47]. During this process, only cells that have acquired heavy and light chain variable region genes that can be translated

into protein will survive, whereas all other cells will undergo apoptosis [47]. Once the BCR is expressed, the lymphocytes leave the bone marrow and become mature, naive B cells.

On antigen-induced B-cell activation, the germinal center reaction in secondary lymphoid tissues is initiated. During the germinal center reaction at least two distinct DNA modifications - somatic hypermutation (SHM) and class switch recombination (CSR) occur. Both reactions are mediated by the B-cell specific enzyme activation-induced cytidine deaminase (AID) [36]. SHM modifies the Ig variable region by introducing mutations, small deletions, or insertions to produce antibodies with increased affinity for the immunizing antigen [18]. In contrast, CSR is a process by which the heavy chain class changes from IgM to IgG, IgA, or IgE. CSR occurs by DNA recombination within highly repetitive switch regions located 5' of each constant region [32]. After the germinal center reaction, B cells develop into memory B cells or plasma cells.

The tightly controlled steps in B-cell development, however, can go awry, and lymphomas may arise. V(D)J recombination, SHM, and CSR especially represent critical processes that might predispose to these malignancies. Examples of translocations occurring during V(D)J recombination are t(14;18) and t(11;14).

The t(14;18), which is detected in virtually all cases of follicular lymphoma and a fraction of diffuse large B-cell lymphoma (DLBCL) cases, involves the *BCL2* gene and the *IgH* locus, leading to dysregulation of BCL [6, 58]. The t(14;18) is mediated by the RAG recombinase proteins, which cleave at J segments in the *IgH* locus and at an unusual non-B-form DNA structure in *BCL2.7*. The t(11;14) juxtaposes the *CCND1* gene to the *IgH* locus, leading to over expression of cyclin D1.

SHM has also been suggested to play an important role in lymphomagenesis. AID can mutate genes in addition to Ig genes. *BCL6* is frequently mutated by aberrant SHM in DLBCL [32]. Some *BCL6* mutations occur in a negative autoregulatory site in the first non coding exon, thereby increasing BCL6 expression by relieving BCL6 of self repression [63]. DLBCLs accumulate AID-dependent somatic mutations in many other genes, including oncogenes such as *MYC* and *PIM1* [44].

CSR also involves DNA breaks, and errors in its regulation can lead to chromosomal switch translocations, which are frequently detected in Burkitt's lymphoma, multiple myeloma, and other lymphoid malignancies [7, 37]. AID is the likely candidate to mediate these translocations, as AID is required for spontaneous *MYC/IgH* translocations in mice [48]. Furthermore, the activated B-cell-like DLBCL subtype is characterized by high AID expression and a high frequency of switch translocations. B-cell lymphomas arise at different stages of differentiation, and accordingly, pregerminal and postgerminal center lymphomas can be distinguished.

Diffuse large B-cell lymphoma (DLBCL) is the most frequently-occurring lymphoma, accounting for an estimated 35% of all lymphoma cases worldwide. In the Western world, nearly 90% of aggressive mature B-cell lymphomas are identified as DLBCL [1, 31, 52-54]. DLBCL is a large B lymphoid cell neoplasm with a diffuse

DLBCL variants, subgroups and subtypes [57]

DLBCL, not otherwise specified
Common morphologic variants: Centroblastic Immunoblastic Anaplastic Rare morphologic variants Molecular subgroups GCB ABC Primary mediastinal large cell lymphoma Immunohistochemical subgroups CD5-positive DLBCL GCB-like non-GCB – like
DLBCL subtypes
T-cell/histiocyte-rich large B-cell lymphoma Primary DLBCL of the CNS Primary cutaneous DLBCL, leg type EBV-positive DLBCL of the elderly
Other lymphomas of large B-cells
Primary mediastinal (thymic) large B-cell lymphoma Intravascular large B-cell lymphoma DLBCL associated with chronic inflammation Lymphomatoid granulomatosis ALK-positive LBCL Plasmablastic lymphoma Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease Primary effusion lymphoma

growth pattern composed of large B-lymphocytes with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of normal lymphocytes. Morphological, biological and clinical studies have identified distinct morphological variants, molecular and phenotypic subgroups and clinico-pathological entities amongst DLBCL [57, 58]. Yet, most DLBCL cases would be finally classified as DLBCL not otherwise specified (NOS), not meeting the classification criteria of a specific subtype as proposed by the current World Health Organisation (WHO) system of classification [58].

The WHO divides DLBCL into subtypes based on clinical, morphological, immunological and genetic features (table 1) [8, 60]. There are three main morphologic variants each with its own characteristic cytological parameters: centroblastic, immunoblastic and anaplastic, with the immunoblastic variant being associated with the worst prognosis [42]. Unfortunately, the identification of immunoblastic variants is often not reproducible [58]. Phenotypically, over 95% of DLBCL cases express pan-B-cell markers, such as CD20 [2]; a few phenotypic markers such as FoxP1 and Cyclin E are consistently associated with poor outcome [61].

Epidemiology DLBCL represents 80% of all aggressive lymphomas [56] and 30 to 40% of all NHL cases in the West and are one of the most frequent in developing countries [64]. NHL is the fifth most common type of cancer in Ukraine, with an incidence of 55,000 cases and over 26,000 deaths per year. Likewise, DLBCL is the most common lymphoma in adults (31%), followed by follicular lymphoma (FL) [14]. The median age at incidence is 60 years and it predominates in males (55%) [17].

According to Friedberg [14], the incidence of DLBCL has been increasing by 3 to 4% per year in both genders, in white and non-white populations, and in all age groups, except for adolescents. Factors such as more sensitive diagnostic techniques, changes in the classification of lymphoproliferative disorders and, particularly, the increase of NHL in HIV patients have contributed to the escalation in the incidence of this disease. Environmental factors, as well as genetic, occupational

and dietary factors, may have contributed to the development of NHL [11]. NHLs are associated with chronic inflammatory diseases such as Sjögren syndrome, celiac disease and rheumatoid arthritis. Indeed, infectious agents are also related to the pathogenesis, but no greater incidence of NHL has been found in individuals who handle organic solvents, organophosphates, benzene or carbon tetrachloride [10]. In DLBCL, factors such as ultraviolet radiation, pesticides, and hair dye are potentially associated with higher risk. In addition, immunosuppression, especially related to HIV, is a risk factor and it may be associated with Epstein-Barr virus [14].

Immunohistochemical Methods Of Classifications Of DLBCL Although GEP is the standard method of evaluating DLBCL COO phenotype, it is currently costly, time consuming, and inaccessible for many centers. Hence, immunohistochemistry (IHC) algorithms were developed. The Hans algorithm [26] stratifies cases as GCB or non-GCB according to protein expression of CD10, BCL-6, and MUM1. The algorithm is prognostic and correlates with GEP-defined subtype in approximately 80% of cases [19]. Subsequent IHC algorithms with minor modifications have been developed [9, 33]. The Choi algorithm incorporates FOXP1 and GCET1 [26], whereas the Tally method substitutes BCL6 for LMO2 [33].

The three algorithms were recently compared to GEP in biopsy samples from 108 patients [20], with results favoring the Hans and Choi algorithms over Tally. The positive predictive value of these IHC classification methods for identifying GEP classified COO ranged from 0.78 to 1.0, with sensitivity of 0.58–0.83; the Tally method was the least sensitive. The Hans and Choi algorithms were significantly predictive of overall survival (OS) and progression free survival (PFS). Although accuracy is less than that of GEP and reproducibility is variable, particularly for BCL6 staining [41], IHC phenotype classification is more readily available and cost effective; hence, it has been more widely adopted both in clinical practice and prospective trial designs.

ABC-DLBCL is frequently associated with constitutive activation of the NF- κ B pathway, resulting in enhanced cell proliferation and decreased apoptosis. NF- κ B pathway signalling occurs through dimerization of NF- κ B transcription factors in the cytoplasm, which migrate to activate transcription of target genes in the nucleus [12, 27]. Cell-line data using RNA interference (RNAi), retroviral transduction and small molecule inhibitors as methods of repressing the NF- κ B pathway show that ABC-DLBCL but not GCB-DLBCL is dependent on the NF- κ B pathway for survival [12, 26, 38]. Mutations affecting the NF- κ B pathway are more frequent but not exclusively present in ABC-DLBCL [11]. An important source of NF- κ B pathway activation in ABC-DLBCL is alteration in genes encoding components of an upstream signaling complex involving CARD11, BCL10, and MALT1 (CBM complex) [27, 38, 39], which also forms part of the BCR-signaling pathway. Missense mutations in *CARD11* occur with higher frequency in ABCDLBCL (10–11%) compared to GCB-DLBCL (4–7%) [11, 27].

Dysregulated B-cell-receptor (BCR) signaling initiated upstream of CARD11 also mediates constitutive NF- κ B pathway activity and is implicated in lymphomagenesis of *CARD11* wild-type (WT) ABC-DLBCL [40]. BCR-signaling is generated by ligand-induced receptor engagement and SRC family kinase phosphorylation of the CD79A and CD79B receptor subunits, leading to activation of spleen tyrosine kinase (SYK) and triggering of a downstream cascade including Bruton's tyrosine kinase (BTK) [12]. Antigenic stimulation of transient BCR-signaling is an essential physiological B-cell process [26]; however, chronic-active BCR-signaling is pathogenetic, as evidenced by the selective lethality of RNAi knockdown of key BCR pathway components in *CARD11*WTABC-DLBCL cell lines [36]. Specific mutations within the CD79B subunit that promote chronic active BCR signaling have also been demonstrated to occur in higher frequency in ABC-DLBCL than in GCB-DLBCL [13]. A20 contributes to termination of NF- κ B pathway signalling and appears to have a tumour suppressor gene role [11, 23]. Inactivating mutations in A20 cause constitutive NF- κ B activity through failure to abort pathway signaling; they occur in approximately 25% of ABC-DLBCL but are rare in GCB DLBCL [11]. Other pathogenic molecular characteristics that are more frequent and of selective functional significance in ABCDLBCL, but not directly associated with the NF- κ B pathway, include 19q amplification, *INK4a/ARF* tumour-suppressor locus deletion, trisomy 3, inactivation of tumor suppressor BLIMP1 (encoded by the *PRDM1* gene), and overexpression of PIM family serine/threonine kinases [16].

Two early GEP-identified recurring genetic alterations exclusive to GCB-DLBCL are the t(14;18) translocation in *BCL-2* and *C-REL* amplification, which occur with a frequency of approximately 25% and 15%, respectively [28, 50]. The t(14;18) translocation causes expression of the antiapoptotic BCL-2 protein and is a hallmark of follicular lymphoma (FL), which also arises from the germinal center—perhaps explaining why transformed DLBCL in the setting of FL is frequently of the GCB subtype. BCL2 protein expression is common in both DLBCL subtypes [21], but there are conflicting data regarding the phenotype for which it has prognostic significance. BCL-2 expression is associated with inferior prognosis in both IHC-defined [57] and GEP defined [40, 62] GCB-DLBCL but not in ABC (or non-GCB) DLBCL.

c-MYC oncogene rearrangements as detected by fluorescent in-situ hybridization (FISH) occur with a frequency of 6–14% [4, 6, 24] in DLBCL; they appear to be more common in GCB-DLBCL using the Hans IHC classification [6, 25, 32, 59]. *c-MYC* rearrangements cause constitutive expression and dysfunction of the transcription controller *c-myc*, and they have been correlated with poor prognosis in patients treated with chemotherapy both with the addition of rituximab [6, 59] and without [24, 32]. The “double-hit” gene rearrangement of both *c-MYC* and t(14;18) is associated with FL histologically transformed to

DLBCL and conveys additively inferior prognosis [3, 31, 32]. High IHC expression of both BCL-2 and MYC is also associated with a poor prognosis. Exome sequencing analyses have recently revealed that mutations in genes involved in epigenetic processes are prominent lymphoma-promoting mechanisms [35, 43, 45]. Inactivating mutations in key histone acetyltransferase (HAT) genes *CREBBP* and *EP300* also occur commonly in GCB DLBCL; they display probable haplo-insufficient tumor suppressor functionality and appear pathogenic by impeding p53 tumor suppressor activity and enhancing BCL6 oncogene activity [43].

Mutations in the mixed-lineage leukemia 2 (*MLL2*) gene occur in biopsy samples with frequency of 27% in GCBDLBCL and 20% in ABC-DLBCL. *MLL2* appears to behave as a haploinsufficient tumor suppressor gene. Mutations at codon 641 of histone methyltransferase gene *EZH2* are almost exclusive to GCB-DLBCL, present in 14–22% of cases [35, 45, 49]. Other GEP-identified potential oncogenic drivers that are exclusive or almost exclusive to GCB-DLBCL are overexpression of the mir-17–92 microRNA cluster amplification in approximately 13% and PTEN deletion in 11% of cases [27]. *TP53* mutations were reported to be negatively prognostic in IHC-defined GCB-DLBCL. *TP53* mutations can provoke activation of the antiapoptotic NF- κ B pathway, which may be more significant in GCB-DLBCL.

The frequencies of other molecular alterations have either not been compared between the GCB or ABC phenotypes or are similar in both. Inactivating mutations leading to absence of expression of immune recognition molecules B2 microglobulin (B2M) and CD58 have been identified in both GCB and ABC / nonclassified DLBCL (B2M: 10–15%; CD58: 6–7%), indicating that cellular immune surveillance is another lymphomagenic mechanism. BCL-6 cytogenetic rearrangements are common in DLBCL [3]. There is conflicting data from studies using the Hans IHC criteria to define subtype with regard to whether these are more prevalent in non-GCB-DLBCL or are similar in both subtypes [3, 59]. Uddin et al. demonstrated that PI3K pathway signaling as assessed by pAKT IHC expression occurs with a frequency of 52% in DLBCL and may represent a therapeutic target; however, the results were not analyzed according to COO subtype.

PMBLs are characterized by amplifications of 9p24 [22, 28]. In contrast, these abnormalities occur significantly less frequently in ABC and GCB DLBCL [28]. 9p24 amplifications are associated with upregulation of JAK2, a tyrosine kinase that regulates cytokine signalling through STAT transcription factors. PD-L1 and PD-L2, which are ligands for the PD receptor on T cells, are also upregulated in PMBL by this amplification [51]. Engagement of the PD receptor by its ligands inhibits signaling through the T-cell receptor, suggesting that amplification of these genes modulates the interaction between PMBL cells and surrounding T cells [51]. Constitutive activation of the NF- κ B signalling pathway is another common feature of PMBL cells [51]. The molecular mechanisms that activate NF- κ B in PMBL are currently not entirely understood. In approximately 30% of PMBL cases, the negative NF- κ B regulator A20 is inactivated [55].

The differentiation and proliferation of B-cells are controlled by transcription factors [29]. Two of these factors are the OCT-1 and OCT-2 proteins that belong to the POU family and are linked to genes involved in B-cell regulation [30]. The OCT-2 protein is little expressed in pre-B-cells, T-cells, myelomonocytic and epithelial cells. However, it is strongly expressed in mature B-cells. On the other hand, the OCT-1 protein is highly expressed in pre-B-cells, suggesting that it may be involved in the early phase of B-cell development [30].

Recent studies have demonstrated, through the RNA interference technique, that OCT factors influence the survival of cells in lymphomas with the t(14; 18). A positive correlation was found between OCT, BOB1 and BCL2 expressions. OCT-2 activates the promoter of the *BCL2* gene and is involved in the malignant transformation in B lymphomas. The low expressions of OCT-1, OCT-2 and BOB1 are inversely proportional to apoptosis [30, 31].

Епідеміологія, патогенез, молекулярна характеристика, класифікація і прогноз при дифузних В-крупноклітинних лімфомах
С.М. Гайдукова, С.В. Видиборець, Ю.Ю. Попович

Эпидемиология, патогенез, молекулярная характеристика, классификация и прогноз диффузных В-крупноклеточных лимфом
С.Н. Гайдукова, С.В. Выдыборец, Ю.Ю. Попович

У статті наведені результати систематичного огляду наукових джерел (пошук проведено і в базах даних JAMA, Scholar, NCBI, Cochrane Library and PubMed, 2007–2018) щодо епідеміології, патогенезу, молекулярної характеристики, класифікації, прогнозу і факторів ризику при дифузних В-крупноклітинних лімфомах (ДВКЛ).

Ключові слова: дифузна В-крупноклітинна лімфома, епідеміологія, патогенез, молекулярна характеристика, класифікація, прогноз, фактори ризику.

В статті приведені результати систематичного огляду літературних наукових джерел (поиск проведено в базах даних JAMA, Scholar, NCBI, Cochrane Library and PubMed, 2007–2018), касаючихся епідеміології, патогенезу, молекулярних характеристик, класифікації і факторів ризику дифузної В-крупноклеточної лімфони.

Ключевые слова: диффузная В-крупноклеточная лимфома, эпидемиология, патогенез, молекулярная характеристика, классификация, прогноз, факторы риска.

Сведения об авторах

Гайдукова Светлана Николаевна – Национальная медицинская академия последипломного образования имени П.Л. Шупика, 04112, г. Киев, ул. Дорогожицкая, 9; тел.: (044) 483-16-61

Выдыборец Станислав Владимирович – Национальная медицинская академия последипломного образования имени П.Л. Шупика, 04112, г. Киев, ул. Дорогожицкая, 9; тел.: (044) 483-16-61

Попович Юрий Юрьевич – Национальный Ужгородский университет, 88000, г. Ужгород, пл. Народная, 3; тел.: (063) 654- 67-89

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