Large B-Cell Lymphoma

Subjects: Oncology

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Diffuse large B-cell lymphomas (DLBCLs) are aggressive B-cell neoplasms with considerable clinical, biologic, and pathologic diversity. The application of high throughput technologies to the study of lymphomas has yielded abundant molecular data leading to the identification of distinct molecular identities and novel pathogenetic pathways.

Keywords: large B-cell lymphoma ; next generation sequencing ; mutations ; pathway activation

1. Overview

The development of high-throughput technologies in recent years has increased our understanding of the molecular complexity of lymphomas, providing new insights into the pathogenesis of large B-cell neoplasms and identifying different molecular biomarkers with prognostic impact, that lead to the revision of the World Health Organization consensus classification of lymphomas. This review addresses the main histopathological and molecular features of large B-cells lymphomas, providing an overview of the main recent novelties introduced by the last update of the consensus classification.

Diffuse large B-cell lymphomas (DLBCLs) are aggressive B-cell neoplasms with considerable clinical, biologic, and pathologic diversity. The application of high throughput technologies to the study of lymphomas has yielded abundant molecular data leading to the identification of distinct molecular identities and novel pathogenetic pathways. In light of this new information, newly refined diagnostic criteria have been established in the fourth edition of the World Health Organization (WHO) consensus classification of lymphomas, which was revised in 2016. This article reviews the histopathological and molecular features of the various aggressive B-cell lymphoma subtypes included in the updated classification.

2. DLBCL

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma worldwide. Patients present with a rapidly enlarging tumor mass involving single, multiple, nodal, or extranodal sites A, and approximately 40% of cases are confined to extranodal sites [1][2].

Histologically, these neoplasms are defined as the presence of lymphoma cells larger than the nuclei of histiocytes present in the same section [3][4]. DLBCL encompasses a wide spectrum of neoplasms with morphological and immunohistochemical heterogeneity. Twenty percent of cases are thought to be sufficiently different, and thirteen different variants have been accepted on the last review of the WHO organization, on the basis of distinctive morphological or immunophenotypic findings or distinctive biological issues associated with their diagnoses. However, 80% to 85% of DLBCL cases are not sufficiently distinctive and are therefore designated as not otherwise specified (DLBCL-NOS) [2][5].

A few changes have been introduced in the fourth edition of the WHO classification regarding DLBCL [2]: (1) the “cell of origin” (COO) classification must be included in the pathology report; (2) CD5, MYC, and BCL2 immunohistochemical expression must be assessed as prognostic factors; (3) the provisional entity “B cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma” has been replaced by two new categories: “high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations” and “high-grade B-cell lymphoma, not otherwise specified”.

3. Diffuse Large-B-Cell Lymphoma, Not Otherwise Specified (Dlbcl-Nos)

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS), accounts for about one-third of all non-Hodgkin’s lymphomas [1]. By definition, DLBCL-NOS is predominantly an aggressive lymphoma that does not belong to a specific subtype and/or variant of DLBCL [2][6]. DLBCL-NOS frequently affects elderly patients with a slight male predominance,

although it can also occur in children and young adults [2][6]. Histologically, the involved tissues show diffuse infiltrates of medium- to large-sized neoplastic cells, displaying a centroblastic appearance in 80% of cases. The immunoblastic variant represents 8–10% of cases, and in the rare anaplastic variant (3% of the cases), the tumoral cells are large, bizarre, and pleomorphic [3][7].

Besides this morphologic subdivision, the COO classification has been shown to identify distinct DLBCL prognostic subgroups, with germinal center B-cell (GCB) subtype DLBCL cases (GCB-DLBCLs), representing 40–50% of DLBCL cases, being associated with a significantly better outcome compared to the activated B-cell (ABC) subgroup (ABC-DLBCL) (50–60% of DLBCL cases) [8]. Approximately 10–15% of cases cannot be included in either of these subgroups and remain unclassified [9].

Consistent with their COO, GCB-DLBCL cases harbor hypermutated immunoglobulin genes with ongoing somatic hypermutation and a high level of BCL6 expression, whereas ABC-DLBCL ones show NF-κB- and BCR-signaling-pathway activation [10]. Therefore, ABC-DLBCLs frequently harbor mutations affecting *MYD88* (~20% of cases), *CD79A*/*B* (~20%), *CARD11* (~10%), *MALT1*, *BCL10*, and *TNFAIP3*, responsible for NF-κB pathway activation [11][12]. Additionally, *PRDM1*/*BLIMP1* mutations are also seen in 30% of DLBCL-NOS cases, exclusively in the ABC subtype. In contrast, the GCB-subtype group more often shows mutations involving histone methylation or acetylation genes (*EZH2*, *EP300*, *CREBBP*, *KMT2D*), B-cell homing genes (*GNA13*, *GNAI2*, *SIPR2*), the PI3K signaling pathway, and the JAK-STAT pathway. *EZH2* mutations are exclusive to the GCB-type, being found in approximately 20% of cases. *EZH2* mutations are gain-of-function mutations leading to an increased expression of the EZH2 protein, which is responsible for the methylation of histone H3 at lysine 27, inducing transcriptional repression and gene silencing [13][14][15][16].

The development of high-throughput technologies in recent years has increased our understanding of the molecular complexity of lymphomas beyond COO classification, defining DLBCL genetic signatures, characterizing new DLBCL subsets, and providing new insights into DLBCL pathogenesis. Initially, six genetic subgroups were defined [17][18][19]: MCD, BN2, N1, EZB, ST2, and A53. MCD and N1 cases were mostly ABC-DLBCL cases, with MYD88L265P and *CD79B* characterizing MCD cases and *NOTCH1* mutations being present in the N1 cases. EZB and ST2 DLBCL cases were mostly GCB-DLBCLs, with recurrent *BCL2* translocations and *EZH2* gene mutations in the EZB subtype cases, and mutations in *SGK1* and *TET2* in the ST2 subtype ones [17][18]. Additionally, a worse-prognosis subtype group (A53) was also defined, with cases showing aneuploidy, *TP53* mutations, and deletions [18]. Later on, whole-exome sequencing (WES) data in 304 primary DLBCLs were used by Chapuy et al. [20] to define five DLBCL subtypes (C1 to C5), allowing the distinction of both ABC and GCB-DLBCL cases in two distinct subgroups, with favorable and adverse outcomes. ABC-DLBCLs subtypes clustered in two different groups: a possible marginal zone origin one (C1) with *NOTCH2* mutations, *BCL6* translocation, and a lower risk, and a higher risk group one (C5) with recurrent mutations in *MYD88*, *CD79B*, and *PIM1* [20]. In the same way, two different GCB-DLBCLs subtypes were also defined, including a C4 subgroup with favorable outcomes and a C3 subgroup with poor prognosis. C4 DLBCLs showed mutations affecting RAS/JAK/STAT pathway members (*BRAF*, *STAT3*), BCR/Pi3K signaling intermediates (*RHOA*, *GNA13*, and *SGK1*), KFkB modifiers (*CARD11*, *NFKBIE*, *NFKBIA*) and immune evasion molecules (CD83, CD58, and CD70) [20]. Conversely, C3 DLBCL cases harbored *BCL2* mutations, as well as mutations affecting chromatin modifiers (*KMT2D*, *CREBBP*, and *EZH2*), B-cell transcription factors (MEF2B, IRF8), BCR-and PI3K-signaling modifiers (*TNFSF14*, *HCNV1*, *GNA13*), and *PTEN*-inactivating mutations [20]. Furthermore, a C2 subgroup associated with genomic instability, *TP53* biallelic inactivation, and *CDKN2A* losses was also described [20].

Cytogenetic analysis is also helpful in DLBCL workup. Complex karyotypes are more common in tumors that are clinically aggressive or resistant to therapy, and specific chromosomal aberrations correlate with COO classification. The most frequent translocation (about 30% of cases) implies *BCL6* at the chromosome 3q27 locus [21][22], often juxtaposed with *IGH* on chromosome 14q32 [3], and tends to occur more commonly in the ABC subtype [11][22]. The t(14; 18)(q21; q32)/IGH-BCL2 can be detected in the GCB type [1][7]. Translocations involving *MYC* at 8q24 also occur in 10–15% of DLBCL cases and are often associated with high-grade morphological features and a complex karyotype [23]. A variable proportion of the *MYC* translocations involve the *IG* loci as partners: *IGH*, *IGK*, or *IGL*. Other partners include non-immunoglobulin loci such as *PAX5*, *BCL6*, *BCL11A*, IKZF1 (IKAROS), and BTG1 [24][25].

It is recognized that GEP is not widely available [26][27], but the classic Hans algorithm utilizing antibodies against CD10, BCL6, and MUM-1/IRF4 is routinely used worldwide in COO classification [28] with variable rates of concordance (65–90%) to the GEP classification scheme. With the development of new IHC antibodies, the panel has been expanded in newer iterations, known as the “Choi”, “Tally”, and “Visco-Young” algorithms [29][30][31]. Recently, Yoon et al. [32] also demonstrated that NanoString technology for formalin-fixed, paraffin-embedded tissue may be a robust, reliable method for predicting the outcome, compared to the Hans algorithm.

Therefore, immunohistochemical assessment is mandatory for DLBCL-NOS diagnosis and COO determination, but different IHC marker expressions have been found to have prognostic significance. CD30 expression, frequently seen in the anaplastic variant of DLBCL [33][34], has been shown to be associated with a favorable outcome [34], while CD5-positive cases exhibit features associated with an aggressive clinical course and poorer survival [35]. DLBLC-NOS cases, in which MYC and BCL2 are expressed in >40% and 50% of neoplastic cells respectively, are known as double-expressor lymphomas (DEL). DEL cases are far more common in the ABC subtype and have been shown to have a worse prognosis [26]. PD-L1 and PD-L2 expression has been reported in about 20–25% of DLBCL-NOS cases, correlating with PD-L1/L2 amplification at chromosome 9p24.1 and response to PD1 inhibitors [36]. P53 expression is seen in 20–60% of cases, suggesting an upregulation of wildtype *TP53* in some non-TP53 mutated cases [37].

Morphologic DLBCL variants have specific molecular features: the centroblastic variant is more frequently found in the GCB subtype, while immunoblastic lymphomas are more often found in the ABC subtype [38]. Additionally, immunoblastic lymphomas have been found to frequently harbor *MYC* translocations [39], which confer a worse prognosis. Li et al. [40] recently indicated the distinctiveness of the anaplastic variant based on genetic analyses. They found a higher incidence of p53 positivity (in 80% of the cases) and expression of both MYC and BCL2 (43%) in association with an aggressive clinical course.

4. Conclusions

New advances in molecular technologies have yielded a tremendous amount of information about lymphoma biology, leading to a refined classification of lymphomas, which is reflected in the revised fourth edition of the WHO classification. Lymphoma diagnosis currently integrates clinical information, morphology, immunophenotypic, and genetic data. This review focuses on specific variants of DLBCL with unique features and for which recognition is important for diagnosis and therapeutic management, as well as on the large category of DLBCL-NOS that represents 80% of all DLBCL cases.

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