

Supplement Article

I. Pathological and clinical diversity in diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the term applied to a constellation of different disorders with specific clinicopathological features [1].

All DLBCL cases are distinguished by a diffuse pattern of infiltration and a cytological composition by large B-cells. Despite these common features, DLBCL cases may have strikingly different clinical presentations, immunophenotype, molecular pathogenesis and response to therapy

Diffuse large B-cell lymphoma, not otherwise specified

This is the term applied to the cases that do not fit into specific variants. A range of morphologies has been distinguished including centroblastic, immunoblastic and anaplastic morphology, a division that has been shown to carry on a prognostic relevance [2]. Thus, Ott and coworkers demonstrated that immunoblastic morphology was as a robust, significantly adverse prognostic factor in multivariate analysis, with this diagnosis showing a good reproducibility among expert hematopathologists. Although specifically-trained pathologists are able to consistently reproduce this morphological subclassification, the overall reproducibility among general pathologists is quite low.

Molecular subclassification of these cases in two main groups has demonstrated a more definite utility [3]. Thus, division in germinal centre (GC) and non-GC phenotypes identifies tumours with distinct molecular pathogenesis and therapeutic targets. Practical application of this approach is limited by the finding that specific markers for routine demonstration of these phenotypes using immunohistochemical markers may lack consistency, but some quite robust models have been proposed and extensively used [4].

There is not a single molecular alteration that distinguishes all DLBCL cases, but in general, these tumours exhibit deregulation of genes involved in cell-cycle control [5], additionally to changes in genes and pathways involved in cell survival and apoptosis regulation. Chromosomal translocations, and other genetic events, segregate with molecular subtypes. Thus, translocations involving *BCL-2* and *C-MYC* oncogene loci have been found in 30–40% cases of CGC-DLBCL, whereas ABC-DLBCL is characterized by the cell dependence on the CBM complex, a signalling hub that includes *CARD11*, *BCL10*, *MALT1* and other proteins [6]. Although initial studies tend to associate the non-GC subtype with NF- κ B activation, it has been recently shown that this phenomenon may take place in both GC and non-GC DLBCL cases [7].

Sequencing studies recently performed in DLBCL cases have revealed recurrent mutations in genes such as *MYD88*, *CARD11*, *EZH2*, *CREBBP*, *MEF2B*, *MLL2*, *BTG1*, *GNA13*, *ACTB*, *P2RY8*, *PCLO* and *TNFRSF14*. Some of these genes have not previously been suspected to play a pathogenic role in DLBCL [8–10].

Diffuse large B-cell lymphoma prognosis has been the subject of numerous studies that have shown that most prognostic models are dependent of the treatment received by the patients and the techniques employed for analyzing the tumours. Molecular subclassification between GC and non-GC types has been shown to be useful in R-CHOP-treated patients exclusively. Quite solid findings have been demonstrated for the adverse prognostic significance of the simultaneous expression of *C-MYC* and *BCL2*, an observation confirmed by different authors [11–14]. A microRNA signature including miR 221, miR22, miR93, miR331 and miR 491 has been shown to identify R-CHOP-treated patients with a more aggressive behaviour [15].

A potential predictive role of the ABC signature, predicting better response to Bortezomib combined with chemotherapy, has been shown in a reduced series and awaits further confirmation [16].

Interestingly, the expression of CD30 has been shown to distinguish a group of DLBCL cases (14%) with a more favourable prognosis, this finding supporting the potential therapeutic use of brentuximab in these patients [17].

Primary mediastinal DLBCL is a distinctive large B-cell lymphoma with a unique clinical presentation and molecular features (CD30 expression and activation of the JAK-STAT pathway) establishing a close relationship with classical Hodgkin lymphoma (HL) [18,19].

Epstein–Barr virus positive age-related DLBCL is a frequent tumour, recently recognized, with aggressive behaviour, diagnosed in patients 50 years and older, in patients with no other causes of immunodeficiency or prior lymphoma. These cases are diagnosed in advanced stages, with more than one extranodal involvement, higher International Prognostic Index risk group and a poorer response to initial treatment. The histology is recognizable because of the polymorphic neoplastic infiltrate and necrosis. Epstein–Barr virus positive large cell lymphomas are excluded from this category, if associated with chronic inflammation or diagnosed as lymphomatoid granulomatosis, plasmablastic lymphoma or primary effusion lymphoma [20,21].

Plasmablastic lymphoma is an aggressive lymphoma type diagnosed frequently in immunosuppressed patients—HIV+, receiving immunosuppressive therapy or elderly people. The tumour involves more regularly oral cavity, gastrointestinal tract or other extranodal tissues. These tumours are characterized by acquisition of the transcriptional profile of plasma cells (with overexpression of PRDM1/Blimp1 and XBP1s, in concert with extinction of the B-cell differentiation programme) by proliferating immunoblasts. C-MYC translocations have been found in up to 49% of these cases [22,23].

Plasmablastic differentiation can be found in a variety of large B-cell lymphomas, including plasmablastic lymphoma, ALK-positive large B-cell lymphoma, primary effusion lymphoma, large B-cell lymphoma arising in human herpesvirus-8-associated multicentric Castleman disease and DLBCL with partial plasmablastic phenotype.

Other DLBCL variants

Numerous DLBCL subgroups have been identified, including the following:

- T-cell/histiocyte-rich large B-cell lymphoma;
- primary DLBCL of the central nervous system;
- primary cutaneous DLBCL, leg type;
- intravascular large B-cell lymphoma;
- DLBCL associated with chronic inflammation;
- lymphomatoid granulomatosis;
- ALK-positive large B-cell lymphoma;
- plasmablastic lymphoma;
- large B-cell lymphoma arising in human herpesvirus-8-associated multicentric Castleman disease;

- primary effusion lymphoma; and
- CD5-positive DLBCL.

All these tumours have specific clinical presentation, histological features and prognosis.

Borderline cases

Intermediate Burkitt's lymphoma (BL)/DLBCL cases: This group was created to allocate those cases, especially in adults, that cannot be definitively classified as BL versus DLBCL, thus avoiding to 'contaminate' the categories of BL and DLBCL with these cases, which may be biologically and clinically different.

This provisional category, termed high-grade B-cell lymphoma, unclassifiable, intermediate between BL and DLBCL, is a heterogeneous category that needs to be further refined and not a distinct entity that allows the classification of cases not meeting criteria for classical BL or DLBCL. In general, these are aggressive, highly proliferative lymphomas with morphological and phenotypic features intermediate between BL and DLBCL, exhibiting increased genomic complexity.

At least three subgroups have been included here:

- double hit involving C-MYC and BCL2 (some of them may represent progressed follicular lymphoma or transformed DLBCL) [24];
- childhood DLBCL cases with MYC translocation; and
- BL cases lacking C-MYC translocation.

Grey zone lymphomas, intermediate DLBCL/HL

This category applies to young men with mediastinal mass, and also other locations that show simultaneous intermediate morphology and immunophenotype. Thus, the tumoural cells express at the same time a B-cell transcriptional programme B (BOB1, OCT2 and PAX5+) and activation antigens (CD30 and CD15). The existence of a grey zone between HL and primary mediastinal large B-cell lymphoma has been strongly suggested by the existence of metachronous and composite cHL and DLBCL cases [25].

Additionally, nodular sclerosis classical HL and primary mediastinal B-cell lymphoma share clinical presentations as mediastinal mass in young adults, and immunophenotypic and genetic features such as the loss of Sig and B-cell receptor signalling, with activation of cytokine JAK-STAT pathway and constitutive NF-kappa B activation with expression of CD30, TRAF1 and nuclear expression of NF-kB subunits

Conclusion

Diffuse large B-cell lymphoma classification includes a bunch of common and rare disorders, some of them with paradoxical clinical behaviour and grey areas with a low reproducibility in diagnosis.

Although DLBCL molecular pathogenesis is being progressively revealed, still the basis for targeted therapies remain to be fully established.

Conflict of interest

The authors have no competing interest.

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