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Large cell non Hodgkin's lymphoma: what is new in the WHO classification?

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non Hodgkin lymphoma (NHL), representing 35-40% of cases. It is a neoplasm constituted of large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte, that has a diffuse growth pattern. Morphological, biological and clinical studies have subdivided diffuse large B-cell lymphomas into morphological variants, molecular and immunophenotypical subgroups and distinct disease entities, which are now quoted in the IV edition of the WHO Classification of Tumours of the Haemopoietic and Lymphoid Tissues (see Table 1). However, a large number of cases remain that may be biologically heterogeneous, and there are no clear and accepted criteria for their further subdivision. These are classified as DLBCL, not otherwise specified (NOS). Importantly, recent gene expression profile (GEP) studies demonstrated that such cases can present with different features, possibly related to a different histogenesis, with relevant prognostic impact. Noteworthy, surrogate markers of GEP can be routinely applied to diagnostic material by immunohistochemistry, being possibly useful for patients' stratification and therapeutic decision.[1-4]

Diffuse large B-cell lymphoma subtypes/entities

T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is characterized by a limited number of scattered, large, atypical B-cells embedded in a background of abundant T-cells and frequently histiocytes.[4]

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL) characterized by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries, with exception of larger arteries and veins.[5]

Primary effusion lymphoma (PEL) is a large B-cell neoplasm usually presenting as serous effusions without detectable tumour masses. It is universally associated with the Kaposi sarcoma herpesvirus (KSHV), also named human herpesvirus 8 (HHV8), most often occurring in the setting of immunodeficiency. Some patients with PEL secondarily develop solid tumours in adjacent structures such as the pleura. Rare KSHV-positive lymphomas indistinguishable from PEL present as solid tumour masses, and have been termed extra-cavitary PEL.[6,7]

Diffuse large B-cell lymphoma of the central nervous system

(CNS DLBCL) represents all primary intracerebral or intraocular lymphomas. Excluded are lymphomas of the dura, intravascular large B-cell lymphoma, lymphomas with evidence of systemic disease or secondary lymphomas, as well as all immunodeficiency- associated lymphomas.

ALK positive diffuse large B-cell lymphoma (ALK positive DLBCL) is a neoplasm of ALK-positive monomorphic large immunoblast-like B-cells, sometimes with plasmablastic differentiation.[8]

Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation is a subtype of DLBCL occurring in the context of long-standing chronic inflammation, and showing association with Epstein- Barr virus (EBV). Most cases involve body cavities or narrow spaces. Pyothoraxassociated lymphoma (PAL) is a prototypic form, and develops in the pleural cavity of patients with long-standing pyothorax.

Large B-cell lymphoma arising in human herpes virus 8 (HHV8)-associated multicentric Castleman disease (HHV-8 MCD) is composed of a monoclonal proliferation of HHV-8 infected lymphoid cells resembling plasmablasts expressing IgM and arising in the setting of multi-centric Castleman disease (MCD). It is usually associated with human immunodeficiency virus (HIV) infection. The term, plasmablastic, is used for this lymphoma, because the cells morphologically resemble plasma cells and have abundant cytoplasmic immunoglobulin; however it corresponds to a naive, IgM-producing plasma cell without IG somatic hypermutation. This lymphoma must be distinguished from plasmablastic neoplasms corresponding to mature, class-switched and hypermutated plasma cells. A primary cutaneous diffuse large B-cell lymphoma composed exclusively of large transformed B-cells, most commonly arising in the leg.

Table 1. Diffuse large B-cell lymphoma subtypes according to the IV edition of the WHO classification of tumours of the haemopoietic and lymphoid tissues.

Diffuse large B-cell lymphoma, not otherwise specified (NOS)
Common morphologic variants
Centroblastic
Immunoblastic
Anaplastic
Rare morphologic variants
Molecular subgroups
Germinal-centre B-cell-like (GCB)
Activated B-cell-like (ABC)
Immunohistochemical subgroups
CD5-positive DLBCL
Germinal-centre B-cell-like (GCB)
Non-germinal centre B-cell-like (non-GCB)
Diffuse large B-cell lymphoma subtypes/entities
Primary mediastinal (thymic) large B-cell lymphoma
T cell/histiocyte rich large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
DLBCL associated with chronic inflammation
ALK positive DLBCL
Large B-cell arising in HHV8-associated multicentric Castleman disease
Plasmablastic lymphoma
Primary effusion lymphoma
Borderline cases
B-cell lymphoma, unclassifiable, with features intermediate bet ween diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate bet ween diffuse large B-cell lymphoma and classical Hodgkin lymphoma

A diffuse large B-cell lymphoma arising in the mediastinum from putative thymic Bcell origin with distinctive clinical, immunophenotypic and genotypic features.[9,10]

Plasmablastic lymphoma (PBL) is a diffuse proliferation of large neoplastic cells most of which resemble B immunoblasts, but in which all tumour cells have the immuno - phenotype of plasma cells. It was originally described in the oral cavity but may occur in other, predominantly extranodal sites.

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References

1. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
2. Rosenwald A, Wright G, Chan WC, 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.
3. Zinzani PL, Dirnhofer S, Sabattini E, et al. Identification of outcome predictors in diffuse large B-cell lymphoma. Immunohistochemical profiling of homogeneously treated de novo tumors with nodal presentation on tissue micro-arrays. Haematologica 2005;90:341-7.
4. Stein H, Chan J, Warnke R, et al. Diffuse large B-cell lymphoma, not otherwise specified. In: Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC 2008:233-7.
5. Ponzoni M, Ferreri AJ, Campo E, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol 2007;25:3168-73.
6. Chadburn A, Hyjek E, Mathew S, et al. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. The American journal of surgical pathology 2004;28:1401-16.
7. DePond W, Said JW, Tasaka T, et al. Kaposi's sarcoma-associated herpesvirus and human herpesvirus 8 (KSHV/HHV8)-associated lymphoma of the bowel. Report of two cases in HIV-positive men with secondary effusion lymphomas. The American journal of surgical pathology. 1997;21:719-24.
8. Delsol G, Lamant L, Mariame B, et al. A new subtype of large B-cell lymphoma expressing the ALK kinase and lacking the 2; 5 translocation. Blood 1997;89:1483-90.
9. Barth TF, Leithauser F, Joos S, et al. Mediastinal (thymic) large B-cell lymphoma: where do we stand? The lancet oncology 2002;3:229-34.
10. Moller P, Herrmann B, Moldenhauer G, Momburg F. Defective expression of MHC class I antigens is frequent in B-cell lymphomas of high-grade malignancy. International journal of cancer 1987;40:32-9.