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Short Communication

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

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Abstract

The 2016 revised World Health Organization (WHO) classification includes several provisional borderline categories for lymphoma cases that do not clearly fit into one entity, such as B-cell lymphoma, unclassifiable (BCLU), with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL). This CARD focuses on lymphomas that are intermediate between DLBCL of the primary mediastinal large B-cell lymphoma (PMLBCL) type and cHL

Keywords: B-cell lymphoma unclassifiable; intermediate lymphomas; diffuse large B-cell lymphoma; primary mediastinal large B-cell lymphoma; classical Hodgkin lymphoma

Clinics and pathology

Disease

Most lymphomas are considered to represent distinct disease entities since they have characteristic immunophenotypic profiles and recurrent genetic abnormalities, and can
accordingly be diagnosed using available techniques. However, the 2016 revised WHO classification has introduced new provisional borderline ("grey zone") categories for cases that do not clearly fit into one entity.

This includes a category termed B-cell lymphoma, unclassifiable (BCLU), with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL).

Another unclassifiable category was created for cases showing features intermediate between DLBCL and Burkitt lymphoma (BL) with the newer recognized categories now termed high grade B-cell lymphoma (HGBL) with and withoutMYC and BCL2 and/or BCL6translocations (the so-called double or triple hit lymphoma).

HGBL, NOS includes cases lacking MYC and BCL2 and/or BCL6 translocations that would formerly have been called BCLU with features intermediate between DLBCL and BL (Figure 1).This CARD focuses specifically on the category of B-cell lymphoma that is intermediate between DLBCL of the primary mediastinal large B-cell lymphoma (PMLBCL) type and cHL (Jaffe et al., 2008, Carbone et al., 2010; Swerdlow et al., 2016).

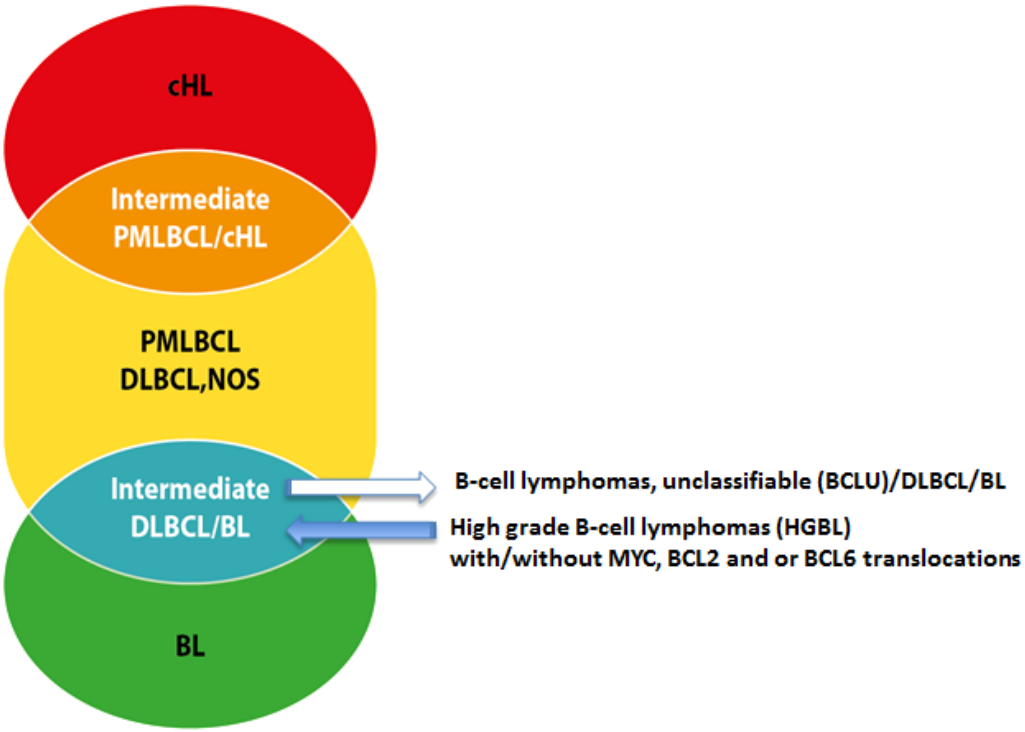

Figure 1. Borderline categories for cases that do not clearly fit into one entity include a category termed B-cell lymphoma, unclassifiable (BCLU), with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL). Another unclassifiable category was created for cases showing features intermediate between DLBCL and Burkitt lymphoma (BL) with the newer recognized categories now termed high grade B-cell lymphoma (HGBL) with and without MYC and BCL2 and/or BCL6 translocations.

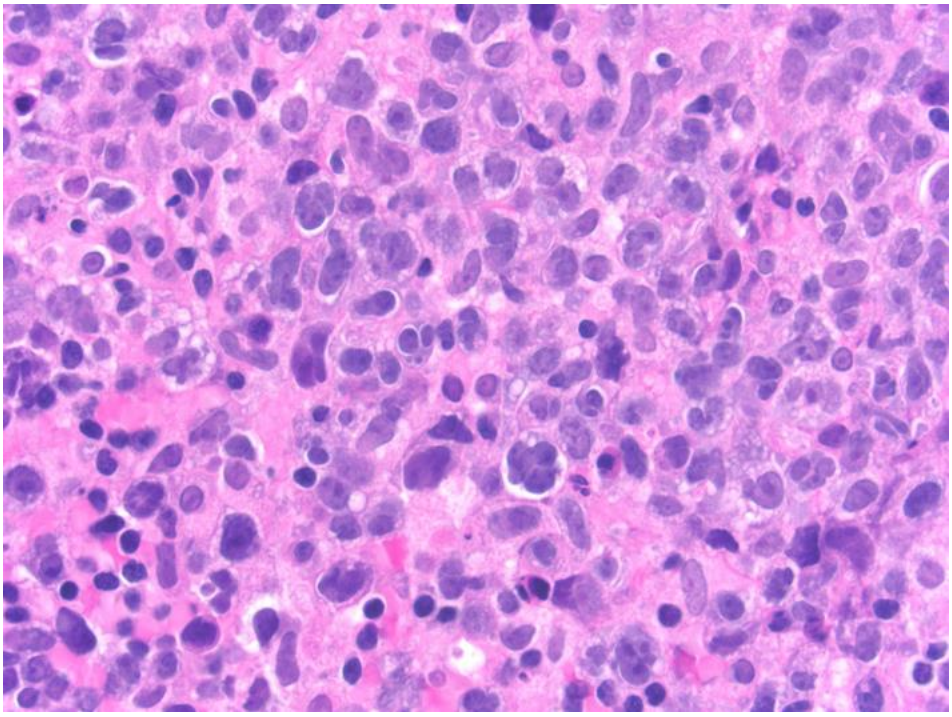

Figure 2. B-cell lymphoma, unclassifiable (BCLU) with features intermediate between DLBCL and cHL This lymphoma has a diffuse growth pattern and is composed of many large atypical cells with distinct nucleoli and a scant inflammatory background. H&E stain, magnification x60.

PMLBCL morphology		
	- Tumour cells	- Large cells with clear cytoplasm and multilobated nuclei - Large cells with Hodgkin Reed-Sternberg (HRS)-like morphology
	-Tumor background	- Contains eosinophils, plasma cells, T-cells. The inflammatory background is less abundant than that of cHL - Fine compartmentalizing alveolar fibrosis
cHL morphology		
	- Tumour cells	- Typical Reed-Sternberg (RS) cells - Mononuclaer Hodgkin cells
	- Tumor background	- Contains admixed T-cells, B-cells, plasma cells, eosinophils, histiocytes, and fibroblasts - Abundant sclerosis (especially in the nodular sclerosis subtype)
BCLU morphology with features intermediate between PMLBCL and cHL		
	- Tumour cells	- Large cells resembling HRS cells, which comprise the majority of the infiltrate - Large cells with clear cytoplasm - Large cells resembling centroblasts
	- Tumor background	- Sparse inflammatory infiltrate with eosinophils, plasma cells, histiocytes, and T-cells - Sclerosis (variable and focal) - Necrosis (frequent)
	- Variation in morphology, with some tumor areas resembling DLBCL and other regions more closely resembling cHL	

Table 1: Morphologic features of the intermediate PMLBCL/cHL B-cell lymphoma overlap between those of PMLBCL and cHL (Gaulard et al., 2008; Stein et al., 2008; Carbone et al., 2010).

PMLBCL	
	- CD30+ (80% of the cases, weak and heterogeneous) - CD15- (occasionally present) - B-cell antigens+ (CD20, CD19, CD22, CD79a) - BCL6+, BCL2+, CD23+, CD10+ (less common) - IRF4/MUM1+
cHL	
	- CD30+ strong (100% of the cases) - CD15+ - CD45- - CD20- - CD40 (consistently positive) - BCL6- - IRF4/MUM1 (consistently positive) - B-cell transcription factors-
BCLU with features intermediate between PMLBCL and cHL	
	- CD30+ (variable amount) - CD15+ (variable amount) - CD45+ - B-cell antigens+ - B-cell transcription factors+

Table 2: Transitional features between PMLBCL and cHL (Gaulard et al., 2008; Stein et al., 2008; Carbone et al., 2010).

DLBCL, NOS	
	- BCL6 gene rearrangement, activation of NFKB pathway, constitutive activation of STAT6
PMLBCL	
	- Activation of the NFkB pathway, altered JAK/STAT signaling, activation of PI3K/AKT pathway - Immunoglobulin (Ig) heavy chain gene rearrangement with high somatic hypermutation (SHM) and class switch recombination (CSR) - No Ig expression
cHL	
	- EBV (a subset of cHL), activation of the NFkB pathway - Altered JAK/STAT signaling, activation of PI3K/AKT pathway - IGH Re non functional. No Ig expression
BCLU with features intermediate between PMLBCL and cHL	
	- Overlap with cHL and PMLBCL

Epidemiology

PMLBCL/cHL usually affects young people; females more than males.

Pathology

See Table 1.

Clinics

Mediastinal presentation with limited stage disease. This B-cell lymphoma is usually aggressive with an intermediate prognosis between DLBCL and cHL.

Other features

Immunophenotype See table2.

Genetics

Specific genetic changes characteristic of BCLU with features intermediate between PMLBCL and cHL have not been definitively shown. Like DLBCL (NOS) and PMLBCL, these lymphomas may demonstrate deregulation of B-cell signaling or transcriptional regulation and apoptosis (e.g. BCL6 gene rearrangement, activation of NFKB pathway, constitutive activation of STAT6) (Carbone et al., 2010; Swerdlow et al., 2016; Carbone and Gloghini 2016).

However, unlike cHL Epstein-Barr virus sequences have been found in fewer (20% or less) cases.

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