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

Disease and pathology

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 without MYC and BCL2 and/or BCL6 translocations (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).
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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.
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

**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
  - Mononucleaer 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).

<table>
<thead>
<tr>
<th>Feature</th>
<th>PMLBCL</th>
<th>cHL</th>
<th>BCLU with features intermediate between PMLBCL and cHL</th>
</tr>
</thead>
</table>
| **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).
**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

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.

**References**


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This article should be referenced as such: