LYMPHOMAS

Gray zone lymphomas

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The term gray zone lymphoma is mostly used for cases of malignant lymphoma which cannot be reliably classified as Hodgkin lymphoma or non-Hodgkin lymphoma [1–3]. As this differential diagnosis has direct implications for management strategies, it is a major problem area for both pathologists and hemato-oncologists [4]. This difficulty is seen in three specific areas as shown in Figure 1.

1. Gray zone between Classical Hodgkin lymphoma (CHL) and diffuse large B-cell lymphoma (DLBCL), in particular primary mediastinal large B-cell lymphoma (MLBCL).
2. Gray Zone between CHL and ALK negative anaplastic large cell lymphoma (ALCL) and/or peripheral T-cell lymphoma (PTCL).
3. Gray zone between CHL or nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (TRLBCL)

Gray zone between CHL and DLBCL

This is the most frequent problem area in gray zone lymphomas. Typically these cases occur in the mediastinum but also, occasionally, in extra-mediastinal sites. In the mediastinum both the CHL and MLBCL are thought to arise from a common precursor, the thymic B-cell. Recent gene expression profiling studies revealed that gene expression profile of MLBCL were distinct from DLBCL occurring at extra-mediastinal sites, but appeared very similar to CHL cell lines [5,6]. This suggests that there is a close biological relationship between these two entities and the pathological features which represent the phenotype will overlap. The presence of both CHL and MLBCL in the same biopsy or consecutive biopsies from the same patient supports this view [7]. Therefore one would expect that at either end of the phenotypical spectrum, differential diagnosis of CHL versus MLBCL will be straightforward where as in the middle, it may be impossible (Figure 2).

There are limited number of tools for the pathologist to make this differential diagnosis. In the absence of a well-characterized genetic abnormality, the diagnosis rests on morphological and immunophenotypical analysis. Virtually all cases of CHL, like MLBCL or DLBCL are of B-cell origin and are composed of large cells. However in CHL, the B-cell phenotype of the neoplastic cells (RS cells and variants) is often incomplete, lacking expression of some pan-B-cell surface markers, B-cell associated transcription factors and immunoglobulin [8,9]. The phenotypic features that are useful in histological diagnosis are listed in Table I.

Gray zone between CHL and ALK negative ALCL

Another problem area for diagnosis of CHL is the differential diagnosis with ALCL that does express ALK. Although there is histological overlap, immunophenotyping is extremely helpful. ALCL is now considered to be exclusively of T or null cell origin and does not express B-cell lineage markers, especially pax-5 which is present in most CHL [3,10].

Gray zone between CHL or NLPHL and TRLBCL

CHL may morphologically overlap with TRLBCL. In TRLBCL, large B cells may occasionally display the morphologic characteristics of Reed-Sternberg cells, Hodgkin’s cells, or variants, but the background cells usually do not include eosinophils, a distinctive feature of CHL. Immunophenotypically, the strong and consistent expression of pan-B-cell markers
CD20, CD79a, and OCT2, the uniform expression of BCL6, the presence of immunoglobulin heavy or light chain expression, the absence or variable weak expression CD30, the lack of CD15 expression, and the absence of EBV gene products should be adequate to establish the diagnosis.

Perhaps more difficult is the differential diagnosis between NLPHL and TRLBCL. Although architectural nodularity and presence of a background of small B-cells favor NLPHL over TRLBCL, in later stages of NLPHL these features are usually lost and the accurate diagnosis may be only possible with clinical parameters.

The immunophenotypic markers for differential diagnosis of CHL or NLPHL and TRLBCL are summarised in Table II [11–13].

### References


**Table I. Features helpful in differential diagnosis of CHL versus MLBCL/DLBC**

<table>
<thead>
<tr>
<th>CHL</th>
<th>MLBCL</th>
<th>DLBC</th>
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<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS cells and variants</td>
<td>All</td>
<td>Occasional</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>Most</td>
<td>Occasional</td>
</tr>
<tr>
<td>Inflammatory background</td>
<td>All</td>
<td>Occasional</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>CD30</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CD15</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>CD45</td>
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<tr>
<td></td>
<td>Fascin</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CD20</td>
<td>-/+</td>
</tr>
<tr>
<td></td>
<td>CD79a</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Bcl-6</td>
<td>+/-, variable</td>
</tr>
<tr>
<td></td>
<td>Pax-5</td>
<td>+, variable</td>
</tr>
<tr>
<td></td>
<td>Oct-2</td>
<td>+/-</td>
</tr>
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<td></td>
<td>B ob-1</td>
<td>+/-</td>
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<td></td>
<td>PU.1</td>
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<tr>
<td></td>
<td>EBV</td>
<td>+/-</td>
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<tr>
<td></td>
<td>immunoglobulin</td>
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**Figure 1. Gray zone lymphomas.**


**Figure 2. Phenotypic spectrum of CHL and MLBC.**

**Table II. Immunophenotype of TRLBCL, CHL and NLPHL**

<table>
<thead>
<tr>
<th>TRLBCL</th>
<th>CHL</th>
<th>NLPHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotype</strong></td>
<td>Centroblasts, L&amp;H-like cells, RS cells, Hodgkin cells</td>
<td>L&amp;H cells</td>
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<tr>
<td>CD20</td>
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<tr>
<td>CD79a</td>
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</tr>
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<tr>
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<td>-/+</td>
</tr>
<tr>
<td>clg</td>
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