Shades of Gray in Hematopathology: Gray Zones, Borderlands, and Badlands in B-cell Lymphomas

Differential Diagnosis and Biological Implications

Nancy Lee Harris, M. D.
Massachusetts General Hospital
Harvard Medical School
Gray Zones in B-cell Lymphomas

- Primary mediastinal large B-cell lymphoma (PMBL) and classical Hodgkin lymphoma (CHL)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (THRBCCL)
- Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL)
Hodgkin Lymphomas and Large B-cell Lymphomas

- Neoplastic cells of both CHL and NLPFHL are B lineage
- Borderline (grey-zone) lymphomas between HL and DLBCL may thus exist
  - HL is characterized by rare malignant B cells in a background of inflammatory cells
  - Most DLBCL are comprised predominantly of neoplastic cells, with few inflammatory cells
- BUT
  - Some cases of HL have large numbers of neoplastic cells
  - Some cases of DLBCL have a background rich in inflammatory cells
- These cases pose a challenge in differential diagnosis and also suggest there is a biological overlap between HL and DLBCL
WHO Classification of Hodgkin Lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
- Classical Hodgkin lymphoma (CHL)
  - Nodular sclerosis (NSCHL)
  - Lymphocyte-rich (LRCHL)
  - Mixed cellularity (MCCHL)
  - Lymphocyte depleted (LDCHL)
Gray Zones in B-cell Lymphomomas

- Primary mediastinal large B-cell lymphoma (PMBL) and classical Hodgkin lymphoma (CHL)
Classical Hodgkin Lymphoma

Pathology

- **Pattern:**
  - Vaguely nodular, diffuse, sclerosis
- **Cytology:**
  - Classical RS cells, histiocytes, eosinophils, lymphocytes; necrosis with neutrophils
- **Immunophenotype:**
  - CD15+ CD30+
  - CD20-/+ Pax5 dim+ Oct2 and/or Bob1-, CD19- CD79a- (B-cell program down-regulated)
  - Bcl6-/+ Mum1+
  - Activation of NFkB, JAK/STAT (TRAF, n-REL)
  - DC marker TNFAIP2+
- **Genetics:**
  - IGH-R, clonal, non-functional
  - EBV+/-(MCCHL)
  - Complex karyotypes, polyploidy
  - Translocation of MHC class II transactivator (CIITA) in 15%
- **Clinical:**
  - NSCHL: adolescent, young adult, mediastinal
  - MCCHL: any age, immunosuppression
  - LRCHL: older adult, peripheral LN
  - LDCHL: rare, elderly, HIV+
Classical Hodgkin’s Lymphoma Subtypes

- NSCHL
- LRCHL
- MCCHL
- LDCHL

Classical Reed Sternberg Cell
Primary Mediastinal Large B-cell Lymphoma (PMBL)

- **Morphology**
  - CB or IB-like cells, multilobated, anaplastic
  - Often “clear” cytoplasm, fine compartmentalizing sclerosis

- **Immunophenotype/genetics**
  - Ig- CD20+ Bcl6+-/ Mum1+-/ CD10- CD30+ CD23+- , TNFAIP2
  - IGH-R, no BCL2, BCL6, MYC-R
  - CGH: gains at 9p24 and 2p15
  - Activation of NFkB and JAK/STAT (TRAF, n-REL)
  - Translocations of MHC class II transactivator (CIITA) in 38%

- **Clinical**
  - Young adults, F=M
  - Locally aggressive
    - Lung invasion
    - SVC syndrome
  - Lymph nodes, BM negative
  - Relapses extranodal
    - CNS, liver, kidney, ovary, GI
**PMBL and NSCHL**

- Both are mediastinal lymphomas common in young adults
- Share immunophenotypic and gene expression profiles
  - Ig-,
  - Loss of B-cell receptor signaling
  - Activation of cytokine JAK-STAT pathway
  - Expression of TNF family members
    - CD30, TRAF1
  - Constitutive NF-kappa B activation
    - REL nuclear localization
  - Activation of tyrosine kinases and the PI3K/ATK pathway
- Translocations involving MHC class II transactivator [CIITA] gene in both
- Borderline, composite, and sequential cases are increasingly recognized by pathologists
- Features suggest a true biological overlap between PMBL and NSCHL
  - This “grey-zone lymphoma” may be a real disease…

B-cell lymphoma, intermediate between DLBCL and CHL (provisional category)

Definition:
A B lineage lymphoma with overlapping features between classical Hodgkin lymphoma (CHL) and diffuse large B-cell lymphoma (DLBCL), especially primary mediastinal large B-cell lymphoma (PMBL).

Morphology and Immunophenotype
Large cells, lacunar, R-S like, in sheets; variable sclerosis, fibrous bands, inflammatory background
CD45+ CD30+ Pax5+ CD20+/- CD79a+/- Oct2/Bob1+ CD15+/- Bcl6+/+ CD10-

Genetics:
Methylation pattern distinctive and intermediate between PMBL/CHL

Clinical:
Young men (20-40), mediastinal
Aggressive, often fatal
?Treat as CHL or PMBL
R-EPOCH, RT

Traverse-Glehen 2005; Eberle 2011
28-year-old woman: mediastinal mass

CD20

CD30

CD15
What’s the Diagnosis?

• Is this grey-zone or composite lymphoma?
• Both morphologic components are intimately admixed.
• In addition, there are transitional areas with features of both PMBL and CHL.
• For these reasons, I would call it grey-zone.
40 year-old man, mediastinal mass
Relapse in lung 4 months post CR
What is the diagnosis?

- PMBL, CD20- (CD30- CD15-), followed by recurrence as CHL (CD15+ CD30+) in adjacent lung and hilar LN post rx
  - Should the original have been called gray-zone because CD20-?
- Salvage CT for DLBCL x2 -> no response
- RT to mediastinum/lung -> CR
- Allo-SCT from matched related donor
  - NED 2 years
28-year-old man

Mediastinal mass 2007

Cervical LN 2011
What’s the diagnosis?

- **PMBL 2007**
  - CD20+ CD30-/+ CD15-
- **CHL 2011**
  - CD20- CD30+ CD15+
- **Diagnosis**
  - PMBL (typical) followed by NSCHL
Borderline cases between NSCHL and PMBL
Diagnostic Evaluation

• Morphology
  - All areas borderline between CHL and PMBL
  - Gradation or admixture of areas resembling CHL and others resembling PMBL
  - “Composite lymphoma” – discrete, separate areas of CHL and PMBL*
  - “Discordant lymphoma” – sequential appearance of PMBL and CHL*

• Immunophenotype panel:
  - CD45, CD20, CD15, CD30, Pax5
  - CD79a, CD19, Oct2, Bob1, Bcl6

*Composite and discordant cases excluded from WHO definition but likely related phenomena
PMBL vs CHL
Algorithm for diagnosis

- **Favors PMBL:**
  - Absence of nodularity, no eosinophils, fine sclerosis
  - CD45+ CD20+ CD79a+ CD19+ CD30 weak CD15-

- **Favors CHL:**
  - Prominent nodularity, sclerotic bands, eosinophils; necrosis with neutrophils
  - CD45- CD20-/+ Pax5 weak CD30++ CD15+ Oct2/Bob1-

- **Favors intermediate PMBL/CHL:**
  - Areas with lacunar cells, eosinophils, sheets of tumor cells resembling PMBL, absence of necrosis with neutrophils
  - CD45+ CD20+ CD79a+ CD30++ CD15+
  - Not all cases of CD20+ CHL belong in this category
    - The more B-cell antigens expressed in a tumor resembling CHL, the more likely it is to be grey-zone
Gray zone between CHL and PMBL

Summary

• Immunophenotypic and genetic similarities between PMBL and CHL
• Occurrence of both PMBL and CHL in the same patient
• Existence of “grey-zone” cases
• All suggest a neoplastic cell with a degree of plasticity
  - Variable morphology and immunophenotype of tumor cells
  - Variable ability of tumor cells to influence or be influenced by the microenvironment
Future Directions

• Validation of additional markers to distinguish CHL from DLBCL and GZL?
  - Mediastinal gray zone lymphoma has a distinct epigenetic profile intermediate between CHL and PMBL but different from that of DLBCL*

• Are “grey zone” cases different from composite or sequential cases?
  - Is there a way to predict which PMBL cases will relapse as CHL or vice versa?

• Development of optimal therapy for grey-zone cases

Gray Zones in B-cell Lymphomas

- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (THRBCL)
Nodular Lymphocyte Predominant Hodgkin Lymphoma

• Morphology
  - Nodular pattern at least partial
  - Diffuse component may rarely predominate
  - LP ("popcorn") cells

• Immunophenotype
  - Large Cells
    ▪ B-cell antigens+ (CD20, CD79a, Pax5, Oct2, Bob1)  CD15- CD30 - Bcl6+
    ▪ IG+, IgD in young males
  - Background lymphocytes
    ▪ Nodular:
      - CD20+ B cells, CD21+ FDC meshworks
      - CD3+ T cells surrounding tumor cells
        = TFH( CD4, CD57, PD1/CD279, Bcl6)
    ▪ Diffuse:
      - T-cell rich; some TFH cells
    ▪ Flow: CD4+ CD8+ T cells
  - Immunoarchitectural patterns:
    ▪ B-cell rich nodular, extrafollicular LP cells, T-cell-rich nodular, THRLBCL-like, diffuse B-cell rich
NLPHEL Immunophenotype

CD21

CD23

CD57

PD1/CD279
Nodular Lymphocyte Predominant Hodgkin Lymphoma

• Genetics
  - IGH genes clonally rearranged, mutated, ongoing mutations, functional
  - BCL6 rearrangements: IGH (20%); other genes (48%)
  - CGH:
    ▪ Recurrent genomic imbalances (average 10.8 per case)
    ▪ Gains: 1, 2q, 3, 4q, 5q, 6, 8q, 11q, 12q, X; loss: 17 (36.8% to 68.4% of cases)

• Clinical
  - 5% of HL, any age, common in pre-adolescent children; male predominance
  - Isolated peripheral lymph nodes
  - Indolent, most patients cured with resection and/or radiation; late relapses occur, but are typically localized and responsive to therapy
  - ABVD may improve outcomes
T/HRBCL

**Morphology**
- **Pattern:** Diffuse, vaguely nodular (spleen=micronodular)
- **Lymphocytes +/- epithelioid histiocytes; rare large neoplastic B cells**
- **Resemble centroblasts, immunoblasts, LP cells, classical HRS cells**

**Immunophenotype**
- **Large cells:** CD20+ CD15- CD30- EMA-/+ EBV-
- **Small cells:** CD3+, CD57-, PD1-; no small B cells/ FDC meshworks, even in nodular areas

**Genetic features**
- IG genes rearranged, mutated, ongoing
- CGH: genomic imbalances (average of 4.7), gains (Xq, 4q13q28, Xp21p11, 18q21); loss (17p)

**Clinical**
- Adults, usually older, occ young
- High stage (liver, spleen, bone marrow)
- Aggressive, similar to other DLBCL at similar stage and IPI
Borderline between NLPHL and DLBCL

- **Transformation of NLPHL to typical DLBCL**
  - ~5% of cases
  - Sheets of large cells not associated with FDC meshworks
  - May resemble LP cells or (more often) other DLBCL
  - Clonal relationship between NLPHL and DLBCL

- **NLPHL resembling THRBCL**
  - Relapse of NLPHL with a partly or entirely diffuse pattern
  - De novo NLPHL with a predominantly diffuse pattern
“Diffuse” NLPHL vs. THRBCCL

- Distinction between diffuse areas of NLPHL and THRBCCL may be impossible
  - Some make a diagnosis of relapsed NLPHL with a diffuse pattern
  - Others make a diagnosis of progression to THRBCCL

- WHO 2008
  - Diagnosis of THRBCCL should be restricted to primary/de novo cases
  - Occurrence or relapse of NLPHL with a partially or entirely diffuse pattern should be called either diffuse LPHL or “NLPHL, THRBCCL-like”
  - Careful search for focal NLPHL important in de novo cases of THRBCCL
    - One nodule of NLPHL rules out THRBCCL
47-Year-Old Man, Inguinal LN

• First biopsy
  - Vaguely nodular to diffuse, T-cell/histiocyte-rich process
  - Large cells: CD20+ CD30-
  - Small cells: CD3+ T cells, many CD57+, admixed small B cells
  - No FDC meshworks even in nodular areas
  - Dx “probably NLPHL but can’t r/o THRLBCL”

• Second biopsy (2 months later)
  - Focal B-cell rich nodules with CD21+ FDC
NLPHEL T-cell rich diffuse

CD21
CD3
CD57
CD20
Foci of NLPHL with B-cell-rich nodules

CD20

CD21
NLPHL predominantly diffuse vs. THRBCl: Algorithm for diagnosis

• **Clinical features:**
  - Young age, isolated peripheral lymphadenopathy favors NLPHL
  - Older age, disseminated disease favors THRBCl

• **Morphology**
  - Evaluation of many sections for nodular areas
  - Morphologic features and immunophenotype of large cells may not be helpful

• **Immunophenotype of background population**
  - FDC antigens (CD21, CD35) (CD23 often negative in NLPHL)
    - Any FDC-rich nodules favors NLPHL
  - T-cell and B-cell antigens
    - B-cell-rich background favors NLPHL-diffuse
  - T-cell subsets (CD4, CD8, CD57, CD279)
    - TFH phenotype favors NLPHL-diffuse
Borderline between NLPHL and THRBCL: Is it “real”?

- **Genetic similarities**
  - Rearranged, mutated IGH genes with ongoing mutations (GCB)
  - Partial gain of 4q, rare in lymphomas

- **Genetic Differences**
  - BCL6 translocations common in NLPHL, not in THRLBCL
  - Number of genomic imbalances greater in NLPHL (10.8 vs 4.7)

- **Since NLPHL has more complex genetic abnormalities than de novo THRBCL**
  - It seems unlikely that THRBCL is a form of progression of NLPHL
Borderline between NLPHL and THRBCCL: Biological implications

- Evidence suggests that de novo THRBCCL is not progressed NLPHL
- NLPHL may lose B-cell rich follicular background, becoming diffuse and T-cell rich
  - Focally or extensively at the time of the diagnosis, or
  - With disease progression
- Suggests some “plasticity” of the tumor cell
  - May require background of a B-cell follicle for survival, or
  - May be able to survive without follicular environment in a T-cell rich background
  - Survival without follicular environment may be due to secondary genetic alterations that could confer a more aggressive phenotype
    - No clear evidence that T-cell-rich cases have a worse prognosis
    - T-cell-rich/diffuse patterns associated with high stage +/- or relapse*

*Fan et al, AJSP, 2003
Borderline between NLPHL and THRBCRL

Future Directions

• Clinical significance of diffuse areas and/or progression to diffuse pattern in NLPHL needs to be defined
  – This is a rare complication of a rare disease
  – Multi-institutional review with clinical follow-up will be required

• Better immunophenotypic and/or genetic markers would be helpful
  – Either to allow better differentiation between NLPHL and THRBCRL
  – Or to show that they are related diseases!
Gray Zones in B-cell Lymphomas

• Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL)
Burkitt Lymphoma

• **Definition**
  - A B-cell lymphoma with monomorphic, medium-sized cells, with a high proliferation fraction

• **Morphology**
  - Starry sky pattern, small-medium sized cells, multiple nucleoli, basophilic cytoplasm, mitoses

• **Immunophenotype:**
  - CD20+ IgM+ CD10+ Bcl6+ Bcl2-
  - Ki 67: >95%

• **Genetics:**
  - t(8;14), t(8;22), t(2;8) [MYC-IG]
  - Simple karyotype (<3 other abnormalities)

• **Clinical:**
  - Endemic: child, Africa
  - Sporadic: child, other areas
  - Immune deficiency
  - Aggressive, extranodal, curable
Borderline between BL and DLBCL

- Most cases straightforward, but some morphologically intermediate (mix of medium and large cells, mitoses, starry-sky pattern)
- Correct diagnosis important to avoid under- or over-treatment
- WHO 3rd ed: “Atypical Burkitt Lymphoma”
  - Morphologically intermediate between BL and DLBCL
    - >95% Ki-67 fraction
    - Immunophenotype of BL (CD10+ Bcl6+ Bcl2-)
    - MYC rearranged, BCL2 germline [if available]
  - Should not make this diagnosis unless you really think it is more likely Burkitt’s than large B-cell lymphoma
- Others: classify as DLBCL
Burkitt lymphoma vs Burkitt-like/atypical Burkitt lymphoma

BL - uniform small cells

ABL/BLL - variable size cells
Three Illustrative cases

All with t(8;14)
All reviewed by a panel of 11 expert international hematopathologists
Typical Burkitt Lymphoma with t(8;14)

Ten of 11 experts who reviewed this case independently made a diagnosis of Burkitt lymphoma; one made a diagnosis of atypical Burkitt lymphoma.
Atypical Burkitt Lymphoma with t(8;14)

Six expert reviewers called this case Burkitt lymphoma; 5 made a diagnosis of atypical Burkitt lymphoma.
DLBCL with t(8;14)

9 experts called this case diffuse large B-cell lymphoma; 2 made a diagnosis of atypical Burkitt lymphoma.
BL and DLBCL – new data since WHO 2001

- Two studies of gene expression profiling in BL defined characteristic molecular BL signatures (mBL)
  - Discrepancies between pathological and GEP classification
    - mBL cases called DLBCL by pathologists (15-30%)
    - Non-mBL cases called aBL by pathologists (<5%)
  - 22% of cases GEP borderline between mBL and DLBCL in one study
  - Borderline and non-mBL cases had either no MYC-R, nonIG-MYC-R, MYC & BCL2-r (“double hit”), BCL2 or BCL6-R, complex karyotypes
  - Suggestion of worse prognosis for non-mBL cases with MYC-R
    - Hummel et al, Dave et al, NEJM 2006
DLBCL vs BL: Clinical Advisory Committee 4th ed (2008)

- Gene expression studies (2006) showed true “grey zone” between BL and DLBCL
- Many cases, especially in adults, cannot be definitively classified as BL vs DLBCL
- Should not “contaminate” DLBCL or BL categories with cases that may be biologically and clinically different
- Provisional category: B-cell lymphoma, intermediate between BL and DLBCL
  - A heterogeneous category that needs to be further refined; not a distinct entity
  - Allows classification of cases not meeting criteria for classical BL or DLBCL
  - Individualized decisions about treatment
High-grade B-cell lymphoma, intermediate between BL and DLBCL (provisional category)

- **Definition**
  - Lymphoma with features of both DLBCL and BL, but that for biological and clinical reasons should not be included in these categories

- **Morphology:**
  - Intermediate between BL and DLBCL (medium-sized cells, large cells)

- **Immunophenotype:**
  - GCB (CD10+ Bcl6+); often Bcl2+
  - Ki67 variable

- **Genetics:**
  - MYC, BCL2, both (double hit), complex karyotypes

- **Clinical:**
  - May occur in pts w/hx FL
  - Adults, high stage, frequent bone lesions
  - Aggressive, short survival (especially DH cases)
  - Individualized treatment

Snuderl et al, 2010
Borderline cases between BL and DLBCL
Diagnostic Evaluation

- **Immunophenotyping panel:**
  - CD10, Bcl6, Bcl2, Myc, Ki67

- **Cytogenetic evaluation:**
  - t(8;14), t(2;8), t(8;22),
  - t(14;18), t(3q27),
  - Complex karyotype

- **FISH Panel:**
  - MYC break-apart
  - BCL2-IGH fusion (if MYC-r)
  - BCL6 break-apart (if MYC-r)
  - IGH break-apart probe (optional)

Snuderl et al, 2010
BL, DLBCL, BCL-U
Algorithm for diagnosis

- **Favors BL**
  - CD10+ Bcl6+ Myc+
  - Bcl2-, Ki67 >95%
  - MYC/IG-R, simple karyotype

- **Favors DLBCL**
  - CD10- Bcl6- Myc-
  - Bcl2+, Ki67<90%
  - MYC neg, BCL6-R, or BCL2-R

- **Favors intermediate DLBCL/BL**
  - CD10+ Bcl6+ Myc+
  - Bcl2+, Ki67 <95%
  - MYC/non-IG-R
  - MYC&BCL2 (double hit)
  - Complex karyotype
## Differential diagnosis: BL, BCL-U, DLBCL

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<tr>
<th></th>
<th>BL</th>
<th>BCL-U</th>
<th>DLBCL</th>
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<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Small/med</td>
<td>Small/med/mix</td>
<td>Large</td>
</tr>
<tr>
<td><strong>Ki67</strong></td>
<td>&gt;95%</td>
<td>60-100%</td>
<td>30-100%</td>
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<tr>
<td><strong>Bcl2</strong></td>
<td>- (or weak)</td>
<td>~50%+</td>
<td>~50%+</td>
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<tr>
<td><strong>Bcl6</strong></td>
<td>+</td>
<td>+</td>
<td>60-90%</td>
</tr>
<tr>
<td><strong>CD10</strong></td>
<td>+</td>
<td>+</td>
<td>30%+</td>
</tr>
<tr>
<td><strong>MYC-R</strong></td>
<td>+ (IG)</td>
<td>50%+ (often non-IG)*</td>
<td>10%+ (often non-IG)</td>
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<tr>
<td><strong>BCL2-R</strong></td>
<td>-</td>
<td>15%*</td>
<td>20-30%</td>
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<tr>
<td><strong>BCL6-R</strong></td>
<td>-</td>
<td>Rare</td>
<td>30%</td>
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*Double-hit MYC/BCL2 may occur*
Gray zone between Burkitt Lymphoma and Diffuse Large B-cell Lymphoma

Summary

• BL and DLBCL are distinct categories
  - They should remain as “clean” as possible for the purposes of management and investigation
  - Cases that don’t “fit” either category should be sequestered and managed and studied separately
  - DLBCL with MYC-R should not be put in the intermediate category (DLBCL with MYC-R).

• Double-hit cases (BCL2 and MYC rearranged) should be considered a distinct category
  - Unclear whether those that resemble DLBCL are as aggressive as those that resemble BL
  - DLBCL that express both MYC and BCL2 proteins have a poor prognosis

• Adult lymphomas that resemble BL but have complex karyotypes appear to be more aggressive than typical BL and should be classified as intermediate BL-DLBCL.
Future Directions

• Validation of additional immunophenotypic markers to distinguish BL from DLBCL?

• Can molecular profiling become part of diagnostic workup?

• Development of optimal therapy for intermediate cases – especially MYC-non-IG-R and MYC&BCL2-R (Double-Hit) cases
I’d be happy to answer any questions....
I’d be happy to answer any questions....
Gray Zones

- CHL and large B-cell lymphomas
  - Particularly NSCHL and PMBL
- NLPHL and large B-cell lymphomas
  - Particularly THRBCCL
- LRCHL and NLPHL
## Differential diagnosis: PMBL, GZL, NSCHL

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<th>PMBL</th>
<th>GZL (Int CHL/PMBL)</th>
<th>NSCHL</th>
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<tbody>
<tr>
<td>Cellular morphology</td>
<td>Sheets of large cells, clear cytoplasm</td>
<td>Sheets of large RS-like or lacunar cells; mix of CHL and PMBL-like</td>
<td>Lacunar cells, focal lymphocyte-eosinophil-histiocyte-rich background</td>
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<tr>
<td>Sclerosis</td>
<td>Fine, compartmentalizing</td>
<td>Nodular or compartmentalizing</td>
<td>Nodular, thick bands</td>
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<tr>
<td>CD45</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>CD20</td>
<td>+</td>
<td>+/-</td>
<td>-/+ (variable, weak)</td>
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<tr>
<td>CD30</td>
<td>+/- weak</td>
<td>+</td>
<td>+ strong</td>
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<tr>
<td>CD15</td>
<td>-</td>
<td>+ or -</td>
<td>+</td>
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<tr>
<td>Other B-cell</td>
<td>(CD19, 79a, 22, Oct2, Bob1)</td>
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<tr>
<td>Bcl6</td>
<td>+</td>
<td>+/-</td>
<td>-/+</td>
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