An update on lymphomas of the upper GI tract

Manuel Rodriguez-Justo
• Primary GI lymphomas account for 1-4% of all GI tumors

• The GI tract is the most common site of extranodal lymphomas (4-20% of all NHL)

• Most commonly these are Non Hodgkin’s lymphomas. Hodgkin's disease usually involve the GIT secondarily.

• In the GI tract they may be associated with other pathologies and complicate the clinical course of the primary pathology (e.g. increase incidence of NHL in IBD patients on immunosuppressive therapy, lymphomas associated with HIV infection…)
Stomach: up to 75%

Small bowel: 10%

Multifocal or >1 site: 6%

Oesophagus <1%
Source: Haematological Malignancy Research Network.
Stomach: up to 75%
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)

Epidemiology: 7-8% of all B-cell lymphomas
50% of primary *gastric* lymphomas

Histopathology:
- Heterogeneous population (centrocyte-like cells, monocytoid cells, scattered larger cells, plasma cell differentiation)
- Lymphoepithelial lesions
Marginal zone MALT lymphoma

- CD20: +
- CD5: -
- CD21: +
- IgM: +
- IgD: +/-
<table>
<thead>
<tr>
<th>Description</th>
<th>Histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal</td>
<td>Scattered plasma cells in lamina propria (LP). No follicles</td>
</tr>
<tr>
<td>1 Chronic active gastritis</td>
<td>Clusters of lymphocytes in LP. No follicles. No lymphoepithelial lesions (LEL)</td>
</tr>
<tr>
<td>2 Chronic active gastritis with florid lymphoid follicle formation</td>
<td>Lymphoid follicles with surrounding mantle zone and plasma cells. No LEL</td>
</tr>
<tr>
<td>3 Suspicious lymphoid infiltrate, probably reactive</td>
<td>Lymphoid follicles surrounded by small lymphocytes that infiltrate LP and occasionally into the epithelium.</td>
</tr>
<tr>
<td>4 Suspicious infiltrate, probable lymphoma</td>
<td>Lymphoid follicles surrounded by marginal zone cells that infiltrate diffusely LP and into epithelium in small groups</td>
</tr>
<tr>
<td>5 MALT lymphoma</td>
<td>Dense diffuse infiltrate of marginal zone cells in LP with prominent LEL</td>
</tr>
</tbody>
</table>

To do IHC +/- molecular
Interobserver variation in the histopathological assessment of malt/malt lymphoma: towards a consensus

Blood Cells, Molecules, and Diseases 34 (2005) 6–16

<table>
<thead>
<tr>
<th>Disease category (0–4)</th>
<th>Pathologist</th>
<th>General (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Simple gastritis</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>(κ 0.38)</td>
<td>(κ 0.42)</td>
</tr>
<tr>
<td>2. Florid hyperplasia*</td>
<td>Fair</td>
<td>Moderate</td>
</tr>
<tr>
<td>Low-grade MALT</td>
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<td>Fair</td>
</tr>
<tr>
<td></td>
<td>(κ 0.35)</td>
<td>(κ 0.30)</td>
</tr>
<tr>
<td>Low-grade MALT with increased blasts</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(κ 0.35)</td>
<td></td>
</tr>
<tr>
<td>3. High-grade lymphoma</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td>with low-grade component</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(κ 0.31)</td>
<td>(κ 0.40)</td>
</tr>
<tr>
<td>High-grade lymphoma</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(κ 0.31)</td>
<td></td>
</tr>
<tr>
<td>Other lymphoma</td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(κ 0.27)</td>
<td>(κ 0.06)</td>
</tr>
<tr>
<td>4. Undecided</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td></td>
<td>(κ 0.07)</td>
<td>(κ 0.01)</td>
</tr>
</tbody>
</table>

H = hematologists, GI = pathologists with special interest in gastrointestinal diseases.
karyotypic alterations

- trisomies 3 (30%) and 18
- translocations $t(11;18)(q21;q21)$, 30-40%
- $t(1;14)(p22;q32)$,
- $t(14;18)(q32;q21)$,
- $t(3;14)(q27;q32)$,
- recently described $t(3;14)(p14.1;q32)$.

$t(11;18)(q21;q21)$ → predicts lack of response to H pylori eradication therapy
H pylori eradication and gastric MALT

• HP is a major factor in the development of MALT-lymphoma.
• Eradication leads to durable remissions in about 80% of selected patients.
• t(11;18)+ patients seem to be unresponsive to HP eradication.
• Relapse triggered by re-infection with HP remains sensitive to eradication
Forty two cases reviewed
Anecdotal and prospective
All *H pylori* positive
Four trials
  • 22/38 (58%) patients achieved complete remission
  • Depth of infiltration and clinical stage important
H pylori eradication on non-gastric MALT lymphomas

Disappearance of rectal mucosa-associated lymphoid tissue lymphoma following antibiotic therapy.
Hori K et al.

Disappearance of a mucosa-associated lymphoid tissue (MALT) lymphoma of the urinary bladder after treatment for Helicobacter pylori
Effect of *H. pylori* eradication on gastric MALT
<table>
<thead>
<tr>
<th>Score</th>
<th>Lymphoid population</th>
<th>LEL</th>
<th>Stromal changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>Absent of scattered plasma cells and small lymphoid cells</td>
<td>-</td>
<td>Normal or empty LP and/or fibrosis</td>
</tr>
<tr>
<td>Probable MRD</td>
<td>Aggregates of lymphoid cells/lymphoid nodules in LP / muscularis mucosa and/or submucosa</td>
<td>-</td>
<td>Empty LP and/or fibrosis</td>
</tr>
<tr>
<td>Responding residual disease</td>
<td>Dense, diffuse or nodular extending around glands</td>
<td>- / +</td>
<td>Focal empty LP and/or fibrosis</td>
</tr>
<tr>
<td>No change</td>
<td>Dense, diffuse or nodular</td>
<td>+</td>
<td>No changes</td>
</tr>
</tbody>
</table>

• Demonstration of **monoclonality** (PCR BIOMED-2 protocols) is **not a prerequisite** for the diagnosis of gastric MALT lymphoma.

• **Histology** is the **first diagnostic choice for H pylori infection** since it is the best diagnostic tool in the case of gastric MALT lymphoma.

• H pylori-negative patients with gastric MALT lymphoma can also undergo anti-H pylori treatment.

• Apparent **B cell monoclonality** has been detected in 1-4% of otherwise **typical chronic gastritis**

• Current evidence does not support a role for assessment of clonality in post-treatment follow-up of gastric MALT lymphomas beyond the research setting.
Small bowel: 10%
Intestinal Lymphomas

B Cell Lymphoma (60% - 70%)

High Grade B cell (70% -80%)

MALT

Low – intermediate grade (20% - 30%)

Others (mainly MCL)

T cell lymphoma

Mediterranean lymphoma Or Immunoproliferative small intestinal disease
Cyclin D1 is overexpressed in 90% of MCL, as a consequence of the t(11;14)(q13;q32)

Rare cases of mantle cell lymphoma are reported that are negative for cyclin D1, but have a gene expression profile consistent with mantle cell lymphoma
Mantle cell lymphoma

- MCL involving spleen and bowel: *multiple lymphomatous polyposis* (polyps 0.5-2cm)
- Histology of MCL in small bowel is identical to MCL at nodal sites
- Intestinal glands may be destroyed by MCL but typical LEL are not seen.
- IHC: CD20 (+), CD19 (+), CD5 (+), IgM (+), IgD (+), Cyclin D1 (+)
Most MCL are positive including the cases of cyclin D1 negative
(CycD1-, CD5+, Sox11+)

Other “Low grade” lymphomas are negative

Some Burkitt lymphoma, lymphoblastic lymphomas and T-prolymphocytic leukemias are positive
CCND2 rearrangements are the most frequent genetic events in cyclin D1- mantle cell lymphoma

- 40 cases of cyclin D1 neg MCL
- SOX 11 was positive in all cases
- 55% CCND2 translocation was found
- No alterations were found in CCND3
Intestinal Lymphomas

B Cell Lymphoma
(60% - 70%)

High Grade B cell
(70% - 80%)

Low – intermediate
grade
(20% - 30%)

MALT

Others (mainly MCL)

T cell lymphoma

Mediterranean lymphoma
Or Immunoproliferative small intestinal disease
• Rare (only 5% of all GI lymphomas)
• Marked geographic variation in incidence: higher in Northern Europe. Same genetic background that predisposes to Coeliac (Similar HLA haplotypes)
• Proximal jejunum the most frequent site
• Most frequently short history of malabsorption
• Less frequently long history of Coeliac
• Obstruction & perforation (50% -30%)
CD3
<table>
<thead>
<tr>
<th>Disease</th>
<th>Histology</th>
<th>IHC / Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>↑IELs, Crypt hyperplasia, Villous atrophy, ↑ inflammatory cells LP</td>
<td>IELs: CD3+, CD7+, CD8+, Polyclonal IELs</td>
</tr>
<tr>
<td>RCD</td>
<td>Same as CD and: Subcryptal inflammation, mucosal thinning…</td>
<td>IELs: CD3+, CD7+, CD8-, CD4-, Monoclonal IELs</td>
</tr>
<tr>
<td>EATCL</td>
<td>Medium-sized cells, angular nuclei, nucleoli, occasional anaplastic cells…</td>
<td>CD3+, cytotoxic markers+, CD30(+, anaplastic cells) Monoclonal</td>
</tr>
</tbody>
</table>

Adapted from Histopathology 2009,54:783-95
Enteropathy Associated T-cell lymphoma EATL
Classical (Type I)

- Large lymphoid cells CD3+, CD7+, CD5-, CD8- (20% +ve), CD4-, CD103+, cytotoxic granules-associated proteins and some are CD30+
- Closely linked to celiac disease, northern European origin
EATL type II (WHO 2008) – monomorphic (10-20%)

- MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA (MEITL) (WHO update 2016)

- No association with celiac disease
- Asians, and Hispanic
- Monomorphic, and usually positive for CD8, CD56, and MAPK
- Gains in chromosome 8q24 involving MYC
- From γδ T-cells
63 Years Old Irish Female

- Refractory coeliac disease
- Cobblestone duodenal mucosa
- Duodenal diverticulum
Ki-67
The clinicopathological features of extensive small intestinal CD4 T cell infiltration

F Carbonnel, H d’Almagne, A Lavergne, C Matuchansky, J C Brouet, F Sigaux, L Beaugerie, J Nemeth, B Coffin, J Cosnes, J P Gendre, J C Rambaud

Small intestinal CD4+ T-cell lymphoma: a rare distinctive clinicopathological entity associated with prolonged survival

Magali Svreck - Laurent Garderet - Virginie Sebbagh -
Michelle Rosenzwaig - Yann Parc - Monique Lagrange -
Malika Bennis - Anne Lavergne-Slove -
Jean-François Fléjou - Bettina Fabiani

- Very low proliferation rate
- No destruction of the glands
- No cytological atypia
- Very bland infiltrate
- Superficial infiltrate confined to mucosa. No invasion of the wall
- Multiple mucosal polyps
- Can affect entire GI Tract (most common small intestine and colon)
Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review

G. Damaj¹*, V. Verkarre¹, A. Delmer², P. Solal-Celigny³, I. Yakoub-Agha⁴, C. Cellier⁴, F. Maurschhauser⁵, R. Bouabdallah⁵, V. Leblond⁶, F. Lefrère¹, D. Bouscary⁶, J. Audouin², B. Coiffier⁶, B. Varet¹, T. Molina², N. Brousse¹ & O. Hermine¹
On behalf of the Groupe d’Etude des Lymphomes de l’Adulte

Primary Follicular Lymphoma of the Gastrointestinal Tract
A Clinical and Pathologic Study of 26 Cases
Jinru Shia, M.D., Julie Teruya-Feldstein, M.D., Dorothy Pan, M.D., Abhijith Hegde, M.D., David S. Klimstra, M.D., R. S. K. Chaganti, Ph.D., Jing Qin, Ph.D., Carol S. Portlock, M.D., and Daniel A. Filippa, M.D.
Gastrointestinal tract FL (variant of FL)

- Frequently in the duodenum (2nd portion)
- Usually presenting as multiple polyps, incidental finding on endoscopy
- Morphology, immunophenotype and genetic features similar to those of nodal FL
- Most patients have localized disease and excellent prognosis even without treatment
- FL in GI tract may show lymphoepithelial lesions and can be mis-diagnosed as MALT lymphomas
• 63 patients, all stage IE
• Uncharacteristic symptoms
• Usually multiple warty polyps along descending part of duodenum
• Limited to mucosa/submucosa in 19 of 20 cases
• No ulcerations, no obstructive lesions

• Grade 1 in 60, Grade 2 in 3 cases
• Typical immunophenotype (bcl-2+, bcl-6+, CD10+, low Ki-67,..)
• t(14;18) by cytogenetics in 4/4 cases, no additional aberrations
Duodenal-type Follicular lymphoma

- localized overt low grade FL, is distinct from other GI tract FL
- Overlap with ISFN (in situ follicular neoplasm) and extranodal marginal zone lymphoma
- excellent outcome
- watch and wait strategy
Extranodal NK/T cell lymphoma, nasal type

- Aerodigestive tract (nasal cavity, paranasal sinuses…)
- Extranasal involvement: GI tract, skin, testis
- Cytological spectrum and morphology very broad
- Highly aggressive, short survival, poor response to treatment.
- IHC: CD2(+), CD4 (-), CD8 (-), CD56 (+), cytotoxic markers (+), EBV (+)
<table>
<thead>
<tr>
<th></th>
<th>Classical EATL</th>
<th>EATL type II MEITL</th>
<th>NK</th>
<th>Indolent LPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Pleomorphic large cells</td>
<td>Monomorphic small cells</td>
<td>Monomorphic small cells</td>
<td>Monomorphic small cells</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>CD3⁺ CD4⁻ CD8⁻</td>
<td>CD3⁺ CD8⁺ CD56⁺</td>
<td>CD3⁺⁻, CD4⁻, CD8⁻, CD56⁺</td>
<td>CD3⁺CD4⁺ or CD8⁺</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>TCR rearrangement</td>
<td>TCR rearrangement</td>
<td>TCR rearrangement</td>
<td>TCR rearrangement</td>
</tr>
<tr>
<td><strong>Mucosa</strong></td>
<td>Villous atrophy</td>
<td>Villous trophy</td>
<td>Villous atrophy in involved areas</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>IELs</strong></td>
<td>Increased CD4⁻/CD8⁻</td>
<td>Increased CD8⁺</td>
<td>Increased in involved areas CD4⁻/CD8⁻</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>EBV</strong></td>
<td>Neg</td>
<td>Neg</td>
<td>Positive</td>
<td>Neg</td>
</tr>
</tbody>
</table>
T-cell lymphomas compared with B-cell lymphomas:

– Frequent need for emergency operations.
– Poorer survival
– Poorer response to chemotherapy
– Tumor progression and death commoner during chemotherapy
– Poorer general condition at presentation preclude any therapy in many
– More frequent and earlier relapses.
• 4th Edition is now >7 years old and out of date

• WHO will not permit a 5th edition until all volumes of the 4\textsuperscript{th} are published

• Update to 4th edition has been allowed
THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

BLOOD, 19 MAY 2016 • VOLUME 127, NUMBER 20
MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukemia / small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic B-cell lymphoma / leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukemia-variant
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T cell / histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL, NOS*
- EBV+ Mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS*
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration*
- High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
- High grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
MATURE T-AND NK-NEOPLASMS

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK cell leukemia
- Systemic EBV+ T-cell Lymphoma of childhood*
- Hydroa vacciniforme-like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- Indolent T-cell lymphoproliferative disorder of the GI tract *
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma

Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Nodal peripheral T-cell lymphoma with TFH phenotype*
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative *
Breast implant-associated anaplastic large cell lymphoma
Formal separation of EATL Types I and II

Introduction of new provisional entities for indolent T-cell LPD’s in the GI tract (and Skin)

Duodenal –type FL: localized overt low grade FL, is distinct from other GI tract FL

New genetics in Mantle cell lymphoma:
• Value of SOX11
• Cyclin D1 negative MCL (Cyclin D2+)
### Rappaport Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular</td>
<td>Lymphocytic, poorly differentiated</td>
</tr>
<tr>
<td>Mixed</td>
<td>Lymphocytic and histiocytic</td>
</tr>
<tr>
<td>Histocytic</td>
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</tr>
<tr>
<td>Diffuse</td>
<td>Lymphocytic, well differentiated</td>
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<td>Lymphocytic and histiocytic</td>
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<td>Histocytic</td>
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<tr>
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<tr>
<td>Burkitts</td>
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<tr>
<td>Non-Burkitts</td>
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</tbody>
</table>

### Kiel Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type</th>
<th>Subtype</th>
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<tbody>
<tr>
<td>Low-grade</td>
<td>B</td>
<td>Low grade:</td>
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<tr>
<td></td>
<td></td>
<td>ML lymphocytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ML lymphoplasmacytic</td>
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<tr>
<td></td>
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<td>ML centroblastic</td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<td>ML centroblastic</td>
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<td></td>
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<td>ML large cell anaplastic</td>
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<td>ML Burkitts</td>
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<td></td>
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<td>ML small cleaved cell</td>
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<td></td>
<td></td>
<td>ML Sezaryysi</td>
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<td></td>
<td></td>
<td>ML lymphoplasmacytic</td>
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<td></td>
<td></td>
<td>ML lymphoblastic (Lennert’s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ML angioimmunoblastic</td>
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<td>ML T zone</td>
</tr>
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<td>ML plasmacytic-small cell</td>
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<tr>
<td>High-grade</td>
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<td>High grade:</td>
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<td>ML plasmacytic-medull large cell</td>
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<td>ML large cell anaplastic</td>
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<td>ML lymphoblastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rare types</td>
</tr>
</tbody>
</table>

### New Working Formulation for Clinical Use

- **Low-Grade**
  - Small lymphocytic (lympho/plasmacytic; plasma/cytoplasmic)
  - Follicular, predominantly small cleaved cell
  - Follicular, mixed, small cleaved and large cleaved cell

- **Intermediate-Grade**
  - Follicular, predominantly large cell, cleaved and/or non-cleaved
  - Diffuse, small cleaved cell
  - Diffuse, mixed, large and small cell
  - Diffuse, large cell, cleaved or noncleaved

- **High-Grade**
  - Large cell, immunoblastic - (B- or T-cell type)
  - Lymphoblastic
  - Small noncleaved cell (Burkitt’s and non-Burkitt’s)
  - Miscellaneous
<table>
<thead>
<tr>
<th>RAPPAPORT CLASSIFICATION</th>
<th>KEL CLASSIFICATION</th>
<th>NEW WORKING FORMULATION for Clinical Use</th>
</tr>
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<tbody>
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<td>Low-grade</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>B cell</td>
<td>Low-grade, cleaved cell</td>
</tr>
<tr>
<td>Mixed, I</td>
<td>Mixed, I</td>
<td>Large cleaved cell</td>
</tr>
<tr>
<td>Histocytoma</td>
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<td>cleaved and/or non-cleaved</td>
</tr>
<tr>
<td>Diffuse</td>
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<tr>
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<tr>
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<tr>
<td>Non-I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NEW WORKING FORMULATION**

- **Low-grade**
  - A. Small lymphocytic (lymphocytic, cleaved or non-cleaved)
  - B. Large cleaved cell
  - Cleaved and/or non-cleaved
  - Mixed cell type

**IM JUST SO CONFUSED**