Updated 2016 WHO Classification of Lymphoid Neoplasms

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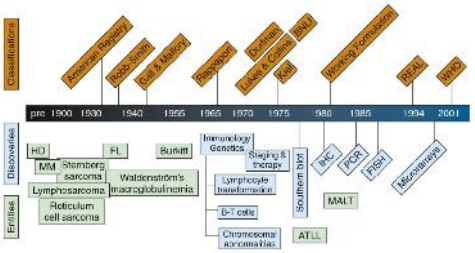
A bit of History….

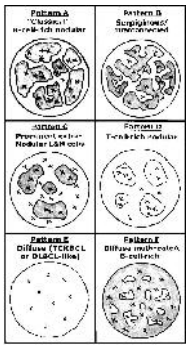


Hematopathology, 1st edition, 2011

Hodgkin Lymphoma

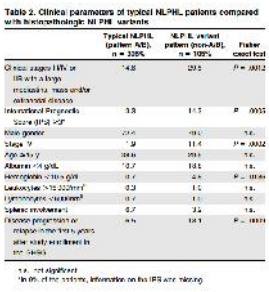
Hodgkin Lymphoma

- No change in classification.
- More emphasis on NLPHL patterns.
- THRLBC-like transformation of NLPHL.
- GEP shown similarities between NLPHL and THRLBCL.



Fan et al, Am J Surg Pathol, 2003

Hodgkin Lymphoma



Hartmann et al, Blood, 2013

Hodgkin Lymphoma

- Lymphocyte-rich CHL has features intermediate between other CHL & NLPHL.
- More frequent expression of B-cell transcription factors.
- Follicular T-cell microenvironment in 50% of cases.
- NF-kB markers were expressed similar to cHL.
- However, CD30 expression is maintained.

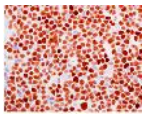
Nam-Cha et al, Mod Pathology, 2009

Mature B-cell neoplasms

CLL/SLL & monoclonal B-cell lymphocytosis (MBL)

- MBL: Monoclonal B-lymphocytes in peripheral blood $\leq 5 \times 10^9$/L.
- Can be found in up to 12% of healthy adults.
- MBL precedes almost all cases of CLL/SLL.
- Divided into:
  - Low-count ($<0.5 \times 10^9$/L).
  - High count.
- Low count MBL has very low risk of progression → No need for extra follow-up.
- High count MBL has 1-2% annual risk of progression → requires yearly follow-up.
- High count MBL has similar phenotypic and molecular features to CLL/SLL.

New Markers in CLL



- **LEF1** (Lymphoid Enhancer binding factor 1)
  - Transcription factor, WNT/ ß-catenin pathway.
  - 100% expression in CLL.
  - Not expressed in other small B-cell lymphomas.

Tandon et al, Modern Pathology, 2011

- **CD200**
  - Ig superfamily.
  - Expressed in CLL, HCL, FL & 24% of indolent MCL.

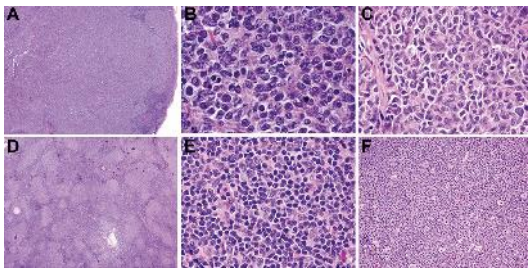
Challagundla et al, AJCP, 2014
Epsinet et al, J Clin Oncol, 201

- **CD49d**
  - Integrin family.
  - Prognostic value independent of CD38/ ZAP70.
  - ? Predictive value for B-cell receptor targeted therapies?

Bulian et al, J Clin Oncol, 2014

Follicular Lymphoma

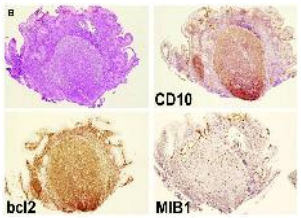
- **FL in situ → In situ follicular neoplasia.**
  - Low rate of progression.
  - However, more often associated with prior or synchronous overt lymphomas → requires additional clinical assessment.
- **Pediatric-type FL:**
  - Nodal localized disease.
  - Large expansile highly proliferative follicles with prominent blastoid follicular center.
  - **No diffuse areas**.
  - BCL2 rearrangements **must not** be present.
  - Lack BCL6 and MYC rearrangements.
  - Nearly all cases are localized and may not require treatment other than excision.



Louissaint Jr et al, Blood, 2012

Follicular Lymphoma

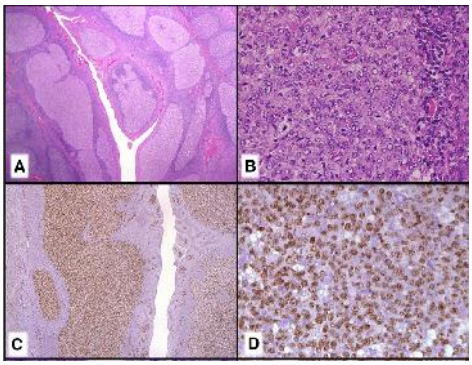
- **Duodenal-type FL:**
  - Localized low-grade FL.
  - CD20+, bcl2+, bcl6+, CD10+.
  - Excellent outcome.
  - Some cases managed with a watch-and-wait strategy.



Schmatz et al, J Clin Oncol, 2011

Follicular Lymphoma

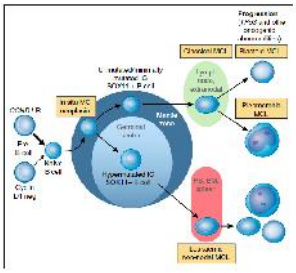
- **Large B-cell lymphoma with IRF4 rearrangement:**
  - Occurs most commonly in children and young adults.
  - Occur in Waldeyer ring &/or cervical lymph nodes.
  - Show follicular, follicular & diffuse, or pure diffuse growth pattern.
  - It resembles FL grade 3B or DLBCL.
  - **IRF4/MUM1+**, Bcl6+, high Ki67.
  - Bcl2 & CD10 can be expressed.
  - IG/IRF4 rearrangements +/- Bcl6 rearrangements.
  - **Lack BCL2 rearrangements**.
  - Require treatment but good prognosis.



Swerdlow et al, Blood, 2016

Mantle Cell Lymphoma

- Mantle cell lymphoma in situ → In situ mantle cell neoplasia.



Swerdlow et al, Blood, 2016

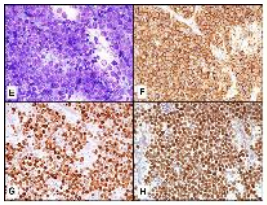
Lymphoplasmacytic Lymphoma

- Role of MYD88 mutation in Dx.
  - MYD88 (L265P) mutation is detectable in:
    - all patients with Waldenström's macroglobulinemia.
    - 47% IgM-MGUS
    - 6% SMZL
    - 4% B-CLPD

Varettoni et al, Blood, 2013

Burkitt Lymphoma

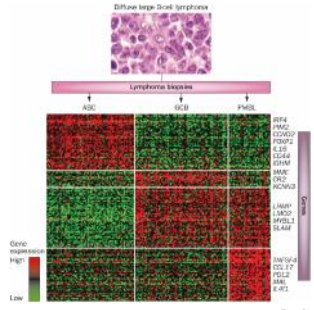
- Burkitt lymphoma (BL) without MYC rearrangement.
- ID3 mutation.
- **Burkitt-like lymphoma with 11q aberration**
  - Morphologically and phenotypically similar to BL.
  - Lack MYC rearrangements.
  - 11q alteration characterized by proximal gains and telomeric losses.
  - More complex karyotype, lower levels of MYC expression & more pleomorphism.
  - Clinical behavior similar to BL.



Swerdlow et al, Blood, 2016

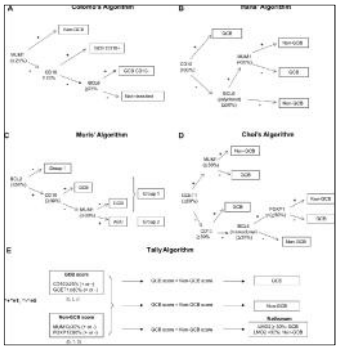
Diffuse Large B-cell Lymphoma

- Determining cell of origin is mandatory.



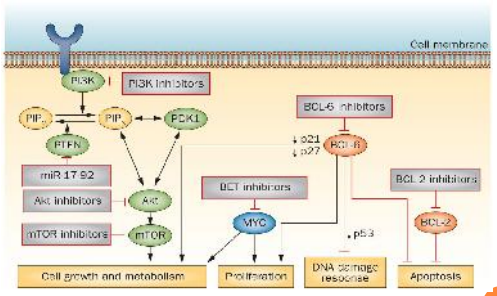
Roschewski et al, Nat. Rev. Clin. Oncol. 2013

Diffuse Large B-cell Lymphoma



Gutiérrez-García et al, Blood, 2011

The key signalling pathways implicated in GCB DLBCL with targeted novel agents in clinical development



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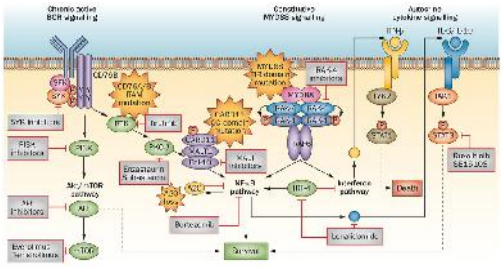
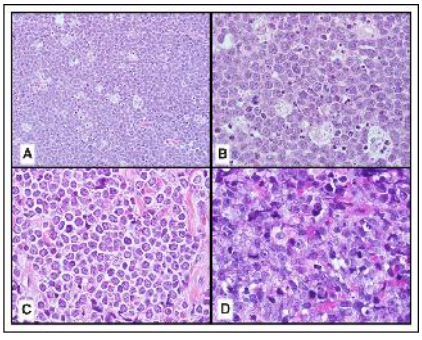


Roschewski et al, Nat. Rev. Clin. Oncol. 2013

Diffuse large B-cell lymphoma

- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU) is removed.
- Now, we have:
  - High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements.
  - High-grade B-cell lymphoma, NOS : Includes blastoid-appearing large B-cell lymphomas & cases lacking MYC & BCL2 or BCL6 translocations that were in 2008 classification called BCLU.

Diffuse large B-cell lymphoma



Swerdlow et al, Blood, 2016

Diffuse large B-cell lymphoma

- Which cases should be tested for MYC rearrangement?
- Screening by immunohistochemistry staining for MYC & bcl-2.
- MYC protein expression is detected in a 30-50% of DLBCL.
- Concomitant expression of BCL2 in 20-35%.
- Double expression without gene aberrations is a prognostic indicator in DLBCL, NOS but not a separate category.

Mature NK/T-cell neoplasms

Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype

- An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype (TFH) phenotype including:
  - Angioimmunoblastic T-cell lymphoma (AITL).
  - Follicular T-cell lymphoma.
  - Other nodal PTCL with a TFH phenotype (2 markers at least).
- May contain B-cell blasts, often EBV+.
- Share recurrent genetic abnormalities (mutations of TET2, IDH2, DNMT3A, RHOA & CD28 and gene fusions of ITK-SYK or CTLA4-CD28).

Anaplastic large-cell lymphomas

- GEP studies have shown that ALK- ALCL has a signature close to that of ALK+ ALCL and distinct from other NK/TCLs.
- ALK- ALCL with rearrangements of DUSP22 and IRF4→ good prognosis.
- ALK- ALCL with TP63 rearrangment → worse prognosis.
- Breast implant–associated ALCL:
  - New provisional entity.
  - Noninvasive disease associated with excellent outcome.
  - Usu. presents as an accumulation of seroma fluid between the implant itself and the surrounding fibrous capsule.
  - Conservative management (removal of the implant & capsule) in most cases.
  - If there is invasion through the capsule, there is risk of lymph node involvement and systemic spread, warranting systemic chemotherapy.

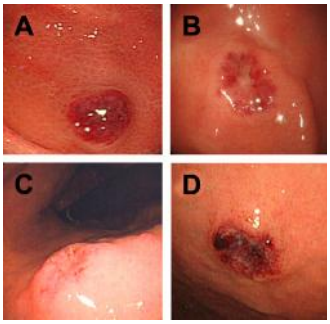
Enteropathy-associated T-cell lymphoma

- EATL Dx is only used for cases formerly known as type I EATL, typically associated with celiac disease.
- Type II EATL → Monomorphic epitheliotropic intestinal T-cell lymphoma.
  - Usu monomorphic.
  - CD8+, CD56+, MATK+.
  - Gains in chromosome 8q24 involving MYC.
  - Most cases are derived from gamma/delta T cells.
  - Mutations in STAT5B.

Indolent T-cell lymphoproliferative disorder of the GIT

- New indolent provisional entity with superficial monoclonal gastrointestinal T-cell infiltrate.
- Takeuchi et al described in 2010, 10 cases of lymphomatoid gastropathy.
- Mansoor et al (Blood, 2011) described 8 cases of NK-cell enteropathy.
- Perry et al (Blood, 2013) proposed the name: Indolent T-cell lymphoproliferative disease of the GIT.
- STAT3 mutation.
- Excellent outcome even without treatment.
- Some cases may progress.

Indolent T-cell lymphoproliferative disorder of the GIT



Takeuchi et al, Blood, 2010

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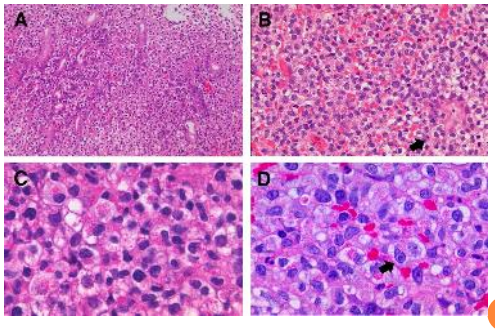

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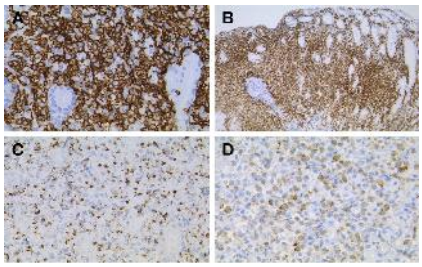

CD7 (A), CD56 (B), granzyme B (C), cytoplasmic CD3ε (D)

Takeuchi et al, Blood, 2010

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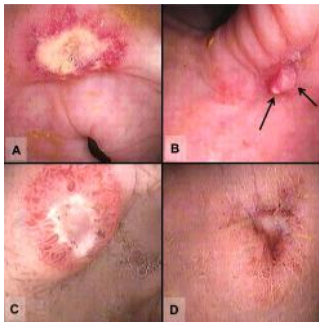

Mansoor et al, Blood, 2011

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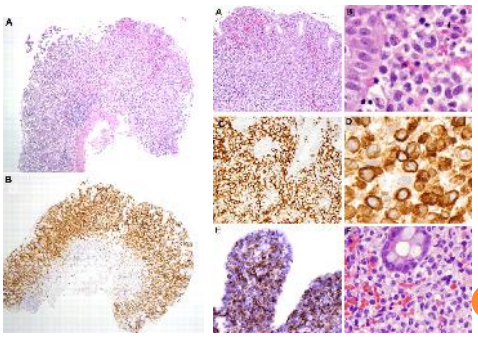

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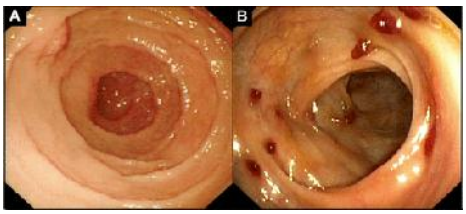

Perry et al, Blood, 2013

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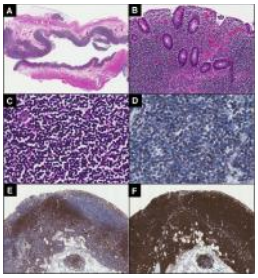

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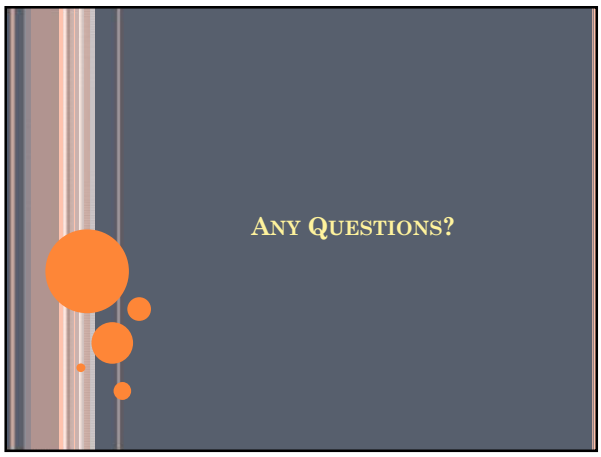
Any Questions?