WHO 4th ED
Classification of Mature B-cell Neoplasms

- Chronic lymphocytic leukemia /Small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukaemia, unclassifiable
- Lymphoplasmacytic lymphoma
- Heavy chain diseases
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Primary cutaneous follicle centre lymphoma
- Follicular lymphoma
- Nodal marginal zone B-cell lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphomas*
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

B-cell Lymphoma 2011

- infectious agents
- early lesions
- site of the disease
- intermediate forms
- prognosis and prediction

humv
HOSPITAL UNIVERSITARIO
MARQUÉS DE VALDECILLA

IFIMAV

B-cell lymphomas associated with infectious agents

- EBV:
  - Immunodeficiencies,
  - Age-related
  - Chronic infections….
- HCV:
  - Marginal Zone lymphoma
  - Monoclonal lymphocytosis +/- cryoglobulinemia
- Paludism
  - Marginal Zone lymphoma
  - Monoclonal lymphocytosis +/- cryoglobulinemia
- Helicobacter pylori,…
  - MALT lymphoma

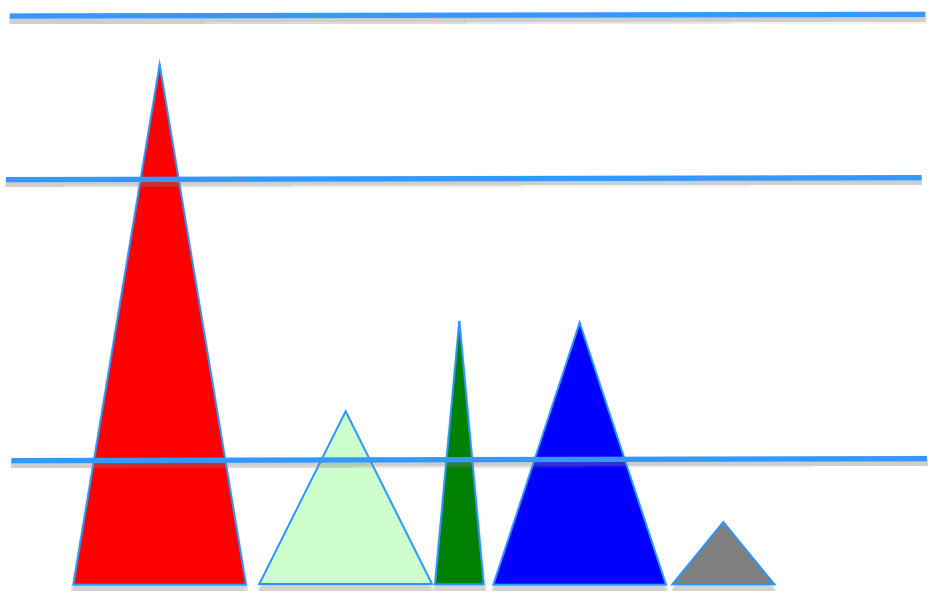
Age-related EBV-associated lymphoproliferative disorders in the Western population: a spectrum of reactive lymphoid hyperplasia and lymphoma

Stefan D. Dojcinov,[1] Girish Venkataraman,[2] Stefania Pittaluga,[2] Iwona Wlodarska,[3] Jeffrey A. Schrager,[2] Mark Raffeld,[2] Robert K. Hills,[4] and Elaine S. Jaffe[2]

[1]All Wales Lymphoma Panel, Department of Pathology, University Hospital of Wales, Cardiff, United Kingdom; [2]Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [3]Center for Human Genetics, K.U. Leuven, Leuven, Belgium; and [4]Department of Haematology, School of Medicine, Cardiff University, Cardiff, United Kingdom

We investigated age-related EBV$^+$ B-cell lymphoproliferations in the Western population. The clinical features, histology, immunophenotype, EBV-encoded RNA in situ hybridization, and clonality by PCR of T-cell receptor gamma and immunoglobulin genes were categorized in 122 EBV$^+$ lesions as follows: (1) reactive lymphoid hyperplasia; (2) polymorphic extranodal or (3) polymorphic nodal lymphoproliferative disease (LPD); and (4) diffuse large B-cell lymphoma (DLBCL). Interphase FISH for *IG* and *PAX5* gene rearrangements was performed on 17 cases of DLBCL. The overall median age was 75 years (range, 45-101 years; 67 men, 55 women), and 67, 79, 73, and 77 years, respectively, for groups 1 through 4. Sixteen of 21 cases of polymorphic extranodal LPD were classified as EBV$^+$ mucocutaneous ulcer. PCR for immunoglobulin genes was polyclonal in reactive lymphoid hyperplasia (84%) and monoclonal in 33%, 63%, and 56% of polymorphic extranodal and nodal LPD cases and DLBCL, respectively. All groups showed restricted/clonal T-cell receptor responses (27%-70%). By FISH, 19% of DLBCLs showed *IGH@* rearrangements, but *PAX5* was unaffected. Disease-specific 5-year survival was 100%, 93%, 57%, and 25% for groups 1-4, respectively, and 100% for patients with EBV$^+$ mucocutaneous ulcer. Disease volume was predictive of therapy response ($P = .0002$), and pathologic subtype was predictive of overall outcome ($P = .001$). Age-related EBV$^+$ B-cell LPD encompasses a wider disease spectrum than previously recognized and includes both reactive and neoplastic conditions. Reduction in the T-cell repertoire may contribute to decreased immune surveillance. (*Blood*. 2011;117(18):4726-4735)

Small Clonal Populations ? Early/Precursor Lesions ?



CLINICAL THRESHOLD

HISTOLOGICAL THRESHOLD

MOLECULAR THRESHOLD

Small Clonal Populations ? Early/Precursor Lesions ?

- New technology allows detection of small clones of lymphoid cells in blood, bone marrow, lymph nodes of healthy persons
  - Immunophenotype (light-chain restriction, CD5, CD10, BCL2)
  - Genetics (IGH-r, BCL2-r)
- May not indicate presence or risk of progressive malignancy
  - Monoclonal lymphocytosis of uncertain significance
  - HCV-lymphocytosis/cryoglobulinemia
  - Intrafollicular neoplasm
  - Other in situ lymphoma (MCL…)
- The term lymphoma should not be used for these conditions, where treatment has not proven benefit. The term *FL- or MCL-like B cells of uncertain significance* has been proposed.
- Guidelines for diagnosis and treatment still provisional (Myeloma, CLL, FL)
- Open field, with new data coming

News on follicular lymphoma 2011

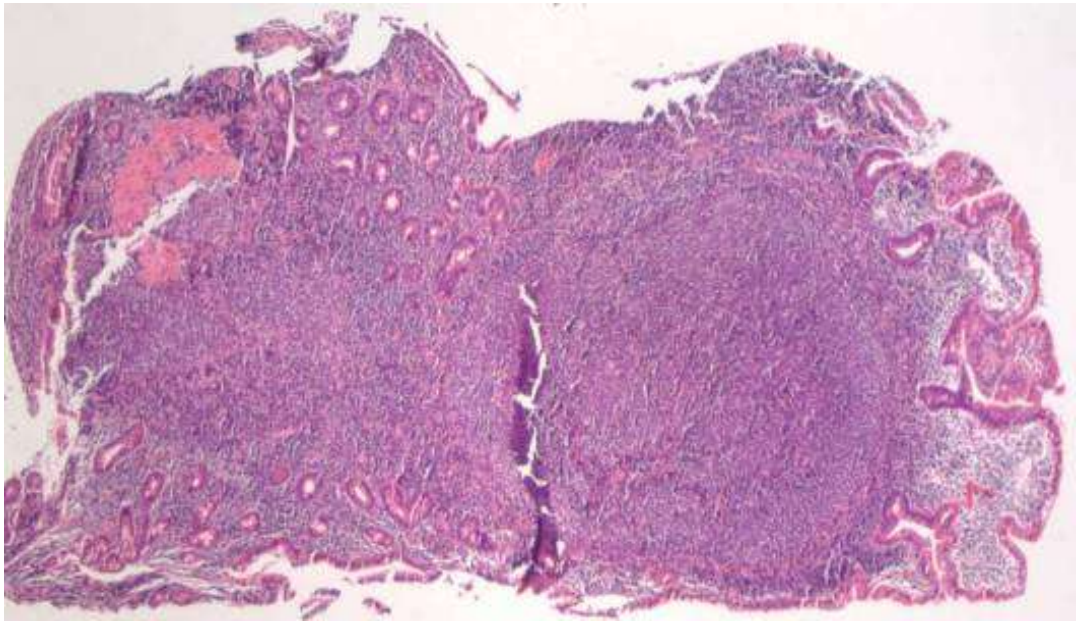
Diversity of clinicopathologic variants:

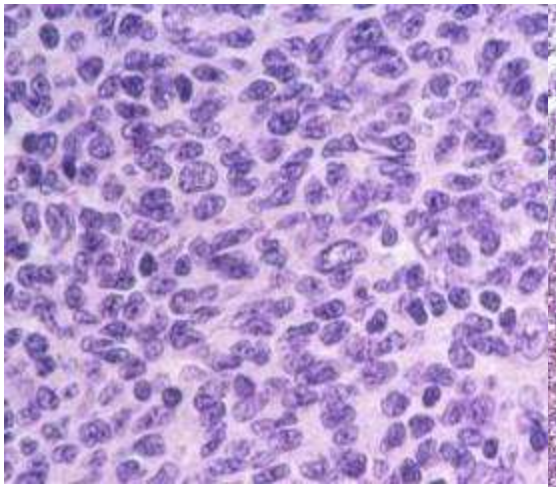
- Nodal FL:
  - t(14;18)+
  - t(14;18)- (IRF4, others)

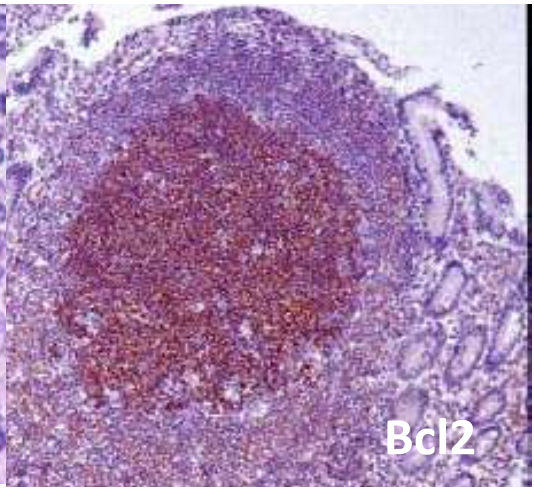
- Extranodal FL:
  - t(14;18)+: duodenal
  - t(14;18)-: cutaneous
    - pediatric
    - testicular

Follicular Lymphoma of the Gastrointestinal Tract

- Small intestine
  - Duodenum: 85%
- Morphology, immunophenotype, genetics similar to nodal FL
  - Bcl2+ CD10+ Bcl6+, often IgA+
- Clinically indolent, localized
  - Asymptomatic (incidental); abdominal pain
  - Most localized (Stage I/II)
  - Curable with resection, often no treatment
  - Systemic recurrence unusual
- Arise from follicular component of MALT ?

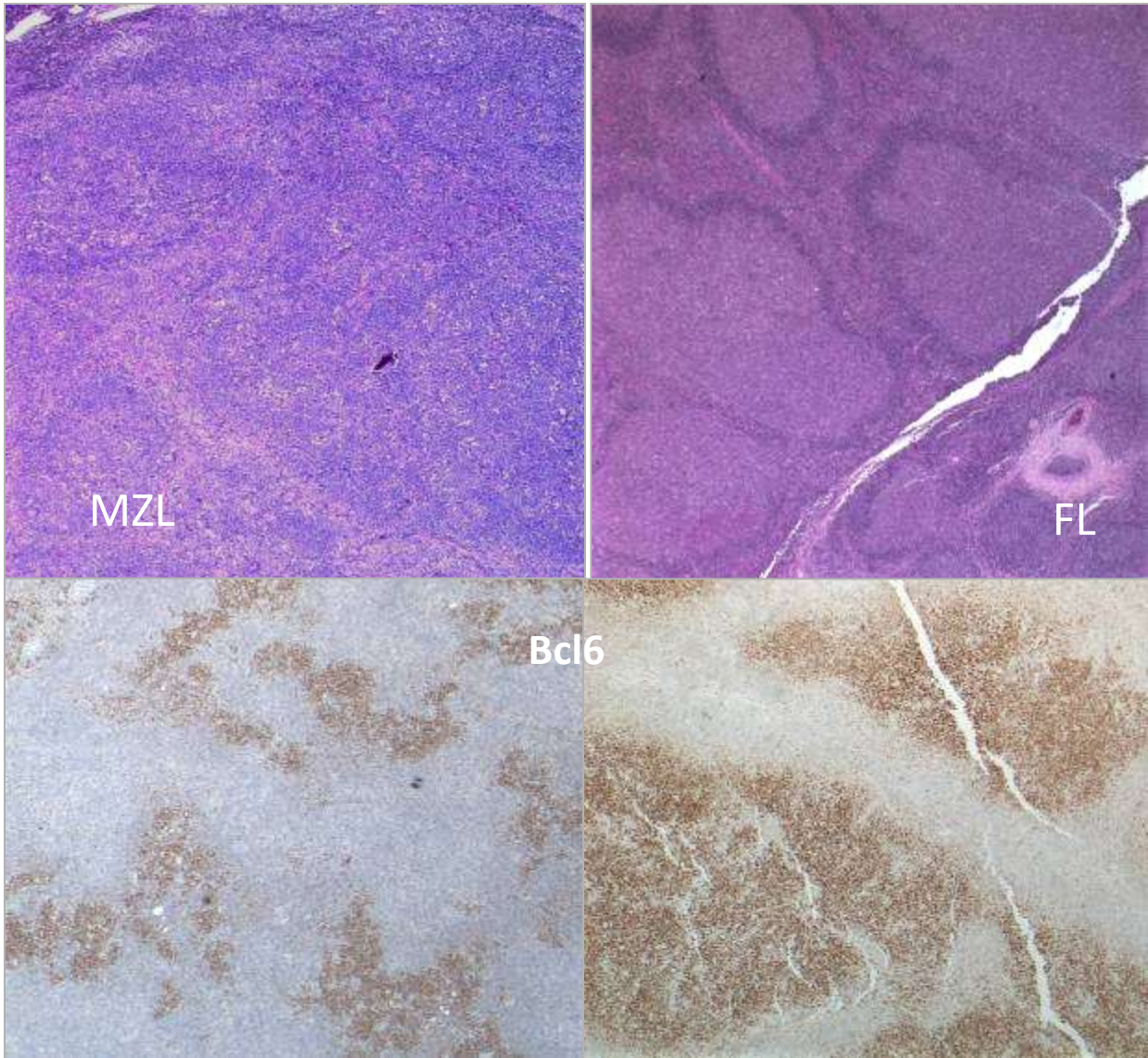






Pediatric Follicular lymphoma
Pediatric Nodal Marginal zone lymphoma

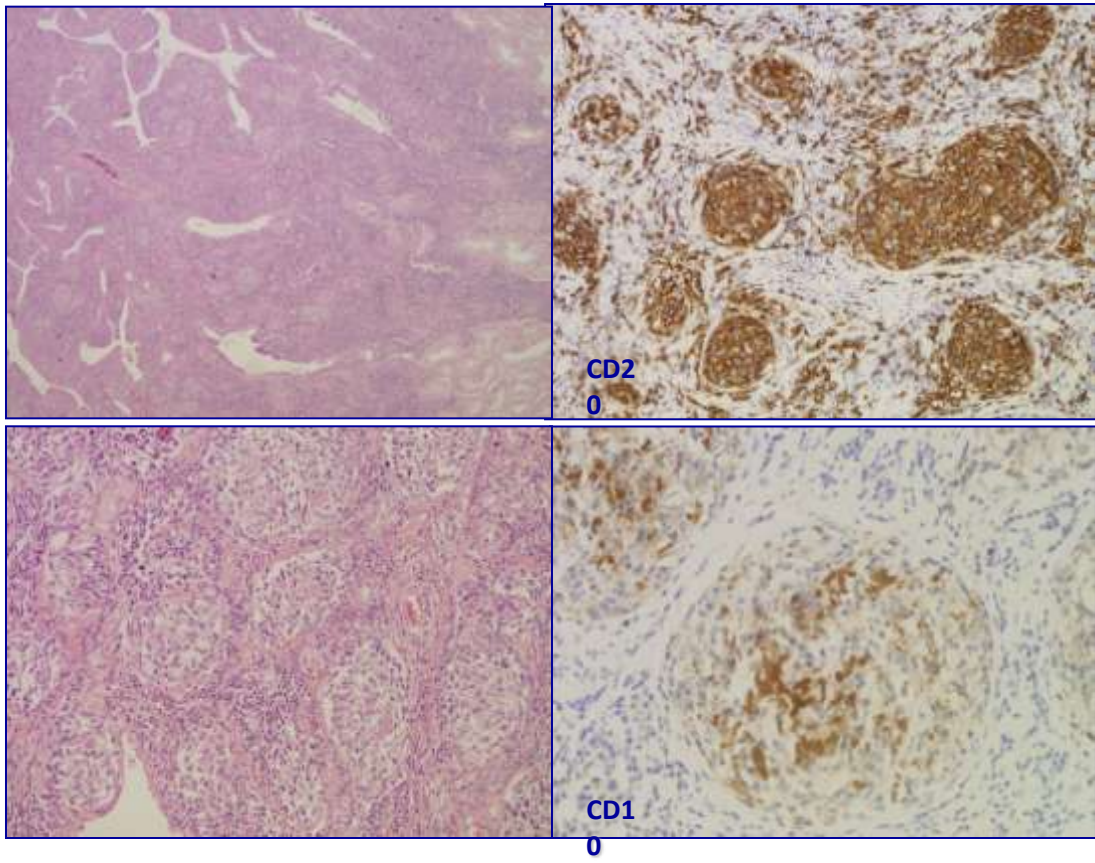
- Adolescent or young adult male; localized peripheral lymph node
- Large follicles, resembling PTGC, follicle lysis; effacement of nodal architecture
- Clonality demonstrated by immunophenotype/PCR
- FL: CD10+ Bcl6+ CD43+ Bcl2-
- MZL: CD10- Bcl6- (residual GC present) Bcl2 +/- clg +/-
- Often cured with minimal therapy; no dissemination
- Are these really malignant?



Testicular Follicular Lymphoma

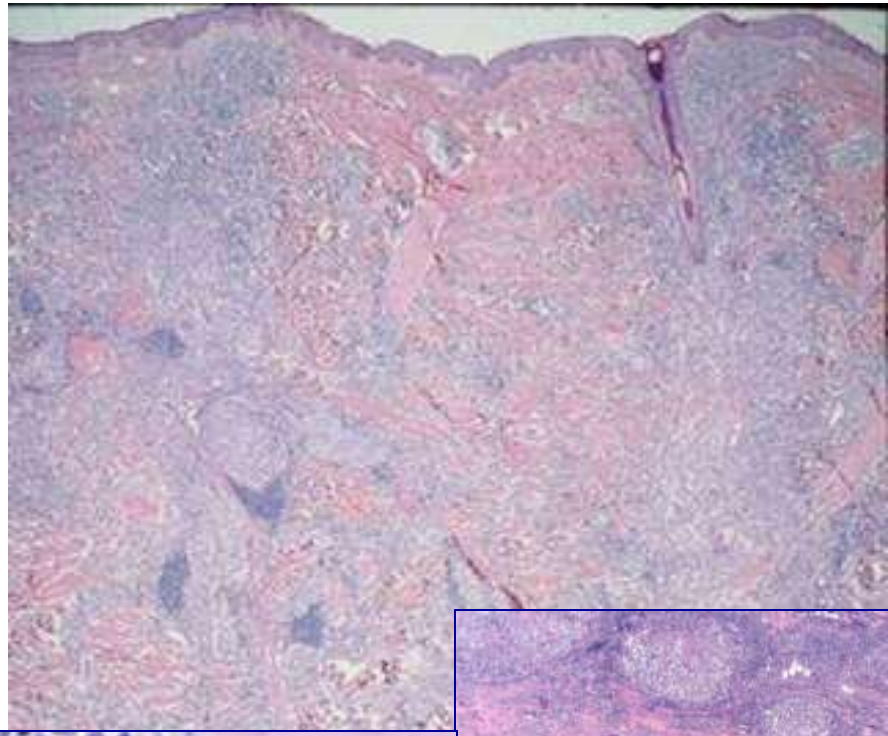
Testicular FL

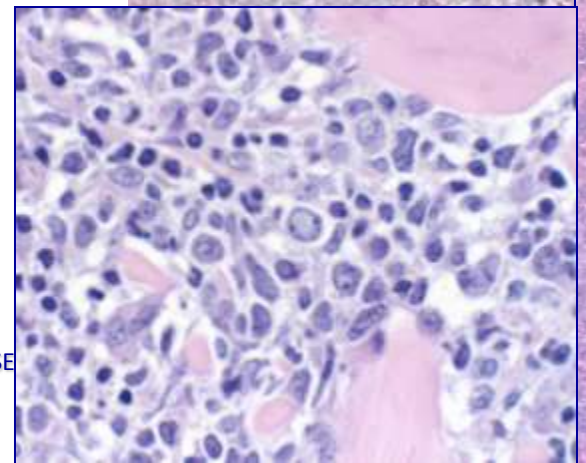
- **Early stages,**
- **Prolonged remissions, favourable response to treatment**
- **Not associated with t(14;18) (<25%)**

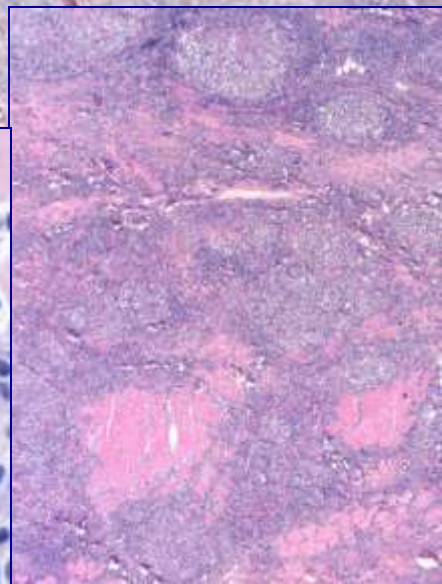


Primary Cutaneous Follicle Center Lymphoma

- Morphology
  - Often diffuse or follicular and diffuse
  - CB and large CC (may be called DLBCL)
    - CB numerous, but not sheets
- Immunophenotype
  - CD20+, Bcl6+ CD10-/+ Bcl2-/+
- Genetics
  - BCL2 usually germline
- Clinical
  - Head and neck, trunk;
  - Indolent, localized; no nodal spread
  - Prognosis independent of grade







- **news on splenic lymphoma 2001**:

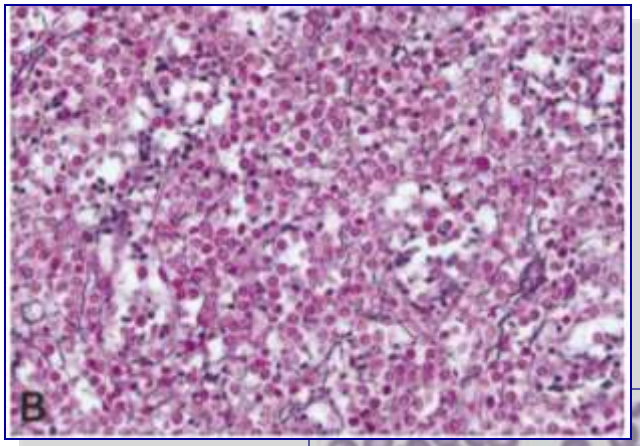
better definition of SMZL

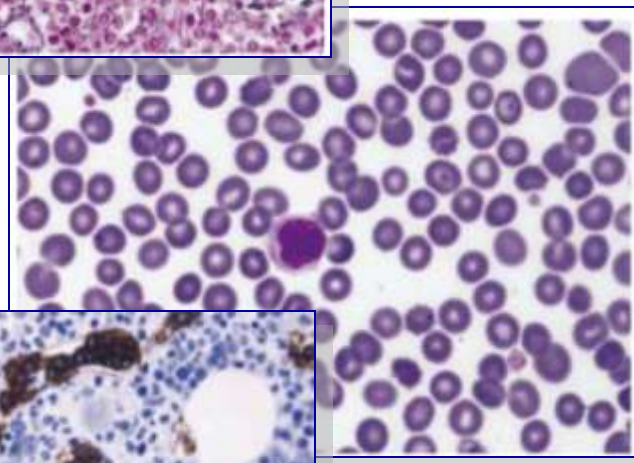
identification of the red pulp diffuse SBCL

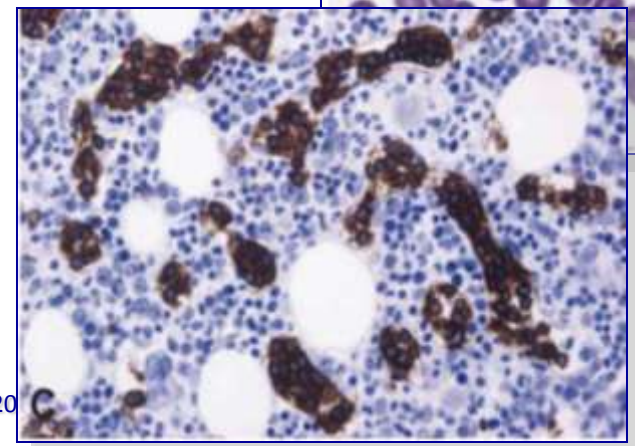
description of HCL variant

Splenic diffuse red pulp small B-cell lymphoma

- Morphology
  - Spleen: diffuse
  - Bone marrow: sinusoidal
  - PB: villous
  - Monomorphous small cell cytology
- Immunophenotype
  - CD20+, DBA44+, IgG+, CyclinD1-
- Genetics
  - Multiple, no characteristic alterations
- Clinical
  - Stage IV
  - Indolent tumor







SPLENIC MARGINAL ZONE LYMPHOMA

Borders of the disease

- Splenic red pulp small B-cell lymphoma
- 7q- monoclonal lymphocytosis
- HCL-variant
- Lymphoplasmacytic Lymphoma
- Splenic FL

B-cell Lymphoma 2011

- news on CLL and PLL

New Definition of CLL

- WHO Classification 2001
  - **Neoplasms of small B-lymphocytes**
  - **Lymphocyte count > $10x10^9$/L or < provide CLL morphology and phenotype**
- NIH Guidelines 1996
  - **Lymphocyte count > 5 $x10^9$/L**
- WHO Classification 2008 (IWCLL-08)*
  - **Presence of $\geq$ 5 $x10^9$/L monoclonal lymphocytes with the CLL phenotype**
  - **Extramedullary tissue involvement and cytopenias allow for lower number of atypical lymphocytes**

Hallek M et al Blood 2008

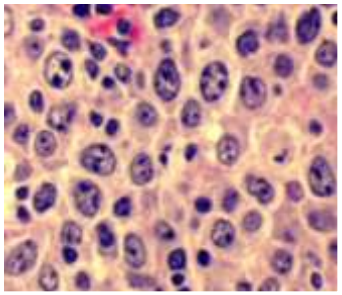
B-cell Lymphoma 2011

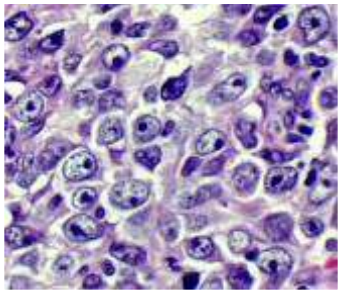
- news on DLBCL

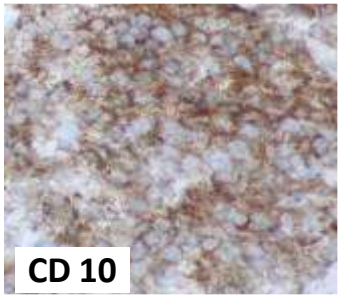
Diffuse Large B-cell Lymphoma

A Heterogeneous Category

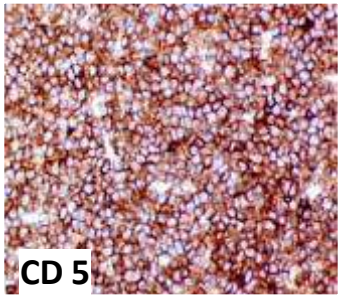
- histology and phenotype
- genetic and molecular alterations
- response to treatment



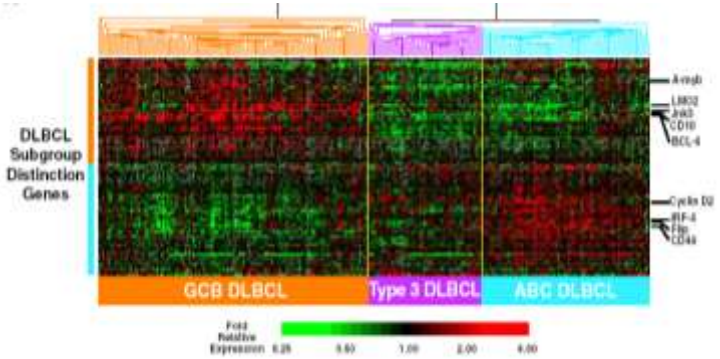




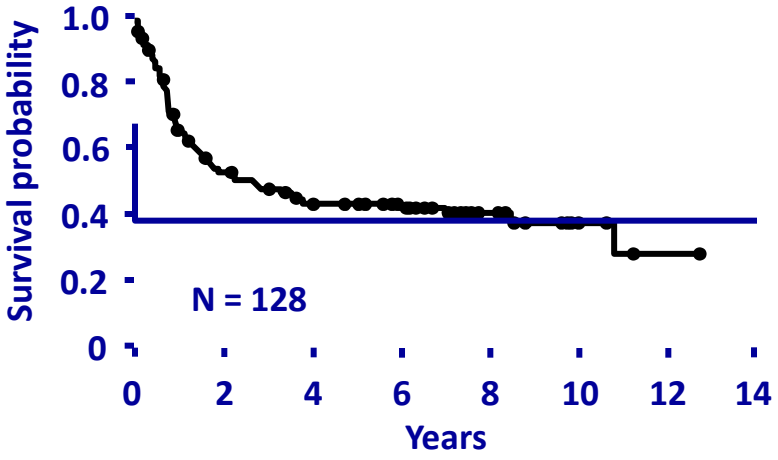
CD 10



CD 5



Response to treatment – CHOP



SEAP-2011

Diffuse Large B-cell lymphoma

Variants and subtypes/entities

Diffuse large B-cell lymphoma, not otherwise specified (NOS)

Morphological variants, Molecular and phenotypic subgroups

Diffuse large B-cell lymphoma subtypes/entities

Topographic site

Terminal B-cell differentiation

Borderline cases

Burkitt and DLBCL

Hodgkin Lymphoma and DLBCL

Diffuse Large B-cell lymphoma
Variants and subgroups

Diffuse large B-cell lymphoma, not otherwise specified (NOS)

Common morphologic variants

- Centroblastic
- Immunoblastic
- Anaplastic

Molecular subgroups

- CD5-positive DLBCL
- Germinal-center B-cell-like (GCB)
- Activated B-cell-like (ABC)

Diffuse Large B-cell lymphoma

Subtypes and Entities

Diffuse large B-cell lymphoma subtypes

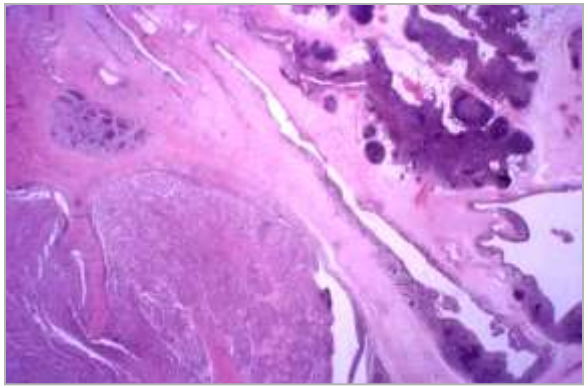
T cell/histiocyte rich large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
EBV + DLBCL of the elderly
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Lymphomatoid granulomatosis
DLBCL associated with chronic inflammation

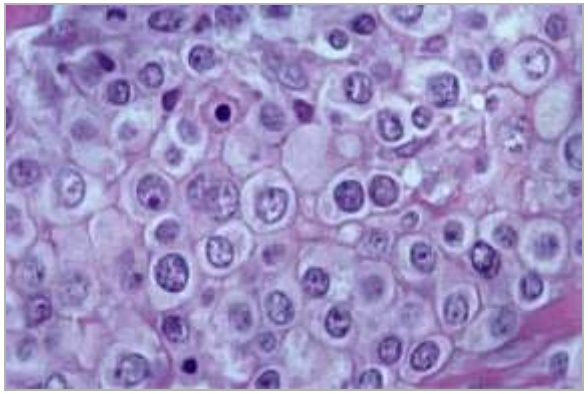
With plasmablastic features:

ALK positive DLBCL
Lymphoma arising in HHV8-associated multicentric Castleman Disease
Plasmablastic lymphoma
Primary effusion lymphoma

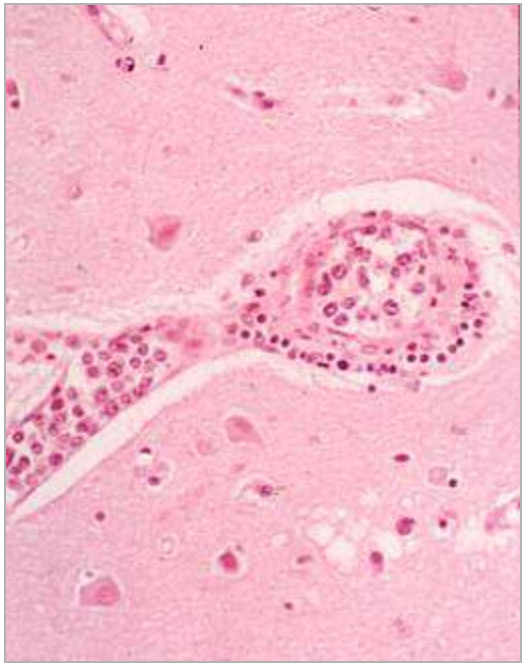
Heterogeneity in DLBCL
Clinico-Patological Entities

Primary Mediastinal

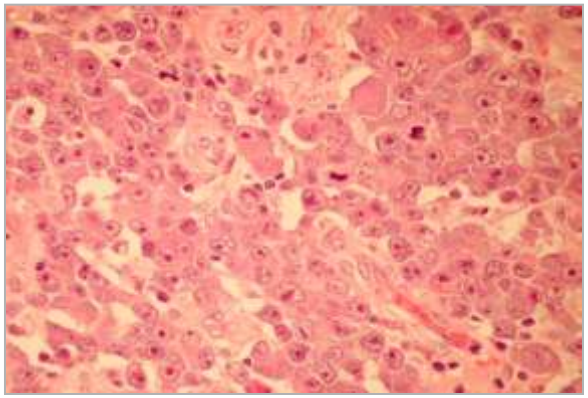


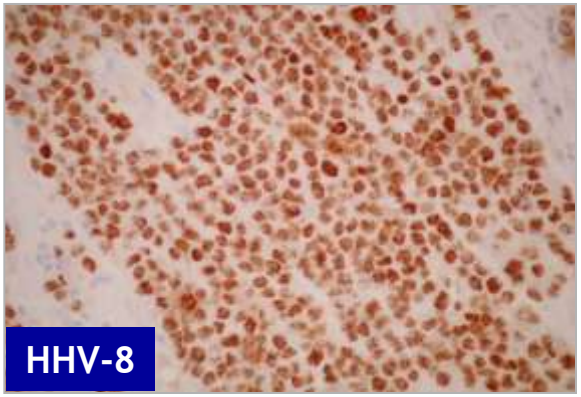


Intravascular

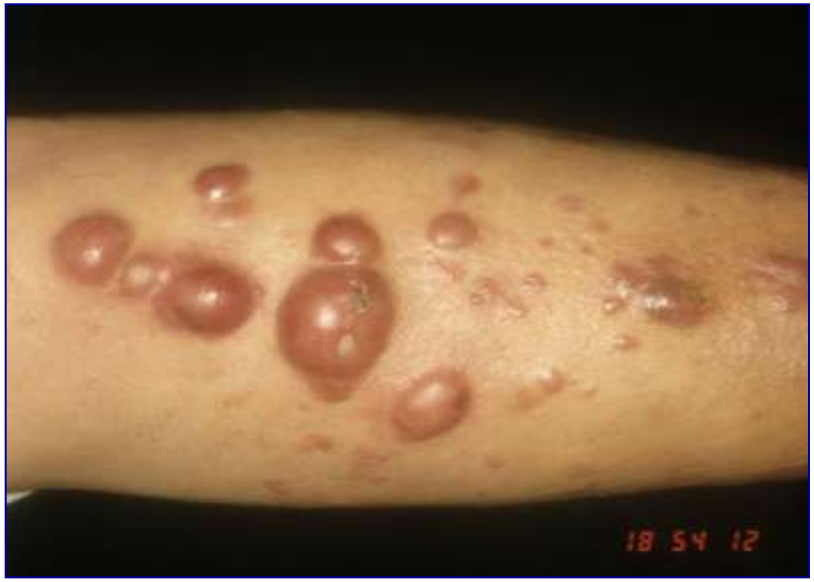


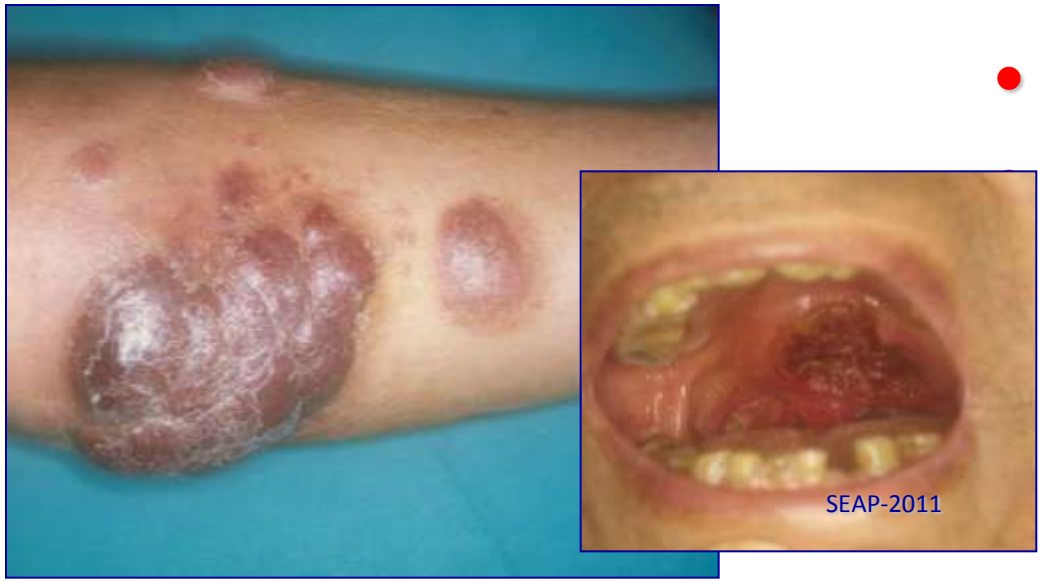
Primary Effusion





Primary Cutaneous Large B-cell Lymphomas
DLBCL Leg Type



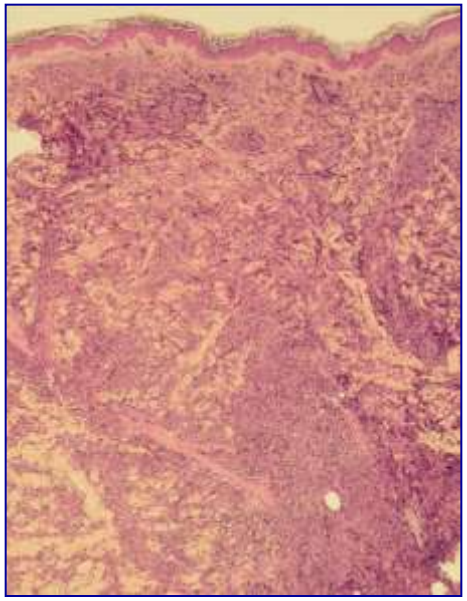


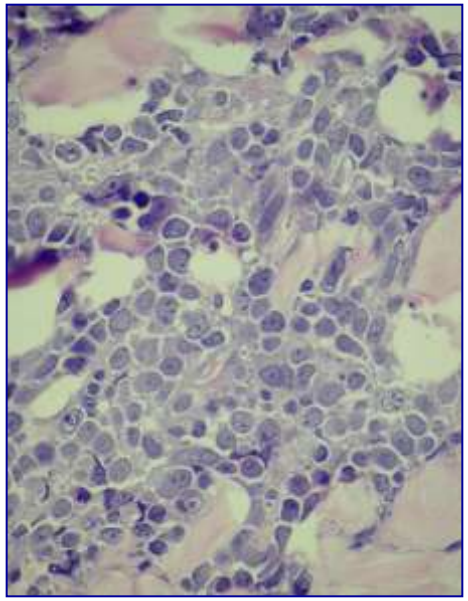
- Elderly females
- Rapidly growing tumors in the legs
- Diseminate to extracutaneous sites
- 5-year survival 55%

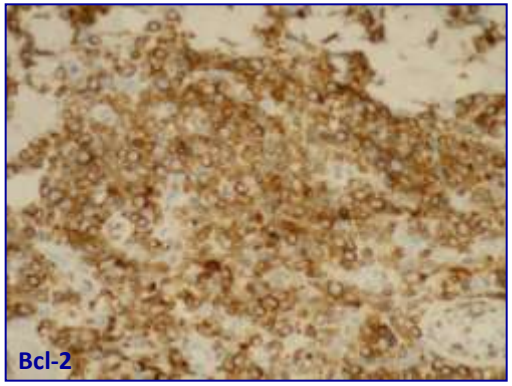
Poor prognosis

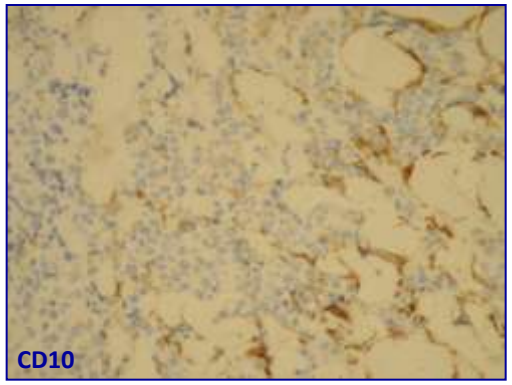
- Multiple skin lesions

Primary Cutaneous Large B-cell Lymphomas
DLBCL Leg Type



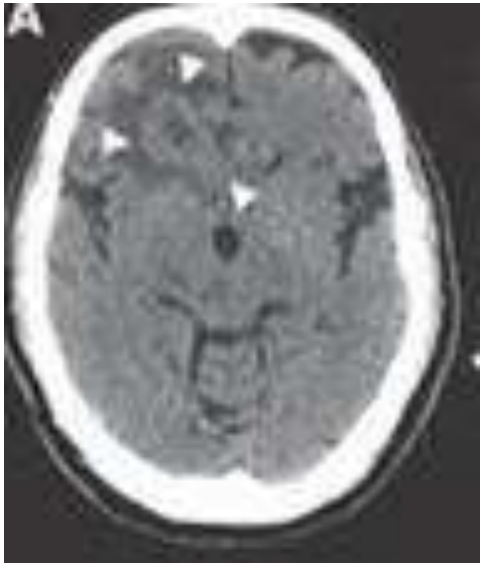




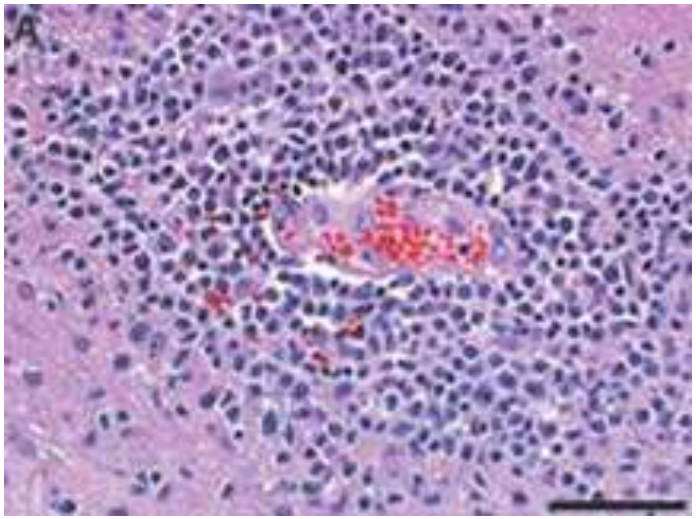


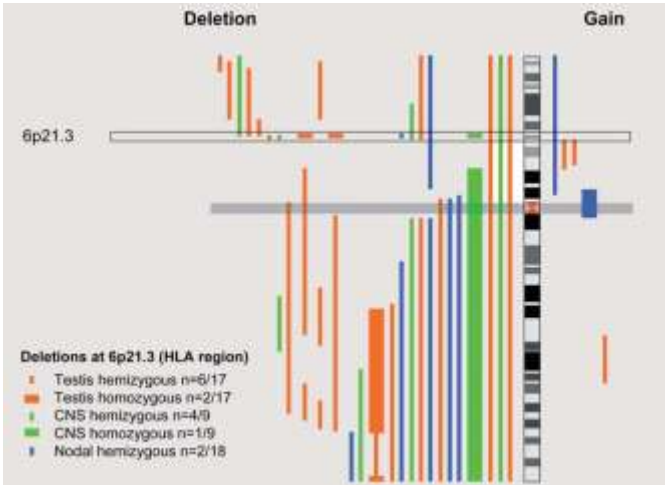
- Diffuse growth pattern
- Monotonous centroblasts or immunoblasts
- Absence of reactive lymphocytes
- Bcl-2 +, MUM1+, CD10-
- Activated B-cell expression profile

DLBCL Central Nervous System



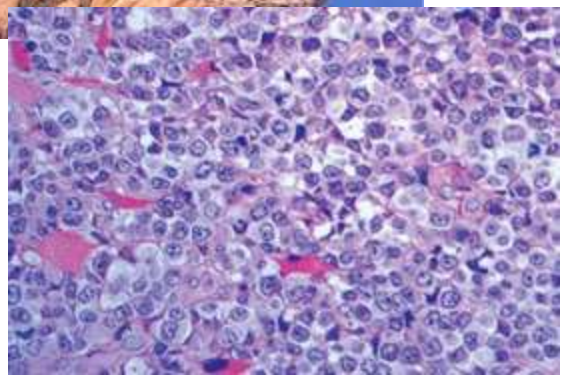
- Immunocompetent host
  - 2-3% of all NHL
  - > 60 yr
  - History of autoimmune disorders neurological or systemic
  - EBV negative
  - Deletions HLA Class I and II, (6p)
  - VH4-34





Hochberg FM et al. Nat Clin Pract Neurol 2007 3: 24–35
Kluin Ph et al WHO 2008

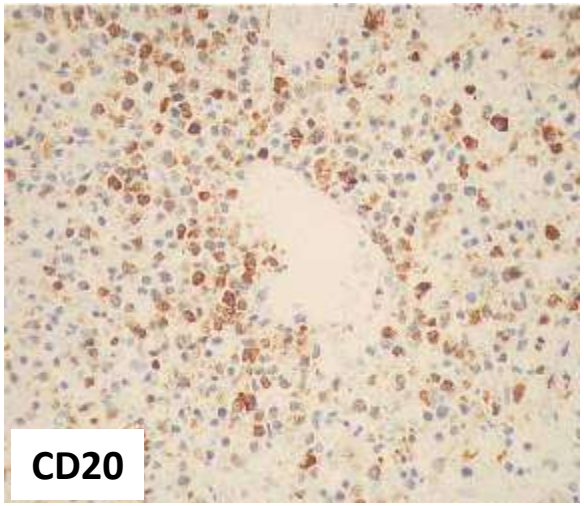
DLBCL Associated with Chronic Inflammation

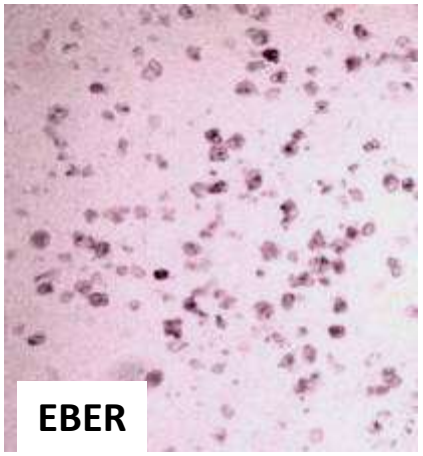


- Pyothorax and other chronic inflammation (> 20 years)
- Eastern countries
- Immunocompetent patients
- Large cell morphology
- CD20+ (-), CD138+
- EBV+ latency III
- HHV8 negative
- 5 yr survival 22%

Aozosa J Clin Exp Hematopatol 2006; 46:5-10
Nakatsuka S J Clin Oncol. 2002;20:4255-60.

Lymphomatoid Granulomatosis





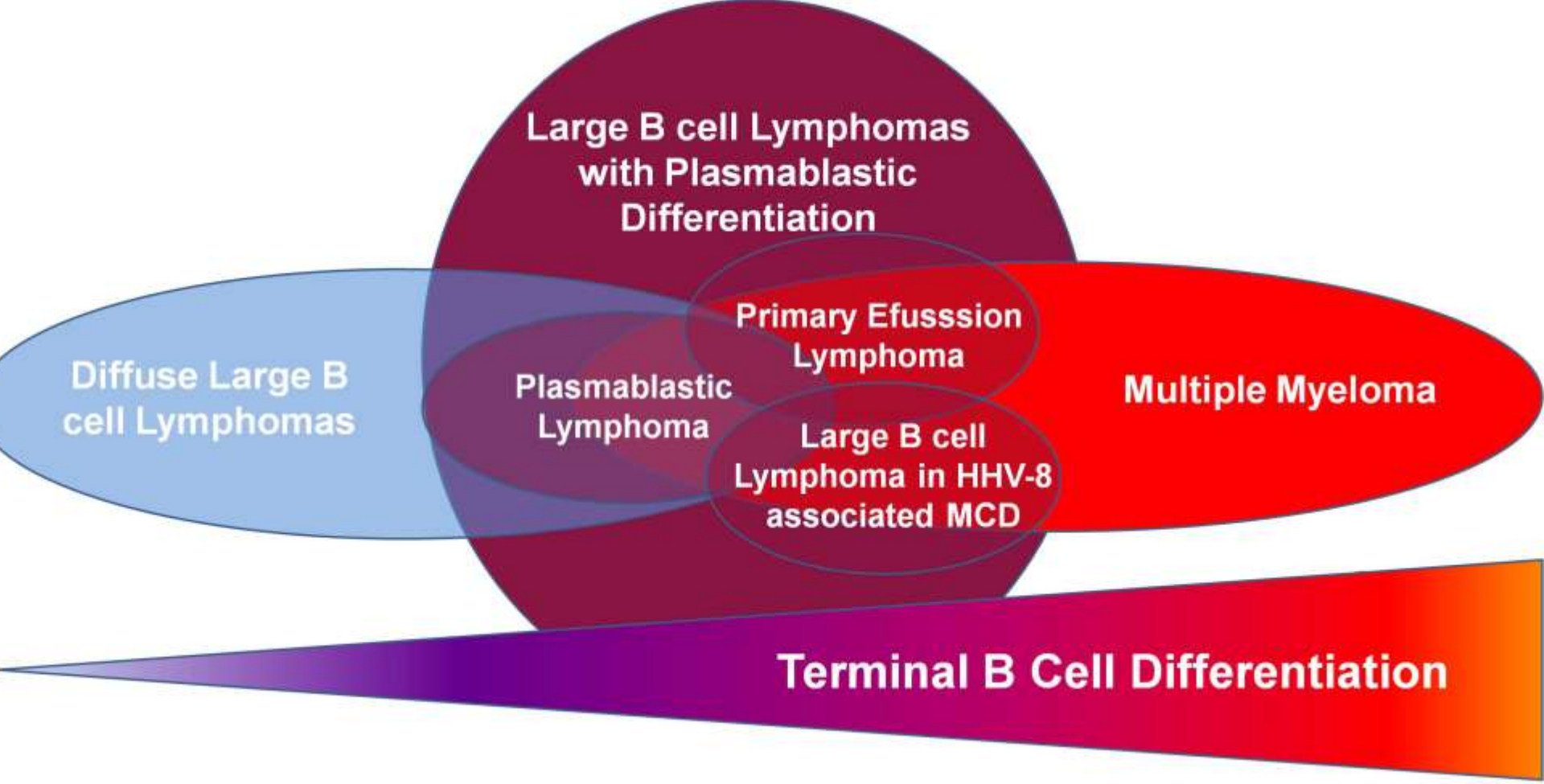
- Lung and other EN sites
- Immunodeficiency states (AIDS, Post-transplant, Wiskott-Aldrich, cytotoxic T-cell function)
- Clinical evolution may be variable from spontaneous regression to aggressive behavior

- Angiocentric and destructive lesions
- Variable number of large B-cells (grades)
- EBV + (latency 2-3
- Abundant reactive T-cells

Location in Lymphoma Classification

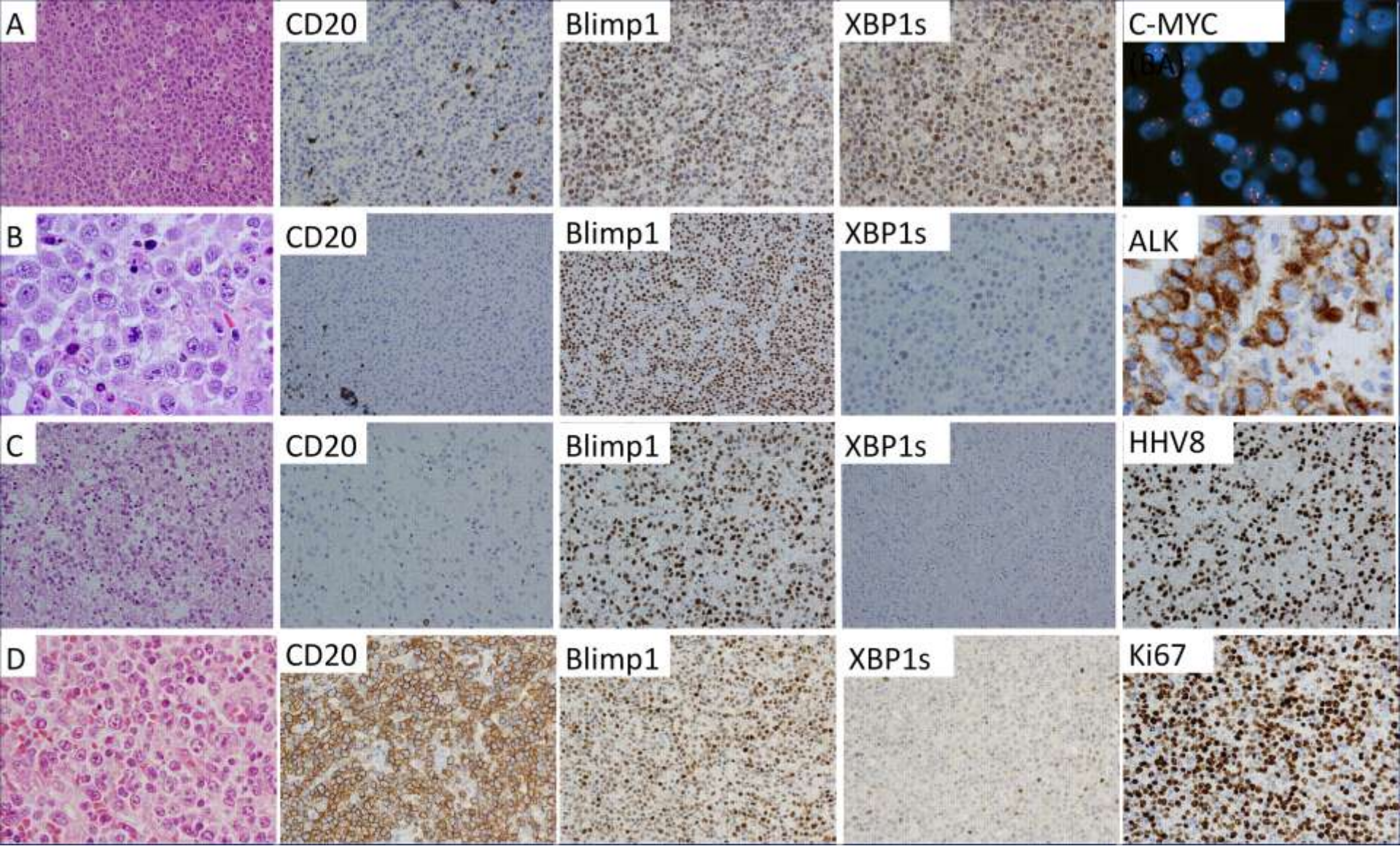
- MALT Lymphomas
- Primary mediastinal large B-cell lymphoma
- Primary cutaneous large B-cell lymphoma
- DLBCL of Immnunoprivileged sites (SNC, testes)
- Follicular lymphoma
  - Children
  - Extranodal sites
  - Duodenum (IgA)
- Skin T-cell lymphomas

- Etio-Pathogenic mechanism
- Cell of origin
- Site related immunological function
- Tumor- host Interaction



Large B Cell Lymphomas with Plasmablastic Differentiation.

Plasmablastic Lymphoma.
ALK-positive large B-cell lymphoma.
Primary Efussion Lymphoma PEL (cavitary or extracavitary).
Large B cell Lymphoma arising in HHV-8 associated Multicentric Castleman Disease.
Diffuse Large B cell Lymphomas with partial plasmablastic phenotype/DLBCL with immunoblastic differentiation.



Large B Cell Lymphomas with plasmablastic differentiation

A.Plasmablastic Lymphoma.

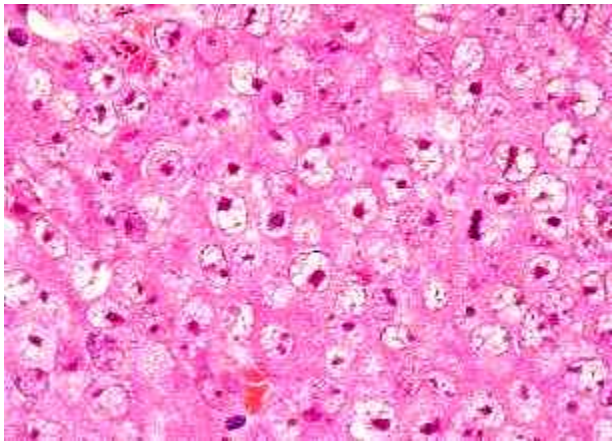
B. ALK positive large B cell lymphoma

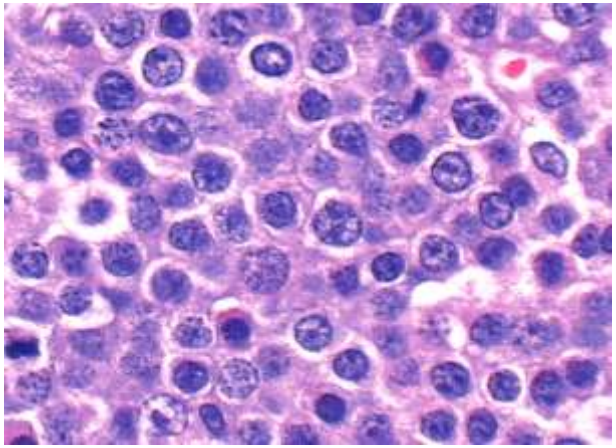
C. Primary Efussion Lymphoma

D. DLBCL with partial plasmablastic phenotype/

SEAP-2011

Plasmablastic Lymphoma

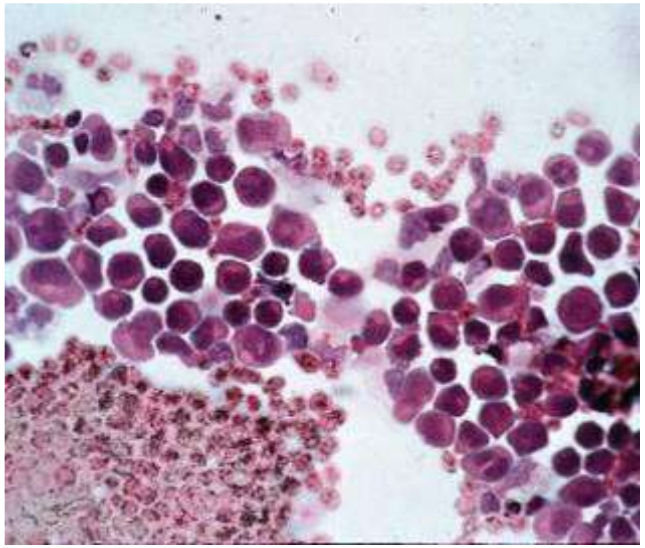




- **Clinical characteristics**
  - **Immunodeficiency: HIV, post-transplant, therapy, elderly**
  - **Frequent extranodal: Oral cavity, Gastrointestinal**
  - **Aggressive clinical course (< 24m)**
- **Phenotype**
  - **B-cell antigens negative**
  - **Plasma cell antigens: XBP1+, BLIMP1+, CD38+, CD138+**
  - **CD 30 (-/+)**
- **Molecular Alterations**
  - EBV + , Latency I (70%)

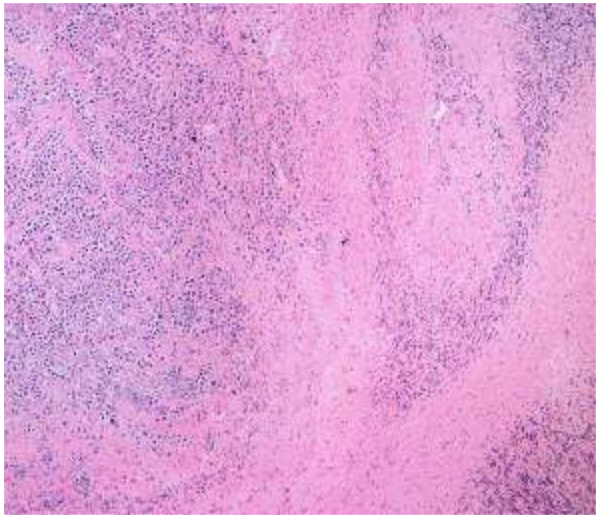
Colomo et al Am J Surg Pathol 2005
Montes et al, Haematologica. 2010

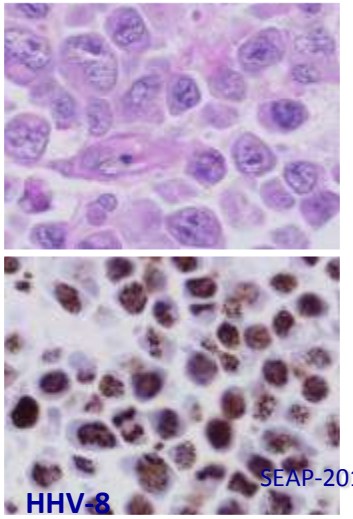
Primary Effusion Lymphoma



Clinical presentation

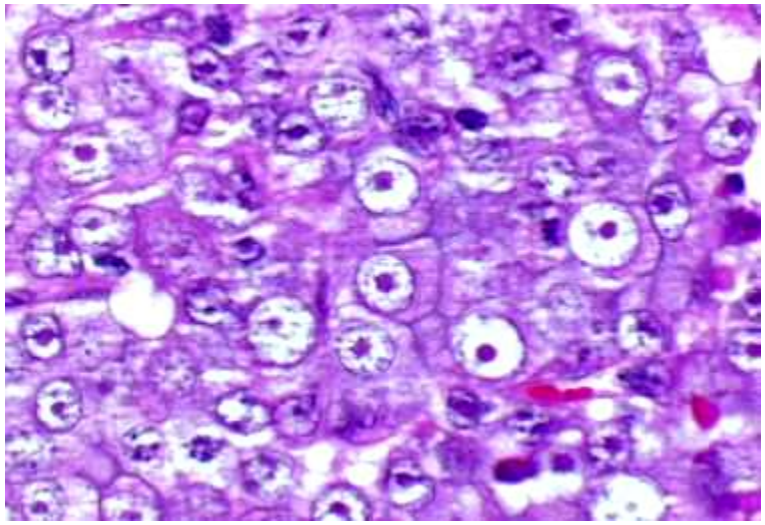
- HIV+ patients, Occasional HIV -
- Cavity Effusion
- Solid tumors: Gastrointestinal
- Rapid clinical course, median survival 5 months

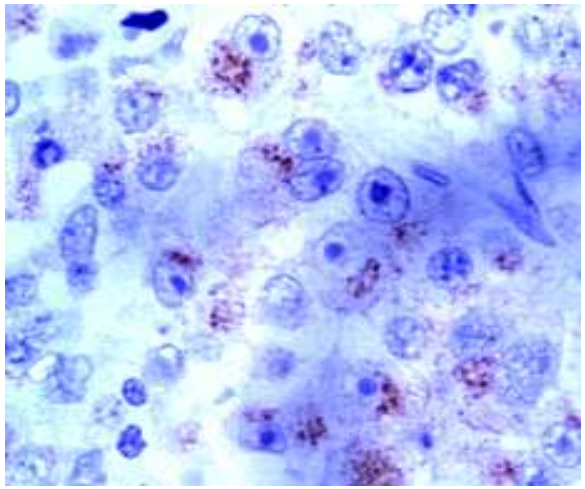




- CD30, CD38, CD138, EMA +
- Mature B-cell markers -
- HHV-8 +, EBV +
- Ig -/+,
- Occasional biphenotypic and bigenotypic (B & T)

DLBCL, ALK +





- **Clinical characteristics**
  - Male predominance, Mean age 51y (15-67)
  - Frequent extranodal involvement (skin, bone, brain)
  - Aggressive clinical course (9-33 months)
- **Phenotype**
  - B-cell antigens (CD20 - , CD79a) negative
  - Plasma cell antigens +: EMA, CD38, CD138
  - IgA (cytoplasmic and seric)
  - CD30 -, CD57+
- **Molecular Alterations**
  - ALK Translocation t(2;17)

Delsol G et al Blood 1997; 89:1483-1490

Burkitt Lymphoma

- Clinically, pathologically and Molecularly highly **Homogeneous** disease

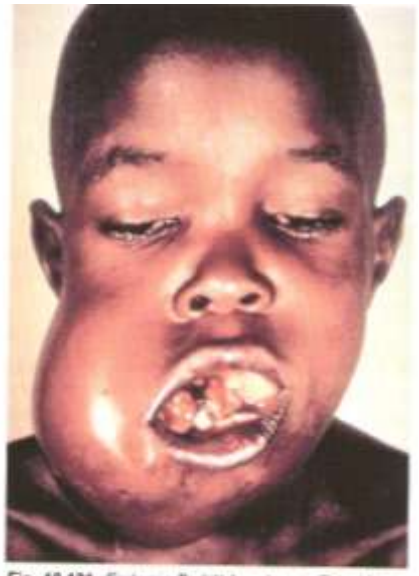


Fig. 10.121 Endemic Burkitt lymphoma. This African patient presented with a large jaw tumour.

Fig. 10.122 Sporadic Burkitt lymphoma with bilateral ovarian tumours.

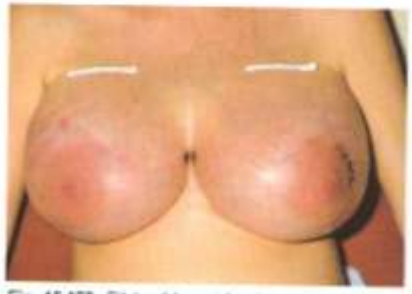
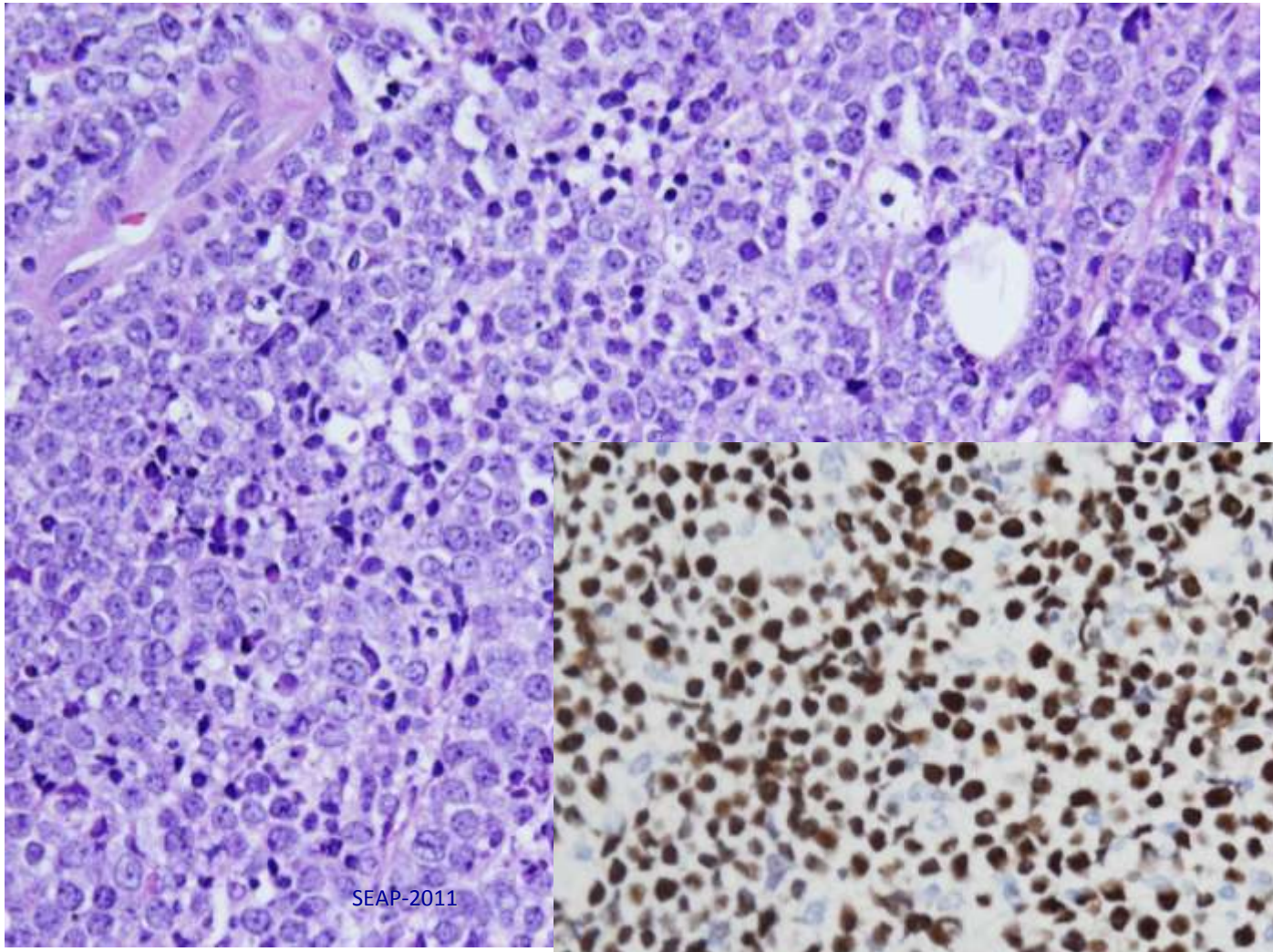
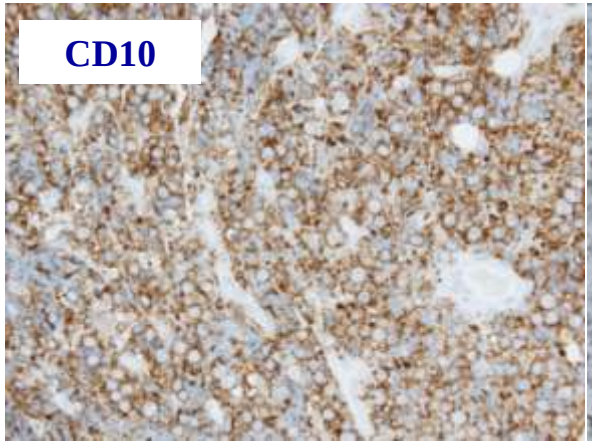
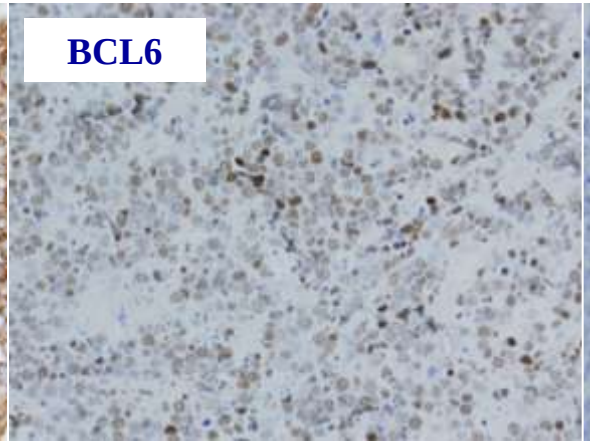


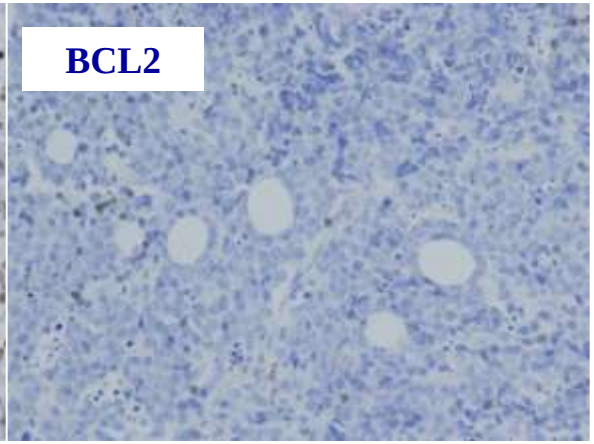
Fig. 10.123 Bilateral breast involvement may be the presenting manifestation during pregancy, and puberty. BL cells have prolactin receptors.

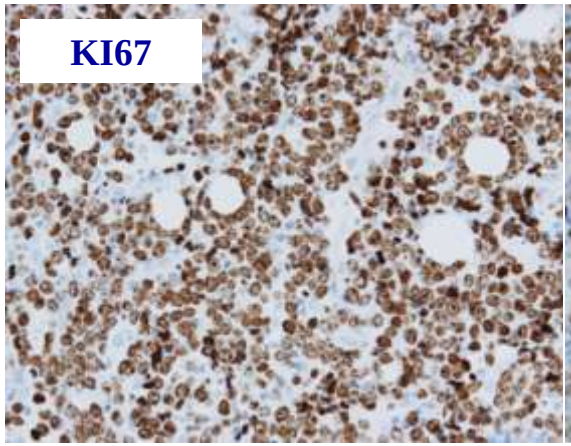


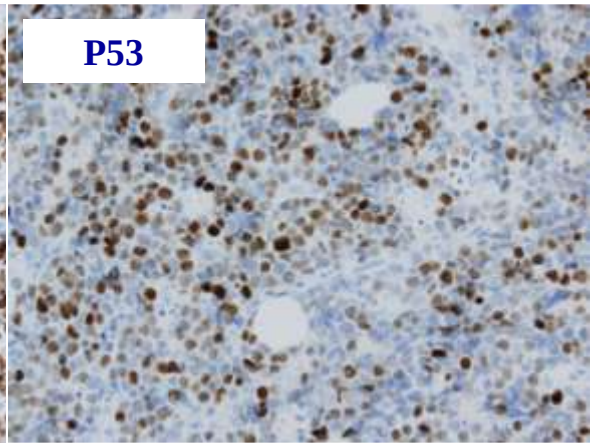
SEAP-2011

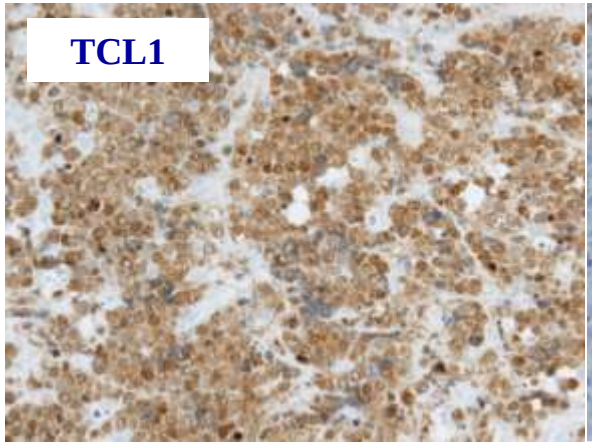

CD10

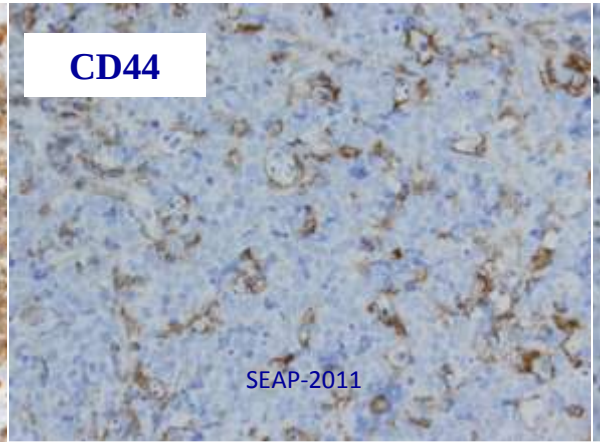

BCL6

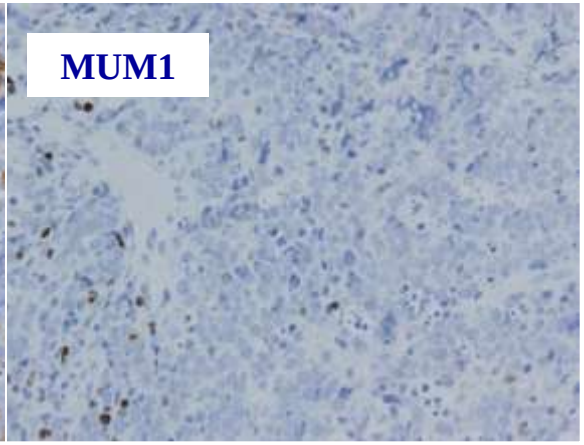

BCL2

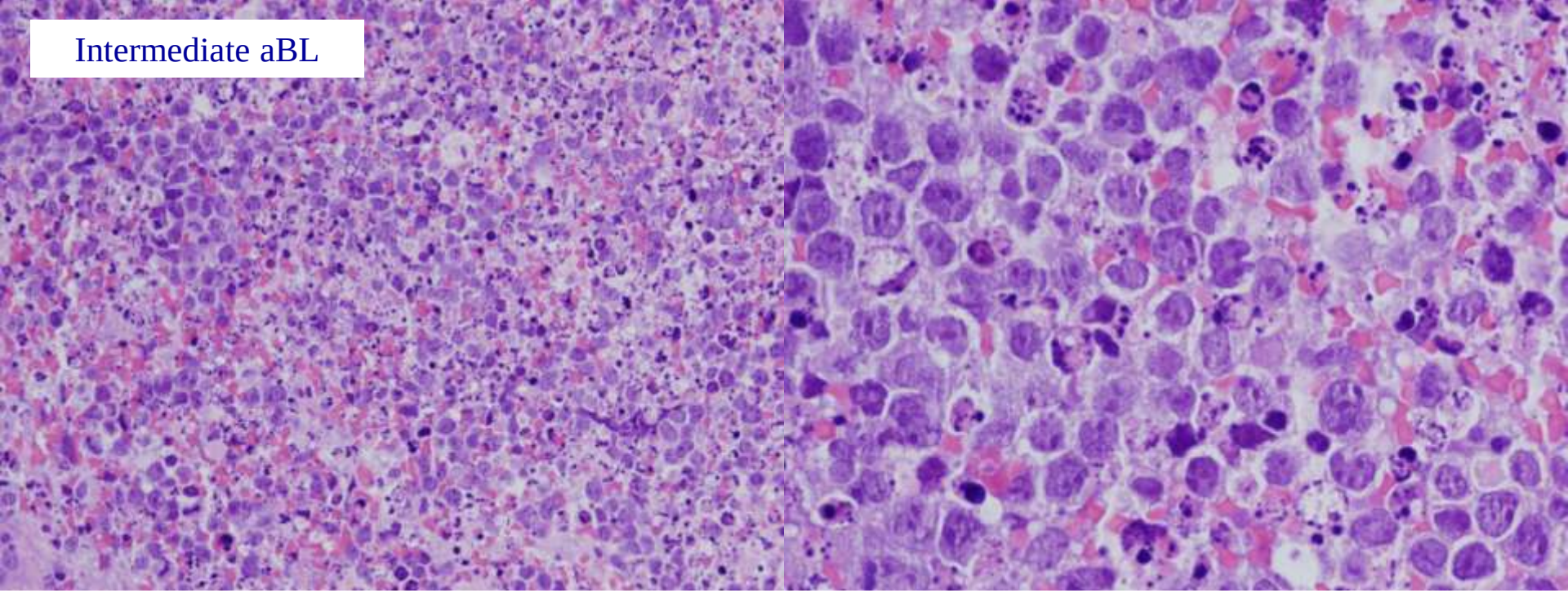

KI67

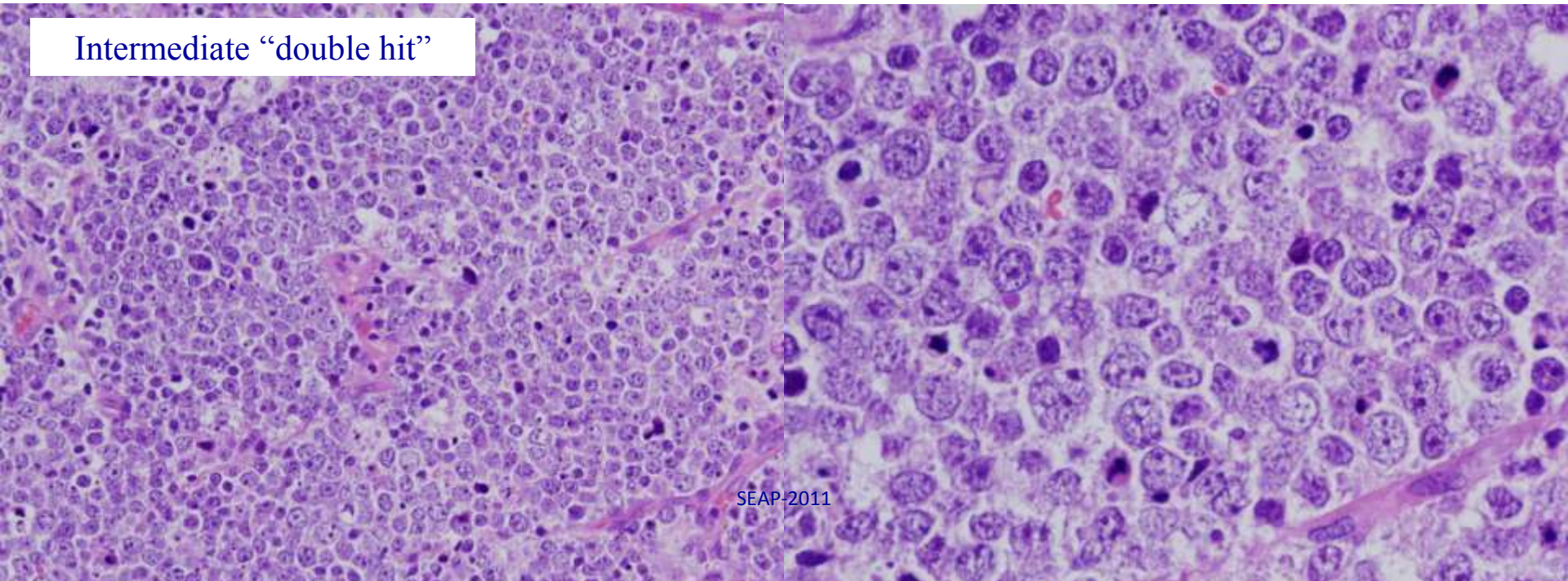

P53


TCL1

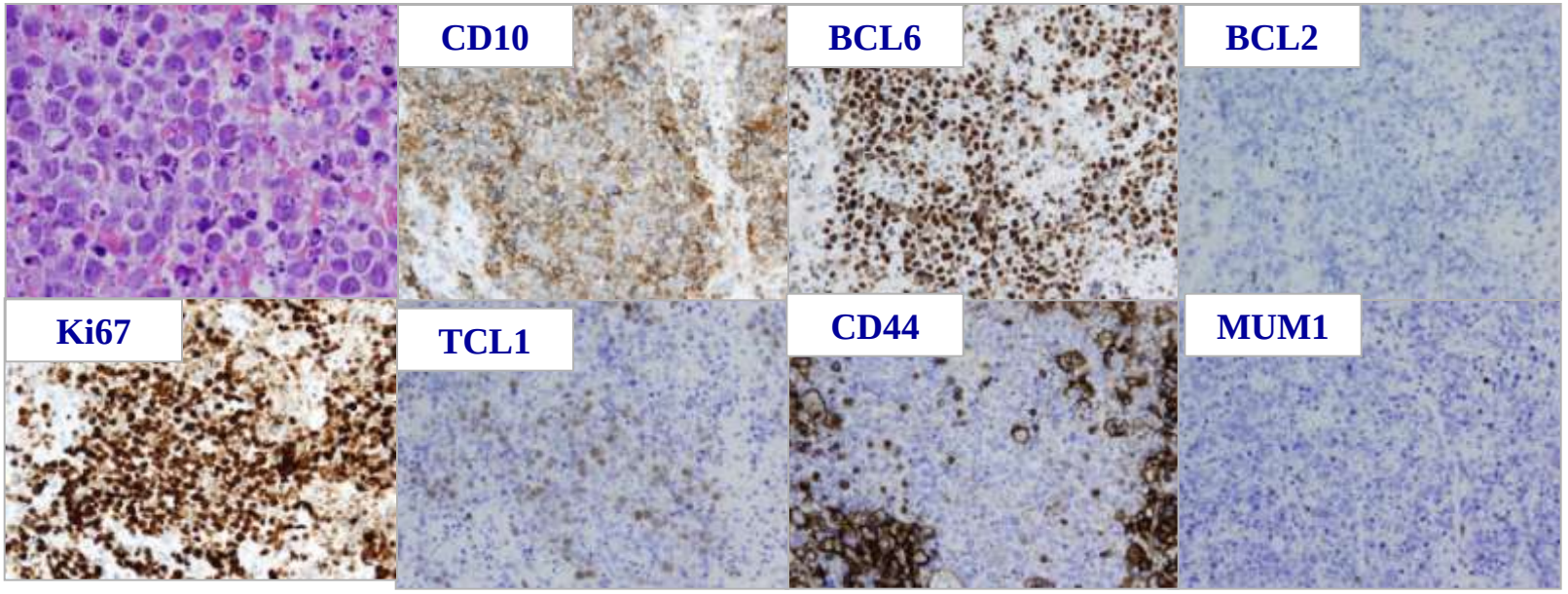

CD44


MUM1

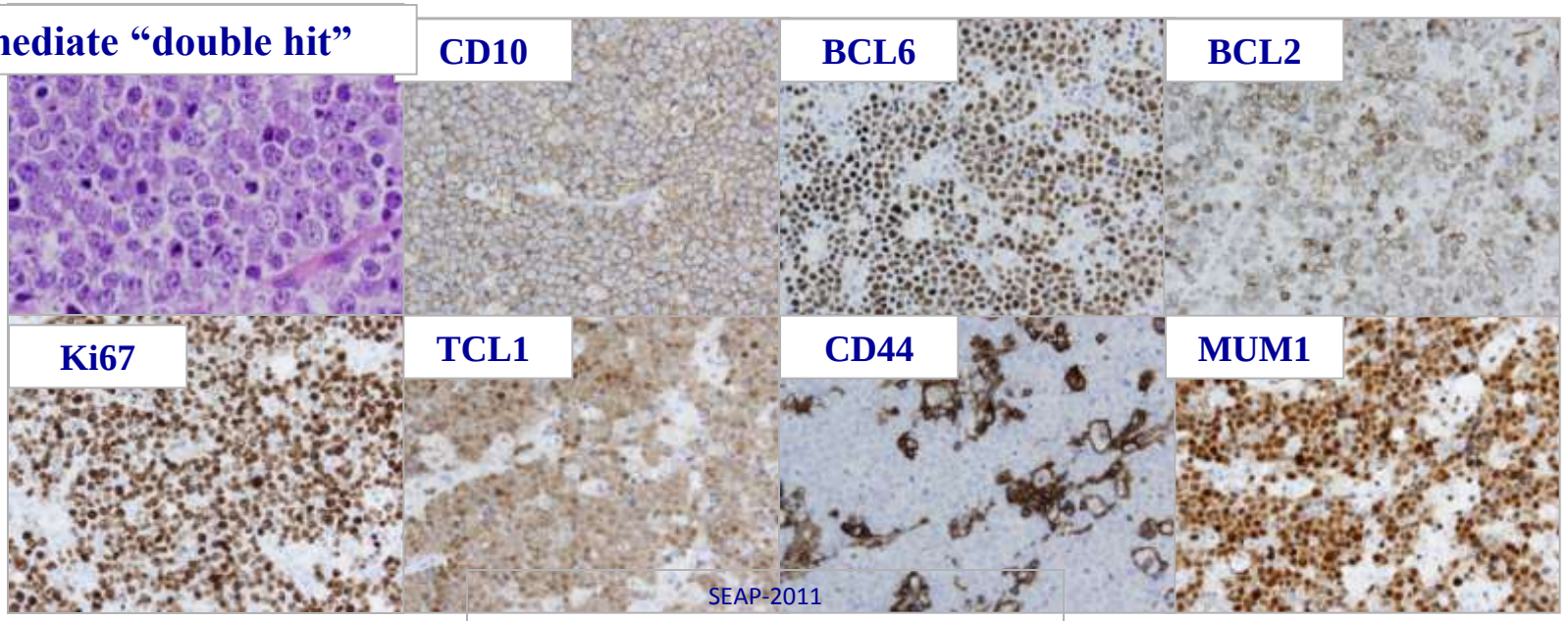

Intermediate aBL


Intermediate “double hit”
SEAP-2011

Intermediate aBL



Intermediate “double hit”



ORIGINAL ARTICLE

Molecular Diagnosis of Burkitt's Lymphoma

Sandeep S. Dave, M.D., Kai Fu, M.D., Ph.D., George W. Wright, Ph.D., Lloyd T. Lam, Ph.D., Philip Kluin, M.D., Evert-Jan Boerma, B.S., Timothy C. Greiner, M.D., Dennis D. Weisenburger, M.D., Andreas Rosenwald, M.D., German Ott, M.D., Hans-Konrad Müller-Hermelink, M.D., Randy D. Gascoyne, M.D., Jan Delabie, M.D., Lisa M. Rimsza, M.D., Rita M. Braziel, M.D., Thomas M. Grogan, M.D., Elias Campo, M.D., Elaine S. Jaffe, M.D., Bhavana J. Dave, Ph.D., Warren Sanger, Ph.D., Martin Bast, B.S., Julie M. Vose, M.D., James O. Armitage, M.D., Joseph M. Connors, M.D., Erlend B. Smeland, M.D., Ph.D., Stein Kvaloy, M.D., Ph.D., Harald Holte, M.D., Ph.D., Richard I. Fisher, M.D., Thomas P. Miller, M.D., Emilio Montserrat, M.D., Wyndham H. Wilson, M.D., Ph.D., Manisha Bahl, B.S., Hong Zhao, M.S., Liming Yang, Ph.D., John Powell, M.S., Richard Simon, D.Sc., Wing C. Chan, M.D., and Louis M. Staudt, M.D., Ph.D., for the Lymphoma/Leukemia Molecular Profiling Project

ABSTRACT

BACKGROUND

The distinction between Burkitt's lymphoma and diffuse large-B-cell lymphoma is crucial because these two types of lymphoma require different treatments. We examined whether gene-expression profiling could reliably distinguish Burkitt's lymphoma from diffuse large-B-cell lymphoma.

METHODS

Tumor-biopsy specimens from 303 patients with aggressive lymphomas were profiled for gene expression and were also classified according to morphology, immunohistochemistry, and detection of the t(8;14) *c-myc* translocation.

RESULTS

A classifier based on gene expression correctly identified all 25 pathologically verified cases of classic Burkitt's lymphoma. Burkitt's lymphoma was readily distinguished from diffuse large-B-cell lymphoma by the high level of expression of *c-myc* target genes, the expression of a subgroup of germinal-center B-cell genes, and the low level of expression of major-histocompatibility-complex class I genes and nuclear factor-κB target genes. Eight specimens with a pathological diagnosis of diffuse large-B-cell lymphoma had the typical gene-expression profile of Burkitt's lymphoma, suggesting they represent cases of Burkitt's lymphoma that are difficult to diagnose by current methods. Among 28 of the patients with a molecular diagnosis of Burkitt's lymphoma, the overall survival was superior among those who had received intensive chemotherapy regimens instead of lower-dose regimens.

CONCLUSIONS

Gene-expression profiling is an accurate, quantitative method for distinguishing Burkitt's lymphoma from diffuse large-B-cell lymphoma.

From the National Cancer Institute (S.S.D., G.W.W., L.T.L., E.S.J., W.H.W., M.B., H.Z., R.S., L.M.S.) and the Center for Information Technology (L.Y., J.P.), National Institutes of Health, Bethesda, Md.; University of Nebraska Medical Center, Omaha (K.F., T.C.G., D.D.W., B.J.D., W.S., M.B., J.M.V., J.O.A., W.C.C.); Groningen University Medical Center, University of Groningen, Groningen, the Netherlands (P.K., E.-J.B.); University of Würzburg, Würzburg, Germany (A.R., G.O., H.-K.M.-H.); British Columbia Cancer Agency, Vancouver, B.C., Canada (R.D.G., J.M.C.); Norwegian Radium Hospital, Norway Hospital Clinic, Oslo (J.D., E.B.S., S.K., H.H.); Southwest Oncology Group (L.M.R., R.M.B., T.M.G., R.I.F., T.P.M.); University of Arizona Cancer Center, Tucson (L.M.R., T.M.G., T.P.M.); Oregon Health and Science University, Portland (R.M.B.); University of Barcelona, Barcelona (E.C., E.M.); University of Oslo, Oslo (E.B.S.); and James P. Wilmot Cancer Center, University of Rochester School of Medicine, Rochester, N.Y. (R.I.F.). Address reprint requests to Dr. Staudt at the Metabolism Branch, CCR, NCI, Bldg. 10, Rm. 4N114, NIH, 9000 Rockville Pike, Bethesda, MD 20892, or at lstaudt@mail.nih.gov.

N Engl J Med 2006;354:2431-42.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 8, 2006 VOL. 354 NO. 23

A Biologic Definition of Burkitt's Lymphoma from Transcriptional and Genomic Profiling

Michael Hummel, Ph.D., Stefan Bentink, M.S., Hilmar Berger, M.D., Wolfram Klapper, M.D., Swen Wessendorf, M.D., Thomas F.E. Barth, M.D., Heinz-Wolfram Bernd, M.D., Sergio B. Cogliatti, M.D., Judith Dierlamm, M.D., Ph.D., Alfred C. Feller, M.D., Martin-Leo Hansmann, M.D., Eugenia Haralambieva, M.D., Lana Harder, M.D., Dirk Hasenclever, Ph.D., Michael Kühn, Dido Lenze, Ph.D., Peter Lichter, Ph.D., Jose Ignacio Martin-Subero, Ph.D., Peter Möller, M.D., Hans-Konrad Müller-Hermelink, M.D., German Ott, M.D., Reza M. Parwaresch, M.D., Christiane Pott, M.D., Andreas Rosenwald, M.D., Maciej Rosolowski, Ph.D., Carsten Schwaenen, M.D., Benjamin Stürzenhofecker, Ph.D., Monika Szczepanowski, Ph.D., Heiko Trautmann, M.S., Hans-Heinrich Wacker, M.D., Rainer Spang, Ph.D., Markus Loeffler, M.D., Ph.D., Lorenz Trümper, M.D., Harald Stein, M.D., and Reiner Siebert, M.D., for the Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe*

ABSTRACT

BACKGROUND

The distinction between Burkitt's lymphoma and diffuse large-B-cell lymphoma is unclear. We used transcriptional and genomic profiling to define Burkitt's lymphoma more precisely and to distinguish subgroups in other types of mature aggressive B-cell lymphomas.

METHODS

We performed gene-expression profiling using Affymetrix U133A GeneChips with RNA from 220 mature aggressive B-cell lymphomas, including a core group of 8 Burkitt's lymphomas that met all World Health Organization (WHO) criteria. A molecular signature for Burkitt's lymphoma was generated, and chromosomal abnormalities were detected with interphase fluorescence in situ hybridization and array-based comparative genomic hybridization.

RESULTS

We used the molecular signature for Burkitt's lymphoma to identify 44 cases: 11 had the morphologic features of diffuse large-B-cell lymphomas, 4 were unclassifiable mature aggressive B-cell lymphomas, and 29 had a classic or atypical Burkitt's morphologic appearance. Also, five did not have a detectable *IG-myc* Burkitt's translocation, whereas the others contained an *IG-myc* fusion, mostly in simple karyotypes. Of the 176 lymphomas without the molecular signature for Burkitt's lymphoma, 155 were diffuse large-B-cell lymphomas. Of these 155 cases, 21 percent had a chromosomal breakpoint at the *myc* locus associated with complex chromosomal changes and an unfavorable clinical course.

CONCLUSIONS

Our molecular definition of Burkitt's lymphoma clarifies and extends the spectrum of the WHO criteria for Burkitt's lymphoma. In mature aggressive B-cell lymphomas without a gene signature for Burkitt's lymphoma, chromosomal breakpoints at the *myc* locus were associated with an adverse clinical outcome.

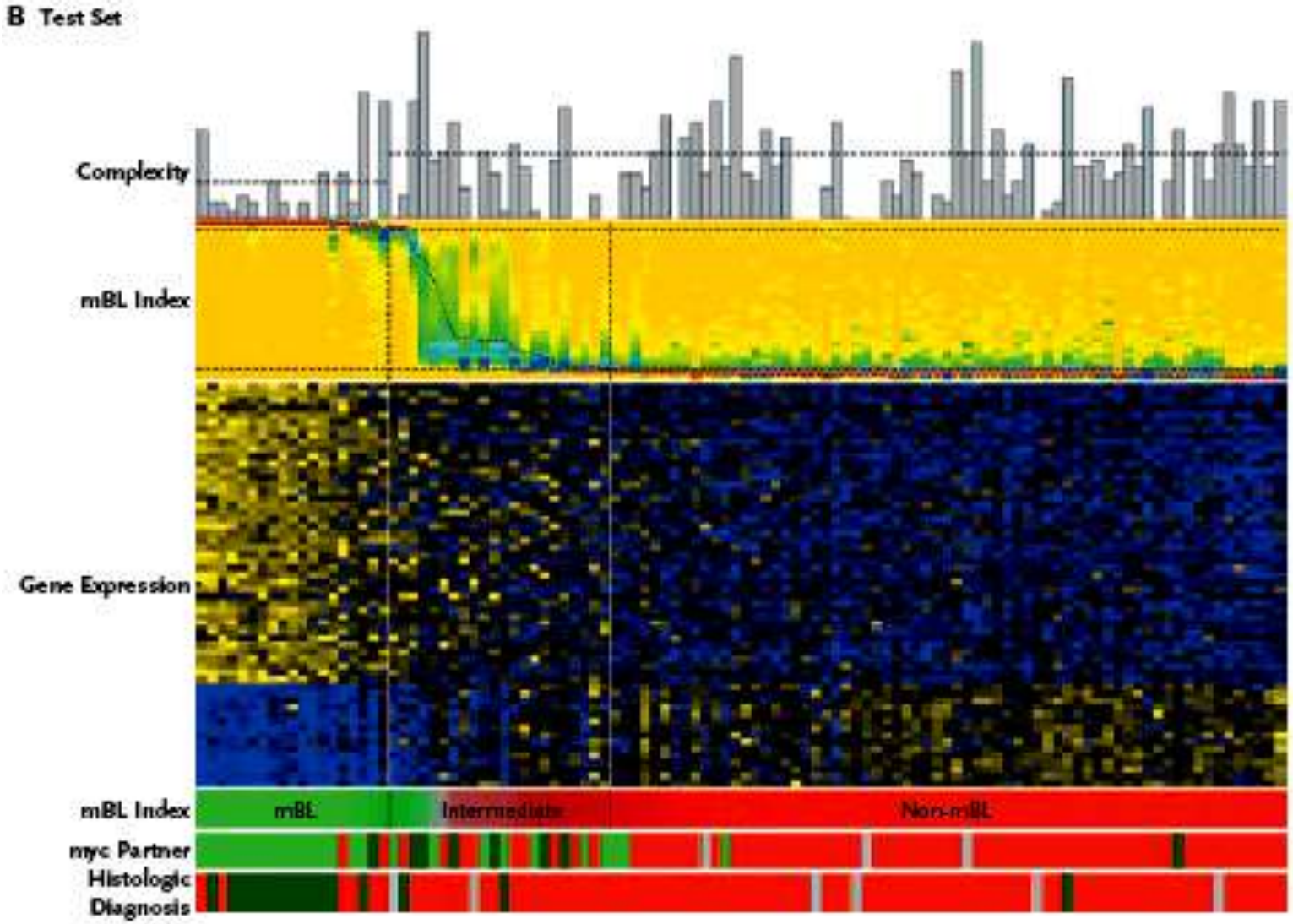
Address reprint requests to Dr. Stein at Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Institute of Pathology, Hindenburgdamm 30, D-12200 Berlin Germany, or at Harald.Stein@charite.de.

Mr. Bentink and Drs. Berger, Klapper, and Wessendorf contributed equally to this article.

*The authors' affiliations and the members of the Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe are listed in the Appendix.

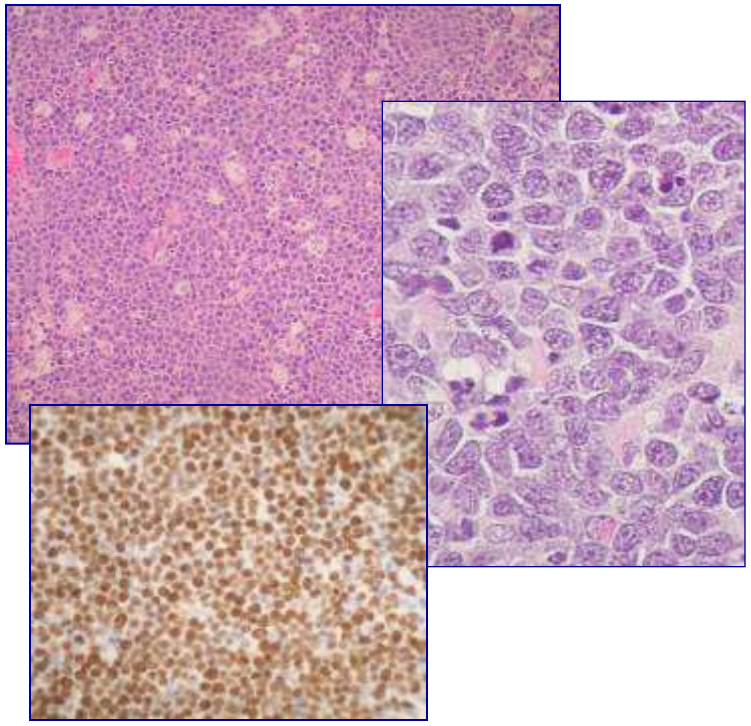
N Engl J Med 2006;354:2419-30.

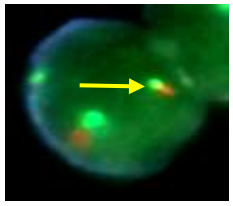
mRNA Expression and Genetic Profile in BL and DLBCL



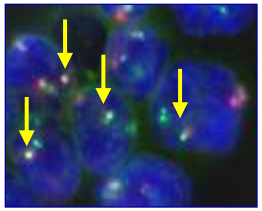
Hummel M et al N Engl J Med 2006

B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and BL





t(8;14)



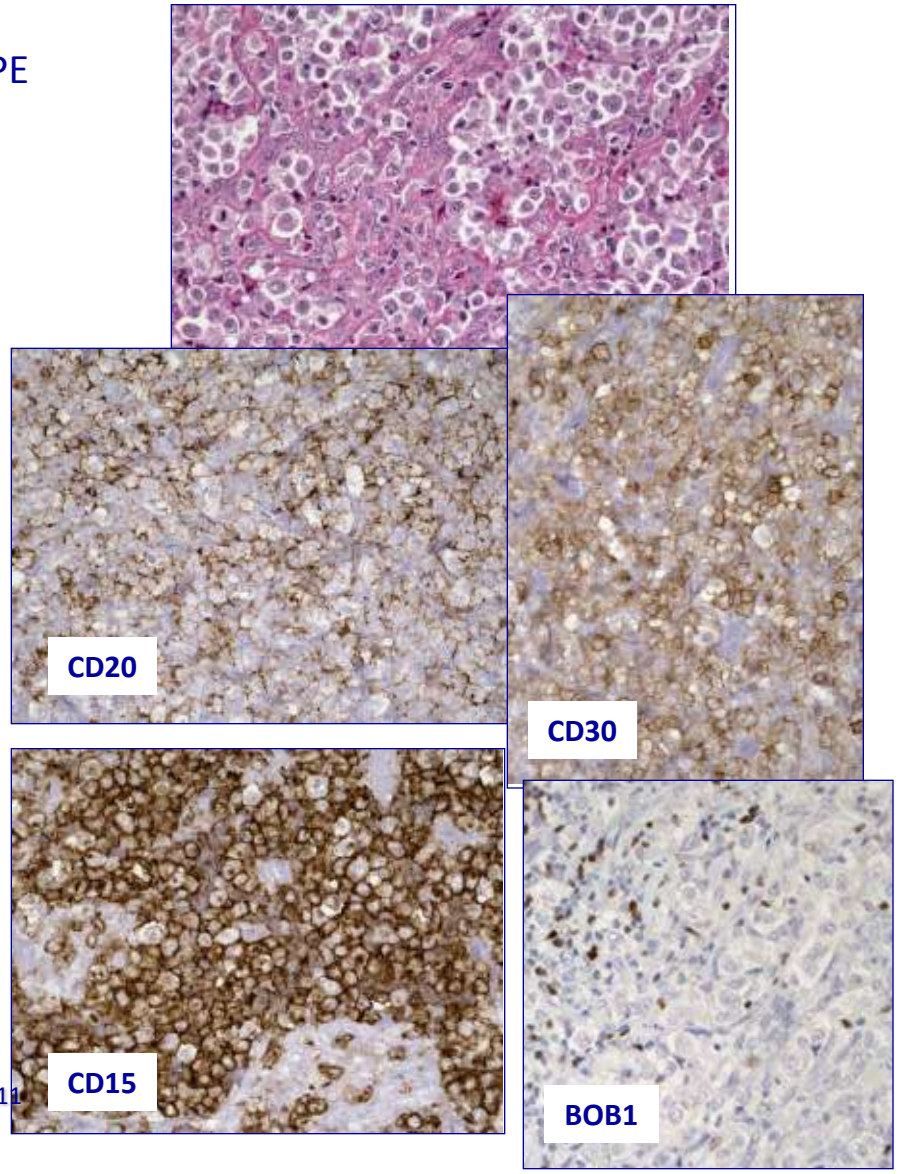
t(14;18)

- Burkitt lymphoma with high molecular complexity, usually associated with advanced age
- Double hit (c-myc + bcl2), including blastoid FL
- To be distinguished from DLBCL with c-myc translocations:
  - Extranodal
  - Plasmablastic

B-cell lymphoma with features intermediate between DLBCL and classical HL

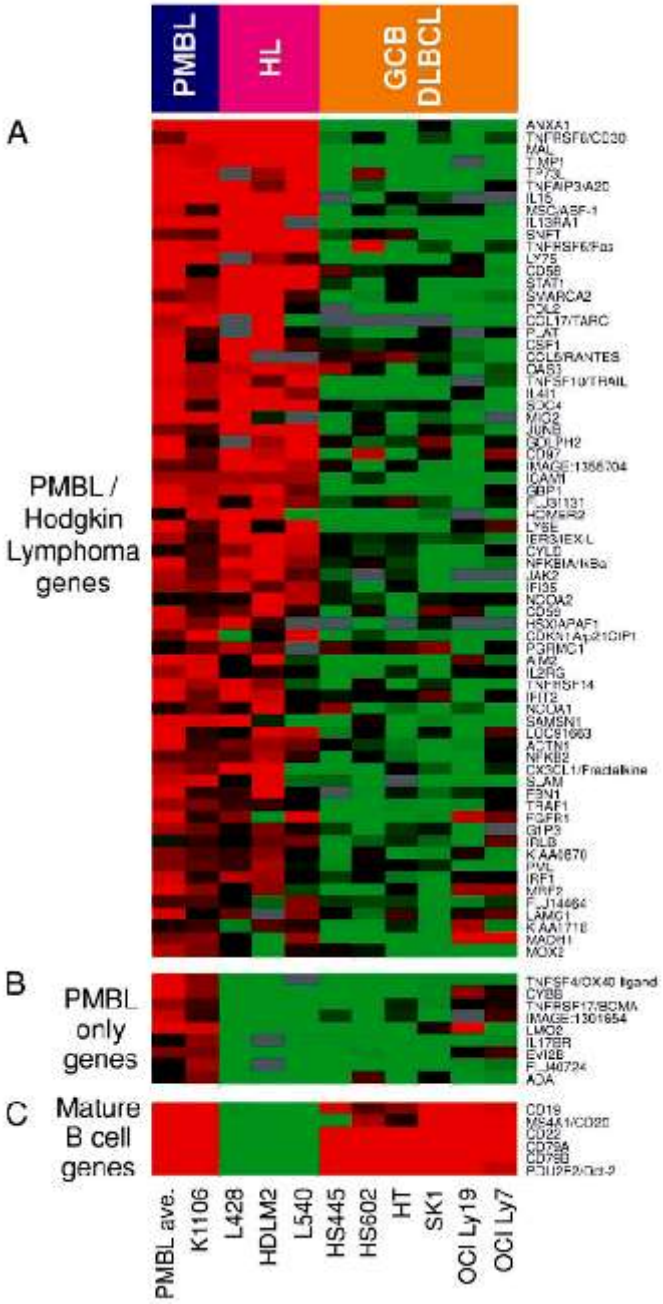
INTERMEDIATE MORPHOLOGY AND IMMUNOPHENOTYPE

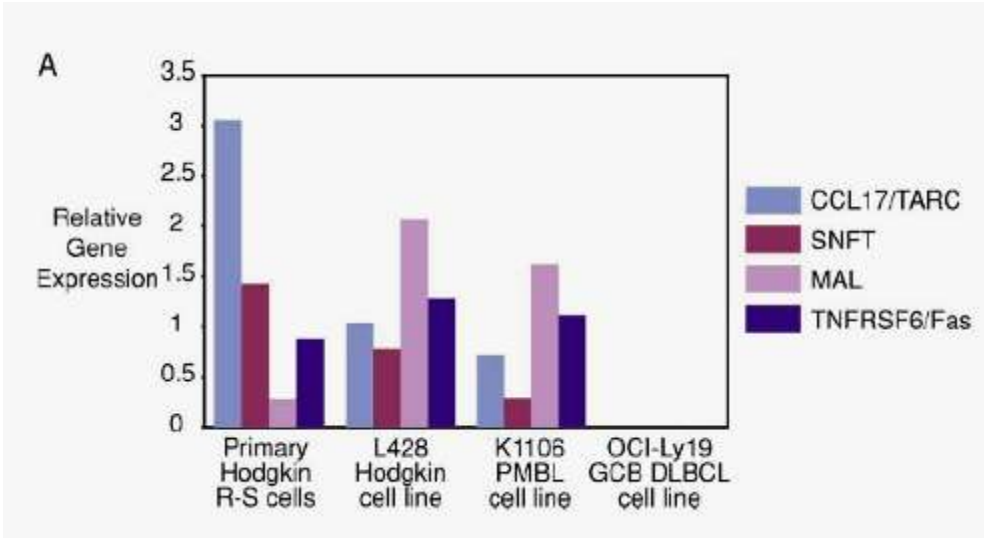
- Young men with mediastinal mass but also other locations
- Metachronus and composite cHL and DLBCL
- Confluent sheets of large and pleomorphic cells with fibrosis and inflammatory infiltrate
- Immunophenotype with transitional features between CHL and PMLBCL: B-cell transcriptional Program activation markers:
  - CD45 and CD20 +
  - CD30 and CD15 +
  - BOB1, Oct2 and PAX5 +
- More aggresive behaviour than cHL or PMBL

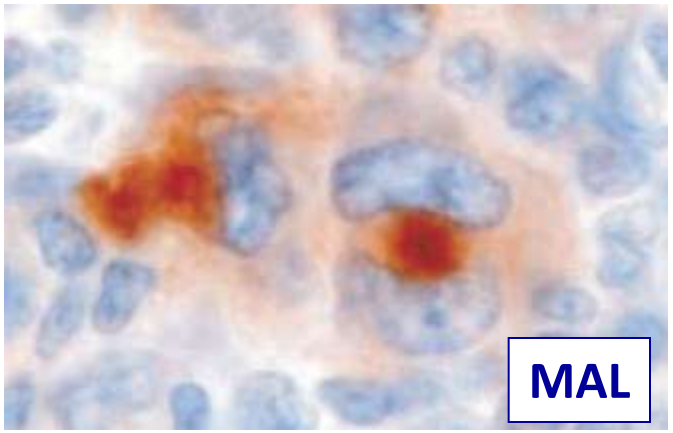


Am J Surg. Pathol. 2005;29:1411-21
Histopathology, 2005;41:107-111

PMBL and Hodgkin Lymphoma







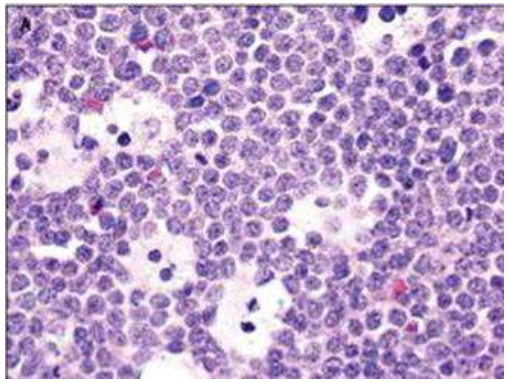
SEAP-2011

Rosenwald et al J Exp Med 2003

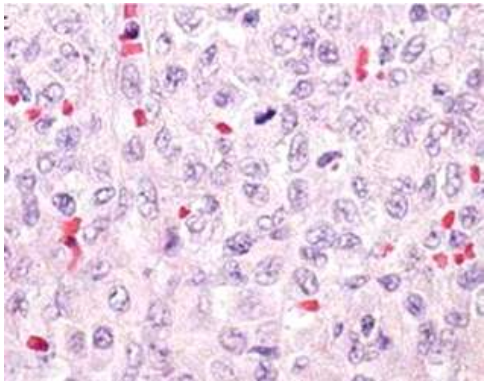
Plasticity and Dynamics of Lymphoid Populations

Are Lymphoma Entities Stable?

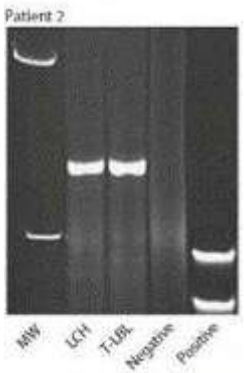
Transdifferentiation and Dedifferentiation in Lymphoid cells



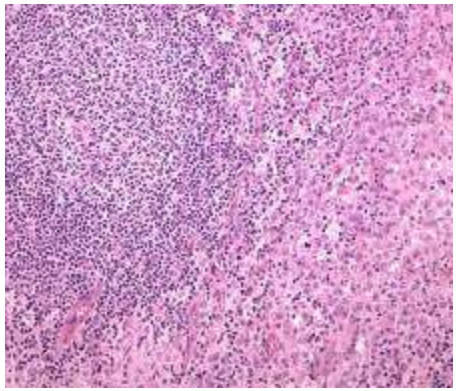
T-LBL



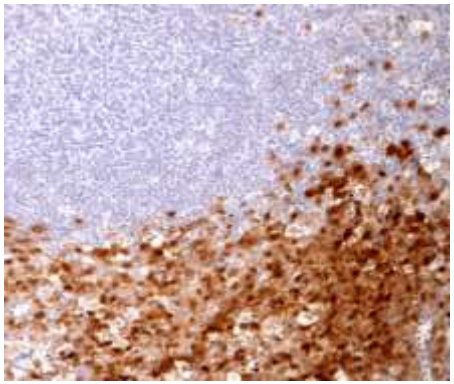
Langerhans Cell Hystiocytosis



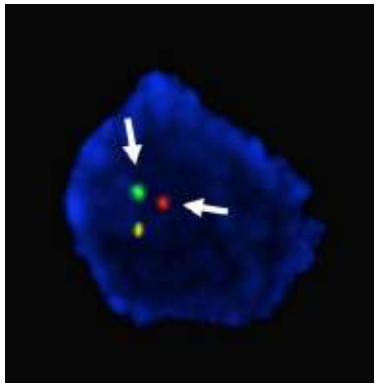
(Feldman et al, Lancet Oncol 2005; 6: 435)



FL & IDCT



S-100



t(14;18)

(Feldman et al, Blood 2008)

Challenges/opportunities

- Lymphoma classification includes
  - premalignant phases, not always requiring therapy
  - advanced stages, progressed forms of the diseases
  - borderline entities
- A western point of view
- For most common lymphoma types, we do not have targeted therapies yet
- Reference experts laboratories and clinical centers are required for proper diagnosis and treatment
- Clinical trials evaluating new drugs with pharmacodynamic endpoints are urgent

Lymphoma Group

S Montes-Moreno [1], N Martinez [1], A Saez [2], C Montalbán [3], MH Rodriguez [1], Sanchez-Espiridión B [1], Pisano D [1], Gomez G [1], Díaz Uriarte [1], García JF [1], L Sanchez [1], A Lopez [4], MC Ruiz-Marcellan [4], M Canales [5], P Mazorra [6], E. Conde [6], M Cruz [7], M Mollejo [7], MA Martinez [8], C Grande [8],GB Lemarbre[9], WM Rehrauer[9], M Waknitz[9], Young KH[9], MA Piris [1].

1 Lymphoma group, Spanish National Cancer Centre (CNIO), Madrid, Spain; 2 Red de Bancos de Tumores de Andalucía, Granada 3 Department of Oncology, Hospital Ramon y Cajal, Madrid, Spain; 4 Departments of Pathology and Oncology, Hospital Vall d´Hebron, Barcelona, Spain; 5 Department of Oncology, Hospital Universitario La Paz, Madrid, Spain; 6 Departments of Pathology and Oncology Hospital Universitario Marques de Valdecilla, Santander, Spain; 7 Departments of Pathology and Oncology, Hospital Virgen de la Luz, Toledo, Spain; 8 Department of Haematology, Hospital Universitario 12 de Octubre, Madrid, Spain; 9 Department of Pathology and Laboratory Medicine, Wisconsin University USA.


SEAP-2011