Avances en hematopatología

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Roche

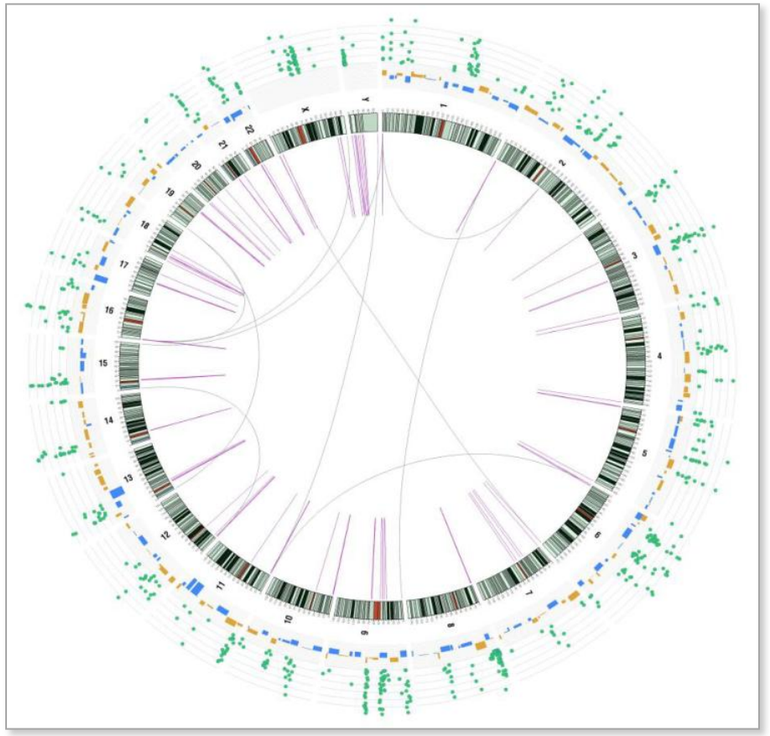
USCAP & AACR HIGHLIGHTS 2012

BIOMARCADORES EN ONCOLOGÍA

- **PRONÓSTICOS**
  - INESTABILIDAD DE MICROSATÉLITES EN CA. COLON
- **PREDICTIVOS**
  - KRAS EN CA COLON
  - BRAF EN MELANOMA
- **FARMACODINÁMICOS**
  - DESARROLLO DE FÁRMACOS

Sequencing studies, what is new?

- LPL: MYD-88 LPL
- HCL: B-RAF V6000 HCL
- CLL: NOTCH1, S3F



[1586] Phospho-ERK$^{Thr202/Tyr204}$ Is Overexpressed in Hairy Cell Leukemia and Is a Useful Diagnostic Marker in Bone Marrow Trephine Sections

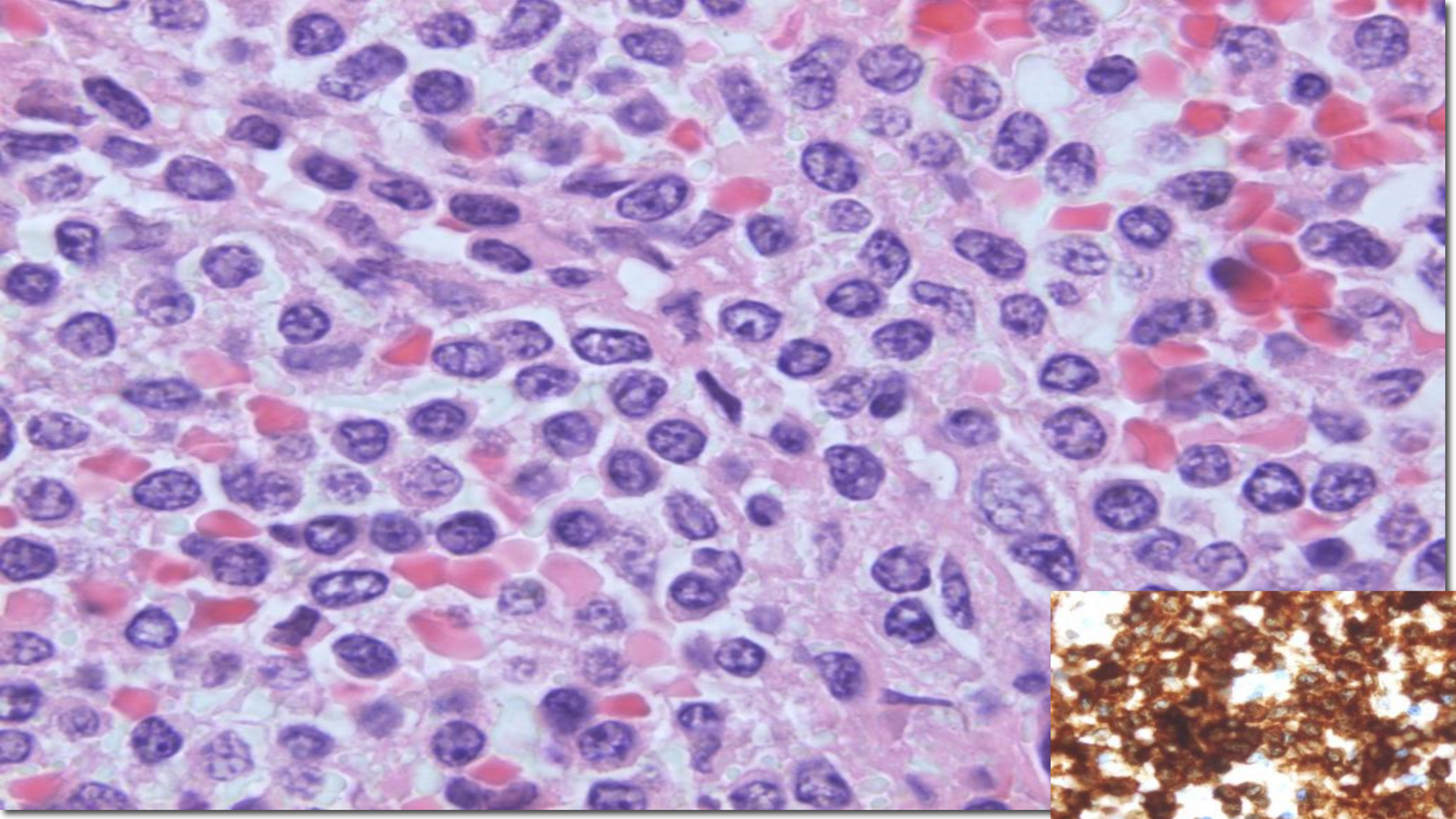
Douglas W Warden, Sarah Ondrejka, Jeffrey Lin, Lisa Durkin, Juraj Bodo, Eric D Hsi. Cleveland Clinic, Cleveland, OH

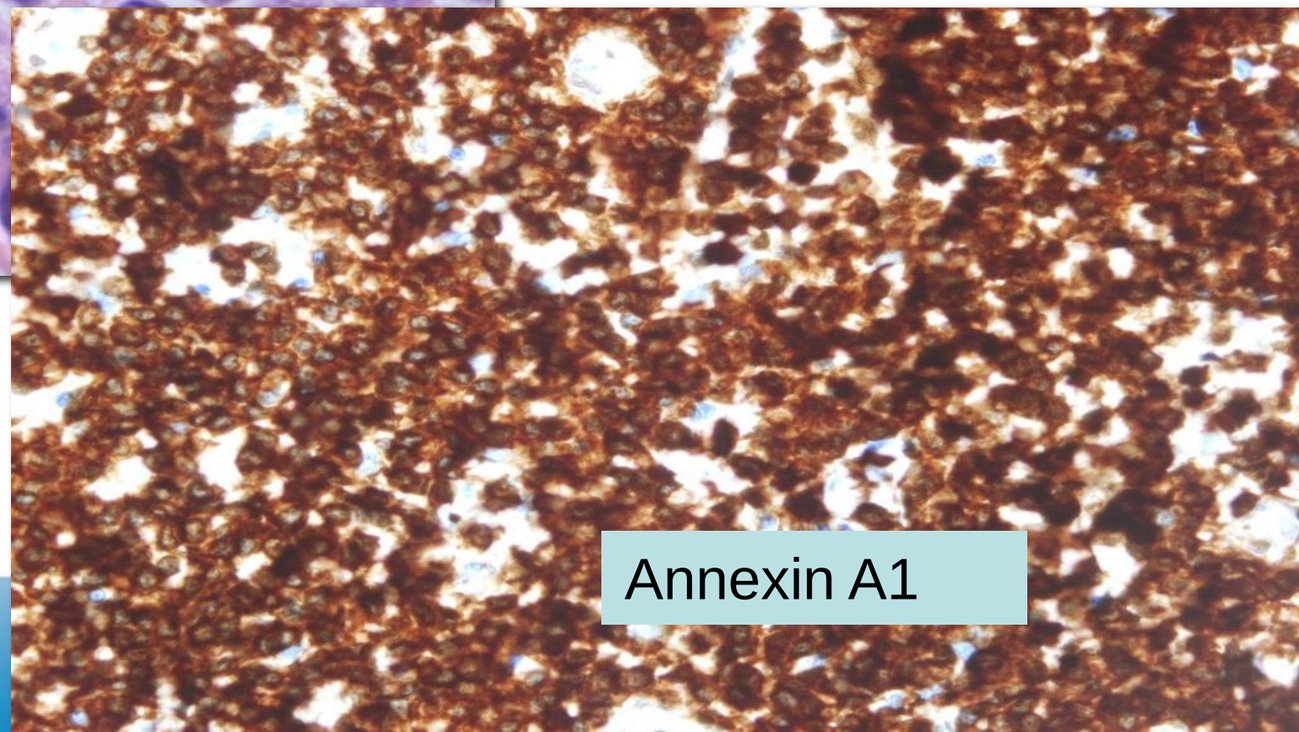
Conclusions: *BRAF* V600E mutations are present in all HCL cases. Immunohistochemistry for pERK can be reliably applied on routinely processed bone marrow trephine sections and is highly sensitive and specific for HCL. It appears to be a useful tool in the differential diagnosis of small B-cell leukemias/lymphomas, and pERK is a surrogate marker for *BRAF* V600E in the rare non-HCL leukemias with this mutation.

[1392] *BRAF* V600E Mutations in Low Grade B-Cell Lymphomas

Eric Duncavage, Lauren Henke, Friederike Kreisel. Washington University, St. Louis, MO; Washington University School of Medicine, St. Louis, MO

Conclusions: We found the *BRAF* V600E mutation in all cases of HCL, but not in cases of SLL or FL, confirming what has been previously reported. In addition we found 2/5 cases of SMZL that were PCR-positive for BRAF V600E mutations, however we could not verify these findings by sequencing. Given the increased sensitivity of PCR-based detection methods over Sanger sequencing and NGS (20% and 10% respectively) it is unclear if the two *BRAF* V600E PCR-positive cases represent low level mutation frequency, tumor cell dilution, or false positive results. However, these finding suggest caution when using PCR-based *BRAF* V600E testing to classify cases as HCL if SMZL is included in the differential diagnosis.




Annexin A1

Lymphoma entities, what is new?

- Intermediate BL/DLBCL

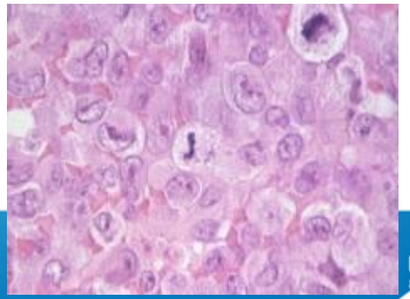
- Breast-implant capsule associated ALCL
- Pediatric Follicular Lymphoma
- Monoclonal lymphocytosis
- Primary cutaneous CD4+ pleomorphic TCL

Breast-implant capsule associated ALCL

[213] Breast Implant Capsule-Associated Anaplastic Large Cell Lymphoma (BIC-ALCL)

Carolyn Mies, Abha Goyal, Adam Bagg, Dale M Frank, Frederic G Barr, Aisner L Dara, Darshan B Roy, Shabnam Jaffer. Hospital of the University of Pennsylvania, Philadelphia, PA; Mount Sinai Medical Center, New York, NY

Background: The US-FDA recently issued preliminary findings of an analysis to assess a possible association between anaplastic large cell lymphoma (ALCL) and breast implants. The analysis was prompted by a small (~30), but growing, number of cases of a rare form of lymphoma in women with breast implants, typically arising within the capsule and causing a clinically-evident peri-implant fluid accumulation. We describe 3 new cases of breast implant-associated anaplastic large cell lymphoma (BIC-ALCL) that highlight its characteristic clinical and pathologic features.
Design: We studied the histopathologic characteristics, molecular pathology and clinical course of 3 cases of BIC-ALCL.



Pediatric Follicular Lymphoma

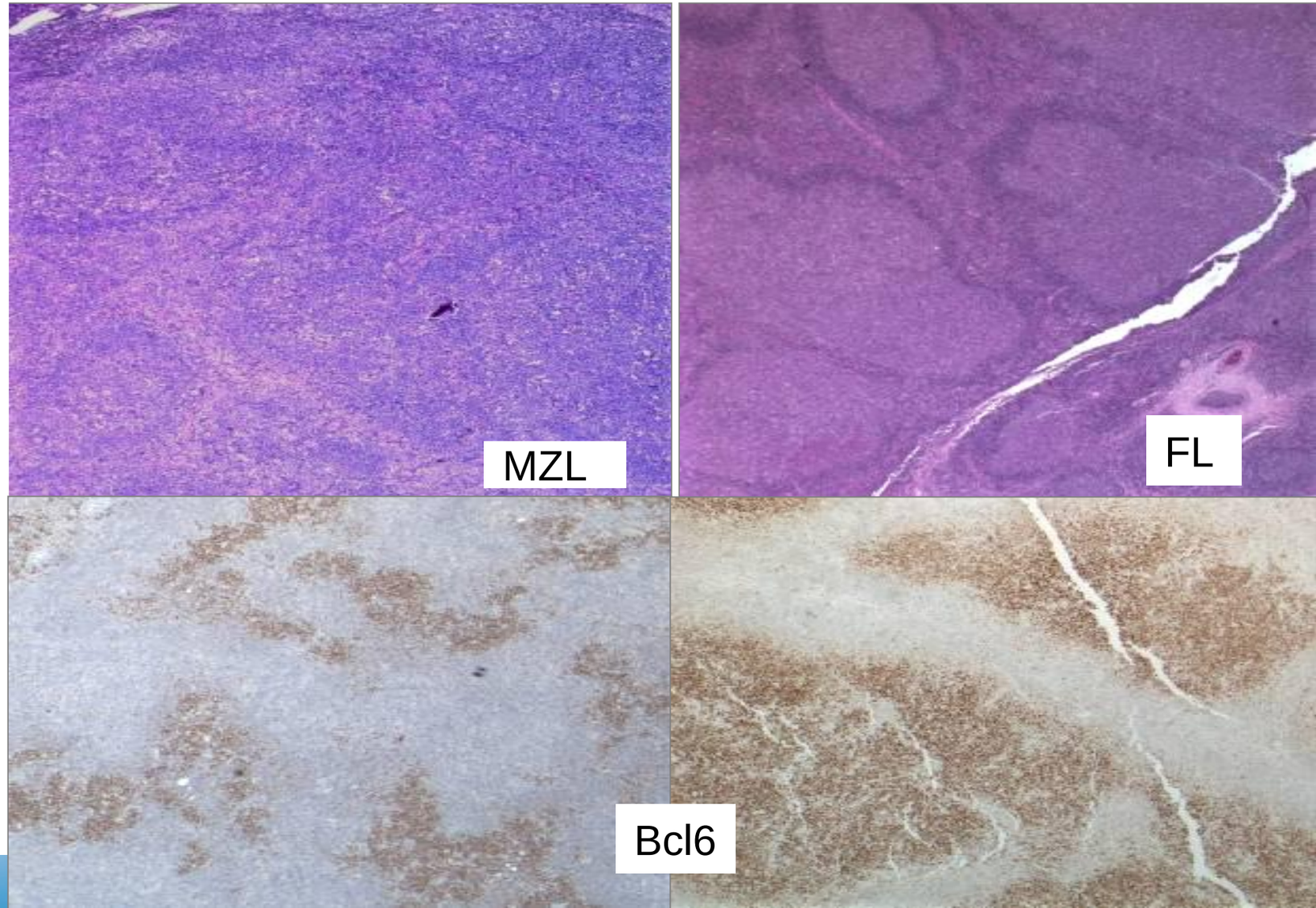
[1483] Pediatric-Type Follicular Lymphoma Occurs in Both Children and Adults and Is Characterized by a High Proliferation Index and the Absence of a BCL2 Gene Rearrangement

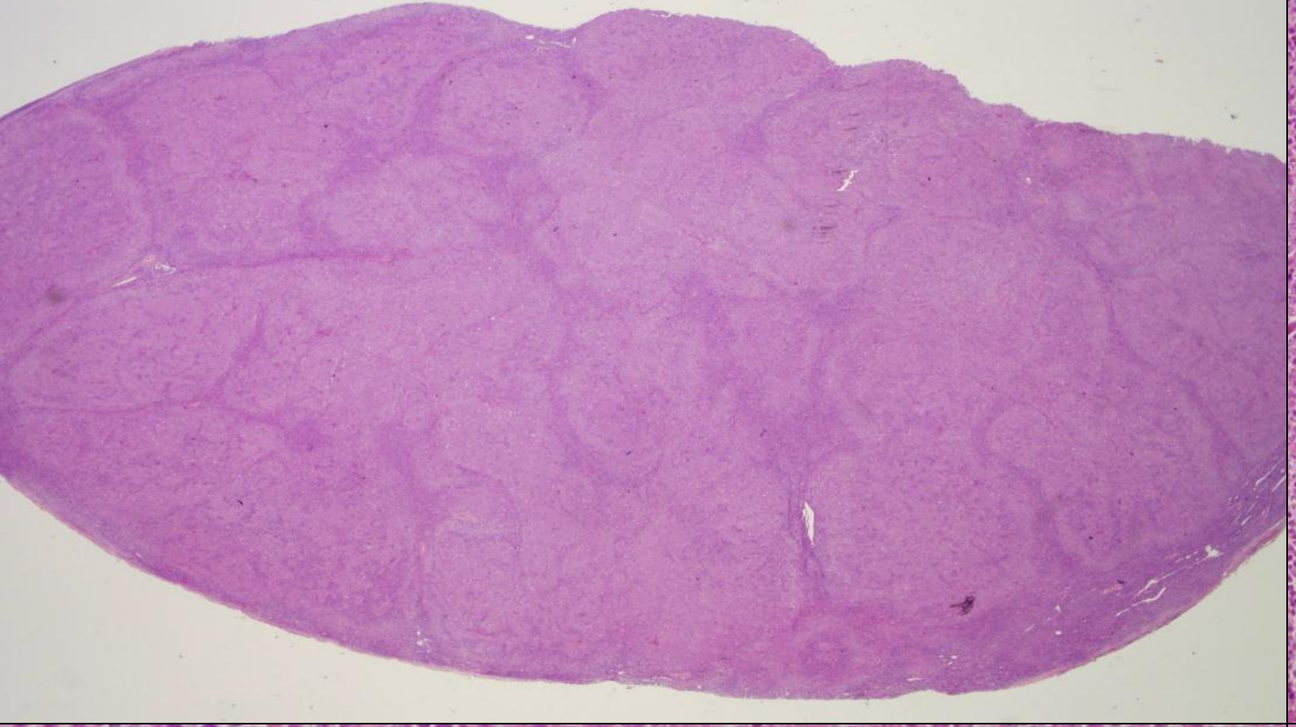
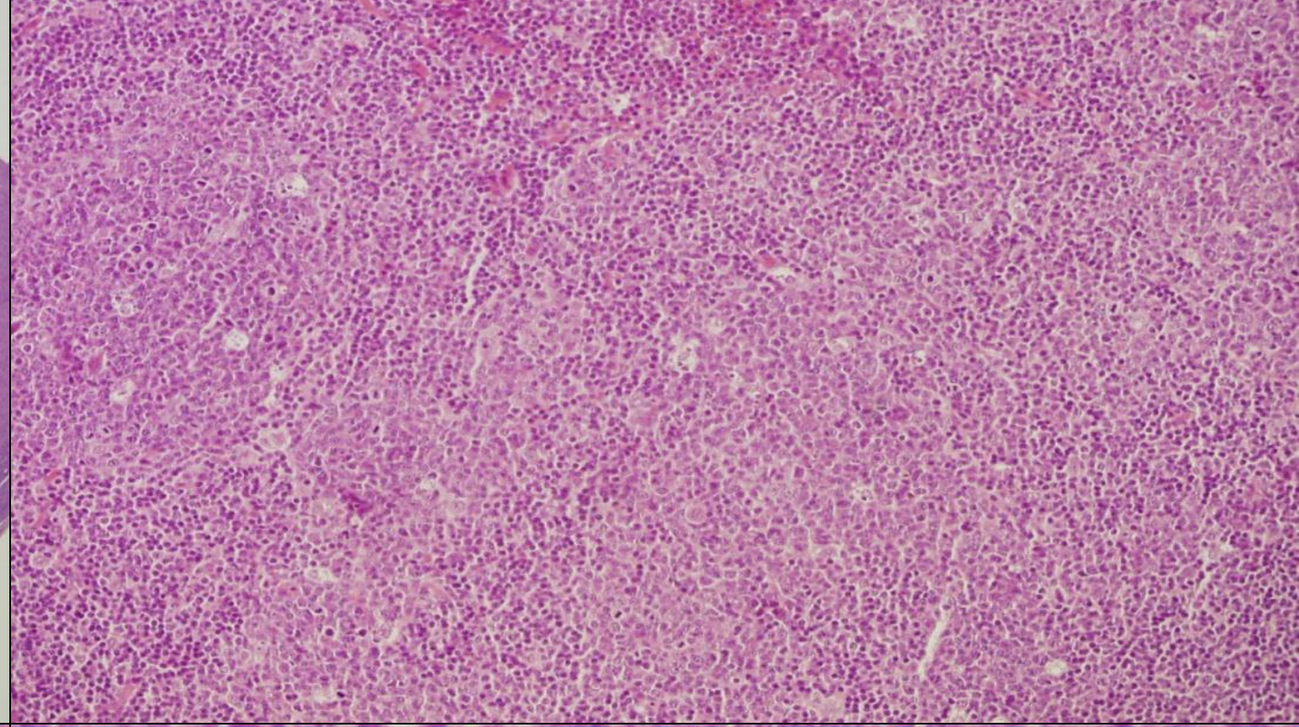
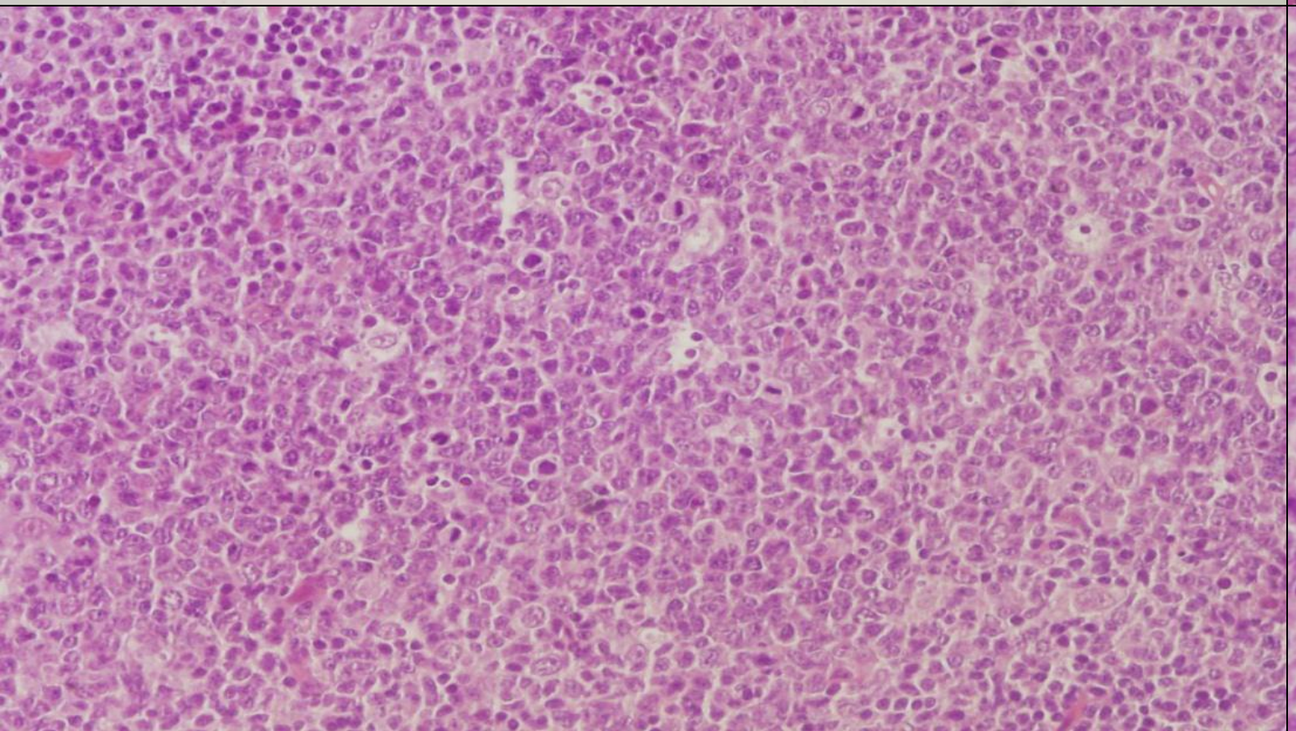
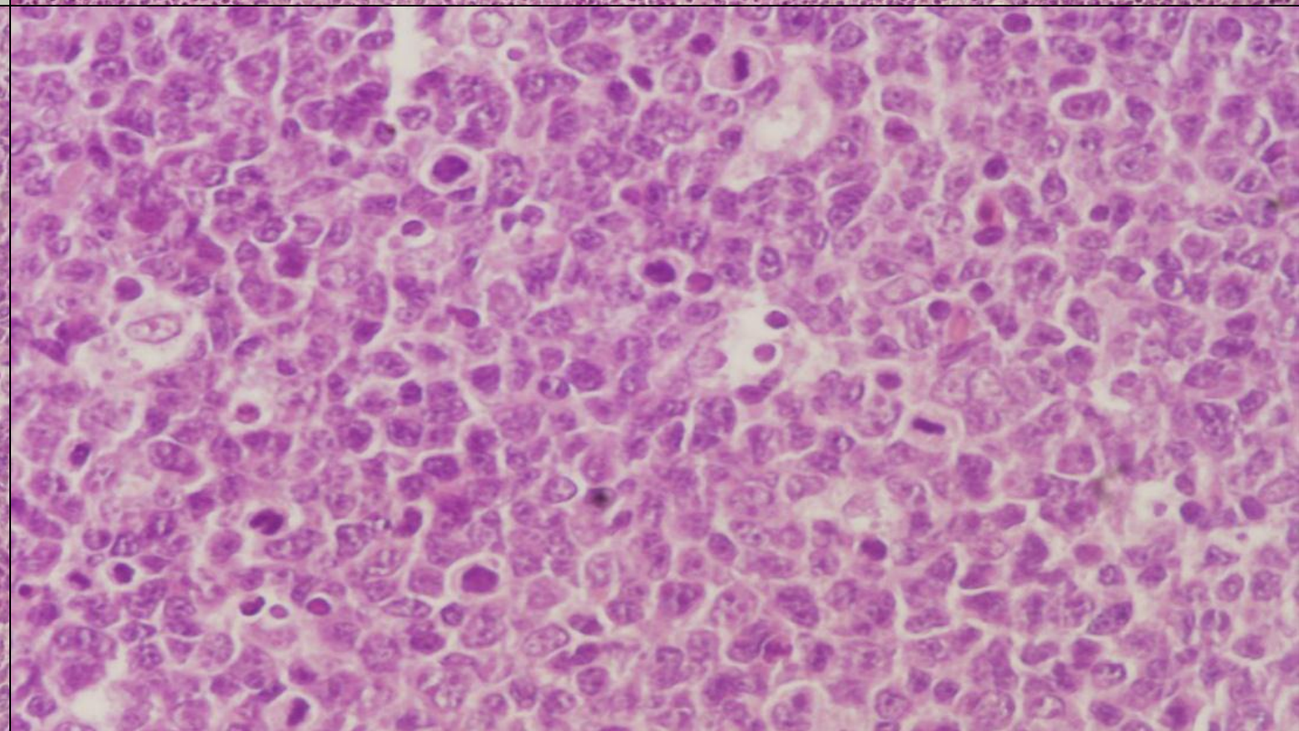
Abner Louissaint, Adam Ackerman, Judith A Ferry, A John Iafrate, Lawrence R Zukerberg, Nancy L Harris, Robert P Hasserjian. Massachusetts General Hospital, Boston, MA

Conclusions: PFL may be defined as an indolent clonal proliferation with a follicular pattern and variable histologic grade and BCL2 protein expression, but that both lacks BCL2 gene rearrangement and has HPI (>40%); large expansile follicles and lack of complete architectural effacement are morphologic clues to identify PFL. Similar indolent clonal follicular proliferations can occur in adults.

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, molecular genetic analysis
- FL: CD10+ Bcl6+ CD43-/+ Bcl2-/+
- MZL: CD10- Bcl6- (residual GC present) Bcl2 +/- cIg +/-
- Often cured with minimal therapy; no dissemination
- Are these really malignant? Should be denominated as lymphoma?

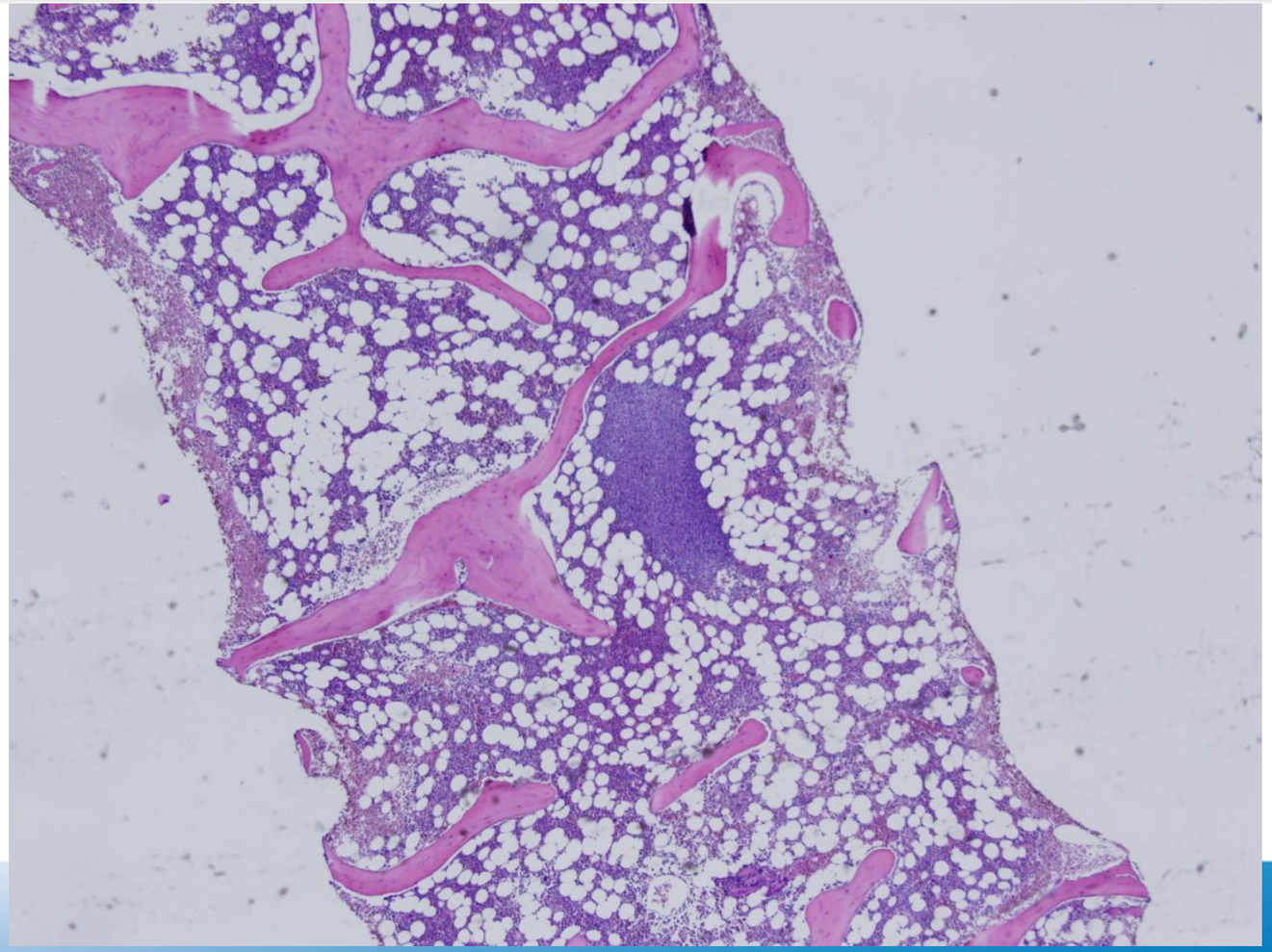


Monoclonal B-cell lymphocytosis

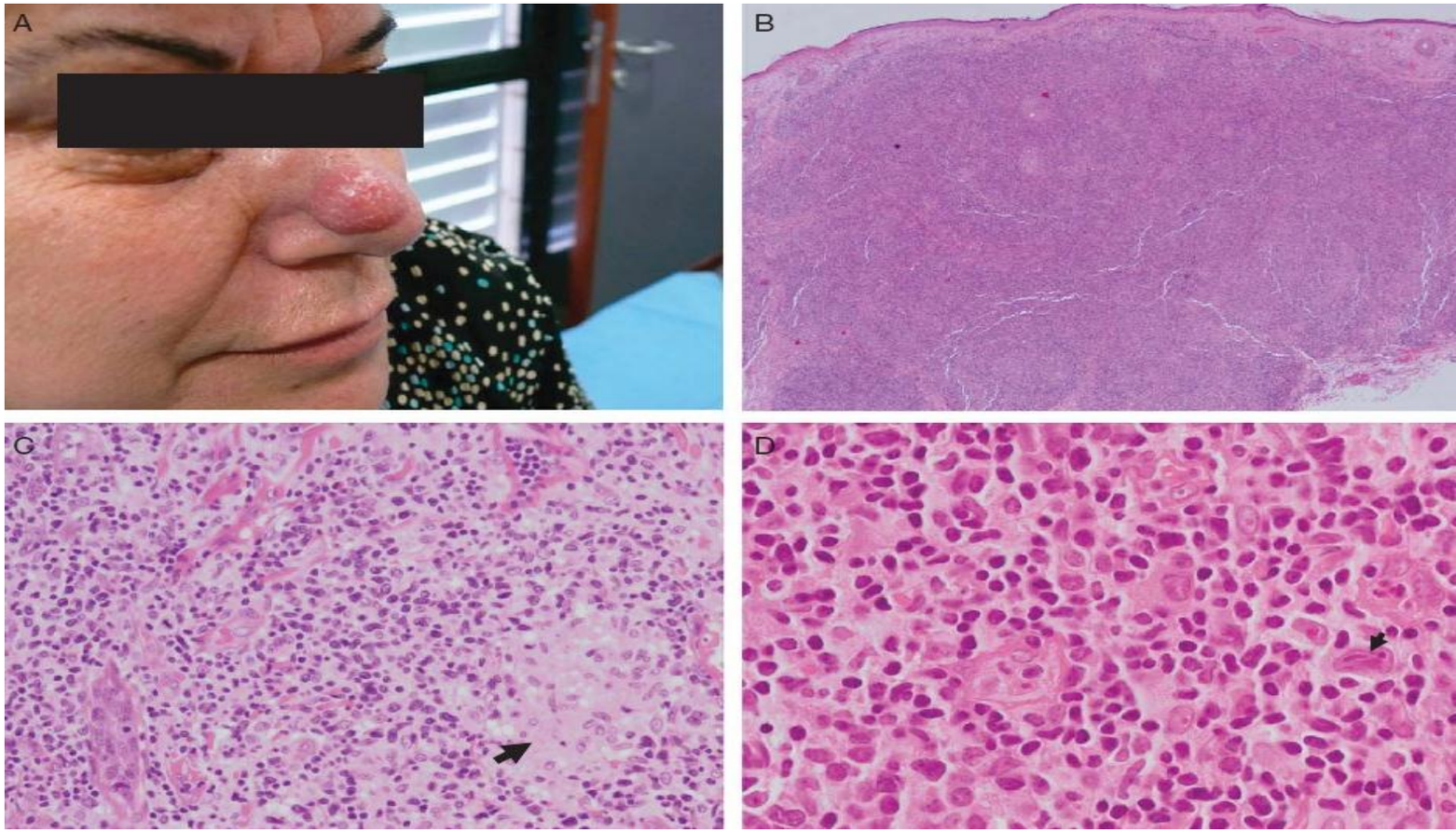
[1345] Characterization of Tissue Findings in Bone Marrow with Small Monoclonal B-Cell Populations

Anmaar Abdul-Nabi, LoAnn Peterson, Beverly Nelson. Northwestern University, Chicago, IL



Primary Cutaneous CD4+ small/medium sized pleomorphic T-cell Lymphoma

- A cutaneous, non-epidermotropic T-cell lymphoma comprised of pleomorphic CD4+ T-cells
- Single lesions (plaque or tumor) in the head and neck.
- CD3+ CD4+ PD1+
- Admixed B-cells.
- TCR monoclonal rearrangements
- Favorable clinical course
- Should be called lymphoma?



IHC markers, what is new?

- C-MYC
- MNDA
- PD1
- GCET1
- BLIMP1

Burkitt Lymphoma

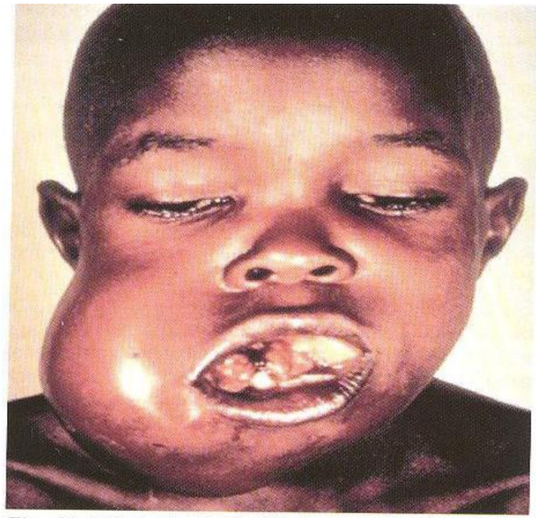


Fig. 10.121 Endemic Burkitt lymphoma. This African patient presented with a large jaw tumour.

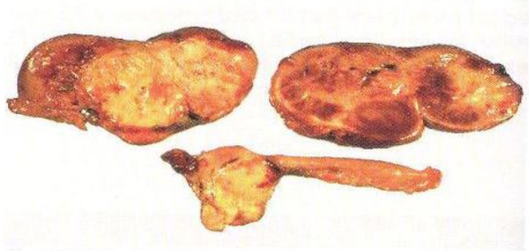


Fig. 10.122 Sporadic Burkitt lymphoma with bilateral ovarian tumours.

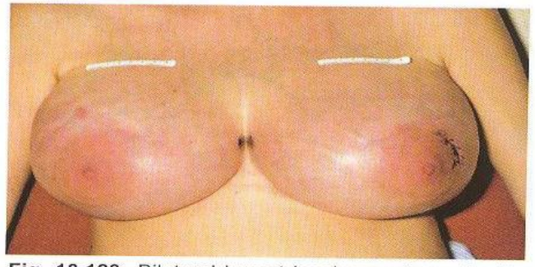
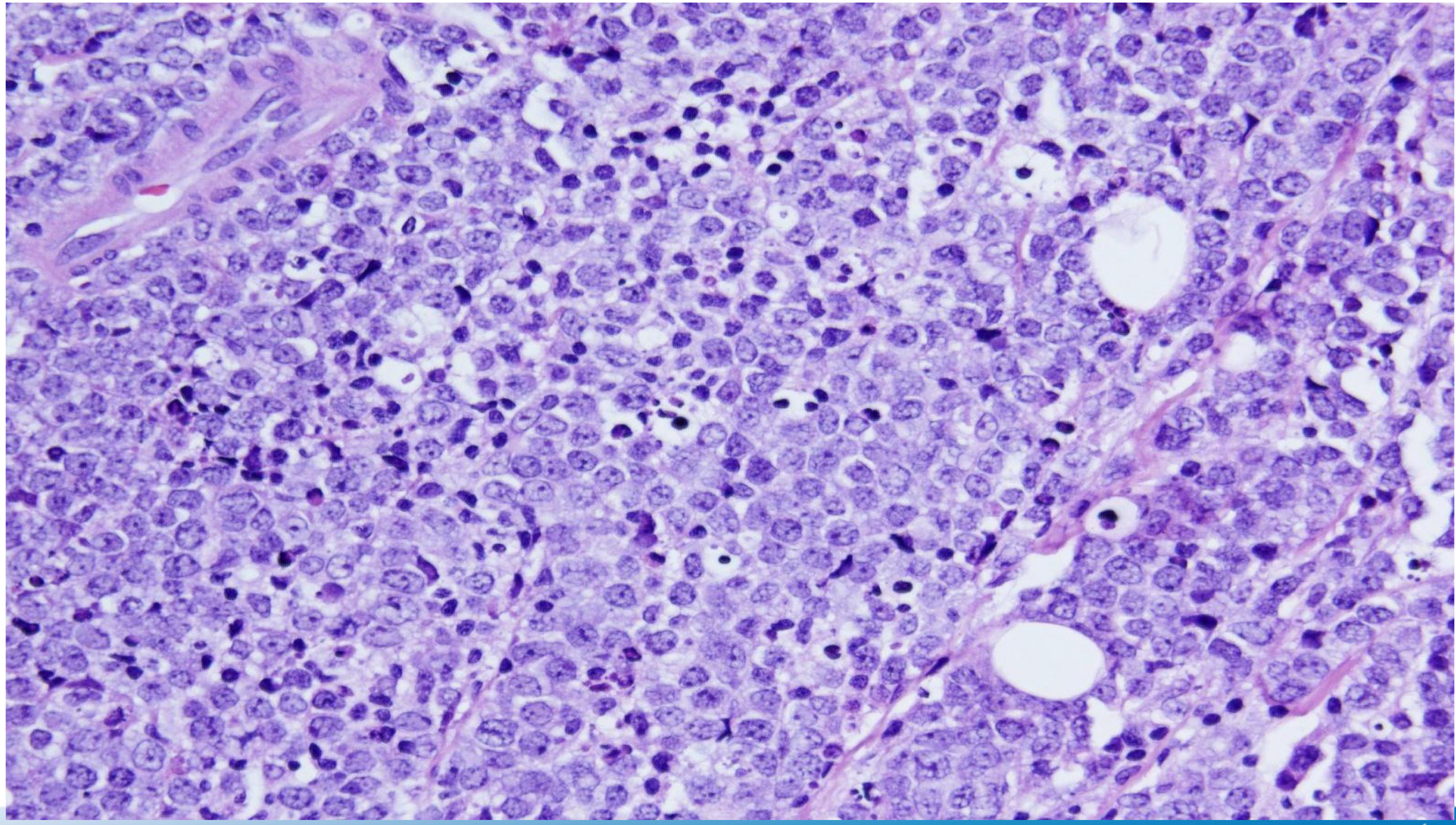


Fig. 10.123 Bilateral breast involvement may be the presenting manifestation during pregancy, and puberty. BL cells have prolactin receptors.



[1359] Correlation of *MYC* Gene Translocation Status with MYC Protein Expression in Burkitt Lymphoma and Diffuse Large B Cell Lymphoma

Ewa B Bajor-Dattilo, Alina Leung, Kieron Dunleavy, Svetlana Pack, Diane Arthur, Mark Raffeld, Wyndham Wilson, Elaine S Jaffe, Stefania Pittaluga. NIH, Bethesda, MD

Conclusions: The above data demonstrates that although strong MYC expression correlates with *MYC* translocation in BL cases, strong MYC expression by IHC is not predictive of *MYC* translocation status in DLBCL. In addition, this data suggests that a mechanism other than *MYC* translocation is responsible for MYC expression in a large fraction of DLBCL patients.

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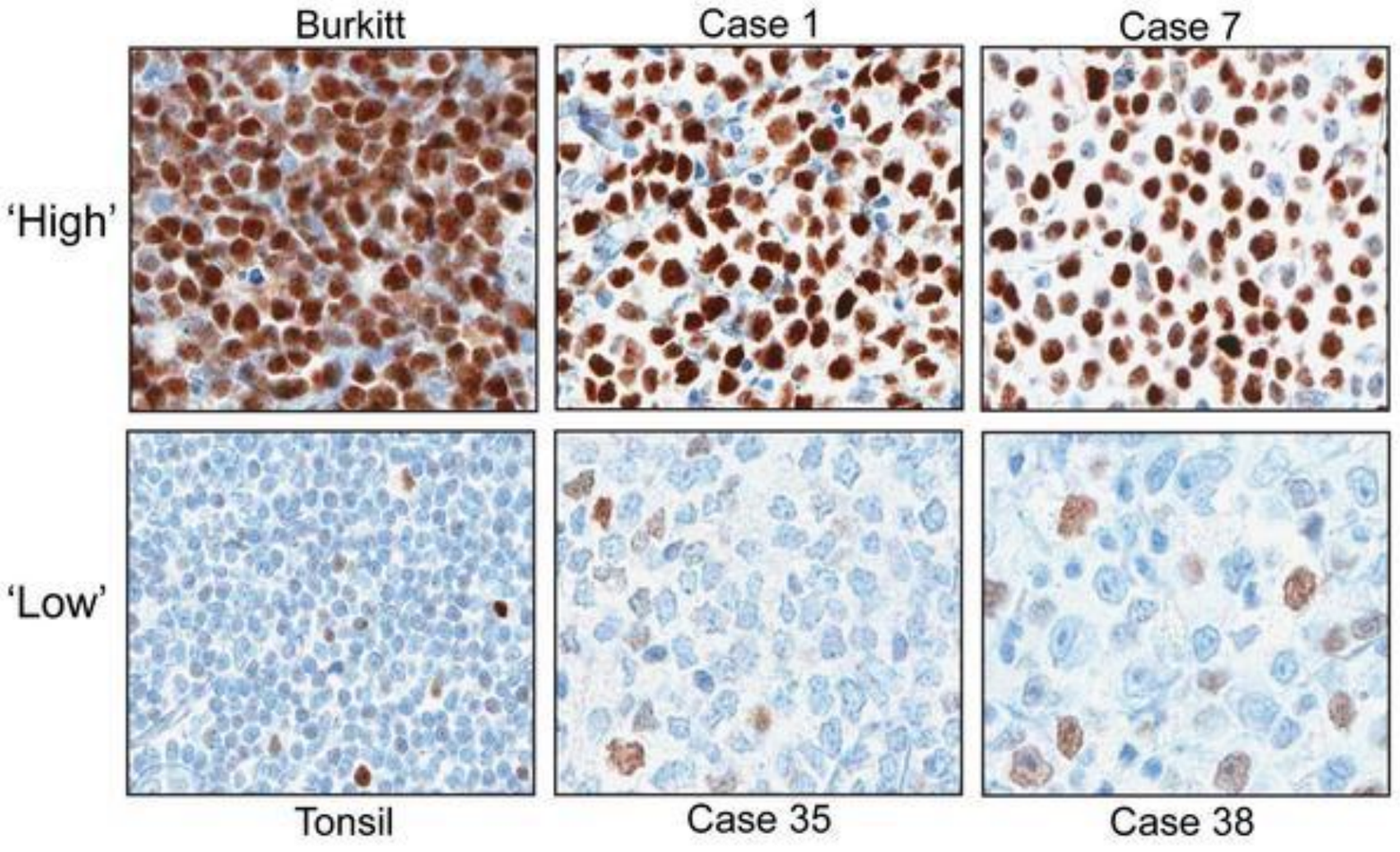
RESEARCH ARTICLE

Immunohistochemical Detection of MYC-driven Diffuse Large B-Cell Lymphomas

Michael J. Kluk[1], Bjoern Chapuy[2], Papiya Sinha[1], Alyssa Roy[1], Paola Dal Cin[1], Donna S. Neuberg[3], Stefano Monti[4], Geraldine S. Pinkus[1], Margaret A. Shipp[2], Scott J. Rodig[1*]

1 Department of Patho
America, **2** Departmer
United States of Amer
Massachusetts, United
Boston, Massachusetts



[1514] Immunostains for C-MYC and BCL2 Protein Predict Survival in Patients with Diffuse Large B-Cell Lymphoma Treated with Rituximab

Anamarija Perry, Yuridia Alvarado-Bernal, Javier Laurini, Lynette Smith, Kai Fu, Patricia Aoun, Timothy Greiner, Wing Chan, Philip Bierman, Gregory Bociek, James Armitage, Julie Vose, Dennis Weisenburger. University of Nebraska, Omaha, NE

respectively). Survival analysis showed that patients who had both BCL2<30% and C-MYC<50% had the best prognosis, whereas the patients with BCL2≥30% and C-MYC≥50% had the worst outcome. In multivariate analysis, the combination of the BCL2 and C-MYC was an independent predictor of OS and EFS (p=0.016 and p=0.006, respectively). The risk of death was 8.7 times greater in cases with BCL2≥30% and C-MYC≥50% as compared to those with BCL2<30% and C-MYC<50%.

[1550] Co-Expression of MYC and BCL2 Protein in R-CHOP Treated *De Novo* Diffuse Large B-Cell Lymphoma Predicts Poor Outcome

Graham W Slack, King L Tan, David W Scott, Susana Ben-Neriah, Nathalie A Johnson, Laurie H Sehn, Joseph M Connors, Randy D Gascoyne. BC Cancer Agency, Vancouver, BC, Canada; McGill University, Montréal, QC, Canada

[1515] High-Grade B-Cell Lymphoma with Features Intermediate between Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma (Grey Zone Lymphoma): A Clinicopathologic Analysis of 39 Cases

Anamarija Perry, Bhavana Dave, David Crockett, Pamela Althof, Lynette Smith, Patricia Aoun, Wing Chan, Kai Fu, Timothy Greiner, Philip Bierman, Gregory Bociek, James Armitage, Julie Vose, Dennis Weisenburger. University of Nebraska, Omaha, NE

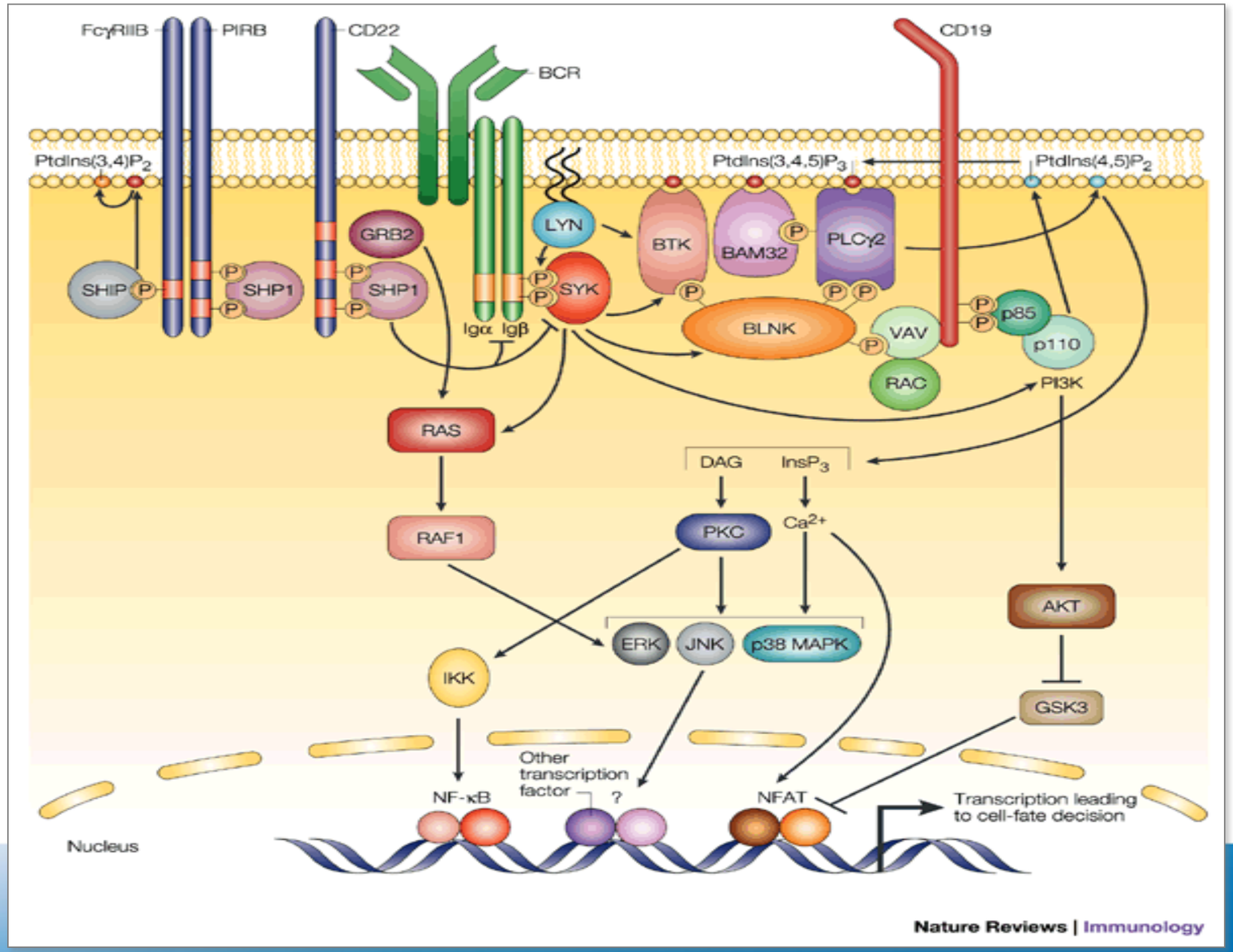
Conclusions: High-grade B-cell lymphoma with features intermediate between BL and DLBCL is a morphologically recognizable entity with an extremely poor prognosis. Most cases fall into the GCB category, with high proliferation, and high BCL2 and C-MYC expression. However, only a subset of cases with BCL2 and C-MYC expression have rearrangement of these genes, suggesting other mechanisms of gene deregulation in this entity.

C-MYC Immunohistochemistry

- Works nicely using the Epitomics antibody
- All C-MYC translocated cases have strong protein expression, but
- there are other causes of C-MYC increased expression
- In DLBCL, double C-MYC and BCL2 expression is an adverse prognostic parametre

Therapeutic targets, what is new?

- BTK
- PKC-delta



[1584] In Vivo CLL Proliferation Is Targeted by BTK Inhibition: ERK Activity Predicts Patient Nodal Response

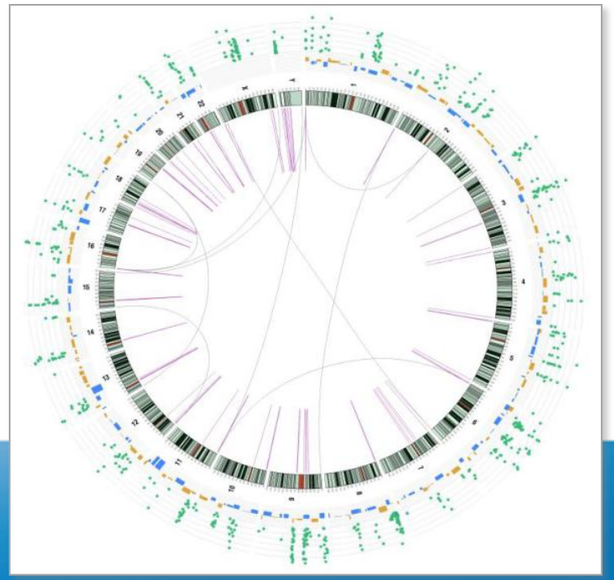
Y Lynn Wang, Shuhua Cheng, Jiao Ma, Ailin Guo, Pin Lu, Lauren Tyrell, Joseph J Buggy, John P Leonard, Richard R Furman. Weill Cornell Medical College, New York, NY; Pharmacyclics Inc., Sunnyvale, CA

Conclusions: These results have several implications: 1) They highlight the key role of cell proliferation in CLL. We demonstrated for the first time that blocking cell proliferation via inhibition of BCR signaling is linked to clinical responses in patients; 2) ERK activity contributes to the in vivo CLL proliferation. ERK signaling pathway, therefore, represents a potential therapeutic target for future interventions; and 3) Ki67 and ERK may be used as response predictors for future trials of BTK inhibitors.

[2152] Next-Generation Pathology: Deep DNA Sequencing and Targeted Therapy for Cancer

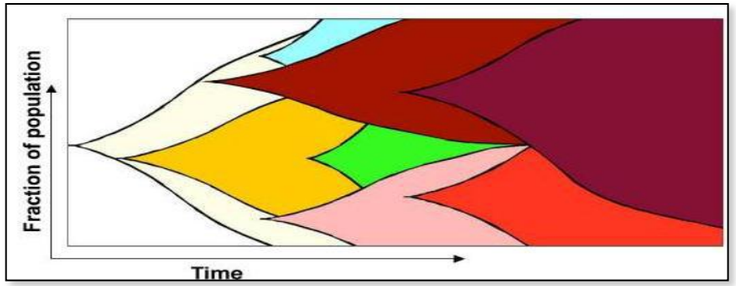
Christine Sheehan, Alex Parker, Mirna Jarosz, Sean Downing, Roman Yelensky, Doron Lipson, Gary Palmer, Maureen Cronin, Jeffrey Ross. Albany Medical College, Albany, NY; Foundation Medicine Inc., Cambridge, MA

Conclusions: NGS of hundreds of cancer-related genes can be reliably performed at a high level of sensitivity and specificity in clinical FFPE samples of solid tumors, can reproduce SOC single gene traditional sequencing results and shows great potential to inform on therapeutic decisions for patients with CRC, NSCLC and MM.



Cancer diagnosis: the situation

- Cancer is a multigenic disorder
  - Therapy targetting mutated genes (CML, B-RAF mutated melanoma, ALK+ lung cancer) has a lower toxicity, and better efficacy
- High molecular diversity of cancer
  - Each tumor sample has an unique combinations of mutated genes
  - Clinical efficay of targetted therapy needs broad target blockage
- Tumor dynamics is dominated by
  - Microclonal competition
  - Collaboration stroma-tumor
  - Cell plasticity



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