

Society for Hematopathology 2017

Session 2

Genetic Testing in the Diagnosis of Lymphoid Neoplasms Summary of the cases

Session Chairs:

Rebecca King and Miguel Piris

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Lymphoma diseases/variants defined by specific mutations

- ALK+ ALCL (C Krishnan 132, SM Rodriguez-Pinilla 153)
- ALK+ DLBCL (J Sidhu 161)
- DH/TH High-grade B-cell lymphoma (T Williams 160, A Jencks 206)
- DUSP22/IRF4+ ALCL (B Bisig 270, C Ho 277)
- IRF4+ LBCL (A Wotherspoon 172, N Aggarwal 341)
- FL with 1p36 deletion (P Khattar 334)
- BL with 11q aberration (V Makarenko 043, R King 058, K Huettl 137, A Louissaint 356)

Useful mutations for recognising B-cell lymphoma diseases

- NOTCH1 (CLL, MCL)
- ATM (MCL, CLL)
- MYD88 (LPL, ABC-DLBCL,...)
- BRAF (HCL, LCH,...)
- BIRC3 (MZL, MALT-type)
- CCND1 (MCL) ([M Wasik, 033](#))
- MAP2K1 (HCLv, Pediatric-type FL)
- NOTCH2/KLF2 (SMZL)
- 7q31 loss (SMZL)
- CCND3 (SRPL)
- EZH2 (FL, GC-DLBCL)
- BCL2 (FL, DLBCL)
- 9p amplifications (PMBL)
- TNFAIP3, SOCS1 and STAT6 (PMBL) ([S Prakash 378](#))
- ID3/TCF3 (BL)

Useful mutations for recognising T-cell lymphoma diseases

- STAT3 (LGL, NKTCL, EBV-neg ANKL) (D Wu 111, P. Rothberg/J. Bennet 0179, M Bansal 190)
- STAT5B (HSTL, EATL)
- DDX3X (NKTCL)
- SETD2 (EATL)
- ALK (C Krishnan 132)
- Ring 7 and other chromosomal imbalances (HSTL) (M Vasef 114)
- TCL1A rearrangement (T-PLL)
- RHOA mutations (AITL)

Prognosis/predictor non class-specific mutations

- TP53
- BTK/PLCG2 (CLL,.....)
- BIRC3 (CLL)
- CARD11, CD79 (DLBCL)
- EZH2 (FL, GC-DLBCL)
- NOTCH2/KLF2 (SMZL)
- CXCR4/MYD88 (LPL)
- TP63+ ALCL
- PLCG (PTCL, CTCL)

The spectrum of frequent lymphoma types goes beyond specific molecular markers:

- BL:
 - MYC translocations
 - 11q aberrations (V Makarenko 043, R King 058, K Huettl 137, A Louissaint 356)
- FL:
 - BCL2 translocation $t(14;18)(q32;q21)$
 - BCL6 translocation $t(3;14)(q27;q32)$
 - Large B-cell lymphoma (LBCL) with IRF4 rearrangement
 - Pediatric-type FL (T Molina 260)
 - Diffuse FL with 1p36 deletion (P Khattar, 334)
 - Duodenal-type FL
 - PCCFL
 - Other extranodal (M Pizzi 154)....

Correlates between IHC and molecular markers

- **ALK in ALCL**
- **CCND1 translocation in MCL and MM**
- CCND3 in SRPL
- MAP2K1-pERK in pediatric-type FL
- IDH2 in AITL ([Gaulard, 377](#))
- BCL2 translocation in FL and DLBCL
- TP53, all lymphoma types
- ID3 in BL
- STAT3 in LGL and others
- MYC in DLBCL and BL
- BRAF and pERK in HCL
- ARID1A in GC-BCL and NKTCL

Gray areas where light seems to emerge

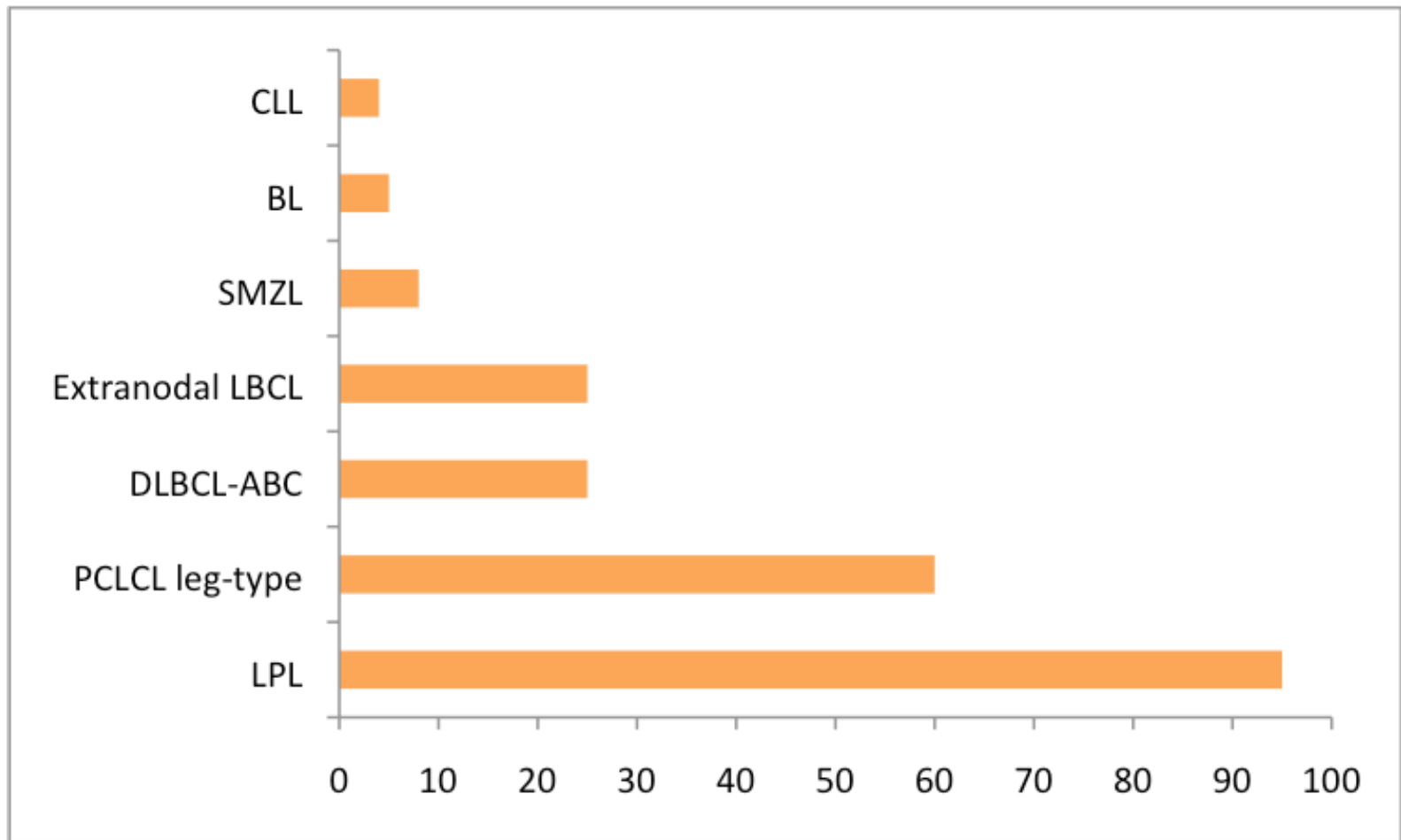
- SRPL-CCND3
- MAP2K1/pERK in pediatric-type FL
- IDH1/IDH2 in AITL
- More precise definition of MZL

Key points from the workshop:

MYD88 L265P

- LPL (M Stump 127)
- ABC-DLBCL
- PCLBCL, leg-type (S Montes-Moreno 191)
- Other extranodal DLBCL
- Orbital and ocular adnexal MZL (S Swerdlow 112)
- Other MZLs (C Roth 046)
- CLL, SMZL

MYD 88 mutation in B-cell lymphoma



Key points from the workshop:

MYD88 L265P

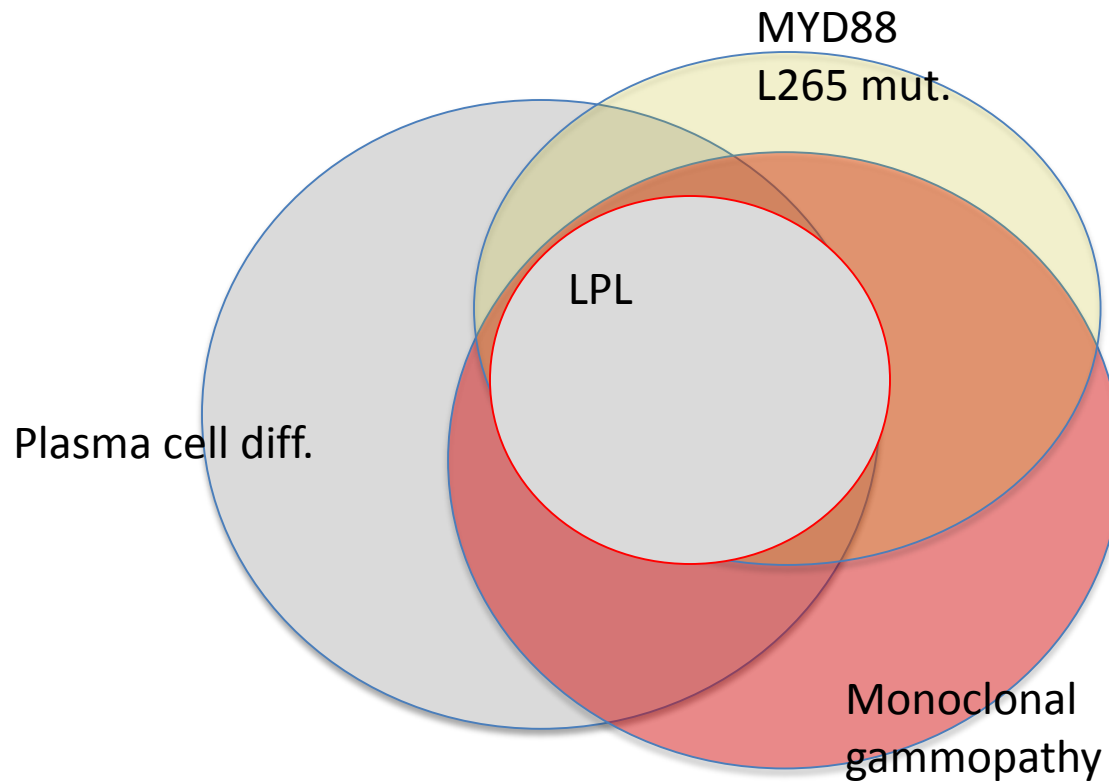
Case **112** (**S Swerdlow**):

Conjunctival lymphoma with plasmacytic differentiation & MYD88 L265P mutation

Ocular adnexal MALT-type marginal zone lymphomas contain MYD88 mutations:

- Oncotarget 2016, Sep 20;7(38):62627-62639 (**18%**)
- Mod Pathol. 2016 Jul;29(7):685-97 (**25%**)
- Am J Hematol. 2013 Sep;88(9):730-5

Key points from the workshop: MYD88 L265P in LPL



Key points from the Workshop:

How to identify....?

- DH/TH High-grade B-cell lymphoma (T Williams 160, A Jencks, 206)
- BL with 11q aberration (V Makarenko 043, R King 058, K Huettl 137, A Louissain 356)
- FL with 1p36 deletion (P Khattar, 334)

Key points from the Workshop:

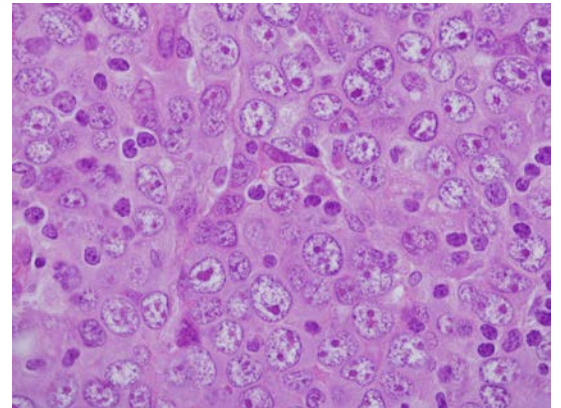
How to identify DH/TH High-grade B-cell lymphoma?

- DLBCL of GCB type which is BCL2 positive and contains >40% MYC-positive cells (IHC)
- FISH for MYC gene could be applied as the initial test. MYC rearranged cases might be further tested for BCL2/BCL6 genes
- CD10+ and Ki67>90%
- FISH for all three genes could be conducted at one time for all DLBCL, HGBCL and BL cases

Key points from the Workshop:

DLBCL Screening for COO

- R-CHOP treated
 - Hans? Choi? Other IHC algorithms?
 - Nanostring (Lymph2Cx)?
- Ibrutinib, Lenalidomide, PI3KDi treated,....
 - IHC algorithms?
 - Lymph2Cx?



Key points from the Workshop:

How to identify....?

FL with 1p36 deletion (P Khattar, 334)

Diagnosis: 1p36 Copy number analysis and/or TNFRSF14 mutation

Screening: CD23 expression and/or inguinal localization
Additional role of STAT6 mutations?

BL with 11q aberrations (V Makarenko 043, R King 058, K Huettl 137, A Louissain 356)

Diagnosis: 11q Copy number analysis

Screening: Low MYC expression and lack of MYC translocation

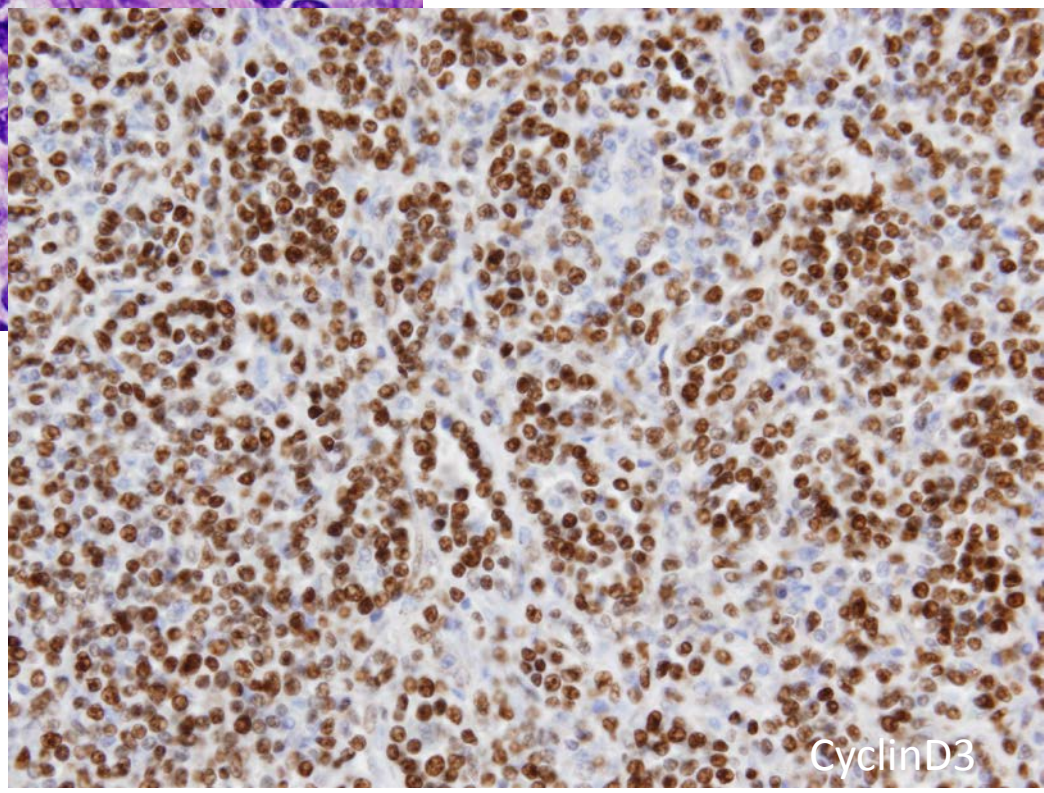
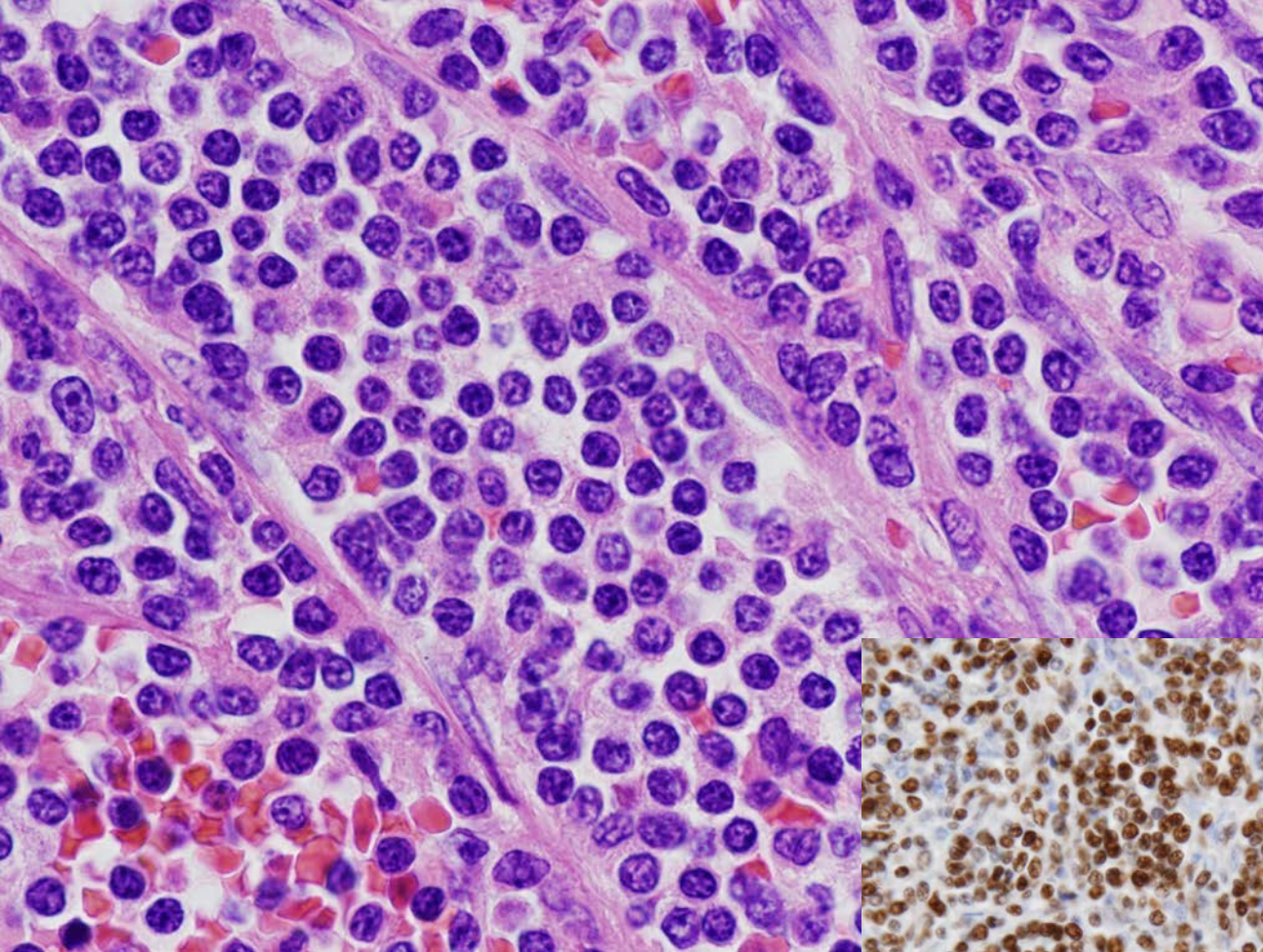
Key points from the Workshop: Splenic BCL other than SMZL

- SRPL ([Piris, 022](#))
Small B-cell lymphoma
CCND3 mt and CyclinD3 expression
- HCLv
Prolymphocytoid variant of HCL ([J Teruya-Feldstein 162](#))
- Splenic B-cell lymphoma, unclassifiable ([H Katerji 198](#), [P Rothberg 208](#))
- CyclinD3-positive Large B-cell lymphoma involving the splenic red pulp ([B Chen, 095](#))

Key points from the Workshop:

Splenic BCL other than SMZL

- Splenic diffuse red pulp small B-cell lymphoma (SDRPL) is an uncommon lymphoma with a diffuse pattern of involvement of the splenic red pulp by small monomorphous B lymphocytes.
- The neoplasm also involves bone marrow sinusoids and peripheral blood, commonly with a villous cytology



CyclinD3

Splenic diffuse red pulp small B-cell lymphoma

Morphology

- Spleen: diffuse
- Bone marrow: sinusoidal
- PB: villous
- Monomorphous small cell cytology

Immunophenotype

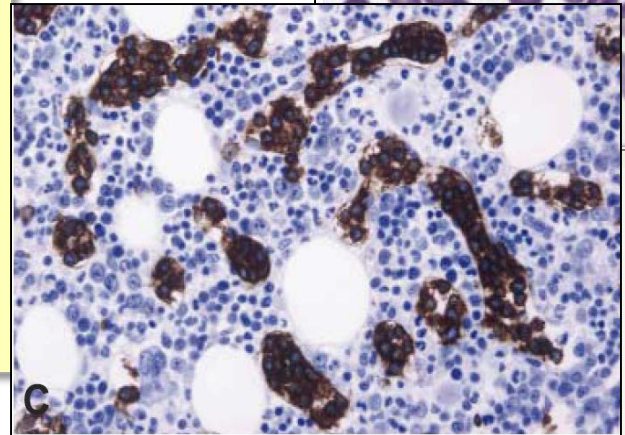
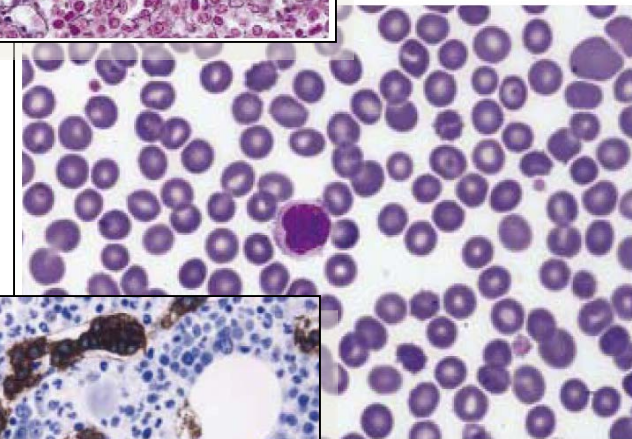
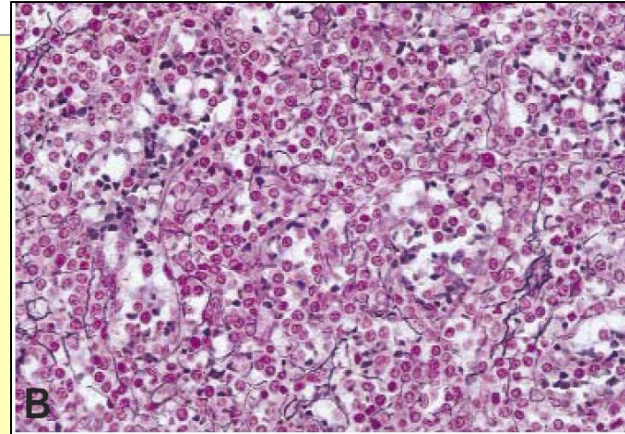
- CD20+, DBA44+, CyclinD1-

Genetics

- CCND3 mutations and
- increased CyclinD3 expression

Clinical

- Stage IV
- Indolent tumour, often preceded by MBL



Key points from the Workshop:

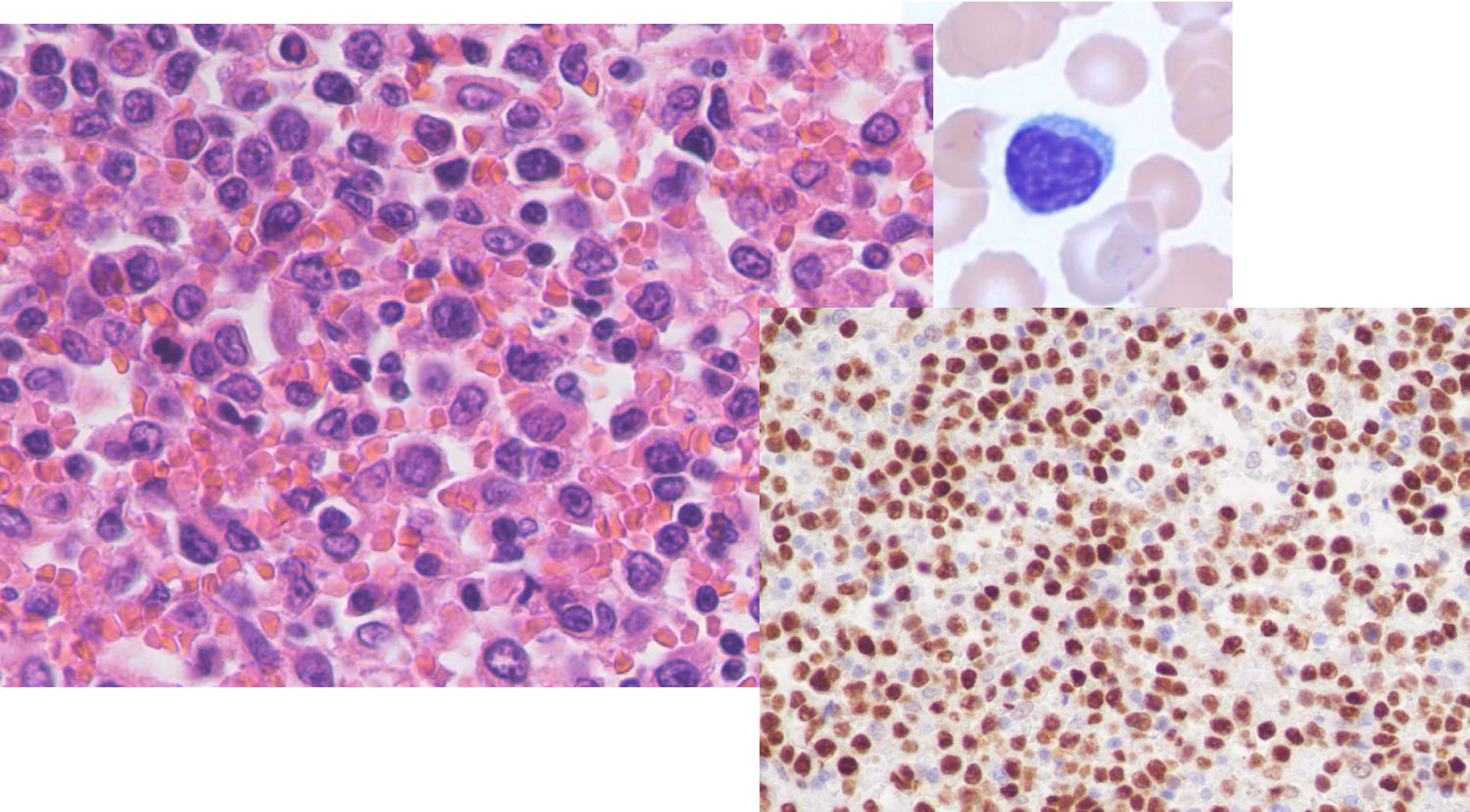
Splenic BCL other than SMZL

- There is some degree of overlap with cases that fulfill the criteria for **hairy cell leukaemia variant**; however, additional studies are required to further evaluate the extent of overlap between these entities,
- Although the rare **large B-cell lymphomas** that involve the splenic and bone marrow sinusoids may be related to SDRPL, they should not be included in this category, which is restricted to indolent lymphomas composed of small lymphocytes

Key points from the Workshop:

Splenic BCL other tan SMZL

CyclinD3-positive Large B-cell lymphoma involving the splenic red pulp (B Chen, 095)



Key points from the Workshop:

Splenic BCL other tan SMZL

Splenic B-cell lymphoma, unclassifiable (H Katerji 198, P Rothberg 208)

HCLv: Studies are limited

- Hybrid features of PLL and classic HCL
- FCM: DBA.44 (CD72), CD11c, CD103, and FMC7
- TP53 and MAP2K1 mutations
- Usage of the IGHV4-34 gene, not a diagnostic feature
- Large number of DNA CNAs, gains on chromosome 5 and losses on 7q and 17p

Key points from the Workshop:

Langerhans cell histiocytosis combined with non-LCH (mixed histiocytosis)

- Cases **S Bhattacharyya 135**, **S Khatri 336** and **N Ozkaya 368**

MYELOID NEOPLASIA

Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the *BRAF*^{V600E} mutation

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Key Points

- The association of both Langerhans cell histiocytosis and Erdheim-Chester disease is not exceptional.
- This association is linked to *BRAF*^{V600E} mutation.

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Key points from the Workshop:

Unusual Molecular and IHC features

- TP53 mutation in an atypical clonal lymphoproliferation: is this sufficient to diagnose a neoplasm? (S Sadigh 115)
- FL with CD5 expression and low somatic mutation burden (C Hudson 204)
- Multiclonal EBV+ lymphoproliferative disorder (DLBCL and marginal zone) arising in the setting of iatrogenic immunosuppression (G Crane 228)
- Burkitt lymphoma/leukemia with aberrant TdT expression (C Griffin 287)
- Hydroa-vacciniforme-like lymphoproliferative disease (J Yan 326)
- TET2/KRAS/TP53-mutated Aggressive Hepatosplenic NK/T Cell Leukemia/Lymphoma with i(7)(q10) (J Sidhu 331)
- ALK positive histiocytosis of infancy (R Lorsbach 380)
- Co-existence of mutations in POT1 and ATR in ALK+ LBCL could be important for the therapy using ATR-inhibitor (J Sidhu, 161)