The differential diagnosis between primary mediastinal B-cell lymphoma and diffuse large B-cell lymphoma

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Large B-cell Lymphoma

- ABC-DLBCL
- GCB-DLBCL
- HGBCL-NOS
- HGBCL-DTH

- IP-DLBCL
- PMBCL
- cHL

The relevance of lymphoma classification

Definition of (clinico-pathological entities – basis of the WHO classification
- based on morphological spectrum, immunofenotypical spectrum, genetic characteristics, clinical characteristics
- class provides information for treatment choices (intensification, radiotherapy)

Dissection of specific oncogenesis
- may provide a basis for specific or targeted treatment
Case 2 – TVU16-5646

14 year old female patient
Presented with bilateral cervical, supraclavicular, anterior mediastinal, hilar and subcarinal and upper abdominal lymphadenopathy
Superior vena cava syndrome
Some right-sided pleural effusion
No hepato-splenomagalie
No other organ localizations
CD79a, PAX5, BCL2 positive
EBER, CD15 negative
### PMBCL vs. DLBCL

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Second line IHC may include: MAL, HLA-II, PDL1/PDL2 and other markers that are rarely routinely available
Molecular features of PMBCL

Molecular features of PMBCL

GCB- and ABC-DLBCL
- BCL6 Tx: 20-40%
- MLL2/MLL3 M: 32-38%
- CREBBP/EP300 M/D: 32%
- B2M/CD58 M/D: 21-29%
- TP53 M: 20%
- MEF2B M: 11%
- FOXO1 M: 8%

GCB-DLBCL
- BCL2 Tx/M: 34%
- GNA13 M: 25%
- EZH2 M: 22%
- BCL6 BSE1 M: 15%
- MYC Tx: 10%
- mir17-92 G: 6-12%
- PTEN D: 6-11%

ABC-DLBCL
- TNFAIP3 M/D: 30%
- MYD88 M: 30%
- CDKN2A/B D: 30%
- BCL2 Amp: 24-30%
- PRDM1 M/D: 25%
- CD79A/B M: 20%
- CARD11 M: 9%

PMBCL
- PDL1/2 Amp/Tx: 49%
- SOCS1 M: 45%
- CIITA Tx: 38%
- STAT5 M: 36%
- TNFAIP3 M: 36%
- JAK2 Amp: 30%
- TP53 M: 20%
- PTPN1 M: 20%

Epigenetic modification proliferation BCL6 deregulation NF-κB/BCR signaling DNA damage response immune escape apoptosis terminal differentiation JAK/STAT signaling cell cycle other
Reflection of the different genetic landscape of PMBCL and DLBCL

Specific structural alterations result in characteristic protein expression patterns

Overall genetic differences result in characteristic gene expression patterns
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<th>Methods</th>
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<td>Gene-expression profile</td>
<td>expression-array, RNAseq, RT-MLPA</td>
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<td>Mutation spectrum</td>
<td>WGS/WES, targeted NGS, (multiplex) PCR-techniques</td>
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<td>Copy number alterations</td>
<td>SNP-NGS, shallow sequencing (off-target), FISH</td>
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<td>Structural alterations</td>
<td>SeqCap-NGS, FISH</td>
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Molecular features in case 2 - TVU16-5646

PD-L1

PD-L2

SE9

PDL2 - 366C.9E5

PDL1 - 22C3
Molecular features in case 2- TVU16-5646

Various gains and losses are noted including large segments, but also focal aberrations:

Losses on chromosome 1, 3, 4q, 7p, 10p12 14q31-32, 19p13 and 20q13.13-13.2.

Gaines on chromosome 5p, 9p24.3-p23 and 20
Molecular features in case 2 - TVU16-5646

A combined assay gives information on copy numbers amplification 9p24
Structural alterations translocation PDL2
Mutation spectrum
Additional (structural) alterations
### Case 2 favor Primary Mediastinal B-cell Lymphoma

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Molecular information, especially isolated PDL2 amplification, adds an additional level to morphology, immunophenotype and clinical information.
Conclusion

• Primary Mediastinal B-cell lymphoma is a distinctly separate disease from Diffuse Large B-cell lymphoma
• Morphological and immunohistochemical markers are characteristic, but not specific
• The copy number landscape and translocation spectrum of PMBCL is characteristic and bears similarities to CHL, but less so to DLBCL
• Additional diagnostic arguments may be needed in equivocal situations

• Custom made and commercial FISH assays for 9p24 are helpful as a diagnostic tool in daily practice
• NGS techniques require a specialized lab, but if available may be an attractive alternative
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The Netherlands

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