Case 7
A tumor of the iris in a patient with CLL

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70-year-old female with a history of CLL, stable without treatment, presented with a tumour of the iris known for 1 year, clinical suspicion of CLL infiltrate

No response to systemic steroid therapy, outside biopsy was insufficient for diagnosis

Resection of the iris tumour

Patient otherwise in good health

Follow-up: Patient had received 6 cycles of R-CHOP with markedly improved visual acuity and no evidence of recurrence
Sonographic study of iris tumor
CD3

MYC

BCL6

LEF1

CD5

MYC
Summary of findings

Morphology:
- Infiltration of the iris by large cells with open chromatin, frequently multiple peripheral nucleoli and high mitotic rate.
- Few admixed small cells and pigmented ciliary cells.

Immunophenotype:
- **Positive**: CD20, MUM1, BCL2, BCL6 (weak, heterogeneous), MYC (weak, heterogeneous)
- **Negative**: CD5, CD3, CD10, CD23, LEF1, EBERs
Differential diagnosis

- Richter transformation of CLL
- Secondary, unrelated DLBCL of non-germinal center type, primary to the iris
Is this discrimination important?

Incidence of RT
0.5%/y, 1%/y in treated patients

15-20% of DLBCL in CLL are clonally unrelated

Show superior prognosis

Rossi et al, Blood 2011
Approach to the diagnosis of discordant lymphomas

<table>
<thead>
<tr>
<th>Lymph-node</th>
<th>Bone-marrow</th>
<th>Clonality studies</th>
<th>Histologically Concordant vs. Discordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>With DLBCL infiltration</td>
<td>infiltration with lymphoma=BMI</td>
<td>Clonally Unrelated</td>
<td>BMI with different histology and different clonality studies = Discordant histology</td>
</tr>
<tr>
<td>Clonally related</td>
<td>Clonally related</td>
<td>BMI with different histology but similar clonality studies = Discordant histology</td>
<td></td>
</tr>
<tr>
<td>Clonally related</td>
<td>Clonally related</td>
<td>BMI with Concordant histology</td>
<td></td>
</tr>
</tbody>
</table>

Brudno et al, Blood 2016

CLL not available for clonality analysis!

Discordant lymphoma is not associated with an increased risk of CNS involvement
Immunohistochemistry of classic RT

**Variable loss of CLL profile**
- CD23-
- CD5- (50%)
- rare CD20-
- loss of p27
- LEF-1 constant

**Upregulation/Expression**
- MIB1
- p53 (60-80%)
- CD10 (5-20%), BCL6 (38%)
- MUM1 (>80%)
- cyclin D1 (25%, variable)

EBV is usually neg. (DD EBV+
- DLBCL, unrelated)

Risk for transformation to Richter syndrome

Unmutated IGH genes, stereotyped BCR, CD38, \textbf{del 17p} and ZAP70 expression are known risk factors for RT

**Genetically** two distinct pathways to Richter transformation

- TP53 and CDKN2A inactivation in 50% of cases
- C-MYC activation in 20-25%, usually co-occurring with TP53 inactivation
- Trisomy 12 and NOTCH1 mutations in 15-30% of cases, mutually exclusive with TP53

Chigrinova et al, Blood 2013
The mutational profile of RT is significantly different from *de novo* DLBCL

Fabbri et al, J Exp Med 2013
Primary intraocular lymphoma

Primary intraocular lymphoma is rare

Most commonly DLBCL of retina and vitreous body - **primary vitreoretinal lymphoma** (PVRL)

PVRL considered a subtype of **PCNSL**

**Primary iridal lymphoma** is extremely rare, most cases are of DLBCL type

Distinction from **primary choroidal lymphoma** usually an extranodal marginal zone B-cell lymphoma with indolent behaviour
Clinical and pathological features of PVRL

Masquerade syndrome – frequently delayed diagnosis

Common affection of both eyes and CNS involvement

Diagnosis by morphology, immunophenotype and clonality analysis difficult

Bonzheim et al, Blood 2015
DLBCL of immunoprivileged sites

Testis and CNS including eye
Poor prognosis
Sanctuary sites, common relapse
Almost always DLBCL of ABC type
High frequency of *MYD88* and *CD79b* mutations

**Key Points**

- *MYD88* mutation analysis significantly improves the detection rate of vitreoretinal B-cell lymphoma (VRL).

Addition of *MYD88* mutation analysis increased sensitivity from 62% to 90.5%
Detection of $\textit{MYD88}^{\text{L265P}}$ mutation in iris DLBCL

Melting temperature

- **WT**: 53.1 °C
- **$\textit{MYD88}^{\text{L265P}}$**: 62.7 °C
Does the $\textit{MYD88}^{L265P}$ mutation exclude a diagnosis of RT?

$\textit{MYD88}$ mutations (majority $L265P$) occur in 2% of CLL patients

Exclusively in CLL with $\textit{IGHV}^{\text{mut}}$ (4%)

Lack of association with $\textit{TP53}$, $\textit{NOTCH1}$ and $\textit{SF3B1}$ mutations

Good prognosis (similar to CLL $\textit{IGHV}^{\text{mut}}$)

Independent prognostic value and association with younger age controversial

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation protein</th>
<th>Mutation cDNA</th>
<th>Allelic frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYD88</td>
<td>p.Leu265Pro</td>
<td>c.794T&gt;C</td>
<td>31,8%</td>
</tr>
<tr>
<td>PIM1</td>
<td>p.His68Tyr</td>
<td>c.202C&gt;T</td>
<td>16,67%</td>
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<tr>
<td>PIM1</td>
<td>p.Gly83Asp</td>
<td>c.248G&gt;A</td>
<td>45,2%</td>
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<tr>
<td>PIM1</td>
<td>p.Glu124Gln</td>
<td>c.370G&gt;C</td>
<td>14,2%</td>
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<tr>
<td>PIM1</td>
<td>p.Leu129Phe</td>
<td>c.385C&gt;T</td>
<td>74,31%</td>
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<tr>
<td>PIM1</td>
<td>p.Ser146Asn</td>
<td>c.437G&gt;A</td>
<td>63,02%</td>
</tr>
<tr>
<td>PIM1</td>
<td>p.Leu174Phe</td>
<td>c.519_520delCCinsTT</td>
<td>10,09%</td>
</tr>
<tr>
<td>PIM1</td>
<td>p.Lys194Pro</td>
<td>c.580_581delAAinsCC</td>
<td>10,17%</td>
</tr>
<tr>
<td>PIM1</td>
<td>p.Val197Ile</td>
<td>c.589G&gt;A</td>
<td>10,35%</td>
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<tr>
<td>BTG1</td>
<td>p.Gly131Arg</td>
<td>c.391G&gt;A</td>
<td>28,61%</td>
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<tr>
<td>BTG1</td>
<td>p.Ala84Thr</td>
<td>c.250G&gt;A</td>
<td>22,15%</td>
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<tr>
<td>BTG1</td>
<td>p.Arg35Ter</td>
<td>c.103C&gt;T</td>
<td>26,85%</td>
</tr>
<tr>
<td>IGLL5</td>
<td>p.Ala23Val</td>
<td>c.68C&gt;T</td>
<td>34,23%</td>
</tr>
</tbody>
</table>
Proposed diagnosis

Primary iridal diffuse large B-cell lymphoma, non-germinal center type, $MYD88^{L265P}$ mutated