Videomicroscopy session

Laurence de Leval
Andrew Wotherspoon
Han van Krieken
59 yo M
Screening colonoscopy, chronic eczema
Colonic biopsies, and a small polyp

https://dih2.chuv.ch/dih/browse.php?token=boxdU0ySUdNS1cyUTuXV01RMGtXejFpcUo1MEZKRDICRk16bzJreE1LV1dNUTBsQlFwNS09LVlqSTNObVU0WWpnMk1UUTFZV1EwTXpWbFlUQXhNVEpoWTJNMVlqUXpObVZtTWpJd1lUa3lPUT09
T-cell lymphoid infiltrates in the GI tract

• T cell represent the major lymphoid component in many reactive conditions
• The majority of lymphomas of the GI tract are of B-cell derivation, T-cell lymphomas are overall rare
• Situations where a T-cell lymphoid infiltrate creates concerns for malignancy or represents lymphoma are relatively uncommon but represent potentially severe conditions
• Specific T-cell lymphoma entities are primary intestinal, but the GI tract can be secondarily involved by any type of systemic lymphoma, and T-cell lymphoma entities other than EATL/MEITL may on occasion present as a GI disease
<table>
<thead>
<tr>
<th>WHO 2008</th>
<th>Enteropathy-associated T-cell lymphoma type I (80-90%)</th>
<th>Enteropathy-associated T-cell lymphoma type II (10-20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 2016</td>
<td>Enteropathy-associated T-cell lymphoma (EATL)</td>
<td>Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)</td>
</tr>
</tbody>
</table>

### Epidemiology
- Northern Europe, association with celiac disease (CD) HLA-DQ2/-DQ8 : >90%
- Celiac disease uncommon
- HLA-DQ2/-DQ8 : nl frequency

### Morphology
- Pleomorphic, medium to large size, some cases anaplastic
- Inflammation, necrosis common
- Monomorphic, small to medium, epitheliotropic
- No inflammation, no necrosis

### Distant mucosa
- Enteropathy
- Increased IEL, no atrophy

### Immunophenotype
- CD3+, CD5-, CD8-/+, CD56-frequently CD30+
- Cytotoxic activated
- MATK+ < 40% of tumor cells
- CD3+, CD5-, CD8+-/-, CD56+-/-
- Cytotoxic activated
- MATK+ > 80% tumor cells
- Coexpression of B-cell antigens (20%)

### TCR expression
- Usually αβTCR
- γδTCR (Vδ1) > αβTCR
<table>
<thead>
<tr>
<th>WHO 2016</th>
<th>Enteropathy-associated T-cell lymphoma (EATL)</th>
<th>Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Northern Europe, association with celiac disease (CD) HLA-DQ2/-DQ8 : &gt;90%</td>
<td>Celiac disease uncommon HLA-DQ2/-DQ8 : nl frequency</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Pleomorphic, medium to large size, some cases anaplastic Inflammation, necrosis common</td>
<td>Monomorphic, small to medium, epitheliotropic No inflammation, no necrosis</td>
</tr>
<tr>
<td><strong>Distant mucosa</strong></td>
<td>Enteropathy</td>
<td>Increased IEL, no atrophy</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>CD3+, CD5-, CD8-/+, CD56- frequently CD30+ Cytotoxic activated MATK+ &lt; 40% of tumor cells</td>
<td>CD3+, CD5-, CD8+/-, CD56+-CD30- Cytotoxic activated MATK+ &gt; 80% tumor cells Coexpression of B-cell antigens (20%)</td>
</tr>
<tr>
<td><strong>TCR expression</strong></td>
<td>Usually αβTCR</td>
<td>γδTCR (Vδ1) &gt; αβTCR</td>
</tr>
<tr>
<td>WHO 2016</td>
<td>EATL</td>
<td>MEITL</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Genomic imbalances</td>
<td>+1q32.2-q41, +5q34-q35.2 +9q -16q21.1</td>
<td>+8q24 (MYC) +9q -16q21.1</td>
</tr>
<tr>
<td>Epigenetics</td>
<td>SETD2 mut. rare</td>
<td>SETD2 inactivation (&gt;90%)</td>
</tr>
<tr>
<td>JAK/STAT pathway</td>
<td>JAK1 mut (20-50%) JAK3 mut (10%) STAT3 mut (20%) STAT5B mut (rare)</td>
<td>JAK1 mut (10-20%) JAK3 mut (35-50%) STAT3 mut (10%) STAT5B mut (50-65%)</td>
</tr>
<tr>
<td>MAPK pathway</td>
<td>KRAS NRAS BRAF mut (20%)</td>
<td>BRAF KRAS NRAS mut (50%)</td>
</tr>
<tr>
<td>GRP signaling</td>
<td></td>
<td>GNAI2 mut (24%)</td>
</tr>
</tbody>
</table>

Tumor suppressor in solid malignancies: ccRCC, breast cancer, GISTS
Often biallelic inactivation (loss-of-function mutations and/or deletion) in > 90%
Potential therapeutic implications: WEE1 inhibitors selectively kill H3K3me3-deficient cancers by dNPT starvation (Pfister SX et al. Cancer Cell 2015)
Differential diagnosis GI tract T-cell lymphomas

- EATL versus MEITL
- Not all gastrointestinal T-cell lymphomas represent EATLs
  - Other specific PTCL entities: PTCL NOS, ENKTCL, ATLL
  - Strong CD30 expression in a variety of intestinal PTCLs
  - Primary ALCL of the GI tract is rare, first exclude EATL
  - Importance of clinical history but EATL might be the first manifestation of celiac disease
- Indolent lymphoproliferative disorders of the GI tract
Indolent T-cell lymphoproliferative disorders of the GI tract

- Important to recognize should not be diagnosed as lymphoma and do not require aggressive therapy
- Mucosal lesions, paucisymptomatic individuals, clinical correlation!
- No mass formation
- **Indolent T-cell lymphoproliferative disorder of the GI tract**
  - Bland cytology, CD4 or CD8 (cytotoxic), clonal TCR
- **NK-cell enteropathy (Lymphomatoid gastropathy)**
  - More aggressive histology, CD56+ CD8-, EBV-, polyclonal TCR
Young adult male patient who presented with diarrhea and had persistent digestive disease for three years. 
Courtesy C Copie Creteil

Indolent T-cell lymphoproliferative disease of the GI tract / CD8+
• 59-year-old Afro-Caribbean female patient, one year history of diarrhea and weight loss
• Gastroscopy: duodenal mucosa slightly nodular
• Courtesy Dr. A. Wotherspoon
- CD2+/CD3+/CD4+/CD7+/CD8-/CD56-/TCR-β+
- No cytotoxic granules, no TFH phenotype
- Clonal TCR-β and TCR-γ rearr.
- Courtesy Dr. A. Wotherspoon
Diagnostic approach

• **Biopsies**
  – Rare diagnoses for a primary diagnosis an extensive workup is recommended;
  – Phenotypic aberrations and clonality analysis
  – Importance of clinical correlations
  – Malignant lymphoma versus indolent lymphoproliferations
  – EATL/MEITL may involve the stomach (even at presentation)

• **Surgical resections** represent the diagnostic specimen in many instances.
Progression from Celiac Disease to EATL-1

CD refractory to gluten-free diet
Ulcerative jejunitis

RCD I
Intraepithelial lymphoma

RCD II

Lymphoma

EATL

<table>
<thead>
<tr>
<th>CD</th>
<th>RCD1</th>
<th>RCD2</th>
<th>EATL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphs</td>
<td>IEL: sCD3+, cCD3+, CD5-, CD8+, CD103+</td>
<td>IEL: sCD3+, cCD3+, CD5-, CD8+, CD103+</td>
<td>Atypical infiltrating: CD3+, CD5-, CD8-, CD30+, Ki67+, CD30+</td>
</tr>
<tr>
<td>Genetics</td>
<td>Polyclonal TCR</td>
<td>Polyclonal TCR</td>
<td>Monoclonal TCR +9q31-16q12</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Indolent</td>
<td>Rather indolent 5-y OS: ~90%</td>
<td>Aggressive 5-y OS: ~50%</td>
</tr>
<tr>
<td>Risk of EATL</td>
<td>0.7% in 5 years</td>
<td>14% in 5-y</td>
<td>33-52% in 5-y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Highly aggressive 5-y survival: ~20%</td>
</tr>
</tbody>
</table>