PRIMARY T-CELL AND NK-CELL LYMPHOPROLIFERATIVE DISORDERS OF THE GASTROINTESTINAL TRACT

XIX EAHP Workshop, Edinburgh September 2018

Maria Calaminici
GI Lymphomas

Low Grade B Cell Lymphomas, MALT Lymphomas, MCL
Duodenal type FL

‘High Grade’ B cell Lymphoma

Extranodal NK-T Cell Lymphomas
Nasal Type

ALK- ALCL

Intestinal T Cell Lymphomas
GI Lymphomas

Primary Gastrointestinal T-Cell and NK-cell Lymphoproliferative Disorders

- Enteropathy-associated T cell Lymphoma (EATL) and precursor lesions (Type 2 Refractory Coeliac Disease, RCD)

- Monomorphic Epitheliotropic Intestinal T Cell Lymphoma

- *Indolent T Cell Lymphoproliferative Disorders of the gastrointestinal tract*

- *NK Cell Enteropathy*
Primary Gastrointestinal T-Cell and NK-Cell Lymphoproliferative Disorders

Refractory Coeliac Disease

- Persistence of clinical symptoms
- Altered villous architecture
- Increased number of intraepithelial lymphocytes (IELs),

Biologically diverse disease currently classified into:

a) Type 1, more frequent (up to 80% of cases), normal phenotype, polyclonal IELs, high 5-year survival rate and low risk of developing EATL.

b) **Type 2**, clonal proliferation of aberrant IELs and considered a *precursor of EATL*.
Refractory Coeliac Disease Type 2 (precursor of EATL)

- Clonal proliferation of aberrant IELs.
- Pleomorphic cells with aberrant T-cell phenotype (CD3+, CD7+, CD103+, granzyme B-/+, TIA1-/+, partial/weak, CD30++).
- T cell receptor gene rearrangement can be present.

- CD30 positivity in intraepithelial T-cells in patients with refractory celiac disease has been associated with transformation to EATL and suggestive of evolution of refractory celiac disease into EATL.
RCD2: mild villous atrophy (villi shortened but preserved). Flow cytometry showed a large fraction of phenotypically aberrant IELs (CD30 was negative).

TCRβ clonality studies showed polyclonal products.

NGS revealed a STAT3 S614R hotspot mutation.
Primary Gastrointestinal T-Cell and NK-Cell Lymphoproliferative Disorders

Enteropathy-associated T cell Lymphoma

• aggressive disease with problematic differential diagnosis in some cases
• directly related to RCD
• frequently large cell anaplastic morphology, prominent angiocentricity, angioinvasion and perineural invasion
Identical monoclonal T-cell receptor gene rearrangement was present in all biopsies indicating a clonal relationship among them.
EATL: RCD1 patient presenting with liver masses 8 months before developing small intestine obstruction (jejunal bx). H&E: large cell morphology in liver.
The lymphomas at the two locations were clonally related (TCR β PCR) but showed different morphology and phenotype. The liver lymphoma exhibited anaplastic morphology and phenotypically resembled ALK- /ALCL which could have led to such diagnosis if the history of celiac disease was not known.
EATL jejunal mass resection. Biphasic pattern with intermediate cells in the mucosa and large cells in the submucosa. The patient had known 5 yrs history of CD and presented with abdominal pain and obstruction.
Neoplastic cells were negative for CD3, CD4, CD5, CD7 and CD8. There was clonal TCR beta and gamma chain rearrangement by PCR. FISH positive for *DUSP22/IRF-4* gene rearrangement in 100% of nuclei, TP63 negative. ?ALK-ALCL
PREVIOUS DUODENAL BIOPSY

- TCR gene rearrangement positive with identical pattern compared to jejunal mass resection specimen
- FISH positive for DUSP22/IRF-4 gene rearrangement (63% of nuclei)

FINAL DIAGNOSIS: EATL WITH DUSP22/IRF4 REARRANGEMENT DEFINED BY PREVIOUS HISTOLOGY PROVEN COELIAC DISEASE.
Primary Gastrointestinal T-Cell and NK-Cell Lymphoproliferative Disorders

Monomorphic Epitheliotropic Intestinal T Cell Lymphoma (MEITL)

• previously known as EATL type 2
• accounts for most cases in Asia and affects males more often than females
• early dissemination to extraintestinal sites
• no clear association with Coeliac Disease
IMMUNOPROFILE: CD2+, cCD3+ CD7+, CD8+, CD56+, TIA-1+, BCL2+; **Negative:** CD4, CD5, CD30, Granzyme B, Tdt, TCR-beta F1; **EBV-ISH (EBER):** negative
MEITL ABERRANT PHENOTYPE: CD8 OR CD56 CAN BE NEGATIVE.
Primary Gastrointestinal T-Cell and NK-Cell Lymphoproliferative Disorders

MEITL MOLECULAR FEATURES

• New mutational analysis in intestinal lymphomas have shown that MEITL has a high proportion of activating mutations in STAT5B (63%) in cases of both gamma-delta and alfa-beta T-cell derivation.

• The most common mutated gene is SETD2 (90%).

• Both mutations seem to be unique to MEITL and not present or rarely described in EATL.
Indolent T cell lymphoproliferative disorders of the gastrointestinal tract

Provisional entity
- Chronic diarrhoea, abdominal pain, nausea and vomiting and weight loss. Some patients are diagnosed and treated as inflammatory bowel disease, irritable bowel syndrome or coeliac disease.
- All patients receive treatments: azathioprine, steroids, antibiotics, CHOP; they all recur.
- Similar histological features in all cases.
- Immunoprofiles: CD3/CD8+, CD3/CD4+, CD4/CD8-.
- Nodal involvement (regional LNs) frequently described: 4/9 workshop cases.
Indolent T cell lymphoproliferative disorders of the gastrointestinal tract

Diffuse dense lymphoid infiltrate mainly confined to the mucosa with minimal spillover to submucosa, without ulceration. The lymphoid infiltrate respects the epithelium and displaces rather than destroys the glandular elements. Mild if any increase in Intraepithelial lymphocytes.
The lymphoid infiltrate in this case was mainly composed of CD3+, CD4+, CD8-, CD56- small cells with aberrant weak CD20 expression, and proliferation rate of less than 5%.
Involvement of regional lymph nodes has been described. Partially preserved architecture with open sinuses, occasional residual lymphoid follicles and slight interfollicular expansion. T-cells show identical immunoprofile to the intestinal lesion.
Molecular studies:
PCR analysis for TCR genes rearrangement of the CDR3-region of the TCR gamma chain gene demonstrated the same monoclonal peak in the small bowel and the lymph node.
Recurrent STAT3-JAK2 fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

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<th>EAHP#</th>
<th>JAK2 BAP FISH</th>
<th>STAT3-JAK2 D-FISH</th>
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*Courtesy of Dr A Feldman, Mayo Clinic*

**JAK2 BAP FISH**
- LYWS174 (split)
- LYWS421 (normal)

**STAT3-JAK2 D-FISH**
- LYWS174 (fusion)
Indolent T cell lymphoproliferative disorders of the gastrointestinal tract

Disease Progression in a Patient With Indolent T-Cell Lymphoproliferative Disease of the Gastrointestinal Tract
Anamarija M. Perry, MD1, Nathanael G. Bailey, MD2, Michelle Bonnett, MD3, Elaine S. Jaffe, MD4, and Wing C. Chan, MD5


- Case report of indolent T-LPD of the GI tract with progression into a clonally related, aggressive T-cell lymphoma.
- Out of 45 cases published, five cases have been described to have progressed into more aggressive T-cell lymphomas: 3 CD4-positive, 1 CD4/CD8 double-negative and 1 CD8-positive. The latter developed a clonally unrelated ALK- ALCL.
- Data still limited but suggest that CD8-positive cases have better long-term prognosis with lower rate of progression.
- CD4+ cases are better characterized molecularly.
- Optimal management presently unknown. Careful long-term follow-up of these patients is essential as some may progress into more aggressive disease.
NK Cell Enteropathy

• Poorly defined entity
• Firstly described in 2006 (Vega et al) as indolent ‘NK-cell LPD of the GI tract’.
• Short series from the US followed defining it as ‘NK-cell Enteropathy’.
• Similar cases were described in Japan and referred to as ‘Lymphomatoid Gastropathy of NK cell type’.
Lymphomatoid gastropathy: random gastric biopsies showed active chronic gastritis positive for H. pylori infection. Patient responded to eradication.
NK Cell Enteropathy

- Dense lymphoid infiltrate in the lamina propria.
- Lymphoid cells are small in size and only show mild atypia.
- There is no epitheliotropism
NK Cell Enteropathy

- Lymphoid cells are positive for CD2, CD3 (cytoplasmic), CD56, TIA1 and granzyme B
- Negative for CD5, CD4, CD8, TCRbeta, TCRdelta, CD25, CD30, PD-1 and EBV. Ki-67 40%.
- Immunohistochemical stain for H. Pylori is negative.
EAHP 252

Novel somatic JAK3 and AXL mutations in NK-cell enteropathy: genetic evidence of a neoplastic process

Wenbin Xiao*, Jinjuan Yao, Kseniya Petrova-Drus, Anita Kumar, Ahmet Dogan
MSKCC, NY

• First report of mutations on NK-cell enteropathy, supporting it as a neoplastic rather than reactive process.

• JAK3 mutations are often seen in NK/T-cell lymphoproliferative disorder/lymphoma.

• AXL is a member of TAM receptor family that has been reported to be indispensable for NK cell development and function in mouse models.


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