Gastrointestinal Lymphoma
MALT-lymphom

BC 24.10.2018
Bern

Universitätsklinik für Viszerale Chirurgie und Medizin
Most difficult question of BC
For the expert: What are dutcher bodies?

Non-specific, non-pathognomonic
In/from plasma-cells – and high-volume production of antibodies......
Most easy question of BC:
What is the mainstay in treatment of gastric MALT?

Failure to answer
Gastrointestinal lymphomas are classified into?

- **B-cell**
  
  Extranodal NHL of MALT
  
  Diffuse Large B-Cell lymphoma (DLCBL)
  
  Mantle-Cell-lymphoma
  
  Burkitt-lymphoma
  
  Follikular lymphoma

- **T-cell**
  
  associated or not with enteropathy and/or atrophy
Epidemiology of primary gastrointestinal lymphoma (PGIL) – incidence, age, location ..?

**PGIL:**
very rare: <1% of all GI-tumors

0.5 – 1.3/100.000

age 50-70 at diagnosis

stomach > small intestine > colon in frequency

90% B-cell-derived

**MALT:**

1:30.000 to 1:100.000 (USA)
GASTRIC B-LYMPHOMA

Extranodale NHL/PGIL -> marginal zone MALT (small B-cells, low malignancy)
Lymph Follicle: sort accordingly to nomenclature

- Germinal Centre
- Benign Mantle Cells
- Marginal Zone Lymphoma
Lymph Follicle: sort accordingly to nomenclature

Germinal Centre

Benign Mantle Cells
outer ring of small lymphocytes

Marginal Zone Lymphoma

*mature B cells proliferate, differentiate, and mutate their antibody genes*

*MZ-B-cells Express polyreactive B-cell-receptors Binding microbial molecular patterns*

*In MALT Derived from Memory B-cells Within the germinal centre*
Diagnosis of MALT-lymphoma is based on?

- **Histopathology**: Latest WHO-classification/definition:
  
  .....composed of morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast-like cells

  - *There is plasma cell differentiation in a proportion of cases*
  - *The infiltrate is in the marginal zone of the reactive B-cell follicles and extends into the interfollicular region.*
  - *In epithelial tissues the neoplastic cells typically infiltrate the epithelium forming lymphoepithelial lesions.*
Endoscopic diagnosis / Gastric mapping – how?

- 1 biopsy from corpus and antrum, resp. for urease test
- 4 biopsies from normal mucosa in antrum and corpus, resp., and 2 biopsies from the fundus

> 10 biopsies from macroscopic visible lesions

No H.pylori eradication before results of reference pathologist is available
Which stains/antibodies to use in diagnosis?

- B-cell marker:
Which stains/antibodies to use in diagnosis?

B-cell marker:

typically CD20
Which stains/antibodies to use in diagnosis?

- **B-cell marker:** typically CD20

- **Neoplastic nature** suggested by:
  - CD 43 (normal B-cells negative)
  - bcl2-protein (reactive germinal centre cells negative)
  - Ki67 (proliferation-associated)
How to stage gastric MALT-lymphoma – What to examine, test, seek?

- Physical exam: Lymph nodes, Waldeyer ring/HNO, liver, spleen...
- Lab work: CBC, LDH, b2-microglobulin, Immunofix, HIV, HCV, HBV
- CT-Tx, Abd, pelvis for LN`s and spreading assessment
- Bone marrow biopsy
  - if no regression after HP-eradication and before oncological treatment
- Ileocolonoscopy should be considered- mapping endoscopically
  - always independent of macroscopic suspicious lesions
Is EUS absolutely needed for staging?

- Only reliable method to stage
- Depth of invasion and
- Separate T1 from T2 and thus
  - I1E from I2E
What staging system to use for gastric MALT-lymphoma?

Infiltration into subserosa + regional lymph node compartment 2 = ?

<table>
<thead>
<tr>
<th>Ann Arbor system, modified*</th>
<th>Paris staging system †</th>
<th>Spreading of lymphoma</th>
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<tbody>
<tr>
<td>I1E</td>
<td>T1N0M0</td>
<td>Mucosa, submucosa</td>
</tr>
<tr>
<td>I2E</td>
<td>T2N0M0</td>
<td>Muscularis propria, subserosa</td>
</tr>
<tr>
<td>I2E</td>
<td>T3N0M0</td>
<td>Serosa penetration</td>
</tr>
<tr>
<td>I2E</td>
<td>T4N0M0</td>
<td>Per continuitatem infiltration of neighbouring organs</td>
</tr>
<tr>
<td>I11E</td>
<td>T1—4N1M0</td>
<td>Regional lymph nodes (compartment I + II)</td>
</tr>
<tr>
<td>I12E</td>
<td>T1—4N2M0</td>
<td>Intra-abdominal distant lymph nodes</td>
</tr>
<tr>
<td>IIIE</td>
<td>T1—4N3M0</td>
<td>Extra-abdominal lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>T1—4 N0—3M1</td>
<td>Diffuse or disseminated infiltration of distant or extra-gastrointestinal organs</td>
</tr>
<tr>
<td></td>
<td>B1</td>
<td>Bone marrow</td>
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T2N1M0 = II1E
H. pylori-eradication – how you do it?

Anti-bacterial Herbs

Manuka Honey

Coconut oil

How to kill H. pylori Naturally
H.pylori-eradication – how you do it?

Success dependend on rate/risk of resistance

• History of antibiotic exposure?
• Geographic/local rate of resistance low to clarithromycin, metronidazole then conventional triple possible
• Dual resistance to clarithromycin+metronidazole > 15% hampers also success of non-bismuth quadruple regimen

Highest Cure Rate else with either

• Bismuth Quadruple with > 90% eradication rate

Malfertheiner et al. Maastricht Gut 2017
What is Bismuth-Quadruple -H. pylori-eradication?

<table>
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<tr>
<th>Drug</th>
<th>Dosage</th>
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<tr>
<td>PPI</td>
<td>Standard dose, bid</td>
</tr>
<tr>
<td>Bismuth subcitrate</td>
<td>420 mg, qid</td>
</tr>
<tr>
<td>Metronidazole/Tinidazole</td>
<td>500 mg, tid</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500 mg, qid</td>
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For 10 – 14 days

Highly effective: Eradication rate 92%
Cost effective: 14d course < 87 CHF
Why H. pylori-treatment in H. pylori-negative MALT?

Eradication in all cases, stages of disease since

- *also other Helicobacter species can cause MALT*
- *diagnostic test has missed H. pylori*

Success-rate reported to be about 19%
When is no good response to H. pylori-eradiation to be expected?

- Translocation t(11,18)
- H. pylori-negative Lymphoma
- Lymphnode positive stage of disease
### Grading-system for post-treatment follow-up?

**GELA: Group d’Étude des Lymphomes de L’Adulte**

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**Legend**

- **Partial Response**
- **Stable Disease/Progression**
Complete Remission is defined as?

2 sequential gastroscopies with mapping Bx and no lymphoma - histomorphologically

Rate of Complete Remission in

IE1 mucosa: > 90%
IE1 submucosa: 78%
IE2: = deeper infiltration: 54%
Follow-up after H. pylori-eradication: Frequency of endoscopy/biopsies/EUS?

- **6 weeks** after HP-eradication endoscopy:
  to rule out progression + to test HP in histology + C13 Breath-test

- **3-6 months** after completion of eradication endoscopy:
  then every 4-6 months for first 2 years/ until CR or pMRD
  - at each endoscopy mapping biopsies

  HP-persistence -> Re-biopsy with culture + susceptibility test

- EUS not generally recommended BUT
Surveillance after complete remission? How long and Why?

Annually endoscopy for up to 10 years
(after 5 years rather arbitrary) due to
Risk of AdenoCarcinom up to 6-fold increased
particularly if intestinal metaplasia, dysplasia present, develops

7.2% suffer relapse (or rather incomplete regression)
Yearly 2.2% relapse rate
Indications for surgery in gastric MALT?

Usually NO

Only complications such as

Perforation, Bleeding

....
When and what further local/systemic treatment after H.pylori-eradication?
Radiation in gastric MALT – when – why - how ?

Localized gastric MALT

I1E- II1E (T1-4, N0/1 M0B0)

MALT radiation sensitive

Cure Rates up to 100%

30 (-40) Gy mostly sufficient (15-20 sessions in fasted state)
Chemo-Tx in gastric MALT – when – why - how?

Rather reserved for disseminated MALT:

For symptomatic disease or other treatment indications:
- overt progression or Bulky disease
- Impending organ damage or patient preference

active irrespective of translocations:
2CdA (Cladribine/prodrug)
Rituximab + Chlorambucil/CHOP
(or Bendamustin)

Cave: Secondary Carcinomas

Alkylating agents: 75% CR (except in t(11,18))
Others: Bortezomib, Oxaliplatin, MTx

Progression-free Survival 72%
Prognostic Index for gastric MALT and CTx

<table>
<thead>
<tr>
<th>N = 400</th>
<th>HR</th>
<th>Standard Error</th>
<th>95% CI</th>
<th>P</th>
</tr>
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<tr>
<td>Stage III-IV</td>
<td>1.79</td>
<td>0.26</td>
<td>1.35-2.38</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &gt;70 y</td>
<td>1.72</td>
<td>0.27</td>
<td>1.26-2.33</td>
<td>.001</td>
</tr>
<tr>
<td>LDH &gt;UNL</td>
<td>1.87</td>
<td>0.37</td>
<td>1.27-2.77</td>
<td>.002</td>
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Risk-factor:

- 0
- 1
- ≥2

Log rank test, P<0.0001
What is the relevance of clonality in MALT-lymphoma?

- Monoclonality by PCR is not a prerequisite for diagnosis
- BIOMED-2-PCR-protocol: in 50% during follow-up still positive despite lack of macroscopic/immunohistochemical lymphoma
  - With clonality: only slightly higher relapse risk =
  - ergo not of major clinical and/or diagnostic relevance
Intestinal B-cell lymphoma: types and treatment

Extranodal marginal-cell B-cell MALT:
very rare, no consensus, if localized watch-and-wait
Chlorambucil + Rituximab and if aggressiv transformation the R-CHOP

Diffuse Large-B-cell-Lymphoma (DLBCL):
as in stomach: CTx plus Rituximab (R-CHOP), 6-8 cycles every 3 weeks

Mantelcell-lymphoma:
most frequent intestinal lymphoma, often multifocal intestinal sites+LN, blood...
< 65 R-DHAX plus autologous-Stemcell-Tx
> 65 R-CHOP plus maintenance Rituximab

Follicular lymphoma: endoscopic aspect of lymphomatous polyposis
If asymptomatic then no treatment – if symptomatic or high tumor mass: R-CHOP

Burkitt-Lymphom
Immunoproliferative small intestinal disease (IPSID)
Immunoproliferative Small intestinal disease is ..... 

• localized small intestine and mesenteric lymph nodes
• affecting the exocrine IgA-mucosal machinery = called
• Alpha chain disease
• Pathogenic role of Campylobacter jejuni
• Stages: Plasmocyte – Intermediate - Immunoblastic
Immunoproliferative Small intestinal disease: TP...

depends on age, general/nutritional status: due to malabsorptive /enteropathy-> substitution of deficiencies (iron, folate, magnesium, calcium....)

> enteral/parenteral nutrition

treatment according to Tumor stage:

A/Plasmocyte/localized intestinal +/- LN-> macrolide and/or tetracycline

B/Intermediate/ Immunoblastic stage C: R-CHOP

(evtl. autologous stem-cell-transplantation)
Who is Who in mucosa-associated ......

Isaacson PG
seen and described histomorphology of MALT first time...

Fischbach W
Meta-Analysis GastroUpdate- „Expert“

MacPherson A
Truely understands B/T-cells and....