The Modern Management of IBD Neoplasia

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carcinoma/dysplasia ?
ALM, ALM-like DALT, DALM, CA,
low grade, high grade
Colitis associated, sporadic
Adenoma, intraepithelial neoplasia
Adenoma-like dysplasia, RLD *

* = raised lesion with dysplasia
# Colitis associated with biologicals

<table>
<thead>
<tr>
<th>Drug</th>
<th>aim</th>
<th>Indication</th>
<th>side effects</th>
<th>colon affection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>anti-CD20</td>
<td>B-NHL</td>
<td>27% kids with nephrot. Syn.</td>
<td>Fever, PMLE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Skin excema</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DD: IBD</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>anti-CD20</td>
<td>Melanoma</td>
<td>40% side effects</td>
<td>Dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uveitis, Nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20% Colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unspecific or UC - like no granuloma</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>anti VEGFR</td>
<td>CRC, NSCLC</td>
<td>case reports</td>
<td>colon perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>insufficiency of anastomosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ischemic colitis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>anti-TNF a</td>
<td>Rheuma</td>
<td>case reports</td>
<td>IBD first manifestation</td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td></td>
<td></td>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UC &amp; CD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Super infections</td>
</tr>
<tr>
<td>Datasinib</td>
<td>anti-Tyr kin</td>
<td>Leukemia</td>
<td>30% colitis</td>
<td>colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea DD: IBD/infection</td>
</tr>
</tbody>
</table>

modified after Freeman HJ. World J Gastroenterol. 18:1871-4, 2012
Colitis-Differential diagnoses

n=1031 Bayreuth

Infectious Colitis          29.6 %
Ulcerative colitis         29.7 %
Crohn‘s disease            18.2 %
Diagnostically unclear     8.4 %
Location of neoplasms in ulcerative colitis

- Transverse: 15 (14%)
- Descending: 10 (9%)
- Sigmoid: 25 (23%)
- Rectum: 20 (18%)
- Unknown site: 13 (12%)
- Ascending / cecum: 27 (25%)
## Details of neoplastic lesions in ulcerative colitis

<table>
<thead>
<tr>
<th>110 neoplastic lesions</th>
<th>25 invisible</th>
<th>After histopathological analysis: 1 CRC, 8 HGD, 16 LGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>85 visible - median size 10mm (range 1-40mm)</td>
<td>At colonoscopy: 74 polypoid, 4 irregular outline, 1 plaque, 6 macroscopic CRC (one only histologically confirmed at colectomy)</td>
<td>Decision after histopathological analysis: 16 DALMs (8 HGD, 8 LGD), 41 TA (33 mild, 8 moderate dysplasia), 12 TVA (8 mild, 4 moderate dysplasia), 11 VA (3 LGD, 4 mild, 3 moderate, 1 villous dysplasia), 5 CRC</td>
</tr>
</tbody>
</table>

Rutter M et al. Gastrointest Endosc 2004
Regression plot of CRC incidence over time

Rutter MD, et al Gastroenterology 2006
Comparison 2001 vs 2011

- 2001: 60 Neoplasms in UC
- 2011: 153 Neoplasms in UC

Vieth et al. 2012
Neoplasia concepts in IBD

Vieth et al. 2012
Polypoid Dysplasia in IBD

Adenoma-like DALM

Classic DALM (non adenoma-like)

Adenoma-like DALM

Polypoid Dysplasia in IBD

DALM

ALM

Warich-Eitel et al. Pathologe 2011

Laine L. et al. SCENIC GI Endoscopy 2015: PARIS classification!
Inflammation - > carcinogenesis

- Bacteria
- Environment
- Proinflammatory cytokines, Chemokines, Oxidative Stress, RONS, Growth factors, ECM Alterations, Angiogenesis
- Genetic and epigenetic Alterations
- Inflammation
- Neoplasia
- T-Cell
- Fibroblast
- Makrophage

Inflammation - > carcinogenesis
Dual effect of Epiregulin in UC carcinogenesis

Role of fibroblasts underestimated!

Sporadic carcinoma

Aneuploidy
Methylation

APC

Normal Epithelium → early Adenoma → Intermediate Adenoma → late Adenoma → Carcinoma

MSI k-ras COX-2

DCC/DPC4

p53

colitis-associated carcinoma

Aneuploidy
CIN/MSI
Methylation

COX-2

p53 mut.

Normal Epithelium → suspicious for Neoplasia → Low grade IEN/Dysplasia → High grade IEN/Dysplasia → Carcinoma

p53 LOH

DCC/DPC4

K-ras

APC

Itzkowitz SH et al- 2004
Mikrosatellite instability (MSI) frequently in UC carcinoma?

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>MSI-L</th>
<th>MSI-H</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=20)</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Indefinite (n=11)</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Dysplasia (n=15)</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>UC-CRC (n=11)</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>0.0015</td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 Jahre</td>
<td>21</td>
<td>4</td>
<td>5</td>
<td>0.084</td>
</tr>
<tr>
<td>≥ 5 Jahre</td>
<td>11</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

## Comparison of molecular alterations of p53, KRAS, BRAF Genes and MSI in Asia

<table>
<thead>
<tr>
<th></th>
<th>MSI</th>
<th>p53</th>
<th>KRAS</th>
<th>BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UC Low risk (n=30)</strong></td>
<td>0</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>UC High risk (n=28)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non progressors (n=22)</td>
<td>0</td>
<td>6 (27.3%)&lt;sup&gt;a)&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>progressors (n=6)</td>
<td>0</td>
<td>3 (50%)&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>1 (16.7%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Sporadic (n=30)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma (n=8)</td>
<td>0</td>
<td>0</td>
<td>2 (25%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>carcinoma (n=22)</td>
<td>5 (22.7%)&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>10 (45.5%)</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Table Notes:**
- a) P<0.05 when comparing p53 gene alterations of UC-HR nonprogressor with UC-LR.
- b) P<0.05 when comparing p53 gene alterations of UC-HR progressor with UC-HR nonprogressor and UC-LR.
- c) P=0.052 showing comparison of MSI in S-CRN vs. UC-LR and UC-HR.

*Shivakumar et al. J Crohns colitis 2012*
Mikrosatellite instability (MSI) frequently in UC carcinoma?

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>MSI-L</th>
<th>MSI-H</th>
<th>P-Wert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indefinite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplasie</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC-Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dauer der Erkrankung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 Jahre</td>
<td>21</td>
<td>4</td>
<td>5</td>
<td>0,0015</td>
</tr>
<tr>
<td>≥ 5 Jahre</td>
<td>11</td>
<td>7</td>
<td>9</td>
<td>0,084</td>
</tr>
</tbody>
</table>

Not to be confirmed in other studies! Situation unclear: to real difference to sporadic carcinoma. Non relevant to differentiate sporadic dysplasia from colitis associated dysplasia! Population dependent?
Ulcerative colitis neoplasia

1. Dysplasia
   - 5% Incidence/10 years
   - 25% Incidence/20 years

2. Carcinoma
   - 3-43% Incidence 25-35 years
     - 5-10% Incidence/20 years
     - 10-20% Incidence/30 years
   - 1-2%/years after 10 years
Lower risk

- Extensive colitis with no active endoscopic/histological inflammation OR left-sided colitis OR Crohn's colitis of < 50% colon

Intermediate risk

- Extensive colitis with mild active endoscopic/histological inflammation OR post-inflammatory polyps OR family history CRC in FDR aged > 50

Higher risk

- Extensive colitis with moderate/severe active endoscopic/histological inflammation OR stricture in past 5 yr OR dysplasia in past 5 yr declining surgery OR PSC/transplant for PSC OR family history CRC in FDR aged < 50

5 yr

3 yr

1 yr
UC Neoplasia

Sporadic Adenoma

are also focal intraepithelial Neoplasms,

but differ grossly and molecularly.

**DALM**

**Sporadic Adenoma-like**
- sessile/stalked
- Sharply delineated
- Smooth surface

**Histology**

**Colitis-associated**
- Often sessile
- Unsharply delineated
- Irregular surface
- velvety, verrucous elevation and/or depression

**Histology**

Schneider u. Stolte 1993; Engelsjerd et al. 1999; Rubin et al. 1999; Vieth et al. 2000; Vieth 2003; Vieth 2003
<table>
<thead>
<tr>
<th></th>
<th>sporadic</th>
<th>colitis-associated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucin vacuoles</strong></td>
<td>regular, apical</td>
<td>irregular, basal, dystro.</td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>palisading, densely packed,</td>
<td>more round, loosely packed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stromal tissue</strong></td>
<td>little, loose stroma</td>
<td>broad and varying amount</td>
</tr>
<tr>
<td><strong>Proliferation zone</strong></td>
<td>apical</td>
<td>basal, horizontal at base possible</td>
</tr>
<tr>
<td><strong>Delineation</strong></td>
<td>sharp</td>
<td>unsharp</td>
</tr>
</tbody>
</table>

Vieth et al. Leber Magen Darm 2000
## UC Neoplasia

<table>
<thead>
<tr>
<th></th>
<th>Adenoma</th>
<th>UC.-Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>66 years</td>
<td>43 years</td>
</tr>
<tr>
<td><strong>Duration UC:</strong></td>
<td>7 years</td>
<td>12 years</td>
</tr>
<tr>
<td><strong>Single lesion:</strong></td>
<td>65%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Pancolitis:</strong></td>
<td>47%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Euploidy:</strong></td>
<td>100%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>p53-Mutation:</strong></td>
<td>4%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>bcl-2-Expression:</strong></td>
<td>76%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Schneider u. Stolte  Z Gastroenterol, 1993
UC neoplasia

365 Patients included

- 148 Adenoma 40.5%
  - 16.3% multifocal
- 137 Colitis-Dysplasia 37.5%
  - 114 low grade Dysplasia
  - 23 high grade Dysplasia
  - 14 Adenoma + C.u.-Dysplasia
  - 77.5% multifocal
- 80 Colitis-carcinoma 22.0%
  - 48.1% multifocal

Vieth et al. Gut 2006
Neoplasia in Ulcerative Colitis

Follow-up Adenoma after Polypectomy:

(n = 88; median Follow-up: 7,1 years)

0 Pat. carcinoma

4 Pat. Dys but other segment: 2xCa in follow-up

3 Procto-colectomy
UC neoplasia

Follow-up low grade Dysplasia

(n = 114; median Follow-up: 5.8 years)

4 Pat. carcinoma same location
6 Procto-colectomy

Conclusion: Dysplasia needs to be treated!

But: How?

Follow-up of carcinoma

(n = 72; median Follow-up: 4.7 years)

47 Pat. Procto-colectomy (11 deceased, 13x relapse)

19 Resection like spor. carcinoma (5 deceased, 8x relapse)

Prognosis:

Relapse more often in partial colectomy

Survival slightly lesser in partial colectomy

Rutter, Riddell 2013
**Indication for surgery with surgical findings**

<table>
<thead>
<tr>
<th>Surgical indication (no. patients)</th>
<th>Findings in surgical-specimen</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nil</td>
<td>Adenoma</td>
<td>LGD</td>
<td>HGD</td>
<td>CRC (%)</td>
</tr>
<tr>
<td>Symptoms (44)</td>
<td>36</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Adenoma (1)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LGD (14)</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>HGD (16)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>CRC (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Total (89)</td>
<td>41</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>27 (30.3)</td>
</tr>
</tbody>
</table>
UC neoplasia

cancer risk after endoscopic resection of a dysplastic lesion

is low and no different from that of a surveillance cohort

Rutter M et al. Gastrointest Endosc 2004
3 easy steps to take home !!

1. Pin on cork or thick paper !
2. Do not stretch !
3. Do not pin through lesion !
4. Fixate in 4% neutral buffered formalin (no alcohol) !

Soetikno et al. J Clin Oncol 2005
3. R-Status by the pathologist in ER-specimen

- **R0 - Resection**
- **R1 - Resection**
- **RX - Resection**
What is it?

Depth of infiltration?
Further risk factors?

Lateral margin (HM)? HM1c, HM1d

Basal margin (VM)? VM1c

C. Langner
M Vieth ESD Guidelines
3. R-status by the pathologist in ER-specimen

Distance to margin in mm

Diagnosis: R0-Resection

Local relapse in piece-meal-ER 10-15%, in ESD <1%

C. Langner
Improvement of colitis diagnostics by change of biopsy technique and clinical informations from 66% correctness to almost 100%

Dejaco et al. Endoscopy 2003
Guidelines

1. Biopsies from at least 5 segments of colon incl. rectum

2. Informations on previous therapies

3. Informations on duration of disease

4. Endoscopic findings ?
Conclusion 1

• 2011 more Neoplasms than 2001

• 2011 earlier stage than 2001

• Different pathways -> different consequences

• No major difference on outcome in ER (Odze et al. 2004, Rutter et al. 2006, 2013)
Practical Conclusion

- Specimen handling in endoscopy
- Localisation
- Gross description
- Specimen handling in pathology
- Primary Diagnosis (aetiology!)
- Resection status
- Risk factors

ensures predictive value of histopathology!
CASE OF THE MONTH

September 2012

Colorectal polyp, measuring 8 mm in largest diameter, obtained from the sigmoid colon of a 76-year-old female.

What is your diagnosis?