Pathology of Malabsorption
dealing with duodenal biopsy

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Outline

• Duodenal biopsy
• Classification of malabsorption
• Gluten Sensitive Enteropathy
• Differential diagnosis
• Reporting

Duodenal biopsy

Bulb

Distal duodenum
• Villi short & blunted
• Villi flat in proximity to Brunner glands or lymphoid follicles
• Foveolar metaplasia
• Peptic injury
• H.pylori

Biopsy orientation

• Mucosal surface upwards on a supporting medium (filter paper, tissue, dental wax)
• Naked eye or dissecting microscope
• Embedded in wax on the side
• Cut through vertical plane
Clinical data

• Age & gender
• Signs and symptoms
• Site of the biopsy
• Endoscopic & radiologic findings
• Clinical diagnosis / impression
• Medical and surgical history
• History of drug intake
• History of immunosuppression
• Findings of previous biopsies

Normal villous/crypt = 2-5/1
Normal IEL count
IEL < 3/10 enterocytes
IEL < 20-25/100 enterocytes
IEL < 5/20 enterocytes at tip of each villous

Artefacts
Classification of malabsorption

- Maldigestion
  - inadequate mixing
  - insufficiency of digestive mediators (brush border enzymes, bile salt deficiencies)

- Mucosal/mural problems
  - decreased mucosa (bowel resection)
  - mucosal disease (GSE, tropical sprue, autoimmune enteropathy, intestinal lymphangiectasia, etc)
  - mural disease (neuromuscular disorders, amyloidosis, diverticula, etc)
  - immunodeficiencies (Congenital ID, AIDS)

- Microbial causes
  - infections

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Malabsorption

- Normal
- Flat mucosa
- IELosis
- Villous shortening
Causes of malabsorption

- GSE and variants
- Infections
- Childhood enteropathies
- Chemical/toxic injuries
- Intramucosal accumulations/infiltrations

Gluten Sensitive Enteropathy (Coeliac Disease)

- Enteropathy in genetically predisposed (HLA-DQ2 or DQ8) individuals characterized by destructive inflammatory reaction to proline-rich proteins in certain grains including gliadin in wheat, secalin in rye, and hordein in barley
Endoscopy

Capsule endoscopy
sens 93% spec 100%
Lidums 2011

Narrow band imaging
sens 93% spec 98%
Singh 2009
Diagnostic difficulty in GSE

- Classification
- "Mild" changes
- Cell counting
- Focal pathology ("patchy" involvement)
- Pediatric cases
- "New comers" in differential

Marsh Classification
**GSE: Classification**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Type 0</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Type 1</td>
<td>Type 1</td>
<td>Grade A</td>
<td>Type 1</td>
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<tr>
<td>Type 2</td>
<td>Type 2</td>
<td>Grade A</td>
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<tr>
<td>Type 3</td>
<td>Type 3a Type 3b Type 3c</td>
<td>Grade B1 Grade B1 Grade B2</td>
<td>Type 2 Type 2 Type 3</td>
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<td>Type 4</td>
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**Marsh classification - Ensari**

- **Type 1**
  - IEL ↑
  - Villi N

- **Type 2**
  - IEL ↑
  - Villi shortened

- **Type 3**
  - IEL ↑
  - Villi flat

*Arch Pathol Lab Med 2010*
Mild changes: IELosis

indefinite
definite
de-crescendo
Normal pattern
crescendo
Abnormal pattern
# IEL counting

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>IEL/100 enterocytes (total of 300-500 cells in 3 fields)</th>
<th>H&amp;E / CD3</th>
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</thead>
<tbody>
<tr>
<td>Upper limit of N</td>
<td>20/100</td>
<td>CD3</td>
</tr>
<tr>
<td></td>
<td>25/100</td>
<td></td>
</tr>
<tr>
<td>Borderline increased</td>
<td>25-29/100</td>
<td></td>
</tr>
<tr>
<td>Definitely increased</td>
<td>&gt;29/100</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Villous “tip” method (5 villi, 20 enterocytes/villous tips, average counts)</th>
<th>H&amp;E / CD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limit of N</td>
<td>5/20</td>
<td>CD3</td>
</tr>
<tr>
<td>Definitely increased</td>
<td>≥6/20</td>
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</tbody>
</table>

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**Figure 1.** Select 4 villi with epithelial nuclei aligned to basement membrane (marked 1-4). To count IELs, from villus 1, count and record IELs/10 enterocytes, starting at base of crypt (arrow), lowest point between 2 adjacent villi, continue till next base (dashed arrow), and continue counts in villi marked 2 through 4.

**Walker (2010) – 25/100**

**Do counting when**
- No serologic correlation
- Not happy with orientation
- No obvious increase
  - OR
  - Do an immuno instead & look for the pattern

3.5/ tip or 18/100
Sens 90, 93; spec 100%
25/100 – miss 25%

Pellegrino 2011
Where & how many?

- Damage starts in the duodenal bulb and extends distally
- Lesions can be patchy
- Severity proximal > distal
- At least 4 biopsies (2 bulbus & 2 distal duodenum)
- Variability in villous morphology in 1/4 of duodenal biopsies

“patchiness”

FIGURE 1. Duodenal biopsies—patient no. 1. A, Biopsy from second part of duodenum showing normal villous architecture. B, Biopsy from the bulb showing villous atrophy and increased intraepithelial lymphocytes.

Levinson-Castiel 2011
Study | Bulb vs distal duodenum
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Vogelsang 2001 | fewer IEL in bulb
Bonamico 2004, & 2008 | 2.4% & 4% only in bulb
Prasad 2009 | Similar in bulb and distal duodenum
Rashid & Mac Donald 2009 | 17.5% normal in bulb
Mangiavillano 2010 | 10.6% only in bulb
Weir 2010 | 9.8% only in bulb
Gonzales 2010 | 13% only in bulb
Walker 2010 | Similar in bulb and distal duodenum
Ravelli 2010 | Similar (proximal-distal gradient of severity)
Levinson-Castiel 2011 | 7% only in bulb - 23% more severe in bulb
Ensari (unpublished) | 10.9 only in bulb

**GSE: serologic tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Anti tissue transglutaminase (tTG)</td>
<td>77-100%</td>
<td>91-100%</td>
</tr>
<tr>
<td>Anti endomysial antibodies (EMA)</td>
<td>86-100%</td>
<td>90-100%</td>
</tr>
<tr>
<td>Anti-gliadin antibodies (AGA)</td>
<td>57-100%</td>
<td>47-94%</td>
</tr>
<tr>
<td>IgG deamidated gliadin peptide + tTG</td>
<td>82.3 -1</td>
<td>88.3-92.8%</td>
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</table>
Current knowledge:
Duodenal biopsy is gold standard for CD diagnosis
TTGA screening is sensitive and specific for CD
TTGA levels correlate with duodenal histology
TTGA $\geq 100$ may be specific for CD in children

New here:
- 96% of TTGA $\geq 100$ had Marsh 3 lesions
- 99% of TTGA $\geq 100$ had at least Marsh 2 changes
- All TTGA $\geq 100$ subjects had evidence of CD
- TTGA $\geq 100$ specific for CD in all ages
- TTGA $\geq 100$ likely diagnostic in at risk subjects

Donaldson, 2007 & 2008

PPV = 75.9%

PPV = 44.3%

Dalgic et al, AJG 2011
Refractory Sprue

- Incomplete or no response to GFD
- Abnormal T cell phenotype
- CD4, CD8, TCR loss
- TCRγ monoclonality
- "In situ" / cryptic T-cell lymphoma?
- Moderate/severe villous loss
- Crypt hypoplasia (mucosal atrophy)
Causes of refractoriness

- Dietary non-compliance
- Unknown gluten source (e.g. pill capsules)
- Wrong initial diagnosis
- Associated or second cause (e.g. collagenous colitis)
- Superimposed complications (Collagenous sprue, “cryptic” T cell lymphoma, EITCL)
Collagenous sprue

• Very rare condition
• Serious complication of coeliac disease
• Refractory to all treatment modalities
• High dose immunosuppression is necessary
• Patients die of malnutrition or malignancy
Collagenous sprue

Infections

cryptococcus
stronglyloides
cmv
cryptosporidium
isospora
giardia
Whipple's disease

- Tropheryma whippelli
- Affects joints, lungs, heart, eyes, and CNS
- Lamina propria filled with foamy macrophages showing PAS + granules
- Villi are blunted and flattened, IEL count can be high

(postinfectious) Tropical sprue

- Seen in Central and South America, West Africa and Southeast Asia
- Bacterial exposure and poor hygiene
- Similar histology with GSE but rarely flat
- Ileal mucosa is also involved
Bacterial overgrowth

- Luminal stasis caused by inflammatory / iatrogenic conditions leads to overgrowth of facultative anaerobic bacteria - *Bacteroides* species
- Elderly patients are affected
- Normal or some villous abnormality
- IELs and neutrophils are increased

Enteropathies of Infancy

### Intractable diarrhoea
- MVID
- “Tufting” enteropathy (Intestinal epithelial dysplasia)
- Autoimmune enteropathy
- “Syndromatic” enteropathies
  - mt DNA disorders
  - congenital disorders of glycosylation

### Protracted diarrhoea
- Congenital immunodeficiencies
- Congenital transport & enzyme dis.
  - Lipid transport dis
  - Disaccharidase deficancy
- Severe infections
- Food allergy
- GSE
Autoimmune enteropathy

- Family of diseases with anti-enterocyte/anti-goblet cell antibodies
- Mostly affects children causing severe intractable diarrhoea
- Histology is similar to GSE except neutrophils are more prominent than IELs
Immunodeficiency

CVID

CD3
CD20
CD79a

GVHD
Peptic duodenitis

NSAID duodenitis

Eosinophilic gastroenteritis
Amyloidosis

Intestinal lymphangiectasia
Reporting

- Include biopsy site & number
- Be brief and descriptive
- Recommend follow-up / re-biopsy
- Give a list of differential diagnosis
- Use the phrase “consistent with……” and
- “clinical/serological correlation is needed…” in your report
Thank you...