The surgical pathology of malabsorption

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Talk Overview

- Biopsy issues
- Classic Histology
- Response to Treatment
- Marsh 1 lesion
- Histologic mimics
  - Peptic duodenitis, Tropical sprue, Bacterial overgrowth, Autoimmune enteropathy
Where to Biopsy?
How many Biopsies?

- Most studies suggest that 4 biopsies are optimum
  - One study suggested 5 with one biopsy being from the bulb
- Recent pediatric studies have found 10% of kids have involvement in the bulb only and that 10% have non-diagnostic findings in the bulb with Marsh 3 lesions more distally.
- Probably best to biopsy both bulb and distal duodenum and put in separate jars

Disorders of Malabsorption Classification

- Normal mucosal histology
- Non-specific inflammatory and architectural changes
- Demonstrable infectious agents
- Immunodeficiency present
- Misc. entities with characteristic findings

Cause of Celiac Disease

- Wheat Flour
  - Starch
  - Fat
  - Fiber
  - Protein
- Water Insoluble Fraction
  - Gluten
- Water Soluble Fraction
- Alcohol Insoluble
  - Glutenin
- Alcohol Soluble
  - Gliadin
Celiac Disease
Histopathology - prior to Tx

- Flat biopsy with surface damage
- Increased Intraepithelial lymphocytes
- Increased lamina propria inflammation
  - Plasma cells
- Increased crypt mitoses
Classification of Celiac Lesions

Marsh 3A  Marsh 3B  Marsh 3C

CELIACS
DO IT
GLUTEN FREE
Celiac Disease
Histopathology - Shortly after Tx

- Marked clinical improvement
- Surface epithelium restored
- Slight return of villi
- Other findings unchanged

Celiac Disease
Histopathology - Long term Tx

- Continued clinical improvement
- Further return of villi
- Mitotic rate subsides
- Chronic inflammation subsides
Celiac Disease

Gluten Challenge

- Epithelial lymphocytes increase
- Epithelial damage to upper villi
- Full-blown lesion develops later

Celiac Disease

Pathogenic Factors

- Genetic Aspects
  - Familial Occurrence (11-22% first degree relative)
  - Identical Twin Concordance (70%)
  - HLA Associations (DQ2, B8)
- Environmental Factors
  - Dietary Gluten
  - Twin non-concordance rate of 30%; separate onsets
  - ?Viral exposure (Adenovirus type 12)
Protein Sequence Homology

Celiac Disease: Adenovirus and Alpha Gliadin

Ad12,Elb
A-Gliadin

Marker | Sensitivity | Specificity
---|---|---
Anti-gliadin | 31-100% | 85-100%
Anti-reticulin | 42-100% | 95-100%
Anti-endomysium | 60-100% | 95-100%
Tissue Transglut | 85-100% | 92-97%

Schuppan D. Gastroenterol 2000:119;234-242
Schuppan et al. Gastro 2009;137:1912-33
Pinier et al, Am J Gastroenterol 105:2551-2561;2010
CD Iceberg

DQ2

CD

Diseased mucosa

latent

Normal mucosa

normal

CD

Diseased mucosa

Normal mucosa

Greenson Sprue
How many IELs are abnormal?

- >25/100 epithelial cells
- >40/100 epithelial cells
- >12/20 epithelial cells on the tips of villi
  - Decrescendo pattern is normal
  - Diffuse pattern is abnormal
- >8/20 epithelial cells in the tips of villi
  - CD3 stains
  - Biagi et al J Clin Pathol 57;835-839, 2004

But what does it all mean?

- 2-3% of small bowel biopsies have normal architecture with increased IELs
- Depending on the type of study and the country the study was carried out in, anywhere from 9 to 40% of such cases represent (pre) celiac disease.
  - Whether such patients need any therapy is controversial


Normal Architecture Increased IELs

- Gluten Sensitive Enteropathy
  - Early type 1 lesion or treated sprue
- Other food hypersensitivity
- H. Pylori (usually only in bulb)
- Autoimmune conditions (RA, SLE, MS, Graves, Hashimoto’s, Diabetes)
- Post-infection
- Drugs (NSAIDs, PPIs??)
- Bacterial Overgrowth
- Obesity
- Crohn’s disease and Ulcerative colitis
Results

Other Diagnoses: Graft versus Host Disease, Combined Variable Immunodeficiency, Diabetes mellitus 1, Juvenile Rheumatoid Arthritis, Systemic Lupus Erythematosis, Tropical Sprue, Ulcerative Colitis

Diseases Associated with Marsh 1 Lesions

- CD, 19
- Idiopathic, 31
- NSAID, 17
- Crohn’s, 7
- Bacterial Overgrowth, 7
- H. pylori, 7
- IBS, 9
- Other, 7

Celiac Disease Complications

- Refractory Celiac Disease
- Ulcers of Small Bowel
- Collagenous Sprue
- Malignancy
  - T cell Lymphoma of gut and regional nodes
  - Adenocarcinoma of small bowel
  - Squamous cell carcinoma of esophagus and oropharynx

Refractory Celiac Disease

- Develops in about 5% of celiac patients
  - Malabsorption, diarrhea, pain, wt loss
- Divided into types I and II
- Type I RCD: IELs are normal / not clonal
  - better prognosis
  - Can progress to Type II
- Type II RCD: IELs are aberrant / clonal
  - 50% mortality rate

Refractory Celiac Disease

- IELs in Celiac disease and type I RCD are CD3 + and CD8 +
- IELs in type II RCD are CD3 + and CD8 -
  - Will have T-cell gene rearrangements
  - Will also loose staining for T-cell receptor αβ
Small Intestinal Ulcers In Celiac Disease
LYMPHOMA IN CELIAC DISEASE
Malabsorption

- Sprue-like Changes
- Gluten Free Diet
- Response
- No Response (Refractory Sprue)
- Remain Well
- Deterioration
- Benign Ulcer
- Refractory Celiac Disease
- Lymphoma

Celiac Disease
Histologic Mimics

- Celiac-related
  - Lymphoma (EATCL)
  - Collagenous Sprue
- Other luminal antigens other than gluten/gliadin
  - Soy protein
- General
  - Peptic duodenitis
  - Tropical Sprue, Bacterial overgrowth
  - Autoimmune enteropathy
  - Infections/immunodeficiencies
  - Crohn’s disease
Tropical Sprue

- Chronic malabsorption after infectious diarrhea commonest in tropical regions
- Bacterial overgrowth with B-12 and Folate deficiencies - often responds to antibiotics and vitamin supplements
- Biopsy findings are variable
  - Sprue-like changes with less intense damage than full blown celiac disease
  - Both Jejunum and Ileum involved
Stasis Syndrome
(Bacterial Overgrowth)

- Crohn’s Disease
- Diverticular Disease
- Scleroderma
- Pseudo-obstruction
- Post-Surgical
  - Blind loop or Pouch
  - Entero-enterostomy
  - Afferent loop
  - Fistulae
  - Adhesions/partial obstruction
Bacterial Overgrowth Biopsy Findings

- Irregular Villi
- Surface cell damage
- Plasmacytosis
- Neutrophils
- Crypt Hyperplasia
- “Doesn’t fit”
Autoimmune Enteropathy

- Childhood onset - usually prior to age 1
  - Intractable diarrhea not relieved by TPN
  - Anti-enterocyte antibodies (requires indirect immunofluorescence)
  - Other autoantibodies (islet cell, parietal cell)
  - FOXP3 mutation
  - X-linked with polyendocrinopathy

- Also Adult onset (not well known)
  - Anti-enterocyte antibodies or anti-goblet cell antibodies
It’s the Surgeon’s Fault!
The Pouch

Baseline Histology

- Increase in lamina propria chronic inflammation
  - Lymphs, plasma cells, eos and histiocytes
- Variable villous atrophy with crypt hyperplasia
- Switch from small intestinal to colonic type mucins over time - “Colonisation”

Pouchitis
**Pouchitis Clinical Symptoms**
- Occurs in 7-50% of pouch patients (avg. 32%)
- Abdominal pain and fever
- Bloody stools, increased frequency, incontinence
- Often responds to antibiotics
- 10-20% refractory to therapy - chronic IBD
  - Much more common in UC than FAP patients
  - Highest incidence in UC patients with PSC

**Pouchitis Clinical Syndromes**
- Responsive to Antibiotics (Flagyl)
  - Bacterial overgrowth
- Refractory Pouchitis
  - Irritable pouch syndrome - no path changes
  - Short strip pouchitis - UC in retained rectal mucosa
  - Chronic primary refractory pouchitis - active inflammation in bxs.

**Pouchitis Histopathology**
- Villous blunting and chronic inflammation are part of the “baseline pouch” and these changes do not correlate with clinical symptoms
- Active inflammation does correlate with clinical symptoms
  - Erosions
  - Ulcers
  - Cryptitis