CELIAC SPRUE
LECTURE SERIES:
PART II

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PART II
DIFFERENTIAL DIAGNOSTIC PROBLEMS IN CELIAC SPRUE

Bibliography for Parts I and II follows

OBJECTIVES

I. To be able to diagnose proximal duodenojejunal biopsies that may resemble CS but do not respond to a GFD.
II. To know why a proximal duodenojejunal biopsy in CS may improve more slowly after a GFD despite an initial dramatic clinical response.
III. To recognize and understand refractory celiac sprue types 1 and 2.
IV. To recognize other small bowel diseases with a specific histologic and/or clinical picture without a GFD response.
I. Duodenal CS-Like Lesions Not Responsive to a GFD

- Kwashiorkor
- Multiple Protein Injury
- Tropical Enteropathy
- Acid-Peptic Injury (Z.E.)
- Tropical Sprue
- Infectious Injury
- Pseudo-obstruction
- Intractable Sprue
- Cow’s Milk or Soy Protein Injury

CS-Like Lesion in Infantile Kwashiorkor, GFD-Unresponsive, Described by Dr. Oscar Brunser in Chile [40]

Villi restored over time by a protein diet containing essential amino acids

Note surface injury and increased IELs

A. Tropical Enteropathy (TE) [19,41]

- A widespread disease in 30-50% of people from certain underdeveloped tropical areas, with largely asymptomatic laboratory evidence of malabsorption.
- Mild nonspecific mucosal changes are:
  - Abnormal surface epithelium in a “comb” pattern at the tip of the villus. Fewer goblet cells.
  - Excess lymphocytes throughout the biopsy
  - Minimally distorted villous architecture
  - Variable loss of villous pleating (scalloping)
  - This is a mild nonspecific lesion. It is not GFD responsive.
Tropical Enteropathy (TE)

Feels well, no steatorrhea [42]

Mild nonspecific lesions
GFD unresponsive

Tropical enteropathy in Thailand

Tropical enteropathy in India

Higher power - Mild nonspecific abnormalities (TE etc.) [19]

Note epithelial "comb" pattern at villous tip & generalized increase in lymphocytes, decreased villous pleating (scalloping) & paucity of goblet cells

B. Tropical Enteropathy (TE) [41, 42]

- Clinical picture varies somewhat geographically
- An acquired disease not present at birth or during infancy
- The nonspecific intestinal abnormalities are much milder than those seen in CS but may be present throughout the length of the small intestine
- The whole length of the small bowel is colonized by microorganisms
- Residence in a temperate climate often improves TE
- Folic acid and vitamin B-12 treatment improves the more severe intestinal mucosal lesions in TE
A. TROPICAL SPRUE (TS) [41, 42]

- Less common than TE
- Overt malabsorption presents with steatorrhea as its hallmark; also anorexia, weight loss, weakness, and anemia – may be megaloblastic.
- GFD unresponsive. Antibiotics plus folic acid heals disease, but it can recur especially in tropical areas.
- Nonspecific panintestinal mucosal lesion, usually less severe than classical flat CS but worse than TE.
- Luminal overgrowth of organisms present throughout intestinal length. Some organisms toxigenic (water secretion increased, solute absorption decreased, mucosa injured.)

B. TROPICAL SPRUE (TS) [42, 43]

- Clinical picture varies somewhat geographically but is more severe in areas of extreme poverty, and can disappear with marked socioeconomic improvement
- TS occurs in adults, mucosa usually normal in young children and fetuses
- Residence in developed countries does not improve TS, but antibiotics and folic acid do
- Sporadic in many tropical countries, but can be epidemic.
- Described in an Indian medical treatise written between 1300 and 600 B.C.

IMPROVING SPECTRUM OF MILD TROPICAL SPRUE IN PUERTO RICO (1970's) [42]

WITH TRANSITION FROM AN AGRICULTURAL TO AN INDUSTRIAL ECONOMY, TS HAS NOW ALMOST DISAPPEARED. NOTE SURFACE INJURY & INCREASED IELs
UNCHANGED SPECTRUM OF SEVERE TROPICAL SPRUE IN IMPOVERISHED HAITIAN ENVIRONMENT (1960s) [44-47]

Severe

Mild to Moderate

CASE 1: TROPICAL SPRUE: UNTREATED ABNORMAL DUODENUM

MILD TO MODERATE NONSPECIFIC LESION IN A WESTERN TRAVELER WITH STEATORRHEA FOLLOWING A SEVERAL MONTH VISIT TO AN UNDERDEVELOPED AREA

NOTE INCREASED SURFACE IELs

CASE 1: TROPICAL SPRUE UNTREATED ABNORMAL ILEUM [42-46]

MODERATELY SEVERE ILEITIS

NOTE INCREASED SURFACE IELs
CASE 1: TROPICAL SPRUE TREATED [45-46]  
NORMAL DUODENUM

AFTER ANTIBIOTICS AND FOLATE, MORPHOLOGY AND ABSORPTION NORMALIZE. MAY RECUR, ESPECIALLY IN TROPICS

PATCHY LESIONS IN PSUEDO OBSTRUCTIONS  
CLASSICAL STUDIES- DR. MICHAEL SCHUFFLER [48]

FLAT  
SOME IMPROVE AFTER ANTIBIOTICS, SOME AFTER RELIEF OF OBSTRUCTION  
NORMAL

COW’S MILK INJURY IN A 10 MONTH OLD

NORMAL VARIANT INFANTILE DUODENAL PATTERN (ABOVE), MODERATE INJURY 10 HRS AFTER COW’S MILK (BELOW)
SEVERE COW’S MILK INJURY
IN A CHILD’S DUODENUM
NOTE SURFACE INJURY & INCREASED IELs

SEVERE SOY INJURY IN A CHILD [49]
NORMAL DUODENOJENAL JUNCTION BEFORE SOY MEAL
SEVERE FLAT I INJURY 12 HOURS AFTER SOY MEAL
FIRST DESCRIBED BY DR. MARVIN AMMENT

TEMPORARY JUVENILE PROTEIN INJURY
• Cow’s milk injury common
• Soy milk injury less common
• Both disappear after childhood
Malabsorption does not improve on GFD, but does on TPN.

We know of only one well-documented adult case of multiple protein injury reported by Drs. Alfred Baker and Irwin Rosenberg.

Chicken, tuna, or egg was tested by adding them individually to TPN and each caused severe intestinal injury and malabsorption. A single exposure to any one of these three food proteins caused frightening episodes of hypotension and cyanosis. Long term exclusion of these three proteins restored normal health.
SUGGESTED PROTOCOL FOR DETECTING UNIQUE NON-GLUTEN PROTEINS THAT INJURE THE INTESTINE

- Biopsy the proximal jejunum to establish the persistence of a severe lesion despite a prolonged strict GFD
- If a severe flat lesion is found, place the patient on complete TPN
- If symptoms regress, rebiopsy proximal jejunum to check for return of villi after TPN, indicating prior dietary injury
- Test individual protein foods one at a time while on TPN. Have a large intravenous access available for emergency treatment.
- Prevent hypovolemia by maintaining blood volume and giving steroids if a severe reaction develops.
- Rebiopsy jejunum within 10-20 hours, as soon as the patient stabilizes, to see if villi have been destroyed by a protein being tested.

SEVERE ACID-PEPTIC INJURY (Z-E)
RESEARCH BY DR. STANLEY SHIMODA AND DAVID SAUNDERS [51]

REVERSED BY PROTON PUMP INHIBITORS
NOTE SURFACE EROSION

HIGHER POWER
ACID-PEPTIC INJURY (Z-E)

SURFACE EROSION
INFECTIOUS ENTERITIS: MODERATE-SEVERE (ABOVE), NORMAL AFTER RECOVERY (BELOW)

INTRACTABLE SPRUE

• Severe NS lesion does not respond to a GFD (excluding CS) or complete TPN (excluding another dietary protein)
• Often fatal.
• Rule out Refractory Celiac Sprue (see below)

INJURIOUS AGENT NOT FOUND BY “TPN TEST”; A SEVERE FLAT LESION, GFD UNRESPONSIVE (HEABS STAIN)
II. UNCERTAIN HISTOLOGIC RESPONSE TO A GFD IN CS [52]

- The most common cause is inadvertent gluten in the “GFD”

- Slow proximal healing, or rare permanently delimited proximal damage to the duodenum on a GFD, nevertheless a dramatic clinical response occurs because of rapid healing of the more distal small bowel.

INADVERTENT GLUTEN INGESTION

- Always look for it, especially if tTG remains elevated despite alleged strict GFD.
- Difficult to avoid gluten in processed foods and restaurants.
- Canned goods with “hydrolyzed vegetable protein” usually means they contain gluten.

SEVERE FULL LENGTH SMALL BOWEL INJURY BY GLUTEN

- Injury is greatest, and the healing often slowest, proximally (may rarely take > 1 year of GFD).
- Injury is least, and the healing after GFD most rapid, distally, explaining the dramatic clinical response to a GFD despite a proximal flat biopsy.
- Rare permanent proximal duodenal injury is also compensated for by rapid healing of the remaining distal small bowel.
- To avoid sampling errors, take 6 biopsies, including the bulb, distal duodenum, and beyond the duodenojejunal junction.
FULL LENGTH GLUTEN INJURY: CS [15]

VERY ILL, UNTREATED CS, SURFACE INJURY & INCREASED IELs

Research of Dr. Walter MacDonald et. al.

DUODENUM
SEVERE FLAT

ILEUM
MODERATE

DELAYED DUODENAL HEALING AFTER A GFD

1 month GFD

3 weeks TPN

DUODENOJ EJUNAL HEALING AFTER 3 WEEKS ON STRICT TPN, WHICH IS AN ABSOLUTE GFD

RARE PERMANENT PROXIMAL DUODENAL CS INJURY

YET CLINICALLY WELL ON A GFD BECAUSE REMAINING BOWEL HEALED.
NOTE: SURFACE INJURY & INCREASED IELs
### III A. REFRACTORY CELIAC SPRUE (TYPE 1) [52]

**Type 1:** Infrequent in younger pts, not progressive, if treated

- Severe duodenjejunal villous loss as in CS, usually unresponsive to a GFD
- The number of aberrant T-cell lymphocytes in the lamina propria is normal, i.e. < 10% by flow cytometry
- Responds to prednisone and/or azathioprine (95% 5 year survival); ? immunopathy
- Does not progress to RCS Type 2, enteropathy associated T-cell lymphoma (EATL), and/or ulcerative ileojejunitis

### III B. REFRACTORY CELIAC SPRUE (TYPE 2) [52-57]

**Type 2:** Approximately 75% of RCS, older patients (>6th decade)

- Initially there is CS with a severe flat proximal small bowel lesion responding to a GFD.
- Eventually cytologically normal appearing T-cell lymphocytes in the lamina propria become aberrant by flow cytometry (> 20%)<br>
- After passage of years, villi disappear and patient is no longer responsive to a GFD. Enteropathy Associated T-cell Lymphoma (EATL) then develops.
- T-cell lymphoma was untreatable and fatal until recently. Some recent reports of long-term survival after chemotherapy followed by autologous hematopoietic stem cell transplant.
- The complicating ulcerative ileojejunitis may be similarly treatable

### SERIAL OBSERVATIONS OVER 29 YRS, BY THE SAME PHYSICIAN FROM CS, TO RCS-2, TO T-CELL LYMPHOMA

1. Initially severe untreated CS, GFD responsive<br>
2. Aberrant T-cells then revealed by flow cytometry despite their normal cytologic appearance.<br>
3. Years later, villi lost and became refractory to a strict GFD<br>
4. Aberrant T-cell clone expanded and became T-cell lymphoma<br>
5. Died of invasive T-cell lymphoma 29 years after initial CS diagnosis
INITIALLY GFD RESPONSIVE CS (LATER RCS 2 & LYMPHOMA)

MALABSORPTION, LOSS OF VILLI
29 YEARS OLD INITIAL DIAGNOSIS OF CS.
NOTE: SURFACE INJURY & INCREASE IELs

UNTREATED CS - LAMINA PROPRIA

INFLAMMATORY LYMPHOCYTE AND PLASMA CELL INCREASE AT HIGHER POWER

GFD RESPONSE IN TREATED CS SHOWN IN PREVIOUS SLIDE

NORMAL VILLI & ABSORPTION RESTORED
NORMAL LP LYMPHOCYTE AND PLASMA CELL CONTENT

INITIAL CS BECOMES GLUTEN UNRESPONSIVE FLAT LESION (RCS 2) MANY YEARS LATER

NORMAL APPEARING LYMPHOCYTES AND PLASMA CELLS BUT ABERRANT T-CELLS BY FLOW CYTOMETRY
RCS TYPE 2 MAY PRESENT AS ULCERATIVE ILEOJEJUNITIS

- Can ulcerate, perforate, bleed, obstruct or become EATL.
- Ulcers can contain EATL.

DEVELOPMENT OF EATL

VILLI BLUNTED, LOSS OF PLEATING, EXCESS LYMPHOCYTES, WITH AN EXPANDING CLONE OF ABERRANT T-CELLS WITHOUT NORMAL SURFACE MARKERS. CAN ULCERATE

DEVELOPMENT OF EATL

ABERRANT T-CELL CLONE WITH LOSS OF NORMAL SURFACE MARKERS
INVASIVE T-CELL LYMPHOMA
FULL THICKNESS LAPAROTOMY SAMPLE

MUCOSA DESTROYED, MUSCULARIS PROPRIA INVADED
AT 58 YEARS OF AGE, 29 YEARS AFTER CS DIAGNOSIS

IV. OTHER DUODENAL LESIONS WITH DIAGNOSTIC HISTOLOGY

- Intestinal Malignancy
- Duodenal Crohn’s
- Common Variable Immunodeficiency (CVI)
- Eosinophilic Enteritis
- Whipple's Disease
- Mycobacterium Avium Intracellulare (often with AIDS)
- Mastocytoma
- Collagenous Sprue
MALIGNANCY IN CELIAC SPRUE [58]

8% of CS develops small bowel T-cell lymphoma (EATL); 70% onset after age 60, 77% T-cell type

1% of CS in North America develops small bowel carcinoma, but not carcinoma outside of GI tract (unlike Europe!)

INTESTINAL LYMPHOMAS

1. Refractory celiac sprue- type 2, becomes T-cell lymphoma (EATL) over time

2. IPSID (Immunoproliferative small intestinal B-cell lymphoma) - also known as heavy chain disease

3. Non-IPSID primary intestinal lymphoma

IPSID LYMPHOMA [59-61]

MALABSORPTION AND B-CELL LYMPHOMA
IPSID: Immunoproliferative Small Intestinal Disease [59-61]
RESEARCH BY DR. SHMUEL EI DELMAN
- Not CS related, endemic in impoverished areas
- Malabsorption, clubbing, weight loss, edema
- Initially massive intestinal infiltration with benign appearing plasma cells that synthesize abnormal heavy chain immunoglobulin
- This early phase may be antibiotic responsive
- Progresses to immunoblastic B-cell lymphoma, located primarily in proximal small bowel
- Nonmetastatic, mostly intra-abdominal except when terminally ill
- Incidence lower with environmental improvement
PRIMARY INTESTINAL LYMPHOMA

- Not endemic, not IPSID, not CS related
- Incidence bimodal - childhood; 5th & 6th decades
- Location mostly ileal, localized masses
- Villi and glands often destroyed
- Constipation, bleeding, obstruction, perforation
- Disseminates from abdomen to the rest of body
- Poorly differentiated histiocytic or “Burkitt’s” cytology

DUODENAL CROHN’S

4 DIFFERENT HISTOLOGICAL FEATURES - SAME PATIENT

FEATURE 1. FOCAL BUT NONSPECIFICALLY AND HISTOLOGICALLY INDISTINGUISHABLE FROM SEVERE CLASSICAL CS. NOTE ABNORMAL SURFACE & INCREASED IELs.

FEATURE 2. ISOLATED GIANT CELL
FEATURE 3. "LOOSE" EPITHELIOID GRANULOMA

FEATURE 3. DEEPER SECTION, HIGHER POWER: NODULAR NATURE OF EPITHELIOID GRANULOMA OBVIOUS

FEATURE 4. FOCALLY NORMAL DUODENUM
DISCOVERED BY DR. MARVIN AMENT: LONG CONFUSED WITH UNTREATED CS BUT NO PLASMA CELLS OR IgA

UNTREATED CVI (COMMON VARIABLE IMMUNODEFICIENCY) [62]

LYMPHOCYTES PRESENT, PLASMA CELLS ABSENT. INCREASED INTRAEPITHELIAL LYMPHOCYTES

UNTREATED CVI “HYPOGAMMA SPRUE”

DUODENAL SMEAR = GIARDIASIS
"HYPOGAMMA SPRUE" (CVI)

Untreated Giardiasis
Villi & absorption abn.
Plasma cells & IgA absent
Immunodeficiency

Giardia eradicated
Villi & absorption are restored
Plasma cells, IgA, & immunodeficiency are not restored

POLYP IN BENIGN LYMPHOID HYPERPLASIA - CVI

Giardia eradicated - villi & absorption return; plasma cells & IgA do not

BENIGN LYMPHOID HYPERPLASIA - CVI

Small bowel X-ray - multiple "polyposis"
CLASSICAL DESCRIPTION BY DR. GARY LEINBACH
VARIABLE VILLOUS DESTRUCTION, CLUMPS OF EOSINOPHILS

EOSINOPHILIC ENTERITIS

EXCESS EOSINOPHILS IN SUBMUCOSA

EOSINOPHILIC ENTERITIS

EXCESS EOSINOPHILS IN LAMINA PROPRIA
EM & HISTOLOGIC STUDY BY DR. JERRY TRIER
LOSS OF VILLI, LAMINA PROPRIA FILLED WITH MACROPHAGES, & DILATED LACTEALS

UNTREATED WHIPPLE’S DISEASE [64]

AFB - PAS+
MACROPHAGES: OBVIOUS ON H & E
NOTE SOLITARY DILATED LYMPHATIC

EM UNTREATED WHIPPLE’S DISEASE
MACROPHAGES AND TROPHYREMA WHIPPELLI
ANTI BIOTIC TREATED WHIPPLE'S
ALMOST NORMAL DUODENUM

MAI VS. WHIPPLE'S IN DUODENUM
ABOVE: WHIPPLE'S MACROPHAGES PAS+, AFB-
BELOW: MAI MACROPHAGES PAS+, AFB+

MAI:
MYCOBACTERIUM AVIUM-INTRACELLULARE
(WITH AIDS)
ACID FAST POSITIVE MACROPHAGES
DUODENAL MASTOCYTOSIS

GI EMASA STAINED MAST CELLS

COLLAGENOUS SPRUE FIRST DESCRIBED [65] BY DR. FRED WEINSTEIN, ET AL.

THICKENED SURFACE SUB-EPITHELIAL COLLAGEN LAYER
COLLAGENOUS SPRUE [65-68]

- Collagenous sprue associated with EATL, ulcerative ileojejunitis & CS. Are they all RCS-2?
- Histologically it looks like severe untreated CS with a collagenous band (>15μM) of collagen underneath the superficial epithelium extending into underlying lamina propria and entrapping vessels and other lamina propria cells. Band continuous, not patchy.
- Tangentially oriented tissue may make collagenous band look thicker than it is when viewed in a biopsy cut at a right angle to the lumenal surface.
- Malabsorption severe and untreatable – often cause of death although they may die of T-cell lymphoma or perforated ulcerative ileojejunitis.

ACKNOWLEDGEMENTS

- Marvin E. Ament
- Alfred L. Baker
- Beach Barrett
- Evelynne Bautista
- Lloyd L. Brandberg
- James R. Brow
- William G. Dobbs III
- Sinmade Edelman
- Arnold L. Fisch
- Rodger C. Haggitt
- Eric Hassall
- Alissa Latimer
- Sum P. Lee
- Gary Leinbach
- Walter C. MacDonald
- John R. Meisel
- Frank R. Parker
- Carrol Sherman: Web Computing Specialist
- R. Anthony Perkins
- Cheryl M. Farmentier
- William A. Panula
- Patricia C. Phelps
- Glyceria Quezon
- Wayne E. Quinlan
- Irwin H. Rosenberg
- David R. Saunders
- Michael O. Schullier
- Stanley S. Shimoda
- Sharon Smithbush
- Hawley C. Taylor, Jr.
- Jerry S. Trier
- Guido N. Tytgat
- Melissa P. Upton
- Wade Volwiler
- Wilfred M. Weinstein
- Rocky Yeh: IT Equipment Manager

END OF PART 2