A Teenager with Complex Crohn’s Disease

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Background

- KL is a 19 year old male
- Crohn’s disease diagnosed age 6
- Gastric and ileal involvement
- Non-smoker
- Symptoms diarrhea and abdominal pain
Timeline of Medical Therapy

- **Diagnosis**: Jan 2001
- **6-MP mesalamine**
- **infliximab**: Jan 2004
- **adalimumab 40 mg EOW**: 2010
- **Diarrhea**
- **LOR to infliximab**
A Change in Symptoms

- Early satiety
- Weight loss ~ 15 lbs over 1 month
- Moderate epigastric pain worse with PO
- See GI who performs an EGD
Endoscopy: Antral Stricture

Balloon dilatation

http://www.gastrolab.net/
Timeline of Therapy

Diagnosis
- Jan 2001

6-MP mesalamine
- Jan 2004

infliximab
- 2010

adalimumab 40 mg EOW
- Feb 2013

balloon dilatation for antral stricture x2
- LOR to infliximab

Diarrhea

Early Satiety and weight loss
Referred to UCMC for 2\textsuperscript{nd} Opinion for ...

Persistent nausea and weight loss
What’s Your next Step?

a) High dose oral/IV steroids
b) Repeat endoscopic dilatation
c) Endoscopic injection of steroids
d) UGI/SBFT
e) Surgical Intervention
What is Your Diagnosis?

a) Menetrier’s disease

b) Intestinal tuberculosis

c) Gastric malignancy

d) Gastroduodenal Crohn’s with small bowel strictures
His Diagnosis is........

Gastroduodenal Crohn’s (GDCD) with three high grade duodenal and jejunal strictures
Which of the Following Statements about GDCD is False?

a) Most remain asymptomatic
b) Pain improves with antacids or PO intake
c) Symptoms include nausea and vomiting
d) Symptoms occur in 5.5% of patients with GDCD
Epidemiology of Gastroduodenal Crohn’s Disease

- **Incidence**
  - Gastro-duodenal involvement occurs in 0.5% to 4% patients of CD $^{1-4}$
  - Isolated stomach and duodenum involvement accounts for less than 0.07% of all cases of CD $^5$

- **Prevalence**
  - Retrospective studies: 0.5-13%
  - Prospective Study: Paucity of data in the literature

Definitions of UGI Specific to Crohn’s Disease


- Esophagus
  - Aphthae
  - Erosions
  - Ulcers

- Stomach: upper and middle
  - Aphthae
  - Longitudinal/irregular erosions and ulcers
  - Bamboo joint appearances

- Stomach: lower
  - Aphthae
  - Longitudinal/irregular erosions and ulcers

- Duodenum: bulb
  - Longitudinal/irregular erosions and ulcers
  - Protruded lesions

- Duodenum: second portion
  - Longitudinal/irregular erosions and ulcers
  - Notch like appearances

* Esophagus: lesions were considered non-CD related when relation with reflux esophagitis was suspected.

* Stomach and duodenum: lesions were considered non-CD related when relation with H. pylori or NSAIDs was suspected.

* Fistula and stricture were considered CD related irrespective of location.
Signs and Symptoms May be Subtle

- Most remain asymptomatic\(^1\)
- Symptomatic GDCD occurs in \(~5.5\%^2\)
- Primary symptoms: nausea and vomiting\(^3\)
- Epigastric pain not relieved antacids or food intake\(^4\)


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Less Common Presentations

- Impairment of linear growth, delayed puberty
- Mouth ulcers, clubbing, chronic iron deficiency anemia
- Extra-intestinal manifestations precedes gastrointestinal symptoms
- Arthritis, arthralgia and osteoporosis

Treatment Options for GDCD

• Proton pump inhibitors
  – No data, but may provide symptomatic relief
  – May be useful in combination w/ immunomodulators

• Mesalamine
  – Not indicated, no data

• Steroids
  – Limited data, likely beneficial for non-obstructing disease

• Methotrexate
  – No data, may be useful

Mottet C et al. Digestion. 2005
Tremaine W. Inflam Bowel Dis. 2003
Treatment Options for GDCD

• 6-MP/azathioprine
  – Steroid sparing
  – Korelitz et al. 100% of GDCD had healing or marked improvement of symptoms

• Anti-TNFα
  – Paucity of data
  – Case reports with mixed results

• Endoscopic Balloon Dilatation
  – Best for single, short and moderately thick stricture

Mottet C et al. Digestion. 2005
Korelitz B et al. Am J Gastro 1993
Matsui et al. Endoscopy 1997
KL’s Course

- UGI series reveals 3 high grade UGI tract strictures
- Admitted to the hospital
- Made NPO
- Surgery service consulted
- Receives methylprednisolone 20 mg IV BID x 48 hrs without improvement
- Undergoes stricturoplasty x 3
Timeline of Therapy

Diagnosis Jan 2001

6-MP mesalamine Jan 2004

infliximab 2010

adalimumab 40 mg EOW Feb 2013

balloon dilatation for antral stricture x2

stricturoplasty x 3 Apr 2013

adalimumab 40 mg/wk MTX 25 mg SC

Diarrhea

LOR to infliximab

Early Satiety and weight loss

Early Satiety and weight loss

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KL presents in September 2013 with...

- Anorexia and 5 lbs weight loss
- Nausea
- Post-prandial abdominal pain and bloating
- Again admitted
- Undergoes repeat UGI series
Partially obstructive, focal circumferential stricture of the mid jejunum
KL Goes Back to the OR…

Exploratory Laparotomy with Upper Endoscopy

- 3 normal appearing stricturoplasty, widely patent.
- Moderate focal stricture within the mid small bowel

Heineke-Mikulicz Stricturoplasty

Timeline of Therapy

Diagnosis

Jan 2001

Diarrhea

Jan 2004

6-MP mesalazine

infliximab

2010

adalimumab 40 mg EOW

balloon dilatation antral stricture x2

LOR to infliximab

Feb 2013

adalimumab 40 mg/wk

MTX 25 mg SC

Early Satiety and weight loss

Apr 2013

stricturoplasty x 3

Sep 2013

stricturoplasty

Early Satiety and weight loss
KL’s Clinical Course

- Feb 2014: Return of symptoms
- UGI Series: 2 short segment areas with focal narrowing in the proximal jejunum
- Adalimumab levels: therapeutic and absence of detectable antibodies
- KL undergoes bypass gastro-jejunostomy
Duodenal Stricturoplasty vs. By-pass Gastrojejunostomy
Birmingham Study: Bypass is Superior

<table>
<thead>
<tr>
<th>Stricturoplasty</th>
<th>By-pass Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=13</td>
<td>N=13</td>
</tr>
<tr>
<td>Early Post-op complications n=9</td>
<td>No immediate post-op complications</td>
</tr>
<tr>
<td>Median Follow-up 143 Months</td>
<td>6/13 late surgeries</td>
</tr>
<tr>
<td></td>
<td>Median Follow-up 192 months</td>
</tr>
</tbody>
</table>

Yamamoto et al. 1999
Cleveland Clinic Study: Approaches Comparable

<table>
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<tr>
<th>Stricturoplasty</th>
<th>By-pass Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=13</td>
<td>N=21</td>
</tr>
<tr>
<td>Early Post-op complications n=2</td>
<td>2/21 immediate post-op complications</td>
</tr>
<tr>
<td>Median Follow-up 42 Months</td>
<td>1/21 late surgeries</td>
</tr>
<tr>
<td></td>
<td>Median Follow-up 96 months</td>
</tr>
</tbody>
</table>

Worsey et al. 1999
Stricturoplasty: Conflicting Data

- **Birmingham Study**: Higher early post-op complications¹
- **Cleveland Clinic Study**: Safe and Effective²
  - Shorter Follow-up
- **Stricturoplasty³**: Strictures in the 2nd or 3rd Part of duodenum
- **By-Pass Surgery³**: Multiple strictures in the 1st or 4th parts of duodenum

1. Yamamoto et al. 1999
2. Worsey et al. 1999
Potential Post-operative complications

- Stricturoplasty causes slow gastric emptying
- Delayed gastric emptying in 24%
- Other complications:
  - Anastomotic leak, enterocutaneous fistula, intra-abdominal abscess, and stomal ulceration
- Meta-analysis results:
  - Overall complication rate for jejunal and/or ileal strictureplasty: 13%
  - Septic complications (eg, leak, fistula, abscess): 4%

By-Pass Surgical Procedures Options

• Commonest indication: Duodenal obstruction\(^1\)
• Gastrojejunostomy \(^2,3\)
• Gastrojejunostomy with highly selective vagotony\(^4\)
• Gastroduodenostomy
• Roux-en-Y-Gastrojejunostomy

What Post-Op Treatment Do You Recommend?

a) Tacrolimus

b) Vedolizumab

c) Repeat endoscopic dilation

d) Exclusive Enteral Nutrition (EEN)
What Post-Op Treatment Do You Recommend?

a) Tacrolimus

b) Vedolizumab

c) Thalidomide

d) Exclusive Enteral Nutrition (EEN)
Exclusive Enteral Nutrition Has All of the Following Effects Except:

a) Down regulates inflammatory cytokines

b) Reduces CRP and ESR

c) Superior mucosal healing compared to corticosteroids

d) Is only effective when using elemental formulas
Exclusive Enteral Nutrition in Crohn’s Disease

- Under used therapy
- Nutrition -> Induction of remission\(^1\)
- Formula: Elemental or Polymeric
- Duration: 6-8 weeks
- Oral or Naso-jejunal route
- Disease location: may impact efficacy, conflicting data\(^2\)\(^-\)\(^6\)
- Useful in children and adults

5. Wall et al. World journal of Gastroenterology 2013
6. Lee et al. IBD 2015
EEN Promotes Mucosal Healing

• Open label RCT: Higher mucosal healing (74%) with the polymeric formulae as compared to corticosteroids (33%)\textsuperscript{1}

• Open label Prospective Study: 84% (clinical remission), 76% (biochemical remission), 58% (early endoscopic remission), and 21% (complete trans-mural remission of ileal CD)\textsuperscript{2}

• Prospective Study: 79\% achieved complete macroscopic and histological mucosal healing in the colon and TI\textsuperscript{3}

\textsuperscript{1} Borelli et al. Clinical Gastroenterology and Hepatology, vol. 4, no. 6, pp. 744–753, 2006.
\textsuperscript{3} Fell et al. Alimentary Pharmacology and Therapeutics, vol. 14, no. 3
EEN Reduces Inflammatory and Improves Barrier Function

• Polymeric formula decreases intestinal permeability and improves tight junction integrity¹

• Down regulates inflammatory cytokines including interleukin-1, interleukin-8 ³

• Reduces serum CRP, ESR, and TNF-α²

Pathophysiology of Action of EEN: Alteration of Gut Microbiota

- **Dysbiosis hypothesis:** a breakdown between the balance of good bacteria and harmful bacteria significantly contributes to the development of IBD

- Significant modification of bacteria -> Anti-inflammatory action

- Effect lasts for Four months

EEN Improves Nutritional Status

- Reversal of growth hormone resistance\(^1-3\)
- Improvement in bone health
- May improve micronutrients

“Why do I have such severe disease and why is it so difficult to treat?”
Other Factors that may Contribute to KL’s Symptoms?

a) Teenage stress/lifestyle/diet

b) Small Intestinal Bacterial Overgrowth

c) Poor motility from medications and previous surgeries

d) Affected Genotype
## Teenagers Are Not Small Adults

<table>
<thead>
<tr>
<th></th>
<th>Adolescents n = 100</th>
<th>Adults n = 100</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn’s disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal</td>
<td>11 (20%)</td>
<td>16 (50%)</td>
<td>P &lt;0.01</td>
</tr>
<tr>
<td>Colonoic</td>
<td>6 (11%)</td>
<td>7 (22%)</td>
<td></td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>37 (69%)</td>
<td>9 (28%)</td>
<td>P &lt;0.0001</td>
</tr>
<tr>
<td>Upper GI tract</td>
<td>15 (28%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

| **Ulcerative colitis** |                     |                |         |
| Left-sided/proctitis  | 11 (33%)            | 24 (61%)       | P <0.01 |
| Pancolitis            | 22 (67%)            | 22 (39%)       | P <0.001 |

| **Indeterminate colitis** | 13 | 12 |         |

| **Behavior** |                     |                |         |
| Inflammatory (B1) | **42 (78%)**       | 19 (59%)       | P <0.001 |
| Stricturing (B2)  | 11 (20%)            | 7 (22%)        |         |
| Penetrating (B3)  | 1 (2%)              | 6 (19%)        |         |
| + Perianal (P)    | **18 (33%)**        | 5 (16%)        | P <0.01  |

Goodhand J. et al. Inflamm Bowel Dis 2010
## Teenagers Have More Severe Disease

<table>
<thead>
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<th>Adolescents n = 100</th>
<th>Adults n = 100</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA for UC</td>
<td>82%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>5-ASA for CD</td>
<td>74%</td>
<td>56%</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>≥ 1 course of steroids</td>
<td>65%</td>
<td>59%</td>
<td>P = 0.87</td>
</tr>
<tr>
<td>Current steroid use</td>
<td>17%</td>
<td>16%</td>
<td>P = 1.0</td>
</tr>
<tr>
<td>Current AZA use</td>
<td><strong>46%</strong></td>
<td>17%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Infliximab</td>
<td><strong>20%</strong></td>
<td>8%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td><strong>46%</strong></td>
<td>14%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>18%</td>
<td>9%</td>
<td>P = 0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Missed appointments (median IQ range)</strong></th>
<th>Adolescents</th>
<th>Adults</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>20% (0-50)</strong></td>
<td>0% (0-14.3)</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Goodhand J. et al. Inflamm Bowel Dis 2010
Genetic Testing for GDCD

*NOD2/Card15* Gene Polymorphisms

- Two allelic variation
- G900R and L1007P
- G900R
- Ileal disease
- Smokers

- L1007P homozygosity
- Strong association
- GDCD
- Younger age at diagnosis

Take Home Points

- Gastro-duodenal Crohn’s Disease is uncommon
- Is usually asymptomatic
- Sx: Nausea and vomiting, weight loss, obstruction
- Little data to guide medical treatment
- Multiple surgical options: depend on location, extent, and past response, local expertise
- EEN is a good long-term option but may be difficult for patient
- Genetics plays a role in this unique phenotype
Take Home Points of GDCD

- **Whom?**
  - Age
  - Co-morbidites
  - Genetic Susceptibility

- **Why?**
  - Inflammation
  - Stricture
  - Obstruction
  - Malnutrition

- **When?**
  - Early vs. late Presentation

- **Where?**
  - Anatomical location
  - Local availability & expertise