New Diagnosis Patient

- 30 yo female presents with 3 month history of perianal pain and drainage. No change in stool habits.
  - Treated empirically with metronidazole with only minimal improvement
  - Colonoscopy with TI intubation and bx are normal
- FH: positive for Crohn’s
- PE: Normal except rectal exam which showed…
Patient asks you if she could have Crohn’s disease and does this happen frequently to CD patients or is she just the unlucky one?

She also wants to know what to expect over her lifetime if this is from Crohn’s disease?
Cumulative Incidence of Crohn’s Fistulas

Frequency of Perianal Fistulas According to the Anatomic Location of Bowel Involvement

Colon only (without rectal involvement) 41%
Rectum only 92%
Small intestine only 12%
Combined ileocolic involvement 15%

Schwartz et al, Gastro 2002
Hellers et al, Gut 1980
Anatomy

Anatomic Relationships in the Pelvis

- Rectal columns
- Dentate line
- Intersphincteric space
- Internal anal sphincter
- External anal sphincter
classification system

park’s classification of perianal fistulas

A: Superficial
B: Intersphincteric
C: Trans-sphincteric
D: Suprasphincteris
E: Extrasphincteric

External anal sphincter
Severe PCD Patient

- 50 yo male presents with long history of perianal pain and drainage. Recently started passing air and stool when he urinates. No change in stool habits.
  - Treated in past with antibiotics, immunomodulators and infliximab
  - Several attempts at surgical treatment without success
  - Colonoscopy with TI intubation and biopsies are normal
- FH: positive for Crohn’s
- PE: Normal except rectal exam which showed…
What is the best approach to this problem?

What are his treatment options (medical and surgical)?
Why is a precise evaluation important?

The key to successful management is to establish adequate drainage of all abscesses and to control fistula healing. An imaging modality should provide a virtual road map for this purpose.

What Happens When Fistulas are Missed at Time of EUA?

- In 52% of patients needed repeat surgery in cases where surgery and MRI disagreed
- Fistula recurrence was always at site predicted by MRI

_Buchanan et al, Lancet 2002_
Study Results

- A prospective triple blinded study compared EUS, MRI and EUA in 32 patients with suspect perianal Crohn’s disease.1
- All three methods showed excellent accuracy in assessing these patients
  - EUS – 91% (95% CI 75% - 98%)
  - EUA – 91% (95% CI 75% - 98%)
  - MRI – 87% (95% CI 69% - 96%)
- Combining either of the imaging modalities with EUA increased the accuracy to 100%

1- Schwartz et al., Gastro 2001

Normal Radial EUS Anatomy
Options for Therapy
Does Controlling Fistula Healing Make a Difference?

Response to Treatment

- Initial Only: 83%
- EUA Before Initial: 100%

Fistula Recurrence

- Initial Only: 78%
- EUA Before Initial: 44%

Requeiro et al, IBD 2003

Comparison of Healthcare Utilization in Patients with CD Perianal Fistulas Treated with Biologics with or without Setons

Schwartz et al. ECCO 2013
With & Without Seton

Are Setons Needed When Using Anti-TNF Agents for CD Perianal Fistulas?

Schwartz, Ghazi et al, DDW 2015
Surgical Treatment

Fistulas
Perianal Crohn’s Disease – Surgical Treatment Options

• Fistulotomy
• Setons
• Advancement Flap
• Fibrin Glue / Fistula Plug
• Diversion / Proctectomy

Setons
Fistulotomy

External Opening
Probe
Incision
Open fistula tract

Fistula
Anus

Fistulotomy
How Setons Help

Seton Placement
Medical Therapy

Medical Therapies

• Antibiotics (metronidazole, ciprofloxacin)
• Immunosuppressives
  – Azathioprine
  – 6-mercaptopurine
  – Cyclosporine
  – Tacrolimus
• Biologic Agents
  – Infliximab
  – Adalimumab
  – Certolizumab
  – Vedolizumab?
Antibiotics Improve Fistula healing in Combination with Anti-TNF Therapy

All patients received adalimumab 160 mg at wk 0, 80 mg at wk 2 and then 40 mg qow. Patients were then randomized to Ciprofloxacin 500 mg bid or placebo.

Azathioprine / 6-MP

• The 5 Controlled trials were summarized in a meta-analysis\(^1\)
  – 22 / 41 (54%) of patients who received AZA/6-MP responded vs. 6 / 29 (21%) who received placebo.
  – Pooled odds ratio was 4.44 in favor of fistula healing

Cyclosporine & Tacrolimus (FK-506)

The double blinded placebo study of 48 patients randomized to receive 0.20mg/kg/day for 10 weeks. Primary endpoint was improvement defined as closure of $\geq 50\%$ fistulas and maintenance of closure for $\geq 4$ weeks.

Week 10 Results

- Only 10% had closure of all fistulas

$\text{Sandborn et al.}, \text{Gastro} \ 2003$
Anti-TNF α Antibody

Infliximab for Crohn’s Perianal Fistulas

Primary endpoint; > 50% reduction in open fistulas

Initial Fistula Response to Infliximab

- 10mg/kg: 56%
  - p = 0.041
- 5mg/kg: 69%
  - p < 0.001
- Placebo: 25%
  - N=94

Present et al., NEJM 1999
Anti-TNF Maintenance Therapy for CD Related Fistulas

**Infliximab**

![Graph showing Infliximab results](image)

**Adalimumab**

![Graph showing Adalimumab results](image)

**Certolizumab**

![Graph showing Certolizumab results](image)

1- Sands et al., NEJM 2004
2- Colombel, Gut 2009
3- Schreiber S, et al. APT, 2011

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Higher Infliximab Trough Levels are Associated with a Higher Rate of Perianal Fistula Healing

**Results:**

- n=117; 17 patients w/seton placement (14.5%)
Future Options?

Vedolizumab

Sandborn et al., NEJM 2013
Adipose Derived Stem Cells – Fistula Healing at Week 24

N = 212

Remission and Response rates higher in TNF/Immunomod pts - 67% v. 47%

Panes, Lancet 2016

How Can We Improve Outcomes for Patients with Crohn’s Perianal Fistulas?
Recurrent Fistula Patient

• 45 yo female presents with 5 year history of Crohn’s disease. Has had perianal fistula that has drain intermittently for 4 years.

• Presents with 2 month history of perianal pain and drainage.
  ▪ Currently on infliximab monotherapy
  ▪ Colonoscopy with TI intubation and biopsies are shows active proctitis

She asks what can be done to get increase her chances of healing and get her fistula to stop draining for good?
The Use of Imaging to Guide Therapy

MRI to Guide Therapy with Infliximab or Adalimumab

Medical therapy was increased if no or partial response seen on MRI

Ng et al. Am J Gastro 2009
MRI to Monitor Therapy

- 41 pts, serial MRIs, 3 years follow-up
- Patients with early response (6 weeks) had 5x ↑ rate of remission (p=0.004)
- All patients (7) who continued the TNF after achieved MRI healing maintained remission

Utilizing EUS to Improve Fistula Healing

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Long-term</th>
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<tbody>
<tr>
<td>Complete Ceo.</td>
<td>85</td>
<td>70</td>
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<tr>
<td>of Drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Fistula</td>
<td>14</td>
<td>24</td>
</tr>
</tbody>
</table>

Schwartz et al, IBD 2005
2 Randomized Prospective Studies Looking at EUS to Improve Outcomes

Initial Prospective Pilot Study

Recent Follow-up Prospective Study

1- Spradlin, Schwartz Am J Gatro 2008
2- Wiese, Schwartz Am J Gastro 2011 (ab)

Conclusion
1. History and physical exam
2. Endoscopy to assess activity of Crohn’s disease
3. Imaging study (EUS or MRI) to delineate perianal disease process
4. Exam under anesthesia (EUA)

Simple fistula without rectal inflammation
- Antibiotics and AZA/6-MP
- Consider anti-TNF

Simple fistula with rectal inflammation
- AZA/6MP & Anti-TNF (consider monitoring healing with repeat imaging study)
  - ? TDM

Complex fistula
- 1. Seton placement
  - 2. Antibiotics, AZA/6-MP, & Anti-TNF (? TDM) (consider monitoring healing with repeat imaging study)

1. Treatment Failure
   - 1. Fistulotomy
     - 2. Consider fibrin glue, fistula plug or endorectal advancement flap
     - 3. If 1 or 2 fails, treat as complex fistulizing process
   - 2. Continue maintenance AZA/6-MP & Anti-TNF (if started)

1. Treatment Success
   - 1. Treat as complex fistulizing process
   - 2. Continue maintenance AZA/6-MP & Anti-TNF

1. Treatment Failure
   - 1. Consider Tacrolimus in selected pts
   - 2. Proctectomy

1. Treatment Success
   - 1. Remove seton
   - 2. Continue maintenance AZA 6-MP & Anti-TNF