Infliximab-Refractory Checkpoint Colitis

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Disclosures

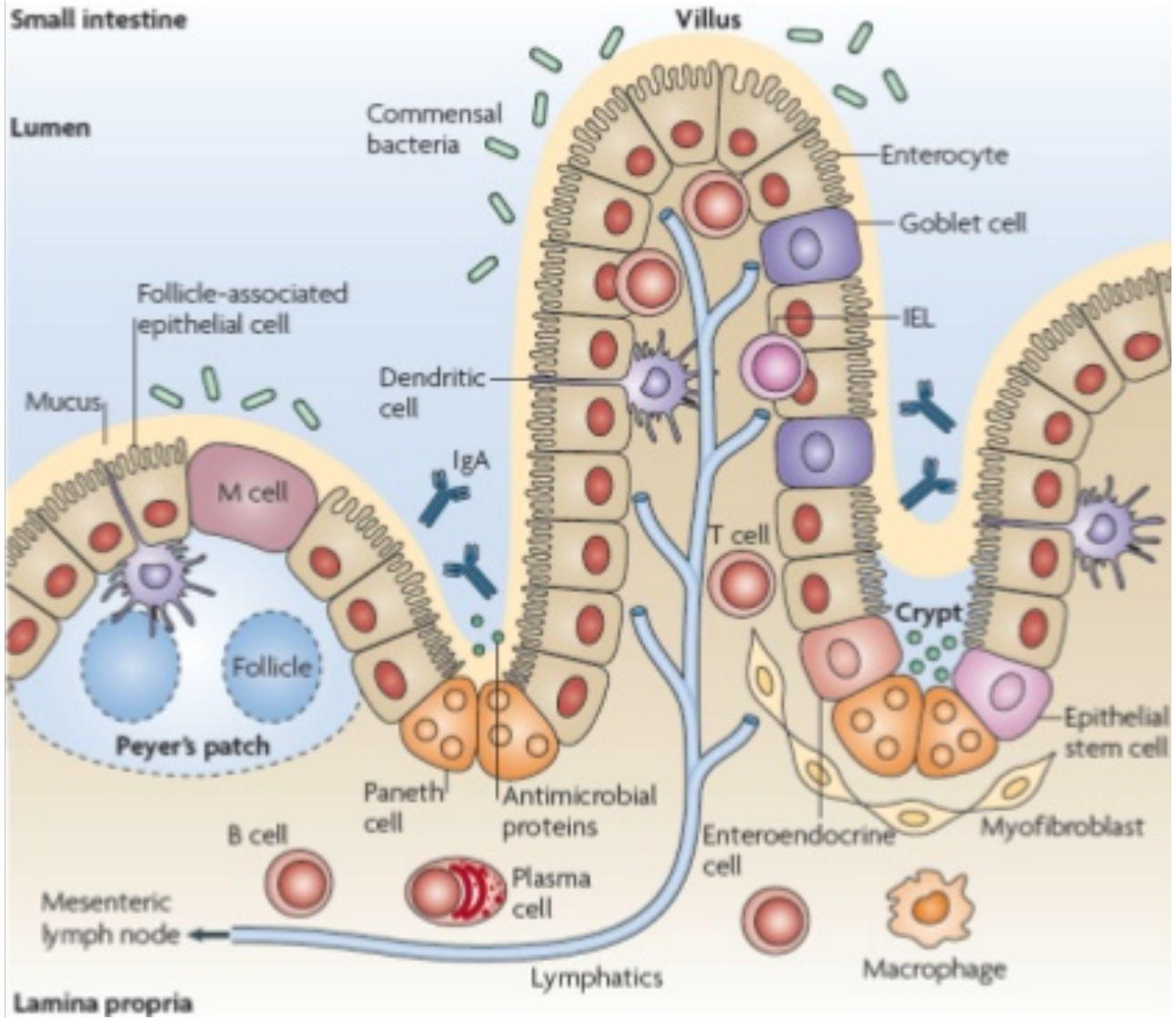
- Novartis (research funding), Genentech (consulting), Tillots (consulting), Moderna (consulting)

- I will be talking about non FDA approved indications for infliximab (and other anti-TNF medications), and vedolizumab

Treatment Refractory Enterocolitis

- DB is a 55 yoW w/ metastatic breast cancer on ipilimumab/nivolumab combination therapy as part of a clinical trial
- Four weeks after completing cycle one, she developed severe, watery diarrhea associated with cramping abdominal pain
- Typical presentation for checkpoint inhibitor enterocolitis

The gut is the most immunologically complex barrier in the body



Abreu et al. Nat. Rev. Imm. 2010

Careful immune regulation is essential

- Dietary proteins
- Commensal bacteria
- Pathogenic microorganisms
- Toxins

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Disruption of immune homeostasis leads to a wide-spectrum of common GI toxicities

(Entero)colitis
Hepatitis

	Ipilimumab	αPD-1[a]	αPD-L1[b]	Ipilimumab + αPD-1
Common toxicities of checkpoint blockade (all grades)				
Constitutional				
Fatigue	15.2–48	10.4–34.2	13.1–25	35.1–39
Asthenia	6.3–11	4.8–11.5	6.6	9
Pyrexia	6.8–15	4.2–10.4	6.6–8	18–20
Dermatologic				
Pruritus	26–35.4	8.5–20	8–10	33.2–40
Rash	14.5–32.8	0.9–25.9	8	40.3–41
Gastrointestinal (GI)				
Diarrhea	22.7–37	7.5–19.2	9.8–15	44.1–45
Nausea	8.6–24	5.7–16.5	6.6–17	21–25.9
Vomiting	7–11	2.6–16.4		13–15.3
Decreased appetite	9–12.5	1.9–10.9	8–8.2	12–17.9
Constipation	9	2–10.7		8–11
Colitis	8.2–11.6	0.9–3.6	2	18–23
Hepatitis	1.2–3.9	1.1–3.8	4	15.3–27
Increased lipase	14–17	0.6		13–18
Musculoskeletal				
Arthalgia	5–9	2.8–14	6–10	10.5–11
Endocrine				
Hypothyroidism	1–15	4.8–11	5–8	15.3–17
Hyperthyroidism	2.3–4.2	3.2–7.8		
Hypophysitis	2–2.3	0.4–0.7		12–13
Adrenal insufficiency	0–2	0.4		5
Pulmonary				
Pneumonitis	0–1.8	0.4–5.8	4	9–11

Dougan M. *Frontiers in Immunology*. 2017.

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The spectrum is dependent on the pathway targeted

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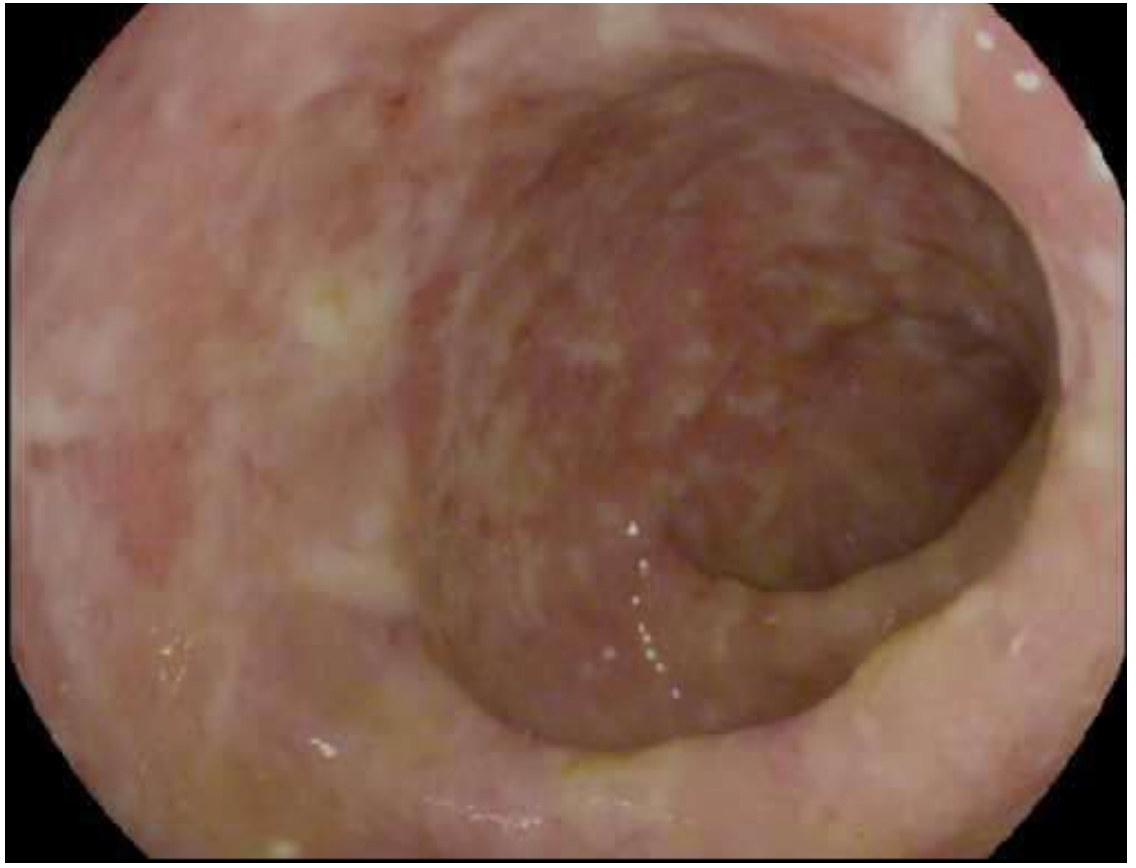
Enterocolitis

- (Entero)colitis is the most common GI toxicity from current checkpoint blocking antibodies (CTLA-4, PD-1, PD-L1)
- Range of severity (many patients have indolent disease)
- Likely responsible for most treatment related diarrhea
- Often isolated to the colon, but can involve the GI tract from stomach to rectum



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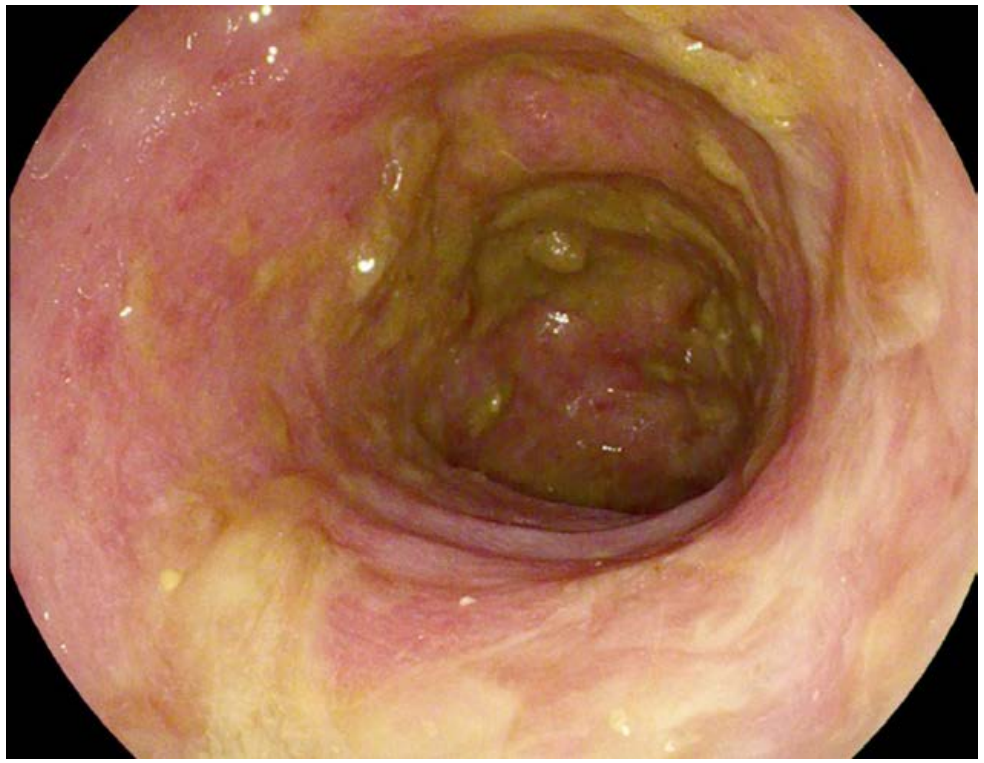
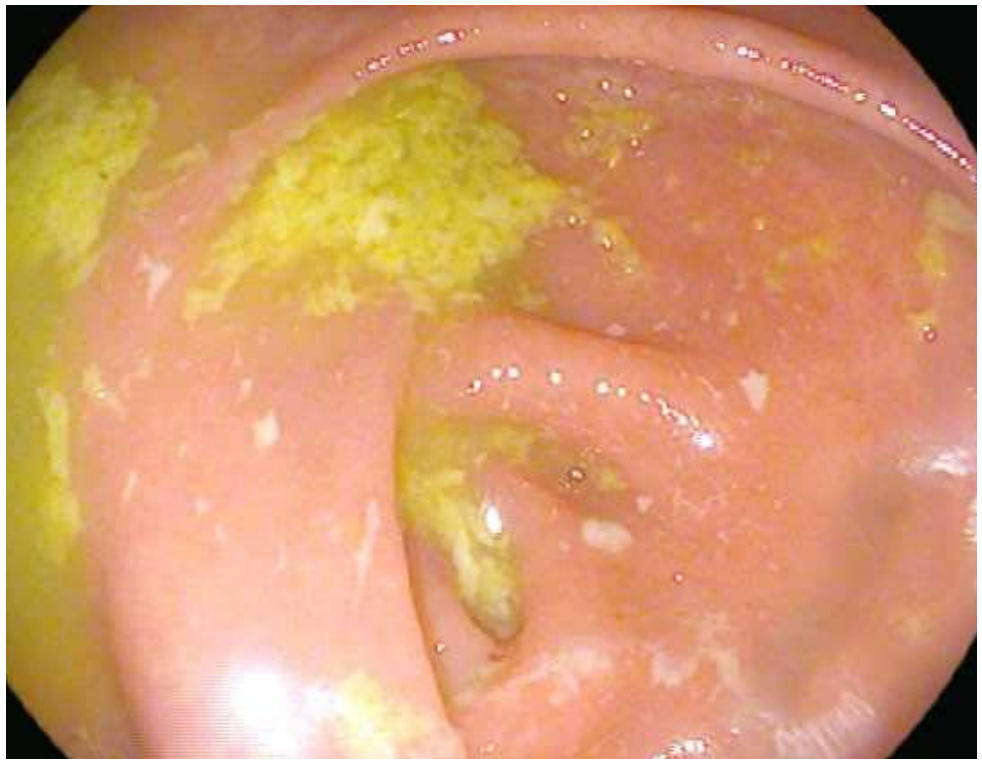
CTLA-4 and PD-1/PD-L1 have different regulatory roles in the gut

Ipilimumab colitis



- More frequent and more severe
- Rapid onset
- Dose-dependent
- Rapidly resolves

PD1-blockade colitis



- more microscopic inflammation
- Indolent course
- Dose-independent (?)
- Slow resolution

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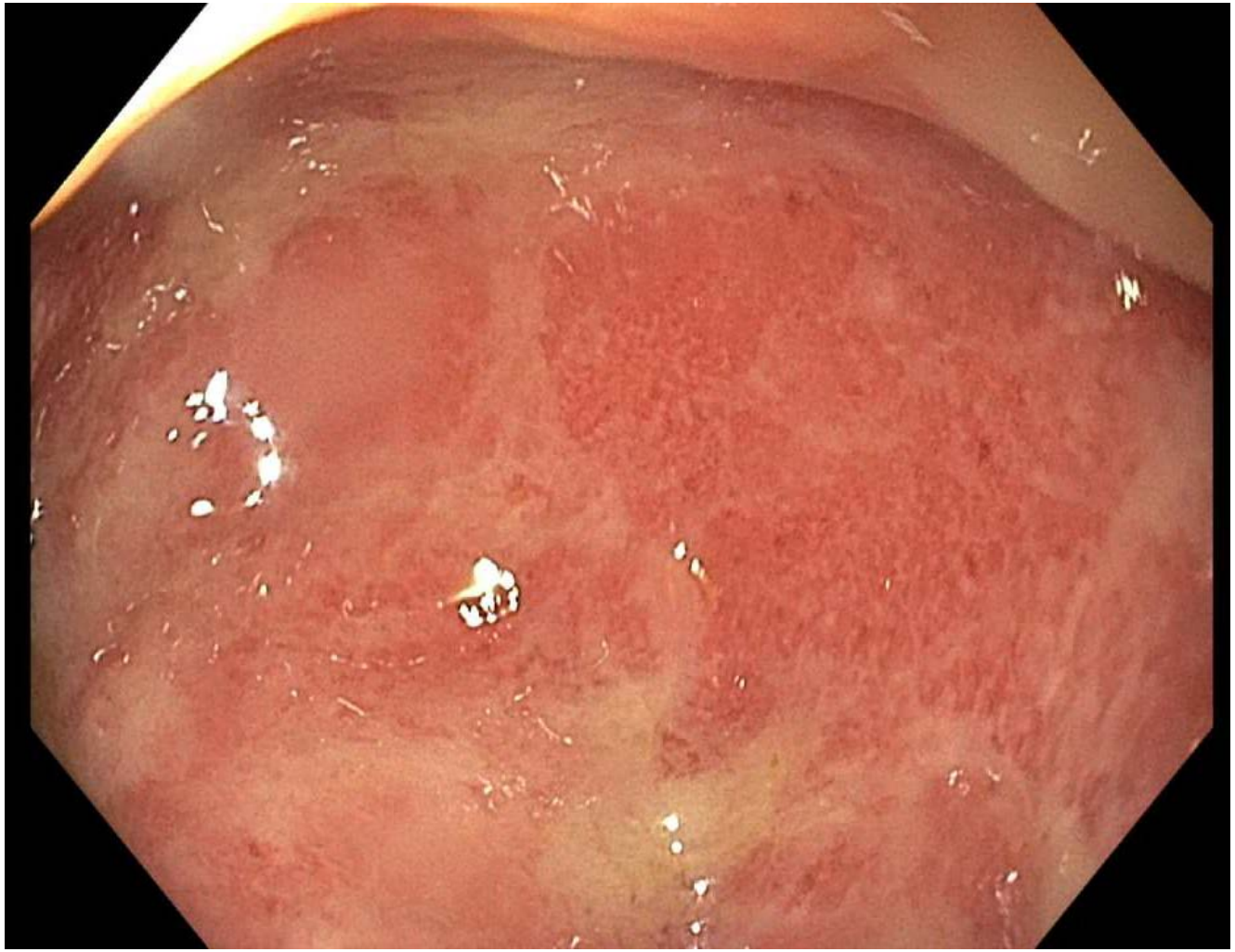
DB underwent endoscopic examination

Severe checkpoint inhibitor colitis was confirmed



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TNFα is likely a key driver of checkpoint colitis

- Most patients with checkpoint colitis respond to steroids
  - 30-40% of severe cases are steroid refractory
- Infliximab (anti-TNFα) is highly effective in ipilimumab and anti-PD1 mediated colitis
  - Suggests a critical functional role for this cytokine in disease pathogenesis
- We have a low threshold for using it (41% of our checkpoint colitis patients go on infliximab)
  - Similar rates for ipilimumab and anti-PD-1 colitis, but ipilimumab colitis seems to respond faster
- Vedolizumab also appears to be effective in some patients (Abu-Sbeih et al. JITC. 2018)
  - Trafficking of new T cells into the gut probably plays a role in maintaining inflammation

Can we predict who is going to need infliximab?

- All current data are retrospective
- Two published case series found an association with **colonic ulceration** (Wang et al. *IBD*. 2018, Geukes et al. *ESMO Open*. 2018)
- In our MGH cohort of 49 patients with detailed endoscopic and oncologic clinical data:
  - Mayo Endoscopic Score is higher in patients who need infliximab (1.14 vs 2.26 out of 3, $p = 0.001$)
  - No association with CTCAE grade (2.05 vs 1.95)
  - MES 3 (ulcers) is associated with an increased need for infliximab ($p < 0.009$)
  - No association with rectal bleeding
  - Patients with enteritis tend to get infliximab more often ($p = 0.08$)
  - No association with pathway inhibited (PD-1 vs CTLA-4)

Corticosteroids were ineffective

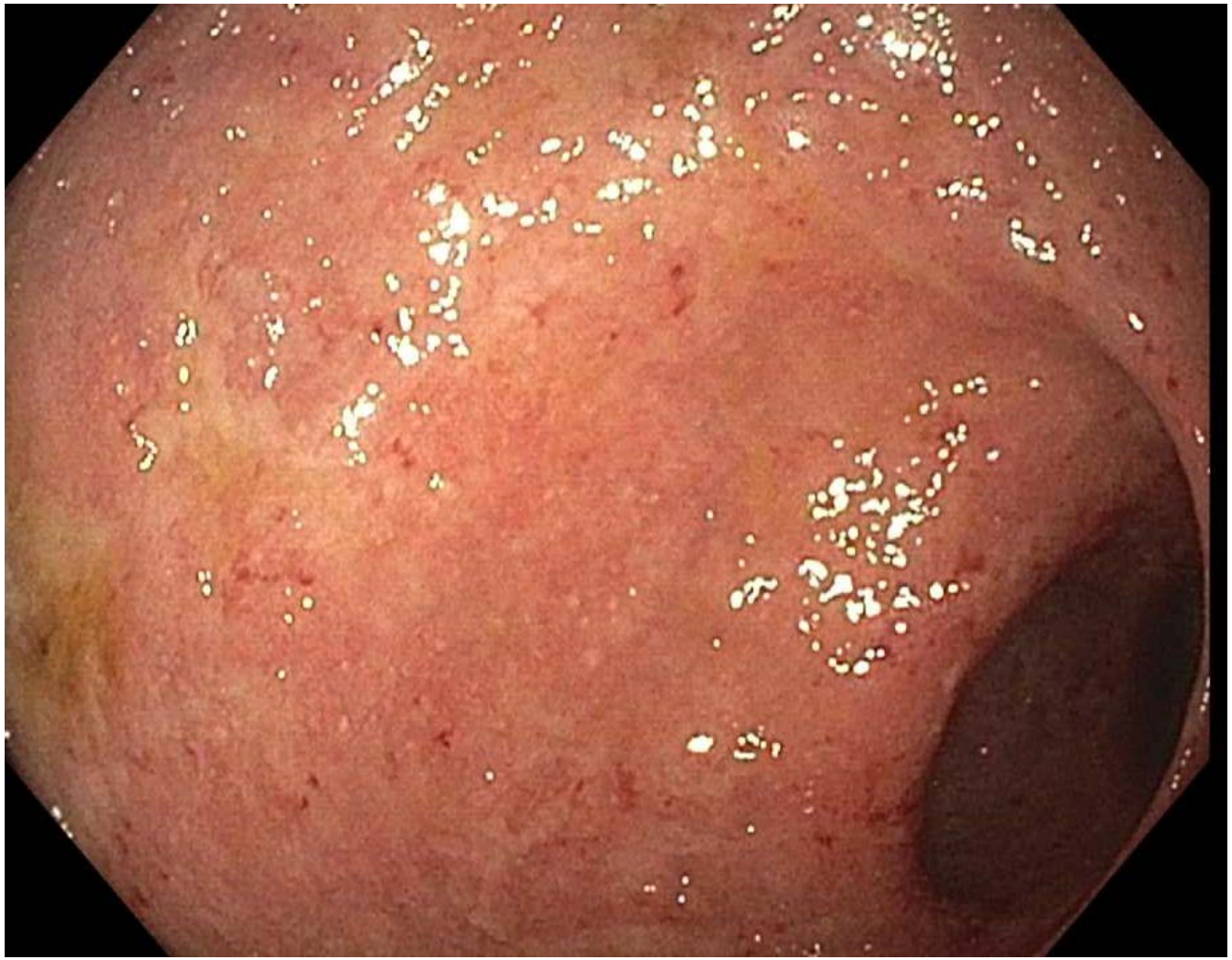
- Within 72 hours of diagnosis, she was started on infliximab (5 mg/kg)
- She received dose 2 one week later for incomplete response
- She received a total of 4 doses (week 0, 1, 2, 6) with an initially good response, but she was unable to taper the steroids below 20 mg daily

What if patients don't respond to infliximab?

- Reconfirm the diagnosis:
- Infections (C Diff, CMV, fungal) happen in a significant fraction of patients
- We have seen treatment emergent Celiac Disease (TTG-IgA+, gluten-free diet responsive)
- Pancreatic insufficiency can occur (Eshet et al. CIR. 2018)

Repeat endoscopy

Persistent checkpoint enterocolitis



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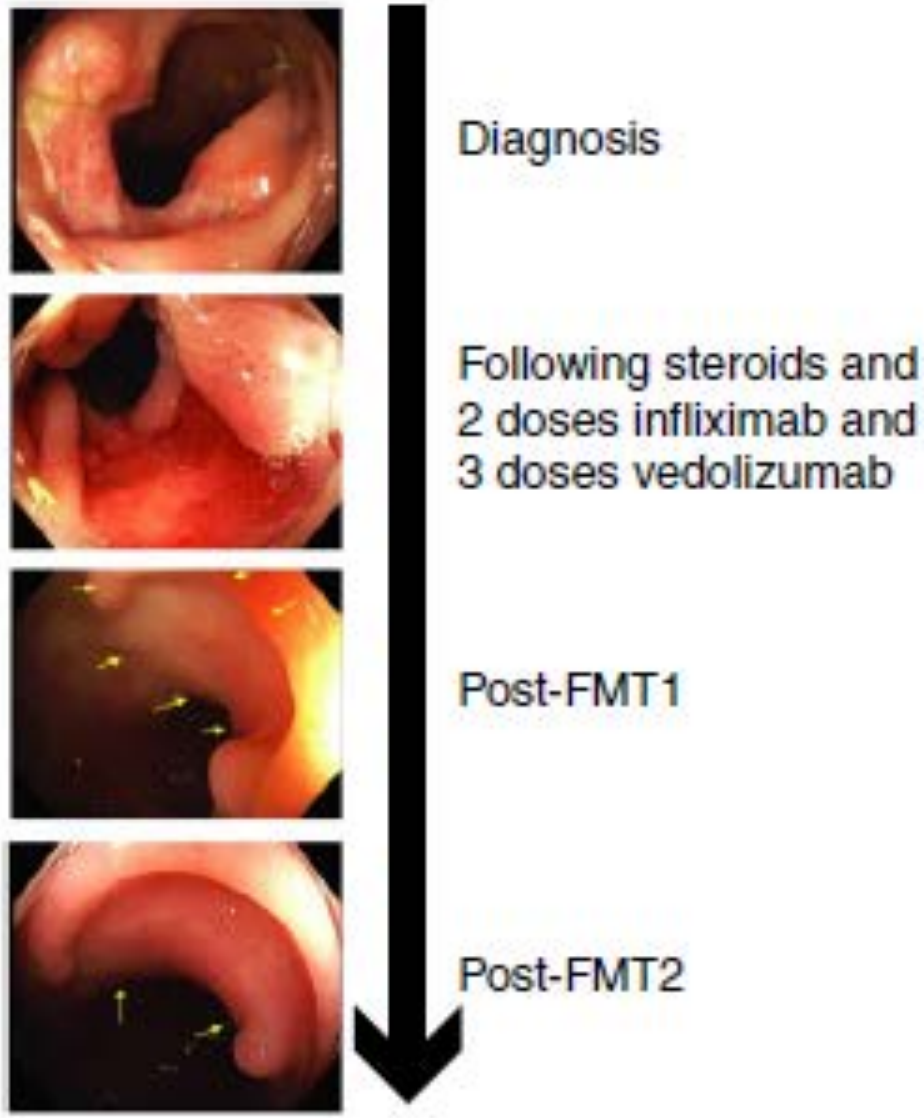
And if checkpoint enterocolitis is reconfirmed?

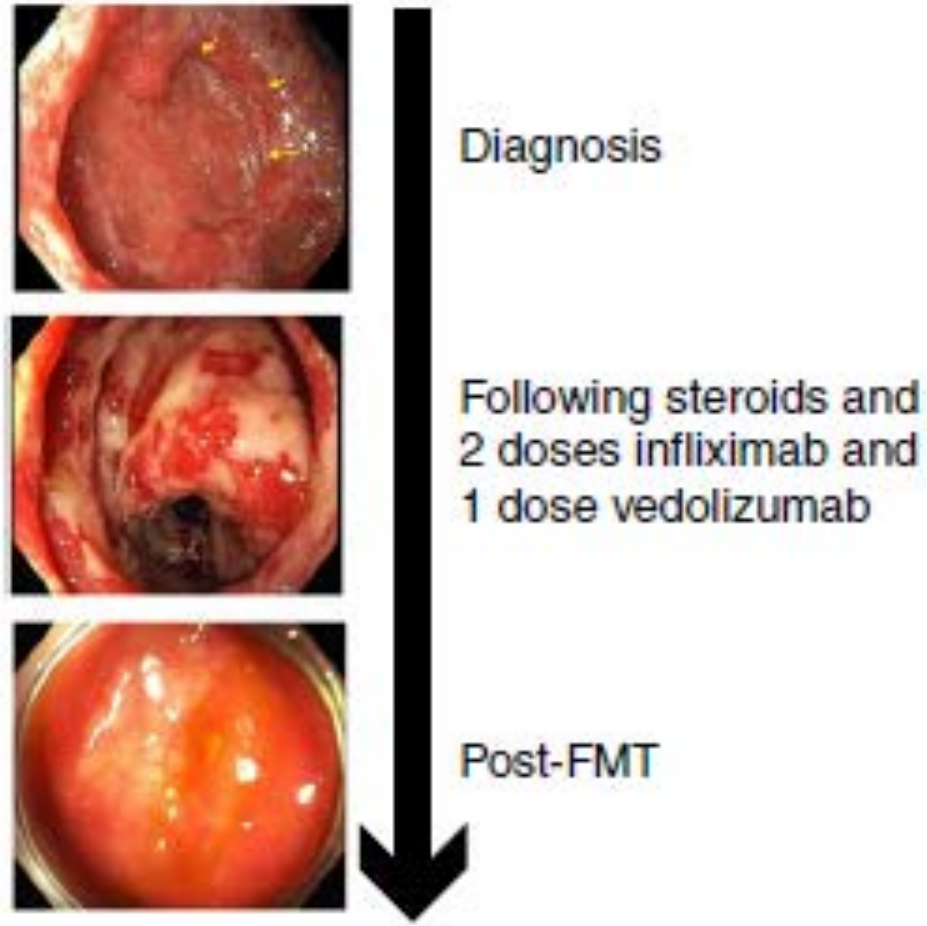
- This question has not been adequately addressed in the literature
- Best data is for vedolizumab (Abu-Sbeih et al. JITC. 2018)
- Vedolizumab has some risks:
  - Often must be given while anti-TNF is still circulating
  - Will block trafficking of immune cells to tumors located in the gut (GI tumors, but also metastatic disease – 5% of melanomas)

What other options do we have?

- Surgery: appropriate for colonic disease, and otherwise healthy patients)
- Ustekinumab (anti-IL-12/23 p40): approved for Crohn's with some activity in UC
- Other cytokine inhibitors (anti-IL-1β, IL-6)
- JAK inhibitors: approved for UC
- CTLA-4-Ig: effective at treating CTLA-4 haploinsufficiency, which is associated with enteritis
- Both JAK inhibitors and CTLA-4Ig likely inhibit the antitumor response

What about FMT?





Wang, Y et al. Nature Medicine. 2019

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Vedolizumab was started

- She responded after the initial dose and has been continued for a full load (weeks 0, 2, and 6)
- Infliximab was stopped
- Steroids have been tapered with recrudescence
- We have also used ustekinumab, abatacept, and FMT successfully in other select situations

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