Cancer Day For Primary Care
Immune checkpoint inhibitors

GI Panel

Medical Oncology: Dr. Benjamin Goldenberg
Gastroenterology: Dr. Charles Bernstein
Radiology: Dr. Christopher Lindquist

10 May 2019

Presenter Disclosure

- **Faculty / Speaker's name: Benjamin Goldenberg**

- **Relationships with commercial interests:**
  - **Grants/Research Support: Co-Investigator on CCMF and CCTG sponsored studies**
  - **Speakers Bureau/Honoraria: nil**
  - **Consulting Fees: nil**
  - **Other: nil**

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Mitigating Potential Bias

- Not making any treatment recommendations

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Community Oncology Program

Presenter Disclosure

Charles Bernstein

- **Relationships with commercial interests:**
  - **Grants/Research Support: Abbvie Canada**
  - **Educational grants: Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada**
  - **Clinical trial contracts: Abbvie, Pfizer, Janssen, Roche, Boehringer Ingelheim, Celgene**
  - **Speakers Bureau/Honoraria: Takeda Canada, Medtronic Canada, Ferring Canada**
  - **Consulting Fees: Mylan Pharmaceuticals**
  - **Advisory Boards: Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada**

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Mitigating Potential Bias

- I will not be advocating on the use of any products made by these companies

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Presenter Disclosure

- Dr. Christopher Lindquist

- **Relationships with commercial interests:**
  - **Grants/Research Support: nil**
  - **Speakers Bureau/Honoraria: nil**
  - **Consulting Fees: nil**
  - **Other: nil**

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GI PANEL OBJECTIVES

- To review indications for, and GI toxicity from, checkpoint inhibitors
- Determine best steps for work up and investigation of Upper and Lower GI symptoms in the presence of immunotherapy
- Understand preferred ways to communicate clinical findings to medical oncologist, gastroenterologist and radiologist

Question 1

Do you think Immunotherapy for metastatic cancer is the miracle cure we've all been waiting for?

A. Yes! Praised be… (the deity of your choice)
B. Heck No! This stuff is like juggling with a plutonium rod…
C. Don't know but it's still exciting and overwhelming
D. Might be for a minority of select advanced cancers, but not all.

GI CASE #1

This is a 58-year-old man from Winnipeg, no other comorbidities, who had a poorly differentiated metastatic melanoma excised from shoulder in Dec 2017.

- Initial post excision imaging, PET/CT and subsequent 9 months surveillance did not reveal any new disease.
- Symptomatically recurred in axilla, pre-excision CT chest revealed new bilateral low volume metastatic lung nodules. CT ABD N. BRAIN N. LDH N. ECOG 0
- Started on ipilimumab/nivolumab as per CHECKMATE-067. Thoroughly counseled on the >50% risk on trial of Grade 3/4 toxicity.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

ABSTRACT

Larkin et al N Engl J Med 2015; 373:23-34.

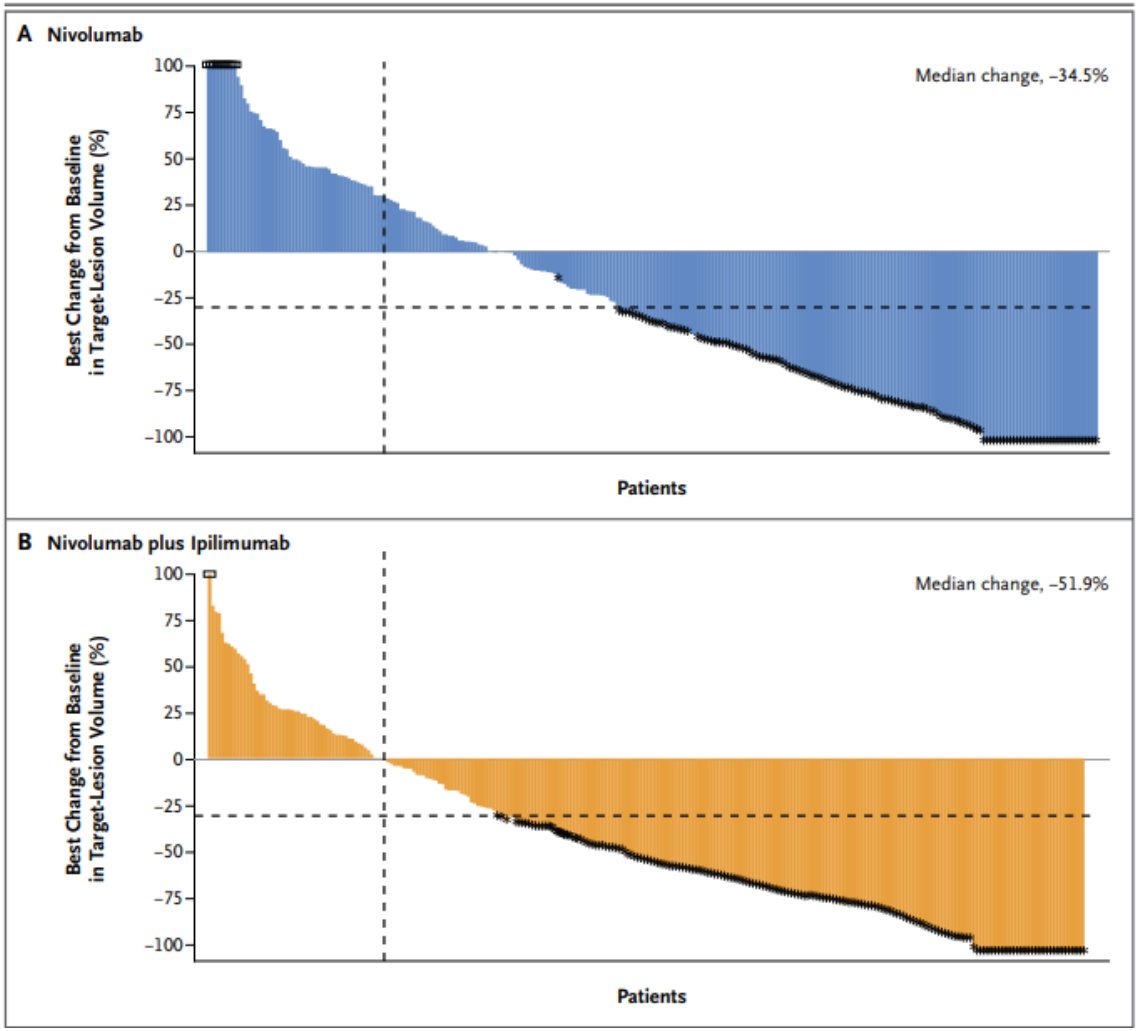
A Nivolumab
Median change, –34.5%
Best Change from Baseline in Target-Lesion Volume (%)
100
75
50
25
0
–25
–50
–75
–100
Patients
B Nivolumab plus Ipilimumab
Median change, –51.9%
Best Change from Baseline in Target-Lesion Volume (%)
100
75
50
25
0
–25
–50
–75
–100
Patients

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

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GI CASE Contd

- After 2 cycles axillary mass flattened, mild fatigue, normal stools. TSH ↓ FT4↑↑ over a span of 3 weeks.
- After 3 cycles, developed episcleritis and hypoT4
- After 4 cycles CT CAP showed marked improvement in lung nodules but new mild jejeunal thickening. Had nausea and 1 episode of vomiting. Otherwise well.
- Given next cycle of nivolumab monotherapy with plans to transition to FPO/CCPN site

GI CASE CONTD

- 2 days post last nivo developed worsening nausea and profuse watery diarrhea.
- Presented to his local tertiary care ED
- Given IV anti-emetics and volume resuscitated; sent home to f/u as outpt at CCMB

Obtained from http://www.owtb.co.uk/topic/46412-have-the-wheels-fell-off/

Question 2

What is the appropriate next step?

A. Move on to next patient in busy ED
B. Contact Med Onc on call or MRP
C. Send outpt referral to WRHA Central Endo Intake
D. Admit to Hospital for Observation and Management

GI Case Contd

- Pt's nausea improved at home but diarrhea continued unabated with imodium, anorexia and dehydration worsened.
- Pt re-presented to same ED
- Admitted now to sub-acute observation unit

Question 3

What else would one want to gather on history?

A. Any blood in stool? Abdominal cramping?
B. How many episodes of diarrhea?
C. Duration of symptoms?
D. Limitations in ADLs?
E. All of the above?

Question 4

What's the most appropriate investigation?

A. Stool culture, C difficile
B. CBC, chem, LFTs, CRP and fecal calprotectin
C. Abdominal X-ray
D. CT ABD
E. Exploratory Laparotomy

GI Case Contd

- Pt symptoms persist despite opiates and loperamide
- Cultures and Cdiff –ve; CRP elevated LFTs midly Abn, Cr inc

Question 5

Whom do you consult first?

A. GI
B. Medical oncologist
C. Surgery
D. ID

CLINICAL PRACTICE GUIDELINES

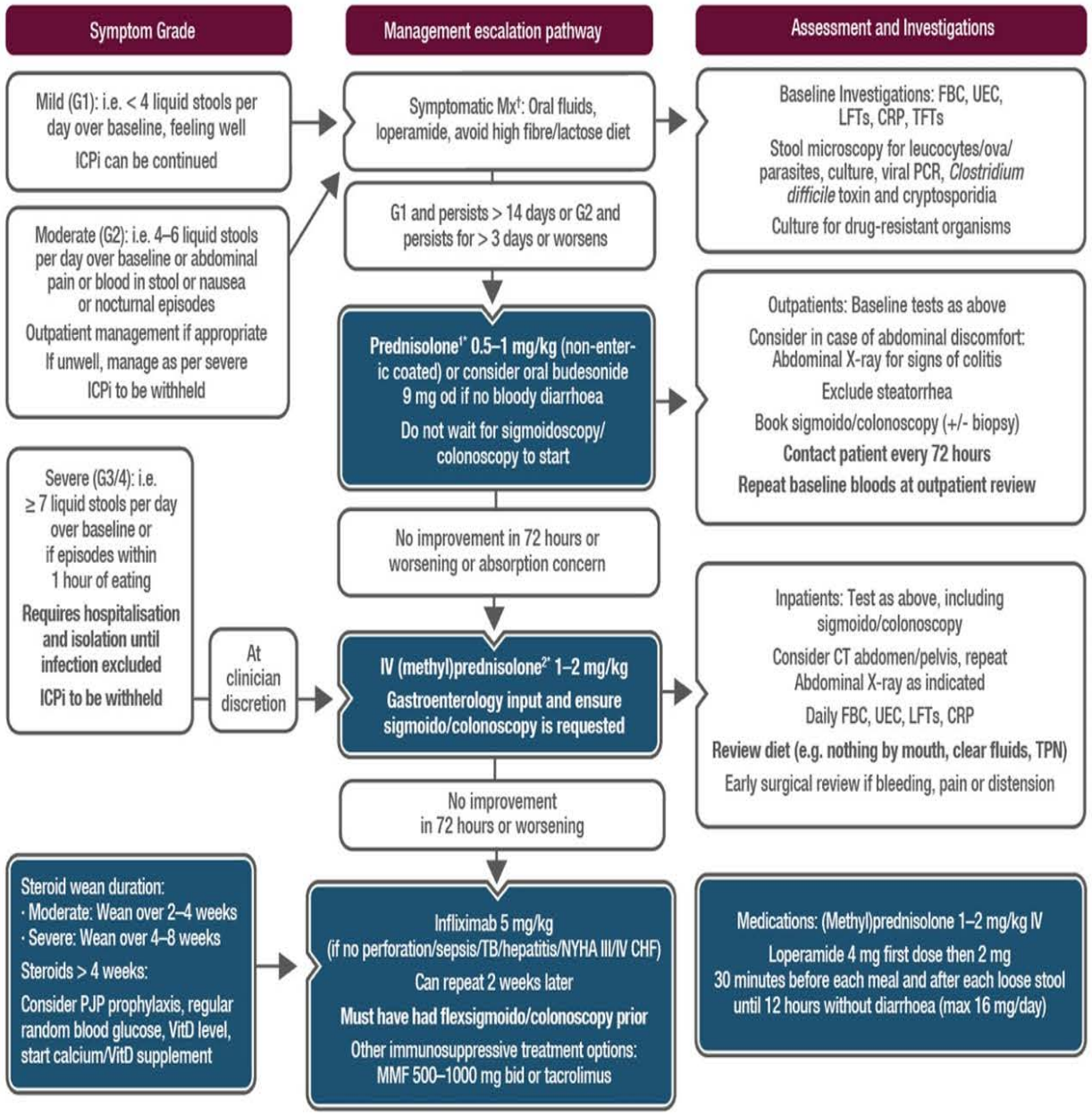
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

†Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:
[1]Moderate: wean over 2–4 weeks
[2]Severe: wean over 4–8 weeks

*Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



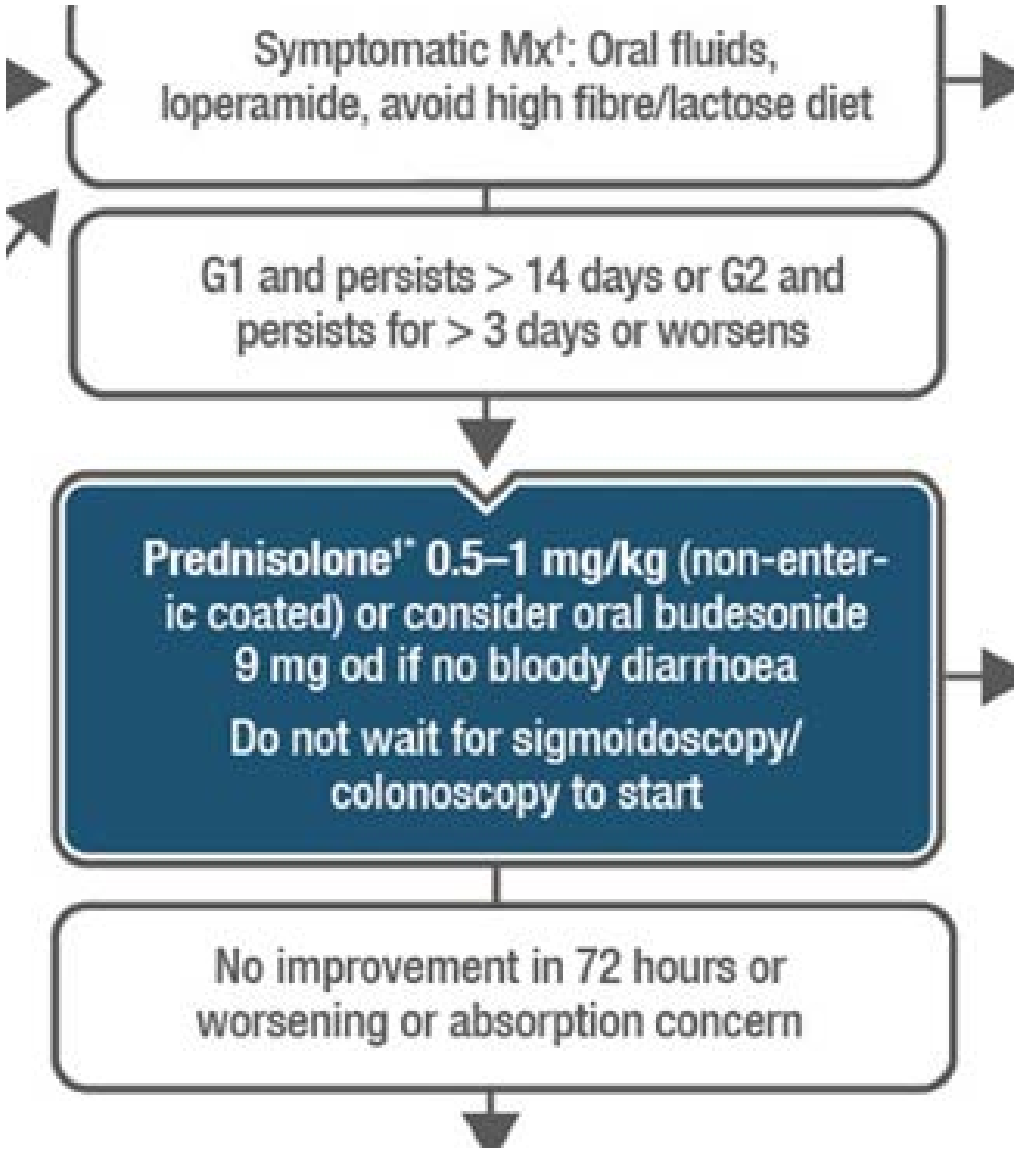
ESMO

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

Question 6

What's the best step in management?

A. Loperamide
B. Oral vancomycin
C. Prednisone
D. Pancrealipase enzymes


Symptomatic Mx†: Oral fluids, loperamide, avoid high fibre/lactose diet
G1 and persists > 14 days or G2 and persists for > 3 days or worsens
Prednisolone†* 0.5–1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg od if no bloody diarrhoea
Do not wait for sigmoidoscopy/ colonoscopy to start
No improvement in 72 hours or worsening or absorption concern

irAE and CTCAE

- Universal Language of Oncology Clinical Trialists – doesn’t always translate appropriately

NCI-CTCAE v4.0

Table 1 National Cancer Institute terminology criteria for diarrhea (1)

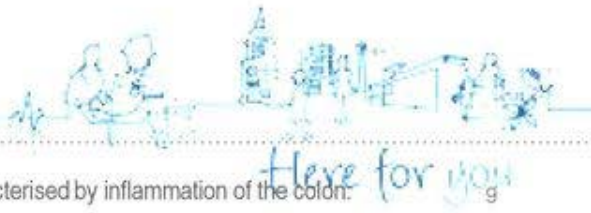
Grade	Description
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared with baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared with baseline
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL[C]
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL[C], activities of daily living.

Grading of Diarrhoea and Colitis

CTCAE v4.03, National Cancer Institute

	Diarrhoea*	Colitis¶
GRADE 1	• Increase of <4 stools/day • Mild increase in ostomy output	• Asymptomatic • Clinical or diagnostic observations only • Intervention not indicated
GRADE 2	• Increase of 4-6 stools/day • Moderate increase in ostomy output	• Abdominal pain • Mucus or blood in stool
GRADE 3	• Increase of ≥7 stools/day • Incontinence • Hospitalisation indicated • Severe increase in ostomy output • Limiting self-care	• Severe abdominal pain • Change in bowel habits • Medical intervention indicated • Peritoneal signs
GRADE 4	• Life-threatening consequences • Urgent intervention indicated	• Life-threatening consequences • Urgent intervention indicated
GRADE 5	• Death	• Death



*A disorder characterised by frequent and watery bowel movements.

¶A disorder characterised by inflammation of the colon.

GI Case Contd

- 100 mgs po daily prednisone did not moderate symptoms after 3 days
- Started at advice of med onc on 200 mg IV solumedrol
- GI consulted

BRIEF INTERLUDE WITH EXPERT GASTROENTEROLOGIST

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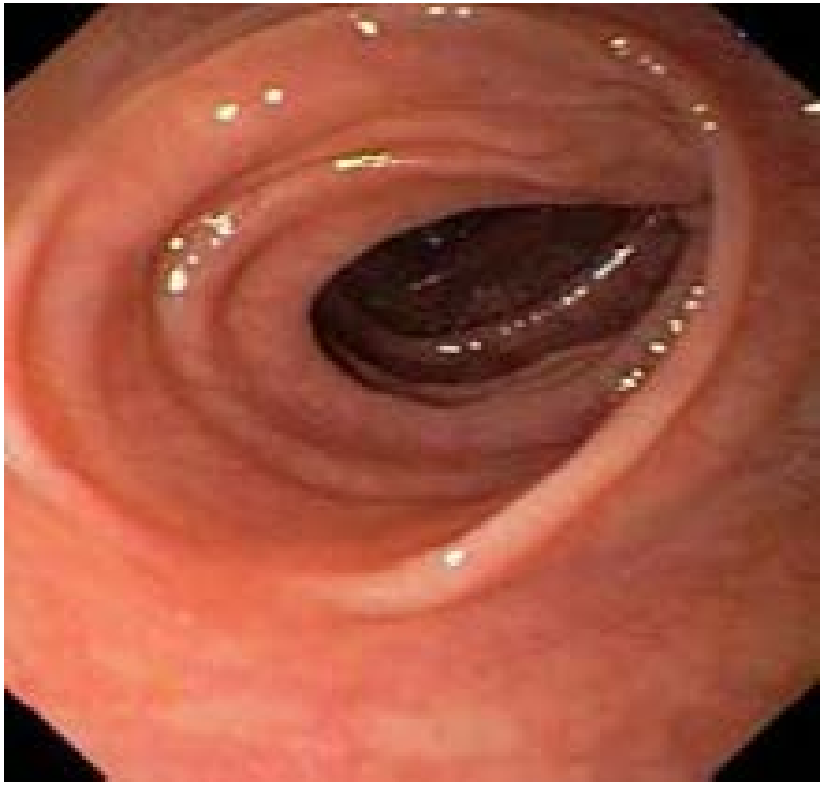
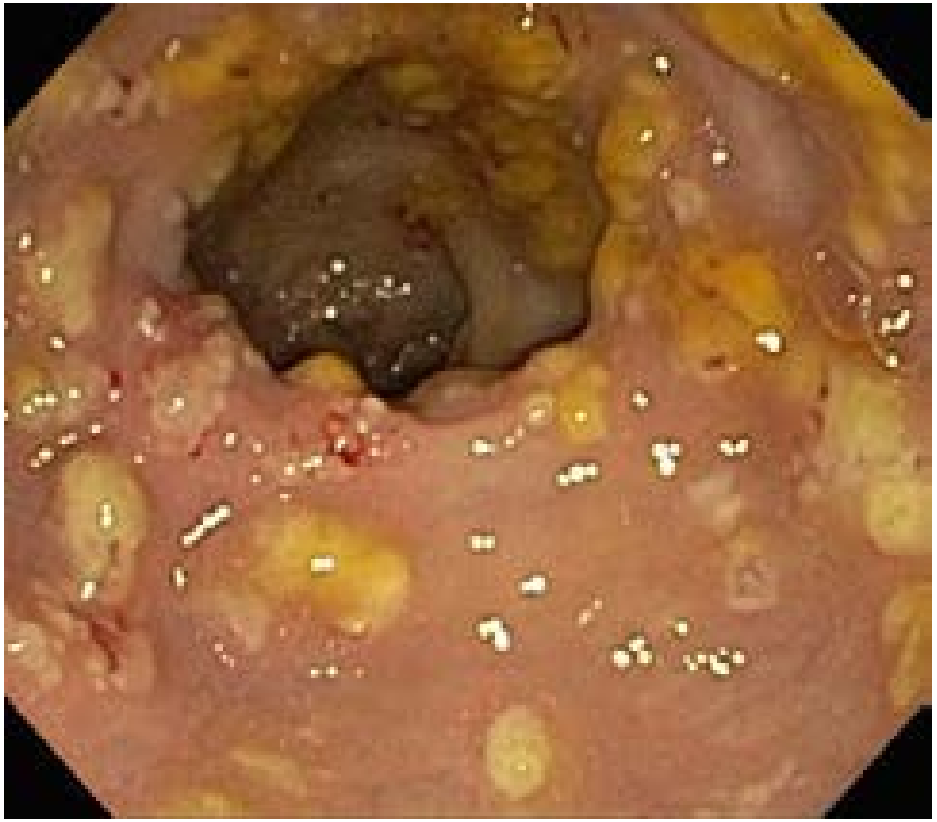
Differential dx is short

- Neutropenic enterocolitis-uncommon; have to be neutropenic. Can be focal
- GVHD; is that in DDX
- Superimposed infection-

  Cdiff- common; oral vanco; not flagyl; other infection- needs testing bloody and non bloody diarrhea C+S

  Nonbloody diarrhea; C diff, C+S, O+P.
- Drug/supplement induced (MMF, elixirs, nutrition supplements, antibiotics)

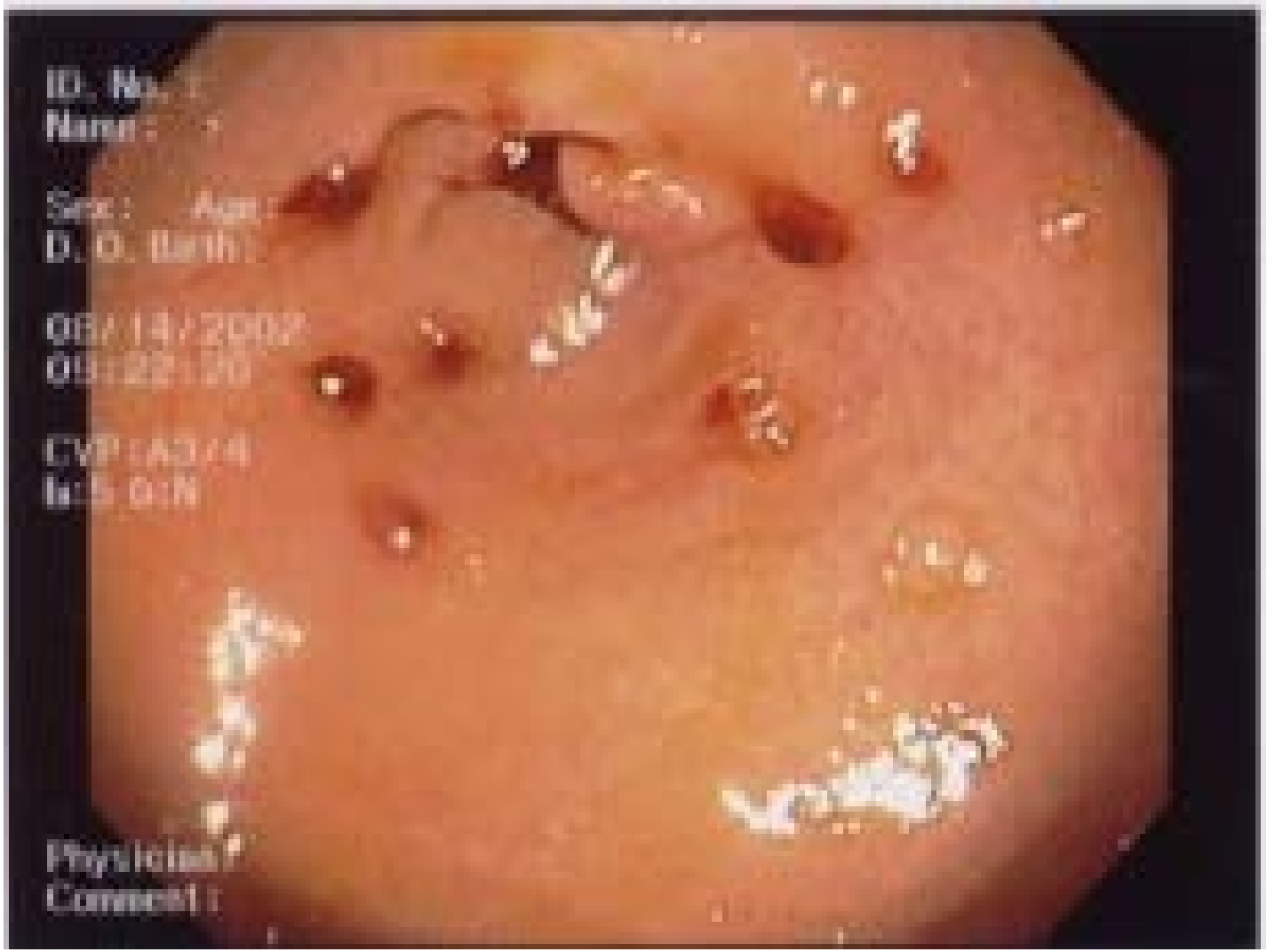




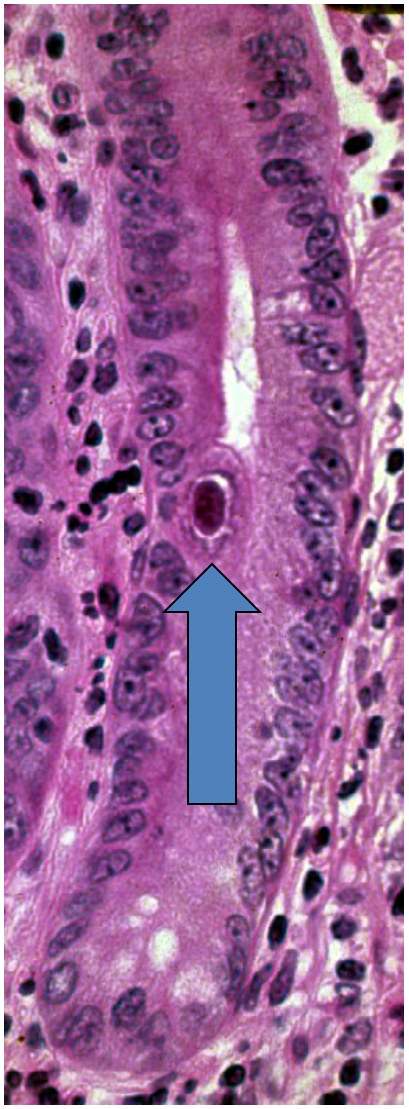
Upper or lower endoscopy

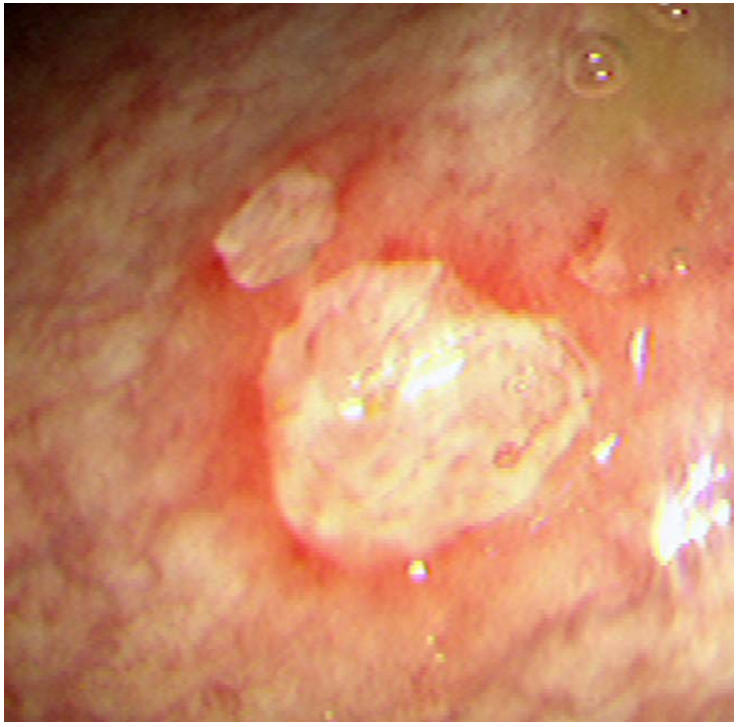
- If secondary to immunotherapy or ?CMV-do lower endoscopy

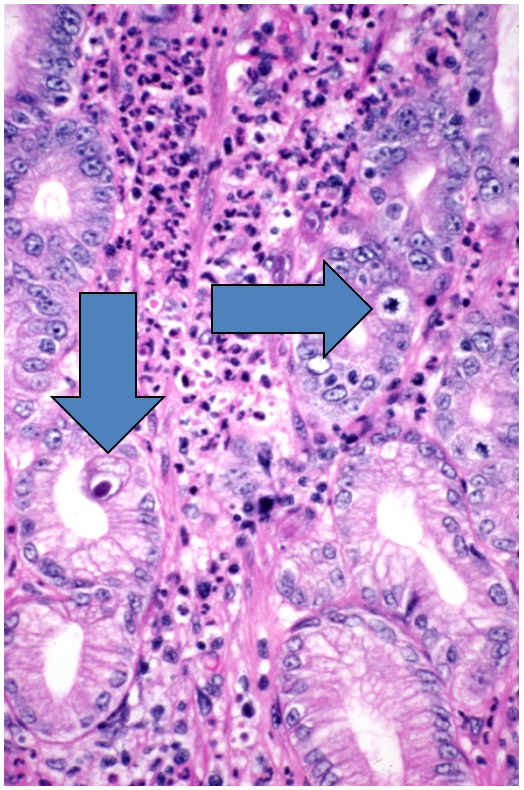
CMV gastritis



CMV colitis







Checkpoint inhibitor induced enterocolitis

- Anti-CTLA4 (ipilimumab), Anti PD-1, anti tyrosine kinase……
- RR 13 for Grade III-IV enterocolitis
- RR 10 for Grade III-IV diarrhea
- RR 3 for intestinal perforation
- RR 2.5 for intestinal related death (Witges, in submission)

Unanswered questions:

- Enteritis/colitis or enterocolitis
- Incidence of chronicity?
- Need for therapy beyond steroids – IS PO PREDNISONE EFFICACIOUS?
- Duration of biological therapy

No infection
?Immunotherapy diarrhea
Tips for RX

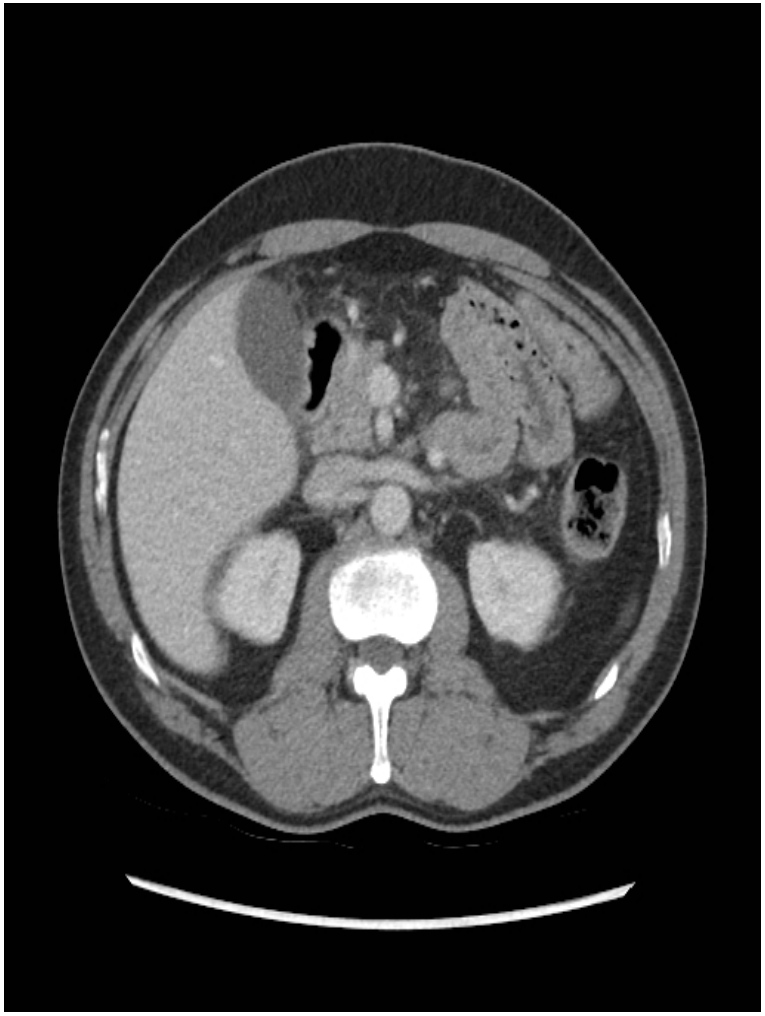
- Oral predinsone for days; if not working-IV
- Switch to oral once diarrhea settles
- Consider anti TNF or anti integrin. If serious worry about systemic infection I would trial vedolizumab.

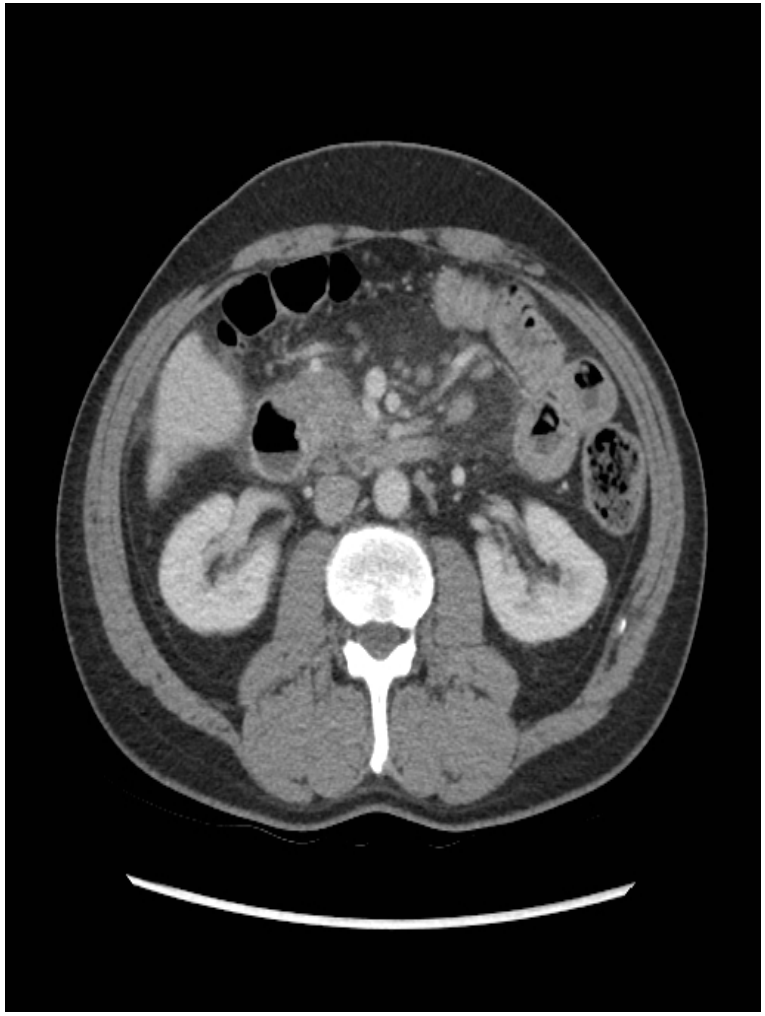
GI Case Contd

- Infliximab was started at 5mg/kg; IV steroids continued
- Pt's diarrhea slowed down by beginning of 3rd week of admission
- Has series of abdominal imaging throughout that time

Radiology slides

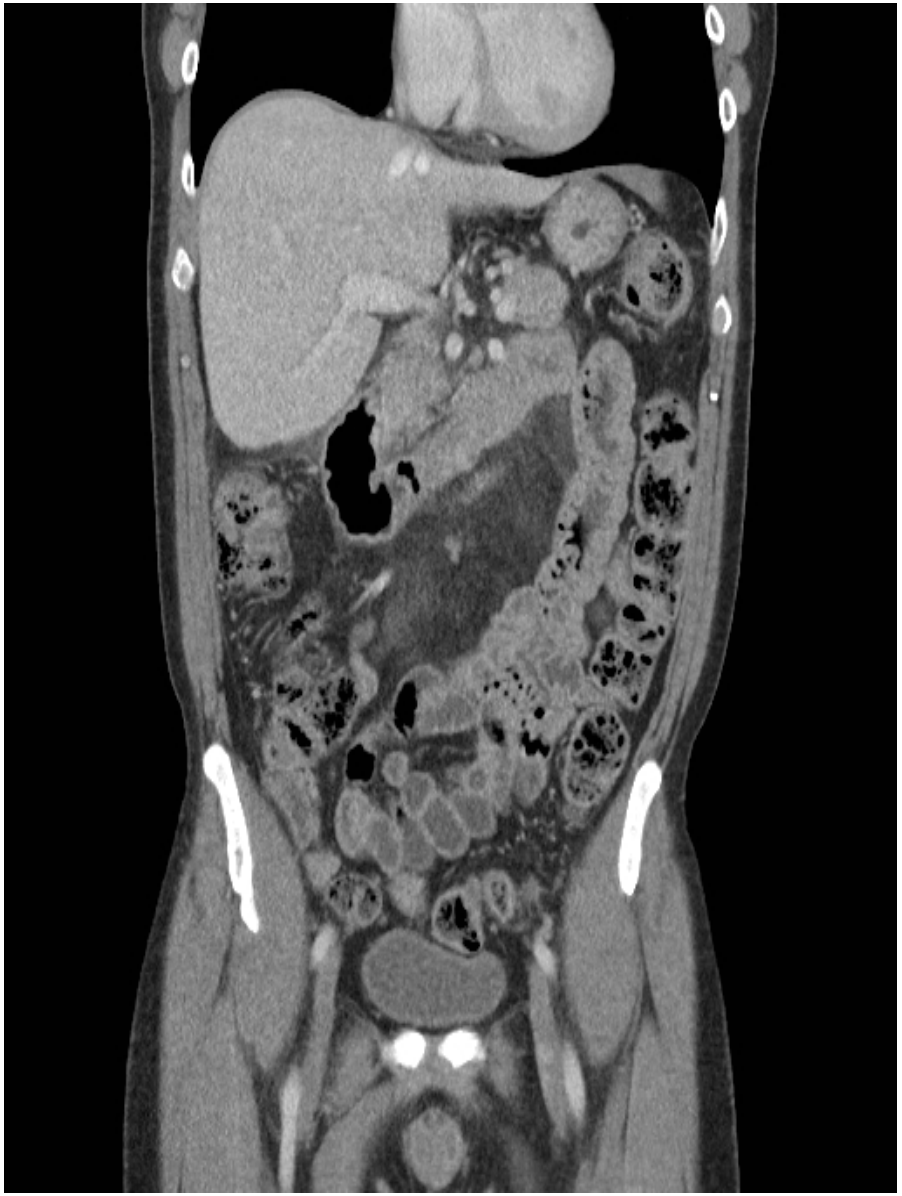
CT April 2019





CT April 2019

- Mildly thickened loops of jejunum in left upper quadrant
- No significant mucosal hyperenhancement
- Colon appears normal
- Mesenteric lymphadenopathy



Differential diagnosis of bowel wall thickening

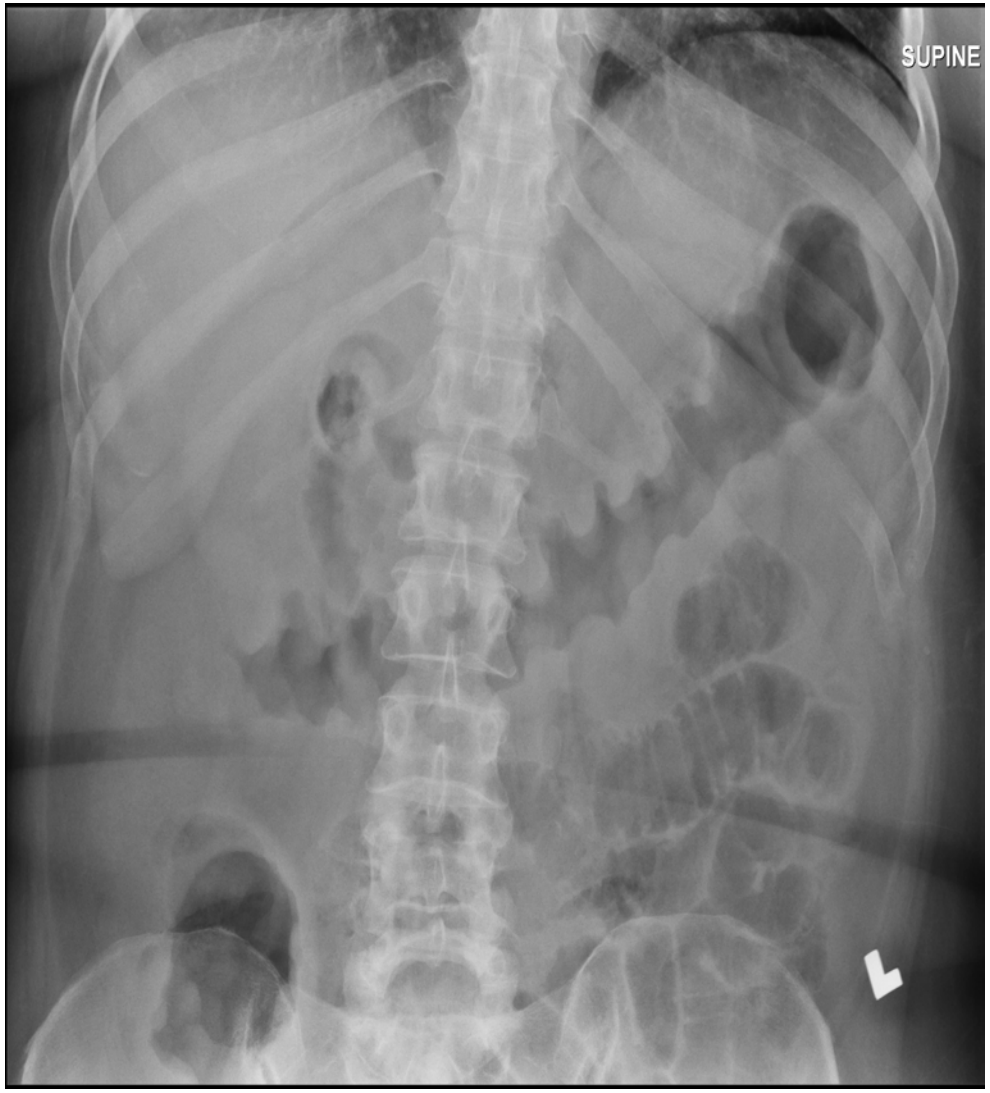
- Infection
  - Infectious colitis
  - Pseudomembranous colitis
- Inflammation
  - UC and Crohn’s disease
- Ischemia
- Neutropenic enterocolitis
- Malignant bowel wall thickening
  - Carcinoma
  - Lymphoma

Infectious colitis

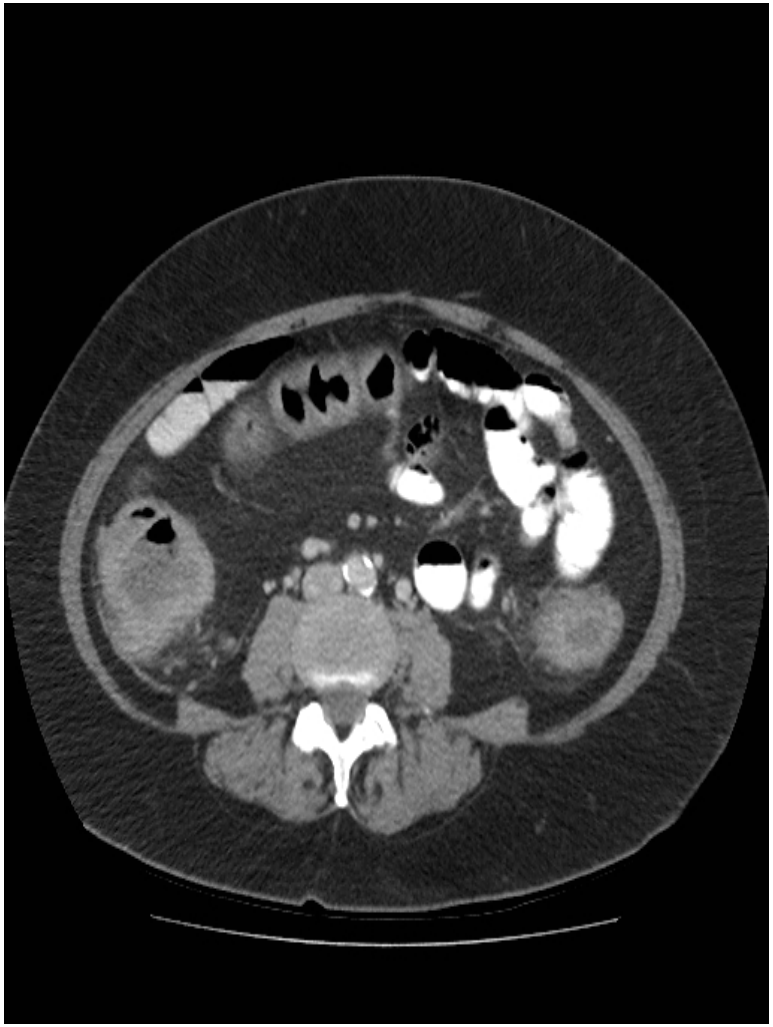
- Typically long segment or diffuse
- CT findings
  - Bowel wall thickening (> 3 mm)
  - Mucosal hyperenhancement
  - Pericolonic fat stranding and edema

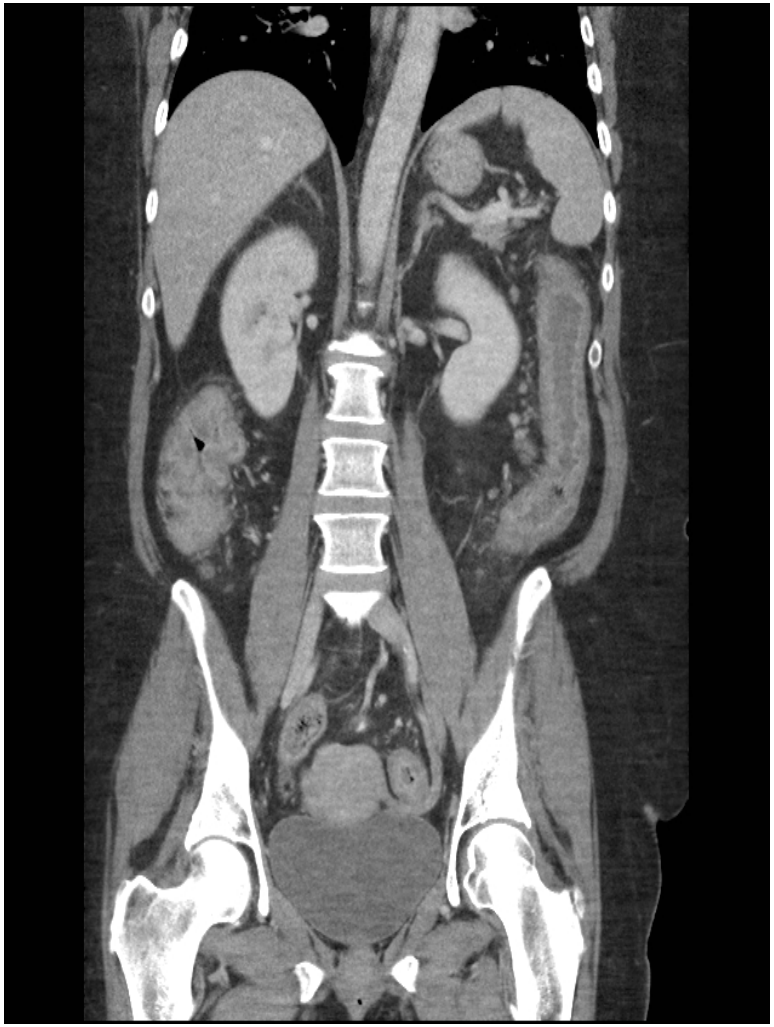
Infectious colitis

- Diffuse thumbprinting of transverse colon seen on AXR
- Mildly dilated small bowel loops in LLQ



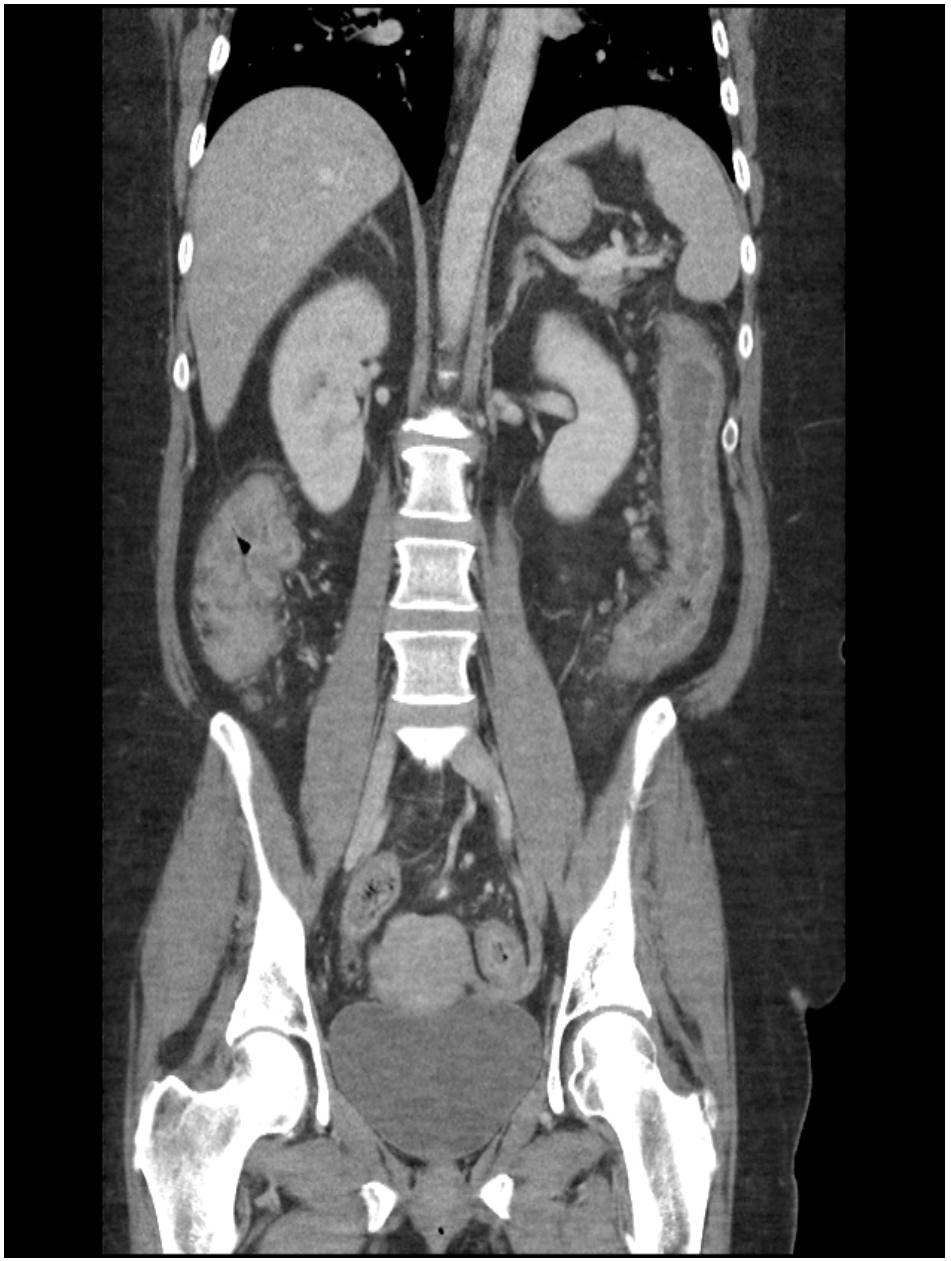
Infectious colitis





Infectious colitis

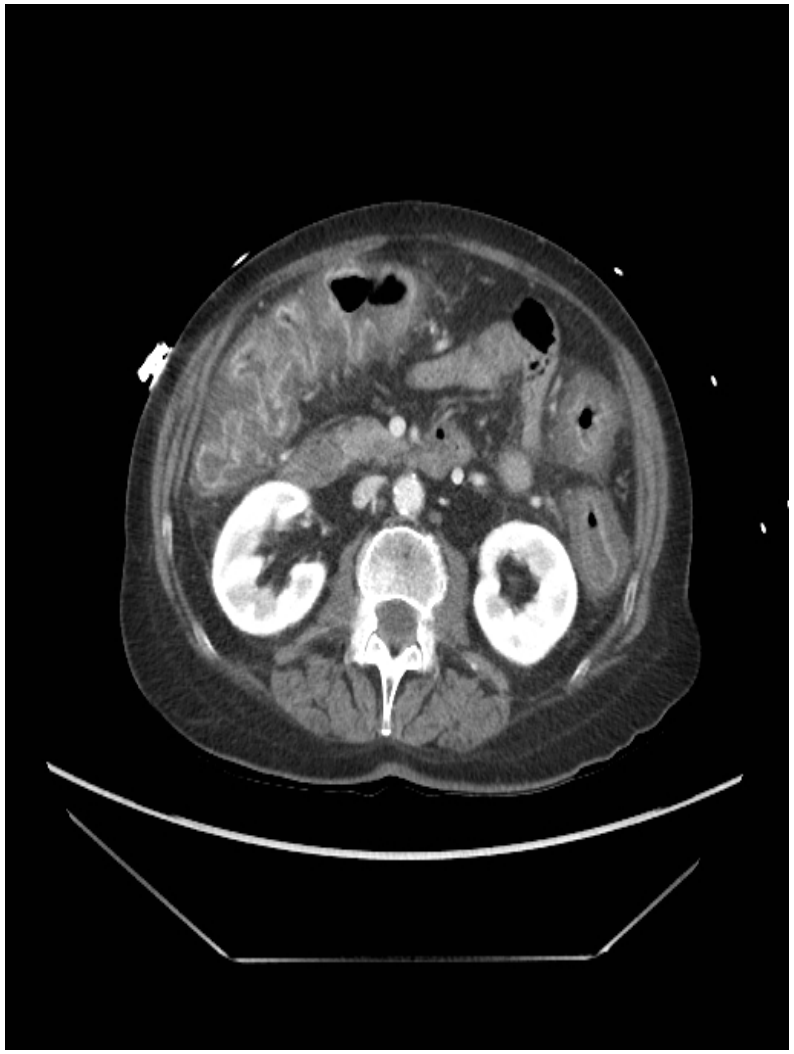
- Diffuse colonic wall thickening and hyperenhancement
- Prominence of vasculature
- Mucosal hyperemia
- Pericolonic fat stranding

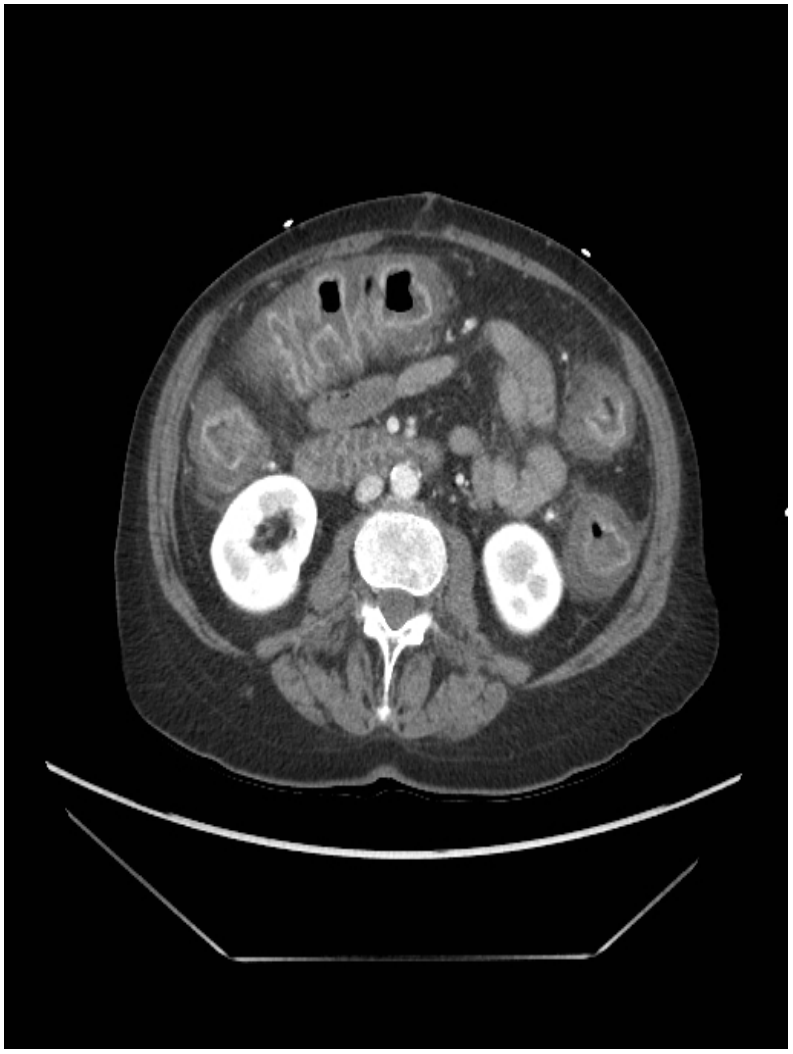


Pseudomembranous colitis

- Specific CT findings seen in pseudomembranous colitis
  - Mucosal hyperenhancement
  - Pancolonic thickening
  - Rectum involved in 90-95%
  - Accordion sign
    - Due to enhancing mucosa trapped between thickened submucosal folds

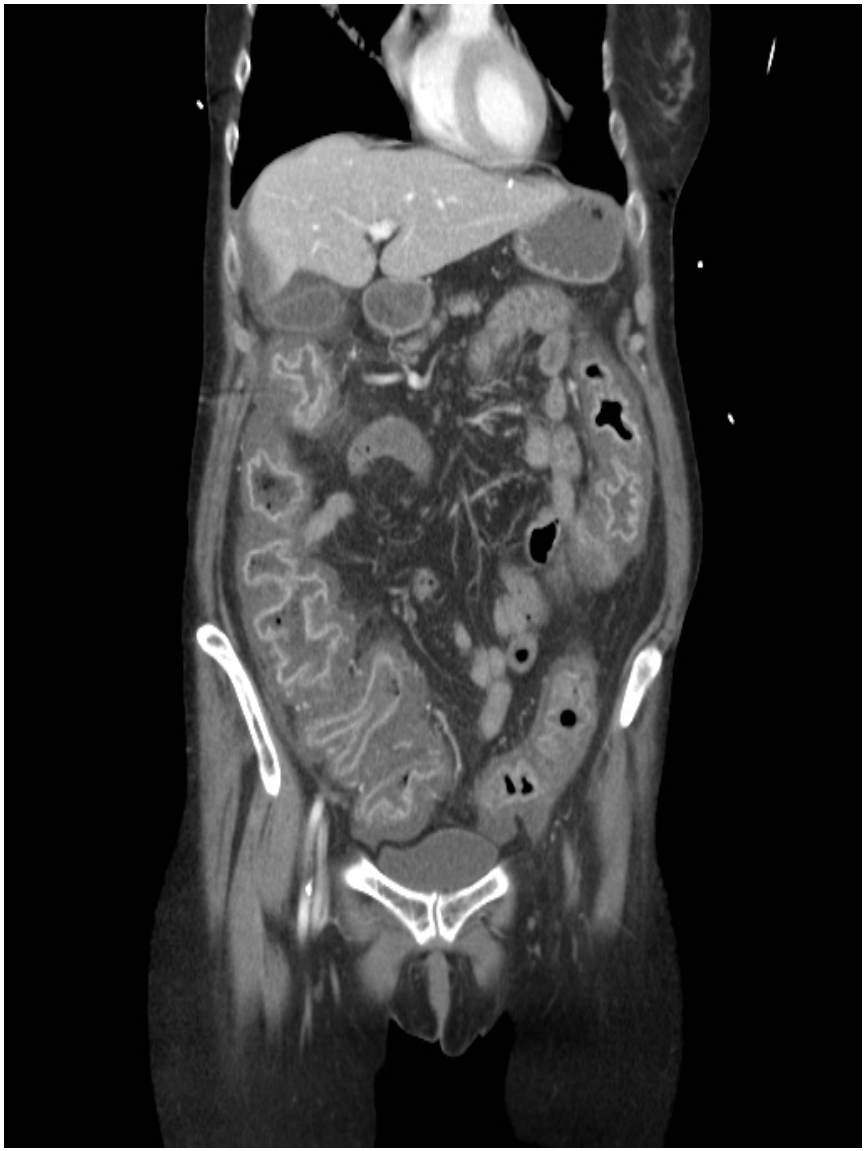
Pseudomembranous colitis





Pseudomembranous colitis

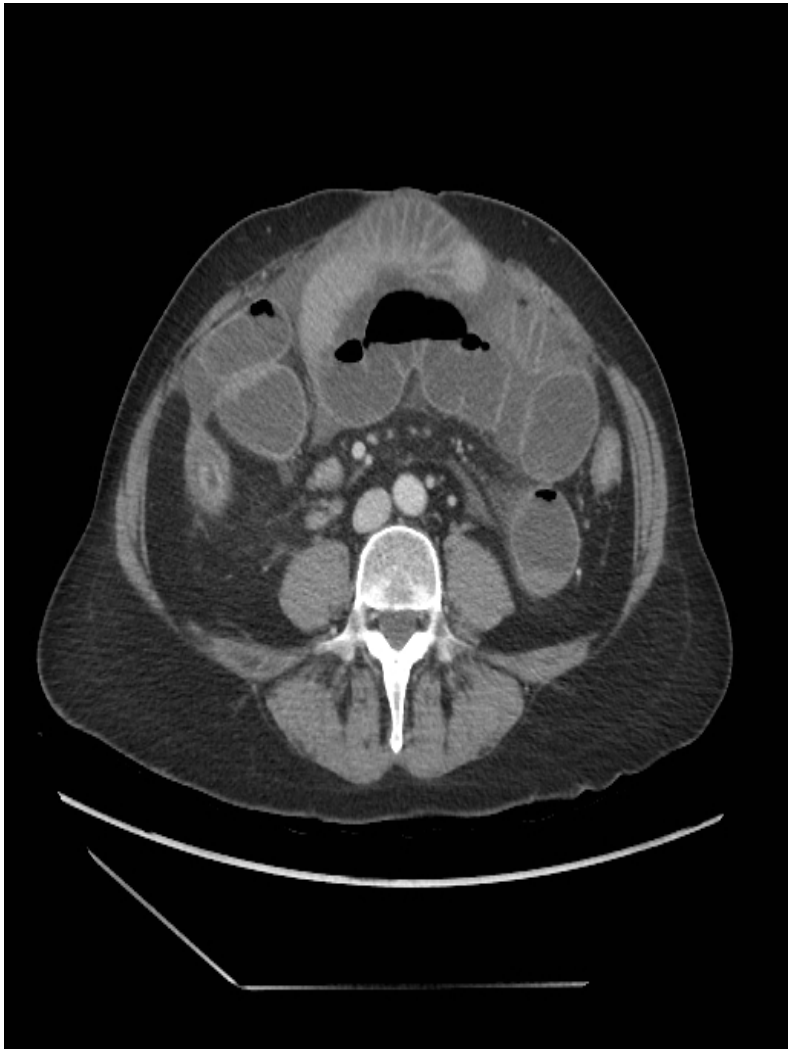
- Severe colonic wall thickening
- Submucosal edema
- Mucosal hyperenhancement
- Pericolonic fat stranding
- Often a pancolitis

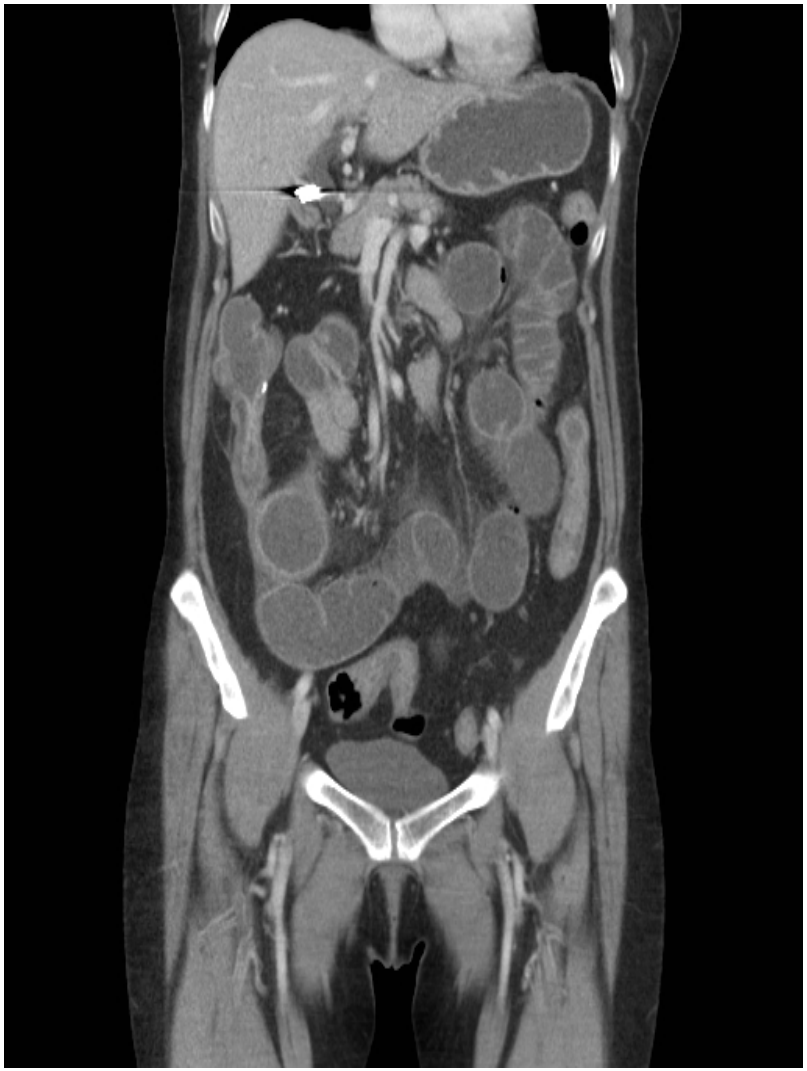


Inflammation

- CT findings include
  - Bowel wall thickening
  - Mucosal hyperemia
  - Prominent of mesenteric vasculature
  - Ahaustral colon
- Distribution can help narrow differential diagnosis
  - Ulcerative colitis
    - Contiguous inflammation
    - Rectum almost always involved
  - Crohn's
    - propensity for involvement of terminal ileum
    - Skip lesions
    - Fistulas, abscess formation
    - Creeping fat

Crohn’s enteritis

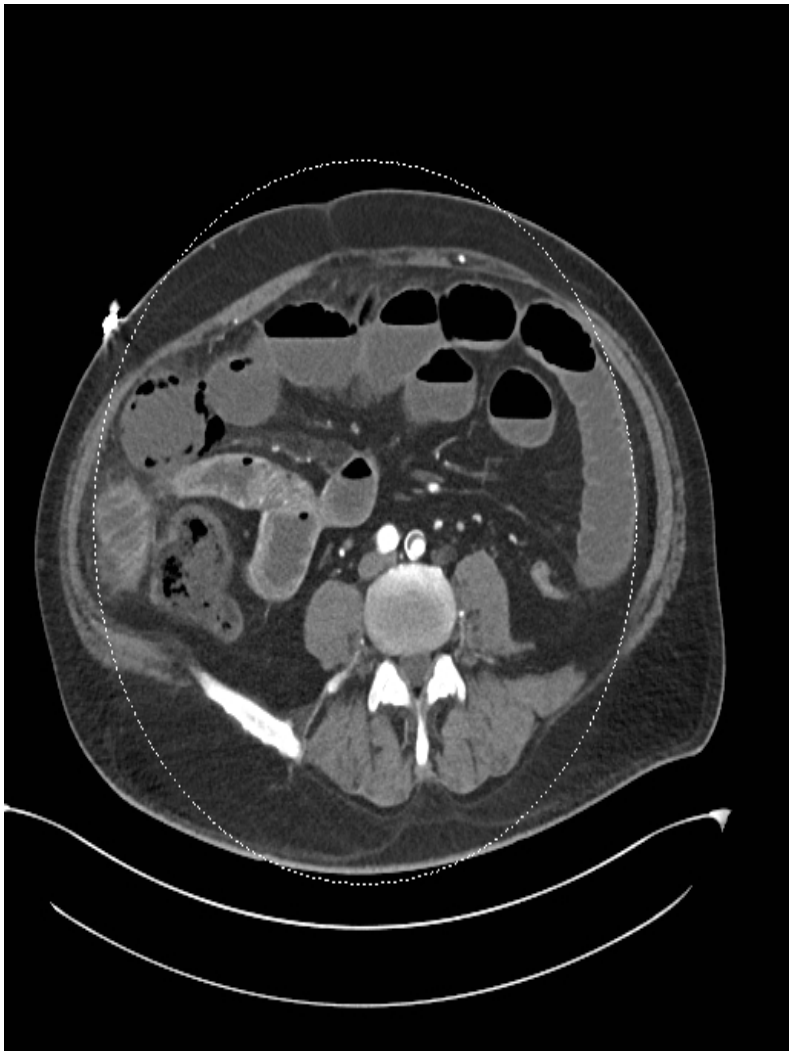


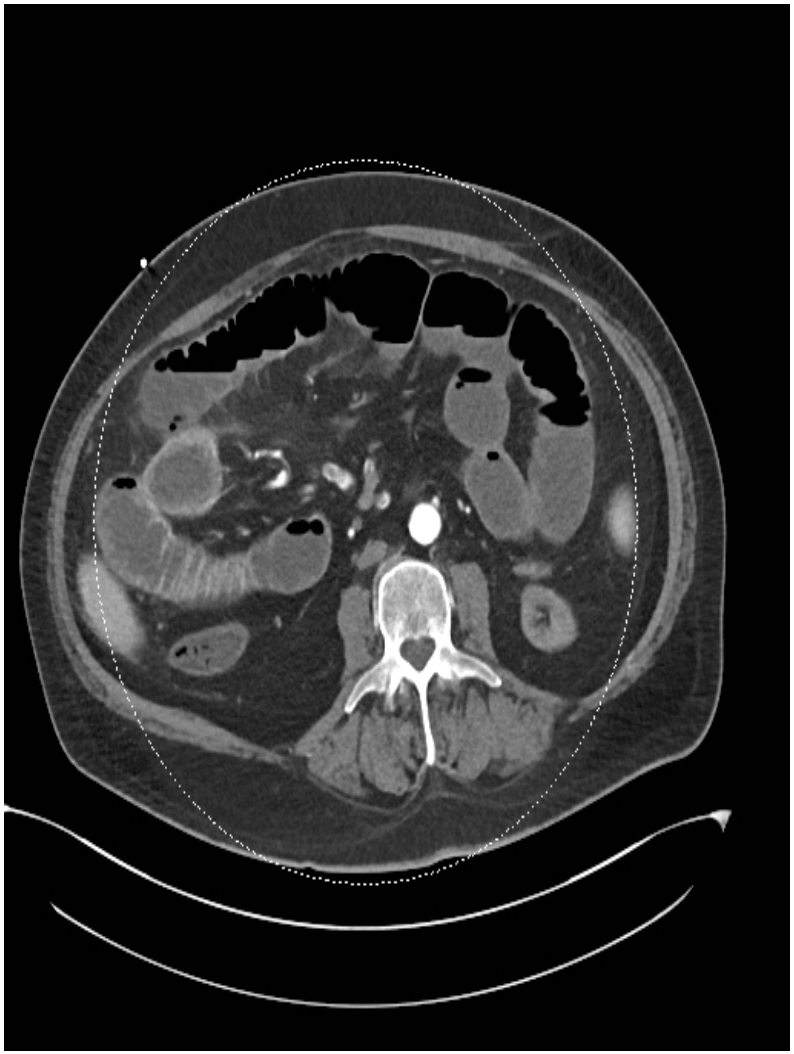


Ischemic colitis

- Due to vascular compromise to large bowel
- Can be occlusive (arterial or venous) or non-occlusive
- Radiographic findings:
  - Pneumatosis, portal venous gas, air fluid-levels
- CT findings
  - Bowel wall thickening
  - Hypoenhancement
  - Pneumatosis
  - Portal venous gas
  - Arterial or venous thrombosis
  - Watershed area involvement in non-occlusive ischemia

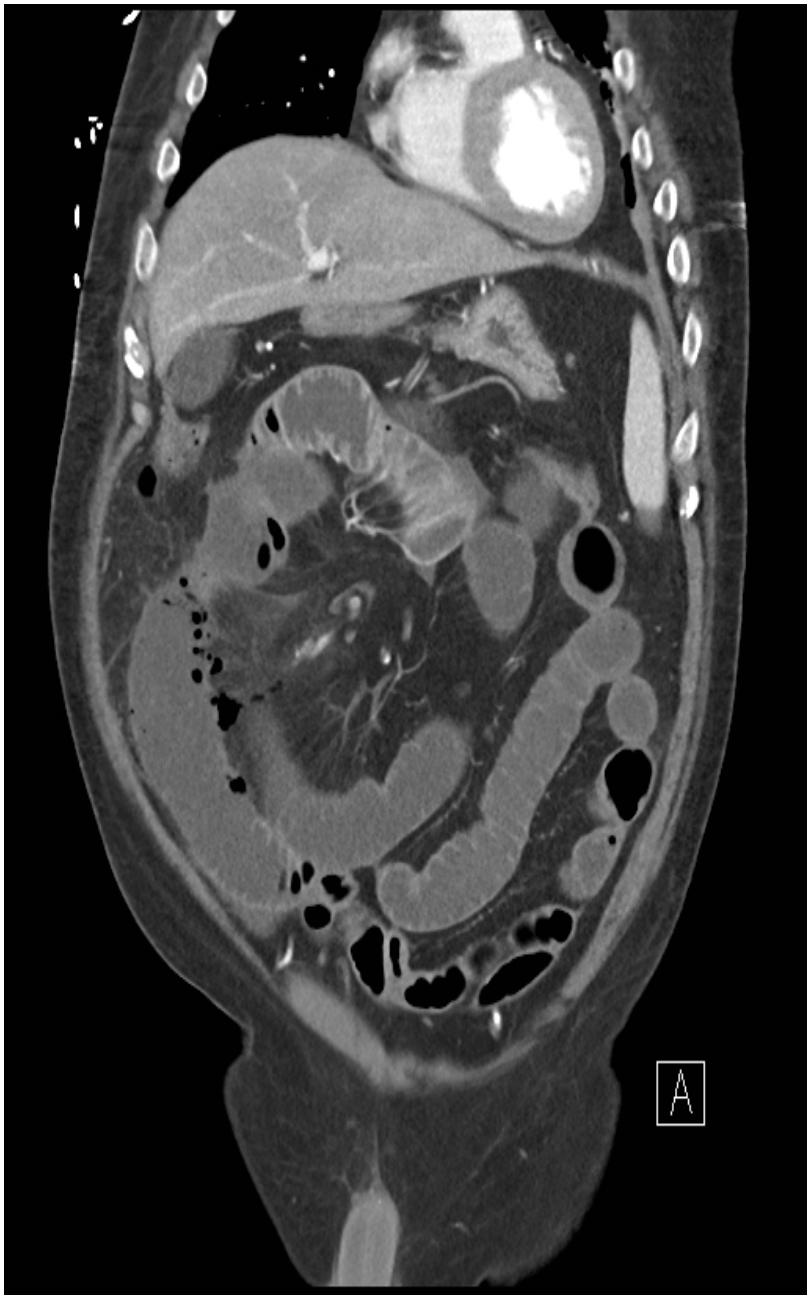
Ischemic enterocolitis





Ischemic enterocol

- Thrombi/emboli in mesenteric arteries or veins
- Mucosal hypoenhancement
- Gas in portal veins or mesenteric veins
- Pneumatosis intestinalis



Clinical history

- Symptoms
  - Diarrhea
  - Abdominal pain
- Clinical setting
  - How sick is the patient?
  - Any episodes of prolonged hypotension?
  - History of malignancy?
- Duration of symptoms
  - Acute or chronic?

Clinical history

- Current medications
  - Recent antibiotic therapy
  - Chemotherapy
- Lab work
  - Neutropenia
  - Elevated serum lactate
  - WBC
  - Stool cultures

Checkpoint inhibitor induced enterocolitis: review of imaging findings

- Diffuse colonic wall thickening
- Mucosal enhancement
- Engorged mesenteric vessels
- Pericolonic fat stranding

Reference: Widman G, Nguyen VA, Plaickner J, Jaschke W. Imaging findings of toxicities by immune checkpoint inhibitors in cancer therapy. Cur Radiol Rep 2017;5(11):59.

Checkpoint inhibitor induced enterocolitis

- These findings are very similar to other enterocolitides
- Clinical history is very important
- Radiologist unlikely to make the diagnosis without the clinical history!

Question 7

Would you restart the nivolumab once patient's diarrhea improves?

A. Yes! With the grace of… (the deity of your choice)
B. Heck No! This stuff is like juggling with a plutonium rod…
C. Don't know but it's still exciting and overwhelming
D. Requires extensive discussion between pt, family, med onc, radiologist, GI and community support

GI PANEL OBJECTIVES

- To review indications of and GI toxicity from checkpoint inhibitors
- Determine best steps for work up and investigation of Upper and Lower GI symptoms in the presence of immunotherapy
- Understand preferred ways to communicate clinical findings to medical oncologist, gastroenterologist and radiologist