Case History:

A 72-year-old male with a history of advanced colorectal carcinoma status post right hemicolectomy, approximately nine years prior to admission, presents now with diarrhea and hematochezia. His past medical history also includes GERD, diabetes mellitus type II, hypertension and hyperlipidemia. He has been treated for the past three years for lung metastases, initially with 5-fluorouracil/bevacizumab and most recently with Nivolumab.

Colonoscopic evaluation shows erythematous, granular and friable rectal mucosa with ulcers and pseudopolyps. Multiple biopsies were obtained. The salient endoscopic and histologic findings are shown below.

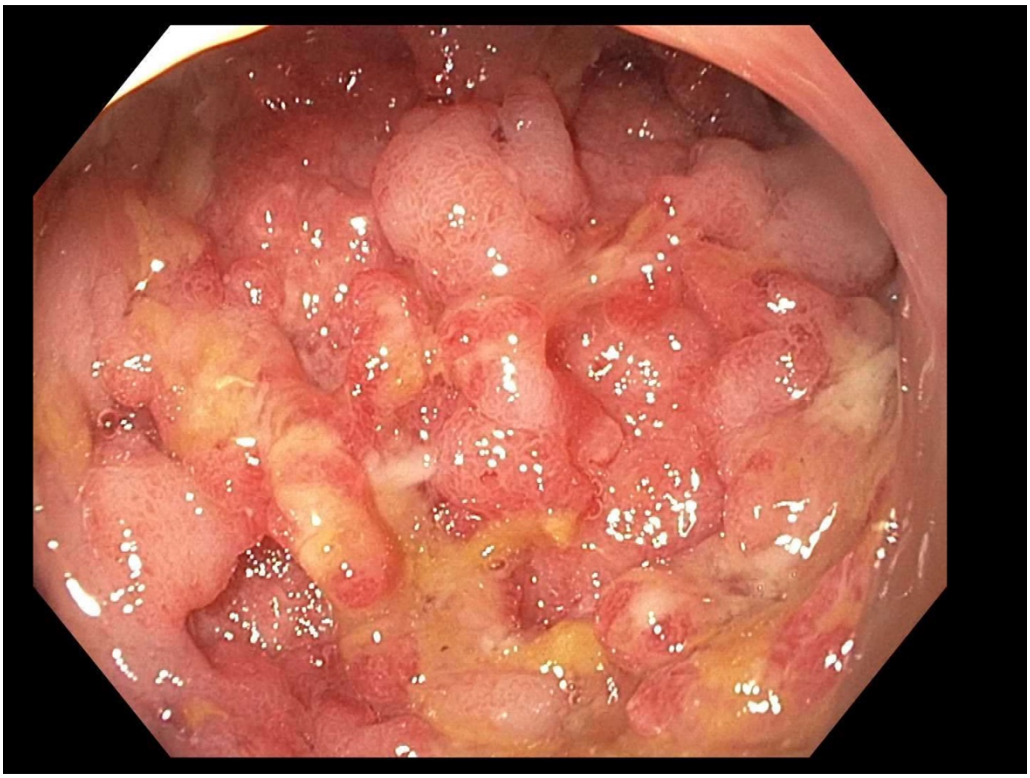

Figure 1. Colonoscopic view of rectal mucosa

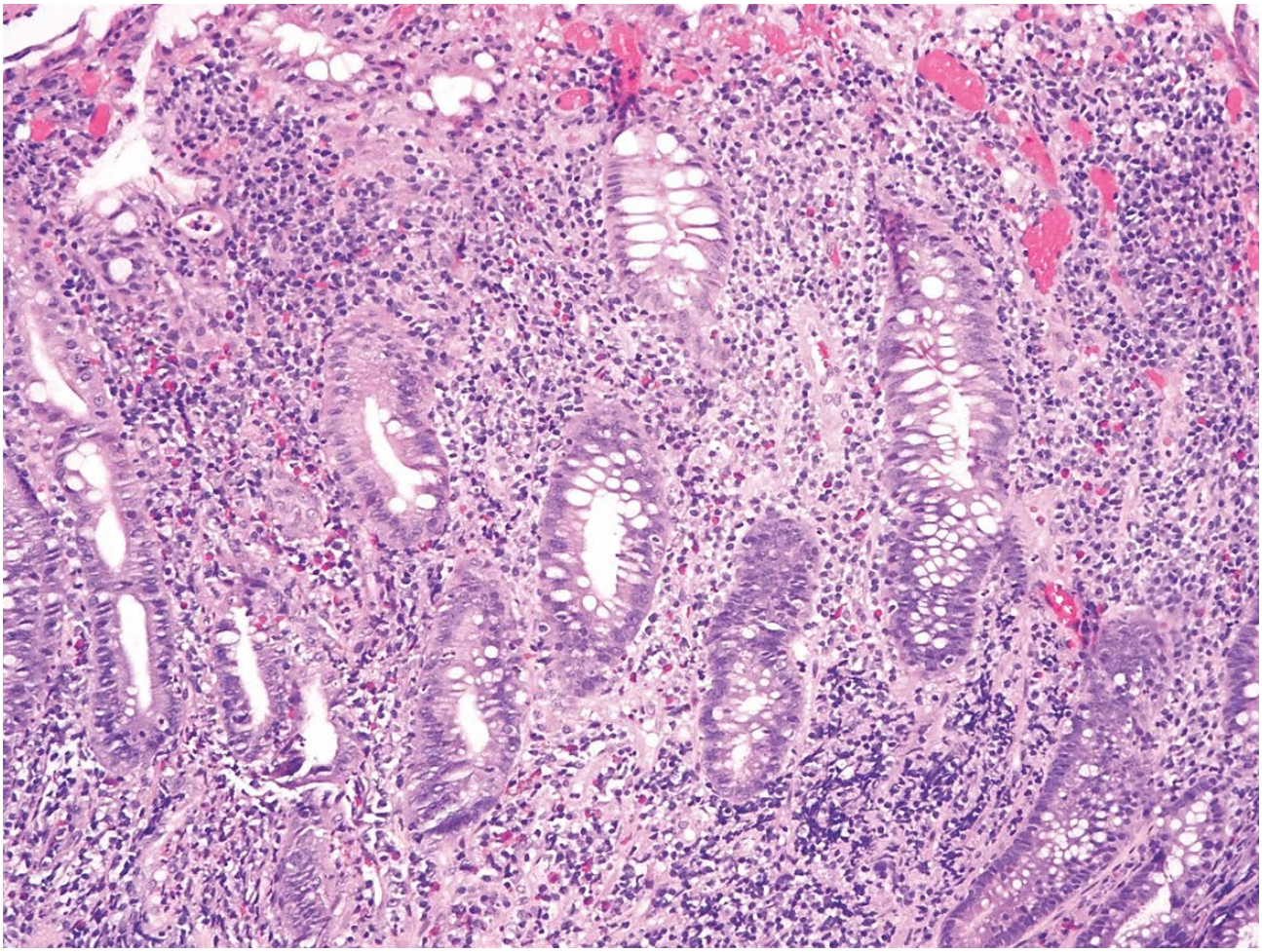

Figure 2. Recto-sigmoid Biopsy, H&E (4x magnification)

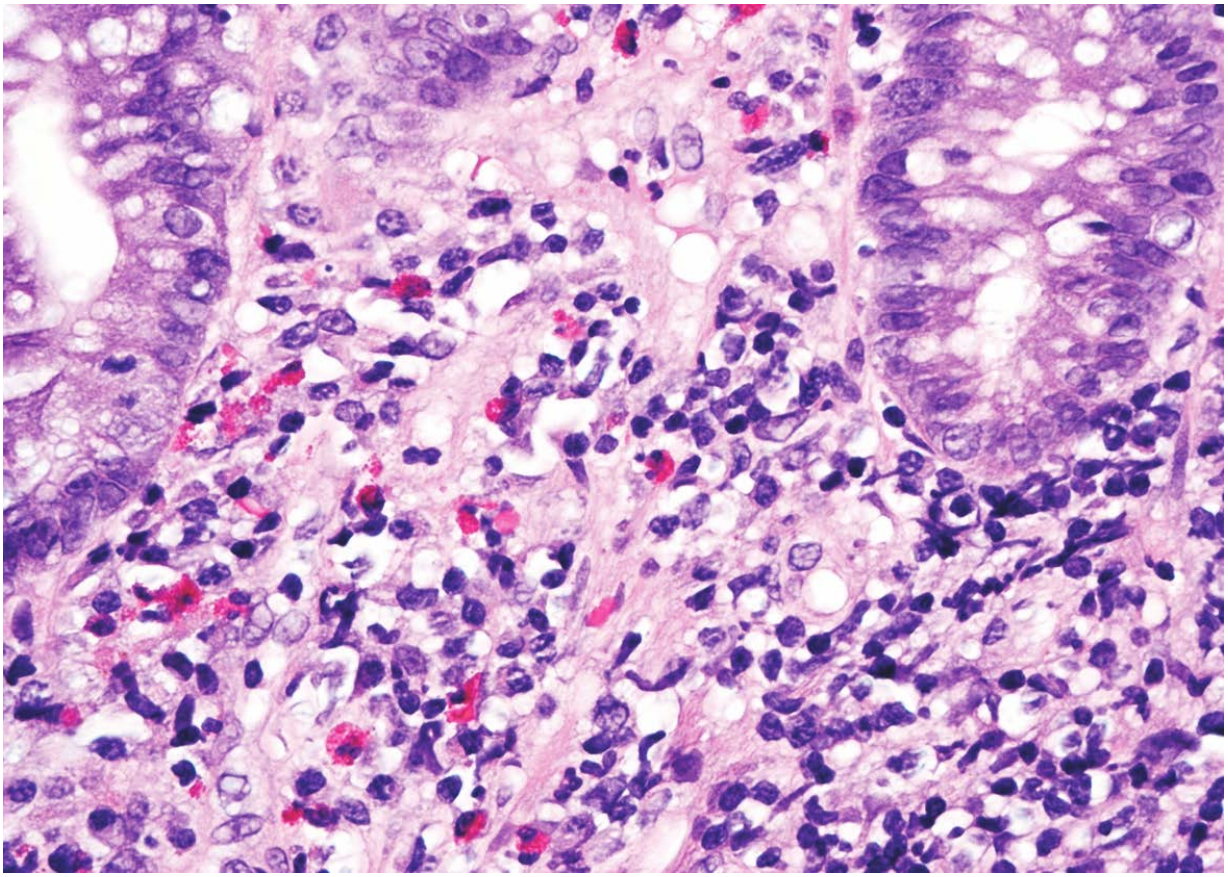

Figure 3. Recto-sigmoid Biopsy, H&E (40x magnification)

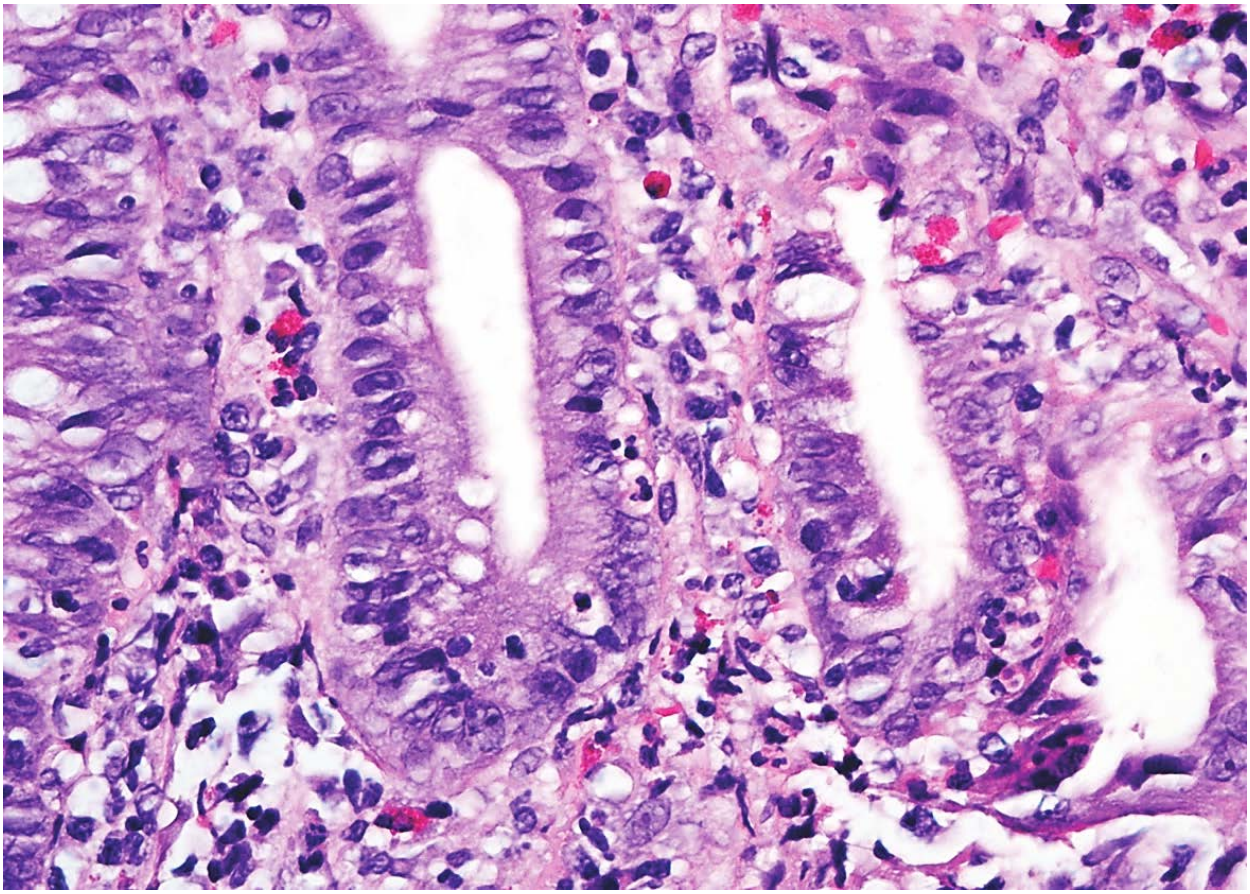

Figure 4. Recto-sigmoid Biopsy, H&E (40x magnification)

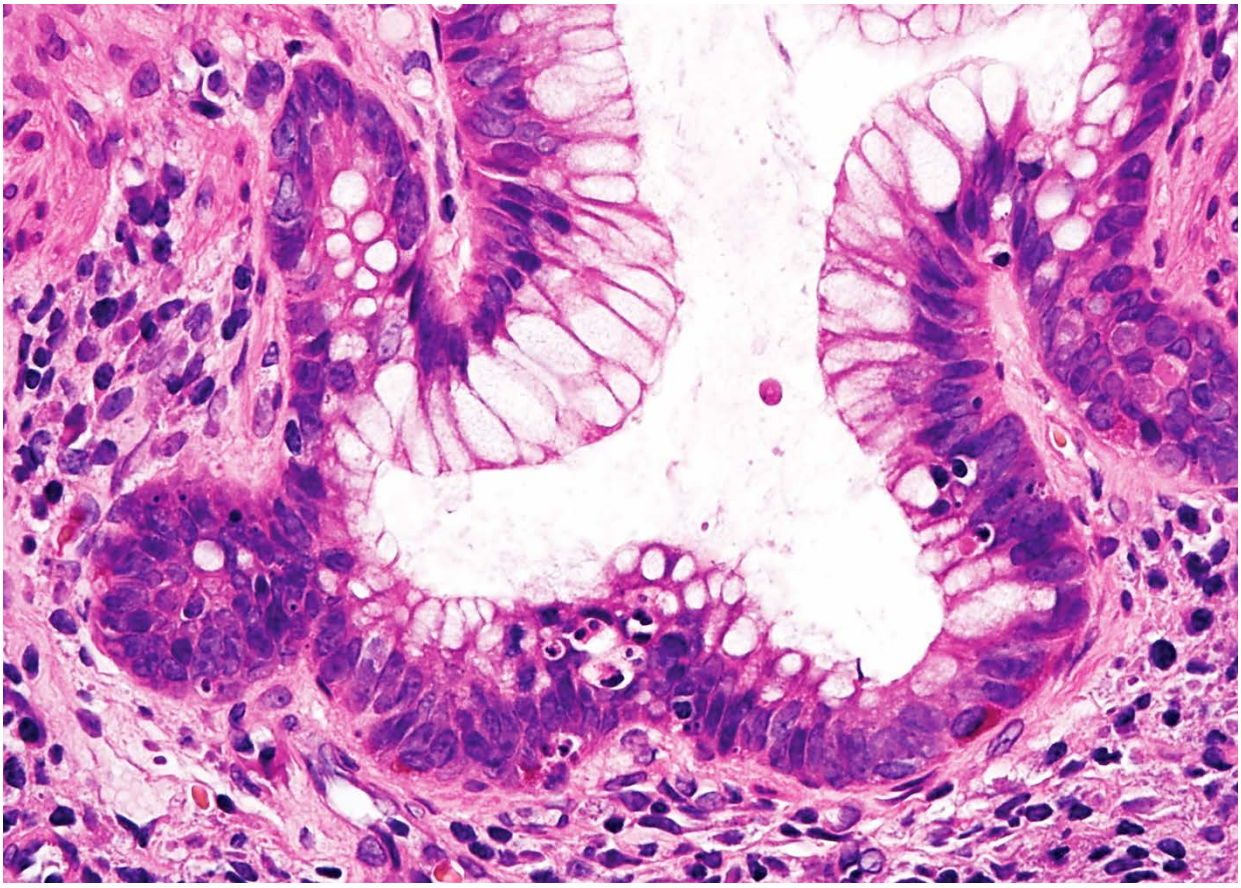

Figure 5. Recto-sigmoid Biopsy, H&E (40x magnification)

What is your diagnosis?

A- New-onset inflammatory bowel disease
B- Cytomegalovirus colitis
C- Colitis due to immunotherapy
D- Graft-*versus*-host disease
E- Mycophenolate-associated injury

Correct answer: C - Colitis due to immunotherapy

Microscopic findings include increased lamina propria cellularity with basal lymphoplasmacytosis. Eosinophils are also easily identifiable in the lamina propria. Foci of cryptitis are present, and apoptotic bodies are prominent in the crypt bases. Crypt architectural distortion is minimal, and granulomas are not identified. These findings and the clinical history of Nivolumab therapy are consistent with immunotherapy-induced colitis.

Immune checkpoint inhibitors enhance immune response to malignancy and are increasingly used to prolong survival in patients with a variety of advanced cancers. This drug class includes ipilimumab [directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)], nivolumab and pembrolizumab [directed against programmed cell death protein-1 (PD-1)], and atezolizumab [directed against programmed cell death protein ligand-1 (PD-L1) receptors]. Checkpoint inhibitor-induced colitis is characterized by dense lymphoplasmacytic lamina propria inflammation with frequent eosinophils, neutrophilic cryptitis and crypt abscesses, and increased epithelial apoptosis. Architectural distortion and Paneth cell metaplasia are not prominent, and granulomas are typically absent. Small intestinal biopsies show villous blunting, lamina propria lymphoplasmacytosis and eosinophilia, neutrophilic cryptitis and villitis, and apoptosis.

Inflammatory bowel diseases may arise de novo in immunosuppressed patients, particularly transplant recipients. However, biopsy samples from these patients are indistinguishable from other forms of inflammatory bowel disease and feature architectural distortion and Paneth cell metaplasia, in addition to basal lymphoplasmacytosis, whereas apoptosis and eosinophils are not prominent **(Answer A: Incorrect)**.

Cytomegalovirus (CMV) colitis should be considered in immunosuppressed patients, particularly when crypt architecture is distorted and numerous apoptotic bodies are present. The inflammatory response to CMV infection depends upon the immune status of the patient and ranges from minimal inflammation to active colitis with ulcers. Characteristic inclusions are absent in this case, and immunohistochemistry for CMV was negative **(Answer B: Incorrect)**.

Apoptotic bodies in deep crypt epithelium are a histologic hallmark of graft-*versus*-host disease, but this patient is not a hematopoetic stem cell transplant recipient **(Answer D: Incorrect).** Similarly, mycophenolate mofetil (MMF) is an immunosuppressant used to prevent graft rejection in transplant recipients that causes colitis marked by frequent apoptotic bodies, crypt loss, and architectural distortion. MMF-induced injury is also associated with increased lamina propria eosinophils. The clinical setting, in this case, excludes this possibility **(Answer E: Incorrect)**.

References:

1. Holtan SG, Pasquini M, Weisdorf DJ. Acute graft-versus-host disease: a bench-to-bedside update. Blood. 2014 Jul 17;124(3):363-73.
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3. Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic features of colitis due to immunotherapy with anti-PD-1 antibodies. Am J Surg Pathol. 2017 May;41(5):643-654.
4. Pittman ME, Jessurun J, Yantiss RK. Differentiating posttransplant inflammatory bowel disease and other colitides in renal transplant patients. Am J Surg Pathol. 2017 Dec;41(12):1666-1674.

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