



Novel Case Report: A Previously Reported, but Pathophysiologically Unexplained, Association Between Collagenous Colitis and Protein-Losing Enteropathy May Be Explained by an Undetected Link with Collagenous Duodenitis

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Abstract

Collagenous colitis (CC) is associated with non-bloody, watery diarrhea, which is pathophysiologically reasonable because normal colonic absorption (or excretion) of water and electrolytes can be blocked by the abnormally thick collagen layer in CC. However, CC has also been associated with six previous cases of protein-losing enteropathy (PLE), with no pathophysiologic explanation. The colon does not normally absorb (or excrete) amino acids/proteins, which is primarily the function of the small bowel. Collagenous duodenitis (CD) has not been associated with PLE. This work reports a novel case of CD (and CC) associated with PLE; a pathophysiologically reasonable mechanism for CD causing PLE (by the thick collagen layer of CD blocking normal intestinal amino acid absorption); and a novel association of PLE with severe COVID-19 infection (attributed to relative immunosuppression from hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and malnutrition from PLE).

Keywords Collagenous colitis · Collagenous duodenitis · Protein-losing enteropathy · Hypoalbuminemia · Anasarca · Malnutrition · COVID-19 infection · SARS-CoV-2 infection

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Table 1 Clinical presentation in seven reported cases of protein-losing enteropathy associated with collagenous colitis (suspected from undiagnosed collagenous duodenitis/enteritis)

Clinical presentation	Laboratory values	Endoscopy and histopathology	Clinical course	Reference (publication type)
<p><i>Initial hospitalization</i> 65 y. o. F with history of tobacco abuse presented with nausea, vomiting, and abdominal pain. PE: BP = 103/65 mmHg, HR = 83 beats/min, RR = 22 breaths/min, T = 36.5 °C. Dry mucous membranes, absent axillary sweat, poor skin turgor, and diffusely mildly tender abdomen</p> <p><i>Later hospitalizations</i> Presented with recurrent nausea, vomiting, and diarrhea. PE: new-onset anasarca (ascites and bilateral upper and lower extremity edema)</p>	<p><i>Initial hospitalization</i> WBC = 6900/mm³, Hb = 13.9 g/dL, BUN = 43 mg/dL, (GFR = 14 mL/min), K = 2.7 mmol/L. Stool tests negative for <i>Clostridioides difficile</i> toxins A & B, and for ova and parasites. Stool tests positive for lactoferrin and calprotectin. Serologic panel for celiac disease: normal</p> <p><i>Later hospitalizations</i> Albumin = 1.4 g/dL, Prealbumin = 10 mg/dL, Normal liver function tests. 24-h urine total protein = 276 mg, stool alpha-1 antitrypsin = 369 mg/dL (normal < 54 mg/dL)</p>	<p><i>Initial hospitalization</i> Colonoscopy: abnormally thick (> 10 µm) subepithelial collagen band (diagnostic of collagenous colitis) and numerous intraepithelial lymphocytes in colonic mucosa</p> <p><i>Later hospitalizations</i> EGD: diffuse nodular mucosa in first and second portion of duodenum. Duodenal biopsy: severe collagenous band (collagenous duodenitis)</p>	<p><i>Initial hospitalization</i> Treated with budesonide and mesalamine, with improving in diarrhea and discharged</p> <p><i>Later hospitalizations</i> Treated with budesonide, mesalamine and azathioprine, with improving diarrhea and discharged</p>	Current report
<p>15-month-old M with history of microcornea admitted for vomiting, diarrhea, and peripheral edema for 4 weeks. PE: ill-appearing, afebrile, and with upper and lower extremity edema</p>	<p>WBC = 14,500/mm³, total protein = 3.6 g/dL, albumin = 2.4 mg/dL. Normal liver and renal function tests. Normal serologic tests for celiac disease. Stool tests: negative bacterial and viral cultures. Stool alpha-1 antitrypsin ≥ 1.33 mg/g (normal < 0.62 mg/g)</p>	<p>EGD: edematous antral and duodenal mucosa. Duodenal biopsy: mildly increased collagenous band, but not thick enough to diagnose collagenous duodenitis. Gastric biopsy: negative for collagen. Flexible sigmoidoscopy: normal-appearing colon and rectum. Biopsies: collagenous colitis</p>	<p>Therapy: budesonide and TPN. Methylprednisolone added due to failed improvement in diarrhea. Weaned off TPN and discharged to take budesonide and methylprednisolone as outpatient</p>	Almadhoun et al. [2]
<p>76 y. o. F. admitted with recurrent diarrhea and edema for 5 months. PE: normal vital signs, tender lower abdomen, swollen face, and pretibial pitting edema</p>	<p>WBC = 7960/mm³, total protein = 4.8 g/dL, albumin = 2.8 gm/dL, normal liver and renal function tests. No proteinuria</p>	<p>EGD: normal-appearing stomach and duodenum. Biopsies: normal villi, no lymphocytic infiltrate, no collagenous duodenitis. Colonoscopy: edematous mucosa. Biopsies consistent with collagenous colitis, with increased lymphocytes and plasma cells. ^{99m}Tc HSA scintigraphy: protein leakage in colon, but not in stomach or small bowel</p>	<p>Therapy: prednisolone 30 mg/day, with improving diarrhea</p>	Sano et al. [3]
<p>82 y. o. F. with CKD admitted for nausea, anorexia, and diarrhea for 1 week. PE: normal vital signs, bilateral pitting edema of lower extremities</p>	<p>Albumin = 1.2 g/dL, (3 months earlier albumin = 3.1 g/dL). Stool positive for occult blood. Stool culture negative for bacteria and viruses. No proteinuria. Normal liver function tests</p>	<p>CT scan: mural thickening of small bowel. ^{99m}Tc HSA scintigraphy: protein leakage from small bowel. EGD: normal-appearing stomach and duodenum. Colonoscopy: edematous mucosa. Biopsies: > 10 µm subepithelial collagenous band (diagnostic of collagenous colitis)</p>	<p>Therapy: loperamide, with improving diarrhea</p>	Nakaya et al. [4]

Table 1 (continued)

Clinical presentation	Laboratory values	Endoscopy and histopathology	Clinical course	Reference (publication type)
63 y. o. F chronically taking lansoprazole admitted with diarrhea and generalized edema for 5 months. No abdominal pain. PE: BP = 128/90 mmHg, HR = 67 beats/min, T = 36.5 °C, swollen face, bilateral pretibial and pedal edema	WBC = 4800/mm ³ , Hb 14.3 g/dL, total protein = 4.6 g/dL, albumin = 2.8 g/dL, normal liver and renal function tests. U/A: no proteinuria	EGD: normal-appearing stomach and duodenum with normal biopsies. Colonoscopy: longitudinal lacerations in descending colon. Biopsies: thick collagen layer (> 10 µm thick), with subepithelial eosinophilic infiltrate. ^{99m} Tc HSA scintigraphy: protein leakage in descending colon	Lansoprazole was discontinued and diarrhea improved. 3 weeks later albumin increased to 3.4 g/dL. No steroids administered	Ozeki et al. [5]
62 y. o. F presented with 6–8 watery stools/day, abdominal cramping, and 4 kg weight loss over 4 months. PE: normal vital signs, non-tender abdomen	WBC = 10,500/mm ³ , K = 4.4 meq/L, total protein = 4.3 g/dL, albumin = 2.24 g/dL, normal liver and renal function tests. No proteinuria. IgA and IgG levels low. Stool for bacterial culture, ova and parasites, and fecal leukocytes were negative. Stool alpha-1 antitrypsin = 214 mL/24 h (normal < 13 mL/24 h)	Abdominal ultrasound: normal-appearing liver, gallbladder, pancreas, and kidneys Small bowel barium series: normal EGD: normal-appearing duodenal mucosa with intact intestinal villi. Small bowel biopsy negative for celiac disease Colonoscopy: grossly normal. Biopsies consistent with collagenous colitis	Therapy: not discussed	Stark et al. [6]
64 y. o. F with breast cancer admitted for 8–10 watery, non-bloody bowel movements/day and 8 kg weight loss over 3 months. PE: normal vital signs, no abdominal pain	Bacterial stool cultures, stool for ova and parasites, fecal leukocytes, and celiac disease panel all negative. Elevated stool alpha-1 antitrypsin in 24 h collection. Low protein C, S, and antithrombin III levels	Abdominal CT scan: right lower lobe pulmonary embolus and renal vein thrombosis EGD: normal-appearing Colonoscopy: normal-appearing. Biopsy: collagenous colitis	Therapy: oral corticosteroids with resolution of diarrhea. Pulmonary embolus treated with IV heparin as bridge to Coumadin	Raimo et al. [7]

y. o. years old, F female, M male, WBC white blood cell (count), Hb hemoglobin, BUN blood urea nitrogen, GFR glomerular filtration rate, K potassium, IgA immunoglobulin A, IgG immunoglobulin G, AP alkaline phosphatase, TPN total parenteral nutrition, U/A urinalysis, CT computed tomography, ^{99m}Tc HSA technetium-99m human serum albumin, PE physical exam, EGD esophagogastroduodenoscopy, HR heart rate, RR respiratory rate, BP blood pressure, T temperature

Introduction

Collagenous colitis (CC) is associated with non-bloody, watery diarrhea, which is pathophysiologically reasonable because normal colonic absorption (or excretion) of water and electrolytes can be blocked by the abnormally thick collagen layer [1]. However, CC has also been associated with six cases of protein-losing enteropathy (PLE) ([2–7]; Table 1), with no pathophysiologic explanation. The colon does not normally absorb (or excrete) amino acids/proteins, which is primarily the function of the small bowel [8].

Collagenous duodenitis (CD)¹ (or enteritis) has not been associated with PLE [9–19].² This work reports a novel case of CD (and CC) associated with PLE; a pathophysiologically reasonable mechanism for CD causing PLE (the thick collagen layer of CD blocks normal intestinal amino acid absorption); and a novel association of PLE with severe COVID-19 infection (attributed to relative immunosuppression from hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and malnutrition from PLE) [3, 6]. A potential association of CD with PLE is clinically important; PLE is a life-threatening, but potentially curable, syndrome.

Case Report

A 65-year-old African American woman with a 50-pack-year history of smoking tobacco, no prior renal insufficiency, and no other medical disorders, presented with nausea, vomiting, and generalized abdominal pain for 3 days; five non-bloody, watery stools/day; and 14 kg involuntary weight loss over the prior 3 months. Physical examination on admission revealed a minimally overweight female (BMI = 27.6 kg/m²); normal vital signs; dry mucous membranes, absent axillary sweat, and poor skin turgor; a non-tender, non-distended abdomen without hepatosplenomegaly; and no fecal occult blood. The leukocyte count was 6900/mm³ (normal: 3500–10,100 leukocytes/mm³), and hemoglobin was 13.9 g/dL (normal: 13.5–17 g/dL). Serum creatinine was 3.61 mg/dL (normal: 0.6–1.3 mg/dL), blood urea nitrogen was 43 mg/dL (normal: 7–25 mg/dL), urine specific gravity was 1.023 (> 1.015 consistent with dehydration), and glomerular filtration rate was 14 mL/min (< 15 mL/min indicates renal failure). Serum potassium was 2.7 mmol/L (normal: 3.5–5 mmol/L). Stool

¹ CD herein denotes collagenous duodenitis and not Crohn's disease.

² Excludes references with collagenous gastritis without collagenous duodenitis, because the stomach is not physiologically an important site of amino acid absorption, and therefore a thickened gastric collagen layer should not pathophysiologically cause protein-losing enteropathy [20–22].

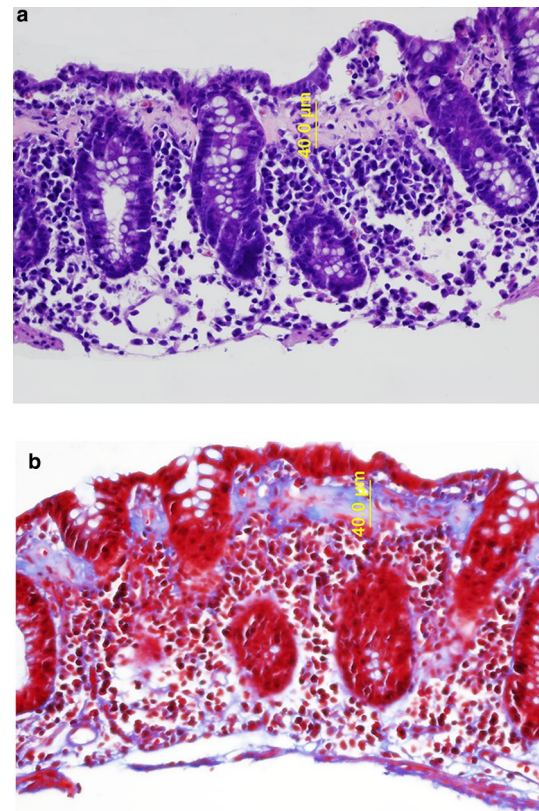


Fig. 1 **a** High-power photomicrograph of hematoxylin and eosin stained section of a random colonic biopsy from endoscopically normal-appearing colon shows a markedly thickened subepithelial collagen (pink) band measuring approximately 40 μ m (diagnostic of collagenous colitis). **b** High-power photomicrograph of the same colonic biopsy stained with Masson's trichrome, which highlights the collagenous band in blue and confirms the thickened (approximately 40 μ m) collagen layer

tests for *Clostridioides difficile* toxins A and B and for ova and parasites were negative. Stool culture for bacterial pathogens was sterile. Stool calprotectin level was 225 mcg/g (normal: 0–50 mcg/g). Abdominopelvic computed tomography (CT) on the initial admission was within normal limits, with no intra-abdominal lymphadenopathy, mural bowel thickening, dilated bowel loops, streaky mesentery, or organomegaly.

The patient received lactated Ringer's solution intravenously at 150 mL/h to reverse dehydration and acute renal failure. Tests for celiac disease revealed tissue transglutaminase immunoglobulin (Ig) A of 8.4 units/mL (normal: 0–19.9 units/mL), and total IgA of 247 mg/dL (normal: 70–365 mg/dL). Colonoscopy, performed for chronic diarrhea, revealed an endoscopically normal colon, but histopathology of biopsies taken throughout the colon showed an abnormally thick (> 10 μ m) subepithelial collagen layer diagnostic of CC (Fig. 1a, b). The patient was initially

treated with oral budesonide 9 mg/day, with gradually decreasing diarrhea, but mesalamine 800 mg twice daily was added as therapy because of persisting non-bloody diarrhea, with subsequent improvement. The patient was advised to cease smoking, as recommended for patients with collagenous colitis [23], but refused.

She was readmitted 1 month later for refractory nausea and vomiting. Physical exam revealed anasarca, manifested by ascites and 3+ pitting edema of all four extremities. Serum albumin was 1.4 g/dL (normal: 3.5–4.9 g/dL), and prealbumin was 10 mg/dL (normal: 18–44 mg/dL). Hypoalbuminemia was not from liver disease: all liver function tests were within normal limits. Hypoalbuminemia was not from protein-losing nephropathy: urine collection revealed only 276 mg of protein/24 h (nephrotic syndrome: > 3.5 g/24 h). Ascites was not from congestive heart failure: electrocardiogram was within normal limits, and chest X-ray did not reveal cardiomegaly. Stool alpha-1 antitrypsin was 369 mg/dL (normal: < 54 mg/dL), a finding diagnostic of PLE [24]; anasarca and hypoalbuminemia were therefore due to PLE. Iron studies were within normal limits. Vitamin B12, folate, and vitamin K were within normal limits, as were cholesterol and triglyceride levels. Vitamin D level was 14 ng/mL (normal 30–100 ng/mL).

Esophagogastroduodenoscopy (EGD) revealed minimally nodular mucosa in the first and second portions of the duodenum (Fig. 2a). Histopathology of duodenal biopsies revealed severe CD [Fig. 2b, c; collagen layer in (c) measuring approximately 332 μm , > 10 μm characteristic of CD)], and of gastric biopsies revealed no *Helicobacter pylori*. Azathioprine was added to the regimen of mesalamine and budesonide. A dietician recommended a protein-rich diet supplemented with medium-chain triglycerides, but patient refused this diet as unpalatable, and was discharged on total parenteral nutrition (TPN).

The patient presented 2 months later with nausea, vomiting, worsening diarrhea, cough, and dyspnea for 7 days. She was taking budesonide, but was noncompliant with azathioprine and mesalamine. Physical examination on admission revealed a mildly thin woman (BMI = 23.47 kg/m²); pulse of 100 beats/min, temperature of 36.6 °C, 18 breaths/min, and O₂ saturation of 99% on room air; dry mucous membranes; moderate ascites; and soft, non-distended, and non-tender abdomen. Laboratory tests revealed 7900 leukocytes/mm³ (normal: 3500–10,100 leukocytes/mm³), creatinine of 0.87 mg/dL (normal: 0.6–1.3 mg/dL), potassium of 2.4 mmol/L (normal: 3.5–5 mmol/L), albumin of 2.3 g/dL (normal: 3.5–4.9 g/dL), prealbumin of 8 mg/dL (normal: 18–44 mg/dL), and serum IgG of 491 mg/dL (normal: 550–1650 mg/dL), findings consistent with malnutrition from PLE. Nasopharyngeal swab was positive for COVID-19 infection by nucleic acid amplification, as confirmed by polymerase chain reaction. C-reactive protein was 48.4 mg/L

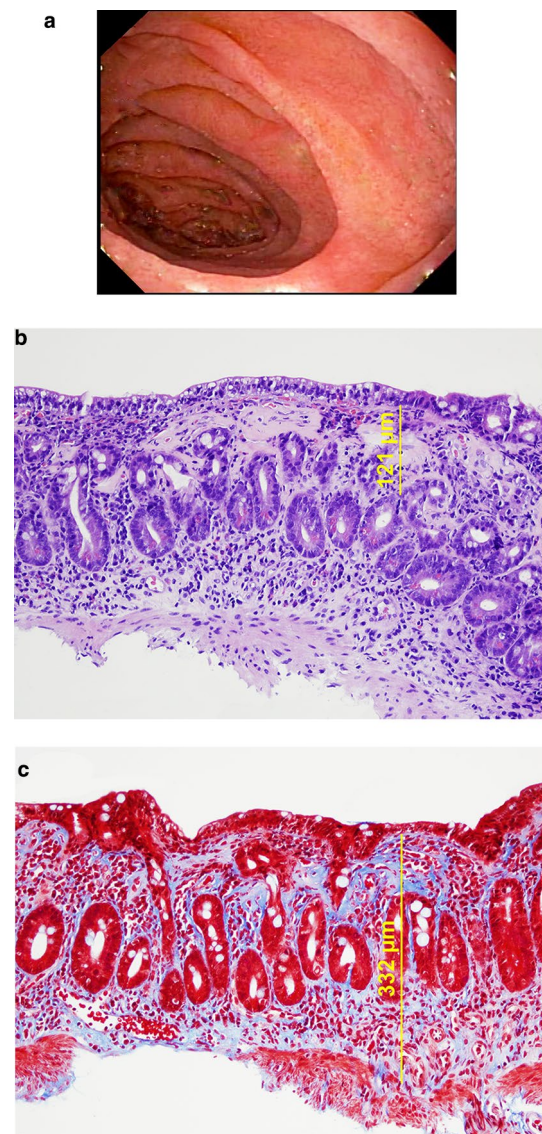


Fig. 2 **a** Esophagogastroduodenoscopy (EGD) revealed endoscopically essentially normal (minimally nodular) mucosa in first and second portions of duodenum, as illustrated for the second portion of the duodenum. **b** Medium-power photomicrograph of hematoxylin and eosin-stained section of a random biopsy of endoscopically relatively normal-appearing second portion of duodenum shows severe to total blunting of the villi, with no appreciable villous height. The collagen band measures approximately 121 microns (> 10 microns diagnostic of collagenous duodenitis). This collagen band is thicker than that observed in the colon (Fig. 1a). **c** Medium-power photomicrograph of the same duodenal biopsy stained with Masson's trichrome, which highlights collagen in blue, shows extensive collagenization of duodenal mucosa, with more discernable collagenization visualized in this stain (measuring approximately 332 μm of entire thickness of the lamina propria) than demonstrated in the hematoxylin and eosin stain

(normal: 0–7.9 mg/L), attributed to active COVID-19 infection. Stool studies for *Clostridioides difficile* toxins A and B and for ova and parasites were negative. Stool culture for bacterial pathogens was sterile. Repeat EGD with duodenal

biopsies revealed persistent CD. She received intravenous hydration, TPN, hydroxychloroquine for COVID-19 infection, and budesonide for CD. She did well without developing respiratory distress and was discharged 11 days after admission.

Discussion

Etiologies of PLE include erosive GI mucosal diseases such as Crohn's disease or GI malignancies; diseases causing intestinal lymphatic fluid loss from lymphatic obstruction, such as primary intestinal lymphangiectasia, or lymphoma; and diseases increasing intestinal mucosal permeability such as Ménétrier's disease [25, 26]. CC is a reported cause of PLE but lacks a pathophysiologic basis. The current work suggests a novel association of CD (and CC) with PLE. Linkage of CC with CD can explain the pathophysiology of PLE by disruption of normal amino acid absorption by the thick intestinal collagen layer in CD (12× upper limit of normal in the current case). Patients with CC and PLE may be reasonably tested to exclude CD by intestinal biopsies. Diagnosing PLE etiology is important to initiate specific therapy.

The current diagnosis of CD was challenging because of negative serology for celiac disease and absence of iron deficiency anemia. CD often occurs with celiac disease [27], which by itself has a mildly increased subepithelial collagen layer [28]. Initiation of a gluten-free diet causes regression of collagen in celiac disease, but not in CD. Collagenous celiac disease (collagenous sprue) has been rarely reported but has not been associated with PLE, even though it has been associated with hypoalbuminemia [29]. Although this patient had severe to total blunting of the intestinal villi (Fig. 2b), the patient did not have collagenous sprue, as shown by negative serology for celiac disease.

Collagen deposition in CC is believed to be immune-mediated; autoimmune diseases, medications, viruses, and bacteria are speculated triggers [19, 28, 30], including one case of *Yersinia enterocolitica* [14]. Collagen deposition and inflammation in CC may extend from the colonic to intestinal mucosa and cause CD by dysfunction of subepithelial myofibroblasts [10, 17]. CC is characterized by an abnormally thick (> 10 µm diameter) subepithelial hyalinized collagen band [19, 21, 27, 30]. Although CC is frequently reported, CD is rarely reported [13]. Because of its rarity, CD is not usually suspected in patients with CC.

Immunosuppression from human immunodeficiency virus infection, cancer, solid organ transplantation, immunomodulatory therapy for autoimmune diseases, and malnutrition can cause severe COVID-19 outcomes, including prolonged hospitalization, intensive care unit admission, renal failure, intubation, mechanical ventilation, and mortality [31–33].

This work suggests that PLE may be associated with severe COVID-19 infection, most likely from severe malnutrition, manifested by hypoproteinemia, hypogammaglobulinemia, hypoalbuminemia, and low prealbumin. Immunosuppression from corticosteroid therapy (budesonide in the current case) is a controversial risk factor for severe COVID-19 infection, because corticosteroids may improve the prognosis of COVID-19 infection.

COVID-19 can affect the digestive system [34–36]. The receptor-binding domain of COVID-19 binds strongly to human angiotensin converting enzyme-2 (ACE-2), which is abundantly expressed in the intestines [37]. Studies have identified COVID-19 RNA in stool specimens of infected patients, suggesting the virus may infect the digestive system [34]. It is interesting to speculate whether COVID-19 infection may be more severe in patients with intestinal disease, such as CD.

This report is limited by its single-case retrospective nature. However, an association of PLE with CD has a solid pathophysiologic basis because the small intestine is the primary site of amino acid (protein) absorption, which should be severely compromised by a thick intestinal collagen layer. In contrast, the colon does not play a physiologic role in amino acid absorption and CC should not affect amino acid absorption. A minor criticism is that the patient's collagenous colitis was treated about 1 year ago with budesonide and mesalamine. Mesalamine has recently been delisted as recommended therapy for collagenous colitis [38]. Strengths of this work include a strongly positive diagnosis of PLE by alpha-1 antitrypsin levels, a strongly positive pathologic diagnosis of CD, and exclusion of other major causes of hypoalbuminemia and anasarca aside from PLE. This work requires confirmation in a large prospective trial, but such a trial may be problematic because CD is relatively rare.

Conclusion

This case demonstrates that presentation of CD (with CC) can result in PLE, attributed to a thick collagen layer preventing absorption of amino acids/proteins in small intestine. Immunosuppression from hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and malnutrition from PLE likely constitutes a high risk factor for severe COVID-19 infection.

Author's contribution The initial draft of the manuscript was written by Drs. IG, AAS, AIE, KR, and MSC. The manuscript was thoroughly revised, and major additions were made by Dr. MSC, who served as the mentor. Drs. KR and MSC provided clinical gastroenterologic care to the patient. Dr. MA provided the histopathology images and description. Drs. IG and MSC are the primary authors.

Compliance with Ethical Standards

Conflict of interest None for all authors. None of the authors received any financial support for writing this case report. In particular, Dr. Cappell, as a consultant of the United States Food and Drug Administration (FDA) Advisory Committee for Gastrointestinal Drugs, affirms that this paper does not discuss any proprietary, confidential, pharmaceutical data submitted to the FDA. Dr. Cappell was also a member of the speaker's bureau for AstraZeneca and Daiichi Sankyo, co-marketers of Movantik until > 2 years ago. Dr. Cappell received one-time honoraria from Shire and Mallinckrodt > 2 years ago. This work does not discuss any drug manufactured or marketed by AstraZeneca, Daiichi Sankyo, Shire, or Mallinckrodt.

Ethical approval Exemption/approval was obtained from the Beaumont Health System Institutional Review Board on June 1, 2020.

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