Protein-Losing Enteropathy in Ulcerative Colitis

Ryan Ungaro\textsuperscript{a}  Mark W. Babyatsky\textsuperscript{a}  Hongfa Zhu\textsuperscript{c}  Jeffrey S. Freed\textsuperscript{b}

Departments of \textsuperscript{a}Internal Medicine, \textsuperscript{b}Surgery and \textsuperscript{c}Pathology, The Mount Sinai School of Medicine, New York, N.Y., USA

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Abstract
Protein-losing enteropathy (PLE) is a debilitating potential complication of ulcerative colitis (UC). We report a case of PLE in a 26-year-old male patient with UC. The patient lost 50 pounds in the setting of a UC flare and was found to have an albumin level of 1.2 g/dl. Although the patient’s UC was clinically controlled with steroids, the weight loss and hypoalbuminemia persisted with the patient’s course complicated by development of deep vein thrombosis and pulmonary embolism. The diagnosis of PLE was confirmed with measurement of stool alpha-1-antitrypsin clearance. The patient’s condition significantly improved following procto-colectomy.

Introduction
Ulcerative colitis (UC), first described in 1875 by Sir Samuel Wilks, has been associated with a plethora of gastrointestinal and extra-intestinal manifestations. UC, a major type of inflammatory bowel disease, is characterized by colonic inflammation that starts in the rectum and can extend proximally to involve various lengths of colon. The inflammation in UC is continuous and limited to the mucosal layer of the bowel wall. In contrast, Crohn’s disease, the other major form of inflammatory bowel disease, can affect any part of the intestinal tract, often has skip lesions, and causes transmural inflammation. UC typically presents clinically as bloody diarrhea with associated abdominal pain, tenesmus, and urgency. Patients with UC may also experience various extra-intestinal manifestations including pyoderma gangrenosum, uveitis, migratory arthritis and primary sclerosing cholangitis. Medical treatment of UC can employ oral or rectal 5-aminosalicylates, oral or rectal glucocorticoids, immunomodulators such as azathioprine and 6-mercaptopurine, or biologic agents such as infliximab and adalimumab. Colectomy can be a potentially curative procedure in severe cases.

Jeffrey S. Freed, MD  Department of Surgery, The Mount Sinai School of Medicine  969 Park Avenue, Suite 1D, New York, N.Y. 10028 (USA)  Tel. +1 212 396 0050, E-Mail jeffrey.freed@mssm.edu
One of the most devastating complications of UC, protein-losing enteropathy (PLE), can further deteriorate the health and well-being of a subset of patients with UC. PLE involves the loss of plasma proteins through the bowel wall into the intestinal tract and can lead to malnutrition, edema, fatigue and weight loss. The association of UC and PLE has been previously described, usually related to severe ulceration of the colonic mucosa or concurrent infection, with agents such as cytomegalovirus [1]. Here, we report a case of existing UC and severe PLE that persisted after the acute clinical phase of UC had been controlled and the procto-colitis symptoms had improved with medical therapy. Although the inflammatory process appeared to be regressing, the loss of protein worsened, prompting this case report and a review of the current understanding of the association of UC and PLE.

Case Report

The patient, a 33-year-old male, was diagnosed with ulcerative colitis in 2001 at the age of 26 after presenting with 2 weeks of mid-abdominal pain and 5–6 loose bowel movements daily that were mixed with mucus and blood. His symptoms improved after 1 month of treatment with mesalamine tablets, with a decrease in bowel movements to 1–2 per day without blood or mucus. He was subsequently changed to balsalazide and continued on this medication for 4 years with good symptomatic control. The patient’s other past medical history was significant only for kidney stones. Both of the patient’s parents had diabetes and there was no family history of inflammatory bowel disease. The patient was married and worked in advertising. He used to smoke cigarettes regularly but stopped smoking a few months prior to being diagnosed with UC. He drank alcohol rarely and never used illicit drugs. There were no known drug allergies.

The patient was changed to Asacol in early 2005 after needing intermittent courses of steroid enemas for mild UC flares characterized by mild diffuse abdominal discomfort and more loosely formed stool mixed with blood. He did not experience another UC flare until 2007 when he had a more severe UC flare in which he had 3–4 bloody bowel movements a day with moderate to severe abdominal pain and significant fatigue. His condition significantly improved with 40 mg of prednisone daily, which was tapered off over the course of 4 months. Between 2001 and 2008, the patient was never hospitalized and maintained a weight of 170 pounds.

His condition deteriorated, however, in early 2008 with increased bleeding and frequency of bowel movements. He was constantly fatigued, had 5–6 bloody bowel movements daily, and suffered from frequent diffuse cramping pain in the abdomen. His weight decreased to 120 pounds, representing a drop in his body mass index from 28 to 20, and he was so debilitated that he was unable to work. On physical exam, the patient was extremely thin, had diffuse mild to moderate abdominal tenderness and 1+ pedal edema bilaterally. Laboratory testing showed iron deficiency anemia with a hemoglobin of 7.1 g/dl. The patient was again started on oral steroids. A colonoscopy at that time revealed retrograde progression of the inflammatory process from the rectum to the transverse colon, with development of pseudopolyps. There was no evidence of dysplasia on multiple biopsies from 2006 through 2008. During this period, his course was complicated by a deep vein thrombosis of the left lower extremity and a pulmonary embolus necessitating treatment with warfarin. Although the oral steroids alleviated his symptoms with resolution of abdominal pain and improvement in frequency of bowel movements to 2–3 daily with only occasional blood, the patient’s serum albumin fell from 4.0 to 1.2 g/dl.

Repeat colonoscopy revealed improvement of the mucosal disease, with no evidence of dysplasia on biopsy. No inclusion bodies consistent with cytomegalovirus colitis were noted on pathologic evaluation. Stool testing was also negative for Clostridium difficile toxin. Even with endoscopic improvement, the patient’s serum albumin continued to be <2 g/dl and he was unable to regain weight from his 50 pound weight loss, leading to a diagnosis of PLE. PLE was confirmed by an elevated stool alpha-1-antitrypsin (A1AT) clearance of 162 ml/24 h, which was greater than 5 times the upper limit of normal of the testing laboratory. He remained severely debilitated and emaciated even though his UC symptoms were controlled. Due to his persistent weakness and PLE, the patient
underwent a 3-stage restorative proctocolectomy, each stage preceded by insertion of a retrievable vena cava filter to prevent pulmonary emboli. At the time of surgery the patient’s UC regimen consisted of Asacol and mesalamine enemas. He underwent closure of his ileostomy and construction of a J-pouch 3 months following his initial surgery and quickly regained weight, which he has maintained with a most recent weight of 200 pounds. The patient has returned to a productive life with an albumin of 4.2 g/dl, 4–5 non-bloody bowel movements daily with no leakage, and no further evidence of PLE. Although the last colonoscopy several months prior to the procedure demonstrated improvement of the inflammatory process, the resected colon did demonstrate active UC with ulceration and extensive inflammatory polyposis from the rectum to the cecum, measuring 0.5–3.0 cm in greatest dimension, as well as one giant inflammatory polyp (fig. 1). There was no evidence of dysplasia.

**Discussion**

There is rapidly accumulating evidence that the etiology of UC is related to both genetic and environmental factors. Genetic associations have been shown for the MHC locus HLA class II alleles. More recently, the gene encoding the interleukin-23 receptor has been associated with susceptibility to developing UC [2]. The multi-drug resistance gene MDR1 has also been implicated as a genetic factor in the development of disease. Intraluminal antigens are of significance as evidenced by a relationship between UC and bacterial flora including Bacteroides and Enterobacteriaceae species. Conversely, cigarette smoking and appendectomy are associated with a decreased incidence of UC. In spite of our growing understanding of the disease, there is yet to be a unified, definitive etiology of UC [3]. Recently developed diagnostic strategies, including the detection of fecal and serologic markers and the use of wireless capsule endoscopy, have expanded our understanding of UC. However, in the absence of specific biomarkers, the definition of UC remains based on clinical, endoscopic and pathologic criteria. Until further specificity regarding pathogenesis is elucidated, specific therapies for UC remain elusive. Further, an overlap of pathophysiologic processes between UC, post-infectious irritable bowel syndrome, Crohn’s disease and other colitides may hinder new therapeutic approaches.

PLE occurs in multiple clinical disease states, all resulting from increased mucosal permeability and excessive transmucosal loss of plasma proteins into the intestinal lumen because of mucosal damage, inflammatory ulceration, or leakage from obstructed lymphatic channels. Interestingly, inflammatory polyposis may contribute to PLE in UC by increasing mucosal surface area and cell turnover [4]. The etiologies of PLE transverse a wide range of conditions including, but not limited to, amyloidosis, viral enteritides, eosinophilic gastroenteropathies, systemic lupus erythematosis, Ménétrier disease, sarcoidosis, schistosomiasis, intestinal lymphangiectasia, Whipple’s disease, non-tropical sprue, UC, superior cava syndrome, bacterial overgrowth, *C. difficile* colitis, giardiasis, congestive heart failure, lymphoma and leukemia, and post-Fontan procedure for congenital atresia of the tricuspid valve [5].

In 1949, Albright et al. [6] demonstrated an increase in protein turnover in patients with PLE. In 1958, Citrin et al. [7] were the first to use radiolabeled tracers to reveal the actual loss of proteinaceous fluid into the gastrointestinal tract. More recently Tc-99m dextran has been used for the same purpose [8]. In PLE, the loss of protein through the gastrointestinal tract (normally <2% of the total serum protein pool) can be as high as 60% of the total albumin pool, resulting in a severe catabolic state. The serum proteins
most often affected by this leakage are those with long half-lives, like albumin, many immunoglobulins and ceruloplasmin. In response to the gastrointestinal losses, the liver can slightly increase the production of rapidly turned-over proteins such as transthyretin (prealbumin), immunoglobulin E, and insulin [9]. Lower concentrations of other substances like lipids, iron and other trace elements can be seen, as well as lymphopenia, especially when lymphatic obstruction is present.

PLE can be caused by conditions with or without mucosal erosions. UC and Crohn’s disease are both inflammatory conditions of the gastrointestinal tract that cause erosions and can lead to PLE. It is thought that protein loss in these conditions is due to enhanced leakage of protein-rich fluids across an ulcerated or eroded mucosal lining. The severity of the condition most often correlates to the extent of protein loss [10]. In fact, the severity of protein loss had been suggested to be an indicator of the severity of inflammatory bowel disease. This correlation is usually confirmed with fecal A1AT clearance, now considered the test of choice to verify the diagnosis of PLE [11].

Our patient certainly demonstrated clinical evidence of PLE with a persistently decreased serum albumin and a markedly elevated A1AT clearance. Fischbach et al. [12] demonstrated that measurement of A1AT levels in the stool was a reliable and simple test for PLE that does not require radiolabeled tracers. A1AT is a protein similar in size to albumin that is produced by the liver and eliminated through the gastrointestinal tract. It is neither degraded nor absorbed in the intestine, allowing it to be excreted intact and detected in stool [5]. Of note, A1AT is broken down in the acidic environment of the stomach when pH is <3, and if a gastric source of protein loss is suspected, patients should be given a proton pump inhibitor prior to measuring A1AT clearance [13]. This approach has identified various conditions that have subclinical PLE as a component of the disease process. Also of note is the fact that our patient, although clinically improved on corticosteroids, continued to have pathological evidence of ongoing colorectal inflammation, placing him in the category of patients with PLE and mucosal erosive disease. Evaluation with urinary excretion studies distinguished the hypoproteinemia as intestinal rather than renal in origin. Identifying that the protein loss is enteric in origin is essential, carefully eliminating kidney and skin as sources of the problem. A due to the enteric source of the protein loss is that unlike skin and the gastrointestinal tract, renal loss of protein is usually limited to small molecules like albumin, whereas the former are much less selective, as evidenced by A1AT loss. Since the liver is responsible for protein synthesis, liver synthetic function must also be assessed in hypoalbuminemic states to make a diagnosis of PLE although stool A1AT clearance would not be elevated in liver disease.

Treatment of PLE in UC usually aims at controlling the underlying inflammatory process. As demonstrated by this case, even when symptomatically improved, persistence of inflammation can still lead to massive loss of protein into the gastrointestinal tract. Treatment options are limited. Anecdotal reports of the use of intravenous heparin and octreotide have been published [14, 15]. However, in UC the mainstay of treatment is to treat the underlying inflammation, even if subclinical.
Conclusion

The incidence and prevalence of PLE in UC remains unknown. Although the etiology appears to be mucosal disruption, PLE can occur in UC even if the symptomatic manifestations of the disease improve with acute treatment. The persistence of underlying inflammation may allow for the development of PLE in a small number of patients as the primary manifestation of UC. This complication may be debilitating, and its presence may be a sufficient indication for surgical intervention.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Fig. 1. Histopathology from the patient’s procto-colectomy. a Photograph of gross specimen showing inflammatory polyposis and one giant inflammatory polyp measuring $6.5 \times 4.5 \times 3.5$ cm located 2 cm from the ileocecal valve. The distal 12 cm of the specimen is largely free of pseudopolyps with edematous changes. b Representative H&E slide of colon at 40× magnification demonstrating severe active idiopathic UC.

References


