CME

Protein-Losing Enteropathy: Case Illustrations and Clinical Review

REVIEW

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Protein-losing enteropathy (PLE) is a rare syndrome of gastrointestinal protein loss that may complicate a variety of diseases. The primary causes can be divided into erosive gastrointestinal disorders, nonerosive gastrointestinal disorders, and disorders involving increased central venous pressure or mesenteric lymphatic obstruction. The diagnosis of PLE should be considered in patients with hypoproteinemia after other causes, such as malnutrition, proteinuria, and impaired protein synthesis due to cirrhosis, have been excluded. The diagnosis of PLE is most commonly based on the determination of fecal α-1 antitrypsin clearance. Treatment of PLE targets the underlying disease but also includes dietary modification, supportive care, and maintenance of nutritional status. In this article, cases illustrating a variety of clinical presentations and etiologies of PLE are presented, and its diagnostic approach and treatment are reviewed.

Am J Gastroenterol 2010; 105:43–49; doi:10.1038/ajg.2009.561; published online 29 September 2009

INTRODUCTION

Protein-losing enteropathy (PLE) is a rare condition characterized by a loss of serum protein into the gastrointestinal tract resulting in hypoproteinemia, which can be complicated by edema, ascites, pleural and pericardial effusions, and malnutrition. Although rare, there are many causes of PLE. The primary causes, however, can be divided into erosive gastrointestinal disorders, nonerosive gastrointestinal disorders, and disorders involving increased central venous pressure or mesenteric lymphatic obstruction (**Table 1**) (1). Owing to a lack of systematic screening and a wide variety of causes of hypoalbuminemia, the prevalence of this condition is poorly understood.

In healthy individuals, loss of protein through the gut epithelium has only a minor role in total protein metabolism; daily enteric loss of serum proteins accounts for approximately 1–2% of the entire serum protein pool and enteric loss of albumin accounts for less than 10% of total albumin (2). Indeed, most endogenous proteins found within the gut are from secretions and sloughed enterocytes. In contrast, gastrointestinal protein loss in PLE has been reported to involve up to 60% of the total albumin pool. This excessive protein loss across the gut epithelium can be due to either mucosal injury, resulting in increased mucosal permeability, or to lymphatic obstruction resulting in direct leakage of protein-rich lymph. The serum protein levels most affected by this process are those with limited ability to rapidly respond to such losses and generally have longer half-lives such as albumin, most immunoglobulins, and ceruloplasmin. Hepatic protein synthesis is maintained or slightly increased in patients with PLE and this is reflected by normal or increased levels of rapid-turnover proteins such as prealbumin, also known as transthyretin, immunoglobulin E, and insulin (3). Lower serum concentrations of other substances such as lipids, iron, and other trace elements are also occasionally encountered in PLE, as is lymphopenia, particularly in the setting of lymphatic obstruction (1).

In the pages that follow, cases illustrating a variety of clinical presentations and etiologies of PLE are presented and the diagnostic approach and treatment of this clinically challenging condition is reviewed.

PATIENT NO. 1: PLE DUE TO CONGESTIVE HEART FAILURE

A 47-year-old man with a 4-year history of non-ischemic dilated cardiomyopathy and end-stage congestive heart failure presented to our institution in August 2008 for a cardiac transplantation evaluation. At that time, he exhibited lower extremity edema but appeared well nourished. He denied any gastrointestinal symptoms and his weight was stable. In the process of the evaluation, he was noted to have markedly decreased levels of albumin and total protein (1.9 and 3.3 g per 100 ml, respectively). Further evaluation of the severe hypoalbuminemia included a 24-h urine protein measurement, serologic testing for celiac disease and intrinsic liver diseases, and abdominal imaging, all of which was normal. Owing to the concerns of possible cirrhosis secondary to severe congestive hepatopathy, additional evaluation of his liver demonstrated a normal portosystemic gradient

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Received 21 June 2009; accepted 31 August 2009

Table 1. Causes of protein-losing enteropathy

Erosive gastrointestinal disease
Inflammatory bowel disease
Gut malignancy
Nonsteroidal anti-inflammatory drug enteropathy
Erosive gastropathy
Acute graft-vs.-host disease
Pseudomembranous enterocolitis
Ulcerative jejuno-ileitis
Intestinal lymphoma
Sarcoidosis
Nonerosive gastrointestinal disease
Celiac disease
Hypertrophic gastropathies
Eosinophilic gastroenteritis
Lymphocytic gastritis
Connective tissue disorders
Small intestinal bacterial overgrowth
Amyloidosis
Microscopic colitis
Tropical sprue
Whipple's disease
Parasitic diseases
Viral gastroenteritis
Increased interstitial pressure
Intestinal lymphangiectasia
Congestive heart failure
Constrictive pericarditis
Congenital heart diseases
Fontan procedure for single ventricle
Portal hypertensive gastroenteropathy
Hepatic venous outflow obstruction
Enteric–lymphatic fistula
Mesenteric venous thrombosis
Sclerosing mesenteritis
Mesenteric tuberculosis or sarcoidosis
Neoplasia involving mesenteric lymph nodes or lymphatics
Chronic pancreatitis with pseudocysts
Congenital malformations of lymphatics
Retroperitoneal fibrosis

of 3 mm Hg and mild sinusoidal dilation in zone 3, but no evidence of significant fibrosis or cirrhosis on biopsy. Bidirectional endoscopy was subsequently completed and was normal including random biopsies of the duodenum and colon. A stool collection for fecal fat was also normal (3 g/day). Finally, fecal α-1 antitrypsin (A1AT) clearance was measured and was found to be markedly elevated at 505 mg per 10 ml (normal, < 27 mg per 100 ml) consistent with PLE. Additional notable laboratory findings included an increased prealbumin and decreased level of both ceruloplasmin and copper. Despite modifying his diet to include a protein intake of at least 2 g/kg/day, his albumin and protein levels did not change. In April 2009, he underwent an uncomplicated orthotopic heart transplant. Six weeks later, his peripheral edema had resolved and his albumin had normalized.

PATIENT NO. 2: PLE FOLLOWING REMOTE FONTAN PROCEDURE

A 26-year-old man with a history of congenital heart disease consisting of a single ventricle, left-sided aortic valve atresia, and transposition of the great vessels underwent a modified Fontan procedure at the age of 7 years. He did well until 2005 when he presented to his local physicians with edema, ascites, and severe malnutrition. Over the course of multiple hospitalizations for worsening edema and ascites, he was eventually diagnosed with PLE. Despite multiple treatment trials, including prednisone, daily albumin infusions, and subcutaneous heparin, none were successful in reversing his condition or improving his symptoms.

When he presented to our institution in November 2007 for consideration of possible surgical correction of his cardiac condition, his weight varied between 130 and 180 pounds depending on the amount of ascites. He denied having diarrhea, nausea, or vomiting but did endorse early satiety and postprandial fullness. He was noted to be severely cachectic on examination, and initial laboratory studies were notable for with an albumin of 1.9 g per 100 ml (normal, 3.5–5.0 g per 100 ml) and a prealbumin of 7.6 g per 100 ml (normal, 18–36 g per 100 ml). Owing to massive ascites, he underwent a diagnostic and therapeutic paracentesis (serum-ascites albumin gradient of 2.1 g per 100 ml). A stool collection did not reveal evidence of fat malabsorption. Fecal A1AT clearance was not rechecked. He was begun on enteral nutrition support using a semi-elemental formula with medium-chain triglyceride and additional protein supplementation to deliver approximately 2–3 g/kg protein daily. Because of a number of other micronutrient deficiencies, he was also started on vitamins A and D, as well as copper, selenium, and iron supplements. Unfortunately, despite these maneuvers his condition progressively deteriorated, and ultimately, it was felt that he was too high risk for surgical correction or cardiac transplantation and he expired about 14 months after his initial presentation to our institution.

Cardiac etiologies of PLE

A number of cardiac diseases may be complicated by the development of PLE. Indeed, one of the first reports of PLE was in a patient with congestive heart failure (4). The pathophysiology of congestive heart failure-associated PLE appears to be secondary to lymphatic obstruction and rupture of lacteals in the gut due to an increase in central venous pressure (4,5). Interestingly, a small case series suggests that PLE occurs rarely in the setting of severe congestive heart failure (2 of 25 patients) and that the presence of PLE does not influence the treatment or prognosis of the heart failure (6).

Protein-losing enteropathy has also been described in the setting of a number of other cardiac conditions including constrictive pericarditis, congenital heart disease, and valvular disease. One of the most frequently described cardiac causes of PLE occurs in the patient who has undergone the Fontan procedure, usually in the remote past. The Fontan procedure is performed in patients born with a functional single ventricle and marked underdevelopment of the left side of the heart, and works to restructure the heart so that the right side can pump enough blood to supply to the body (7–10). PLE is said to occur in approximately 3–15% of patients after the Fontan operation and, unfortunately, as illustrated by our patient, carries a high risk of morbidity and mortality (7,10,11). As the pathophysiology of post-Fontan PLE remains incompletely understood, one hypothesis suggests that elevation in the systemic venous pressure leads to dilation of the lymphatics within the gastrointestinal tract with subsequent protein leakage into the gut lumen. Another theory combines the concept of elevated venous pressure with low cardiac output and suggests that the diminished cardiac output leads to decreased intestinal perfusion and a compromised mucosa, thus causing increased epithelial permeability and protein leakage into the lumen (7,9). Recently, increased levels of tumor necrosis factor-α were demonstrated in these patients along with a compromised intestinal epithelial barrier and an increased flux of albumin across the mucosa (8,12); however, the cause-and-effect relationship between the increased level and PLE remains to be determined. Both preoperative and postoperative factors appear to predispose post-Fontan patients to develop PLE. Preoperative risk factors include ventricular anatomy other than a dominant left ventricle, increased preoperative ventricular end-diastolic pressure, and longer operative time (11). Postoperative risk factors were evaluated in a recent study by Silvilairat *et al.* (10) who showed that reduced ventricular area change on echocardiogram was more prevalent in PLE compared with non-PLE patients. They also found that lower serum albumin and higher New York Heart Association classification were associated with higher mortality in the Fontan patients with PLE.

PATIENT NO. 3: PLE IN THE SETTING OF LYMPHOMA

A 68-year-old man was in good health until December 2006 when he developed generalized fatigue associated with a 10-pound weight loss. The following month, his weight began to rise and he developed progressive abdominal distension. An evaluation by his local physician demonstrated the presence of ascites. He was begun on diuretics and referred to our institution for further evaluation. He was found to have ascites with substantial peripheral edema and muscle wasting. Laboratory evaluation revealed a mildly increased serum creatinine and mild proteinuria. Both serum albumin and total protein were decreased at 2.4 and 5.1 g per 100 ml, respectively. A computed tomography scan of his chest, abdomen, and pelvis demonstrated a large left pleural effusion, a moderate amount of ascites, and extensive mesenteric lymphadenopathy that was felt not to be "pathologically enlarged." Diagnostic paracentesis was notable for a serum-ascites albumin gradient of 0.9 g per 100 ml. Additional testing did not demonstrate a renal, cardiac, or liver cause of the anasarca and severe hypoalbuminemia; however, he was noted to have a markedly elevated CA-125 level (5,310 U/ml; normal, < 35 U/ml). This prompted the performance of a diagnostic laparoscopy with peritoneal and mesenteric biopsies. The laparoscopy was normal as were the biopsies.

Despite an absence of gastrointestinal complaints, colonoscopy, upper endoscopy, and video capsule endoscopy were then performed, all of which were normal including random biopsies from the duodenum and colon. Fecal A1AT clearance was found to be markedly abnormal at 299 mg per 100 ml (normal, < 54 mg per 100 ml), consistent with PLE. Fat malabsorption was also found to be present (29 g/day; normal, 2–7 g/day). Numerous micronutrient deficiencies were identified including copper, zinc and selenium, and vitamins A and D. Given the finding of PLE without a defined cause, an excisional lymph node biopsy was performed and revealed chronic lymphocytic leukemia/small lymphocytic lymphoma. This was confirmed on a subsequent bone marrow examination. He was subsequently treated with chemotherapy and his ascites and edema were gradually resolved. At his last follow-up visit in May 2008, his ascites and edema were absent, albumin level was normal, previous micronutrient deficiencies were resolved, and a repeat fecal fat collection was nearly normal at 10 g/day. Fecal A1AT clearance was not repeated.

PATIENT NO. 4: PLE DUE TO MENETRIER'S DISEASE AND POORLY CONTROLLED ULCERATIVE COLITIS

A 35-year-old man with a 6-year history of ulcerative colitis was referred to our institution in November 2006 for management of refractory colitis symptoms including frequent, nonbloody diarrhea, and abdominal pain. He also described a 1-month history of nausea and vomiting and a 70-pound weight loss over the past year. Initial laboratory studies were notable for an albumin of 1.8 g per 100 ml and a total protein of 4.0 g per 100 ml. Flexible sigmoidoscopy showed moderately active colitis, and upper endoscopy demonstrated markedly thickened gastric folds (**Figure 1**). Mucosal biopsies demonstrated nonspecific

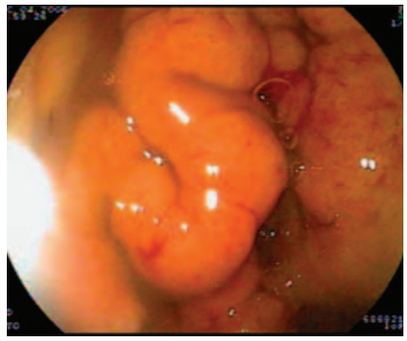

Figure 1. Upper endoscopy photograph demonstrating enlarged gastric folds.

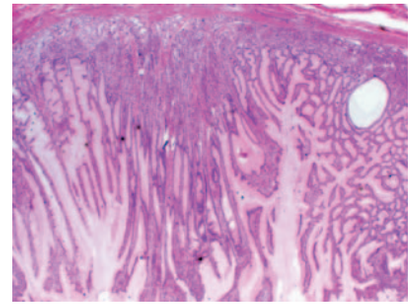

Figure 2. Gastric biopsy specimen demonstrating characteristic findings of Menetrier's disease. Note the elongated and dilated gastric crypts and diminished glandular component. Courtesy of Dr Giovanni De Petris.

foveolar hyperplasia. Immunostaining for *Helicobacter pylori* was negative. Endoscopic ultrasound with mucosal resection was subsequently performed and found uniform thickening of the mucosal and submucosal layers with normal underlying muscularis propria throughout the stomach. Pathology demonstrated marked foveolar hyperplasia, cystic atrophy of the specialized gastric antral and fundic glands, mild superficial active chronic inflammation (including eosinophils), and smooth muscle extension into the lamina propria (**Figure 2**). These histologic changes, in conjunction with the endoscopic appearance, were felt to be strongly supportive of Menetrier's disease.

Further investigation confirmed PLE with a fecal A1AT clearance while taking a daily proton pump inhibitor of 70 mg per 100 ml; however, it remained unclear whether the PLE was due to Menetrier's, refractory ulcerative colitis, or both. Despite trials of subcutaneous octreotide, cetuximab, which he received under an investigational protocol for Menetrier's disease, parenteral nutrition support, and aggressive treatment of his ulcerative colitis, his symptoms, namely, peripheral edema and inability to eat, persisted. He subsequently underwent a total gastrectomy in January 2008 and experienced a rapid resolution of his edema, normalization of his laboratory parameters, and weight gain. As of January 2009, his colitis was in remission on 6-mercaptopurine and he had not required a colectomy.

Gastrointestinal etiologies of PLE

There are two categories of gastrointestinal diseases that lead to PLE—those with and those without mucosal erosions (**Table 1**). Even without mucosal erosions, conditions that lead to surface epithelial cell loss or malabsorption can cause excess protein loss. The most common nonerosive gastrointestinal condition that may be complicated by the development of PLE is Menetrier's disease, also known as giant hypertrophic gastropathy. This is a rare, acquired disorder characterized grossly by giant rugal folds in the stomach and histologically by foveolar hyperplasia, cystic dilation/pits, and reduced numbers of parietal and chief cells. The reduced number of parietal cells usually results in hypochlorhydria. An increase in intracellular permeability and wider tight junctions between cells leads to protein loss, and the presence of protein-rich exudates in the stomach (13). Recent evidence implicates increased signaling of epidermal growth factor receptor by transforming growth factor-α in the pathogenesis (13,14). Patients with Menetrier's commonly present with symptoms of abdominal pain, nausea, vomiting, and weight loss. Menetrier's may be suspected during upper endoscopy because of the finding of abnormally large gastric folds, although this finding is not specific. Endoscopic mucosal resection or full-thickness biopsy may be needed to confirm the diagnosis. Treatment of the disorder is difficult and many of the available treatments (e.g., subcutaneous octreotide) improve symptoms only transiently and generally do not resolve the underlying pathologic process (13). Because of an association between both *H. pylori* and cytomegalovirus infection with Menetrier's disease, it may be reasonable to test and treat for these possibilities (14–17). Recently, the use of monoclonal antibodies to epidermal growth factor receptor (e.g., cetuximab) has been suggested to be effective in some patients with Menetrier's potentially obviating the need for gastrectomy (18). Our patient no. 4 received treatment with cetuximab for approximately 6 months, but this was unsuccessful in halting his protein loss and he eventually underwent definitive surgical therapy in the form of a total gastrectomy. This is often the case in Menetrier's, whereby gastrectomy becomes necessary (13). Other nonerosive gastrointestinal processes that have been reported to be complicated by PLE include eosinophilic gastroenteritis, microscopic colitis, small intestinal bacterial overgrowth, celiac disease, and *H. pylori* infection.

Both ulcerative colitis and Crohn's disease are classic examples of erosive gastrointestinal disease leading to PLE. Other examples are listed in **Table 1**. The mechanism of protein loss in these conditions is thought to relate to enhanced leakage of protein-rich fluids across the eroded epithelium. The degree of mucosal involvement typically correlates with the severity of protein loss (19). Indeed, gastrointestinal protein loss has been suggested to be a marker of the severity of activity in inflammatory bowel disease, with fecal A1AT clearance being suggested as the test of choice (20–22).

Granulomatous involvement of the lymph nodes in Crohn's disease has also been demonstrated to lead to dilation of the lymphatics with leakage of lymph across the epithelium, thus, resulting in additional protein loss (19). A similar process due to the extensive mesenteric lymphadenopathy related to lymphoma could be postulated to be responsible for the PLE noted in our patient no. 3. Although rare, there have been several case reports of coexisting ulcerative colitis and Menetrier's disease (23,24). Interestingly, the diagnosis of ulcerative colitis generally predates the diagnosis of Menetrier's, a finding we also observed in patient no. 4.

Finally, although most PLE cases due to lymphatic obstruction or increased lymphatic pressure are the result of cardiac etiologies, a rare disorder of the gut, primary intestinal lymphangiectasia (Waldmann's disease), may also be responsible. This disorder is characterized by the presence of tortuous, dilated lacteals in the mucosa, and submucosa, which result in loss of protein-rich lymph into the small bowel lumen. Patients with this disorder usually present in childhood with edema, weight loss, diarrhea, and lymphopenia.

Clinical features and diagnosis of PLE

The clinical manifestations of PLE are highly variable, being related to the underlying cause, but tend to mainly consist of edema. Diarrhea and other gastrointestinal symptoms are frequently not present. The main laboratory findings are reduced serum concentrations of albumin, protein, γ-globulins, fibrinogen, transferrin, and ceruloplasmin. Although the hypoalbuminemia contributes to the primary clinical manifestation of edema due to diminished plasma oncotic pressure, the reductions of other serum proteins rarely cause clinically significant problems. Importantly, PLE may also be associated with fat malabsorption and fat-soluble vitamin deficiencies caused by the primary disease.

The initial step in the evaluation of the patient with hypoproteinemia and/or hypoalbuminemia is to exclude other, more common, etiologies such as malnutrition, liver, and renal diseases. Importantly, as with our second case illustration, malnutrition may also occur as a feature of PLE, thereby, complicating the diagnosis. When no other cause has been identified and there is concern of possible PLE, at present, the most commonly used and reliable method to determine enteric protein loss is to determine the clearance of A1AT from plasma. A1AT is a protein synthesized in the liver that is neither actively secreted nor absorbed, has a molecular weight similar to albumin, and does not undergo proteolysis or degradation in the gut, thereby allowing for its intact elimination and detection in feces. The measurement of A1AT clearance requires both a blood sample to determine plasma A1AT level and a 24-h stool collection to determine stool volume and stool A1AT level (note that a 72-h stool collection is not required for stool A1AT clearance). The analysis of fecal A1AT concentration is not a reliable substitute for measurement of A1AT clearance (25). Normal A1AT clearance is ≤27 ml/24 h. Importantly, diarrhea from any cause can increase the clearance of A1AT. Therefore, in the setting of diarrhea, the normal A1AT clearance increases to ≤56 ml/24 h (19). In addition, this test does not distinguish between intestinal and gastric sources of protein loss. Because A1AT is degraded in environments with a pH < 3.5, if a gastric source of protein loss is suspected or an acid hypersecretory state is known to be present, it is recommended that the test be performed while the individual is receiving acid suppressive therapy (26,27).

Nuclear radiology testing has also been used, albeit primarily as a research tool, to quantitate enteric protein loss. The use of technetium-99m-labeled albumin to scintigraphically document protein loss in the gut has been shown to be useful not only for diagnosis but also in monitoring response to treatment (28–30). The overall accuracy of this and other scintigraphic tests, however, has yet to be determined. Magnetic resonance imaging has also recently been studied as a diagnostic test for PLE, primarily in children with lymphangiectasia. Imaging was clearly able to detect abnormalities in both mesenteric and intestinal swelling and document the presence of dilated/prominent lymphatics. It was suggested that these findings in the setting of an appropriate clinical presentation could be used to support the diagnosis of PLE without having to proceed to invasive testing such as biopsy and/or endoscopy (31).

Treatment of PLE

Following confirmation of PLE, an evaluation is necessary to identify the underlying cause (1). As there is no specific treatment of PLE, its treatment should be directed at the underlying condition; however, careful monitoring and treatment of malnutrition and micronutrient deficiencies, if present, is also necessary. Fortunately, most causes of PLE can be readily diagnosed and treated. Treatment options may include dietary, pharmacological or surgical intervention, or a combination of these.

Protein-losing enteropathy associated with cardiac diseases can generally be improved with medical and surgical management of the underlying cardiac condition. Similarly, protein loss from the stomach, small bowel, or colon should be treated according to the underlying disease present. For example, in cases of hypertrophic gastropathy, evidence of an infection with *H. pylori* should be sought and treated if present (15,16). Investigational treatment with cetuximab or gastrectomy should be considered in cases of Menetrier's disease (13,18). Acquired intestinal lymphangiectasia should be treated by correction of the underlying cause (32). Small intestinal bacterial overgrowth, Whipple's disease, and other infectious causes of PLE should be treated with appropriate antibiotic therapy, whereas cancer-induced PLE requires therapy directed against the cancer. Immunosuppressive therapies may be useful in the management of PLE caused by inflammatory diseases such as Crohn's disease, ulcerative colitis, collagenous colitis, gut graft-vs.-host disease, or systemic lupus erythematosus (33). Surgery may be needed in refractory inflammatory cases. Despite a lack of quality

evidence supporting their efficacy in PLE, anecdotal reports suggest that other therapies such as intravenous heparin (34) and octreotide (35) may be useful to decrease fluid secretion and protein exudation from the bowel. The use of intermittent intravenous infusions of albumin is generally unhelpful in the long-term.

A high-protein diet is generally recommended. In some circumstances, a low-fat diet may also be recommended usually along with medium-chain triglyceride supplementation in hopes of offsetting at least some of the reduction in calories caused by the decrease in fat. Congenital intestinal lymphangiectasia is one such condition that may benefit from such dietary changes. These dietary modifications may beneficially effect albumin metabolism and diminish the need for lymphatic transport of fatty acids, thus decreasing pressure on the lymphatic system and decreasing lymph leakage (32,33). The ability to correct hypoalbuminemia is dependent upon the type and severity of the underlying disease. Normal protein requirements are generally 0.6–0.8 g/kg/day. In PLE, this value may increase to 2.0–3.0 g/kg/day to achieve positive protein balance. High protein intake within this range can usually be achieved through changes in the diet and use of commercially available protein supplements. Although it is always preferable to use the gut for feeding, in certain conditions such as severe erosive disease or intestinal dysmotility, parenteral nutrition support may be necessary.

Finally, supportive care to avoid complications resulting from peripheral edema with support stockings, vigilant monitoring for skin breakdown, and adequate ambulation to prevent deep vein thrombosis is recommended. In contrast, diuretics are not generally useful as the edema relates to a reduction in plasma oncotic pressure.

CONCLUSION

Protein-losing enteropathy is a syndrome of gastrointestinal protein loss, which may complicate a variety of diseases, most commonly cardiac or gastrointestinal conditions. The diagnosis of PLE should be considered in patients with hypoproteinemia in whom other causes, such as malnutrition, proteinuria, and impaired protein synthesis due to cirrhosis have been excluded. The diagnosis of PLE is most commonly based on the determination of fecal A1AT clearance. The prognosis of PLE depends upon the underlying condition responsible. Treatment of PLE targets the underlying disease but also includes dietary modification, supportive care, and maintenance of nutritional status.

CONFLICT OF INTEREST

Guarantor of the article: John K. DiBaise, MD, FACG.
Specific author contributions: S.B.U.: collecting patient information, reviewing the literature, and drafting the manuscript; J.K.D.: supervising the study and revising the manuscript.
Financial support: None.
Potential competing interests: None.

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