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Protein-Losing Enteropathy - Diagnostic Challenge, Unusual Pathologies and Literature Review

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Abstract

Introduction: Protein-losing enteropathy (PLE) is a rare condition in clinical practice that can be present in a variety of diseases, including those primarily from the gastrointestinal tract (GIT) or not. The mechanisms possibly involved in its pathogenesis are: erosive and non-erosive mucosal disease, increased central venous pressure and mesenteric lymphatic obstruction. This diagnosis must be considered in patients with severe hypoalbuminemia in which proteinuria, liver disease and malnutrition were excluded.

Aim: Present unusual causes of PLE, its clinical management and literature review. Methods: retrospective study, in which we describe seven cases of PLE with uncommon etiologies and its treatment approaches.

Conclusion: The prognosis of these patients depends mainly on the primary disease and its specific treatment. However, in situations in which the etiology cannot be defined, protein loss can be stopped with approaches based on its possible physiopathological mechanisms.

Keywords: Protein-losing enteropathy; Physiopathological mechanisms; Hypoalbuminemia; Serum proteins; Gastrointestinal tract

Introduction

Protein-losing enteropathy (PLE) is a rare condition in clinical practice [1]. It is characterized by excessive loss of serum proteins in the gastrointestinal tract, leading to hypoalbuminemia and generalized edema, among other clinical manifestations [2]. Several mechanisms are involved in its process, including erosive and non-erosive mucosal disease and increased central venous pressure or mesenteric lymphatic obstruction [3,4] (Table 1).

Table 1: Most frequent causes of PLE according to mechanisms possibly involved in its pathogenesis.

Erosive Mucosal Disease	Non-Erosive Mucosal Disease	Increased Central Venous Pressure and Mesenteric Lymphatic Obstruction
Inflammatory bowel disease	Celiac disease	Congestive heart failure
Pseudomembranous enterocolitis	Allergic gastroenteropathy	Intestinal lymphangiectasia
Ulcerative jejunoileitis Amyloidosis	Lymphocytic gastritis/colitis	Intestinal endometriosis
Graft versus host disease	Parasitosis	Enteric lymphatic fistula
Gastrointestinal carcinomas	Collagen colitis	Portal hypertensive gastroenteropathy
Ischemic colitis	Systemic lupus erythematosus	Mesenteric venous thrombosis
Sarcoidosis	Whipple's disease	
	Hypertrophic gastropathy	

As protein loss is not selective, serum albumin, globulin, fibrinogen, lipoproteins, alpha-1 antitrypsin, transferrin and ceruloplasmin are decreased. Lymphopenia is also observed in cases in which lymphangiectasia is the mechanism involved in the protein loss. Despite the humoral and cellular deficiency, an increased susceptibility to opportunistic infections is not common [5,6]. This diagnosis must be considered in patients with severe hypoalbuminemia in which proteinuria, liver disease and malnutrition have been excluded [6,7]. Alpha 1-antitrypsin is a glycoprotein with molecular weight similar to albumin, also synthesized by the liver. In gastrointestinal tract, alpha-1-antitrypsin is resistant to proteolysis, so it is not absorbed neither secreted. Under physiological conditions, its concentration in feces is low. Thus, its faecal excretion dosage is useful in the diagnosis of PLE [4,8].

99mTc-labeled human serum albumin scan can detect protein loss into the gut and thus confirm suspected protein losing enteropathy and provide anatomical imaging to confirm the precise site of protein loss [4,5,8-10]. Losing enteropathy protein treatment consists primarily in the management of primary disease and its complications, such as malnutrition. Based on knowledge of the involved mechanism in intestinal protein loss, some therapeutic alternatives have been proposed, although more studies are still needed to set them as specific treatment [4].

Heparin, in vitro studies, has shown increased lymphangiogenesis mediated by growth factor in addition to an antiinflammatory effect. It is believed that, based on these effects, it can restore the integrity of the basement membrane and selective permeability in the gut. The exact mechanism is still unclear, and only a few patients have shown good response to its use [4,11]. In the same way, corticosteroids don´t have the mechanism by which can modify LPE evolution well defined. It is often observed a response in the first six months of treatment, with long-term relapse [4,7]. Some authors believe it is more frequently in patients who are in maintenance treatment with corticosteroid alone than in those who are on combined therapy with immunomodulator agents [5].

Octreotide is also an option. Its use has been described in association with corticosteroids in cases of refractory PLE secondary to amyloidosis [12]. Its mechanism of action is not fully understood, and more research is needed for this setting [13].

Aim

Present rare causes of protein-losing enteropathy, its management and literature review.

Case Reports and Discussion

Protein-losing enteropathy by erosive mucosal disease.

Case 1

Male, 52 years old, referred to Gastroenterology from Nephrology service due to anasarca frame, malnutrition, hypoalbuminemia (serum albumin: 1,9mg/dL). He had no diarrhea, and renal causes for the symptoms had been discarded. Protein-losing enteropathy was confirmed by 99mTc-labeled human serum albumin scan that showed protein loss in the topography of the right flank (Figure 1). Endoscopy showed duodenal subestenosis and local mucosal erosions. Anatomopathologic study of these lesions was unspecific. Barium contrast radiography showed multiple stenoses along small intestine. Enteroscopy showed multiple superficial erosions, and stenosis dilatation was performed. Colonoscopy was macroscopically normal, and biopsies showed in specific chronic ileitis and colitis (Table 2). Corticosteroid therapy was started, and clinical improvement was observed. But the patient gave up treatment, returning after worsening of edema and malnutrition. He was admitted for a possible bowel resection, but because of diffuse intestinal protein loss at that moment, the surgery could not be realized. Intravenous corticosteroid therapy was initiated, and azathioprine prescribed later. As there was no response, Infliximab was initiated. There was a significant clinical worsening, pyoarthritis and pneumonia been diagnosed. Despite antibiotic therapy and nutritional support, the patient died.

Table 2: Clinical presentation and diagnostic methods.

	Clinical Presentation	Diagnostic Methods
Case 1 Male 52-years-old	Anasarca, malnutrition, hypoalbuminemia, no diarrhea or renal disease	Serum albumin: 1,9mg/dL 99mTc-labeled human serum albumin scan: protein loss in right flank. Upper digestiva endoscopy: duodenal subestenosis with mucosal erosions. Biopsies were unspecific. Barium contrast radiography: showed multiple stenoses along small intestine. Enteroscopy: multiple superficial erosions. Colonoscopy: no anormalities; biopsies showed inespecific chronic ileitis and colitis.
Case 2 Female 60-years-old	Diarrhea, abdominal pain, swelling in limbs and weight loss (BMI 11). History of uterine cervix cancer 10 years ago with radiotherapy at the time.	Serum albumin: 1,7mg/dL Colonoscopy: erythema and ulcerations in terminal ileum. Biopsies: actinic ileitis. Magnetic resonance: diffuse wall thickening in ileus.

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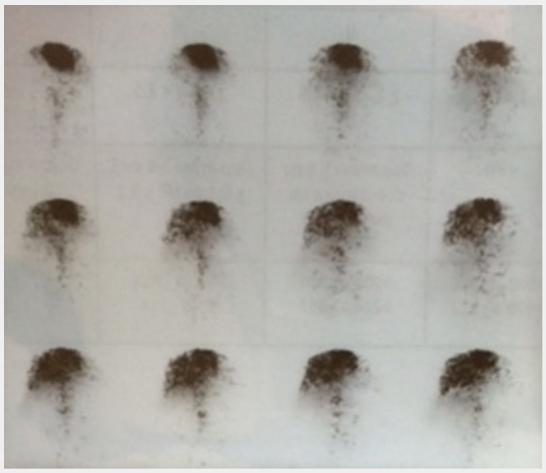

Figure 1: 99mTc-labeled human serum albumin scan showing protein loss in right flank.

Case 2

Female, 60 years old, started four years ago a clinical condition including diarrhea, crampy abdominal pain, swelling in limbs and weight loss (10kg in six months). She had a previous history of cervical neoplasia 10 years ago and underwent radiotherapy at the time. She developed severe malnutrition frame (30Kg; BMI 11), an important muscle weakness and lower limbs and abdominal wall swelling. She was hospitalized at the time, and laboratory tests showed albumin 1.7 mg/dL, prealbumin 12mg/dL, Hb 8.0, K 2.1mg/dL and Mg 0.89mg/dL, with normal ESR and CRP 2mg/dL. Colonoscopy showed erythema and ulcerations in the terminal ileum, and pathologic study showed actinic ileitis. Resonance revealed diffuse wall thickening in ileal loop (Table 2). Oligomeric enteral diet and corticosteroids were started. She was discharged with serum albumin level and clinical improvement ((alb 3.8mg/dL; weight = 34.5Kg). The patient presented intestinal subocclusion and was hospitalized for nutritional support and surgical intervention. Bowel resection target in three areas of ileal stenosis was performed. She progressed well, in good nutritional status. pneumonia been diagnosed. Despite antibiotic therapy and nutritional support, the patient died.

Discussion

Protein-losing enteropathy originating in the gut can be classified into erosive and non-erosive. Ulcerative colitis and Crohn's disease are the classic examples of the erosive form. The mechanism includes an increased fluid passage rich in proteins through the damaged epithelium, and the degree of protein loss is relating directly to the lesion mucosa [3].

Idiopathic ulcerative jejunum ileitis is a rare disease, which etiology is not well known [14,15]. Its presentation ranges from mucosal inflammation to involvement of deeper layers, causing ulceration and stenosis. It is an unusual and exclusion diagnosis, since over 50% of patients with ulcerative jejunum ileitis are diagnosed as Crohn's disease, celiac disease, lymphoma or infectious diseases [16]. Although little thing is known about its pathophysiology, it is believed to be the participation of T lymphocytes, with extensive mucosal infiltration, and prednisone, azathioprine and biological being therapy options for these pacientes [16,17]. Our patient, although had receive immunosuppression therapy and heparin, did not provide satisfactory answers and evolved to death due to infectious complications, probably due to the immunosuppression associated with severe malnutrition.

Actinic enteritis is a complication of pelvic radiation therapy used to treat cancer with an estimated incidence ranging 3-15% [18], mainly affecting the ileum, rectum and sigmoid [19]. The pathophysiology includes damage to epithelial cells and connective tissue by radiation, leading to obliterans endarteritis and tissue ischemia. The consequences range from mucosal ulceration to necrosis of the intestinal wall, and the symptoms may arise during the first 5 to 10 years, but up to 30 years later [18-21]. In case 2, the patient presented ulcerations of the intestinal mucosa in the distal ileum and substenosis areas as manifestations of enteritis actinic. She achieved good performance with the use of corticosteroids and nutritional therapy, being submitted to bowel resection.

Protein-losing enteropathy by non-erosive mucosal disease

Case 3

Female, 62 years old, was admitted for investigation of diarrhea and anasarca. She had previous episode of acute pulmonary edema due to cardiac tamponade and diagnosis of celiac disease at that time. She displayed anemia, serum alb 2.0 mg/dL, prealbumin 17.6mg/dL and increased PCR. During hospitalization, she evolved with deep vein thrombosis in the left arm, receiving anticoagulation therapy. It was started empirical treatment with corticosteroids, with improvement in diarrhea, and gluten-free diet was maintained. Colonoscopy showed only diverticular

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disease of the colon, and upper endoscopy with biopsy of the second duodenal portion didn´t show suggestive findings of celiac disease. Endoscopic capsule detected no changes of intestinal mucosa. Laboratory tests showed albumin 3.6 mg/dL, and genetic screening of HLA-DQ2 and DQ8 was negative (Table 3). There was clinical worsening with the decrease in corticosteroid dose, progressing to anasarca, diarrhea return and serum albumin of 1.2 mg/dL. After increasing dose of prednisone to 30 mg day, there was a significant improvement, reaching serum albumin of 4.0 mg/dL. Nowadays, the patient is in use of Azathioprine 150mg/day alone, remaining asymptomatic, with no ascites and normal serum albumin for a year.

Table 3: Protein-losing enteropathy due to non-erosive mucosal disease. Clinical presentation and diagnostic methods.

	Clinical Presentation	Diagnostic Methods
Case 3 Female 62-years-old	Diarrhea, anemia and anasarca. Gluten-free diet due to celiac disease diagnosis some years ago.	Serum albumin: 2.0mg/dL Upper digestive endoscopy: normal. Biopsies of second duodenal portion without findings of celiac disease. Endoscopic capsule: detected no changes of intestinal mucosa. Colonoscopy: diverticular disease. HLA-DQ2 and DQ8: was negative
Case 4 Female 61-years-old	Diarrhea, ascites, pleural effusion, and livedo reticularis. Pan-hysterectomy due to the diagnostic of ovarian tumor (ovarian fibrotecoma) in other medical service, three years ago. Maintaining diarrhea, and after six months, ascites returned.	Serum albumin: 1.9mg/dL CA-125: 1366UI/mL C3 complement: low levels 99mTc-labeled human serum albumin scan: protein loss Upper digestive endoscopy and colonoscopy: normal. Capsule endoscopy: normal

Case 4

Female, 61 years old, presenting with diarrhea for three years associated to ascites, weakness and weight loss. At that time, it was diagnosed an ovarian tumor. She was submitted to pan-hysterectomy, and pathological results in left ovarian fibrotecoma. She progressed well, although maintaining diarrhea. After six months, because of returned ascites frame, she underwent exploratory laparotomy with biopsies of intestinal serous and peritoneum, and study of ascites: all negative for malignancy. She was than referred to our clinic for research, presenting with ascites, pleural effusion, emaciated, with livedo reticularis and keeping interspersed diarrhea with constipation. Laboratory tests showed alb 1.9 mg/dL, gamma globulin 0.58mg/dL, VHS 103/mm^3, increased CRP, CA-125 1366UI/mL and C3 below the lower limit of normal. After liver and kidney causes for anasarca were excluding, protein-losing enteropathy was confirmed through 99mTc-labeled human serum albumin scan. Upper and lower endoscopy showed no findings that justify the frame. The capsule endoscopy also showed no mucosal lesion, and autoantibodies tests were negative (Table 3). Steroid therapy was started. During follow-up, she developed deep vein thrombosis in the left arm, and anticoagulation with heparin was started. During its use, along with steroids, the patient evolved with clinical and laboratory improvement. The patient keeps on using of corticosteroids, with significant reduction in CA-125 and improvement in complement serum level.

Discussion

Even without mucosal erosions, conditions that lead to loss of surface epithelial cells may cause loss of proteins in excess in the gastrointestinal tract. Among them, the most common is Menetrier's disease, wherein the enlargement of intercellular junctions leads to an increased mucosal permeability [3]. Other non-erosive causes of LPE are eosinophilic gastroenteritis, microscopic colitis, celiac disease, among others [9]. These are clinical conditions that, although do not occur frequently, the inflammatory process leads to increased vascular permeability.

When associated with autoimmune diseases, a hypothesis for its mechanism is that there must be a direct relationship with vasculitis, leading to increased permeability of protein trough the intestinal vessels. Another hypothesis is that inflammatory mediators may cause vasodilation, with a consequent increase in vascular permeability [5]. Ong et al. [7] reported a case of a patient with LPE, increased CA-125 and low levels of C3, as well as ascites and edema in the lower limbs as the initial presentation of systemic lupus erythematosus. In case 4, although the investigation has not been completed, the presence of livedo reticularis associated to high CA-125 levels and low levels of complement, with improvement of these parameters after the use of corticosteroids, suggest that it must be an autoimmune process, consistent with the hypothesis of vasculitis as a mechanism of protein loss in this case.

Besides been a demonstration of a variety of diseases, LPE may occur as an idiopathic disease [5], as in case 3, in which even after thorough investigation, an underlying disorder were not diagnosed. The treatment of LPE, as said before, primarily consists on resolution of underlying disease. However, even when the primary cause of protein loss is not identified, steroid therapy is an option, as seen in cases 3 and 4.

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Protein-losing enteropathy by vascular disease (increased interstitial pressure)

Case 5

Female, 29 years old, diagnosed with Whipple's disease with enteric and lymph node involvement. The diagnosis was confirmed by upper endoscopy with duodenal biopsy and inguinal lymph node. Besides in use of sulfamethoxazole-trimethoprim since the last year, she kept diarrhea board and anasarca, associated with hypoalbuminemia (1.5mg/dL) and decreased levels of immunoglobulins. Scintigraphy with 99mTc-labeled human albumin showed protein loss in the right abdomen (terminal ileum / cecum / ascending colon). In addition to the protein loss, had elevated inflammatory markers (Table 4). Sulfamethoxazole-trimethoprim was suspended and a new treatment with ceftriaxone was started and maintained for 15 days, in addition to nutritional therapy with medium-chain triglycerides (MCT). There was improvement in bowel habits and gradual reduction of edema associated with the use of diuretic.

Table 4: Protein-losing enteropathy by vascular disease (increased interstitial pressure). Clinical presentation and diagnostic methods.

	Clinical Presentation	Diagnostic Methods
Case 5 Female 29-years-old	Diarrhea and anasarca, besides the use of sulfamethoxazole-trimethoprim for Whipple disease (diagnosed by upper endoscopy with duodenal biopsy and inguinal lymph node biopsy).	Serum albumin: 1,5mg/dL 99mTc-labeled human serum albumin scan: protein loss in the right abdomen (terminal ileum / cecum / ascending colon)
Case 6 Male 58-years-old	Hypoalbuminemia, asthenia and malaise, with no change in bowel habits. He had chronic pancreatic insufficiency secondary to alcohol, and surgical history (pancreatojejunal branch and Nissen fundoplication 20 and 15 years ago).	Serum albumin: 1,1mg/dL Intestinal transit: showed subocclusion at various levels and adhesions of the small bowel. 99mTc-labeled human serum albumin scan: diffuse protein loss in small bowel. Magnetic Resonance: suggested encapsulating peritonitis.
Case 7 Male 40-years-old	Ascites, lower limbs edema and mental confusion. Two years ago, he had deep vein thrombosis in lower limb and was treated with oral anticoagulation.	Serum albumin: 2,9mg/dL AST: 698U/L ; ALT: 826U/L ; INR:5,15 Anti-HCV, HbsAg, anti-HIV: negative Abdominal Doppler-ultrassonography: portal vein thrombosis and ascites. Angiography by computerized tomography: hepatomegaly and acute thrombosis of the portal and hepatic veins - acute Budd-Chiari Syndrome (figure 3). 99mTc-labeled human serum albumin scan: protein loss across the small intestine (figure 3).

Case 6

Male, 58 years-old, referred to our service because of hypoalbuminemia (serum albumin 1.15mg/dL). He had a history of chronic pancreatic insufficiency secondary to alcohol, diabetes mellitus, hypertension, and surgical history pancreatojejunal branch in 1992 and Nissen fundoplication in 1999. He complained of asthenia and malaise nonspecific, with no change in bowel habits. On physical examination, the patient presented lower limb edema without ascites. Intestinal transit showed subocclusion at various levels and adhesions of the small bowel. Due to the hypothesis of protein-losing enteropathy, scintigraphy with 99mTc-labeled human albumin was performed, and diffuse protein loss in small bowel was confirmed, in addition to diffuse bowel distension with air-fluid levels, suggesting a subocclusive bowel frame. Magnetic Resonance suggested the possibility of encapsulating peritonitis (Figure 2, Table 4). He was submitted to surgery, and pathology of the surgical specimen showed vascularized fibrous connective tissue fragments with diffuse infiltration of polymorphonuclear organization and hyaline fibrosis in the wall, confirming the diagnosis. Postoperatively return, the patient was without asthenia and edema, with serum albumin 3.1mg/dL.

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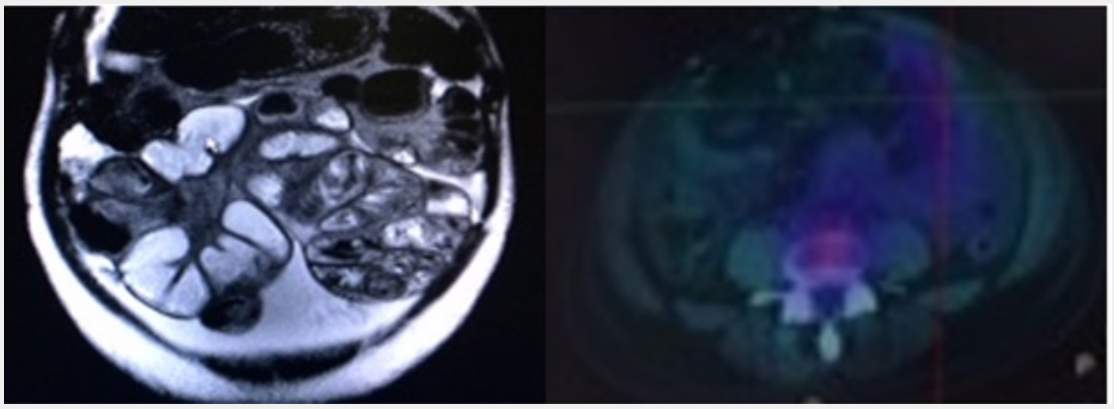

Figure 2: Left: Magnetic Resonance suggesting encapsulating peritonitis; right: 99mTc-labeled human serum albumin scan showing protein loss especially in left flank.

Case 7

Male, 40 years-old, previously healthy, presented ascites, oliguria, lower limbs edema and mental confusion. He had a history of deep vein thrombosis in the right lower limb two years ago and received oral anticoagulation at the time. Laboratory tests showed: alb 2.9 mg/dL, BT 5.73 mg/dL, ALT 698 U/L, AST 826 U/L, INR 5.15, and serological tests for virus hepatitis B and C and HIV were negative. Abdominal USG-Doppler showed portal vein thrombosis and ascites. Angiography by computerized tomography showed hepatomegaly with acute thrombosis of the portal and hepatic veins, consistent with the diagnosis of acute Budd-Chiari Syndrome. A 99mTc-labeled human serum albumin scan was performed (Figure 3), which showed an important protein loss across the small intestine, compatible with protein-losing enteropathy of vascular origin (Table 4). The patient remained on worsening of liver function and died from septic shock.

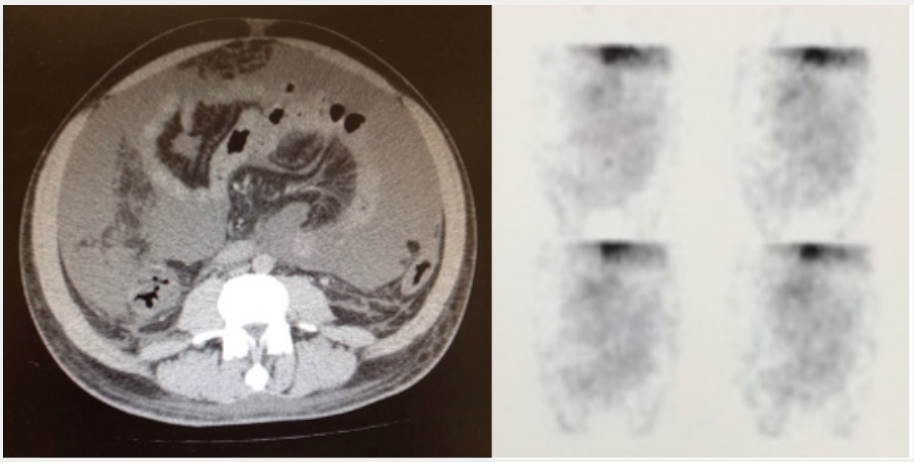

Figure 3: Left: Computerized tomography showing mesenteric congestion; right: 99mTc-labeled human serum albumin scan with protein loss across the small intestine.

Discussion

Physiologically, when proteins pass through the gastrointestinal mucosa, reaching its light, new proteins are synthesized in a compensatory manner. In normal situations, enteric protein loss accounts for only 1 to 2% of the proteinaceous shell, with albumin losing accounting for less than 10% of the total catabolism. In patients with PLE, this enteric albumin loss can reach 60% of the total albumin body reserve [1]. One of the first reports of PLE was a patient with congestive heart failure. The mechanism includes lymphatic obstruction due to increased central venous pressure (CVP) in these patients. A high pressure in lymphatic vessels would cause stroke of rich protein content into gastrointestinal tract light [3].

Although more commonly associated with congestive heart failure, any situation that leads to increased CVP may be associated with PLE by vascular disease as a complication. For example, constrictive pericarditis, non-cardiac valve diseases or other conditions as described above in cases 5, 6 and 7. Whipple's

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disease may be associated with hypoalbuminemia, usually secondary to intestinal malabsorption and malnutrition. However, the ascites is found only in 5% of cases in which there is a lymphatic system involvement [22-26]. However, although studies reveal up to 66% of cases with lymphadenopathy, PLE as a manifestation of Whipple's disease is not common. Case 5 exemplifies this situation, presenting with hypoalbuminemia secondary to PLE (confirmed by scintigraphy with labeled albumin).

Table 5: Complementary exams, etiologic diagnosis, mechanisms involved and instituted therapy of the seven cases of protein-losing enteropathy (PLE) presented in this study.

	Complementary Exams	Etiologic Diagnosis	Mechanism Involved	Instituted Therapy
Case 1 Male 52-years-old	Serum albumin: 1.9mg/dL 99mTc-labeled human serum albumin scan: protein loss in right flank. Upper digestiva endoscopy: duodenal subestenosis with mucosal erosions. Biopsies were unspecific. Barium contrast radiography: showed multiple stenoses along small intestine. Enteroscopy: multiple superficial erosions. Colonoscopy: no anormalities; biopsies showed inespecific chronic ileitis and colitis.	Idiopathic ulcerative jejunoileitis	PLE due to erosive mucosal disease	Intravenous corticosteroids, and azathioprine was associated later. Because of no response, Infliximab was introduced.
Case 2 Female 60-years-old	Serum albumin: 1.7mg/dL Colonoscopy: erythema and ulcerations in terminal ileum. Biopsies: actinic ileitis. Magnetic resonance: diffuse wall thickening in ileus.	Actinic enteritis	PLE due to erosive mucosal disease	Oligomeric enteral diet and corticosteroids were administrated, preparing the patient for surgical intervention.
Case 3 Female 62-years-old	Serum albumin: 1.9mg/dL CA-125: 1366UI/mL C3 complement: low levels 99mTc-labeled human serum albumin scan: protein loss Upper digestive endoscopy and colonoscopy: normal. Capsule endoscopy: normal	Idiopathic PLE	PLE due to non-erosive mucosal disease	Corticosteroid and azathioprine
Case 4 Female 61-years-old	Serum albumin: 1.9mg/dL CA-125: 1366UI/mL C3 complement: low levels 99mTc-labeled human serum albumin scan: protein loss Upper digestive endoscopy and colonoscopy: normal. Capsule endoscopy: normal	Autoimmune disease (vasculitis)	PLE due to non-erosive mucosal disease	Corticosteroids and heparin
Case 5 Female 29-years-old	Serum albumin: 1.5mg/dL 99mTc-labeled human serum albumin scan: protein loss in the right abdomen (terminal ileum / cecum / ascending colon)	Whipple's disease with lymphatic system involvement	PLE by vascular disease (increased interstitial pressure)	Ceftriaxone for 15 days and nutritional therapy with medium-chain triglycerides (MCT).
Case 6 Male 58-years-old	Serum albumin: 1.1mg/dL Intestinal transit: showed subocclusion at various levels and adhesions of the small bowel. 99mTc-labeled human serum albumin scan: diffuse protein loss in small bowel. Magnetic Resonance: suggested encapsulating peritonitis.	Encapsulating peritonitis	PLE by vascular disease (increased interstitial pressure)	Surgical intervention
Case 7 Male 40-years-old	Serum albumin: 2.9mg/dL AST: 698U/L ; ALT: 826U/L ; INR:5.15 Abdominal Doppler-ultrassonography: portal vein thrombosis and ascites. Angiography by computerized tomography: hepatomegaly and acute thrombosis of the portal and hepatic veins - acute Budd-Chiari Syndrome. 99mTc-labeled human serum albumin scan: protein loss across the small intestine.	Acute Budd-Chiari Syndrome	PLE by vascular disease (increased interstitial pressure)	The patient remained on worsening of liver function and died from septic shock (there was no time for introduction of specific therapy).

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Encapsulating peritonitis, first described in 1907 by O'Wtschinnikow [27], can be classified as idiopathic or secondary, the latter one being more common. While most commonly related to peritoneal dialysis, any inflammatory process, whether infectious or not, can lead to this complication. Its most frequent manifestation consists in abdominal pain associated with bowel subocclusion [27,28], being PLE an unusual presentation, as is the case 6. The surgical interventions led to a chronic inflammation of the peritoneum, forming a fibrous capsule surrounding the bowel. This imprisonment led to a persistent and ongoing inflammatory process, damaging the intestinal mucosa, increasing its permeability, but mostly, this process also caused a lymphatic obstruction, contributing to the PLE presented by this patient. In case 7, what was observed was an increased pressure venous secondary to portal and hepatic veins thrombosis, leading to a sub-acute increased lymphatic pressure. In this situation, treatment options would be the clearing of the portal system through TIPS or liver transplantation. Both were unfortunately not possible (Table 5).

Conclusion

Protein-losing enteropathy is a clinical condition that can complicate a variety of gastrointestinal and systemic diseases, with pathophysiological mechanism still poorly elucidated. The most commonly described causes in literature are inflammatory bowel disease, systemic lupus erythematosus and Fontan operation.

Here we describe a variety of uncommon etiologies of this disease and treatment approaches. It has been shown that the prognosis of these patients depends mainly on the primary disease and its specific treatment. But in some situations, where it is not possible to define the associated disease, protein loss can be stopped with measures based on its possible pathophysiological mechanisms.

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