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Does intestinal obstruction influence hypo-albuminemia: assessment of the physio-pathogenesis of protein-losing enteropathy with literature review

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Abstract. – BACKGROUND: Non-steroidal anti-inflammatory drug (NSAID) use may cause diaphragm-like lesions in the bowel. Although NSAID-enteropathy is among the causes of protein-losing enteropathy (PLE), intractable hypoalbuminemia is rare.

CASE REPORT: Here, we discuss a case of NSAID-enteropathy with a diaphragm-like disease that presented with Protein Losing Enteropathy (PLE) rather than obstruction. The hypoalbuminemia recovered immediately after resection of the obstructive segment, despite ongoing annular ulcerations in the early postoperative period. Thus, it was not clear whether obstructive mechanisms influenced resistant hypoalbuminemia besides the ulcers. We also reviewed the English-written literature for "diaphragm-type lesion, NSAID-enteropathy, obstruction, and protein-losing enteropathy". We noted that the role of obstruction in the pathophysiology of PLE was not clear.

CONCLUSIONS: As our case and a couple of cases reported in literature, slow-onset obstructive pathology seems to contribute to well-known factors: inflammatory response, exudation, tight-junction dysfunction, and increase in permeability in the physiopathology of NSAID-induced PLE. Factors such as distention-induced low-flow ischemia and reperfusion, cholecystectomy-related continuous bile flow, bacterial overgrowth-related bile deconjugation and concomitant inflammation are among other potential influencers. The possible role of a slow-onset obstructive pathology in the physiopathology of NSAID-induced and other PLE needs to be further elucidated.

Key Words:
NSAIDs, Protein-losing enteropathy, Hypoalbuminemia, Obstruction, Diaphragm-type lesion.

Introduction

Protein-losing enteropathy (PLE) can be defined as the loss of serum proteins in more than physiologic amounts from the gastrointestinal (GI) tract with clinical consequences, such as hypoalbuminemia and associated edema. Non-steroidal anti-inflammatory drugs (NSAIDs) have GI adverse effects that may range from small aphthous ulcerations to rare circumferential ulcers with various degrees of luminal narrowing called diaphragm-like lesions, and result in GI protein loss[1].

Here, we present a patient with NSAID-related distal small bowel ulcers on diaphragm-like lesions and severe intractable hypoalbuminemia. The relative narrowing of the small intestinal lumen was the possible leading cause. Furthermore, we reviewed the literature of NSAID-enteropathy, obstruction, and protein-losing enteropathy for possible pathophysiological mechanisms and we discussed the possible physiologic mechanisms behind intractable hypoalbuminemia in mild small bowel obstruction due to NSAID-enteropathy.

Case Presentation

A 57-year-old male patient presented with a complaint of swelling in his legs (for 4 months)

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and watery diarrhea 5-6 times per day (for the last 1.5 years). He reported 15 kg weight loss in the last 6 months. His medical history was unremarkable except for a cholecystectomy performed 22 years ago. He had been habitually using paracetamol/diclofenac/flurbiprofen five times per week in various combinations for nearly 35 years. He told he was using these analgesics for headache and foot pain. Detailed investigations could not reveal any cause for his chronic leg pain and headache. The patient was hospitalized and all NSAIDs were stopped. Physical examination revealed pretibial edema, moderate ascites, and bibasilar crackles. Laboratory tests showed a very low level of serum albumin (1.82 g/dL). We noticed that the albumin level could be temporarily increased to 2.5 g/dL with aggressive intravenous albumin replacement, but it decreased to basal levels very rapidly within 2-3 days. Abdominal ultrasonography (USG) and Doppler evaluation revealed ascites as only pathology. The ascites albumin and total protein levels were 0.4 g/dL and 0.7 g/dL, respectively. The serum ascites albumin gradient was 1.4. There was no urinary protein loss in the 24-hour urine specimen. Initial laboratory test results are summarized in Table I. Diagnostic tests for celiac disease, connective tissue disorders, and vasculitis were negative. Inflammatory bowel disease (IBD) or particularly Crohn disease (CD) suggestive markers, p-ANCA, c-ANCA, and ASCA were also negative. Cardiac functions were evaluated using transthoracic echocardiography, which showed no abnormalities with an ejection fraction of 55%. Upper and lower GI endoscopy were normal. There were no signs of lymphangiectasia, amyloidosis, celiac, or Whipple disease in the biopsies taken from the duodenum, terminal ileum, and various colon segments. Alpha-1-antitrypsin (AAT) clearance assessment was not performed, because it was not available in the institution. Nano-colloid lymphoscintigraphy resulted as heterogeneous activity in the distal colon and rectosigmoid lumen in the late (24 h) series, which was highly suggestive for intestinal protein loss. Due to the lack of scintigraphy positivity in the early period, we could not determine the exact location of the protein loss. However, late phase positivity in the colon indicates a protein loss proximal to this area, and intestinal origin. Abdominal magnetic resonance imaging (MRI) showed wall thickening in a small segment pelvic ileal loop, and ileal dilatation up to 4 cm in diameter proximal to this segment. During 8 weeks of inpatient care, despite nutritional support and albumin replacement, the patient had persistently low serum albumin levels. Finally, a diagnostic laparoscopy was planned for the ileal segment with the wall thickening. Laparoscopy revealed edema and stiffness suggesting intussusception in a 10 cm ileal segment, which was approximately 100 cm proximal to the ileocecal valve. An ileal segment of 17 cm was resected, and a double barrel-shaped ileostomy was done. Immediately after the resection, despite the relatively high-volume discharge of ileostomy, the patient's albumin level started to increase. Without any further albumin support, serum albumin levels reached 3.5 g/dL 2 weeks after the resection (**Supplementary Figure 1**). The fecal calprotectin level of proximal ileal stool was 180 mcg (normal <50 mcg). A follow-up endoscopic evaluation revealed normal

Table I. Initial laboratory findings of the patient.

Parameter	Value	Parameter	Value
Hemoglobin (g/dL)	9.7	Sodium (mmol/L)	131
Hematocrit (%)	30.5	Potassium (mmol/L)	3.8
Mean corpuscular volume (fL)	70	Chlorine (mmol/L)	89
Leukocyte (10^3/µL)	9.7	Phosphorus (mg/dL)	3.4
Neutrophil (10^3/µL)	6.6	Magnesium (mg/dL)	1.69
Thrombocyte (10^3/µL)	731	Calcium (mg/dL)	6.8
Albumin (g/dL)	1.82	Lactate dehydrogenase (U/L)	143
Total protein (g/dL)	3.7	Iron (µg/dL)	21
INR	1.2	Total iron binding capacity (µg/dL)	114
AST (U/L)	9	Ferritin (ng/mL)	18
ALT (U/L)	8	Vitamin B12 (pg/mL)	570
Alkaline phosphatase (U/L)	69	Folic acid (ng/mL)	11
Gamma-glutamyl transferase (U/L)	10	C-reactive protein (mg/L)	9.5
Total bilirubin (mg/dL)	0.36	Urea (mg/dL)	30
Direct bilirubin (mg/dL)	0.21	Creatinine (mg/dL)	0.8

ileal mucosa at the distal loop of the double-barrel ileostomy, but four annular ulcers were observed within 15 cm of the proximal (afferent) loop. Ulcers were situated on diaphragm-like circumferential thickening of the lumen.

The last evaluation through the ileostomy was at post-op 6 months, all annular ulcers were spontaneously healed, and serum albumin level was 4.0 g/dL. Closure of the ileostomy was performed.

Histopathology

There was a 1 cm annular fibrotic segment of obstruction in the resected ileum. The submucosal connective tissue increases, and hypertrophic muscularis propria in this segment were consistent with a diaphragm-like lesion. There were ulcerations limited to the submucosa, starting from the obstruction site, and extending to the proximal ileum. There were also multiple erosions in this region. The distal surgical margin showed congestive findings, while the proximal margin had erosive enteritis. An increased submucosal collagen-predominant connective tissue [elastin van Gieson (EVG) – Masson trichrome], neuronal proliferation, and lymph node edema were also noted in the resection specimen. No sign of chronic structural destruction suggestive of CD was reported. There was no amyloid accumulation, no specific infectious agent, and no granuloma in serial sections [Kongo, periodic acid-Schiff (PAS), diastase-PAS staining].

Post-operative endoscopic mucosal biopsies of the distal ileum, and endoscopically normal mucosa between the annular ulcerations of the proximal ileum showed no significant pathology; biopsies of the ulcer margin revealed granulation tissue, thickening of the muscularis mucosa, and an increase in peri-cryptal connective tissue.

Review of Literature

Protein Losing Enteropathy (PLE) may be a complication of many GI and non-GI diseases. Sustained loss of even small amounts of albumin may cause hypoalbuminemia. The clinical picture in most patients with PLE, can also be complicated by ascites, pleural effusions, and malnutrition of various degrees. Increased alpha-1 antitrypsin (AAT) clearance may be used to show protein leakage from the GI tract, but it cannot estimate the exact location of the protein loss. In our case, we were able to demonstrate the protein loss from the GI tract, and its cause through imaging studies and surgical intervention. Among diagnostic tests, functional (scintigraphy) imaging can show intestinal protein loss[2]. In our patient, accumulation in the late images showed that the pathology was in the GI tract, even though we could not point exact location with early scintigraphy positivity.

PLE etiologies are summarized in Table II[3,4]. Rupture of lymphatic ducts into the intestinal lumen due to increased interstitial or lymphatic pressure, tight junction dysfunction or exudation from erosive-ulcerative lesions may be the causes behind the GI protein loss. In our case, the inflammatory pathology, including the residual annular ulcers, and surgically removed obstruction, was restricted to approximately 30 cm segment of the distal ileum. More than half of the mucosal lesions were outside the resected segment. The mucosa between these lesions were both endoscopically and histologically normal. The resistant hypoalbuminemia improved briskly after the resection. Thus, it is not clear whether exudation from a few local ulcerations was the only cause of the PLE or if other obstruction-related mechanisms had any influence on the hypoalbuminemia (Figure 1).

Obscure bleeding increased intestinal permeability, mucosal erosions, and specifically annular ulcerations are associated with NSAID use[1,5]. Diaphragm disease, which is considered the only pathognomonic sign of NSAID enteropathy, may occur with chronic NSAID use and is a rare complication[6]. In a study performed with capsule endoscopy, the prevalence of diaphragm disease was 2% among chronic NSAID users[7]. Diaphragm-like lesions are more commonly observed in the ileum (sparing the terminal ileum) rather than the jejunum. These lesions can be multiple and close to each other. In our case, the diaphragm-like lesion, and four annular ulcerations with normal mucosa in-between, were all compatible with NSAID-enteropathy. As in our case, thickened submucosa and increased connective tissue may be regarded as the precursor of diaphragm-like lesions. The histologic assessment of the mucosa in between each diaphragm-like lesion is typically normal[8,9].

How NSAIDs cause PLE is not clear. Exudation from erosive, and ulcerative lesions is the generally accepted major factor. Animal experiments and *in-vitro* studies[10-12] have shown that luminal microorganism burden and bile acids enhance NSAID-enteropathy by stimulating intestinal inflammation and increasing tight junction dysfunction. In our case, the cholecystectomy-related sustained bile flow, and relatively increased levels of locally deconjugated bile acids

Table II. Etiologies of protein-losing enteropathy[3,4].

Erosive and ulcerative diseases	Non-erosive diseases
Inflammatory bowel disease	Celiac disease, Tropical sprue
GI tract malignancy, lymphoma	Hypertrophic gastropathies
NSAID enteropathy	Eosinophilic gastroenteritis
Infections (bacterial, viral, parasitic)	Lymphocytic gastritis
Pseudomembranous enterocolitis	Microscopic colitis
Erosive gastropathy	Connective tissue disorders
Ulcerative jejuno-ileitis	Small intestinal bacterial overgrowth
Graft-vs-host disease	Amyloidosis
Sarcoidosis	Whipple's disease
	Parasitic/viral infections
Increased interstitial pressure, lymphatic abnormalities	
Intestinal lymphangiectasia	Mesenteric venous thrombosis
Congestive heart failure	Sclerosing mesenteritis
Constrictive pericarditis	Mesenteric tuberculosis or sarcoidosis
Congenital heart diseases	Neoplasia involving mesenteric lymph nodes
Fontan procedure for single ventricle	or lymphatics
Portal hypertensive gastroenteropathy	Chronic pancreatitis with pseudocysts
Hepatic venous outflow obstruction	Congenital malformations of lymphatics
Enteric–lymphatic fistula	Retroperitoneal fibrosis

(induced by bacterial overgrowth due to sub-clinical obstruction) may support bile acid induced augmentation of NSAID enteropathy[13]. Irregularities of tight junctions and increased mucosal permeability also contribute to the process of albumin loss[14,15]. However, evident protein loss and the development of overt hypo-albuminemia are among the less common complications of NSAID-enteropathy. Resistance to intense albumin support was never mentioned in previous reports[16-18]. In a report of a 57-year-old female patient, hypoalbuminemia, which persisted despite NSAID discontinuation, regressed spontaneously after balloon dilation of the NSAID-induced

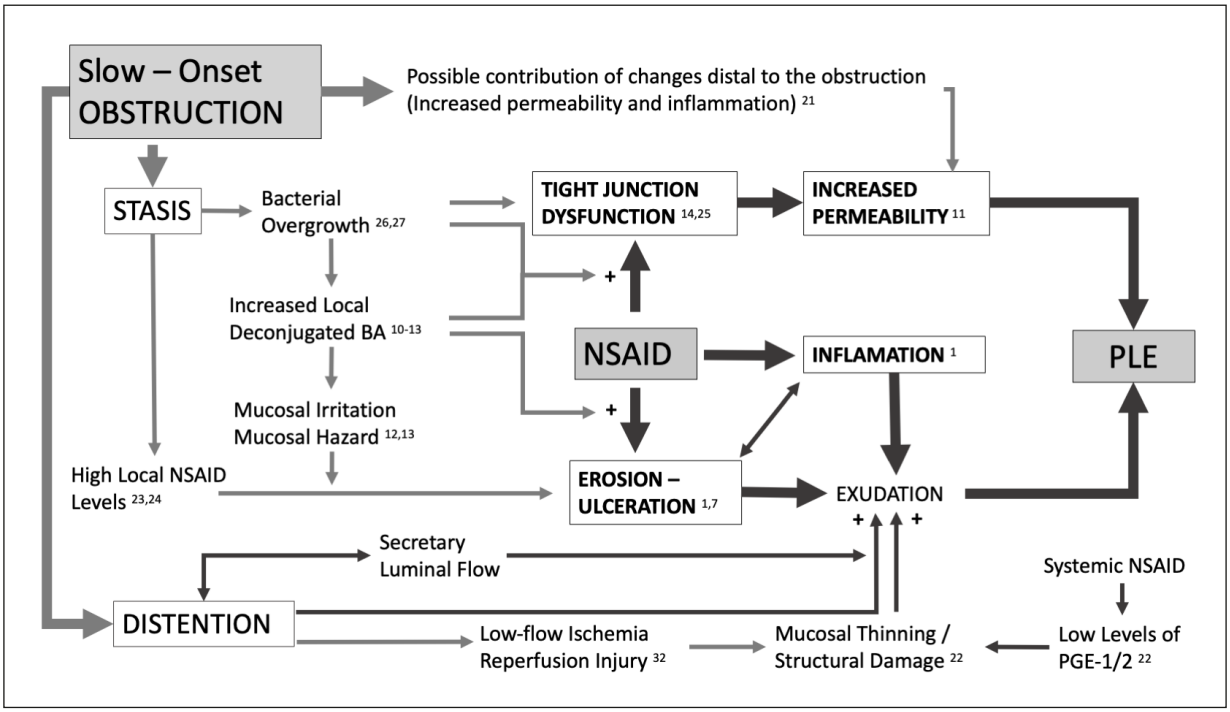

Figure 1. Interactions of slow-onset obstruction with NSAID-induced PLE pathogenesis.

Table III. Comparison of the presented case with reported cases in which PLE improved with the treatment of diaphragm disease-related obstruction.

Case	Bakkaloglu et al [Case presented]	Kamata et al[19]	Desmond et al[20]
Patient:	57 years old, M	57 years old, F	46 years old, F
Clinical presentation:	* Lower leg edema * Watery diarrhea * Weight loss	* Initially lower leg edema * Then nausea and vomiting	* Progressive obstructive symptoms * Weight loss
Laboratory:	* Replacement resistant hypoalbuminemia * Positive 99mTc-human albumin scintigraphy * Increased AAT clearance	* Hypoalbuminemia (Resistance data N/A) * Positive 99mTc-human albumin scintigraphy	* Hypoalbuminemia (Resistance data N/A) * Increased AAT clearance
Diagnostic modality:	* MR enterography	* Double balloon enteroscopy	* MR enterography
Localization of the diaphragm disease:	* Distal ileum	* Proximal and distal jejunum	* Mid-distal jejunum
Treatment modality:	* Surgical resection	* Endoscopic balloon dilatation	* Surgical resection * Surgical stricturoplasty

diaphragm-like lesions (Table III)[19]. Another patient presented with significant hypoalbuminemia and recovered totally after surgical resection and strictureplasty of multiple intestinal diaphragm-like lesions (Table III)[20]. These two case reports are in line with our observation and suggest that NSAIDs may cause hypoalbuminemia due to the disruption of luminal bowel flow. However, the authors in both cases did not mention whether any albumin replacements were administrated. In our case, hypoalbuminemia recovered immediately after the resection of the obstructive segment. Although the annular ulcerations persisted for at least 5 months following the segmental resection, attaining normal albumin levels suggests that the obstructive pathophysiology may have an effect on PLE, and hypoalbuminemia.

The possible contribution of obstruction to the pathophysiology of PLE has not been elucidated in the literature. In the experimental models, obstruction-induced luminal changes are more pronounced proximally, but they are not limited to there. In a rat model of intestinal obstruction, inflammatory change in the distal were also seen, and there was an increase in the mucosal permeability for horseradish peroxidase in the intestinal wall distal to the obstruction site[21]. Experimental intestinal obstruction in rats induces thinning in the mucus layer, structural damage, increased bacterial load and translocation. Prostaglandin E1 and E2 have ameliorating effects on obstruction-induced mucosal injury. Thus, NSAID-induced mucosal injury may be more pronounced in an obstructive background[22]. The fact that NSAID-induced colopathy is more common with enteric-coated or slow-release pills underlines the importance of local drug concentrations[23,24]. The slowed passage due to obstruction may cause the proximal of stenotic area to be more susceptible to NSAID enteropathy. *In-vitro* experiments[25] reported that NSAIDs and acetylsalicylic acid cause decreased expressions of cell junction proteins. Electron microscopy images illustrated severe distribution of electron-dense material of the tight junction ultrastructure[25]. Obstruction-induced bacterial overgrowth, which is more pronounced in the ileum than the jejunum, may also influence enteropathy[26,27]. Bacterial overgrowth may cause the above-mentioned increase in deconjugated bile acids, which further potentialize NSAID toxicity[13]. These factors contribute to inflammatory changes, destructs mucosal integrity, increases intestinal permeability for small molecules, and stimulates plasma-like fluid secretion into the lumen[26,28,29]. This secretion can be modified by adrenoreceptor blockage. So, in addition to inflammation, enteric neuronal stimulation may also contribute to this process[30]. An animal study[31] showed that luminal distention could decrease blood and oxygen delivery to the bowel wall, may result in low-flow ischemia, and related reperfusion injury after decompression. This ischemia and reperfusion injury cycle may further contribute to mucosal injury in recurrent sub-clinical obstructions. In our case, even though the ulcerations persisted, the quick normalization of albumin levels after the obstruction was eliminated suggests a prominent effect of the obstructive pathology in intestinal protein loss.

This supports the need to investigate the possible pathologic role of obstruction in PLE in more detail (Figure 1). Additional influence of the bacterial overgrowth-related inflammation in bowel permeability and albumin loss cannot be ignored. However, with the control of inflammation and normalization of CRP level after antibiotic treatment, the persistence of hypoalbuminemia suggests this factor has a minor influence.

Another well-known GI disease that can cause ulcerations, protein loss, obstructive pathology is Crohn's disease (CD). Our patient's clinical presentation, histopathology, and laboratory markers were not consistent with CD. CD may cause long-segment mucosal involvement with deep ulcerations, and frequently be complicated with obstruction. The exudation from erosion or ulceration, increase in lymphatic pressure due to granulomatous inflammation, or the development of lymphangiectasia, may all contribute to intestinal protein loss and eventually hypoalbuminemia in CD[32]. However, despite mucosal lesions are common, severe PLE resistant to albumin support is a very rare phenomenon in stenosing CD. Rare cases of PLE in patients with stenosing CD, with the normalization of albumin levels after resection have been reported[32-34]. In CD, due to the submucosal involvement and full-thickness fibrotic disease, the destruction or blockage of lymphatics may be seen. This possibly has a restrictive effect on intestinal protein loss[35-37]. This gradual destruction of the intestinal wall and lymphatic obstruction may be why we do not usually see severe and resistant hypoalbuminemia in CD.

Finally, severe intractable hypoalbuminemia is quite rare in acute obstructive pathologies, such as adhesive ileus. The development of NSAID-related obstruction is a much slower process, gradually disturbing the intestinal flow. However, the relatively protected mucosal integrity in rapidly developing obstructions, suggest that various parameters would have been necessary for the development of PLE.

Conclusions

Here we discussed a case of NSAID enteropathy with a diaphragm-like disease, which presented with PLE. Our patient had severe intractable hypoalbuminemia rather than prominent obstructive symptoms. Although NSAID enteropathy is cited among the causes of PLE, accompanying intractable hypoalbuminemia is very rare. The possible contribution of the slow-onset obstructive pathology to the well-known factors (such as inflammatory response in the intestinal wall, exudation from mucosal injury, and increase in intestinal permeability), needs to be elucidated more in the physiopathology of NSAID-induced PLE. With the review of the limited literature, and through this case we finally conclude that the obstruction may have a role in severe albumin loss on top of already-established NSAID enteropathy and may have created a vicious circle that resulted in resistant hypoalbuminemia.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Informed Consent

Patients gave full consent for clinical and histopathologic information relating to this study and agreed this information to be reported in a medical publication.

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