Protein-losing Enteropathy in Crohn's Disease

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Abstract

Protein-losing enteropathy (PLE) is a rare but severe complication of Crohn's disease (CD) and hypoalbuminemia can be one of the presenting symptoms of this illness. The diagnosis of PLE can only be made after exclusion of malnutrition and liver or kidney failure. Significant intestinal leakage can be caused by mucosal injury, increased lymphatic pressure or dilated lymphatics and has been reported in a large number of diseases. The protein-losing can be diagnosed by assessing the excretion of different radiolabeled macromolecules in the faeces or by the clearance of alpha-1-antitrypsine in stools. The primary approach should be the optimization of the nutritional status. Medical treatment of the underlying disease is primordial. In other cases surgical resection of the most affected areas is inevitable.

We report a case of a 21-year-old male with a 4 year history of CD, who developed significant hypoproteinemia with pitting oedema, initially in the absence of any other sign of severe disease activity. A ^{51}Cr-chloride albumin excretion confirmed our hypothesis of protein-losing enteropathy. Because of sub-obstruction signs some months later, a laparotomy was performed which revealed a severely affected loop with dilatation of the proximal jejunum. Interestingly, multiple large lymph nodes and dilated lymphatics were seen. A partial jejunal resection was performed for stricturing Crohn's disease. Histology showed severe mesenteric granulomatosis, dilated lymph vessels and granulomatous vasculitis. After the resection our patient improved without further albumin infusions and the oedema resolved. (Acta gastroenterol. belg., **2006**, 69, **384-389**).

Key words : Crohn's disease, inflammatory bowel disease, protein-losing enteropathy, diagnosis, therapy.

Introduction

Albumin is the predominant product of hepatic protein synthesis and one of the more abundant plasma proteins. The serum albumin concentration reflects the rate of synthesis, the degradation, and the volume of distribution. Hypoalbuminemia is a common problem among persons with acute and chronic medical conditions. It can be caused by various entities, including nephrotic syndrome, hepatic cirrhosis, hearth failure, malnutrition and protein loss.

Since the potential causes of hypoalbuminemia are numerous, thorough patient's history taking and physical examination are primordial and will guide the further investigations. Laboratory studies might include inflammatory parameters (C-reactive protein and erythrocyte sedimentation rate), factors of malnutrition (lymphocyte count, blood urea nitrogen, transferrin), a 24-hour urine collection for protein analysis (cfr nephrotic syndrome), liver function test (cfr cirrhosis), faecal fat studies (cfr malabsorption), serum electrophoresis, ... Imaging studies may comprise liver ultrasound, small bowel series, echocardiogram, ... In cases were cirrhosis or nephrosis is suspected, a biopsy might confirm the tentative diagnosis.

Hypoalbuminemia can also be caused by gastrointestinal protein loss, but this diagnosis can only be considered after exclusion of malnutrition and both renal or liver disease. Some disease will influence the albumin status by several mechanisms. Gastrointestinal amyloidosis, for example, may lead to malabsorption due to mucosal infiltration, but is also associated with protein-losing enteropathy due to increased permeability and lymphatic vessel obstruction (1-4).

In this article we present a case of protein loosing enteropathy in a patient with Crohn's disease.

Case report

In December 2003 a 21-year old man presented for the first time to our out-patient clinic, after he had moved to a neighbouring city. The diagnosis of Crohn's disease (CD) with involvement of the entire gastrointestinal tract, had been established in 1999. The first gastroscopy revealed ulcerative disease of the stomach and the duodenum and the consecutive ileocolonoscopy showed aftoid lesions and small ulcerations in the entire colon and terminal ileum. Histology was suggestive of CD. The patient had initially been treated with 5-aminosalicylates and prednisolone. He had a positive family history with a diagnosis of CD in both his brother and grandmother. In February 2000 he underwent a laparoscopy because of radiological evidence of multiple mesenterial adenopathies. Pathological examination of full thickness biopsies revealed active ulcerative ileitis and the affected lymph nodes showed 'tuberculoid' granulomas suggestive of morbus Crohn. From 2000 till 2003 he was treated with azathioprine, oral

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Table 1. — **Blood and urine analysis**

	3 months prior to surgery	1 week prior to surgery	2,5 months after surgery	
Haemoglobin	12.8	12.1	12.6	(14.0 – 18.0 g/dL)
MCV	82.2	79.0	79.8	(76.0 – 96.0 fL)
MCH	25.3	24.9	25.0	(27.0 – 32.0 pg)
WBC	8.2	10.3	6.5	(4.0 – 10.0 10^9/L)
Neutrophils	78.4	79.1	66.4	(38.0 – 77.0%)
	6.4	8.1	4.3	(2.5 – 7.8 10^9/L)
Lymphocytes	8.5	8.4	15.8	(20.0 – 50.0%)
	0.7	0.9	1.0	(1.5 – 3.5 10^9/L)
CRP	36.8	56.4	18.9	(< 5.0 mg/L)
Urea	19	23	20	(< 50 mg/dL)
Creatinin	0.73	0.93	0.90	(0.70 – 1.30 mg/dL)
Total protein	50	43	57	(66 – 87 g/L)
Albumin	24.3	20.7	33.4	(35.0 – 52.0 g/L)
Iron	28	11	33	(65 – 175 µg/dL)
Transferrin saturation	–	7	13	(16 – 45%)
Ferritin	52	109	23	(15 – 300 µg/dL)
Vitamin B12	169	234	258	(170 – 800 ng/L)
Folic acid	137	186	146	(170 – 480 µg/L)
Proteinuria	0.26	0.07	–	(< 0.12 g/L)

budesonide, methotrexate and infliximab, after exclusion of tuberculosis. Except for oral budesonide and his first infusion of infliximab, all of these had proven to be ineffective. Because of persisting hypoproteinemia and iron deficiency anaemia, he needed regular infusions with human albumin and iron sucrose. A radiological barium follow-through in 2003 showed severe ulcerative ileitis and jejunitis without strictures or bowel dilatation.

At the first visit to our clinic the patient reported slumbering abdominal discomfort with normal stools and a stable weight under 6 mg of oral budesonide. When he presented the patient was pale and he had pitting oedema at both ankles. The abdominal examination was normal. Blood analysis (Table 1) showed minor inflammation, lymphopenia, hypoproteinemia with hypoalbuminemia, hypochromic anaemia with possible iron deficiency, normal liver and kidney function without any sign of proteinuria on a urine sample. There were also signs of malabsorption (low Vitamin B12, low folic acid). We continued oral budesonide and supportive treatment with iron sucrose and human albumin monthly. Substitution with Vitamin B12 and folic acid was started.

A stool collection after administration of 884.21 counts of ^{51}Cr-chloride radiolabeled albumin intravenously was used to confirm our hypothesis of protein losing enteropathy. 416.12 counts or 49% of the administered dose was found in a 4 day stool collection, suggestive of major protein loss in the gastro-intestinal tract (normally less than 1%). To exclude vasculitis abdominal MRI angiography was done. No large vessel vasculitis was demonstrated.

Because of the treatment failure with increasing stool frequency and abdominal discomfort we restarted anti-TNF treatment, early January 2004. He initially reported significant improvement after the first doses, but at the end of that month he was hospitalized with signs of sub-obstruction under 9 mg of oral budesonide. The lower abdomen was very painful on clinical examination, but there was still normal peristalsis. The initial inflammation had increased and the patient was still hypoalbuminemic (Table 1). A plain radiograph of the abdomen showed multiple air-fluid levels and dilated small bowel loops. The diagnosis of sub-obstruction was confirmed by a computed tomography, which showed multiple Crohn's lesions, predominantly in the proximal ileum and the duodenum. A barium enteroclysis revealed segmental enteritis and two or three significant short strictures with prestenotic dilatation (Fig. 1).

We decided to refer the patient for abdominal surgery. During laparoscopic exploration a severely affected loop of about 60 cm was found, 2 meters proximal to the ileocecal valve and some smaller skip lesions more proximally in the jejunum. The proximal jejunum was dilated (Fig. 2). Interestingly dispersed areas of dilated lymphatics were apparent on the serosal coat, without evidence of lymphangiomata (Fig. 2) but with multiple large lymph nodes in the mesenterium of these loops. A partial jejunal resection was performed.

Pathological examination confirmed the diagnosis of stricturing CD with dilated lymphatic vessels suggestive of lymphatic obstruction (Fig. 3A) and granulomatous vasculitis. The resected mesenteric lymph nodes showed non-caseating epithelioid granulomas (Fig. 3B).

Two and a half months after the resection the patient was free of oedema without further need for human albumin infusion. The albumin and lymphocyte levels were increasing (Table 1) and the iron levels had improved, but remained rather low.

Discussion

The case presented in this paper illustrates the role of severe mesenteric granulomatosis in refractory hypoalbuminemia as one of the presenting symptoms in Crohn's disease.

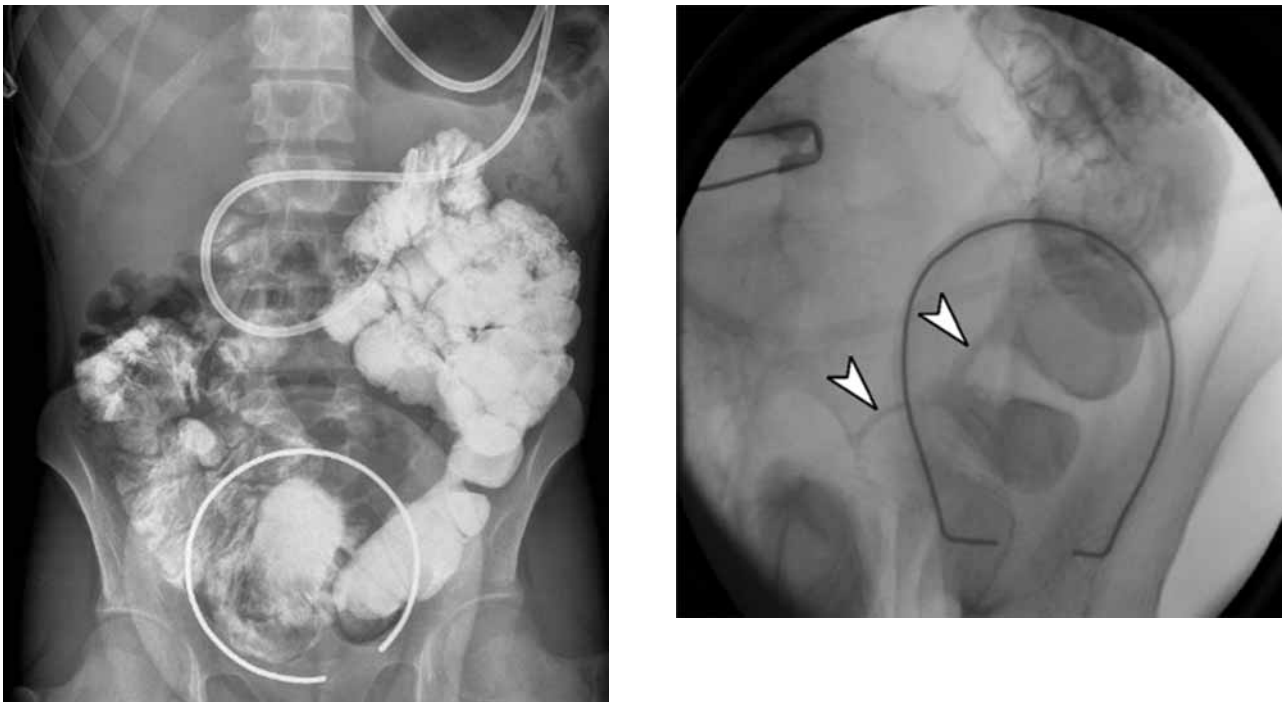

Fig. 1. — Enteroclysis. Left : Asymmetrical ileal strictures with prestenotic dilatation. Right : Two short important strictures (arrowheads) with a pseudodiverticulum and prestenotic dilatation.

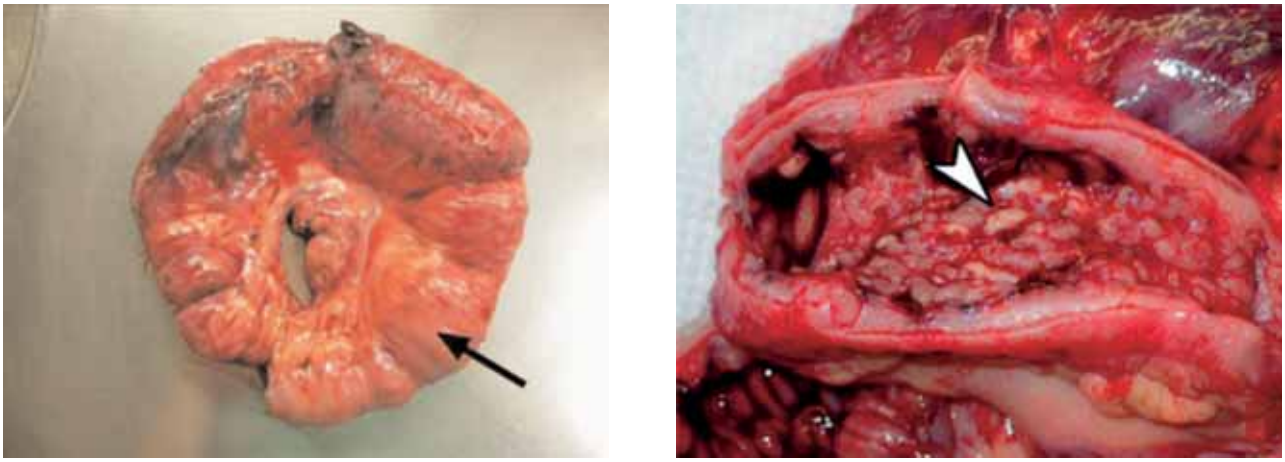

Fig. 2. — Peroperative photographs of affected jejunal segments. Left : dilated bowel loops with lymphatics at the serosal side (arrow). Right : jejunal segments with exposed mesenterium containing enlarged lymph nodes (arrowhead).

Hypoproteinemia has been recognized as a complication of Crohn's disease for more than forty years, but there has been a longstanding debate on the precise origin of low serum albumin levels. Theoretically, hypoalbuminemia and hypoproteinemia originating from the gastrointestinal tract may have three different aetiologies : decreased albumin synthesis in the liver due to an acute phase response, malabsorption of proteins and amino acids and, finally, intestinal protein losing. As indicated in the recent review by *Belaiche and Louis*, Crohn's disease is one of the major causes of malabsorption (5).

Although malabsorption is common in Crohn's disease, *Steinfeld et al.* reported already in 1960, that malabsorption alone is probably not the dominant reason for the hypoproteinemia seen in CD, because severe malnutrition in healthy volunteers provoked only slight reduction in levels of plasma protein and amino acids (6). This observation confirmed an old hypothesis of protein exudation in the inflamed bowel wall, currently known as protein-losing enteropathy (PLE).

Protein-losing enteropathy is characterized by an excessive loss of serum proteins into the gastrointestinal tract which results in typical signs as hypoalbuminemia, anasarc oedema, and sometimes pericardial and pleural effusions. Loss of other proteins like gamma globulins, fibrinogen, transferrin and ceruloplasmin are also

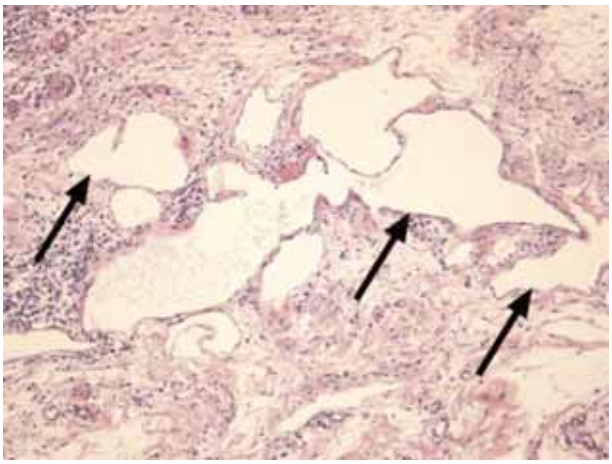

Fig. 3A. — Light microscopic photograph of dilated lymphatic channels (arrows) in the inflamed jejunal serosa (HE ×100).

observed, even as secondary fat and carbohydrate malabsorption with fat-soluble vitamin deficiencies. The diagnosis can only be considered after exclusion of malnutrition and renal or liver disease.

Three mechanisms have been proposed as a cause for the increase in intestinal leakage of plasma proteins (Table 2). First, mucosal injury with or without frank erosions or ulcerations such as in inflammatory bowel disease and celiac disease, may be the cause of protein losses. Alternatively, it may be secondary to increased lymphatic pressure in the gut due to granulomatous or neoplastic involvement of the lymphatic system. Moreover, in patients with lymphatic obstruction, loss of lymphocytes into the gut can produce significant lymphocytopenia, like in our patient. Finally, in intestinal lymphangiectasia, dilated lymphatics leak protein in the mesenteric space or in the gut lumen (7).

To confirm the diagnosis of PLE numerous diagnostic tests have been proposed. Steinfeld *et al.* used I^{131}-labeled albumin excretion in stools (6). Because of the possible thyroid toxicity with I^{131} alternative scintigraphic methods with radiolabeled macromolecules have been proposed, such as nuclear imaging of PLE after intravenously administration of 99m-Technecium (8-10). One of the main disadvantages of the latter procedure is the need for serial image acquisition during the first 24 hours.

The assessment of alpha-1-antitrypsine (A1AT) clearance and ^{51}Cr-albumin excretion in stools have also been validated to test for PLE (11-15). Alpha-1-antitrypsin clearance is the only non-isotopic method for the detection of PLE and also the most inexpensive. A1AT is an endogenous protein marker and it can be measured in faeces and blood by radial immunodiffusion. Hospitalization is not required.

The ^{51}Cr-albumin test, as performed in this case, has been developed in 1972 by Beeken *et al.* (11). They found an excessive loss of protein in a subgroup of patients with CD. In some of them the impact of protein loss on serum protein levels was relatively modest, probably because of sufficient compensation through synthesis in the liver. Nordgren *et al.* studied 69 patients with CD (12). After intravenous injection of trace amounts of $^{51}CrCl_3$-human albumin they investigated a 5-day stool collection. They found a close correlation between faecal excretion of ^{51}Cr and the extent of the small-intestinal disease as measured at laparotomy. This test appears to be the most accurate at this moment and is used as the golden standard.

Florent *et al.* reported that the sensitivity of the A1AT test for PLE compared to ^{51}Cr is 93.3%, specificity 90%, positive predictive value 97.7% and negative predictive value 75% (13). But Quigley *et al.* only found a sensitivity and specificity of 58% and 80% respectively (14). They concluded that faecal A1AT excretion indeed correlated with ^{51}Cr-albumin for a whole group of patients, but was not reliable for the measurement of enteric protein loss in an individual person.

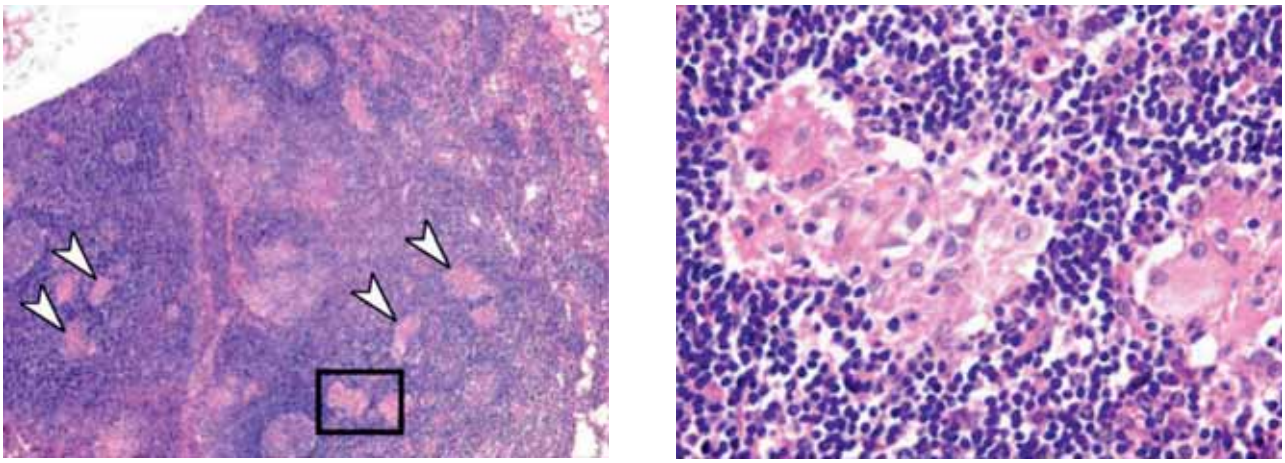

Fig. 3B. — Left : Light microscopic photographs showing a mesenteric lymph node with multiple non-caseating epithelioid granulomas (arrowheads) (HE ×50). Right : Enlargement of a granuloma (HE ×400).

Table 2. — **Major causes of protein-losing enteropathy**

Inflammatory exudation due to mucosal erosions or ulcerations
Inflammatory bowel disease
Gastro-intestinal malignancy
Pseudomembranous colitis
Erosive gastritis and multiple gastric ulcers
Post-chemotherapy
NSAID enteropathy
Increased permeability due to mucosal disease without erosions or ulcerations
Celiac disease
Tropical sprue
Giant hypertrophic gastritis
Lymphocytic gastritis
Secretory hypertrophic gastropathy
Amyloidosis
Infections
Rheumatic diseases
Allergic gastroenteropathy
Eosinophilic gastroenteritis
Collagenous colitis
Intestinal loss of lymphatic fluid due to lymphatic obstruction
Intestinal lymphangiectasia
Right-sided hearth failure
Cirrhosis
Hepatic venous outflow obstruction
Enteric-lymphatic fistula
Mesenteric tuberculosis or sarcoidosis
Intestinal lymphoma
Chronic pancreatitis with pseudocysts
Crohn's disease
Whipple's disease

In addition, the amount of protein loss may be an alternative for the CDAI to assess disease activity. Some authors propose to use gut lavage test in children, patients with a stoma, stricturing disease and in psychiatric patients in whom CDAI is not accurate (16). Biancone *et al.* recently suggested the use of faecal A1AT clearance as a marker to predict clinical relapse in patients with CD (15).

The first and obvious treatment of PLE is the maintenance of the nutritional status. In some cases correction of the underlying disease, e.g. gluten-free diet in celiac disease, will already resolve the symptoms. Surgical resection of the most affected areas can ameliorate this condition but carries the risk of repeated resection and short bowel. Albumin substitutions and total parenteral nutrition may be an alternative. In very severe cases with a short bowel syndrome, small bowel transplantation should be considered.

Our patient had an important hypoalbuminemia at diagnosis without signs of severe inflammation. Therefore, the degree of hypoproteinemia was incongruent with the severity of the Crohn's disease. Radiological findings a year after diagnosis, however, revealed important mesenterial adenopathies. These were confirmed at laparoscopy, which showed multiple large lymph nodes in the mesenterium. Indeed, during laparoscopy and laparotomy three years later dilated lymphatics were visible at the serosal side of the bowel wall in segments with severe mesenteric involvement. On histology, granulomas were abundant in these large lymph nodes and dilatation of lymphatics was confirmed. Therefore, the hypoalbuminemic status was probably aggravated by lymphatic pressure. Granulomatous vasculitis, as diagnosed in our patient, is seen in about 20% of the CD patients (17). It probably is a secondary phenomenon of the disease and not the primary lesion in the inflammatory cascade of CD. Also, multiple strictures were observed in the intestine, but only with barium enteroclysis. The severe stenotic disease had not been diagnosed on barium follow-through 6 months earlier.

Using Medline we have come across only two case reports describing PLE as the predominant cause of hypoalbuminemia in the absence of severe inflammatory CD. Raju *et al.* presented a 43-year old patient with severe anaemia and hypoproteinemia without any gastrointestinal complaints or signs of inflammation (18). The hypoalbuminemia couldn't be explained by malnutrition, liver or renal failure. Of the intravenously administered ^{51}Cr EDTA 4.5 % was excreted in the faeces (normal < 3%). A barium meal showed two small bowel strictures and dilated proximal loops of jejunum. After resection the albumin and haemoglobin levels normalized. Final histological examination diagnosed CD.

A more recent case of hypoproteinemia in a 22 year old known CD patient was reported by Baert *et al.* (9). The patient was hospitalized for weight loss despite a normal diet. He had melena, microcytic anaemia, a prothrombin time of 3% (INR > 8) suggestive of vitamin K deficiency, no significant proteinuria and normal liver tests. Further examinations revealed stenotic strictures at the level of the sigmoid, transverse colon, terminal ileum and proximal jejunum. A functional study of the lymphatic system with 99m-Tc showed leakage of chyle into the intestinal lumen, contributing to the severe deficiencies of protein, fat and lymphocytes. This patient was helped with a low-fat, high-protein diet, substitution with iron, calcium and vitamins, and immunosuppressive therapy with azathioprine. At that moment the biochemical and clinical parameters improved without the need for surgical intervention.

We conclude that protein-losing enteropathy is a rare but severe complication of Crohn's disease. In some patients it may be the main clinical feature at diagnosis. Our case illustrates that an extensive diagnostic assessment is needed to define the most appropriate treatment strategy. Although surgical resection is not curative in CD, in patients with severe mesenteric involvement and stenotic disease it may be the best choice to ascertain clinical improvement, including correction of protein loss. Post-operative medical follow-up with immune modulator therapy in case of remaining active disease, however, is of paramount importance.

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