Child with protein losing enteropathy as presentation of collagenous duodenitis and eosinophilic gastroenteritis

K. van Hoeve[1], M. De Keukelaere[1], G. De Hertogh[2], I. Hoffman[1]

(1) Department of Pediatric Gastroenterology & Hepatology & Nutrition, University Hospitals Leuven, KU Leuven, Leuven, Belgium; (2) Department of Anatomopathology, University hospital Leuven, KU Leuven, Leuven, Belgium.

Abstract

Background: **Collagenous duodenitis and gastritis are rare histopathological findings in children.**

Patients and methods: We describe a four-year old girl, who presented with non-bloody diarrhea for two months and progressive edema with an albumin of 16g/dl.

Results: **The diagnosis of a protein losing enteropathy was made. Extensive investigations withheld only an infectious cause of the protein losing enteropathy (cytomegalovirus and adenovirus). However, the patients still required repetitive albumin infusions 3.5 months after onset of symptoms without spontaneous recovery. Therefore, a new endoscopic work-up was performed. Duodenal biopsies revealed collagen deposition, in association with a high number of eosinophils and mast cells throughout different parts of the gastrointestinal tract.**

Conclusions: **The collagen deposition seems to be triggered by an eosinophilic gastrointestinal disorder. Treatment was started with amino acid-based formula, oral iron therapy, an antihistamine, and a proton pomp inhibitor that resulted in persistent normalization of serum albumin already after 1.5 weeks.** (Acta gastroenterol. belg., **2023, 86, 363-366**).

Introduction

Collagenous gastroenteritis is a rare histopathological finding in children. Colletti and Trainer (1) first described this disorder in 1989. Since then, only 45 cases have been reported worldwide with absence of solid recommendations for treatment management so far (2). We report a four-year-old girl, who presented with protein losing enteropathy (PLE) associated by this condition.

Case report

A previously healthy four-year-old girl was transferred to our hospital with progressive orbital and peripheral edema of the lower limbs. She had abdominal pain, non-bloody diarrhea and intermittent vomiting for two months. Previous tests revealed negative stool samples for bacterial cultures, virology (adeno-, rota-, norovirus) and parasites. Lactose-free diet prior to admission failed to ameliorate symptoms.

Physical examination showed generalized edema with 10% weight gain. Blood pressure was within the normal range for age and length. Initial laboratory findings (see table 1) showed mild iron deficient anemia in addition to decreased total serum protein concentration of 38 g/L (60-80g/L) and albumin of 16.3g/L (35-52 g/L). The hepatic

panel, creatinine, blood urea nitrogen, electrolytes, and C-reactive protein were within normal ranges. Urinalysis revealed no proteinuria. Functional imaging with Tc-99m serum albumin confirmed the diagnosis of PLE.

Extensive investigations (see table 1) withheld only an infectious cause: acute co-infection of cyto-mega-lovirus (blood, urine and nasopharyngeal swab) and adenovirus (stool sample and colonic biopsy) proven with PCR-testing. Broad screening for malignant neoplasms and autoimmune disorders were negative, including normal tissue transglutaminases. Initial eso-phagogastroduodenoscopy and sigmoidoscopy were normal, however the biopsies in the small bowel were only superficial and of minor quality. Negative anti-parietal cell antibodies and normal serum gastrin excluded an autoimmune atrophic gastritis. Serum-specific immunoglobulin E (IgE) testing showed normal total serum IgE, with mildly elevated values for egg white, cow's milk, and wheat. However, skin tests for these allergens were negative. Tryptase was also normal. During follow-up, peripheral eosinophilia increased progressively up to $1.7 * 10^9$/L.

The initial treatment consisted of albumin infusions (2-3 times a week) in combination with loop diuretics. Despite this supportive treatment, no positive evolution was seen 3.5 months after onset of symptoms, contrary to what one would expect in a case of PLE triggered by an infection which can last for up to two months (3).

Therefore, an endoscopy was repeated and showed macroscopic view of white dots suggestive of lymph-angiectasia, however not on histology. Instead, an increased number of eosinophils in the lamina propria of the stomach (40-50/high power field (HPF)), bulbus duodeni (70-80/HPF), second duodenum (120-130/HPF), and colonic mucosa (90/HPF) were reported in addition to increased mast cells in duodenum (80/HPF) and colonic mucosa (50/HPF), suggestive for an eosinophilic gastroenteritis. Esophageal biopsies were normal. Helicobacter pylori staining was negative. Discrete signs

Correspondence to: Karen van Hoeve, Department of Pediatric Gastroenterology & Hepatology & Nutrition, University Hospitals Leuven. Herestraat 49. 3000 Leuven. Belgium. Phone: +003216 343843. Fax: +003216 343842.
Email: karen.1.vanhoeve@uzleuven.be

Table 1. — **Summary of investigations**

Blood analysis		Ref. value			Ref value
Albumin (g/L)	16.3	35.0-52.0	IgG (g/L)	2.72	4.78-11.29
Total protein (g/L)	38	60-80	Tissue-transglutaminase (CU)	< 1.9	≤ 20.0
Creatinine (mg/dl)	0,37	0.26-0.42	ANA, ANCA, ASCA	Negative	
Ureum (mg/dL)	22	≤39	Smooth muscle, LKM-IgG	Negative	
Haemoglobulin (g/dL)	11.5	11.5-13.5	TPO, TSH, anti-parietal cell IgG	Negative	
Iron binding capacity (%)	5	16-45	NSE (µg/L)	15.6	≤ 16.3
Ferritin (µg/L)	10	13-150	Chromogranine A (µg/l)	187	< 84.7
WBC count ($10^{**}9$/L)	7.58	5.50 - 15.50	Peripheral blood smear	Normal	
Eosinophils (%)	1.8%	<3%	TSH (mIU/L)	1.73	0.27-4.20
CRP (mg/L)	2.5	<5	T4 (pmol/L)	11.9	12.9-23.2
ESR (mm/h)	<2	<20	Sialotransferrine	Negative	
Serology	EBV IgM EBV IgG EBV PCR	Positive Negative Negative	Tryptase (µg/L)	4.8	<11
			IgE total (kU/L)	143	<224
			Egg white (kU/L)	1.88	<0.10
	CMV IgG	Positive	Cows milk (kU/L)	0.73	<0.10
	CMV PCR	Negative	Wheat (kU/L)	0.12	<0.10
Urine analysis					
12 WBC/µl	Culture	CMV positive	Total protein/creatinine ratio	24 h catecholaminecollection	
0 RBC/µL	negative	(antigen + PCR)	normal	normal	
Stool analysis					
Bacterial culture	Clostridium	Adenovirus PCR	Entero- and Norovirus PCR	Negative parasite, Cryptosporidium, Giardia lamblia, Entamoeba histolytica PCR	
negative	negative	positive	negative		
Other investigation					
Tc-99m serum albumin confirmed PLE	Abdominal ultrasound and echo-cardiography normal		Barium swallow upper GI test normal	Histology of gastro- and sigmoidoscopy normal*	

* Two biopsies from five different locations were taken during the endoscopy (second duodenum, bulbus duodeni, stomach, distal oesophagus and sigmoid).
Legend: ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, ASCA: anti-*Saccharomyces cerevisiae* antibody; CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr-virus; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; h: hour; Ig: immunoglobuline; LKM: liver kidney microsome; NSE: neuron-specific enolase; PCR: polymerase chain reaction; PLE: protein losing enteropathy; RBC: red blood cell; Tc-99m: technetium-99m; TPO: thyroid peroxidase antibody; TSH: thyroid stimulating hormone; WBC: white blood cell.

of (intra)-epithelial damage were seen, without acute inflammation or villous atrophy. Thickened subepithelial collagen bands in the bulbus duodeni stained positively with tenascin, suggestive for collagenous duodenitis (Figure 1).

Hence, PLE was associated with collagenous duodenitis, probably triggered by an underlying food allergy as suggested by infiltration of eosinophils and mast cells in the gastrointestinal tract.

An exclusive amino acid-based diet (administered through a nasogastric tube) and an oral antihistaminicum were started to treat the underlying food allergy. In addition, high doses of proton pump inhibitor (2 mg/kg/day) were added to achieve an anti-inflammatory effect and iron-deficient anemia was treated with iron supplementation (both orally and intravenously). Clinical improvement was seen rapidly, with normalization of

serum albumin within 1.5 weeks, and this remained stable during a 1.5-year follow-up without extra albumin infusions. Gradually histological improvement was seen, with reaching a full histological remission of the eosinophilic duodenitis three months after changing treatment strategy. Since then, sequential reintroduction of different food groups was performed at a timely matter without relapse. At this time, cow milk and egg white are still eliminated from the food.

Discussion

We report a four-year-old girl who presented with PLE associated with collagenous duodenitis and eosinophilic gastroenteritis most likely triggered by food allergens. Although both disorders are rare in children, the combination of them is extremely rare and is more than fortuitous.
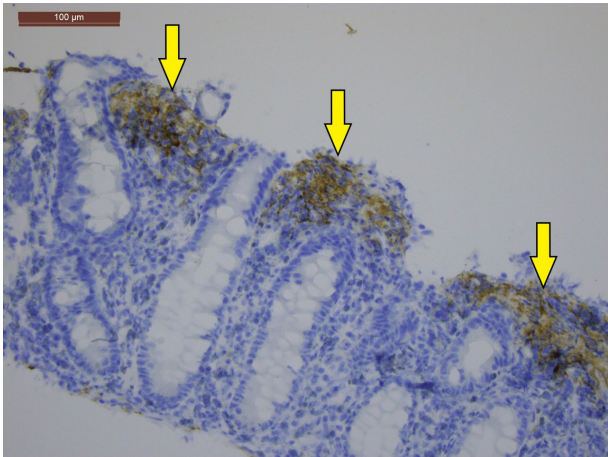
Figure 1. — Tenascine immunohistochemistry in the bulbus (arrows).

PLE is an uncommon condition characterized by an excessive loss of proteins into the gastrointestinal tract with diverse underlying causes. Several viral pathogens such as rotavirus, herpes simplex virus, or cytomegalovirus have been associated with PLE (4-5). As in our case, an infectious cause of the PLE (cytomegalovirus and adenovirus) was initially proposed.

However, the lack of spontaneous recovery after 3.5 months should raise one's suspicion for an alternative diagnose.

Collagenous depositions can affect multiple parts of the gastrointestinal system. Typical histopathological findings are: collagen band thickness > 10μm in the subepithelial mucosa, increased inflammatory cell infiltration in the lamina propria, and surface epithelial damage (6). This entity has a different presentation in adults than in children: in pediatric patients collagen deposition is preferentially limited to the stomach, where in adults the colon is more frequently involved (7). The adult phenotype is also more often associated with autoimmune diseases. Clinical presentation varies widely, ranging from abdominal pain and diarrhea to a more severe clinical picture with malabsorption and PLE. Persisting iron deficiency anemia can be the only presenting symptom due to bleeding from superficial capillaries entrapped in collagen (8).

The underlying pathogenesis is unknown. Several hypotheses have been proposed to explain the collagen deposition: (A) as a result of chronic inflammation and/or an autoimmune mechanism, (B) abnormalities of the pericryptal fibroblast sheath or proteins, and (C) fibrinogen leakage with increased collagen replacement due to a primary vascular abnormality with increased vascular permeability (1,9). The immune-mediated hypothesis is the most popular theory because of the frequent association with autoimmune disorders and overexpression of HLA-DR by epithelial cells and CD25-positive cells in the lamina propria as a sign of continued inflammation (10). These activated immune cells will produce cytokines and growth factors that in turn stimulate the extracellular matrix-producing myofibroblasts. It is presumed that a luminal agent (infectious agents or toxins), or allergic reactions to environmental or dietary antigens act as a trigger for chronic inflammation and will initiate this fibro-inflammatory condition.

The present case demonstrated beside collagen deposition, also infiltration of eosinophils and mast cells in the lamina propria with resolution of the clinical picture after starting an exclusion diet and an antihistaminicum. This would suggest that food allergens had triggered the development of an eosinophilic gastroenteritis with ultimate evolution to collagen deposition. Although, this was not confirmed with provocation tests to strengthen this diagnosis.

Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of the bowel wall in different segments of the gastrointestinal tract, with the stomach and small intestine being the most commonly affected (11). Histological examination remains the cornerstone of the diagnosis (>20 eosinophils/HPF) with exclusion of other potential causes for intestinal eosinophilia (12). Clinical manifestations will depend strongly on the affected site of the gastrointestinal tract and on the main location of the eosinophils in the bowel wall, most commonly resulting in abdominal pain and nausea. Concomitant allergic disorders are common and 70-80% of patients will have peripheral eosinophilia and/or elevated serum IgE levels (13). Furthermore, a family history of atopic diseases is seen in up to 64% of cases.

The pathogenesis of this disorder has yet to be fully elucidated, but intestinal dysbiosis and food allergies have been suspected of causing an immune dysregulation (14). Eosinophils are recruited to the gastrointestinal tract and will trigger an inflammatory response by producing and secreting several inflammatory mediators that are cytotoxic to the gastrointestinal epithelium. This will result in mast-cell degranulation in addition to the release of cytokines, chemokines, lipid mediators and neuromediators (15).

Moreover, eosinophils seem to play an important role in the pathophysiology of collagenous colitis/duodenitis (10). Eosinophilic degranulation will not only cause tissue damage, but it is also known to stimulate DNA synthesis, matrix and collagen production in dermal fibroblasts and could thus lead to the production of collagenous bands (16).

To our knowledge, the combination of both these rare entities are previously only described by Benchimol et al. (14). They reported a girl with chronic diarrhea due to collagenous colitis and eosinophilic gastritis. Being unresponsive to 5-aminosalicylates and exclusion diets, the diarrhea only disappeared after treatment with an H1 class of antihistaminicum, stabilizing mast cells and potentially impairing eosinophilic migration to target organs (16).

As collagenous gastroenteritis is a rare finding with many causes, there is as yet no standardized treatment. Most treatment modalities consist of oral

iron supplementation, anti-secretory therapy, and anti-inflammatory agents (mesalazine or steroids). Clinical response rates vary widely, but some improvement is seen with most therapeutic regimens. Gluten-free or other restriction diets or even parenteral feeding were often tried in vain (9,16). In eosinophilic gastroenteritis, empirical food-elimination diets and steroids are considered first-line treatments, however in patients with combined eosinophilic gastroenteritis and collagenous colitis/duodenitis, the benefit of elimination diets or steroids may be larger. In addition, supportive treatment with either mast cell inhibitors, leukotriene receptor antagonists, antihistaminica, or anti-interleukin-5 are described with some success (15).

The natural history of both disorders is not yet known, most likely due to the broad pathogenesis making a consensus for optimal treatment strategy difficult. Despite clinical improvement and even resolution of inflammation, the collagen disposition in collagenous duodenitis will most likely remain. Preliminary data shows a rather benign course of collagenous gastritis in children. In contrast to collagenous sprue, there is no evidence for increased risk of malignancy (2).

Conclusion

As collagenous gastroenteritis in children is a rare finding, little is known about the triggers, natural course and most effective treatment of this disease. In our case, food allergens are proposed as a potential trigger for eosinophilic gastroenteritis with eventual collagen deposition, possibly leading to protein-losing enteropathy. Although this condition is extremely rare, gastroenterologists and pathologists need to be aware of the different conditions it is associated with to enable accurate diagnosis, so that appropriate therapy can be started in a timely manner.

Conflict of Interest Disclosures (includes financial disclosures)

The authors have no conflicts of interest relevant to this article to disclose.

References

1. COLLETTI RB., TRAINER TD. Collagenous gastritis. *Gastroenterology*, 1989,**97**:1552-1555.
2. DE RONDE O., DELOS M., JESPERS S., GILLAIN C., DE RONDE T. Collagenous gastritis: about two paediatric cases and literature review. *Acta Gastroenterol. Belg.,* 2020,**83**:41-45.
3. GOODGAME RW. Gastrointestinal cytomegalovirus disease. *Ann. Intern. Med.*, 1993,**119**:924-935.
4. BRAAMSKAMP MJ., DOLMAN KM., TABBERS MM. Clinical practice. Protein-losing enteropathy in children. *Eur. J. Pediatr.*, 2010,**169**:1179-1185.
5. IWASA T., MATSUBAYASHI N. Protein-loosing enteropathy associated with rotavirus infection in an infant. *World J. Gastroenterol.*, 2008,**14**:1630-1632.
6. KOIDE T., MOCHIZUKI T., KAWAI N., YASHIRO K., INOUE T., TSUJIMOTO M., *et al.* Collagenous gastroduodenitis with recurrent gastric ulcer in 12-year-old girl. *Pediatr. Int.*, 2015,**57**:754-757.
7. MATTA J., ALEX G., CAMERON D.J.S., CHOW C.W., HARDIKAR W., HEINE R.G. Pediatric collagenous gastritis and colitis: a case series and review of the literature. *J. Pediatr. Gastroenterol. Nutr.*, 2018,**67**:328-334.
8. COTE J.F., HANKARD G.F., FAURE C., MOUGENOT J.F., HOLVOET L., CEZARD J.P., *et al.* Collagenous gastritis revealed by severe anemia in a child. *Hum. Pathol.*, 1998,**29**:883-
9. BAJIRA R.U., JOSHI A., HEIKENEIN J.B. Successful treatment of collagenous gastritis in a child with gluten-free diet. *W.M.J.,* 2015,**114**:271-273.
10. PULIMOD A.B., RAMAKRISHNA B.S., MATHAN M.M. Collagenous gastritis and collagenous colitis: a report with sequential histological and ultrastructural findings. *Gut.*, 1999,**44**:881-885.
11. YANG X.M., HE S.Q., YANG H., ZHENG H.H., ZHU H.L., ZHOU S.K., *et al.* Clinical features and treatment outcomes of eosinophilic gastroenteritis: an analysis of 28 cases. *Acta Gastroenterol. Belg.*, 2019,**82**:5-10.
12. PINETON DE CHAMBRUN G., DUFOUR G., TASSY B., RIVIERE B., BOUTA N., BISMUTH M., *et al.* Diagnosis, Natural History and Treatment of Eosinophilic Enteritis: a Review. *Curr. Gastroenterol. Rep.*, 2018,**20**:37.
13. GONSALVES N. Eosinophilic Gastrointestinal Disorders. *Clin. Rev. Allergy Immunol.*, 2019,**57**:272-285.
14. MISHRA A., HOGAN S.P., BRANDT E.B., ROTHENBERG M.E. IL-5 promotes eosinophil trafficking to the esophagus. *J. Immunol.*, 2002,**168**: 2464-2469.
15. ZHANG M., LI Y. Eosinophilic gastroenteritis: A state-of-the-art review. *J. Gastroenterol. Hepatol.*, 2017,**32**:64-72.
16. BENCHIMOL E.I., KIRSCH R., VIERO S., GRIFFITHS A.M. Collagenous colitis and eosinophilic gastritis in a 4-year-old girl: a case report and review of the literature. *Acta Paediatr.*, 2007,**96**:1365-1367.