Collagenous gastritis : about two paediatric cases and literature review

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Abstract

Background and study aims : **Collagenous gastritis is a rare entity divided in two subgroups (paediatric and adult). In the paediatric population, it often causes anaemia and abdominal pain. Therapy remains the most challenging part as no randomized clinical trial exists and long-term outcome is not well established.**

Patients and methods : **We reviewed the 43 paediatric patients with diagnosis of collagenous gastritis reported in Pubmed from 1989 to mid 2019 to analyse clinical and histological response depending on the treatment choice.**

Results : **In 43 patients (M/F ratio 1:2), a clinical response was observed in 85.7% of patients and a histological response in 20.8% of patients. PPI treatment associated with oral iron supplement was the most frequent choice with clinical improvement in 78.5% of patients. Other treatments such as gluten-free diet or corticoids showed relatively good rates of clinical improvement. Histological remission seems difficult to achieve and recurrence of symptoms after treatment interruption was often reported.**

Conclusions : **Collagenous gastritis in children is mainly characterized by symptoms of anaemia, abdominal pain or diarrhea. Gastroscopy with fundic biopsies helps to confirm diagnosis and treatment with PPI's (associated with oral iron supplement in case of anaemia) seems to be the most efficient choice to achieve clinical and sometimes histological remission. Long-term outcome of these young patients is unknown. A better understanding of the pathogenesis could lead to new medications focusing on this histological remission.** (Acta gastroenterol. belg., **2020**, 83, **41-45**).

Key words : collagenous gastritis, anaemia, paediatrics, enteritis.

Introduction

Collagenous gastritis is a rare entity that may lead to severe anaemia especially in children. Its natural history and the links with adult collagenous infiltration diseases are not well understood.

We report herein the cases of two young patients with severe microcytic anaemia. Significant improvement with PPI's and iron supplementation were observed just as prompt recurrence after stopping.

Case report

The first patient is a 15 years old boy with a history of significant microcytic anaemia (Hb 7.5 g/dl with MCV 58.8 fL) and daily rectal blood loss mixed with normal stool. No others symptoms were mentioned.

Previous tests were made one year ago concluding to a collagenous gastritis based on gastric biopsy samples. Ileo-colonoscopy showed no abnormalities including normal histological findings. Fecal calprotectin level was slightly elevated (223 µg/g faeces with upper normal values of 200 µg/g faeces), stool examination was positive for blood. A Technetium scintigraphy excluded Meckel's diverticulum and an entero-Magnetic Resonance Imaging was normal too. Absence of anti-transglutaminase antibodies excluded coeliac disease.

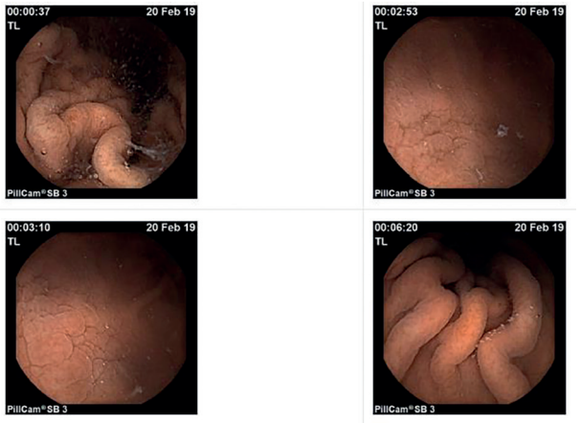

Fig 1. — Fundic aspect of patient 1 (videocapsule).

The blood tests in June 2018 showed a chronic iron deficiency (iron 7µg/dl (nv 59-158), ferritin 1.5 ng/l (nv 28-365), reticulocyte count 33 900/µl (nv 25 000-75 000), B12 vitamin 408 pg/ml (nv 193-982).

His medication included oral iron supplement started a year ago but he stopped PPI's several months before with recurrence of anaemia (11.5g/dl).

Therefore, in the beginning of 2019, a new endoscopic work-up was performed. The rectoscopy revealed a slightly hemorroïdal congestion explaining the red blood losses. The ileo-colonoscopy was normal, including histological analysis. Both gastroscopy and videocapsule showed normal oesophagus, antrum and duodenum, with normal biopsies (especially normal duodenal villi) but a nodular/pavimentous aspect of the fundus (figures 1 and 2*)*. Helicobacter pylori was not found. The fundic biopsies showed a significant thickening of the basement

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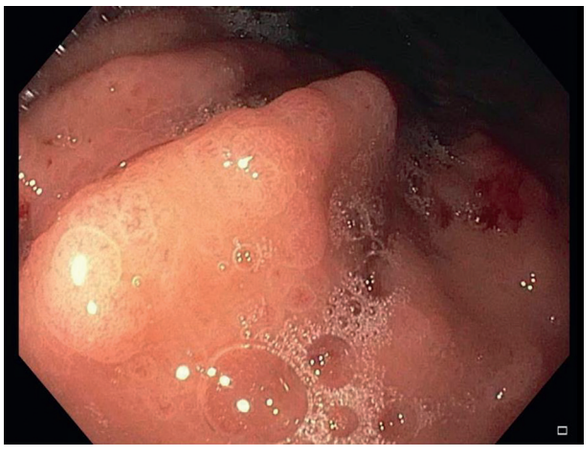

Fig. 2. — Fundic aspect of patient 1 (gastroscopy) with nodular pattern.

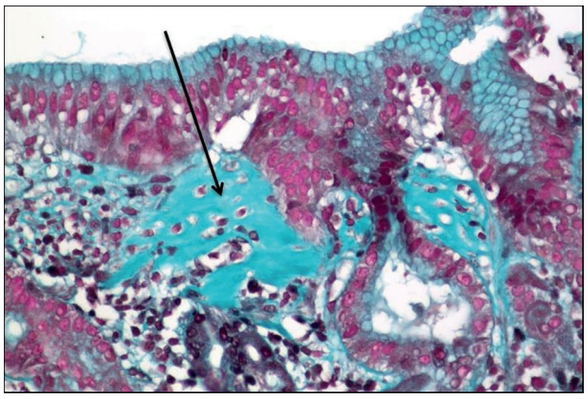

Fig. 3: fundic biopsy (Masson's trichrome) showing in blue/green the collagenous thickening of the basal membrane (black arrow).

membrane (>10µm) with chronic inflammatory infiltration of the chorion and some stripping of the surface epithelium (figure 3). All these aspects were leading to the diagnosis of collagenous gastritis.

Under oral iron supplement (iron sulfate 80 mg a day) and PPI's (esomeprazole 40mg a day), anaemia resolved within 3 months, the haemoglobin value reached 13,5g/dl and MCV increased to 78 fL.

The second patient is a 10 years old girl with a history of fatigue, pallor, irritability and recurrent upper airways infections. She complained 6 months earlier about epigastric pain without symptoms of gastro-oesophageal reflux or other digestive tract symptoms, no signs of melena or hematemesis.

Microcytic anaemia was diagnosed (Hb 6.9 g/dl (nv 12-15), MCV 62 fL (nv 80-88), serum iron 15 µg/dl (nv 59-158), ferritin 5 µg/l (nv 4-67), normal B9 and B12 vitamins serum values).

Haemoglobin level increased up to 13.7 g/dl after blood transfusion and iron supplements. Three months after transfusion, under oral iron supplement only, haemoglobin level was 11.4 g/dl.

But six months after transfusion and three months after stopping iron supplement, haemoglobin decreased again to 9.7 g/dl in parallel with decreased serum iron and ferritin (low range of the normal values). Reticulocyte count was increased at 105 700/µl (nv 25 000-75 000). Other results were within normal range, including coeliac disease serology (anti-transglutaminase antibodies).

The gastroscopy performed at this point showed a diffuse erosive and nodular pattern of the gastric fundus with a small fundic ulcer showing signs of recent bleeding. Ileo-colonoscopy was macroscopically and histologically normal.

Histology of the fundic samples showed a thickening of the basement membrane and a chronic inflammatory infiltration of the chorion. Helicobacter pylori was not found. No other abnormalities were described on antral and duodenal samples and the diagnosis of collagenous gastritis was made.

Discussion

The spectrum of collagenous diseases in the digestive tract is divided in three categories: collagenous gastritis, collagenous sprue and collagenous colitis (1). The last one is the most frequent with an overall annual incidence of 5.2 cases per 100.000 and may cause chronic diarrhea in elderly patients (2).

Collagenous gastritis is a rare disorder characterized by the collagenous thickening of subepithelial bands (>10µm) associated with mucosal inflammation (3). Colletti and Trainer reported the first case, a 15 years old girl, in 1989 (4), about 60 cases were published until 2015 (5) and currently up to 80 patients were reported in mid-2019, according to the PubMed search.

Etiology of the disease remains unclear. Usual causes of chronic gastritis (such as toxic gastritis, allergic gastritis, eosinophilic gastritis, sarcoïdosis, hystiocytosis, ischemic gastritis, lymphomatous gastritis, chronic granulomatosis…) are absent. Helicobacter pylori does not seem to be part of the pathogenesis and eradication does not improve the collagenous gastritis course (4,6).

A possible explanation could be an increase in subepithelial deposition of collagen. This is a consequence of chronic inflammation and auto- immunity (peri-cryptal fibroblast sheath and proteins and fibrinogen leakage with increased collagen replacement) (7).

We may consider two different subgroups since the phenotype seems to differ between the paediatric and adult populations (8): paediatric patients presenting preferentially with pure gastric involvement and severe anaemia (frequent nodular pattern on endoscopy) and adults presenting more often with chronic watery diarrhea caused by collagenous colitis associated with a collagenous gastritis. This adult type has also been described in association to autoimmune disorders such as ulcerative colitis, Sjögren syndrome, coeliac disease or lymphocytic gastritis/colitis (9).

Table I. — **Summary of the 43 patients**

Ref	Age (years)	Sex (M/F)	Symptoms	Treatment	F-up (years)	Clinical response	Histological response
(3)	13	F	Anaemia	/	/	/	/
(3)	14	F	Nausea	PPI	/	No	/
(3)	15	F	Anaemia, abdominal pain	Steroids	3.4	Yes	Yes
(4)	15	F	Anaemia, abdominal pain, GI bleeding	H2 receptor-antagonist	2	/	No
(6)	9	F	Anaemia, retrosternal pain	PPI, Steroids, sucralfate	1.1	No	No
(7)	1.25	F	Abdominal pain, diarrhea, generalized oedema	PPI, oral iron supplement, steroids, azathioprin	0.75	Yes	/
(8)	11	M	Anaemia	/	8	/	Yes
(10)	7	F	Anaemia, abdominal pain	PPI, oral iron supplement	0.5	Yes	Yes
(10)	11	M	Anaemia, abdominal pain	PPI, oral iron supplement	5	Yes	Yes
(11)	16	F	Anaemia, abdominal pain	PPI, H2 receptor-antagonist, oral iron supplement	6	Yes	No
(12)	9	F	Abdominal pain	Oral iron supplement	4	Yes	Yes
(13)	9	F	Abdominal pain	Oral iron supplement	/	Yes	/
(13)	15	M	Diarrhea	PPI, steroids, mesalazine	/	Yes	No
(14)	9	F	Abdominal pain	Mesalazine	/	No	/
(15)	12	F	Nausea	PPI	1	No	No
(15)	12	F	Abdominal pain	PPI	6	Yes	/
(15)	12	F	Abdominal pain	PPI	0.17	Yes	/
(16)	12	F	Anaemia	Oral iron supplement	/	/	/
(17)	14	F	Abdominal pain	PPI, sucralfate	12	No	No
(18)	15	F	Anaemia	PPI, oral iron supplement, steroids	0.83	Yes	No
(19)	0.75	M	Diarrhea	Steroids, parenteral nutrition	/	Yes	No
(20)	2	M	Diarrhea	PPI, steroids, mesalazine, bismuth	/	Yes	No
(21)	9	M	Anaemia, abdominal pain	Oral iron supplement	2	/	/
(22)	12	F	Abdominal pain, nausea	PPI, oral iron supplement	0.5	Yes	/
(23)	12	F	Haematemesis	H2 receptor-antagonist	4	/	No
(24)	15	M	Gastric perforation	Oral iron supplement	3	Yes	/
(25)	13	M	Abdominal pain, diarrhea	Gluten-free diet	3	Yes	Yes
(26)	10	F	Anaemia, diarrhea	PPI, steroids, mesalazine	1	Yes	/
(27)	11	M	Nausea	Oral iron supplement	1.5	Yes	No
(28)	14	F	Anaemia, abdominal pain, nausea	Oral iron supplement, gluten-free diet	2	Yes	No
(28)	12	F	Upper GI bleeding	PPI, oral iron supplement	6.5	Yes	No
(28)	15	F	Retrosternal pain	/	/	/	/
(28)	13	M	Anaemia	PPI, oral iron supplement	0.5	Yes	No
(28)	10	F	Anaemia	PPI, oral iron supplement	/	/	/
(28)	5	F	Anaemia, diarrhea	Oral iron supplement, gluten-free diet	5	Yes	No
(28)	10	F	Anaemia, abdominal pain	Oral iron supplement	3	Yes	No
(28)	9	M	Anaemia	Oral iron supplement, 4-food elimination diet	5	Yes	No
(28)	13	M	Anaemia, abdominal pain, diarrhea	Oral iron supplement, gluten-free diet	/	Yes	/
(29)	8	M	Anaemia, abdominal pain, nausea	PPI, H2 receptor-antagonist, oral iron supplement, steroids	2.5	Yes	/
(29)	11	M	Anaemia	Oral iron supplement	/	Yes	No
(29)	15	F	Anaemia	PPI, oral iron supplement	/	Yes	/
Cur.	15	M	Anaemia, abdominal pain, diarrhea, GI bleeding	PPI, oral iron supplement	0.25	Yes	/
Cur.	10	F	Anaemia, abdominal pain	Oral iron supplement	0.5	Yes	/

M : male – F : female – PPI : Proton pump inhibitor – GI : gastro-intestinal – H2 : Histamine-2 – Cur. : current case report

Our two cases fit the paediatric subtype with severe anaemia and/or epigastric pain without other digestive involvement. The nodular pattern of the gastric fundus is also one of the supporting criteria of this diagnosis (10) as this pattern reflects areas of remaining undamaged mucosa and the depressed surrounding mucosa reflects the atrophic changes and collagen deposition.

Therapy is challenging in collagenous gastritis.

With the small amount of patients and the two different subgroups, there is no randomized clinical trial available to establish a standard of care.

Table II. — **Summary of results**

Population		
Characteristics		
n	43 (100%)	
M/F ratio	15/28 (34.9%/65.1%)	
Mean age (years)	11,07 (0.75-16)	
Mean duration of follow-up (years)	3.03 (0.25-12)	
Symptoms :		
- Anaemia	15 (34.9%)	
- Abdominal pain	27 (62.8%)	
- Nausea	20 (46.5%)	
- Diarrhea	6 (14%)	
- Others	9 (20.9%)	
Treatment	*Clinical response*	*Histological response*
Overall	30/35 (85.7%)	5/24 (20.8%)
Subgroups :		
- PPI	16/21 (76.2%)	2/21 (9.5%)
+ iron supplement	11/14 (78.6%)	2/14 (14.3%)
+ steroids	6/7 (85.7%)	0/7 (0%)
+ others	6/7 (85.7%)	0/7 (0%)
- Gluten-free diet	4/4 (100%)	1/3 (33.3%)
- Steroids	8/9 (88.9%)	1/5 (20%)
- Iron supplement	22/22 (100%)	2/22 (9.1%)
- Others	12/17 (70.6%)	0/17 (0%)

Literature review, methods

We searched PubMed database using the words 'collagenous gastritis' and limited the articles to case reports and reviews written in English.

We further limited the articles to those including reports of patients under 18 years old (paediatric population) for the treatment analysis. In this analysis, primary endpoint was clinical and histological response based on reporter's evaluation.

Results

We collected the data of 43 patients under 18 years old reported between 1989 and mid-2019 (Table 1), 15 males and 28 females (M/F ratio 1:2), mean age was 11.07 years old and mean duration of follow-up was 3.03 years (Table 2).

Whatever the treatment choice, a clinical response was observed in 85.7% of patients (30/35) and a histological response in 20.8% of patients (5/24).

PPI treatment was tested in 48.8% of patients (21/43) with clinical response in 76.2% (16/21) and histological response in 9.5% (2/21).

Further analysis showed that PPI's combined with oral iron led to similar values (clinical response 78.5% (11/14) and histological response 14.3% (2/14).

PPI's associated with steroids (budesonide,…) or with other molecules showed clinical response in 85.7% (6/7) but no histological response.

Gluten-free diet was evaluated in 4 patients, all with clinical response (4/4) but only one of three showing a histological response.

The most common treatment was oral iron supplement (58.1% (25/43)) related to anaemia in 20 of these 25 patients. In this subgroup, clinical response was observed in 100% of patients (22/22), mainly related to improvement of anaemia, histological response was found in 2 of 5 patients but in association with PPI's.

Conclusion

Collagenous gastritis is a rare entity but is now recognized as a cause of severe anaemia in the paediatric population, encouraging discussing the usefullness of gastroscopy in this specific population.

The adult subtype is mainly associated with collagenous colitis or other autoimmune disorders and further investigations such as colonoscopy are often necessary.

The histological findings are well established, the endoscopic findings in paediatric patients are less specific but the nodular aspect of the fundus surrounded by inflammatory/atrophic areas is frequently reported.

The challenging point remains to find the adequate therapy to improve symptoms and stop the collagenous proliferation that is a response to the chronic gastric inflammation (11).

Many drugs or diets have been empirically tested but a randomized clinical trial is still needed to establish for this rare entity an evidence-based standard of care. The most frequent combination is PPI's and oral iron supplement, sometimes combined with steroids (such as budesonide) or Histamine-2-receptor-antagonists.

Actual goal of treatment is to achieve a gastric anti-inflammatory effect (PPI's, steroids, mesalazine,…). But these drugs fail to achieve a sustained histological

improvement even if they have significant benefits on symptoms.

Interruption of treatment often leads to clinical recurrence as described in several case reports including our two patients.

The natural history of collagenous gastritis, the follow-up of paediatric patients and their evolution during adulthood remain also unclear and require more dedicated studies.

Conflict of interest

All the authors declare that they have no conflict of interest.

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