Collagenous gastritis: reports and systematic review

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Collagenous gastritis is a rare disorder first described in 1989. After encountering two cases, we decided to review the literature and evaluate the collagen band. A systematic review of PubMed and EMBASE databases was performed. Twenty-eight cases have been previously described and two patterns of presentations are identifiable: children or young adults (median age 12 years, range 2–22 years) presenting with symptoms attributable to the gastritis (anaemia and pain); and older adults (median age 52 years, range 35–77 years) presenting with loose stools, often associated with collagenous colitis or coeliac disease. Our two cases (one child and one adult) matched this pattern. Immunostaining of the collagen band for collagens II, III, IV and VI, and tenascin showed that the band in our cases was predominantly tenascin. In conclusion, collagenous gastritis is a rare entity whose presentation depends on the age of the patient. An autoimmune aetiology seems possible given its associations. Treatment is empirical. The 30 cases now reported show that the disorder can relapse or persist for years. *Eur J Gastroenterol Hepatol* **21:1419–1424**

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Introduction

Collagenous gastritis (CG) is a rare disorder first described in 1989 [1]. When we encountered two cases, we reviewed the literature. A total of 28 cases have been reported. It is clear that there are two patient groups: 16 cases are in children or young adults (ages 2–22 years) group and 12 in older adults (ages 35–77 years) group, characterized (apart from age) by different presentations and summarized in Tables 1 and 2 [1–20]. Children and young adults tend to present with anaemia and abdominal pain, whereas older adults present with loose stools, frequently associated with collagenous colitis (CC), coeliac disease or both. There are exceptions: a 2-year-old child has been described with profound diarrhoea secondary to collagenous gastroduodenocolitis [12]. There do not seem to be characteristic endoscopic appearances, although endoscopy in younger patients is always described as abnormal, most commonly with a nodular appearance in the stomach. The diagnosis is invariably unexpected given the nonspecific symptoms and made by the histopathologist after examining gastric mucosal biopsies. CG is defined as thickening of the gastric subepithelial collagen layer to more than 10 μm, in association with an inflammatory cell infiltrate in the lamina propria [2]. The purpose of this report is to describe our two cases, to review the literature so that awareness of this rare condition is raised, and report on the nature of the collagen band.

Case 1

A 16-year-old Caucasian girl presented with a severe episode of epigastric pain radiating to her left shoulder. She described passing black stools 2 days before admission. There was a history of dysmenorrhoea (but not menorrhagia), for which she took mefanamic acid, as well as a previous diagnosis of irritable bowel syndrome. Physical examination was unremarkable. Routine blood tests showed a haemoglobin of 6.0 g/dl, mean cell volume 82 fl, white cell count 6.2×10^9/l (normal differential) and raised inflammatory markers (C-reactive protein 26 g/l, erythrocyte sedimentation rate 110 mm/h). Her urea, electrolytes, liver function tests, amylase and a coagulation screen were all normal. Endomysial antibody (EMA) serology was negative. Stool microscopy and culture was negative for pathogens, ova, cysts and parasites. Upper gastrointestinal endoscopy at that time was normal, with no source of bleeding found. Gastric biopsies were taken to exclude focal active gastritis in case of Crohn's disease and to exclude *Helicobacter pylori*. Histopathology of the gastric biopsies revealed patchy CG (Fig. 1, arrows to collagen band) without *H. pylori*. Distal duodenal biopsies were normal, with no intraepithelial lymphocytosis or villous atrophy. The colonic mucosa was normal to the caecum at colonoscopy, but no biopsies were taken at that time. Both ultrasound and a computed tomography scan of the abdomen were normal.

She was treated with ranitidine, omeprazole, iron sulphate and cessation of NSAIDs. The haemoglobin and the inflammatory markers returned to normal over the next 6 weeks, although symptoms of epigastric pain did not disappear completely. There was no change in

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Table 1 Cases of collagenous gastritis in children and young adults

Year	Age	M/F	Abdominal pain	Anaemia	Diarrhoea	Earlier use of NSAIDs or PPIs	Treatment	OGD appearance	Collagenous colitis	Collagen type	References
1989	15	F	Yes	Yes	No	No	H_2 antagonist, sucralfate – no improvement	Nodular/granular gastric body	No	Not done	[1]
1998	9	F	No	Yes	No	No	PPI, sucralfate, corticosteroids – no improvement	Erythema of gastric mucosa	Not investigated	Not done	[2]
1999	20	M	Yes	Yes	Yes – 6 years later	No	H_2 antagonist, oral iron, antihelminthics	Nodular gastric mucosa	Initially normal, later developed	Not done	[3]
2001	11 and 22	M and F	No	Yes	No	No	Not commented	Nodular mucosa	No	Not done	[4]
2001	11 and 12	ND	No	Yes	No	No	Unavailable	Gastritis	Not investigated	Not done	[5]
2003	11	F	Yes	No	No	No	Proton pump inhibitor – no improvement	Atrophic areas and scarring	No	Positive for III, VI. Negative for I, IV, laminin	[6]
2005	11	M	Yes	Yes	No	No	Oral iron, antacid	Nodular hemorrhagic mucosa	No	Not done	[7]
2007	19	F	No	Yes	Yes	No	Prednisone – improved	Diffuse nodular pattern	No	Not done	[8]
2007	12	F	Yes	Yes	Yes	No	PPI, iron – no improvement	Nodular, friable mucosa	No	Not done	[9]
2007	12	F	Yes	Yes	No	No	PPI, iron – no improvement. Prednisone – improved	Nodules and plaques	No	Not done	[9]
2007	12	F	Yes	No	No	No	PPI	Gastric erosions	Not investigated	Not done	[9]
2007	21[a]	M	Yes	No	No	No	Nil	Diffuse Nodularity	No	Not done	[10]
2007	9	F	Yes	Yes	No	No	PPI oral iron	Nodularity	No	Negative for collagen IV	[11]
2008	2	M	No	No	Yes	No	IV steroids – improved then relapsed; PPI; bismuth subsalicylate – improved	Erythema, petechiae	Yes	Not done	[12]
2008	16	F	Yes	Yes	No	Yes, mefanamic acid	H_2 antagonist, PPI, oral iron	Irregular gastric mucosa	No	Tenascin	Current

Where available, the symptomatic response to treatment has been noted. There is no documented case of improved histology after treatment of CG.
F, female; M, male; ND, not documented; OGD, oesophagogastroduodenoscopy; PPI, proton pump inhibitor.
[a]At initial presentation and endoscopy.

bowel pattern. Repeat endoscopy 7 months later revealed a slightly irregular gastric mucosa on the greater curve with erythema (Fig. 2). Biopsies were again consistent with CG. An exclusion diet was started and symptoms resolved completely, although no reproducible food sensitivity could be identified. About 6 years later, she represented (age 23 years) with epigastric pain, fatigue and possible melaena, but without diarrhoea. There were no precipitating factors and no ingestion of NSAIDs. She was again anaemic (haemoglobin 10.5 g/dl) and repeat endoscopy within 24 h of presentation showed erythema and an irregular, nodular, gastric mucosa. Histopathology of biopsies from the antrum, body and fundus of the stomach showed persistent CG. Biopsies from the distal duodenum were normal. Flexible sigmoidoscopy and colonic mucosal biopsies were normal, with no evidence of a colonic collagen band. The patient recovered on a further course of oral iron, in addition to combined therapy with an H_2 antagonist and proton pump inhibitor.

Case 2

A 39-year-old Caucasian woman presented with iron deficiency anaemia (haemoglobin 8.0 g/dl, mean corpuscular volume 68.2 fl) and fatigue. She had been anaemic through each of her three pregnancies. She reported a normal diet, no history of menorrhagia and no gastrointestinal symptoms at that time. There was no other past medical history and she was on no medication apart from occasional ibuprofen for headaches. On examination, she was pale and had angular stomatitis.

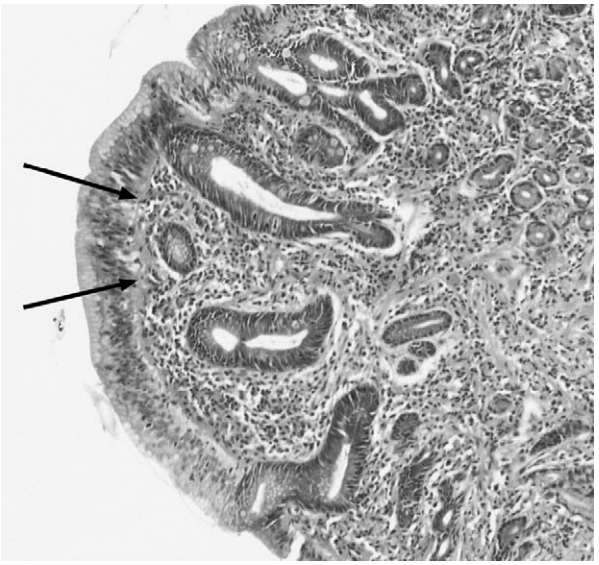
Further investigation revealed a low vitamin B12 (132 pg/ml, normal 220–1130 pg/ml), negative EMA and negative autoimmune profile including anti-gastric parietal cell and intrinsic factor antibodies. Upper gastrointestinal endoscopy was macroscopically normal. Biopsies from the second part of the duodenum showed normal villous architecture, but minimal lamina propria inflammation and an increased number of intraepithelial lymphocytes. No gastric biopsies were taken at the initial endoscopy.

Table 2 Cases of collagenous gastritis in older adults

Year	Age	M/F	Abdominal pain	Anaemia	Diarrhoea	Earlier use of NSAIDs or PPIs	Treatment	OGD appearance	Coeliac disease	Collagenous colitis	Collagen type	References
1989	67	F	No	No	Yes	No	Loperamide, no response	Normal	No	Yes	Not done	[13]
1989	54	F	No weight loss	No	No	No	Prednisone, H_2 antagonist, carbenoxolone, metoclopramide	Severe gastritis with mucosal friability	No	No	Not done	[14]
1990	75	F	No	No	Yes	No	Not commented	Normal	No	Yes	Not done	[15]
1996	35	F	No	No	Yes	No	Sucralfate, sulfasalazine, H_2 antagonist	Oedema and submucosal nodules	No	No, Lymphocytic colitis	Not done	[16]
1999	57	F	No	No	Yes	Yes – NSAID	Prednisone – initial improvement then relapse	Patchy erythema, atrophic mucosa	No	Yes	Negative for collagen IV	[17]
2000	57	M	No	Yes	Yes	No	Mesalamine, gluten-free diet	Erythema	Yes	No. Ulcerative colitis.	Not done	[18]
2001	52	F	No	Yes	No	No	Not commented	Normal	No	No	Negative for collagen IV	[4]
2001	40	F	No	No	Yes	No	Prednisone, salazopyrin, total parenteral nutrition	Normal	No	Yes	Negative for collagen IV	[4]
2001	77	M	No asymptomatic – endoscoped before surgery	No	No	No	None	Erosions	No	Not investigated	Negative for collagen IV	[4]
2001	36	M	ND	ND	ND	ND	ND	ND	ND	ND	ND	[4]
2001	42	M	Yes – cramps	Yes	Yes	No	Gluten-free diet	Gastric erythema	Yes	No	Not done	[19]
2004	37	M	No weight loss	No	Yes – post prandial	No	Prednisone, azathioprine, metronidazole, ciprofloxacin	Nodular and erythematous mucosa	No	No	Not done	[20]
2008	39	F	No	Yes	Yes	Yes – NSAID	Gluten-free diet – improved	Normal	Yes probably	No	Tenascin	Current

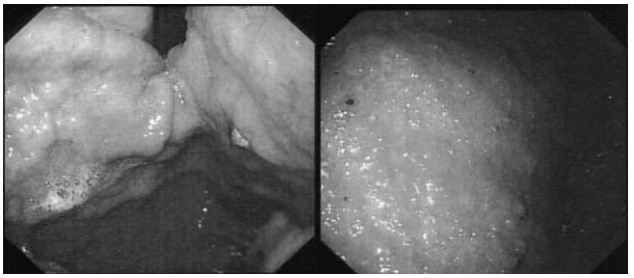
Where available, the symptomatic response to treatment has been noted. There is no documented case of improved histology after treatment of CG.
F, female; M, male; ND, not documented; NSAID, nonsteroidal anti-inflammatory drug; OGD, oesophagogastroduodenoscopy; PPI, proton pump inhibitor.

Fig. 1



Histopathology (haematoxylin and eosin stain, ×200) of the gastric mucosa in case 1, showing patchy collagenous gastritis (arrows to collagen band).

Fig. 2



Endoscopic appearance of the stomach in case 1, 7 months after presentation, showing a slightly irregular gastric mucosa on the greater curve with erythema.

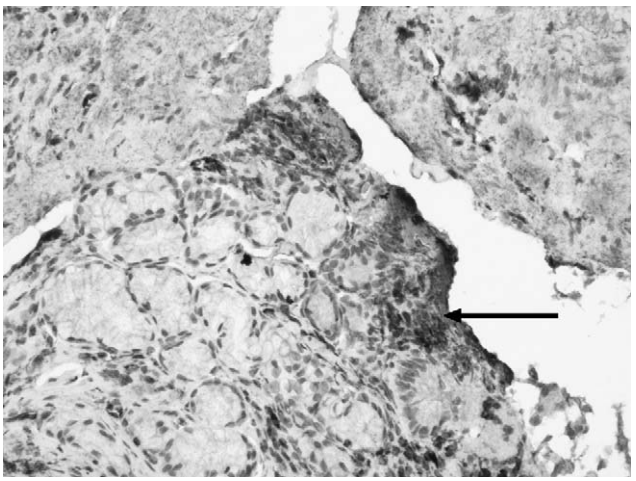
She continued a normal diet and initially responded well to iron and B12 replacement. Iron deficiency, however, recurred twice over the next 4 years and two further endoscopies with distal duodenal biopsies revealed a persistent intraepithelial lymphocytosis, although her EMA remained negative. She was referred for a further opinion regarding possible coeliac disease. Systems review revealed a stool frequency of 2–3 times per day, with a

tendency to loose motions which were sometimes pale and buoyant. A fourth endoscopy was again normal, but on this occasion, gastric biopsies revealed changes consistent with CG. *H. pylori* were not found. In view of the persistent distal duodenal intraepithelial lymphocytosis, a diagnosis of atypical coeliac disease, Marsh type I, was made, in conjunction with CG. Colonoscopy was macroscopically normal, but of seven colonic biopsies, one showed an increase in inflammatory cells and thickening of the subepithelial membrane with collagen, raising the possibility of CC. Terminal ileal biopsies were normal. Lactulose hydrogen breath test was negative for bacterial overgrowth. Thyroid function revealed hypothyroidism (thyroid stimulating hormone 45.5 mU/l and T4 10.8 μg/dl). The patient is now well on a gluten-free diet and thyroid replacement.

Gastric collagen band immunostain

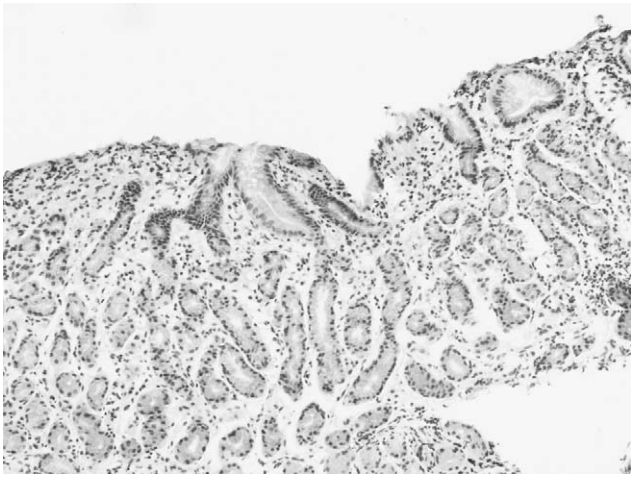
An attempt to type the collagen bands in our cases, examined by two gastrointestinal pathologists, produced equivocal results. Two attempts at staining at optimal dilutions revealed positive results for tenascin alone (Fig. 3, arrow), and negative for collagens II, III, IV and VI (Fig. 4, collagen III stain). Both cases showed the same pattern of staining. This was unexpected. It suggests either that tenascin was indeed the dominant component of the band, or that the staining was suboptimal due to focal thickening of the subepithelial collagen, or that the collagen in CG is of an unusual type (other than II, III, IV or VI) that is not stained by conventional methods.

Fig. 3



Tenascin immunohistochemistry (arrow shows positive staining, ×400). Immunohistochemical stains were performed on formaldehyde-fixed paraffin-embedded tissue. Sections were cut at 5 μm thickness and stained for five types of collagen at the optimal dilution, including tenascin. The optimal dilution for each collagen type was obtained after staining control tissue with different dilutions and obtaining the dilution showing the best staining quality with minimal background staining. After obtaining the optimal dilutions, the test tissue from the two cases were stained. Collagen III (Novocastra 1/1000 dilution), tenascin (Novocastra 1/1200), collagen VI (Novocastra 1/200), collagen IV (Novocastra 1/200), collagen II (Novocastra 1/200).

Fig. 4



Collagen III immunohistochemistry (background staining without discernible uptake, ×100).

Systematic review and comment

A systematic review of PubMed and EMBASE was performed, using the terms 'collagenous gastritis', 'gastritis', 'collagenous' and 'collagen'. Free text and Medical Subject Heading (Mesh) strategies were deployed. Exclusion criteria were: those inaccessible to Oxford University e-resources and those unrelated to humans or irrelevant to the topic. Twenty-eight cases were found and two patterns of presentation of CG were identifiable (Tables 1 and 2). Children or young adults aged up to 22 years report definite symptoms (abdominal pain most notably, sometimes with weight loss) or anaemia attributable to CG. The endoscopic appearances of the gastric mucosa invariably seem to be abnormal (17 out of 17 cases, including the current case on the second endoscopy). Evaluation of these 17 cases shows a median age 12 years (range 2–22 years), and 60% female predominance (sex not recorded in two out of 17). Over half (10 out of 17) presented with abdominal pain and the large majority (13 out of 17) were anaemic (Table 1). The colon was initially normal both macroscopically and microscopically in those 12 out of 17 who had a colonoscopy, apart from the recently described infant case [12]. One of the young adults subsequently developed CC [3], which raises the possibility of disease progression, because a colonic collagen band is generally a feature of older adults with CG.

In contrast, the 13 older adults had a median age of 52 years (range 35–77 years), with a similar female percentage (62%). A predilection for women to have CC is well established in the Swedish [21] and Oxford [22] cohorts (in 45 out of 51 and 21 out of 32 female patients, respectively). The same seems true for CG. In older adults, the endoscopic appearance of the gastric mucosa

was described as normal in six out of 13 cases. The majority of adult patients had diarrhoea (eight out of 13), but all had a good reason to explain their presentation other than the CG – CC or lymphocytic colitis (a variant of microscopic colitis that can interchange with CC [23]) in five out of 13 [4,13,15–17], ulcerative colitis and coeliac disease in one out of 13 [18], and coeliac disease alone in two out of 13 [19]. In these older patients, the CG seems to be a marker of a more extensive inflammatory disorder of the gastrointestinal tract. Of the remaining five cases, one was anaemic, one asymptomatic and another had no available history [4], whereas two cases presented with weight loss as the predominant feature [14,20].

These data raise two main possibilities. The first is that the collagen band is the end result of different pathological processes in the two groups. In children, the collagen band may be a localized response to a specific, perhaps ingested, insult (in our case that may have been mefanamic acid) leading to inflammation, pain and anaemia. In adults, however, it might be part of a panenteric response to a given stimulus, although the involved stomach has a limited impact on symptoms. This theory is less plausible in the light of the recently described infant with diarrhoea and panenteric collagen deposition. The second possibility is that the collagen bands arise through the same pathological process in susceptible individuals, but that the response in a child's gastric mucosa predominates, whereas in adults, it is generally more severe in the colon. This may explain not only the discrepancy in the cohorts, but also the overlap case [3] of the 20-year-old male who originally presented as a child with anaemia and pain with normal colonic mucosa, but who later developed CC.

The aetiology and pathogenesis of CG is not understood. Speculation that it is related to other collagen disorders is implausible for several reasons. There is no evidence of an association of CC with, and there are no symptoms attributable to, a systemic collagen disorder. CC has been related to drugs (predominantly NSAIDs or proton pump inhibitors), bacteria and autoimmunity [23]. The acidic and relatively sterile environment of the stomach is vastly different to the colon, so a bacterial stimulus for both the gastritis and colitis is hard to envisage. Case reports have shown no clear association with *H. pylori* or other gastric pathogen. Furthermore, although NSAIDs have been implicated in up to 61% of CC compared to 13% in controls [24], only three out of 29 with CG were taking NSAIDs (Tables 1 and 2), including both of our patients. Conjecture about an autoimmune aetiology is based on reported associations between CC and rheumatoid arthritis [25,26], thyroid disease and coeliac disease [27]. Our adult case of CG had both coeliac disease and hypothyroidism, whereas a total of three out of 13 adult cases of CG have documented coeliac disease (Table 2). An association between CG and Sjogren's syndrome has been described [14] and the female preponderance (overall CG documented female : male ratio is 18 : 27, with the sex in 2 cases not reported) also suggests a link to autoimmunity.

It is not clear how any of the above might lead to collagen deposition, nor whether this is a by-product or a cause of symptoms. The most likely explanation is collagen synthesis by an abnormal pericryptal myofibroblast sheath [28], although impaired degradation of collagen has been postulated [29]. The subepithelial band of collagen in CC is composed of type III collagen, with reduced type I collagen [30]. Type III collagen is produced by subepithelial fibroblasts for repair in inflammatory processes. The basement membrane of the normal gastrointestinal tract consists of type IV collagen, which implies that the increased collagen synthesis in CC is not a primary process, but reparative. Others have found the band to be predominantly tenascin (an extracellular matrix glycoprotein) and type VI collagen, together with some type III collagen [28]. Tenascin is considered a marker for mesenchymal cell proliferation and migration [29], so this implies a high turnover of the extracellular matrix to produce an immature, loosely connected interstitial collagenous matrix. Type VI collagen filaments help to bridge cells and the extracellular matrix [31]. This may explain why the collagen band in CC can be degraded as well as formed.

The collagen band in CG has been typed in only six cases, including our two cases. There is agreement that the collagen band is not type IV [4,11,17] and, like CC, may be type III with some type VI collagen [6]. In contrast, our cases showed positive staining for tenascin alone and were negative for collagens II, III, IV and VI. The expression of the extracellular matrix glycoprotein tenascin is transient and restricted to embryonic development. In the embryo, tenascin expression occurs in defined areas such as the neural crest and later at sites of skeletal tissue formation [32]. It is re-expressed in certain adult tissues during normal and pathological tissue remodelling, such as oncogenesis or wound healing [33]. In this instance, it would seem most likely that the tenascin is present as part of a reparative process after tissue damage and inflammation, rather than having any aetiological role in the CG. This is similar to the conclusion regarding the collagen band in CC. It is interesting to note, however, that although tenascin-rich fibrous tissues can be remodelled (whereas tenascin-poor fibrous tissues such as strictures in Crohn's disease have little reversibility), the reversibility of the collagen band in CG seems to be poor [34]. This implies either continued exposure to an offending stimulus and ongoing tissue injury, inadequate available treatment, or perhaps

the presence of a more durable (and unidentified) component of the CG band.

CG is a distinct and rare entity whose presentation depends on the age of the patient. Children or young adults characteristically present with abdominal pain or anaemia, whereas adults usually present with colonic symptoms related to coexistent CC. An autoimmune aetiology seems possible, given associations with coeliac disease, thyroid disease and a female preponderance. The type of collagen or tenascin, deposited may be a consequence of reparative processes driven by myofibroblasts in the subepithelial layer, whether in the colon or stomach. Treatment is empirical and has been for the most part unsuccessful. There are now 30 reported cases, with reports that the disorder can relapse or persist for years.

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