Collagenous gastritis and collagenous colitis: a report with sequential histological and ultrastructural findings

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Abstract
The case is reported of a young adult man with collagenous gastritis, an extremely rare disorder with only three case reports in the English literature, who subsequently presented with collagenous colitis. Sequential gastric biopsies showed a notable increase in thickness of the subepithelial collagen band. Ultrastructural study of gastric and rectal mucosa showed the characteristic subepithelial band composed of haphazardly arranged collagen fibres, prominent degranulating eosinophils, and activated pericryptal fibroblasts.

Collagenous gastritis, an extremely rare entity, and the more commonly encountered collagenous colitis are both characterised by the deposition of a subepithelial collagen band in the mucosa. Only three cases of collagenous gastritis have been reported in the English literature. One occurred in isolation\(^1\), one with synchronous collagenous colitis and collagenous duodenitis,\(^2\) and the third with synchronous lymphocytic colitis.\(^3\) We report, with ultrastructural findings, the case of a young adult man who presented initially with features of collagenous gastritis and was subsequently found to have collagenous colitis.

Case report
A 20 year old man presented with a two year history of epigastric pain, vomiting, easy fatiguability, and malaise. The symptoms were noticed after an acute febrile illness, the treatment details of which are not known. Physical examination disclosed pallor and angular stomatitis. Routine blood and stool examination showed a haemoglobin level of 6.3 g/dl, a total white blood cell count of \(8.5 \times 10^6/dl\) with 13% eosinophils, and hookworm ova in the stools. On upper gastrointestinal endoscopy, diffuse nodularity of the gastric mucosa was seen with no abnormalities in the oesophagus or duodenum. Biopsy specimens from the body and antrum of the stomach were obtained for routine histopathological examination. Rigid sigmoidoscopy performed at the same time gave normal results and biopsy specimens were not taken. The patient was treated with \(H_2\) receptor blockers, antihelminthics, and oral iron, but he continued to have recurrent symptoms over the next four years. Upper endoscopy repeated at three months and three years after the initial presentation continued to show the same findings. On both occasions, biopsy samples from the gastric body and antrum were processed for routine histopathology, and on the second time the samples were also fixed in glutaraldehyde for ultrastructural study.

Six years after the onset of the illness, the patient presented with diarrhoea and weight loss of two months duration. Stool occult blood at this time was strongly positive (3+). On upper endoscopy and sigmoidoscopy, the
gastric mucosa continued to show diffuse nodularity. The rectal mucosa still did not show any abnormality. Biopsy specimens were obtained from the antrum, duodenum, and rectum for histopathological study and from the antrum and rectum for ultrastructural study.

**Pathology**

**LIGHT MICROSCOPY**

Gastric biopsy specimens obtained at the time of presentation and three months later showed diffuse chronic gastritis of the body and antrum with focal moderate to severe atrophy of glands, in both the body and the antrum. The foci of atrophy were associated with notable fibrosis of the lamina propria and smooth muscle upgrowth from the muscularis mucosa (fig 1). The surface epithelium in these areas was partly detached and there was neutrophilic infiltration of both the epithelium and the lamina propria. In the mucosa away from the sites of atrophy, short bands of hyalinised collagen 15–43 µm thick, with entrapped capillaries, lymphocytes, and eosinophils (fig 2A), were seen below the surface epithelium or at the level of the foveolae. These bands of collagen stained blue with the trichrome stain and negative for amyloid with congo red stain. The epithelium overlying these bands appeared normal in some areas and shortened and detached in others. There was no increase in intraepithelial leucocytes. Modified Giemsa stain did not show any evidence of *Helicobacter pylori*.

Gastric biopsy samples obtained three and four years after presentation also showed chronic gastritis with foci of atrophy and subepithelial collagen bands. The width of these bands ranged from 23 to 225 µm (fig 2B,C) and they extended over greater lengths of the mucosa than the bands seen in the earlier specimens. The cellularity of the lamina propria and the degree of atrophy were similar to that seen in the previous samples. *H pylori*
were not seen. Duodenal biopsy specimens showed only mild chronic inflammation.

Rectal biopsy specimens obtained after the onset of watery diarrhoea showed a mild chronic colitis with patchy subepithelial collagen bands 20–30 µm thick (fig 3). In some areas the band was located deeper in the mucosa. The surface epithelium was shortened in foci over the deposited collagen and showed a few intraepithelial leucocytes. The lamina propria had a mild infiltrate of plasma cells, lymphocytes, eosinophils, and neutrophils. Crypt architecture was preserved and there were no other significant findings.

ULTRASTRUCTURAL STUDY

Ultrastructural examination of the gastric biopsy specimens obtained three and four years after the first presentation showed a patchy subepithelial band of haphazardly arranged collagen fibres (fig 4). Capillaries, lymphocytes, eosinophils, mast cells, and fibroblasts were seen entrapped in this band. The overlying surface epithelium showed focal decrease in mucous granules, widening of intercellular spaces, and detachment from the basement membrane in some areas.

Fibroblasts entrapped in the subepithelial collagen bundles and located around foveolae and glands did not show significant alterations. Many of the entrapped eosinophils and those present in the superficial and deep lamina propria showed evidence of prominent degranulation: by necrosis and release of granules, by piecemeal degranulation (partial or complete loss of individual granule contents), or by the fusion of granule chambers with each other and the surface membrane to release contents, a process similar to anaphylactic degranulation of mast cells (figs 5 and 6). Mast cells entrapped in the collagen band and located in the lamina propria also showed evidence of degranulation, predominantly of the piecemeal type (fig 5).

There was atrophy of glands, and the deep lamina propria showed large collagen bundles composed of uniformly oriented fibres. Some of these glands showed reduplication of their basement membranes (fig 7), a finding that was also noted in superficial and deep blood vessels.
Ultrastructural study of the rectal biopsy specimens obtained after the onset of watery diarrhoea also showed a subepithelial band of haphazardly arranged collagen fibres. The overlying surface epithelium did not show any significant alterations. Pericryptal fibroblasts were enlarged (fig 8), with prominent rough endoplasmic reticulum, well developed Golgi, large mitochondria, and occasional lipid bodies. Eosinophils in the mucosa showed evidence of piecemeal degranulation. Mast cells did not show any significant alterations. There was focal duplication of basement membranes, both of crypts and blood vessels.

Discussion

Collagenous gastritis is an extremely rare disorder and little is known about its aetio-pathogenesis and natural history. The three previous reports described this condition (a) in isolation, \( \text{b} \) with synchronous lymphocytic colitis, \( \text{c} \) and (c) with synchronous collagenous colitis and collagenous duodenitis. \( \text{d} \) This is the first report of a case presenting initially with collagenous gastritis and subsequently with features of collagenous colitis.

The clinical, endoscopic, and histological features in our case are similar to those described by Colletti and Trainer. \( \text{e} \) Both patients were young and presented with epigastric pain and gastrointestinal bleeding. Our patient, however, presented with chronic anaemia which did not improve with \( \text{f} \) receptor blockers, antihelmintic treatment, and iron supplements, suggesting chronic blood loss. This was unlike the acute upper gastrointestinal bleeding seen in the patient described by Colletti and Trainer. Our endoscopic finding of gastric nodularity had been noted in two of the three previous reports, \( \text{g} \) but involvement of the mucosa was more extensive in our case. Histologically also, atrophic gastritis and deposition of the subepithelial collagen band was seen in both the body and antral biopsy specimens of our patient, unlike the previous report \( \text{h} \) where only the body was involved.

There was an eightfold increase in thickness of the subepithelial collagen band noted in the gastric mucosa of our patient in the three year period between the initial and the last two sets of biopsies. The linear extent of the band was also increased in the second set of samples. The simultaneous notable increase in thickness of the gastric collagen band and the onset of symptomatic involvement of the colon in this young man suggests that histologically the disease was probably progressing. Colonic/rectal biopsy specimens from the period before the onset of diarrhoea, however, were not available to rule out definitely pre-existing disease. The fact that the thickness of the rectal collagen band seen within two months of the onset of diarrhoea was similar to that in the gastric mucosa at the time of initial presentation also suggests that the disease process in the colon was still in its early stages.

Three major theories have been postulated for the pathogenesis of the subepithelial collagen band: \( \text{a} \) inflammatory origin; \( \text{b} \) local abnormality of the pericryptal collagen sheath; \( \text{c} \) autoimmune injury. \( \text{d} \) The histological and ultrastructural findings in our case appear to concur with the first two theories. The initial and all subsequent gastric biopsy specimens from our patient showed a non-progressive patchy atrophic gastritis. This was associated with neutrophilic infiltration of the mucosa and thin subepithelial collagen band deposition in the first two sets of biopsy samples, but absent neutrophils and a noticeably thickened collagen band in the next two obtained three and four years later. These findings suggest that the original stimulus for the atrophic gastritis and the collagen band deposition was possibly the same, but once triggered, the subepithelial collagen deposition continued to progress irrespective of the course of gastritis in the rest of the mucosa. This would imply that a local defect was responsible for the specific subepithelial collagen deposition, and, as the periepithelial fibroblastic sheath is the source of collagen in this zone, the defect would in all probability lie in the functioning of these cells. Activated fibroblasts were noted in the rectal mucosa of our patient, as described in previous ultrastructural reports, \( \text{e} \) and an inherent metabolic defect in these pericryptal fibroblasts, either in their production or breakdown of collagen, would also explain the synchronous or metachronous occurrence of collagenous colitis and collagenous gastritis in this and other patients.

Collagenous colitis is occasionally associated with lymphocytic colitis, and they have been postulated to be different stages of the same disorder. \( \text{f} \) Lymphocytic gastritis on the other hand has been reported in only one patient with collagenous colitis \( \text{g} \) and was not described in any of the previous reports of collagenous gastritis.

The gastric mucosa of our patient showed prominent degranulating eosinophils in the lamina propria on ultrastructural study. This observation was also made in one of the earliest reports of collagenous colitis. \( \text{h} \) At the light microscopic level, authors have described the increase in mucosal eosinophils in patients with collagenous gastritis and colitis. \( \text{i} \) Eosinophils are known to produce tissue damage and are associated with some fibrosing disorders. \( \text{j} \) It is possible that they may play a role in the aetiopathogenesis of collagenous disorders of the gastrointestinal tract, although their activation could also be a byproduct of a non-specific inflammatory response.

The gastric mucosa of this patient also showed many degranulating mast cells. Mast cells are believed to play a role in wound healing and fibrotic disorders of the skin, \( \text{k} \) heart, \( \text{l} \) and lung. \( \text{m} \) In the appendix mild mucosal fibrosis was associated with a threefold increase in mast cell numbers. \( \text{n} \) Mast cells induce migration and proliferation of fibroblasts \( \text{o} \) and also stimulate collagen synthesis. \( \text{p} \) It is possible that the mediators released by the degranulating mast cells in the gastric mucosa of our patient could have contributed to the pathogenesis of the thickening collagen band. Mast cell activation, through the release of eosinophil chemotactic
factor and the resulting eosinophilic infiltrate could also indirectly play a role in the laying down of excessive collagen.

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