DOI: 10.7860/JCDR/2023/64706.18778

Case Report

Pathology Section

Collagenous Enterocolitis: A Rare Condition with Simultaneous Involvement of the Upper and Lower Gastrointestinal Tract

ANKITA ASTHANA[1], VINAYA INGAVALE[2], SUYOG RATNAPARKHI[3], KOMAL BAGHLA[4], RACHANA CHATURVEDI[5]

ABSTRACT

Collagenous colitis is a form of microscopic colitis, while Collagenous Sprue (CS) is a malabsorptive disorder that mimics celiac disease. Both conditions show increased Intraepithelial Lymphocytes (IELs) and basement membrane thickening due to collagen deposition. The simultaneous occurrence of both disorders is rare, and only a few such cases have been reported in the literature. A 60-year-old female presented with chronic, non bloody diarrhoea persisting for two years. Investigations revealed megaloblastic anaemia and hypoalbuminaemia. Gastroenteroscopy showed flattening and atrophy of the small intestinal mucosa. Biopsy results showed increased IELs, normal crypt architecture, and stripping of the epithelium. There was also patchy deposition of hyalinised band subepithelially, confirmed to be collagen through Masson's stain. As both the upper and lower Gastrointestinal (GI) tracts were involved, a diagnosis of collagenous enterocolitis was made. A 70-year-old female presented with intermittent watery diarrhoea for the past 10 days, accompanied by urgency and tenesmus. She had a history of colicky abdominal pain four years ago, which improved with steroids, but the symptoms recurred. Clinically, she was considered to have inflammatory bowel disease, with recurrent anaemia. Both gastroduodenoscopy and colonoscopy were normal. Mapping biopsy showed increased IELs and focal atrophy in the duodenum, while the colon exhibited mild mononuclear inflammation with occasional minimal activity. Focal, irregular deposition of subepithelial collagen was also observed and confirmed through Masson's stain. A diagnosis of collagenous enterocolitis was made. She is currently being monitored for any recurrence of symptoms, after which steroid treatment will be initiated. Collagenous colitis, CS, and collagenous duodenitis share similar histological features and can rarely co-exist. Further studies are needed to better understand their aetiology and association.

Keywords: Collagenous sprue, Intraepithelial lymphocytes, Malabsorption, Microscopic colitis, Subepithelial collagen

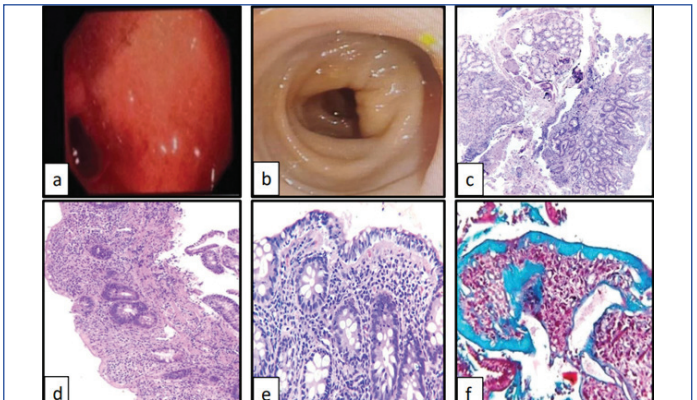
CASE REPORT

Case 1

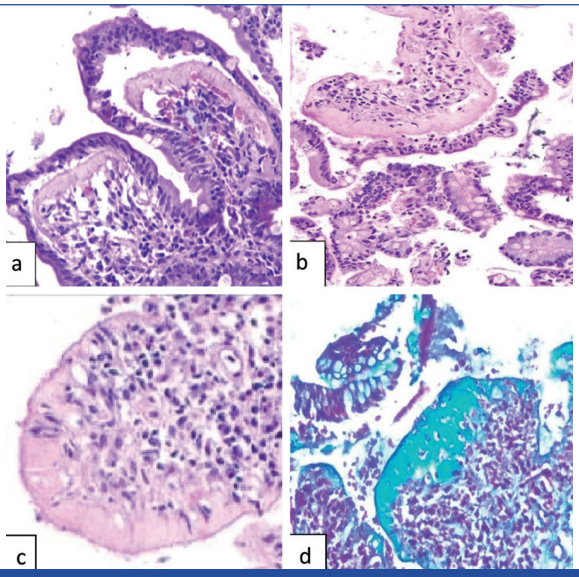
A 60-year-old female, known to be diabetic and hypertensive, presented with watery diarrhoea for the past two and a half years, sometimes occurring at night, with a stool frequency of 4-5 times per day and associated urgency. There is no history of blood or mucus in the stool, tenesmus, or incontinence. Laboratory investigations revealed megaloblastic anaemia {Haemoglobin: 6.6 gm/dL, Mean Corpuscular Volume (MCV): 108 fL} and hypoalbuminaemia with an albumin level of 2.9 g/dL (Reference range: 3.5-5.5 g/dL). Stool examination revealed mucus, 4-6 pus cells per High-Power Field (HPF), and no blood. Colonoscopy examination showed no abnormalities, while upper GI endoscopy revealed flattened duodenal and ileal folds [Table/Fig-1a]. Consequently, a clinical diagnosis of coeliac sprue was made. Focal flattening of the duodenal and ileal mucosa was observed [Table/Fig-1c,d]. All biopsies, including colonic samples, showed increased IELs (30-40/100 enterocytes) and a locally thickened subepithelial collagen band (>10 um), which was confirmed by Masson's trichrome staining [Table/Fig-1e,f]. Focal stripping of the epithelium, entrapped capillaries, stroma, and inflammatory cells were also present [Table/Fig-2a-d], and Congo red stain was negative. Therefore, a diagnosis of "Collagenous enterocolitis" was made. The patient was started on steroids and a gluten-free diet, which provided symptomatic relief. After correcting the hypoalbuminaemia and receiving folate therapy, she was discharged with instructions for follow-up. However, due to the pandemic, she could not attend the follow-up appointment. According to recent telephonic communication, she is partially compliant, taking medication only when symptomatic and stopping whenever she experiences relief.

Case 2

A 70-year-old female presented in January 2023 with intermittent watery diarrhoea, both large and small bowel type, in the last 10 days. She experienced a large stool volume and a frequency of 10-12 times per day, along with urgency and tenesmus. Four years ago, she had a history of anaemia and periumbilical colicky abdominal pain that worsened after meals, as mentioned in her papers from outside. This pain was relieved with the administration of steroids, such as budesonide, at a dose of 3 mg three times daily for six weeks. However, she presented again with similar symptoms and was clinically considered to have inflammatory bowel disease with recurrent anaemia (haemoglobin around 6.5 g/dL). Her gastroduodenoscopy and colonoscopy showed normal results [Table/Fig-1b]. On mapping biopsy, the duodenum showed a significant increase in IELs with focal mild villous atrophy, while the ileum showed only non specific mucosal



[Table/Fig-1]: Endoscopy of ileum showing flattened mucosa (a, Case 1) and normal (b, Case 2). Microscopy showing flattened duodenal (c) and ileal (d) mucosa (H&E, 40x) and thickened subepithelial collagen band in ileum and colon (d,e) highlighted by Masson's trichrome (f) (H&E, 400x).



[Table/Fig-2]: Ileal mucosa showing stripping of the epithelium with the thickened collagen band; a,b); (H&E, 100x); inflammatory infiltrate in the stroma with entrapment of capillaries; c); (H&E, 400x); irregular collagen deposition highlighted by Masson's trichrome; d) (H&E, 200x).

inflammation. The colonic mucosa exhibited features similar to the first case, along with minimal focal neutrophilic activity. Therefore, a diagnosis of collagenous enterocolitis was made. The patient became asymptomatic immediately after admission and was not put on any treatment. She was discharged within a week and is currently being followed-up to monitor the reappearance of symptoms, in case steroids need to be initiated.

DISCUSSION

Collagenous colitis is a form of microscopic colitis that typically presents in elderly women and is characterised by watery diarrhoea [1]. CS, a rare malabsorptive disorder of the small intestine, mimics coeliac disease [2]. The exact aetiology of these disorders remains unknown, and biopsies reveal a characteristic thickening of the subepithelial collagen layer, with or without an increase in IELs [3]. The occurrence of these disorders simultaneously is very rare but has been reported as early as 1988, leading to the suggestion of the term "Collagenous enterocolitis" [4]. This indicates that the unusual mucosal process may be highly heterogeneous and more extensive in the intestinal tract than previously recognised. The present cases also showed involvement of both the upper and lower gastrointestinal tracts. Six cases have been reported where CC was associated with Protein-Losing Enteropathy (PLE) [5,6]. Here, the authors report two such cases of collagenous enterocolitis in elderly women presenting with watery diarrhoea, one with recurrent symptoms, and involvement of both the upper and lower gastrointestinal tracts, as suggested by the clinical features and confirmed by histopathology.

The term "Collagenous colitis" was first described in 1976 by Lindstrom and is characterised by collagen deposition beneath the surface epithelium of the colorectal mucosa [7]. Classically, the mucosa appears normal during endoscopy, although ulcerations may be observed in a few cases. The mean age of presentation is 63 years, with a predominance of females, and the common symptom is chronic watery, non bloody diarrhoea lasting for more than 24 months. CS is a rare disease of the small bowel, first described in 1947, occurring in a younger age group and characterised by patchy villous atrophy as a hallmark endoscopic finding. It is associated with persistent diarrhoea, progressive weight loss, and severe malabsorption, leading to multiple nutrient deficiencies [8]. Similar features were observed in our cases as well. In the first case, diarrhoea, anaemia, and hypoalbuminaemia were present, suggesting malabsorption, while the second case had only anaemia.

Although collagenous colitis is typically considered "benign," a few serious colonic complications have been reported. These include the spontaneous development of peritonitis associated with free perforation of the colon, submucosal dissection, and colonic "fracturing," particularly during endoscopic procedures. Extensive ulcerative colitis progressing from collagenous colitis may occur within one to two years of the initial diagnosis [8]. On the other hand, CS carries a guarded prognosis with a substantial risk of malabsorption that could be fatal.

The exact aetiology of both the aforementioned disorders is unknown. Genetic sensitivity, hypersensitivity to a specific food component, medication, and environmental factors may all contribute. Certain drugs such as Non Steroidal Anti-inflammatory Drugs (NSAIDs), proton pump inhibitors, Angiotensin Receptor Blockers (ARBs), and autoimmune conditions have also been associated [9,10]. Other causes include paraneoplastic syndrome due to colon cancer, Yersinia infection, and Hashimoto's thyroiditis [11]. The first patient had diabetes and was also on long-term ARB for hypertension. However, in the second patient, no obvious cause could be identified.

Histologically, both of these disorders exhibit increased IELs in the mucosa, irregular deposition of subepithelial collagen bands demonstrated by Masson's trichrome staining (with a thickness greater than 10 µm, approximately the diameter of two lymphocytes), negative Congo red staining, and characteristic entrapment of capillaries, stroma, and inflammatory cells. Additionally, flattening and/or atrophy of the villi in the small intestine can be observed in CS. Similar findings were present in the cases as well. Both collagenous colitis and CS typically respond to steroids. Other medications used include bismuth nitrate, sulfasalazine, and a lactose- or gluten-free diet [12]. The patients also showed a response to steroids with a decrease in the frequency of stools. Details of only 12 cases [Table/Fig-3] [4,5,9-11,13-19] were found after an extensive review, and these cases have been tabulated.

Case no.	Name of author	Place of study	Year of study	Age (years)	Sex	Presentation	Aetiology/associated history	Site of histological involvement	Treatment
1.	Eckstein RP et al., [4]	Australia	1988	78	Female	Profuse watery diarrhoea, malabsorption, Weight loss	Not mentioned	Duodenum, colon	Sulfasalazine therapy
2	McCashland TM et al., [13]	Omaha	1992	62	Female	Diarrhoea, malabsorption	Not mentioned	Duodenum, colon	Gluten/lactose-free diet, oral prednisone, sulfasalazine
3	Chatti S et al., [14]	France	1994	67	Female	Not mentioned	Symptomatic after *NSAID treatment.	Duodenum, colon	Not mentioned
4	Castellano VM et al., [15]	Spain	1999	57	Female	Watery diarrhoea for 6- months	low serum proteins, increasedfaecal alpha1-antitrypsin	Antrum, fundus, duodenal bulb, colon, rectum	Prednisone
5	Stolte M et al., [16]	Bayreuth, Germany	1990	75	Female	Watery diarrhoea for six months	Not mentioned	Stomach, duodenum, colon	Treatment not mentioned
6	Meier PN et al., [17]	Hanover, Germany	1991	53	Female	Chronic watery diarrhoea	Aetiology unknown	Ileum,duodenum, colon	Therapeutictrial with bismuthnitrate

7	Freeman HJ and Berean KW, [11]	Canada	2006	52	Female	Severe watery diarrhoea, weight loss	†CA colon, anaemia, hypoalbuminaemia	Small and large intestine	Asymptomatic after CA colon resection
8	Navarro-Llavat M et al., [18]	Spain	2007	-	Male	Chronicdiarrhoea	Intestinal yersiniosis, IgG deficiency	Duodenum, ileum, colon	Not mentioned
9	Macaigne G et al., [19]	France	2010	75	Female	Chronic diarrhoea, weight loss	Hashimoto's thyroiditis, chronic atrophic gastritis.	Stomach, ileum, colon	Budesonide
10	Hunter JM et al., [9]	Australia	2014	37	Female	Watery diarrhoea, malabsorption	Type 1 diabetes, acute kidney injury	Stomach, small bowel, colon	Systemic steroidtherapy
11	Kaneko S et al., [10]	Japan	2021	73	Male	Severe diarrhoea for 2 months, weight loss	Olmesartan treatment	Duodenum, ileum	Within 3 weeks of Olmesartandis continuation, symptoms improved.
12	Gill I et al., [5]	Royal Oak, USA	2021	65	Female	Nausea, vomiting, abdominal pain	Dry mucous membrane, absent sweat, anasarca	Duodenum, Colon	Budesonide, mesalamine, azathioprine
13	**Present case 1**		**2023**	**60**	**Female**	**Watery diarrhoea for 2 and half years**	**Long term ‡ARB drug, anaemia, Hypoalbuminaemia**	**Colon, ileum, duodenum**	**Steroids and gluten free diet**
14	**Present case 2**		**2023**	**70**	**Female**	**Intermittent watery diarrhoea, tenesmus for 10 days**	**Colicky abdominal pain 4 years back, recurrent anaemia**	**Duodenum, colon**	**Symptomatic treatment**

[Table/Fig-3]: Review of the 12 cases reported in the literature [4,5,9-11,13-19].
*NSAID: Non-steroidal anti-inflammatory drug; †CA: Carcinoma; ‡ARB: Angiotensin receptor blocker

CONCLUSION(S)

In conclusion, the clinical presentation of collagenous colitis can be misleading at times. The disease can occasionally involve both the upper and lower gastrointestinal tracts simultaneously, which can pose a diagnostic challenge. However, histopathological examination is crucial for arriving at a definitive diagnosis. Limited reporting of such cases has been done so far, and the present report will contribute further to the existing literature.

Acknowledgement

The authors would like to thank Department of Gastroenterology, Seth GS Medical College and KEM Hospital, Mumbai.

REFERENCES

[1] Dietrich CF. Lymphocytic and collagenous colitis (microscopic colitis): Clinical manifestations, diagnosis, and management. UpToDate. Waltham, MA: UpToDate; September 11, 2018.
[2] Zhao X, Johnson RL. Collagenous sprue: A rare, severe small-bowel malabsorptive disorder. Arch Pathos Lab Med. 2011;135(6):803-09. Doi: 10.5858/2010-0028-RS.1. PMID: 21631278.
[3] Boland K, Nguyen GC. Microscopic colitis: A review of collagenous and lymphocytic colitis. Gastroenterol Hepatol (N Y). 2017;13(11):671-77. PMID: 29230146; PMCID: PMC5717882.
[4] Eckstein RP, Dowsett JF, Riley JW. Collagenous enterocolitis: A case of collagenous colitis withinvolvement of the small intestine. Am J Gastroenterol. 1988;83(7):767-71. PMID: 2898210.
[5] Gill I, Shaheen AA, Edhi AI, Amin M, Rana K, Cappell MS. Novel case report: A previously reported, but pathophysiologically unexplained, association between collagenous colitis and protein-losing enteropathy may be explained by an undetected link with collagenous duodenitis. Dig Dis Sci. 2021;66(12):4557-64. Doi: 10.1007/s10620-020-06804-3. Epub 2021 Feb 4. PMID: 33537921; PMCID: PMC7857935.
[6] Xiao Z, Dasari VM, Kirby DF, Bronner M, Plesec TP, Lashner BA. Collagenous sprue: A case report and literature review. Gastroenterol Hepatol (N Y). 2009;5(6):418-24. PMID: 20574500; PMCID: PMC2886398.
[7] Lindstrom CG. "Collagenous colitis" with watery diarrhoea-a new entity? Pathol Eur. 1976;11(1):87-89. [PubMed] [Google Scholar].
[8] Freeman HJ, Berean KW, Nimmo M. Evolution of collagenous colitis into severe and extensive ulcerative colitis. Can J Gastroenterol. 2007;21(5):315-18. Doi:10.1155/2007/950154. PMID: 17505568; PMCID: PMC2657714.
[9] Hunter JM, Lee HJ, Dettrick A, Tan C. Collagenous enterocolitis, and maturity onset type 1 diabetes manifesting as uraemia, malabsorption, and extreme weight loss. BMJ Case Reports. 2014;2014:bcr-2013200409. Doi: 10.1136/bcr-2013-200409. PMID: 25056300; PMCID: PMC4112348.
[10] Kaneko S, Matsuda K, Mizuta Y, Shiratori S, Kishi K, Nakamura A, et al. Severe spruelike enteropathy and collagenous colitis caused by olmesartan. BMC Gastroenterol. 2021;21:350. https://doi.org/10.1186/s12876-021-01926-y.
[11] Freeman HJ, Berean KW. Resolution of paraneoplastic collagenous enterocolitis after resection of colon cancer. Can J Gastroenterol. 2006;20(5):357-60.
[12] Mahajan D, Goldblum JR, Xiao SY, Shen B, Liu X. Lymphocytic colitis, and collagenous colitis: A review of clinicopathologic features and immunologic abnormalities. Adv Anat Pathol. 2012;19(1):28-38.
[13] McCashland TM, Donovan JP, Strobach RS, Linder J, Quigley EM. Collagenous enterocolitis: A manifestation of gluten-sensitive enteropathy. J Clin Gastroenterol. 1992;15(1):45-51. PMID: 1500661
[14] Chatti S, Haouet S, Ourghi H, Belkahla N, Kchir N, el Ouertani L, et al. Collagenous enterocolitis. Apropos of a case and review of the literature. Arch Anat Cytol Pathol. 1994;42(3-4):149-53. French. PMID: 7857133.
[15] Castellano VM, Muñoz MT, Colina F, Nevado M, Casis B, Solís-Herruzo JA. Collagenous gastrobulbitis and collagenous colitis. Case report and review of the literature. Gastroenterol. 1999;34(6):632-38. Doi: 10.1080/003655299750026128. PMID: 10440616.
[16] Stolte M, Ritter M, Borchard F, Koch-Scherrer G. Collagenous gastroduodenitis on collagenous colitis. Endoscopy. 1990;22(4):186-87. Doi: 10.1055/s-2007-1012837. PMID: 2209504.
[17] Meier PN, Otto P, Ritter M, Stolte M. Collagenous duodenitis and ileitis in a patient with collagenous colitis. Leber Magen Darm. 1991;21(5):231-32. German. PMID: 1758239.
[18] Navarro-Llavat M, Domènech E, Masnou H, Ojanguren I, Mañosa M, Lorenzo-Zúñiga V, et al. Collagenous duodeno-ileo-colitis with transient IgG deficiency preceded by Yersinia enterocolitica intestinal infection: Case report and review of literature Duodeno-íleo-colitis colágenaprecedida de infección intestinal por Yersinia enterocolitica: revisión de la literatura a propósito de uncaso. Gastroenterol Hepatol. 2007;30(4):219-21. Doi: 10.1157/13100588. PMID: 17408550.
[19] Macaigne G, Boivin JF, Harnois F, Chayette C, Dikov D, Cheaib S, et al. Collagenous gastritis and ileo-colitis occurred in autoimmune context: Report of a case and review of the literature. Gastroenterol Clin Biol. 2010;34(8-9):e01-06. French. Doi: 10.1016/j.gcb.2009.06.020. Epub 2010 Jul 15. PMID: 20637552.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Seth GS Medical College and KEM Hospital, Thane, Maharashtra, India.
2. Fellow, Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.
3. Fellow, Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.
4. Resident, Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.
5. Associate Professor, Department of Pathology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Rachana Chaturvedi,
Zeon B 403, Ajmera Bhakti Park, Wadala East, Mumbai-400037, Maharashtra, India.
E-mail: rachanachaturvedi@yahoo.co.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 17, 2023
- Manual Googling: Jun 20, 2023
- iThenticate Software: Oct 07, 2023 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Apr 15, 2023**
Date of Peer Review: **May 24, 2023**
Date of Acceptance: **Oct 10, 2023**
Date of Publishing: **Dec 01, 2023**