CASE REPORT

Collagenous enterocolitis and maturity onset type 1 diabetes manifesting as uraemia, malabsorption and extreme weight loss

Jonathan Michael Hunter,^{1,2} Hui Jean Lee,^{2,3} Andrew Dettrick,^{2,4} Christopher Tan^{1,2}¹Department of Medicine, Redcliffe Hospital, Brisbane, Queensland, Australia²School of Medicine, University of Queensland, Brisbane, Australia³Department of Medicine, The Prince Charles Hospital, Brisbane, Queensland, Australia⁴Department of Anatomical Pathology, The Prince Charles Hospital, Brisbane, Queensland, Australia**Correspondence to**

Dr Jonathan Michael Hunter, jonhunter@live.com.au

Accepted 7 July 2014

SUMMARY

A 37-year-old patient with type 1 diabetes had been recently diagnosed with collagenous colitis (CC) after sigmoidoscopy. She rapidly progressed from a fortnight of watery diarrhoea, to a malabsorptive state with severe dehydration and acute kidney injury. This necessitated admission to an intensive care unit for emergency dialysis. She was subsequently diagnosed with collagenous enterocolitis affecting gastric, small bowel and colonic mucosa which required systemic steroid therapy. Physicians caring for patients with CC should be aware of the potential extreme manifestations of upper gastrointestinal collagenous deposition.

BACKGROUND

This is only the fifth reported case of collagenous enterocolitis in the literature and the first requiring emergency renal replacement therapy with admission to an intensive care unit.

It further adds support that collagenous enterocolitis has an autoimmune aetiology.

It emphasises the subsequent problems and guarded prognosis these patients face with regard to long-term malabsorption, weight loss and steroid dependency.

It highlights to physicians the need to screen for collagenous deposition in the upper gastrointestinal (GI) tract if collagenous colitis (CC) is diagnosed.

CASE PRESENTATION

A 37-year-old woman presented with an initial 2-month history of watery diarrhoea. There had been no known enteric infectious contact or recent antibiotic use. An initial diagnosis of CC had already been established following an earlier sigmoidoscopy and colonic biopsy. She had been prescribed oral mesalazine and loperamide with outpatient follow-up. However her condition rapidly deteriorated with progression to severe, large-volume diarrhoea and also frequent emesis resulting in representation to hospital. On this occasion, the patient was anuric with blood investigations revealing severe acute kidney injury and metabolic acidosis (table 1). She required intensive care unit management with prolonged intravenous fluid replacement and also 3 days of renal replacement therapy. Empiric therapy with intravenous hydrocortisone and also octreotide were started to treat the patient's large-volume diarrhoea with an estimated 5000 mL loss daily. She also required intermittent parental replacement of potassium,

magnesium and phosphate for severe electrolyte deficiency.

Her medical history was remarkable in being diagnosed with maturity onset type 1 diabetes mellitus 6 years earlier. At that time she had serological proof of autoimmune diabetes mellitus with elevated antglutamic acid decarboxylase and anti-IA2-antibodies. Glycaemic control was initially poor with a glycated haemoglobin (HbA1c) of 11.8%. There were no known diabetic microvascular or macrovascular complications, with prior normal renal function and no albuminuria.

She had a history of anxiety and depression on treatment with a selective serotonin reuptake inhibitor.

Her other medications consisted of insulin lispro 8–12 units three times daily, insulin glargine 70 units nocte and paroxetine 40 mg daily.

She was a current smoker at the time with a 30 pack-year smoking history, and was unemployed with two children.

After 2 weeks of intensive care management, the patient's hypovolaemia, large volume diarrhoea and renal function improved. She underwent upper endoscopy and colonoscopy to review her diagnosis. The resultant histological samples were diagnostic of collagenous enterocolitis with marked thickening of the subepithelial collagen plate in the stomach, duodenum, terminal ileum and colon. The patient was started on an indefinite gluten-free diet and oral budesonide 9 mg daily. Her paroxetine was changed to escitalopram while inpatient due to prior case report associations with collagenous enterocolitis. Gradually her diarrhoea settled from 5000 mL loss daily to around 300 mL. This coincided with improved renal function, with her serum creatinine stabilising at 140 µmol/L.

The patient's malnutrition was also addressed with a short course of parental nutrition and oral nutritional supplements under dietician supervision.

INVESTIGATIONS

Serial blood investigations (table 1) show development of hyponatraemia, hypokalaemia, hypoalbuminaemia, an acute kidney injury and metabolic acidosis.

Interestingly, human leucocyte antigen (HLA) typing revealed DQA1:05 and DQB1:02 with negative coeliac serology including anti gliadin (deamidated) IgG and tissue transglutaminase IgA antibodies.

CrossMark

To cite: Hunter JM, Lee HJ, Dettrick A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200409

Table 1 Initial and subsequent blood investigations

	8 January 2012	18 January 2012	1 February 2012	5 February 2012	28 February 2012	22 March 2012	22 November 2012	22 May 2013
Na ⁺ (135–145 mmol/L)	136	124	125	120	135	140	136	138
K ⁺ (3.5–5.1 mmol/L)	3.5	3.1	2.7	3.5	3.7	2.9	4	5.4
Urea (2.1–7.1 mmol/L)	5.3	9	11.4	23.4	6.3	4.8	7.3	22.7
Creatinine (46–90 µmol/L)	70	149	223	816	139	137	121	299
HCO ₃ ⁻ (22–32 mmol/L)	20	18	16	11	21	20	20	22
Albumin (35–50 g/L)	39		21	24	<15	17	16	27
Phosphate (0.81–1.45 mmol/L)		0.43			0.86	1.14	1.26	
Mg (0.7–1.0 mmol/L)		1.05			0.62	0.55	0.47	
Alt (<40 U/L)	12			10	17	80	20	35
INR				1.5		1.7		1.4
Retinol (1.6–2.3 µmol/L)						1.5	1.1	
Vitamin D (50–150 nmol/L)						42	52	
Retinol binding protein (1.4–2.9 µmol/L)						1.9	2.3	
Echis time (8–16 s)								20
Selenium (0.7–1.4 µmol/L)						0.4	0.4	
Zinc (8–18 µmol/L)						22	7	

INR, international normalised ratio.

The initial sigmoidoscopy macroscopically revealed non-specific mucosal hyperaemia with marked loss of normal vascular patterns.

Endoscopic biopsies were obtained from the stomach, duodenum, terminal ileum and colon and were stained using both H&E and Masson's trichrome.

The biopsies obtained at the initial sigmoidoscopy, the gastro-colonoscopy 4 weeks later and gastrocolonoscopy at 10-month follow-up were all very similar. The features of the last set of biopsies will be described in detail, as they are representative of all biopsies and are arguably the most significant because they demonstrate failure to respond to gluten-free diet and medication.

In the stomach mucosa, the outstanding abnormality was marked by thickening of the subepithelial collagen plate (Masson's trichrome positive, Congo red negative) ([figure 1](#)). Although patchy, it is measured as much as 200 µm thick and contained dilated and entrapped capillaries. There was also a moderate mixed inflammatory infiltrate predominantly in the lamina propria but also with some extension into the surface epithelium. Lymphocytes were only a part of the intraepithelial

inflammation and did not reach criteria for intraepithelial lymphocytosis (being well below 25/100 epithelial cells). Other changes included flattening and focal detachment of the surface epithelium. No *Helicobacter* were seen. The changes were typical for collagenous gastritis.¹

The duodenal mucosa showed a similarly remarkable subepithelial collagen plate, measuring up to 130 µm thick, containing entrapped capillaries ([figure 2](#)). This was accompanied by villous flattening, inflammation in the lamina propria and intraepithelial mixed inflammation. The intraepithelial inflammation included lymphocytes, eosinophils and occasional neutrophils. Regardless of which of the several published criteria were applied, the number of lymphocytes fell below the diagnostic threshold for intraepithelial lymphocytosis. Though, intraepithelial lymphocytes are an accepted feature of collagenous sprue.² Neither convincing crypt hyperplasia nor *Giardia* were seen. The features were typical for collagenous sprue.²

Terminal ileal mucosa was similar in most respects to the duodenum with the collagen measuring up to 90 µm thick ([figure 3](#)). Possible mild crypt hyperplasia was present, though not surprising given the surface damage.

Figure 1 Stomach mucosa showing markedly thickened subepithelial collagen plate (up to 200 µm thick), moderate mixed inflammation in the lamina propria, flattened and detached epithelium, and intraepithelial lymphocytes <25/100 enterocytes. Entrapped capillaries are clearly demonstrated.

Figure 2 Duodenal mucosa displaying markedly thickened subepithelial collagen plate, villous flattening, inflammation in the lamina propria and mild intraepithelial mixed inflammation.

In the colon, the subepithelial collagen plate measured as much as 90 μm and there was focal separation of the surface epithelium from the underlying connective tissue (figure 4). The number of intraepithelial lymphocytes was within normal limits. There was no crypt damage and no parasites were seen.

OUTCOME AND FOLLOW-UP

Although her large volume diarrhoea initially responded well to treatment, there remain on-going issues of chronic diarrhoea, malabsorption, malnutrition and severe lethargy.

Her renal function (table 1) unfortunately has never returned to baseline function with development of chronic kidney disease. We presume her mild coagulopathy results from impaired vitamin K absorption as evidenced by a prolonged echis time.

She has suffered unintentional weight loss of 70 kg. Owing to fastidious glucose control coupled with improved insulin sensitivity from reduced adiposity, her HbA1c is currently 6.7%.

She is now obstinate from cigarette smoking.

Despite prolonged immunosuppression, she has required intermittent hospitalisation for parental nutrition and hydration. She currently remains corticosteroid dependent, with a guarded prognosis.

DISCUSSION

The term CC was first coined in 1976 by Lindstrom³ and is characterised by collagen deposition under the surface epithelium of colorectal mucosa. Classically the mucosa is macroscopically unremarkable under endoscopic visualisation. The annual incidence of CC has been reported, in several European studies,

to be 0.6–5.2/100 000 with a prevalence of 10–15.7/100 000.^{4 5}

The years following its initial report have been plagued by uncertainty and controversy with regard to sampling error and apparent overlap with the other ‘microscopic colitis’,⁶ lymphocytic colitis.

Diagnosis of CC depends on demonstrating the thickened collagen band. An absolute minimum measurement to constitute ‘thickened’ has not been settled on by the international literature with a wide range quoted (10–70 μm) normal subepithelial collagen plate is 3–7 μm thick. Regardless of which of the published criteria are adopted, the current case has clearly demonstrated a markedly thickened collagen plate.

Gastric mucosal collagen banding in our case was as thick as 200 μm in places. This is also in keeping with prior case reports and series citing gastric collagen band deposition from 15 to 225 μm in diameter.^{1 7}

In this case and CC generally, there are also signs of chronic inflammation, frequently with a more marked eosinophilia in the lamina propria.⁴ Chronic inflammation is such a usual component of CC such that the diagnosis should be made with caution if there is none.

The phenomenon of collagenous sprue was first reported in 1947⁸ when it was believed to be simply a form of refractory coeliac disease (CD). It was not until 1970 that this entity was termed collagenous sprue by Weinstein *et al*⁹ in a female patient who later died from malabsorption.

Classically collagenous sprue presents with chronic diarrhoea, malabsorption and weight loss with multiple nutritional deficiencies,¹⁰ intimately associated with CD and a strong

Figure 3 Terminal ileal mucosa showing thick subepithelial collagen plate, detached epithelium and mild inflammation of the lamina propria. An entrapped capillary is clearly shown on the trichrome stain.

Figure 4 Colonic mucosa with thick subepithelial collagen plate and some intraepithelial lymphocytes (not reaching diagnostic threshold).

association with autoimmune disease. A variable severity of villus atrophy often occurs (as in this case), with a distinct subepithelial collagen deposition¹¹ which is very similar histologically to CC.

In the largest case series of collagenous sprue from the Mayo clinic, the most common associated risk factor was CD.¹² They also concluded in most patients the disease could be controlled with a combination of steroids and a gluten-free diet. Interestingly both conditions have been associated with positive antiendomysial antibodies as well as hyposplenism.¹³ HLA typing in our patient revealed CD-susceptibility haplotype DQA1:05 and DQB102 (+HLA DQ2 status) genotype.

Interestingly, high prevalence of this HLA type has also been found in collagenous sprue patients. Consequently, gluten immunological sensitivity has been postulated as causal to the clinical overlap between the two conditions.^{7 14}

Conversely, mild thickening of the subepithelial collagen is common and associated with a poorer prognosis in gluten enteropathy¹⁵ though a diagnosis of collagenous sprue should not be made unless the collagen band is $>10\text{ }\mu\text{m}$ thick with capillary entrapment.² A clinically similar disease entity to collagenous sprue has recently been termed collagenous enterocolitis describing coexistent CC with small bowel collagen deposition and malabsorption.^{7 16 17}

Its aetiology again remains obscure though there is a case report of histologically proven collagenous enterocolitis resolving, following surgical removal of a coexistent bowel cancer.¹⁸ The authors postulated that their case of collagenous enterocolitis was a reversible paraneoplastic phenomenon.

In fact collagen deposition throughout the GI tract either in true isolation or associated with the more common CC has now been described.^{19–26}

Generally those features that would be suggestive of an autoimmune involvement would be: (1) an association with other autoimmune disorders, (2) an association with specific HLA haplotypes, (3) circulating disease-specific autoantibodies (4) a prominent lymphocytic infiltrate at the site of active disease, with induced epithelial expression of HLA class I antigens and (5) corticosteroid responsiveness.

In keeping with our case, observational studies have constantly suggested an association of CC with autoimmune disease such as autoimmune thyroiditis, diabetes and seronegative arthritides.^{27 28}

A study at the Royal Melbourne Hospital, as well as showing a strong association of coexistent CD and CC (in keeping with several prior case reports and the Mayo case series), revealed intraepithelial CD8 T cells in higher than expected numbers. CD8 T cells also show major histocompatibility complex class I

restriction, and in this context the antigen presented is usually a processed peptide of an endogenous antigen.²⁹

Bohr *et al*³⁰ in 1996 showed that the patients with CC as well as having significantly higher serum IgM levels were numerically more likely to have a positive antinuclear antibody titre as compared to the control group. Interestingly this was consistent with three smaller studies also finding high frequency of positive antinuclear antibody titres associated with CC. To date however, no specific autoantibody or common HLA to the disease has been found.³¹

Given the unknown aetiology of CC, treatment has historically been empirical, consisting of antidiarrheal agents and escalating anti-inflammatory/immunosuppressive regimes.³² This patient, however, was initially unresponsive to mesalazine and loperamide. Although regrettable, this perhaps was not unsurprising, given lack of randomised control trials and the cited 50% response rate of mesalazine from retrospective data.³³

She was finally stabilised with budesonide therapy following intravenous hydrocortisone.

Corticosteroids, specifically oral budesonide, remain the mainstay treatment of all forms of collagen deposition in the gut. Presently clinical trials evaluating utility of budesonide for enteric collagen deposition have only occurred with CC. In the largest randomised controlled trial of around 50 CC patients evaluating budesonide with placebo, clinical remission and histological improvement was achieved in 86.9% vs 13.6% and 60.9% vs 4.5%, respectively.³⁴ A smaller Belgian study reported a response rate with budesonide of 57.2% versus a placebo rate of 21.4%.³⁵ One population study³⁶ comparing treatment of microscopic colitis showed an 82.5% vs 52.9% remission rate with budesonide over prednisolone. Also unlike prednisolone,³⁷

Learning points

- ▶ Collagenous enterocolitis is rare and an extreme spectrum of collagenous colitis that general physicians may encounter.
- ▶ Collagenous enterocolitis may manifest with acute severe diarrhoea, malabsorption and rarely, as in this case, acute kidney injury.
- ▶ Endoscopic detection of focal collagen deposition in the gut should prompt physicians to look elsewhere in the gastro-oesophageal tract for more extensive disease.
- ▶ Currently, first-line therapy is immunosuppression with corticosteroids yet the prognosis remains guarded, with need for further research.

long-term budesonide therapy does not significantly suppress adrenal function³⁸ and is associated with better preserved bone mass.³⁹ This feature is related to budesonides high first pass hepatic metabolism and is a useful characteristic should the need arise for maintenance therapy in CC.

As described earlier, interval endoscopy and histology findings have remained consistent despite adherence to a gluten-free diet and an initial clinical response to corticosteroid therapy. This is in keeping with previous findings of persisting endoscopic abnormalities and poor clinical correlation.⁴⁰

Contributors JMH was responsible for research, organisation and the predominant writer of the case. HJL helped with initial research and was added later to the author list after providing extensive writing time and research to help answer the reviewers' comments/queries. AD prepared all the histological sections and contributed significantly to writing and shaping the article. CT had the original idea to write up the case, performed the necessary biopsies and contributed significantly to the writing.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Lagorce-Pages C, Fabiani B, Bouvier R, et al. Collagenous gastritis: a report of six cases. *Am J Surg Pathol* 2001;25:1174–9.
- Maguire AA, Greenon JK, Lauwers GY, et al. Collagenous sprue: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 2009;33:1440–9.
- Lindstrom CG. 'Collagenous colitis' with watery diarrhoea—a new entity? *Pathol Eur* 1976;11:87–9.
- Lazenby AJ, Yardley JH, Giardiello FM, et al. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. *Hum Pathol* 1989;20:18–28.
- Baert F, Wouters K, D'Haens G, et al. Lymphocytic colitis: a distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis. *Gut* 1999;45:375–81.
- Read NW, Krejs GJ, Read MG, et al. Chronic diarrhea of unknown origin. *Gastroenterology* 1980;78:264–71.
- McCashland TM, Donovan JP, Strobach RS, et al. Collagenous enterocolitis: a manifestation of gluten-sensitive enteropathy. *J Clin Gastroenterol* 1992;15:45–51.
- Schein J. Syndrome on non tropical sprue with hitherto undescribed lesions of the intestine. *Gastroenterology* 1947;8:438–60.
- Weinstein WM, Saunders DR, Tytgat GN, et al. Collagenous sprue—an unrecognized type of malabsorption. *N Engl J Med* 1970;283:1297–301.
- [No authors listed]. Collagenous sprue. *BMJ* 1971;2:65–6.
- Brandborg LL. Histologic diagnosis of diseases of malabsorption. *Am J Med* 1979;67:999–1006.
- Rubio-Tapia A, Talley NJ, Gurudu SR, et al. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol* 2010;8:344–49.
- Freeman HJ. Hyposplenism, antiendomysial antibodies and lymphocytic colitis in collagenous sprue. *Can J Gastroenterol* 1999;13:347–50.
- Fine KD, Do K, Schulte K, et al. High prevalence of celiac sprue-like HLA-DQ genes and enteropathy in patients with the microscopic colitis syndrome. *Am J Gastroenterol* 2000;95:1974–82.
- Bossart R, Henry K, Booth CC, et al. Subepithelial collagen in intestinal malabsorption. *Gut* 1975;16:18–22.
- Eckstein RP, Dowsett JF, Riley JW. Collagenous enterocolitis: a case of collagenous colitis with involvement of the small intestine. *Am J Gastroenterol* 1988;83:767–71.
- Chatti S, Hauet S, Ourghi H, et al. [Collagenous enterocolitis. Apropos of a case and review of the literature]. *Arch Anat Cytol Pathol* 1994;42:149–53.
- Freeman HJ, Berean KW. Resolution of paraneoplastic collagenous enterocolitis after resection of colon cancer. *Can J Gastroenterol* 2006;20:357–60.
- Borchard F, Niederau C. [Collagenous gastroduodenitis]. *Dtsch Med Wochenschr* 1989;114:1345.
- Castellano VM, Munoz MT, Colina F, et al. Collagenous gastrobulbitis and collagenous colitis. Case report and review of the literature. *Scand J Gastroenterol* 1999;34:632–8.
- Jin X, Koike T, Chiba T, et al. Collagenous gastritis. *Dig Endosc* 2013;25:547–9.
- Macaigne G, Boivin JF, Harnois F, 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:e1–6.
- Rustagi T, Rai M, Scholes JV. Collagenous gastroduodenitis. *J Clin Gastroenterol* 2011;45:794–9.
- Wang HL, Shah AG, Yarian LM, et al. Collagenous gastritis: an unusual association with profound weight loss. *Arch Pathol Lab Med* 2004;128:229–32.
- Zhang HJ, Jin Z, Lin SR, et al. [A case report of collagenous gastritis in a young Chinese woman and literatures review]. *Zhonghua Nei Ke Za Zhi* 2010;49:688–90.
- O'Brien BH, McClymont K, Brown I. Collagenous ileitis: a study of 13 cases. *Am J Surg Pathol* 2011;35:1151–7.
- Kao KT, Pedraza BA, McClune AC, et al. Microscopic colitis: a large retrospective analysis from a health maintenance organization experience. *World J Gastroenterol* 2009;15:3122–7.
- Bohr J, Tysk C, Eriksson S, et al. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. *Gut* 1996;39:846–51.
- Armes J, Gee DC, Macrae FA, et al. Collagenous colitis: jejunal and colorectal pathology. *J Clin Pathol* 1992;45:784–7.
- Bohr J, Tysk C, Yang P, et al. Autoantibodies and immunoglobulins in collagenous colitis. *Gut* 1996;39:73–6.
- Giardiello FM, Bayless TM, Jessurun J, et al. Collagenous colitis: physiologic and histopathologic studies in seven patients. *Ann Intern Med* 1987;106:46–9.
- Madisch A, Morgner A, Stolte M, et al. Investigational treatment options in microscopic colitis. *Expert Opin Investig Drugs* 2008;17:1829–37.
- Alberti-Flor JJ, Howell S. Olsalazine in collagenous colitis. *Br J Clin Pract* 1994;48:158–9.
- Miehke S, Heymer P, Bethke B, et al. Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002;123:978–84.
- Baert F, Schmit A, D'Haens G, et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002;122:20–5.
- Gentile NM, Abdalla AA, Khanna S, et al. Outcomes of patients with microscopic colitis treated with corticosteroids: a population-based study. *Am J Gastroenterol* 2013;108:256–9.
- Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;41:209–14.
- Hanauer S, Sandborn WJ, Persson A, et al. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005;21:363–71.
- Schoon EJ, Bollani S, Mills PR, et al. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin Gastroenterol Hepatol* 2005;3:113–21.
- Vakiani E, Arguelles-Grande C, Mansukhani MM, et al. Collagenous sprue is not always associated with dismal outcomes: a clinicopathological study of 19 patients. *Mod Pathol* 2010;23:12–26.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow