Macroscopic endoscopic lesions in microscopic collagenous colitis : double case report and review of the literature

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Abstract

Collagenous colitis is a cause of chronic diarrhea of incompletely elucidated origin, defined by normal laboratory tests, a normal endoscopic appearance of colonic mucosa and specific microscopic inflammatory features on colonic biopsies. We report two cases of macroscopic endoscopic lesions observed in patients suffering from chronic diarrhea, whose biopsies confirmed a diagnosis of collagenous colitis and who were successfully treated in that setting, achieving clinical and endoscopic remissions. By means of a literature review, we summarize what is known about collagenous colitis. We particularly discuss macroscopic findings in that context, drawing attention on the so called "microscopic colitis" in the differential diagnosis of that type of lesions. (Acta gastroenterol. belg., **2011**, 74, **454-461**).

Key words : collagenous colitis, endoscopy, ulcerations, mucosal tears.

Introduction

Collagenous colitis is a well recognised cause of chronic diarrhea. It is classified as microscopic colitis as its diagnosis requires typical pathological features on biopsies taken from a usually macroscopically normal colonic mucosa. We describe two cases of macroscopic endoscopic lesions of this mucosa observed in patients suffering from chronic diarrhea and whose biopsies confirmed a diagnosis of collagenous colitis. By means of a literature review, we summarize what is known at present about collagenous colitis and particularly discuss the associated macroscopic lesions.

Case report number one

A seventy-year-old man consulted in September 2002 for recent dyspepsia, long lasting hypogastric discomfort and stool disturbance, alterning diarrhea and constipation. Systematic questionnaire and physical exam were uncontributive.

His past medical history was marked by hypertension treated with an association of lisinopril-hydrochlorothiazide and hyperuricemia treated with allopurinol.

Gastroscopy and colonoscopy were performed, showing a Los Angeles grade A oesophagitis and a normal colonic mucosa. No biopsies were taken. Pantoprazole was prescribed.

Four months later, the patient came back, complaining of diurnal and nocturnal explosive diarrhea with fecal incontinence, which started two months earlier and occurred six to seven times a day, but without significant weight loss or general status deterioration. Relevant data from systematic anamnesis included a switch from pantoprazole to lansoprazole three months ago and a recent addition of bisoprolol for uncontrolled hypertension. Physical exam remained uncontributive and blood tests, including thyroïd tests, were normal.

Assumption was made that these complaints may be due to previously well-described lansoprazole-associated microscopic colitis. An ileocolonoscopy was performed immediately without preparation. Curiously, this showed blood stains in the transverse and right parts of the colon combined with strange colonic mucosal tears, mimicking "cat-scratch" lesions (Fig. 1). These lesions predominantly involved the right part of the colon, but were also present in the left part of it and in the terminal ileum, suggesting a possible alternative diagnosis of IBD, especially atypical Crohn's disease. Biopsies were taken and the patient was advised to stop lansoprazole.

Bacterial cultures of biopsies showed a normal colonic flora associating E. Coli and Streptococcus bovis ; histology showed an important thickening ($> 10\ \mu$m) of the subepithelial basement membrane (Fig. 2), enhanced by Picro-Sirius coloration, suggestive of a diagnosis of collagenous colitis.

Clinical, endoscopic and microscopic evolutions were favourable concomitantly with lansoprazole withdrawal, with complete relief of symptoms after 24 hours, normal aspect of the colonic mucosa at control endoscopy two months later and normal control biopsies. Lansoprazole was switched back to pantoprazole, without recurrent complaints.

Eighteen months later, in December 2004, the patient consulted again for explosive diarrhea, still without any "alert symptom" or general status deterioration. A recurrence of collagenous colitis had to be excluded, especially as systematic anamnesis pointed out reintroduction one month earlier of a proton-pump inhibitor, omeprazole at that time, for recurrent pyrosis following pantoprazole cessation due to administrative reimbursement problems.

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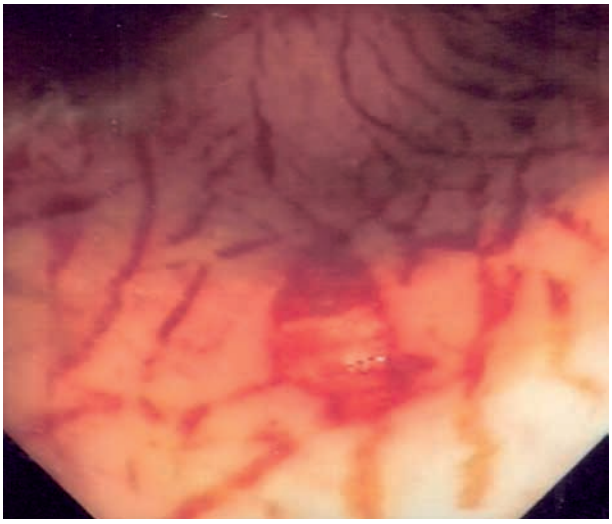

Fig. 1. — Case 1 : endoscopic colonic mucosal tears mimicking "cat-scratch" lesions (2003).

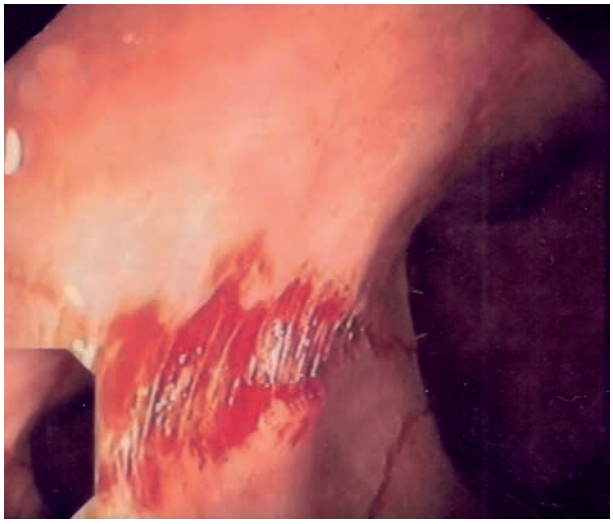

Fig. 3. — Case 1 : recurrence of endoscopic colonic "cat-scratch" lesions (2004).

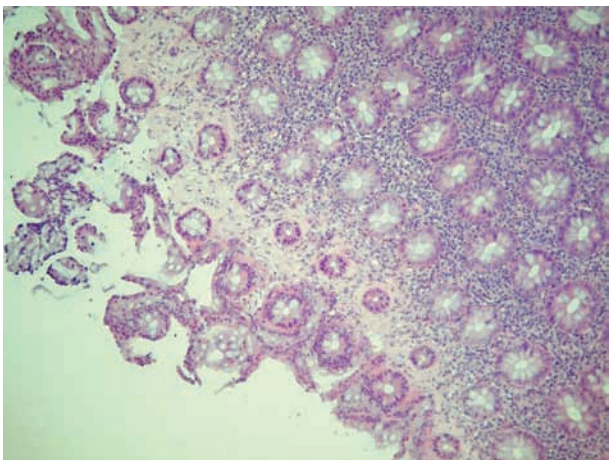

Fig. 2. — Case 1 : marked thickening of the basal membrane in a slightly inflamed colonic mucosa (H&E ×100).

Colonoscopy showed recurrence of the previously described macroscopic lesions (Fig. 3), even more impressive at that time, and biopsies confirmed recurrent collagenous colitis. The patient was advised to stop omeprazole and was completely free of symptoms a few days later. A control colonoscopy performed one month later was normal, although biopsies showed persistence of focal stains of collagenous colitis. The patient was then lost to follow-up.

Case report number two

A fifty-six-year old woman consulted in September 2008 in the emergency department for repeated episodes of hematochezia for 48 hours, adding further to frequent episodes of diurnal and nocturnal loose stools with fecal incontinence occurring for 3 months. There was no abdominal pain, pyrosis, fever, nor unusual fatigue, but post-prandial nausea and dyspepsia, and an 8 kg weight loss during the same period. She had not travelled recently, took no new medication and had not changed her nutritional habits. There was no epidemic context of gastroenteritis within her relatives.

Her past medical history was marked by diabetes mellitus, hypercholesterolemia, epilepsia, chronic atrial fibrillation, mitral valve replacement, VVI-defibrillator implant for syncope and transient cardiac arrest following ventricular fibrillation, and cholecystectomy. She smoked twenty cigarettes per day and had no excessive alcohol consumption. Her daily medication was glimepiride, atorvastatine, valproic acid, bisoprolol, acenocoumarol, acetylsalicylic acid, perindopril and trazodone chlorhydrate. She had a recent consumption of NSAIDs for arthralgia.

Hemodynamic parameters at admission were normal and physical exam was unremarkable except for a small degree of dehydration.

Biological tests showed a moderate inflammatory syndrome with a CRP level of 6,4 mg/dl, normal complete blood count, normal glycosylated haemoglobin level of 6.5%, normal thyroïd tests, signs of moderate renal dysfunction due to dehydration (with urea and creatinine levels of 87 and 2,9 mg/dl respectively, returning to normal values after normosaline solution perfusion, as it was for CRP level in parallel), and coagulation disturbance with excessive prothrombine time, expressed by international normalized ratio superior to 7, due to excess of acenocoumarol. ANCA and ASCA were negative. Normal serum levels of iron and liposoluble vitamins and normal steatocrite excluded malabsorption. Stool cultures and search for parasites were negative.

Abdominal X-ray showed some insignificant hydroaeric transition levels without ileal or colic dilation, abdominal CT-scan showed a normal appearance of the small bowel and the colon, except for minor sigmoid diverticulosis with no signs of inflammation.

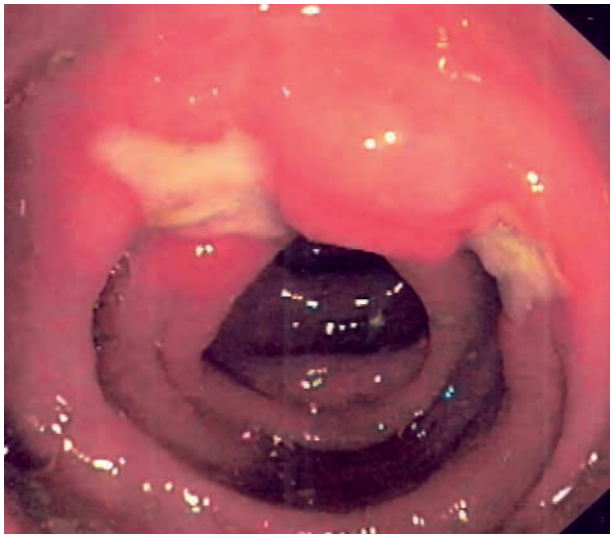

Fig. 4. — Case 2 : endoscopic large round ulcerations in the left part of the colon.

Gastroscopy showed mild atrophic aspect of gastric mucosa and two Forrest III ulcers located on the small and large gastric corporeal flexures, all biopsied. Rectoscopy showed sigmoid diverticules and normal stools. Colonsocopy showed aspecific mucosal inflammatory patches in the sigmoid part of the colon, two large round ulcerations (Fig. 4) endoscopically suggestive of either drug-induced or Crohn's disease or ischemic ulcerations in the left part of the colon, and "cat-scratch" mucosal dilacerations, oozing blood, throughout the transverse and right parts of the colon (Fig. 5-6). All these lesions were biopsied. Barium small bowel X-ray was normal. Isotopic gastric emptying time measurement showed mild gastroparesis, consistent with possible diabetes mellitus' neuropathy. Small intestinal bacterial overgrowth was excluded in that context by normal hydrogen breath test with lactose. Celiac disease, giardiasis, Helicobacter Pylori, eosinophilic gastritis, Menetrier's disease and Zollinger Ellison's syndrome were excluded by normal appropriate laboratory tests and/or normal gastric or duodenal biopsies.

All colonic biopsies showed the same microscopic aspect of a normal cryptic colonic mucosa (for samples coming from inflammatory patches and non-ulcerated mucosa) or a fibrinoleucocytic necrotic ulcerated mucosa (for samples coming from linear or round ulcerations) laying on a thickened subepithelial basement membrane, in places largely exceeding 10 μm, enhanced by a Picro-Sirius coloration (Fig. 7). These data confirmed the diagnosis of collagenous colitis and excluded the hypotheses of Crohn's disease or patchy ischemic colitis as suggested by the macroscopic endoscopic exam.

The patient was discharged with a prescription of domperidone for gastroparesis and 9 mg daily budesonide for collagenous colitis, and with recommendation to avoid the use of NSAIDs. Evolution was rapidly favourable, with complete relief of symptoms.

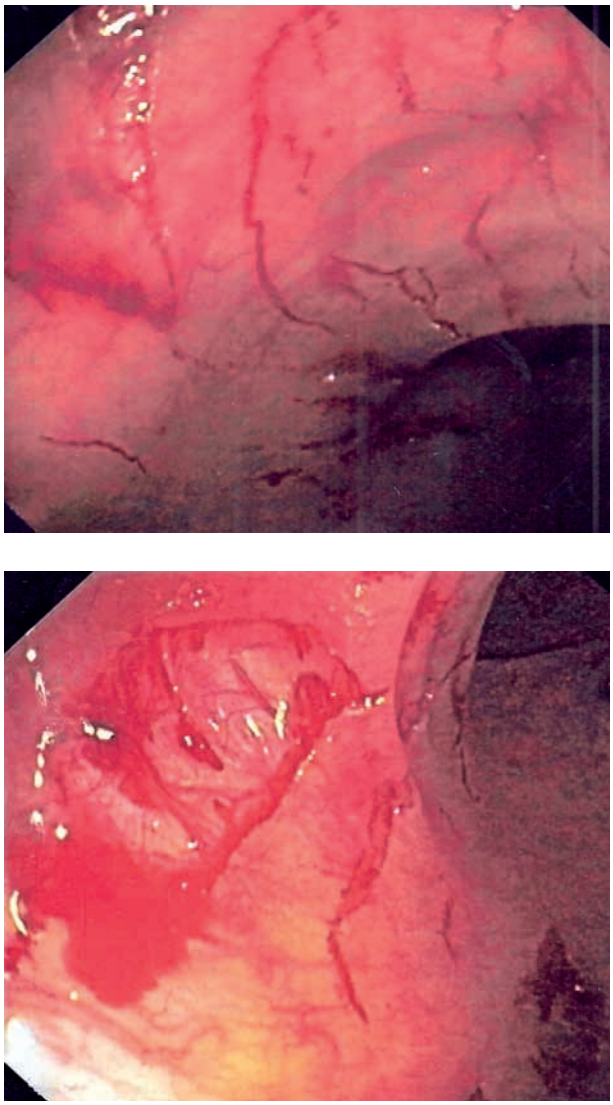

Fig. 5 and 6. — Case 2 : endoscopic "cat-scratch" ulcerations oozing blood in the right part of the colon.

A control colonoscopy performed three months later, in December 2008, showed complete mucosal healing, and multiple biopsies confirmed absence of residual collagenous colitis.

Discussion

1. *Definition of collagenous colitis, epidemiology and clinical presentation*

First described by Lindström in 1976 (1), collagenous colitis is an uncommon (2) chronic inflammatory bowel disease of unknown origin, predominantly affecting middle-aged women (2,3,4,5,6,7), with a mean female-to-male ratio of approximately 7:1 (6) and a mean age of 55 (2,3,4) to 68 (4) years at diagnosis. The incidence rate ranges from 1 to 15/100.000/year (4,7).

In 20% (8) of patients, it is associated with a dysimmune context and immune pathologies such as celiac

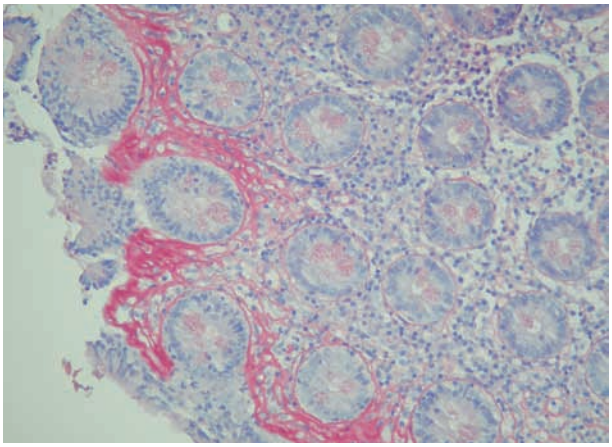

Fig. 7. — Case 2 : Picro-Sirius coloration showing the thickened basal membrane (in red) with entrapped lymphocytes (Picro-Sirius ×200).

disease (3,4,5,8), dysthyroïdy (3), rheumathoïd arthritis (3,4), seronegative polyarthritis (3), HLA-B27-positive oligoarthritis (3), Horton's arteritis (3), myasthenia gravis (9), lupus erythematosus (3), amyloïdosis (10), Sjögren's syndrome (10), CREST syndrome (11,12), psoriasis (3) or plane lichen (3).

Clinically, collagenous colitis causes watery and non-bloody diarrhea (3,4,5,7,13) defined as semi-loose or loose stools with a minimal frequency of 3/24h (or 21/week) (13). Up to 50% of patients complain of crampy abdominal pain (3) and bloating (13), and some report anal incontinence (5,7). There is usually no dramatic repercussion on general status, except for a possible loss of weight (3,5,7) assessed in the most severe cases as 5,2 +/- 3,4 kg (3). These disabling symptoms do not always resolve under symptomatic medication and may evolve on a chronic or a remitting-relapsing mode (13), urging patients to consult for further diagnostic procedures and management.

2. *Diagnostic tools and differential diagnosis for collagenous colitis*

Microscopic colitis accounts for 4 to 13% of patients investigated for chronic diarrhea (7). The diagnosis of collagenous colitis is mainly suspected on the basis of exclusion criteria, and is positively confirmed by colonic biopsies.

The clinical differential diagnosis of collagenous colitis is that of all causes of chronic watery diarrhea, which includes : a) laxative medications, b) hormonal disturbances (hyperthyroidism, Zollinger Ellison's syndrome, carcinoïd tumours), c) exocrine pancreatic insufficiency, d) infectious diseases (duodenal giardiasis, colonic bacterial/viral/parasitic infections), e) inflammatory diseases (especially Crohn's disease), f) celiac disease, g) Menetrier's disease, h) villous hypersecretant colonic tumours, i) parietal neurologic or muscular disorders, medications and previous surgical procedures responsible for small bowel bacterial overgrowth (diabetes mellitus associated neuropathy, amyloïdosis, sclerodermia, anti-Parkinson, anticholinergic and morphinic drugs, Billroth II gastric resection, bariatric surgery). All these diagnoses were excluded in our cases by anamnestic, clinical, biological, radiological and endoscopic data.

The up-to-now recognised paraclinical diagnostic criteria for collagenous colitis are a normal or near normal (mild edema with or without loss of normal vascular pattern) (4,5,7,14) endoscopic macrosopic appearance of the colonic mucosa, in contrast with histological lesions, characterised by a thickening of the subepithelial collagen band, exceeding 10 μm on a perpendicular section (4,7,14) presenting as a subepithelial hyaline deposit (5) enhanced by a trichrome or Picro-Sirius coloration (14). According to these criteria, collagenous colitis is classified as microscopic colitis, such as lymphocytic colitis (characterised by normal findings on colonic macroscopic endoscopy associated with an excessive number of intraepithelial lymphocytes in a normal or slightly inflammatory colonic mucosa without increased collagen deposit in the lamina propria) (4,7).

Other microscopic findings confirming collagenous colitis are a preserved normal crypt architecture (6,15,16), red blood cells and/or lymphocytes trapped within the collagen band (7,15,16), a ragged pattern of the latest's inferior margin (7,15,16), an increased mixed inflammatory cell infiltrate in the lamina propria (6,17), possibly including eosinophil white cells (17), and a possible associated increased number of intraepithelial lymphocytes exceeding 10 per 100 epithelial cells (6), parallel to lymphocytic colitis. A certain degree of epithelial cell damage may also be observed, including cell flattering and vacuolization and detachment of the surface epithelium (7,17).

Nevertheless, diagnosis of collagenous colitis is sometimes rendered more difficult by a segmental distribution (2,16). It is observed that the disease predominantly affects the right and transverse parts of the colon, with a collagen layer thickness gradually increasing from the rectum (usually not involved (4,6,16)) to the transverse (15) or proximal colon (2), and that the collagen deposit tends to be patchy rather than continuous in mucosal distribution (2,5,15,16). It is therefore important to systematically perform biopsies in all parts of the colon during endoscopy and at least as proximal as the transverse colon (15) to definitively confirm or exclude the diagnosis. Besides, a thickened collagen band may also be observed in association with diabetes mellitus, with or without clinical diarrhea, probably secondary to protein glycosylation. Immunohistochemical staining can help to differenciate both conditions : in collagenous colitis, the collagen band consists of collagen fibers type I, III and VI and tenascine (18,19) as opposed to collagen fibers type IV, fibronectine and laminine in case of thickening associated with diabetes mellitus (18). Response to treatment also differs, with no corticoid-induced remission in case of fibrosis related to diabetes. Response to budesonide and a normal level of glycosylated haemoglobin in our second case are in favour of collagenous

colitis. Finally, as observed in our patients, some macroscopic endoscopic lesions mimicking "cat-scratch" lesions correspond to collagenous colitis, calling into question the "microscopic" status of collagenous colitis. These macroscopic lesions will be discussed later.

3. *Physiopathology and etiologies of collagenous colitis*

Physiopathology of collagenous colitis remains unclear. Several hypotheses have been proposed, supported by observational data.

The main hypothesis is that of an inflammatory disease precipitated by an undetermined foreign agent, probably a noxious luminal factor as suggested by observed disease remission in case of fecal stream diversion by ileostomy and recurrence after restoration of intestinal continuity (20). This noxious agent may be of dietary (8), infectious (4,6,7,8), metabolic (biliar salts) (21) or iatrogenic origin. The latest includes several medications which were associated with development of collagenous colitis (4,5,6,7,8,14,22,23,24,25,26) : NSAIDs, ticlopidine, flutamide, ranitidine, cimetidine, omeprazole, lansoprazole, gold salts, carbamazepine, less evidently lisinopril (27), simvastatine (7) and maybe some antibiotics (28). The foreign agent would be responsible for immunologic cross-reactivity with an endogenous antigen produced by enterocytes. Fibrosis observed in biopsies would result from a local pathologic excess of collagen synthesis, leading to an increased subepithelial collagen deposition (18,29) and from possible reduced fibrolysis (19).

Tobacco may also play a noxious role since cigarette smoking seems more common in collagenous colitis patients (7) and a possible hormonal influence is not excluded given the female predominance of the disease (7).

Other hypotheses support either a possible etiologic role of genetic factors suggested by observed familial cases of collagenous colitis (5,7,8), or a possible reversible paraneoplastic phenomenon as some authors (8) reported complete remission of a collagenous involvement of the small and large intestine of a patient following resection of a coincidental colon cancer.

As for the pathogenesis of diarrhea in collagenous colitis, it seems correlated to the mucosal inflammatory process and a currently not completely elucidated secretory mechanism in which the collagen band may play the role of a cofactor acting as a diffusion barrier (5).

With regard to proton-pump-inhibitors, the most frequently incriminated molecules of drug-associated collagenous colitis are lansoprazole and omeprazole (23), in accordance with what was observed in our first patient. Lymphocytic colitis was also associated with lansoprazole (30,31), with notably two cases reported in our centre (31). According to observational data (23), the median time to developing symptoms after the start of lansoprazole or omeprazole treatment is 2 months and 85% of patients improve after cessation of treatment alone, as it occured in our first patient. We therefore firmly believe that in our first case, PPIs (lanzoprazole and omeprazole but not pantoprazole) were responsible for collagenous colitis. He also used lisinopril, which was incriminated in microscopic colitis, but this was used chronically and was never withdrawn. In the second case, recent use of NSAIDs was pointed out, possibly responsible for collagenous colitis, for nephrotoxicity with acute renal failure in a context of associated dehydration, and for coagulation disturbances secondary to drug-interaction with acenocoumarol, all three conditions observed at admission.

4. *Macroscopic endoscopic lesions in collagenous colitis : the "cat-scratch colon"*

a) Definition, epidemiology and physiopathology

"Cat-scratch colon", as named by W.M. Mcdonnell *et al*. in 2007 (32), is defined as bright red linear marks occasionally seen during colonoscopy and also described as longitudinal mucosal lacerations, mucosal tears (33,34,35,36) or shallow linear and sharply demarcated bleeding ulcers (9,28,37). It corresponds to superficial breaks in the colonic mucosa.

Colonic linear mucosal ulcerations are relatively rare : in a single endoscopy center report (32), over a two year period, they were observed in 22/8277 cases, i.e. an incidence rate of 0,25%. After comparison with histological findings in the same cases, the authors noted a significantly higher prevalence of collagenous colitis in case of linear ulcerations (14% vs 0,15%), suggesting an association between these lesions and collagenous colitis. Mucosal ulcerations remain however unfrequent in collagenous colitis : in a large series of 469 cases of collagenous colitis diagnosed at the Mayo Clinic between 1992 and 2000, only 9 cases showed mucosal ulceration (i.e. a prevalence of 1,9%) (27).

Mucosal tears predominantly affect the right side of the colon (ascending and transverse colon) (9,28,33,34), involvement of the left side being extremely rare as some authors described the so-called first case and to our knowledge unique case reported in the literature in 2009 (38) ; our first patient would then be the second one. Moreover, there is to our knowledge no previous literature report of ileal macroscopic lesions in a context of collagenous colitis, as observed in our first case. A differential diagnosis of Crohn's disease was excluded in this patient through unsuggestive biopsies and rapid clinical and endoscopic remissions after single withdrawal of lansoprazole, remissions not achieved in Crohn's disease without immunosuppressive treatment.

Physiopathologically, it is supposed (33,34,37,39) that collagen deposits and submucosal fibrosis are responsible for increased stiffness and loss of elasticity in the colonic areas involved, making them susceptible to linear fractures. Right predominance of the disease may be explained by the locally thicker collagen band (gradient of thickness from the left to the right parts of the colon as mentioned before) and by a greater wall tension because of a larger diameter of the right side of the

colon (9,38,40) (according to Laplace's law : tension on the wall of a cylindric vessel is proportional to its radius).

It is of note that macroscopic endoscopic lesions associated with collagenous colitis do not seem to be limited to linear ulcers. Our second patient also presented more classical round ulcers whose pathological exam however confirmed a diagnosis of collagenous colitis.

b) Differential diagnosis of cat-scratch lesions

As observed by McDonnell *et al*. (32), mucosal tears are strongly associated with (14% vs 0,15%) but are not specific of collagenous colitis.

Colonic linear mucosal defects may represent traumatic lesions after endoscopic instrumentation, possibly related to air insufflation and secondary barotrauma (8) or to insertion of barium contrast agents (8). In these cases, however, lesions typically involve the distal colon (8), as compared to lesions observed in our patients which predominantly involved the right part of the colon. Moreover, our patients did not receive any intrarectal fleet before endoscopy. Linear ulcers may also be observed in other conditions (28,41) including infectious colitis, Crohn's disease and ischemic colitis, urging clinicians to perform biopsies to confirm diagnosis and appropriately define management. It is of note that in ischemic colitis, margins of linear mucosal defects are irregular and defects are usually accompanied by circumferential mucosal edema as opposed to ulcerations described in collagenous colitis (28), allowing endoscopic distinction between both conditions.

Some authors (27) report that collagenous colitis presenting with macroscopic ulcerations is strongly associated with concomitant NSAIDs' use, suggesting that these are responsible for ulcerations rather than collagenous colitis itself, NSAIDs being known to induce ulcers in the whole digestive tract. This may be true in our second patient, who had concomitant Forrest III gastric ulcers, but not in our first patient who did not take any NSAID.

Other authors (28) suggest that linear mucosal defects may be characteristic of lansoprazole-associated collagenous colitis, as they observed, in a cohort of 13 collagenous colitis patients, that this endoscopic finding appeared in 78% of patients using lansoprazole versus in 0% of patients not using it ($p = 0,02$). Our second patient argues against this assumption as she had never taken any proton-pump inhibitor at the time of diagnosis. Moreover, our first patient experienced recurrent lesions with omeprazole, also illustrating that these are not specific for lansoprazole-associated microscopic colitis. It is to note that mucosal tears are not the only macroscopic lesions associated with lansoprazole. Some authors (11) indeed described a diffuse cloudiness of the colonic mucosa mimicking ulcerative colitis, which turned out to be collagenous colitis.

c) Pathology

Biopsies from colonic linear ulcerations in collagenous colitis show the same thickened subepithelial basement membrane with collagen deposits and inflammatory infiltrate as that observed in biopsies consistent with collagenous colitis taken from macroscopically normal sites of the colonic mucosa (28,33,34,41). Besides, they sometimes show a characteristic artificial detachment of the overlying surface epithelium (38) because of the decreased wall compliance due to the subepithelial deposits.

It is to note that, with regard to the association with NSAIDs, pathologic data in collagenous colitis are questionable. Some authors (41) who took biopsies from ulcerations in a patient with collagenous colitis taking NSAIDs described a histological aspect of acute and chronic inflammation associated with granulation tissue as observed in "classical" ulcers, without signs of collagenous colitis in these samples, as opposed to the at random biopsies taken from other parts of same patient's colonic mucosa. In our experience (case 2), biopsies taken from linear and more classical round ulcerations observed in the colon of our patient taking NSAIDs also showed an ulcerated mucosa but this was laying on a thickened basement membrane with collagen deposits. These conflicting findings open a debate about the possible etiologic role of NSAIDs in some cases of collagenous colitis or their potential superimposed noxious role in cases of collagenous colitis of other etiologies, maybe leading to these different microscopic appearances. The relevance of this needs further investigation.

d) Complications due to cat-scratch lesions

The main risk associated with colonic cat-scratch lesions is air dissection of the colonic wall (9,34,35,37) leading to colonic perforation, a risk enhanced by colonoscopic air insufflation. Extreme caution is mandatory during the procedure if such lesions are observed. However, this complication affects less than 1% of collagenous colitis patients (9). Typically, patients develop a progressive (+/- 24 hours) clinical peritonitis due to progressive transmural air dissection and dilaceration of the colonic wall (34,37). Acute peritonitis occurring during or immediately after endoscopy is less frequent (2/12 cases (9) ; 3/12 cases (35)).

This progressive wall dilaceration is confirmed by colonic wall emphysema (9,38,39) visible on CT-scan or double-contrast barium enema radiographs as a submucosal trapping of gas reflecting cleavage of the colonic wall alongside the collagen layer.

This complication occurs most frequently in the right and transverse parts of the colon (9), in accordance with the right colonic predilection of collagenous colitis and in opposition to the predominantly left-sided iatrogenic colonic perforations.

5. *Treatment of collagenous colitis and evolution*

Long-term studies (8) suggest that collagenous colitis usually runs a benign clinical course with possible spontaneous remission (7,8,13,14,21,42) (up to 20%

of patients in a cohort of 37 patients (14)) allowing first-line symptomatic treatment (loperamide) (6,7,8, 13,21,42) and high-fiber diet (8)). In suspected drug-induced cases, incriminated drugs have to be withdrawn, especially proton-pump-inhibitors as 85% of patients experience clinical improvement after cessation of that treatment alone (23). Co-existence of celiac disease has also to be excluded (6).

In case of refractory disease, severe disease or relapsing and remitting symptoms, oral budesonide is recommended as first-line specific therapy (6,13,14,43), at the dose of 9 mg daily tapered weekly after clinical response. In two double-blind placebo-controlled clinical trials involving 28 (13) and 51 (43) patients respectively, the group who received budesonide 9 mg daily showed significant amelioration of stool consistency ($p = 0,05$ and $< 0,001$ respectively), significant reduction of the histologic inflammatory infiltrate in the lamina propria ($p < 0,001$ in both studies) and, although not significant, a trend to reduction in the mean thickness of the collagen band on biopsies after 8 and 6 weeks of treatment respectively, as compared to the placebo group. Observational data (28,38) and a meta-analysis (44) confirmed these data with rapid disappearance of diarrhea within 1 to 2 weeks and normalization of control biopsies after 3 months of treatment, proving that budesonide is effective for inducing clinical and histological responses. We observed the same results with our second patient together with endoscopic remission and mucosal healing (disappearance of cat-scratch lesions and ulcerations). Besides, budesonide undergoes a 90% metabolism during first pass through the liver (7,43), giving the advantage of low systemic activity and consecutively few systemic adverse effects even if used for a long time (6,7,14,43). There is however up to now no clear consensus on the most appropriate duration of treatment, varying from several weeks (usually 8 weeks (6,13)) to several months (13) depending on clinical response. Moreover, as relapses are possible (up to 30% at 3 years of follow-up in a cohort of 37 patients (14)) and unpredictable (4,5,8,13), maintenance therapy at the dose of 6 mg daily is proposed by some authors as it has proven effective on maintaining remission over at least 6 months. Alternatively,treatment may also be prescribed on an on-demand basis (4,13). Five-ASA compounds (sulfasalazine (4,6,7,21,42) or mesalazine (6,7,14,42,44)), bismuth subsalicylate (6,7,13,44) and NSAIDs (13,21) have also successfully been tried, but with less relevant results and with cautious recommendation for NSAIDs as they are incriminated as potential causative agents for collagenous colitis.

In case of non-response or intolerance to budesonide, a second-line immunosuppressive treatment is proposed, usually azathioprine (5,6,7) at standard dose of 1,5 to 2,5 mg/kg.

Because of the possible role of noxious luminal agents in the physiopathology of the disease, probiotics (5,44), antibiotics (metronidazole and erythromycine (5,7,18, 20)), and biliar salts chelators (cholestyramine (5,6,7, 14,18,21,44)) were also proposed,but showed no consensus in terms of efficacy.

As ultimate therapy and as mentioned above, fecal stream diversion by means of an ileostomy has proven effective on reducing symptoms and collagen layer thickness, but with recurrence after restoration of intestinal continuity (20), implying a need for permanent ileostomy in drug-refractory cases. Colectomy with restorative pelvic pouch surgery is also performed in that context (5,6,7,12).

It is to note that clinical and histological remissions do not always occur in parallel : histological remission occurs in only 50 to 82% of treated patients (14), even if they are asymptomatic and/or on maintenance therapy. Possible benefits of achieving histological remission are not proven at this time.

Despite a usually benign course, some complications related to collagenous colitis have been described : associated involvement of the gastric, duodenal and/or small intestinal mucosa (5,7,8,45) ; long-term altered mucosal permeability leading to protein-losing enteropathy (7,8, 45) ; evolution into ulcerative colitis or Crohn's disease, with then disappearance of the collagen deposition, suggesting that collagenous colitis could be a pattern or a precursor of these diseases (10,46,47,48) ; submucosal dissection and colonic perforation as discussed above. The risk of developing colorectal cancer seems similar to that of the general population (5,6,7,8), but data are less clear about secondary lymphoproliferative disorders (8) and intestinal carcinoïds (5), due to insufficient follow-up of large series of patients up to now. Again, possible benefits of achieving histological remission in this context are not proven at this time. Mortality rate is also similar to that expected in the general population (6).

Conclusion

We report here two cases of collagenous colitis diagnosed in patients complaining of chronic diarrhea, incriminating pantoprazole, omeprazole and NSAIDs as etiologic factors, and whose colonoscopies showed colonic mucosal tears. This macroscopic finding is unusual as collagenous colitis is classified as a microscopic colitis. These lesions, particularly present in the right part of the colon, are supposed to be due to a local stiffness of the colonic wall secondary to the collagen deposit in the mucosa.

We also further report lesions in the left colon and terminal ileum that are unusual sites for macroscopic lesions in that setting.

Finally, besides linear lesions, we report round ulcers in the colon of one patient showing typical collagen band on microscopic exam.

Both patients were successfully treated following literature recommendation in the setting of collagenous colitis and achieved clinical and endoscopic remissions.

According to these findings, confirming previous reports and adding new types and locations of macroscopic lesions, the term "microscopic colitis" may be rather restrictive for collagenous colitis. Macroscopic features should also incite endoscopists to evoke this diagnosis.

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