

CASE REPORT***Escherichia coli*-associated granulomatous colitis in a cat**Alexander M. Safian | Timothy Bolton 

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Email: timothy18@vt.edu**Abstract**

A 6-year-old male castrated domestic shorthair cat was evaluated for a 6-month history of haematochezia, mucoid diarrhoea, tenesmus and rectal prolapse. Colonic histopathology revealed multifocal mucosal ulceration and lamina propria infiltration with large numbers of periodic acid-Schiff-positive macrophages. Large clusters of intracellular *Escherichia coli* were confirmed with fluorescence in situ hybridization testing, similar to that seen in dogs with granulomatous colitis. An 8-week course of marbofloxacin resulted in resolution of clinical signs; however, recurrence occurred 4 weeks later. A 12-week course of marbofloxacin resulted in disease remission for which the cat still remains free of clinical signs (15 months). *Escherichia coli*-associated granulomatous colitis, although reported with rarity in this species, is an important infectious cause of chronic large intestinal disease in the cat.

BACKGROUND

Granulomatous colitis (GC) is an infectious large intestinal disease that primarily affects young Boxers and French Bulldogs, although it has been reported in other dog breeds too.^{1–4} Clinical signs associated with GC include tenesmus and frequent, small-volume diarrhoea containing frank blood or mucus.⁵ Histopathologically, GC is characterized by mucosal ulceration and submucosal infiltration by a mixture of lymphocytes, neutrophils and macrophages, the latter of which are periodic acid-Schiff-positive (PAS+).^{2,6,7} Originally thought to be an immune mediated disease, GC was recently determined to be caused by mucusally adherent and invasive *Escherichia coli*.¹ Disease remission is contingent upon eradication of bacteria within PAS+ macrophages, usually achieved with a fluoroquinolone antibiotic such as enrofloxacin.^{1,2,8}

To date, only three feline cases of GC have been reported, a 5-year-old Persian, a 4-year-old domestic shorthair, and a 10-year-old domestic shorthair.^{9–11} All cases had colonic histopathology lesions identical to that of canine GC and long-standing remission following the administration of either a fluoroquinolone^{9,10} antibiotic or chloramphenicol.¹¹ The primary goal of this report is to provide additional documentation and heightened awareness of GC as an underreported cause of chronic large bowel disease in the cat. Like prior cases, this report also confirms both a bacterial aetiology and successful response to antimicrobial treatment for GC in the cat.^{9–11}

CASE PRESENTATION

A 6-year-old male castrated domestic shorthair cat was referred for investigation of a 6-month history of haematochezia, mucoid diarrhoea, tenesmus, and rectal prolapse.

There was no weight loss and the cat maintained a normal appetite throughout the duration of the illness. The cat had an otherwise unremarkable medical history. Physical examination was unremarkable, and the cat was in a good body condition.

A high fibre diet trial (Royal Canin fibre response) and metronidazole (20 mg/kg orally every 12 h for 5 days) administered prior to referral resulted in no improvement in the clinical signs. No additional diagnostic tests nor therapeutic trials were performed prior to the referral.

INVESTIGATIONS

Complete blood count, serum biochemistry and routine urinalysis were within normal limits. A faecal sample investigating for parasites via zinc sulphate flotation and PCR for *Tritrichomonas foetus* and *Giardia* spp. were negative. Abdominal ultrasound abnormalities included a diffusely thickened colon wall (3.0–4.0 mm) containing hypoechoic nodules (1.0–2.0 mm) in the submucosal layer, a diffusely thickened cecal wall, and enlarged colic lymph nodes. A colonoscopy revealed an irregular mucosa with multifocal superficial erosions (Figure 1). Multiple endoscopic biopsies of the colon and cecum were obtained.

Colonic histopathology revealed mucosal ulceration and infiltration of the lamina propria by a mixture of lymphocytes, neutrophils, plasma cells, and large epithelioid macrophages (Figure 2a). The macrophages contained abundant eosinophilic cytoplasm that stained PAS+ (Figure 2b). Also present in the colonic biopsy specimens were decreased numbers of goblet cells. Other causes of granulomatous intestinal inflammation, such as fungi and acid-fast bacteria, were excluded based on negative special stains (Gomori methenamine silver and acid-fast stain, respectively). Cecal

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histopathology revealed mucosal ulceration and lamina propria infiltration by variably sized lymphocytes. No epithelioid macrophages were present.

Following the colonic histopathology findings, fluorescence in situ hybridization testing using *E. coli*-specific probes was performed as previously described.¹ Clusters of *E. coli* were present within the PAS+ lamina propria macrophages, thus establishing a definitive diagnosis of GC (Figure 3). No colonic biopsy or swab was submitted for bacterial culture.

DIFFERENTIAL DIAGNOSIS

Abdominal ultrasound findings were consistent with an infiltrative process in the colon and caecum. In a young cat with no overt systemic signs, the top differential diagnosis was an immune-mediated process such as inflammatory bowel disease. However, gross findings on endoscopic examination made a neoplastic or infectious process of equal likelihood. Given the insensitivity of both ultrasound and gross endoscopic findings to differentiate between these infiltrative disease processes, biopsies were necessary for a definitive diagnosis.

TREATMENT

Based on the high index of suspicion for GC following routine histopathology findings, the cat was started on marbofloxacin (4.5 mg/kg orally every 24 h) pending fluorescence in situ hybridization analysis results. The duration of marbofloxacin treatment was extended to 8 weeks following confirmation of the diagnosis. Follow-up was recommended at the mid-point (4 weeks) of treatment.

OUTCOME AND FOLLOW-UP

At the 4-week follow-up, all clinical signs had resolved. The cat was asymptomatic as early as 1 week following treatment initiation. However, 4 weeks after antibiotic completion, all clinical signs recurred. A recheck examination at that time revealed the cat to still be in a good body condition. No new physical examination abnormalities were present. Diagnostic tests to ascertain the cause for the relapse were recommended but declined. Consequently, the cat was started on a 12-week course of marbofloxacin (4.5 mg/kg orally every 24 h). Fortunately, this again led to the resolution of all clinical signs, with remission to date (15 months).

DISCUSSION

To date, this represents only the fourth reported adult cat with confirmed PAS+ GC.^{9–11} In this particular case, the presence of severe macrophage infiltration on colonic histopathology prompted concern for an infectious aetiology. Faecal PCR testing and special stains on the biopsies excluded parasitic, fungal, and other noninvasive bacteria as causes for the granulomatous colonic infiltrate. Diagnosis confirmation was achieved after fluorescence in situ hybridization revealed clusters of *E. coli* bacteria within PAS+ macrophages. The

LEARNING POINTS/TAKE-HOME MESSAGES

- Granulomatous colitis is most likely an underreported cause of chronic large intestinal disease in cats, as evidenced by an increase in case reports of this disease over the last 3 years.
- Consequently, granulomatous colitis should be considered a differential diagnosis in cats with chronic large intestinal signs, especially when colonic wall thickening is present on abdominal ultrasound and/or superficial ulcerative lesions are visualized on endoscopy.
- A definitive diagnosis requires the demonstration of *E. coli* organisms within PAS+ macrophages, as accomplished with fluorescence in situ hybridization.
- Treatment with a fluoroquinolone safe in cats, such as marbofloxacin, appears to result in long-term disease resolution.

clinical signs, in conjunction with the colonic histopathologic changes, were compatible with GC as seen in dogs such as Boxers and French Bulldogs.^{1–3,5–7}

Previously considered an autoimmune disease, GC has recently been linked to *E. coli* in dogs.^{1,3,8} Given the relatively few dog breeds affected by GC, a genetic susceptibility to colonic mucosal invasion by *E. coli* is strongly suspected. In fact, mutations in a candidate gene (NCF2) responsible for conferring microbicidal capability to macrophages have been identified.⁵ An absence of such capability prevents macrophage elimination of phagocytized pathogens, thus reinforcing ineffective macrophage eradication of phagocytized *E. coli* as the most likely mechanism for GC development in dogs. Additionally, human NCF2 gene mutations result in chronic granulomatous disease (CGD), an inherited immune deficiency disorder that predisposes to recurrent infections.¹² Humans with CGD can develop colitis that is histopathologically similar to GC in dogs, including the presence of PAS+ macrophages.^{13,14} Although the specific bacteria involved in CGD colitis development are poorly characterized, the striking histopathologic similarity to GC in dogs might suggest a potential role for *E. coli* in this human disease. In cats, despite no genetic basis for GC to date, this and other case reports demonstrate intracellular *E. coli* within granulomatous colonic lesions.^{9–11} This would seem, at least in part, to support *E. coli* as the causative agent for GC in cats. Studies investigating cats for a potential underlying genetic basis, such as candidate gene NCF2 mutations in humans and dogs, are needed.

Additional support for *E. coli* as the causative agent of GC in this cat was the robust clinical improvement following treatment with an antibiotic of known efficacy against the bacteria based on results of a bacterial culture or extrapolated from dogs with GC.^{1,3,8–10} Similar to dogs, this cat responded rapidly to treatment, with clinical signs resolving as early as 1 week following treatment commencement.⁸ The decision to treat with a fluoroquinolone was extrapolated from the current recommendations in successfully treated dogs and two prior feline case reports.^{5,9,10} One of the limitations in this

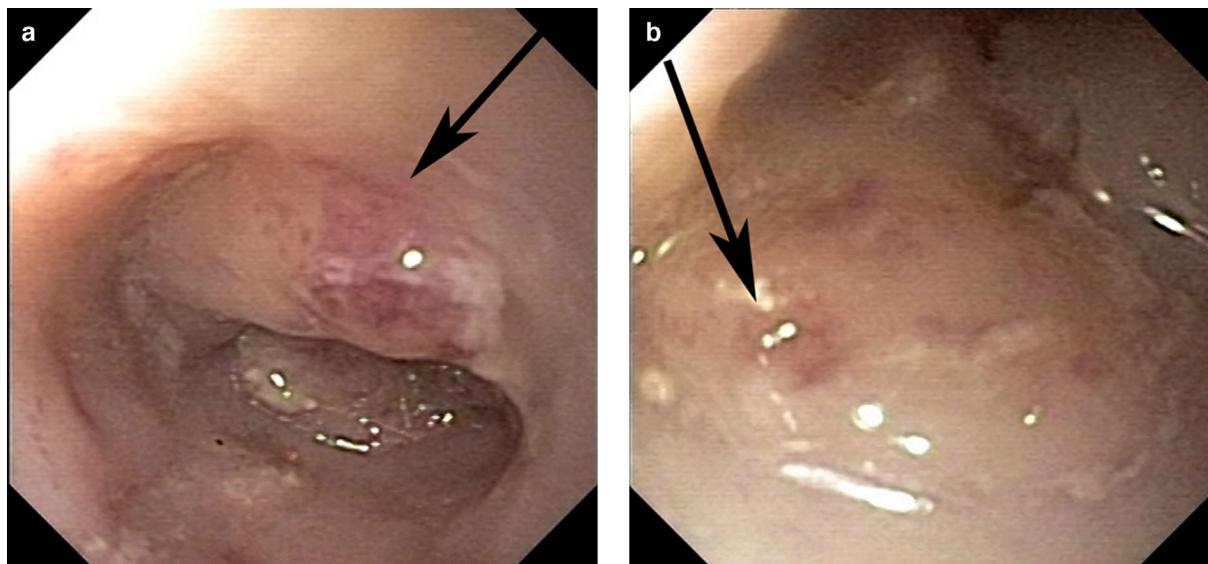


FIGURE 1 Colonoscopy images showing superficial erosions and ulceration (black arrows)

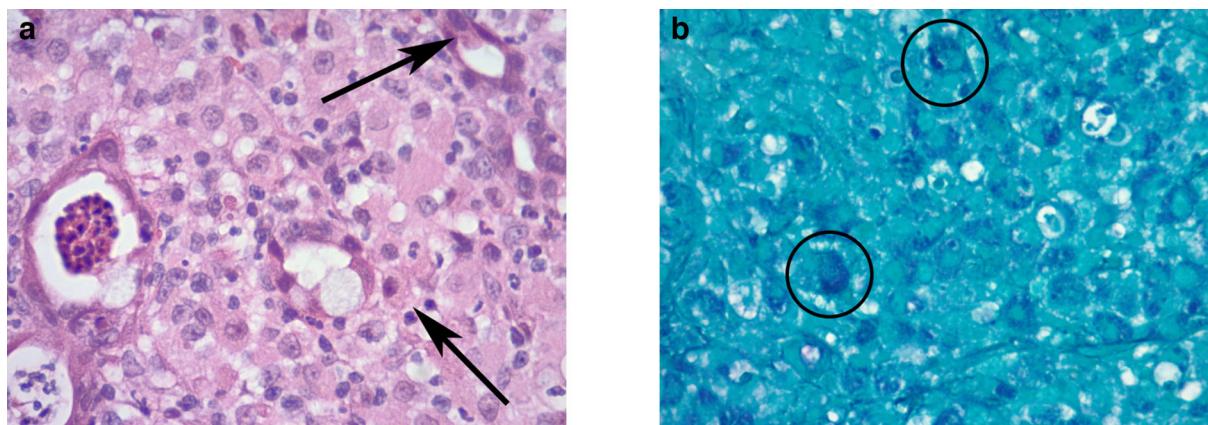


FIGURE 2 Histopathology of the colon. (A) Abundant numbers of macrophages with eosinophilic cytoplasm (black arrows). Haematoxylin and eosin. (B) Abundant numbers of macrophages with periodic acid-Schiff (PAS)-positive material (black circles) within the cytoplasm.

case was the lack of a bacterial culture for guiding antibiotic selection. In dogs, obtaining this information prior to starting treatment is important because of fluoroquinolone resistance, particularly when administered prior to a definitive diagnosis.¹⁵ The unexpected finding of GC in a cat, due to its lack of consideration at the time of patient evaluation, and the positive response to fluoroquinolone therapy by the time GC was confirmed account for the lack of a culture in this case. As additional cases of GC are diagnosed, fluoroquinolone resistance is likely to develop in cats too. Thus, a colonic swab or biopsy submitted for bacterial culture is recommended in feline cases where suspicion for GC is high.

There were several other limitations in the diagnostic work-up of this case. Recurrence of clinical signs occurred 4 weeks following the initial 8-week course of fluoroquinolone therapy; however, repeat biopsies were not performed to definitively prove that GC was the cause of the relapse. Instead, the cat was re-started on a longer duration of the same antibiotic, resulting again in rapid and clinical resolution to date. Based on the response, the most likely reason for clinical sign recurrence was incomplete eradication of the *E. coli*. The possible reasons for this failure include an insufficient antibiotic dose (4.5 mg/kg) when compared to that recommended in

dogs with GC (5.0 mg/kg), utilization of a fluoroquinolone (marbofloxacin) that has not yet been proven to induce disease remission, or an insufficient duration of treatment. The last reason is most likely given that the cat remains in disease remission to date.

Histopathological follow-up after disease resolution was also not performed in this case. In dogs, macrophages can remain PAS+ for more than 6 months following clinical disease resolution; however, it is unknown if the same occurs in cats.⁸ Repeat biopsies would have been necessary to determine this; however, because the cat was free of clinical signs, it was determined to not be of clinical value.

This report describes, to date, a rare infectious cause of colitis in the cat. The clinical signs, endoscopic and microscopic findings, and clinical response to fluoroquinolone therapy resemble GC in dogs. Thus, it appears this disease can also infect cats, making this an important differential diagnosis to consider in a cat with chronic large bowel signs. Although suspicion for the disease is initially obtained on routine histopathology, fluorescence in situ hybridization is required for a definitive diagnosis. Prognosis appears to be good based on the response to treatment in this case and others.^{9–11}

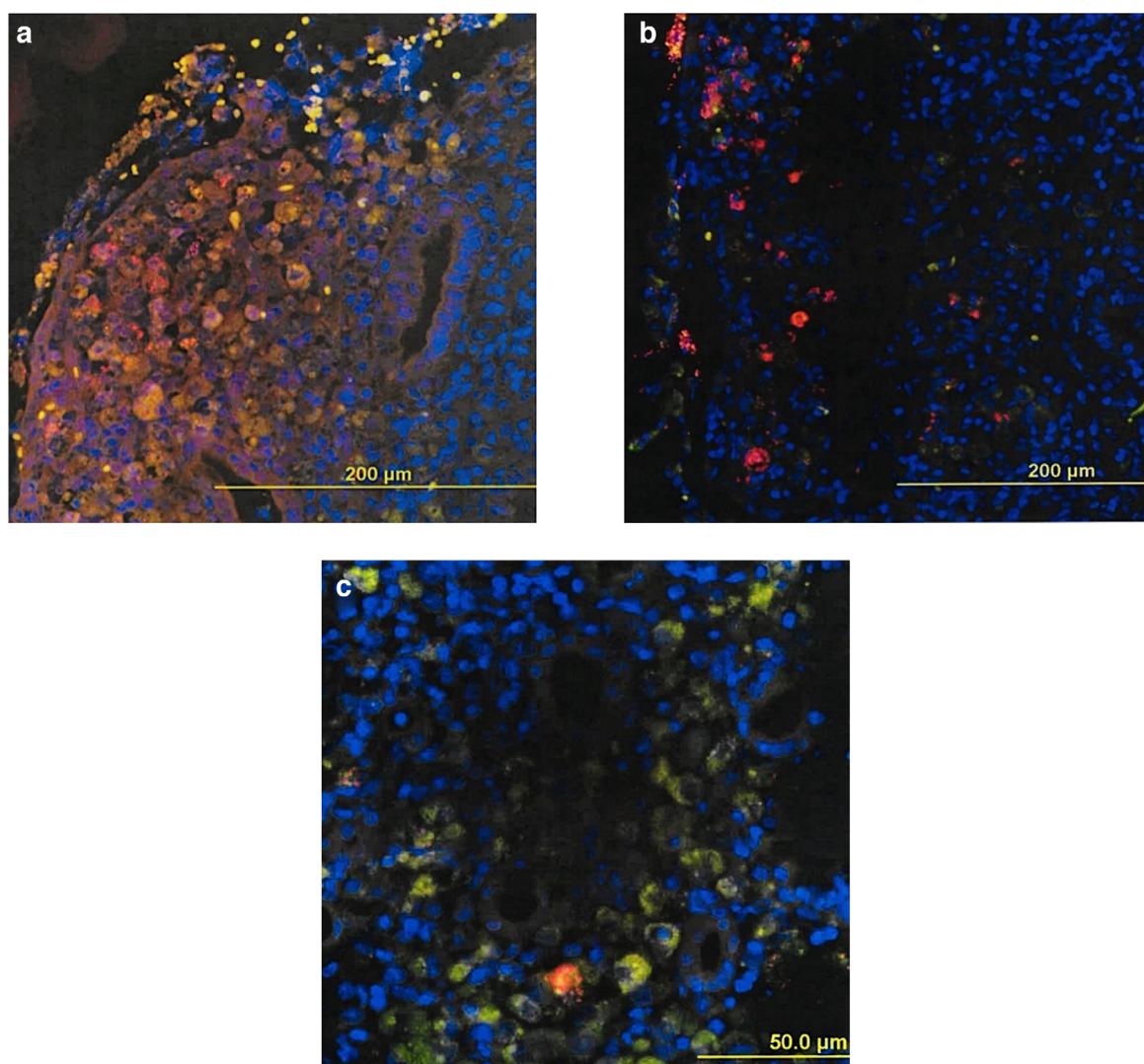


FIGURE 3 Fluorescence in situ hybridization of colonic biopsies revealing multifocal clusters of invasive intracellular rod bacteria consistent with *Escherichia coli*. The bacteria hybridized to an *Escherichia coli* bacterial probe. Bacteria (*Escherichia coli*) stain red and nuclei/DNA blue

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