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Granulomatous colitis in two French bulldogs unresponsive to fluoroquinolone antimicrobials: a case report

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ABSTRACT: Two cases of granulomatous colitis in two French bulldogs were found to be unresponsive to fluoroquinolones. The granulomatous colitis diagnosis was made on the basis of PAS-positive histiocytes in the lamina propria of the colonic mucosa in biopsy samples taken at colonoscopy. Remission of granulomatous colitis has been reported using fluoroquinolones leading to the idea that invasive *Escherichia coli* strains in the colonic mucosa are involved. Oral enrofloxacin (Baytril 150 mg, Bayer, Spain) at 10 mg/kg per day for eight weeks was prescribed to both dogs in this study. A first course of therapy resolved the problem in dog No. 1, which, however, was followed by relapse three months later without enrofloxacin response. No clinical remission was seen in dog No. 2 and 4.4 mg/kg marbofloxacin (Marbocyl P 20 mg, Vetoquinol, Spain) per day for 10 weeks was administered but without any response. From both dogs, biopsy samples from the colonic mucosa were taken during colonoscopy. Samples were homogenised for microbial culture in different agar media to identify invasive microbes. *Escherichia coli* were largely isolated and antibiotic sensitivity testing (MIC of *E. coli* to selected antimicrobials, CLSI 2013) was carried out. In both cases, *E. coli* was resistant to fluoroquinolones. In dog No. 1 *E. coli* was susceptible to amoxicillin-clavulanate, cefazolin, amikacin and gentamicin whereas in dog No. 2 it was susceptible to doxycycline and amoxicillin-clavulanate. Clinical remission was achieved in dog No. 1 with amoxicillin-clavulanate (Synulox 250 mg, Pfizer, Spain) therapy for eight weeks. No response was found in dog No. 2 with any of the antimicrobials alone or combined with metronidazole.

Keywords: enrofloxacin; *Escherichia coli*; colonoscopy; PAS-positive histiocytes; dog

Granulomatous colitis (GC), also known as histiocytic ulcerative colitis, is a chronic inflammation of the colonic mucosa seen in young Boxer dogs (Davis et al. 2004; Craven et al. 2010; Manchester et al. 2013) and in French bulldogs, a breed ancestrally related to Boxer dogs (Van der Gaag et al. 1978; Tanaka et al. 2003; Manchester et al. 2013). Clinical signs include chronic diarrhoea with increasing frequency of defecation, haematochezia, mucus and tenesmus (Stokes et al. 2001; Hostutler et al. 2004; Craven et al. 2010; Manchester et al. 2013). Severe cases also exhibit hypoalbuminemia and cachexia (Manchester et al. 2013). In the past, most GC cases failed to respond to any therapy. However, since the association between GC and *E. coli* strains within the colonic mucosa in affected dogs was reported, the condition has been successfully managed with enrofloxacin therapy (Mansfield et al. 2009; Craven et al. 2010; Lechowski et al. 2013; Manchester et al. 2013). The aim of this study was to describe two cases of GC in French bulldogs that failed to respond to any fluoroquinolone therapy.

Case description

Two privately owned French bulldogs were studied. A female, aged 17 months (dog No. 1), was presented with chronic diarrhoea, with increased frequency of defecation, haematochezia, tenesmus

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and abdominal pain. A male, aged 11 months (dog No. 2), presented with haematochezia since birth. Both dogs were fed twice a day with different commercial hypoallergenic diets and specific diets for gastrointestinal problems and which slightly improved clinical signs. Different therapies with metronidazole, sulfasalazine and prednisolone were prescribed in both cases but without any clinical response. Results of blood and urine analysis were normal in both cases. A thickened colonic mucosa and an enlargement of the regional lymph nodes were detected on ultrasonography surveys. A colonoscopy was performed in both dogs showing an irregular, ulcerated and hyperaemic colonic mucosa. Several biopsies samples were taken to confirm the diagnosis of GC and thus oral enrofloxacin (Baytril 150 mg, Bayer, Madrid, Spain) at 10 mg/kg per day for eight weeks was prescribed as recommended (Mansfield et al. 2009). Dog No. 1 recovered with this therapy but clinical signs relapsed three months later without any clinical response to enrofloxacin at this time. Dog No. 2 did not respond to the initial course of enrofloxacin therapy and received 4.4 mg/kg marbofloxacin (Marbocyl P 20 mg, Vetoquinol, Madrid, Spain) per day for 10 weeks but again without response. Subsequently, biopsy samples from the colonic mucosa were taken from both dogs, ground and homogenised for microbial culture in different agar media (Blood agar, Chocolate agar, Schaedler agar, Cled, Sabouraud and thioglycolate broths; Idexx Laboratories, Barcelona, Spain) to identify invasive microbes. Predominantly *E. coli* organisms were isolated and antibiotic sensitivity testing (MIC of *E. coli* to selected antimicrobials, interpreted by Clinical Laboratory Standards Institute 2013; Idexx Laboratories, Barcelona, Spain) was carried out. In dog No. 1, the *E. coli* strain was resistant to fluoroquinolones, doxycycline, tetracycline and trimethoprim-sulphamethoxazole but susceptible to amoxicillin-clavulanate, cefazolin, amikacin and gentamicin. Clinical remission was achieved with oral amoxicillin-clavulanate (Synulox 250 mg, Pfizer, Madrid, Spain) at 20 mg/kg every 8 h for eight weeks. The dog No. 1 remains currently in good condition.

The *E. coli* strain in dog No. 2 was resistant to fluoroquinolones, tetracycline and trimethoprim-sulphamethoxazole but susceptible to doxycycline and amoxicillin-clavulanate. No response was found when oral amoxicillin-clavulanate (Synulox 250 mg, Pfizer, Madrid, Spain) at 20 mg/kg every 8 h was administered alone or combined with oral sulfasalazine at 20 mg/kg every 8 h or when 10 mg/kg per day of oral doxycycline alone and combined with oral metronidazole at 10 mg/kg twice a day were administered. Other combinations of antimicrobials and prednisone were prescribed but none improved the condition of dog No. 2.

DISCUSSION AND CONCLUSIONS

GC is a severe chronic disease mostly seen in Boxer dogs (Mansfield et al. 2009; Craven et al. 2010) and French bulldogs (Van der Gaag et al. 1978; Tanaka et al. 2003; Manchester et al. 2013). It has also been reported in the Mastiff, Alaskan malamute, Doberman pinscher, English bulldog (Manchester et al. 2013) and Beagle (Carvallo et al. 2015). Young dogs are predominantly affected with clinical signs which are similar to those observed in other forms of chronic colitis (Sherding 2003). The definitive GC diagnosis is made on the basis of PAS-positive histiocytes in the lamina propria of the colonic mucosa (Tanaka et al. 2003; Hostutler et al. 2004; Mansfield et al. 2009; Craven et al. 2010). The cause of GC is not still clear. In only one report (Manchester et al. 2013), was GC in French bulldogs associated with the invasion of the colonic mucosa by *E. coli*. GC in dogs is remarkably breed-specific and, thus, a heritable anomaly in mucosa immunity that confers susceptibility to invasion and persistence of invasive *E. coli* within the colonic mucosa may be an important predisposing factor (Mansfield et al. 2009; Craven et al. 2010). To optimise the treatment of GC a specific antimicrobial would be needed to eliminate *E. coli* within these cells. Its ability to effectively penetrate cells to kill *E. coli* might explain the positive results obtained with enrofloxacin (Mansfield et al. 2009; Craven et al. 2010; Lechowski et al. 2013; Manchester et al. 2013).

In the two cases reported here invasive *E. coli* were isolated from the colonic mucosa and enrofloxacin was prescribed for eight weeks at a dose of 10 mg/kg body weight per day as previously reported (Mansfield et al. 2009; Manchester et al. 2013). However, both dogs failed to respond to enrofloxacin therapy although dog No. 1 did respond initially. Further, dog No. 2 also failed to respond to marbofloxacin therapy.

In a previous study in French bulldogs (Manchester et al. 2013), five out of six dogs were reported to be susceptible to enrofloxacin and one case responded

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to marbofloxacin. However, it has also been reported that over 43% of Boxer dogs with GC were reported to be resistant to fluoroquinolones and over 50% of cases were resistant to one or more non-fluoroquinolone antimicrobials (Craven et al. 2010). Our results suggest the possibility of similar antibiotic resistance of GC in French bulldogs. Resistance to fluoroquinolone antimicrobials was described when short courses (less than eight weeks) were followed (Craven et al. 2010; Manchester et al. 2013). The relatively rapid resolution of GC-associated clinical signs and the potential adverse effects of enrofloxacin on cartilage development in skeletally immature dogs could lead to prematurely discontinued antimicrobial administration (Manchester et al. 2013). It could be possible that in dog No. 1 a longer treatment of enrofloxacin would have been needed to control GC. In dog No. 2, the unresponsiveness of GC to fluoroquinolones could be due to resistant invasive *E. coli* in the colonic mucosa, perhaps as a result of the widespread use of these antimicrobials in both human and veterinary medicine (Craven et al. 2010). In such refractory cases, a combination of two or more antimicrobials could be useful (Craven et al. 2010). However, in dog No. 2 no response was achieved with any of the effective antimicrobials or a combination of them. This leads us to speculate that invasive *E. coli* may not always be involved in the pathogenesis of GC in French bulldogs. Rather, it is possible that a heritable anomaly in mucosa immunity, which has been described in GC, might confer susceptibility to invasion of other microbes within the colonic mucosa. It would therefore be interesting to investigate the occurrence of rare microbes such as *Histoplasma* spp., *Candida* spp. or *Prototheca* spp. that can also be responsible for difficult-to-control chronic colitis (Sherding 2003), such as that observed in the cases described here.

In conclusion, our report describes cases of GC in which no response to fluoroquinolone antimicrobials could be found, thus highlighting potential difficulties in controlling this condition in French bulldogs. To optimise outcomes, it would be useful to take colonic mucosa biopsies and to perform antibiotic sensitivity testing of invasive *E. coli*. However, in some cases no clinical recovery could be achieved which leads us to suggest that invasive *E. coli* might not always be involved in the pathogenesis of GC in French bulldogs.

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