**Case Series**

**Idiopathic eosinophilic colitis lesions of the equine small (descending) colon**

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**Summary**

Five horses with a primary surgical lesion of the small (descending) colon were diagnosed with eosinophilic colitis based on visual and histopathological examination. These were evident as visibly striking, hyperaemic, focal lesions of the small colon with serosal petechiation, oedema and marked thickening of the intestinal wall at the site. Some areas of focal necrosis were also evident. The gross appearance of the lesions were considered to be sufficiently severe in all cases to merit resection, due to concerns about intestinal necrosis and septic peritonitis. An inability to fully exteriorise the affected portion of intestine to perform a resection and anastomosis necessitated intraoperative euthanasia of one horse. Three horses survived to hospital discharge. Eosinophilic colitis lesions are a rare cause of severe small colon disease but should be considered in cases with similar visual characteristics.

**Introduction**

Focal and multifocal idiopathic eosinophilic lesions are an uncommon but important cause of gastrointestinal disease in the horse. They have been previously described as causes of acute abdominal pain (colic) as a result of either lesions in the large colon, described as segmental eosinophilic colitis lesions (Bertone *et al*. 1996; Edwards *et al*. 2000) and as idiopathic focal eosinophilic enteritis (IFEE) lesions of the small intestine (Scott *et al*. 1999; Southwood *et al*. 2000; Stanar *et al.* 2002; Swain *et al*. 2003; Archer *et al*. 2006; Perez Olmos *et al*. 2006). Focal eosinophilic infiltration of the small colon has been briefly reported in the literature (Mäkinen *et al.* 2008; de Bont *et al.* 2013), but there have not been any detailed reports of the clinical and histopathological features, nor of the outcome in these cases. Primary lesions of the small (descending) colon account for a relatively small percentage (2.8-4.2%) of colic cases requiring surgical treatment (Edwards 1992; Mair *et al.* 2005). Eosinophilic colitis lesions affecting the small colon represent a small proportion of these, having been identified in 6% (5/84) of horses undergoing exploratory laparotomy for treatment of colic which was due to a primary lesion of the small colon in one study (de Bont *et al*. 2013). The aim of this study was to detail the clinical and histopathological features of focal, idiopathic eosinophilic colitis of the small colon.

**Case Details**

***Signalment***

Five horses where a surgical and histopathological diagnosis of eosinophilic colitis of the small colon as the primary cause of colic was made, were identified in case records at the Philip Leverhulme Equine Hospital, between August 2004 and August 2010. The signalment, clinical and clinicopathological findings of all horses are summarised in Table 1. There was no evidence of age, breed or sex predisposition when compared to the general hospital population. None of the horses had a history of previous colic signs and there did not appear to be any characteristic pre-surgical findings indicative of an eosinophilic colitis lesion. The median age was 11 years (range 7-21 years). The decision to perform an exploratory laparotomy was based on abnormal rectal and ultrasonographic findings, clinical parameters and/or persistent pain despite the administration of analgesics. Abdominocentesis was not performed in any of the cases prior to surgery due to other clinical findings indicating that exploratory laparotomy was required.

***Surgical findings***

At exploratory laparotomy the lesions were evident as visibly striking, hyperaemic, focal lesions of the small colon with serosal petechiation (Fig. 1) and were considered to be the primary cause of abdominal pain. There was evidence of oedema and marked thickening of the intestinal wall at the site. Other findings included gaseous distention of the small colon, oedema of the mesocolon and impaction of ingesta orad to the lesion. Due to the degree of mural thickening and evidence of focal necrosis already developing at the site, leaving the affected portion of colon in situ was considered likely to result in a poor prognosis for survival, due to the risk of developing septic peritonitis. Resection was therefore undertaken in four horses and a two-layer hand sewn end-to-end anastomosis was performed (Rakestraw and Hardy 2012). Examination of the resected portions of intestine revealed a green appearance to the mucosa and submucosa, consistent with tissue necrosis. The length of resection ranged from 15cm to 180cm. One horse (Horse 5) was euthanased intraoperatively due to the extent of the lesion and an inability to sufficiently exteriorise the affected portions in order to expose healthy tissue margins.

***Histopathology***

The lesions represented a focal severe eosinophilic and granulomatous colitis. Mucosal regions were characterised by varying degrees of ulceration, intense hyperaemia and moderate multifocal haemorrhage, with moderate mixed cellular infiltrates of plasma cells, lymphocytes, macrophages and often mild but sometimes moderate infiltrates of eosinophils (Fig. 2a). Moderate infiltrates of neutrophils accompanied ulcerated areas. The submucosa was markedly hyperaemic, with multifocal haemorrhage and severe diffuse oedema with lymphangiectasia and fibrin exudation. Severe multifocal to coalescing aggregates of primarily perivascular macrophages and eosinophils dominated on a background of diffuse cellular infiltration (Fig. 2b). The muscularis was characterised by multifocal to coalescing aggregates of eosinophils and macrophages, sometimes with mild infiltrates of neutrophils. Additionally there were multiple foci of homogenous eosinophilic debris, surrounded by macrophages and multinucleated giant cells with an outer rim of lymphocytes (eosinophilic granuloma). Occasionally these foci were associated with inflammatory tracts extending between muscle layers, coalescing with follicular lymphoid aggregates (Fig. 2c). Serosal regions were intensely hyperaemic, with moderate diffuse eosinophil dominated cellular infiltrates and fibroblast activation (Fig. 2d). There was no evidence of an aetiologic agent on examination of these portions of small colon using standard (haematoxylin and eosin) stains.

***Outcome***

Following an initial good recovery from surgery, Horse 1 deteriorated rapidly 11 days post-operatively and developed marked abdominal pain that was non responsive to analgesia. The owner did not want repeat laparotomy to be performed and the gelding was euthanased on day 12. Post mortem examination revealed multiple adhesions between the small intestine and small colon anastomosis site resulting in a small intestinal obstruction. A small 3-4mm defect was evident in the anastomosis once the adhesions had been dissected. Horses 2, 3 and 4 recovered uneventfully and were discharged at a mean of 10.33 days postoperatively (short term survival of horses recovered from surgery was 75%). Horse 2 was euthanased 184 days postoperatively due to recurrent colic episodes but no post-mortem examination was performed. Horse 3 was still alive at the time of writing, with no further signs of colic observed. Horse 4 was euthanased 257 days post-operatively following an acute injury and fracture associated with the cubital joint.

**Discussion**

This study is the first to describe the clinical and histopathological features of a series of focal eosinophilic lesions of the small colon. The lesions were visibly striking in appearance and should be considered as a rare but possible cause of simple obstruction of the small colon, when there is no evidence of a primary intraluminal obstruction, which may necessitate intestinal resection. There are both similarities and differences between the clinical and histological features of focal eosinophilic lesions of the small colon, when compared to those previously described in both the large colon (Edwards *et al*. 2000) and the small intestine (IFEE) (Archer *et al.* 2006).

The lesions in the current series were evident as visibly striking, focal, hyperaemic lesions with serosal petechiation, oedema and marked thickening of the intestinal wall, characterised histologically as a focal and severe eosinophilic and granulomatous colitis. Eosinophilic colitis lesions identified in the large colon have been reported to have marked thickening and oedema of the colon wall, with variable serosal changes from petechiation, erythema to discrete, well defined area of serosal necrosis, and with histopathological abnormalities of varying severity (Edwards *et al*. 2000). IFEE lesions are characterised as single or multiple, palpably thickened and hyperaemic focal serosal plaques or circumferential bands with histological evidence of submucosal oedema, haemorrhage and mucosal swelling (Archer *et al.* 2006). In contrast to colitis lesions, serosal necrosis has not been described as a characteristic of IFEE lesions. A clear demarcation between affected and normal bowel at the edge of the segmental lesion has been reported in the large colon (Edwards *et al*. 2000), which is similar to the lesions identified in the small colon and those affecting the small intestine (Archer *et al.* 2006).

The lesions described in the current study had several similarities with those occuring in the large (ascending) colon. In a series of horses with eosinophilic colitis lesions of the large colon, partial colon resection was performed in 16/22 (72%) cases, where the external appearance of the serosa and transmural necrosis indicated lack of tissue viability (Edwards *et al*. 2000). Large colon resection was considered unnecessary in 5 cases where the appearance of the intestine was relatively normal and luminal occlusion was minimal, but the authors considered that there was a risk of progressive intestinal necrosis postoperatively in cases that did not undergo intestinal resection (Edwards *et al*. 2000). Short term survival (defined as discharge from the hospital) for horses with eosinophilic colitis of the left dorsal colon was 82% (18/22), with 73% (16/22) alive at 3 months to 7 years postoperatively (Edwards *et al*. 2000).

Resection of IFEE lesions was previously considered necessary and was undertaken in 10/12 cases in one series, with rates of short-term survival to discharge of 83% (10/12) and 58% survival at 13 months postoperatively (Archer *et al.* 2006). However, a separate study suggested that these lesions could be left in situ, with resection and anastomosis only performed in 1/28 cases of IFEE in which 100% of cases survived to hospital discharge (Perez Olmos *et al*. 2006). In the authors’ hospital IFEE cases now routinely undergo manual decompression only and are not resected unless intestinal viability or severe luminal obstruction is a concern. This suggests that IFEE lesions would appear to have different characteristics with regard to mucosal barrier function and progression of lesion necrosis when compared to eosinophilic lesions of the small or large colon.

Resection of the affected portion of small colon was performed in 4 out of 5 of the horses in this series. Due to the degree of mural thickening and concerns about focal necrosis already developing at the site, leaving the affected portion of colon in situ was considered likely to result in a poor prognosis for survival. Several factors should be considered when undertaking resection of small colon including the frequent large amounts of adipose tissue in the mesentery making vessel identification and ligation more difficult and the need to ensure that the mesenteric portion of the anastomosis is secure to prevent leakage occurring (Rakestraw and Hardy 2012). High concentrations of collagenase and bacteria within the bowel, along with the mechanical stress endured by movement of hard faecal balls within the lumen post operatively may also result in the potential for leakage of the anastomosis to occur (Rakestraw and Hardy 2012). In humans, small colon bacterial populations are rich in aerobic and anaerobic bacteria and contain a high level of matrix metalloproteinases (MMPs), with abnormal up-regulation of MMPs and disturbances in the extracellular matrix identified in human patients with anastomotic leakage following colorectal surgery (Stumpf *et al.* 2005). Complications following enterotomy or resection and anastomosis of the small colon in horses however are rare, being reported to occur in just under 5% of cases (Prange *et. al*. 2010), including dehiscence of part of the anastomosis which occurred in one case in the present study. Median survival times following small colon resection have been reported at just under 3 years, which is lower when compared with horses with a primary lesion of the small colon not requiring resection, reported at just under 8.5 years (de Bont *et al.* 2013).

The histopathological findings reported in focal eosinophilic lesions affecting the large colon (Edwards *et al*. 2000), are similar to the lesions of the small colon described in the present case series, but there are some contrasting findings compared to histopathological features of focal lesions affecting the small intestine. Necrotic mucosa in the small colon cases contained neutrophils and eosinophils, with bacterial colonisation on the surface of devitalised mucosa, consistent with similar lesions in the large colon (Edwards *et al*. 2000). In contrast, IFEE lesions typically had a moderate diffuse inflammation of the lamina propria of the mucosa, with mild to moderate changes associated with the lamina epithelialis mucosae, represented by short, stubby or shattered villi and focal necrosis or erosion of villous tip epithelial cells (Mäkinen *et al.* 2008). In the latter lesions, lymphocytes dominated the inflammatory infiltrate, followed by macrophages, eosinophils, plasma cells and neutrophils in decreasing numbers (Mäkinen *et al.* 2008). The submucosal regions of the large colon lesions reported by Edwards et al 2000 were again similar to the lesions of the small colon described in the current study and were characterised by oedema, fibrinous exudation, lymphatic dilatation and thrombosis, with eosinophilic infiltrates of varying intensity. In addition variable features included small numbers of neutrophils, submucosal fibroplasia and granulation tissue formation (Edwards *et al*. 2000). In contrast, the transmural inflammatory infiltration within the submucosa of IFEE lesions was dominated by eosinophils and macrophages, with smaller numbers of lymphocytes, plasma cells and neutrophils (Mäkinen *et al.* 2008). Diffuse oedema and hyperaemia was often noted, with occasional focal areas of necrosis representing degenerate eosinophils (Mäkinen *et al.* 2008). The muscularis of the large colon was generally well preserved in eosinophilic colitis lesions with variable focal necrosis, oedema and fibrinous exudate (Edwards *et al*. 2000). The transmural inflammatory infiltration within the muscularis of IFEE lesions was dominated by eosinophils and macrophages (Mäkinen *et al.* 2008), which was similar to findings in the muscularis of the small colon in the current series. In addition swelling, vacuolation and necrosis of the muscularis was evident in IFEE lesions (Archer *et al.* 2006). Histologically the serosal surfaces of large colon lesions were hyperaemic, oedematous and infiltrated by variable numbers of eosinophils (Edwards *et al*. 2000), again similar to the lesions described in the current study, which were intensely hyperaemic. Focal inflammatory infiltrate was reported to often but not always extend to the serosal layer of IFEE lesions (Mäkinen *et al.* 2008).

The cause of the focal lesions in the current series and those affecting the large colon (Edwards *et al*. 2000) and small intestine (Archer *et al.* 2006; Mäkinen *et al.* 2008; Archer *et al.* 2015), remains unknown and requires further research. There was no evidence of a primary cause for the eosinophilic infiltrate in the current series based on histopathological examination. Eosinophilic gastrointestinal disease (EGID) is uncommon in humans and is characterised by either focal or diffuse eosinophilic infiltrate within the gastrointestinal tract, without evidence of known causes of eosinophilia including parasitism, drug reactions and malignancy (Rothenberg 2004; Sheikh *et al.* 2009). Gastroduodenal involvement is most commonly seen, with cases rarely affecting the colon (Sheikh *et al.* 2009). Indeed eosinophilic colitis represents the least frequent manifestation of EGID, irrespective of whether or not other segments of the gastrointestinal tract are involved (Guajardo *et al*. 2002). The disease has been classified into mucosal, submucosal (transmural) and serosal forms, based on the predominant location of eosinophilic infiltrate (Klein *et al*. 1970; Talley *et al*. 1990). Gastrointestinal obstruction is uncommon and is associated primarily with the transmural form of the disease, manifesting as gastric outlet or duodenal obstruction and intestinal thickening (Sheikh *et al.* 2009). The transmural form has also been associated with intussusception, volvulus and perforation (Fraile *et al*. 1994; Box *et al*. 1997; Velchuru *et al*. 2007) and may therefore be most similar to the lesions seen in the small and large colons in horses. The serosal form is distinguishable by the presence of eosinophilic ascites, with up to 88% eosinophils seen on fluid analysis (Kravis *et al*.1982). Peripheral eosinophilia has also been reported in up to 80% of cases (Khan & Orerstein 2008). Mucosal predominant disease results in mucosal dysfunction and manifests clinically as protein-losing enteropathy, malabsorption and diarrhoea (Okpara *et al*. 2009). Eosinophils were reported in peritoneal fluid in 4/6 (67%) of horses presenting with IFEE (Southwood *et al*. 2000). Eosinophil levels were not measured in the peritoneal fluid in this series. Since eosinophils are not normally identified in the peritoneal fluid of healthy horses or horses with simple or strangulating intestinal obstructions, it would be interesting to see whether peritoneal fluid analysis could be used to predict the likelihood of the presence of a focal eosinophilic lesion.

**Conclusions**

The visual and histological features of focal eosinophilic lesions of the small colon causing intestinal obstruction are similar to those previously described in both the large colon (Edwards *et al*. 2000) and the small intestine (Archer *et al.* 2006; Mäkinen *et al.* 2008). However, the primary difference between lesions in the small and large colons and those that occur in the small intestine appears to be in the degree of mucosal and serosal necrosis. Eosinophilic colitis lesions are rare but should be considered as a potential cause of obstruction of the small colon, which may progress to development of septic peritonitis. Surgical resection of these lesions can result in a successful outcome. The underlying cause of focal eosinophilic lesions affecting the equine small intestine, large colon and small colon has not been determined and further research is required.

**Authors’ declaration of interests**

No conflicts of interest have been declared.

**Source of funding**

No sources of funding.

**Tables**

Table 1. Case signalment, pre-operative clinical parameters and outcome of the five horses with focal eosinophilic colitis lesions of the small colon.

**Figures**

Fig. 1. Gross appearance of focal eosinophilic colitis lesions identified in the small colon at exploratory laparotomy demonstrating the degree of serosal hyperaemia, and petechation evident together with focal areas of mural necrosis. .

Fig. 2.

A: Haematoxylin and Eosin [H&E] photomicrograph of mucosal layer showing intense hyperaemia and mixed cellular infiltrate (few eosinophils), with extensive loss of mucosal epithelial cells and sloughing into the intestinal lumen. Bar = 50 μm.

B: H&E photomicrograph of submucosal layer with eosinophil dominated diffuse cellular infiltrate (arrows). Bar = 100 μm.

C: H&E photomicrograph of muscularis layer with multifocal infiltrate with a focal central accumulation of eosinophilic debris, surrounded by macrophages, and lymphocytes. Bar = 100 μm.

D: H&E photomicrograph of serosal layer with hyperaemia and diffuse eosinophilic infiltrate. Bar = 20 μm.

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