Case Report

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Hormone Therapy for Treatment of Colonic Vascular Ectasia in 2 Dogs

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Case History 1: A 10-year-old sexually intact male mixed breed dog was examined because of a 5-year history of intermittent melena, hematochezia, and a chronic microcytic anemia. In the 5 months before examination, the hemorrhagic episodes had increased in frequency and intensity, requiring 3 whole blood transfusions for stabilization. On physical exam, a grade III/VI left apical systolic murmur was ausculted. Physical examination also revealed tachycardia, tachypnea, and pale mucous membranes. Rectal examination revealed evidence of melena and hematochezia. Treatment before admission included prednisone (2.5 mg/kg, [1.25 mg/lb], PO q24h), azathioprine (3.1 mg/kg [1.4 mg/lb], PO q24h), metronidazole (21 mg/kg, [10 mg/lb], PO q12h), famotidine (1.25 mg/kg [0.56 mg/lb], PO q12h), and sucralfate (62.5 mg/kg [28 mg/lb], PO q12h).

CBC results revealed a severe microcytic (MCV 59 fl; reference range 60–75 fl), normochromic (MCHC 33 g/dL; reference range 32–36 g/dL) anemia (HCT, 12.5%; reference range 37–55%) with poor evidence of regeneration (reticulocyte count 54,000; reference range >60,000) and a total protein of 4.5 g/dL (reference range; 6.0–8.0 g/dL). Red blood cell (RBC) morphology was characterized by a 1 + anisocytosis, polychromasia, and Howell Jolly bodies. The remainder of the clinicopathologic results was unremarkable as were results of diagnostic imaging.

A crossmatch was performed and a packed-RBC transfusion (12 mL/kg [5.6 mL/lb]) was administered. PCV and total solids improved after the transfusion to 22% and 8.0 g/dL, respectively. The tachypnea, tachycardia, and murmur resolved after administration of the transfusion.

Endoscopic evaluation revealed a small gastric ulcer and a friable, hyperemic duodenal mucosa. Colonoscopy revealed multiple bundles of tortuous, dilated vessels, which were found diffusely throughout the length of the colon.

A diagnosis of colonic vascular ectasia was made from the characteristic gross morphologic abnormalities visualized during endoscopy. The diffuse distribution and number of vascular lesions made laser coagulation or electrocautery an inappropriate method of treatment. Subtotal colectomy was considered as an option for treatment, but hormone therapy alone was eventually chosen because of the owner's desire to avoid the potential morbidity associated with surgery. The prednisone and azathioprine therapy was tapered and discontinued and hormone therapy was initiated.

Diethylstilbestrol (DES) was instituted at 0.33 mg/kg (0.15 mg/lb), PO q24h, then tapered to twice weekly after a 5-day loading period. The bleeding episodes decreased in severity over the next 3 weeks, but did not resolve, and the dog was administered an additional transfusion of packed-RBCs (12 mL/kg [5.6 mL/lb]). Altrenogest[a] (a synthetic progestin) was added to the twice weekly estrogen therapy at 0.04 mg/kg (0.02 mg/lb), PO q24h, for 7 days, and then increased to 0.08 mg/kg (0.04 mg/lb), PO q24h. Once the combination estrogen-progesterone therapy had been initiated, the dog improved clinically. Any significant hemorrhage subsided in approximately 1 week and the PCV stabilized between 35 and 40%. Over the next several weeks the microcytosis resolved. One episode of melena and hematochezia occurred 7 months later, after Dog 1 was treated with prednisone and carprofen by the referring veterinarian during an acute onset of ataxia and circling.

Dog 1 was examined 8 months after diagnosis for acute neurologic signs localized to the brainstem. CBC performed at this time revealed a mild normocytic, normochromic anemia because the hematocrit was 34% (reference range 37–55%). The owner declined advanced diagnostics and elected to take the dog home. The estrogen-progesterone therapy was reduced to DES 0.17 mg/kg (0.07 mg/lb) twice weekly and altrenogest 0.33 mg (0.15 mg/lb) every other day, and the dog was released from the hospital. Two weeks later, Dog 1 collapsed at home and suffered acute cardiopulmonary arrest. A necropsy was not performed.

Case History 2: A 10-year-old recently castrated male English Springer Spaniel was examined because of a 12-week-history of a nonregenerative anemia, intermittent melena, and hematochezia that had not improved with medical treatment. Treatment during that time period included amoxicillin (23 mg/kg [10.5 mg/lb], PO q12h), prednisone (0.3 mg/kg [0.15 mg/lb], PO q12h), sucralfate (57 mg/kg [26 mg/lb], PO q8h), famotidine (0.6 mg/kg [0.3 mg/lb], PO q12h), and metronidazole (14.3 mg/kg [6.5 mg/lb] PO q12h). Upon presentation, significant physical examination findings included hepatomegaly, prostatomegaly, and pale mucous membranes. Capillary refill time was within normal limits.

Remarkable findings included a microcytic (MCV 51; reference range 58–79 fl), normochromic (MCHC 30 g/dL;

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reference range 30–38 g/dL), nonregenerative (reticulocyte count 14.76 × 103/μL; reference range > 100 × 103/μL) anemia (HCT 25%; reference range 36–60%). RBC morphology was characterized by a 1 + anisocytosis, 1 + hypochromasia, and target cells were noted.

Gastroduodenoscopy revealed multiple small erosions and ulcerations diffusely distributed throughout the gastric mucosa. The proximal duodenum was grossly unremarkable.

Colonoscopy, to the level of the cecum, identified multifocal areas of raised, tortuous vascular lesions, which were present 15 cm orad to the anus in the transverse colon and extended to the ileocolic valve. Multiple biopsy specimens were collected from the stomach, duodenum, and colon. The colonic vascular lesions bled profusely when biopsied, but the normal appearing colonic mucosa did not.

Histopathologic evaluation of the colonic specimens revealed thin-walled, variably dilated, and ectatic venous vessels in the submucosa. The venous walls were flaccid and tortuous, with occasional, slight projections and outpouches. In some vessels there was variation in thickness of the smooth muscle wall, with focal or segmental poorly delineated areas of subtle eosinophilia and nuclear pyknosis. Thicker-walled vessels, apparently arterioles, showed similar features. Affected vessels were variably blood filled, and some vessels appeared dilated with blood. A diagnosis of colonic vascular ectasia was made based on the endoscopic appearance of the aberrant vasculature and was supported by histopathologic analysis.

The dog was stable upon discharge; however, the hematochezia continued to wax and wane over the next 3 weeks. The hematocrit decreased from 25 to 16%. At that time Dog 2 developed clinical signs attributable to the anemia, and the dog was administered 100 mL (5.7 mL/kg [2.6 mL/lb]) of whole blood. After the transfusion, the hematocrit improved to 26% (reference range 37–55%). Melena, which was present upon initial evaluation, resolved with medical treatment for gastric ulceration and discontinuation of the prednisone.

The large number of diffusely distributed colonic vascular lesions made endoscopic treatment utilizing argon plasma laser coagulation or electrocautery not an ideal option. Subtotal colectomy was discussed with the owner, but because of the risk of surgical complications, the owner elected to attempt medical management with hormone therapy.

A commercially available combination ethinyl estradiol and norethindrone acetate tablet was prescribed. Each tablet of OvCon[b] 35 contains 35 μg of ethinyl estradiol and 400 μg norethindrone acetate. This corresponded to an ethinyl estradiol dose of 2 μg/kg (1 μg/lb) PO q24h and a norethindrone acetate dose of 23 μg/kg (10.4 μg/lb) PO q24h. Ferrous sulfate was initiated at 18.6 mg/kg (8.5 mg/lb) PO q24h because of the chronic gastrointestinal blood loss and suspected iron deficiency component of the anemia.

Within 7 days of initiating hormone therapy, the hematochezia had improved, and the hematocrit stabilized. Over the next 6 weeks, the hematocrit continued to improve to as much as 35% and the feces had intermittent evidence of a small quantity of frank blood.

Eight weeks after instituting hormone therapy, the hematochezia had resolved. Colonoscopy revealed that the vascular lesions were grossly unchanged from the previous evaluation. Subjectively the lesions were more resistant to manipulation than at the previous procedure and hemorrhaged less with the passage of the endoscope. Hematochezia induced by the endoscope improved in the days after the procedure and was not severe, and the hematocrit continued to improve.

Twenty-four months later, the hematocrit was 40% (reference range 37–55%) and the microcytosis had resolved. The hematochezia had completely resolved other than 1 other incident of hematochezia in the prior 24 months, associated with a temporary decrease in the dosage of ethinyl estradiol.

Discussion: Colonic vascular ectasia is defined in both the human and veterinary literature as dilated arteries, veins, and lymphatics lined with a single layer of endothelial cells within the mucosa and submucosa of the colon.[1–4] Hemorrhage is caused by disruption of these fragile dilated mucosal vessels, often simply by the passage of feces. The hematochezia can become chronic and intermittent in nature, resulting in an iron deficiency anemia characterized by microcytosis and hypochromasia.[5] Melena is also present if the ectatic lesions extend into the ileum and jejunum.

The exact etiology of CVE is currently unknown in dogs and humans. However, the most widely accepted theory for the development of CVE in humans is that chronic colonic distension and contraction (from chronic constipation) lead to submucosal venous occlusion. Concomitantly, colonic arterial inflow is maintained, further increasing the submucosal venous pressures, and resulting in dilation of these vessels. Continuous back pressure and dilation cause a loss of precapillary sphincter competency and ultimately form an arteriovenous shunt.[6] It is interesting to note that while chronic constipation has been associated with the development of CVE in humans, neither dog reported here had a history of constipation or tenesmus. Other proposed etiologies of acquired colonic vascular ectasia include aortic stenosis, renal failure, type IV collagen abnormalities, malignancy, and parasitism.[7–10]

Diagnosis of colonic vascular ectasia is dependent upon endoscopic evaluation of the mucosal surface of the colon. The lesions are typically not visible on or from the serosal surface of the gastrointestinal tract and therefore cannot be identified during exploratory celiotomy. Histopathologic confirmation of mucosal vascular abnormalities is helpful, but the presence of the vascular lesions on the mucosa of the colon is definitive for the disease.

Although colectomy is considered the preferred method of treatment in dogs,[1–3] this procedure is reserved for humans with life-threatening hemorrhagic lesions that are unresponsive to minimally invasive procedures. Most physicians prefer endoscopic-assisted argon plasma laser coagulation[5] of the vascular bundles in combination with oral estrogen-progesterone therapy. Estrogen-progesterone

therapy does not lead to lesion regression, rather it has been associated with a reduction in the number of blood transfusions necessary to maintain stable to normal hemoglobin levels as well as decrease the number and severity of bleeding episodes. Ethinyl estradiol (50 μg) and norethisterone (1 mg) administered for 6 months to 1 group of transfusion-dependent human patients with bleeding gastrointestinal vascular malformations appeared to be efficacious.[11] The mean transfusion requirement before entry to the study was 16 units of packed cells per patient per year. While on hormone therapy, the transfusion requirement dropped to 2.8 units per patient over 6 months. Patients on placebo therapy had a transfusion requirement of 11.2 units per patient over 6 months. The mechanism of action of this drug combination has not been confirmed, but a number of theories have been proposed. These theories include induction of squamous metaplasia, restoration of the continuity of the endothelium of abnormal vessels, primary effects on blood coagulation, especially in patients suffering from concurrent vWF deficiency, and stasis of blood in the mesenteric microcirculation.[11–15]

The current treatment of choice for CVE in the veterinary literature is surgical resection of the affected portion of the colon to control hemorrhage. Although there are no large studies evaluating complications associated with subtotal colectomy in dogs, reported complications in cats include dehiscence, tenesmus, chronic diarrhea, and fecal incontinence.[16] In two of the veterinary CVE case reports, one reported resolution of hemorrhage with no significant postoperative morbidity, whereas in the other report intestinal hemorrhage persisted despite multiple surgical procedures in 1 dog. The dog developed fecal incontinence and was euthanized. In the current report, the owners' desire to avoid the morbidity associated with surgery prompted the use of medical management, so hormone therapy was used as an alternative to surgery. Both dogs need transfusions before initiation of hormone therapy; after initiation of hormone therapy, hematochezia resolved and no further transfusions were necessary.

Dogs are more sensitive to estrogen and progestins than humans. The optimal estrogen : progesterone ratio for dogs is approximately 1 : 1,000–1 : 3,000.[17] Bone marrow toxicity is the most common side effect of estrogen administration in the dog. The mechanism of estrogen toxicity is unknown, but the cytologic pattern of development of this toxicity is unique. Pancytopenia and hypoplastic marrow develop at 3–4 weeks postexposure and are often fatal with dogs succumbing to secondary infection.[18] Toxicolgy studies determined that the no-observed-effect-level for ethinyl estradiol-induced hematotoxicity in dogs is between 0.04 and 0.2 mg/kg/day (0.02–0.1 mg/lb/day).[17] The most prominent effects of long-term administration of ethinyl estradiol-norethindrone acetate in dogs are alopecia, cystic endometrial hyperplasia, and pyometra at dosages of 21–525 μg/kg/day (9.5–240 μg/lb/day). These published levels were used when developing the hormone regimen for Dog 2. The low end of the dose for both ethinyl estradiol and norethindrone acetate was utilized in the second case with clinical success.

Surgical resection of ectatic lesions has been considered the treatment of choice in veterinary patients diagnosed with colonic vascular ectasia. This case report describes oral estrogen-progesterone therapy as a viable alternative to surgery in the treatment of colonic vascular ectasia in dogs. Oral hormone therapy was well-tolerated long-term in both patients with no indications of bone marrow toxicity at the prescribed dose. Oral hormone therapy effectively decreased the severity and frequency of hematochezia in both patients, controlled their clinical signs, and maintained a normal hematocrit without surgical intervention.

Footnotes

[a] Regu-Mate, Schering-Plough, Kenilworth, NJ
[b] OvCon 35, Warner Chilcott, Rockaway, NJ

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