RCCV
Revista Complutense de Ciencias Veterinarias

PULMONARY THROMBOEMBOLISM IN A DOG WITH INFLAMMATORY BOWEL DISEASE
TROMBOEMBOLISMO PULMONAR EN UN PERRO CON ENFERMEDAD INFLAMATORIA INTESTINAL

García-Sancho M., Sainz A., Rodríguez-Franco F., Villaescusa A. and Rodríguez-Bertos A.

Departamento de medicina y Cirugía Animal. Facultad de Veterinaria, UCM. Avenida Puerta de Hierro s/n 28040-Madrid, Spain. Corresponding author: mercgarc@vet.ucm.es

ABSTRACT

A 4-year-old 4-kg male Yorkshire Terrier was brought for a re-evaluation of inflammatory bowel disease (IBD) diagnosed two years before. The dog presented with a four-week history of diarrhoea, biliary vomiting, weight loss and ascites. Laboratory analysis revealed hypoproteinemia and a neutrophilic leucocytosis. An upper gastrointestinal endoscopic examination was performed. During the endoscopic procedure, the animal died due to a cardiopulmonary arrest. The necropsy confirmed the presence of a pulmonary thromboembolism. Extraintestinal manifestations of IBD are well reported in humans, but rarely appear in dogs. In Human Medicine, a very common extraintestinal manifestation of IBD is the presence of thromboembolisms. Further studies are needed to evaluate the tromboembolism risk in dogs with IBD.

KEYWORDS: Inflammatory bowel disease (IBD), pulmonary thromboembolism, dog, ascytis.

RESUMEN

Se describe el caso clínico de un perro macho de raza Yorkshire de 4 años de edad que acude a la consulta para una revisión de su enfermedad inflamatoria intestinal (EII) diagnosticada hace 2 años. El animal se presenta con una historia de diarrea, vómitos biliosos, pérdida de peso y ascitis de 4 semanas de duración. Los análisis de sangre mostraron la presencia de hipoproteinemia y leucocitosis. Se lleva a cabo una exploración endoscópica del tracto digestivo

superior durante la cual el animal muere. El examen postmortem confirma la presencia de un tromboembolismo pulmonar. Las manifestaciones extraintestinales de la EII se describen con frecuencia en humanos pero no en perros. Entre estas, los tromboembolismos son muy frecuentes en medicina humana. Sería de interés realizar más estudios con el fin de profundizar en el riesgo de la aparición de tromboembolismos en perros con EII.

PALABRAS CLAVE: Enfermedad inflamatoria intestinal (EII), tromboembolismo pulmonar, perro, ascitis.

Inflammatory bowel diseases (IBD) are a group of idiopathic disorders characterized by the presence of gastrointestinal clinical signs and histological evidence of intestinal inflammation (Guilford 1996).

The most frequent clinical signs of IBD in the dog are chronic diarrhoea, vomiting, weight loss, anorexia or polyphagia. In human medicine, many extraintestinal signs have been described in the literature; however, in veterinary medicine, they are rarely reported (Guilford 1996a). Polyarthritis (Pedersen *et al* 1976, Bennet 2005), inflammatory hepatic disease, pancreatitis, nephritis (Weiss *et al* 1996) and polydipsia (Henderson and Elwood 2003) have been detected in small animals with IBD. Thrombocytopenia and anaemia have also been reported (Ridgway *et al* 2001, Ristic and Stidworhty 2002). The pathogenesis of these extraintestinal signs is not well understood; immunoregulatory defects have been related with some of these extraintestinal signs (Ridgway *et al* 2001).

The occurrence of thromboembolisms is a serious complication in human IBD (Talbot *et al* 1986, Jackson *et al* 1996). Deep vein thrombosis of the leg and pulmonary emboli are the most frequent events (Talbot *et al* 1986). The aetiopathogenesis of these complications has been widely discussed, being the presence of hypercoagulable state as the suggested cause for thromboembolism in humans with IBD (Schapira *et al* 1999).

Here we describe a clinical case of pulmonary thromboembolism in a dog with IBD associated with a protein-losing enteropathy.

CASE DESCRIPTION

A 4-year-old 4-kg sexually intact male Yorkshire Terrier was referred to the Veterinary Medicine Teaching Hospital of the Complutense University of Madrid for a re-evaluation of inflammatory bowel disease.

Two years before, the dog presented with chronic diarrhoea, biliary vomiting, weight loss, and ascites. Blood analysis showed hypoproteinemia (plasma proteins: 3.1 g/dL, albumin: 1.7 g/dL). A histopathological study of endoscopic biopsies had shown a severe lymphocytic-plasmacytic infiltrate in the duodenum, edema in the lamina propria and lymphangiectasia. The dog was initially treated with prednisone (1 mg/kg PO q12 hours for 10 days, 0.5 mg/kg PO q12 hours for 10 days, 0.5 mg/kg PO q24 hours for 10 days, and 0.5 mg/kg PO q48 hours for 60 days), and metronidazole (10 mg/kg PO q12 hours for 21 days). Dietary management using a prescription diet for gastrointestinal disease was administered.

Clinical response after therapy was favourable, obtaining normal values of plasma proteins and albumin after treatment. No medical therapy was administered for two years. Clinical signs were absent for this period of time, until a four-week history of chronic diarrhoea, biliary vomiting, weight loss and ascites was presented. At that time, physical examination revealed some abnormal findings: rectal temperature 36.7ºC, slight dehydration (4%), and ascites. Pulse, capillary refill time, and heart and pulmonary sounds were normal. No jugular pulses were detected. Blood analysis showed: PCV: 47%, hemoglobin: 15.5 g/dL, RBC count: $6.85 \times 10^6/\mu L$, platelets: $420 \times 10^3/\mu L$, WBC count: $21.3 \times 10^3/\mu L$, neutrophils: $20.4 \times 10^3/\mu L$, lymphocytes: $0.4 \times 10^3/\mu L$, eosinophils: $0.4 \times 10^3/\mu L$, glucose: 97 mg/dL, urea: 55 mg/dL, creatinine<0.5 mg/dL, total protein: 2.8 g/dL, albumin: 1.9 g/dL, ALT: 15 IU/L, alkaline phosphatase: 63 IU/L, Na^+: 137 mmol/l, K^+: 3.7 mmol/l, Cl^-: 103 mmol/l, fibrinogen: 116 mg/dL. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal; antithrombin III was not evaluated. Serology for *Leishmania infantum* and *Ehrlichia canis* was negative. Urine analysis was normal. Protein/creatinine ratio was 0.09 g/mmol. 300 ml of abdominal fluid were removed and analyzed; the specific gravity was of 1.008, total proteins value was 200 mg/dL, 12 nucleated cells/μL were found, and lipids and bacteria were absent. Examination of faeces for parasites was negative. Abdominal ultrasound revealed a significant thickening of the small bowel wall (> 6 mm), though the layered appearance of the bowel wall was maintained.

An upper gastrointestinal endoscopic examination was planned. Metronidazole (10 mg/kg BID) and Hetastarch (20 ml/kg/day IV) were administered for one day prior to the procedure. Pre-anaesthetic electrocardiography was normal. An IV bolus of fentanyl (10 µg/kg) and diazepam (0.2 mg/kg) was administered as pre-anaesthetic. Isoflurane was used for induction (5% MAC) and maintenance (0.5% MAC). The endoscopy revealed erythemic mucosa with a granular appearance and some erosions in the stomach, and erythemic, granular, irregular

and friable mucosa in the duodenum. A cardio-respiratory arrest occurred while finishing the endoscopic procedure, and resuscitation manoeuvres were unsuccessful.

Subsequent necropsy revealed a poor body condition, presence of yellowish-fluid in the abdominal cavity, and a severe thickening of the gastric and bowel wall. Some erosions were present in the gastric body and pyloric antrum. Lymphangiectasia was observed in different points of the small bowel (Figure 1). The most important finding in thorax cavity was a thrombosis in the pulmonary artery (Figure 2).

The histopathological study of the endoscopic biopsies revealed a moderate lymphocytic-plasmacytic infiltrate in the duodenum, severe oedema in the lamina propria and marked lymphangiectasia. Histopathology of the liver and kidneys didn't show any significant lesion.

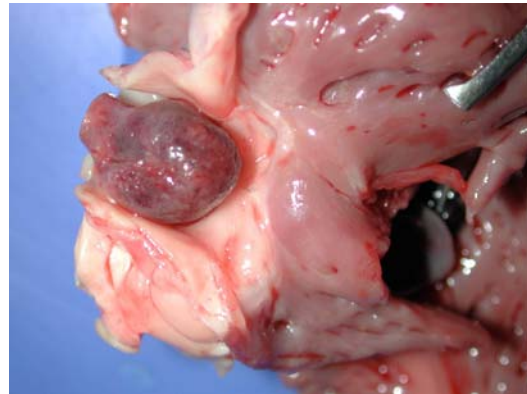Figure 1.- Bowel lymphangiectasia on the serosa.

Figure 2.- Thrombus attached to the pulmonary artery.

DISCUSSION

In human medicine, many extraintestinal manifestations of IBD have been reported, such as musculoeskeletal signs, specially arthritis and ankylosing spondilitis (Rankin 1990, Levine and Lukawski-Travish 1995, Bernstein *et al* 2001). Other alterations commonly associated to human IBD are ocular signs (iritis/uveitis), hepatobiliary signs (primary sclerosing cholangitis), and cutaneous signs (pyoderma gangrenosum, and erythema nodosum) (Rankin 1990, Levine and Lukawski-Travish 1995, Bernstein *et al* 2001). Neurological (Lossos *et al* 1995), respiratory (Mahadeva *et al* 2000), urinary (Wester *et al* 2001), cardiac (Hyttinen *et al* 2003), and pancreatic alterations (Huang and Lichtenstein 2002) have also been described.

Thromboembolic events and other vascular and haematological signs have been described in humans with this disease (Talbot *et al* 1986, Jackson *et al* 1997, Novaceck *et al* 1999). Both Crohn's disease and ulcerative colitis are thought to be associated with a high risk of thromboembolisms (Bernstein *et al* 2001). In fact, the risk of developing deep venous thrombosis

or pulmonary embolism is three times higher in patients with IBD (Bernstein *et al* 2001). This risk is especially higher in young patients with active disease.

In veterinary medicine, extraintestinal manifestations of IBD are rarely noticed (Guilford 1996). Polyarthritis (Pedersen *et al* 1976, Bennet 2005), inflammatory hepatic disease, pancreatitis and nephritis (Weiss *et al* 1996) have been described in small animals. Pruritic concurrent skin diseases have also been reported (Guilford, 1996). These lesions could be due to the immune complex deposition in different organs, secondary to aberrant immunological responses in IBD, though the ethiopathogenesis of these signs is not well understood (Center 1996). Thrombocytopenia and anaemia have also been described in dogs with IBD (Ridgway *et al* 2001, Ristic and Stidworthy 2002).

In dogs, many diseases lead to prothrombotic tendencies. Diseases that cause endothelial damage, blood stasis or systemic hypercoagulability have a thromboembolic potential (Good and Manning 2003). The common methods used to assess hemostasis are more effective in documenting a trend toward hypocoagulability than one toward hypercoagulability (Good and Manning 2003). Although it is not used commonly in veterinary patients clinically yet, thromboelastography provides a method for identifying hypercoagulable patients (Goggs and others 2009). Hypercoagulability can be due to many factors, including decreased levels of Antithrombin III (ATIII). ATIII deficiency is common in glomerular diseases due to protein loss (DiBartola and Meuten 1980, Greco and Green 1987, Cook and Cowgill 1996, Ritt *et al* 1997). This deficiency may also occur in diseases causing protein loss through the gastrointestinal tract, like parvoviral enteritis (Otto *et al* 2000). Protein-losing enteropathies frequently allow the extravasation of larger proteins than in a protein-losing nephropathy. In this case, the haemostatic balance may not be altered because of the simultaneous loss of both large procoagulant factors and small anticoagulant factors in equal amounts (Green 1984). Therefore, protein-losing enteropathies could be less frequently involved with thromboembolic risk (Good and Manning 2003).

This could explain the limited information available in the literature about thrombotic events in dogs with protein-losing enteropathy. Femoral thrombosis has been previously described in a dog with intestinal lymphosarcoma and hypoproteinemia (Ihle *et al* 1996). Distal aortic thrombosis has also been reported in one case of protein-losing enteropathy (Clare and Kraje 1998). Interestingly, pulmonary thromboembolism was suspected in 2 Yorkshire terriers with protein-losing enteropathy (Kimmel *et al* 2000). To the author's knowledge, this is the first clinical and pathological description of canine pulmonary thromboembolism associated with IBD.

Diseases most commonly associated with pulmonary thromboembolism in dogs are: heart disease (including heartworm disease), glomerular disease, neoplasia, disseminated intravascular coagulopathy, immune-mediated haemolytic anemia, pancreatitis, sepsis, trauma, hyperadrenocorticism, hypothyroidism, and diabetes mellitus (Burns *et al* 1981, Klein *et al* 1989, LaRue and Murtaugh 1990, Corlouer 1994, Kittleson and Kienle 1998, Good and Manning 2003). Prothrombotic tendencies can be exacerbated by immunosuppressive therapy with corticosteroids (Good and Manning 2003).

Pulmonary thromboembolism was not suspected in our case, due to the absence of clinical signs and abnormalities found in the physical examination compatible with this disease. These difficulties have also been described in human medicine. In a recent report, the most frequently underdiagnosed disease in human autopsies (in 61% of cases) was pulmonary thromboembolism (Ermenc 1999).

Taking into account this case report and the incidence of thromboembolic events in human patients with IBD, further studies are required to investigate the rate of thromboembolism or hypercoagulability in dogs with inflammatory bowel disease.

REFERENCES

Bennet, D. (2005): Immune-mediated and infective arthritis. In: Textbook of veterinary internal medicine. 6th edn. Eds S.J. Ettinger, E.C. Feldman. W.B. Saunders, Philadelphia, pp 1958-1965.

Bernstein, C.N., Blanchard, J.F., Rawsthorne, P., Yu, N. (2001): The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. American Journal of Gastroenterology, 96, 1116-1122.

Burns, M.G., Kelly, A.B., Hornof, W.J., Howerth, E.W. (1981): Pulmonary artery thrombosis in three dogs with hyperadrenocorticism. Journal of the American Veterinary Medical Association, 178, 388-393.

Center, S.A. (1996): Diseases of the gall bladder and biliary tree. In: Strombeck's Small Animal Gastroenterology. 3rd edn. Eds W.G. Guilford, S.A. Center, D.R. Strombeck, D.A. Williams, D.J. Meyer. W.B. Saunders, Philadelphia, pp 860-888.

Clare, A.C., Kraje, B.J. (1998): Use of recombinant tissue-plasminogen activator for aortic thrombolysis in a hypoproteinemic dog. Journal of the American Veterinary Medical Association, 212, 539-543.

Cook, A.K., Cowgill, L.D. (1996): Clinical and pathological features of protein-losing glomerular disease in the dog: a review of 137 cases (1985-1992). Journal of the American Animal Hospital Association, 32, 313-322.

Corlouer, J. (1994): Thromboembolie pulmonaire chez le chien. Pratique Médicale et Chirurgicale de l'Animale de Compagnie, 29, 71-84.

Dibartola, S.P., Meuten, D.J. (1980): Renal amyloidosis in two dogs presented for thromboembolic phenomena. Journal of the American Animal Hospital Association, 16, 129-135.

Ermenc, B. (1999): Minimizing mistakes in clinical diagnosis. Journal of Forensic Sciences, 44, 810-813.

Goggs R, Benigni L, Fuentes VL, Chan DL: Pulmonary thromboembolism. J Vet Emerg Crit Care (San Antonio) 2009; 19:30-52.

Good, L.I., Manning, A.M. (2003): Thromboembolic disease: predispositions and clinical management. Compendium on Continuing Education for the Practicing Veterinarian, 25, 660-674.

Greco, D.S., Green, R.A. (1987): Coagulation abnormalities associated with thrombosis in a dog with nephritic syndrome. Compendium on Continuing Education for the Practicing Veterinarian, 9, 653-658.

Green, R.A. (1984): Clinical implications of antithrombin III deficiency in animal diseases. Compendium on Continuing Education for the Practicing Veterinarian, 6, 537-545.

Guilford, W.G. (1996): Idiopathic inflammatory bowel diseases. In: Strombeck's Small Animal Gastroenterology. 3rd edn. Eds. W.G. Guilford, S.A. Center, D.R. Strombeck, D.A. Williams, D.J. Meyer. W.B. Saunders, Philadelphia, pp 451-486.

Henderson, S.M., Elwood, C.M. (2003): A potential causal association between gastrointestinal disease and primary polydipsia in three dogs. Journal of Small Animal Practice, 44, 280-284.

Huang, C., Lichtenstein, D.R. (2002): Pancreatic and biliary tract disorders in inflammatory bowel disease. Gastrointestinal Endoscopy Clinics of North America, 12, 535-559.

Hyttinen, L., Kaipiainen-Seppanen, O., Halinen, M. (2003): Recurrent myopericarditis in association with Crohn's disease. Journal of Internal Medicine, 253, 386-388.

Ihle, S.L., Baldwin, C.J., Pifer, S.M. (1996): Probable recurrent femoral artery thrombosis in a dog with intestinal lymphosarcoma. Journal of the American Veterinary Medical Association, 208, 240-242.

Jackson, L.M., O'Gorman, P.J., O'Connell, J., Cronin, C.C., Cotter. K,P., Shanahan, F. (1996): Thrombosis in inflammatory bowel disease: clinical setting, procoagulant profile and factor V Leiden. The Quarterly Journal of Medicine, 90, 183-188.

Kimmel SE, Waddell LS, Michel KE. Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire terriers: five cases (1992-1998). J Am Vet Med Assoc 2000; 217: 703-706.

Kittleson, M.D., Kienle, R.D. (1998): Thromboembolic diseases. In: Small Animal Cardiovascular Medicine. 1st edn. Eds M.D. Kittleson and R.D. Kienle. Mosby, St. Louis. pp 540-551.

Klein, M.K., Dow, S.W., Rosychuk, R.A. (1989): Pulmonary thromboembolism associated with immune-mediated haemolytic anemia in dogs: ten cases (1982-1987). Journal of the American Veterinary Medical Association, 195, 246-250.

Larue, M.J., Murtaugh, R.J. (1990): Pulmonary thromboembolism in dogs: 47 cases (1986-1987). Journal of the American Veterinary Medical Association, 197, 1368-1372.

Levine, J.B., Lukawski-Travish, D. (1995): Extraintestinal considerations in inflammatory bowel disease. Gastroenterology Clinics of North America, 24, 633-646.

Lossos, A., River, Y., Eliakim, A., Steiner, I. (1995): Neurologic aspects of inflammatory bowel disease. Neurology, 45, 416-421.

Mahadeva, R., Walsh, G., Rower, C.D.R., Shneerson, J.M. (2000): Clinical and radiological characteristics of lung disease in inflammatory bowel disease. The European Respiratory Journal, 15, 41-48.

Novacek, G., Vogelsang, H., Genser, D., Moser, G., Gangl, A., Ehringer, H., Koppensteiner, R. (1996): Changes in blood rheology caused by Crohn's disease. European Journal of Gastroenterology and Hepatology, 8, 1089-1093.

Otto, C.M., Rieser, T.M., Brooks, M.B., Russell, M.W. (2000): Evidence of hypercoagulability in dogs with parvoviral enteritis. Journal of the American Veterinary Medical Association, 10, 1500-1504.

Pedersen, N.C., Weisner, K., Castles, J.J., Ling, G.V., Weiser, G. (1976).:Noninfectious canine arthritis: the inflammatory, non-erosive arthritides. Journal of the American Veterinary Medical Association, 169, 304-310.

Rankin, G.B. (1990): Extraintestinal and systemic manifestations of inflammatory bowel disease. The Medical Clinics of North America, 74, 39-50.

Ridgway, J., Jergens, A.E., Niyo, Y. (2001): Possible causal association of idiopathic inflammatory bowel disease with thrombocytopenia in the dog. Journal of the American Animal Hospital Association, 37, 65-74.

Ristic, J.M.E., Stidworthy, M.F. (2002): Two cases of severe iron-deficiency anaemia due to inflammatory bowel disease in the dog. Journal of the Small Animal Practice, 43, 80-83.

Ritt, M.G., Rodgers, K.S., Thomas, J.S. (1997): Nephrotic syndrome resulting in thromboembolic diseases and disseminated intravascular coagulation in a dog. Journal of the American Animal Hospital Association, 33, 385-391.

Schapira, M., Henrion, J., Ravoet, C., Maisin, J.M., Ghilain, J.M., De Maeght, S., Heller, F. (1999): Thromboembolism in inflammatory bowel disease. Acta Gastro-Enterologica Belgica, 62, 182-186.

Talbot, R.W., Hepell, J., Dozois, R.R., Beart, R.W. Jr. (1986): Vascular complications of inflammatory bowel disease. Mayo Clinic Proceedings, 61, 140-145.

Weiss, D.J., Gagne, J.M., Armstrong, J.P. (1996): Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis and nephritis in cats. Journal of the American Veterinary Medical Association, 209, 1114-1116.

Wester, A.L., Vatn, M.H., Faausa, O. (2001): Secondary amylodiosis in inflammatory bowel disease: a study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962 to 1998. Inflammatory Bowel Disease, 7, 295-300.