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Aortic thromboembolism. A different predisposing disease in four dogs: a case report

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Abstract: Four dogs had signs of pelvic limb lameness, pain, and collapse resulting from an occlusion of the distal aorta or the iliac arteries by thrombi. The diagnosis of an aortic thromboembolism was based on the absence or weakness of a femoral pulse, and the two-dimensional and Doppler ultrasonography of the abdominal aorta, iliac, and femoral arteries. Three dogs had a concurrent disease predisposing to thrombosis, including hyperadrenocorticism, protein losing nephropathy, neoplasia, and cardiac disease. Three dogs were treated with a tissue plasminogen activator (t-PA) in an attempt to lyse the thrombosis; two regained pelvic limb function. The other two dogs died shortly after the diagnosis of a thrombosis. A complete description of the history, clinical signs, laboratory analysis and imaging studies is included. Moreover, a review of the aortic thromboembolism, a diagnosis protocol and the options for its treatment are discussed.

Keywords: arterial thrombosis; tissue plasminogen activator; pelvic weakness; hind-limb paresis

Aortic thromboembolism (ATE) occurs commonly in cats with cardiomyopathy and is one of the most common causes of hind-limb paresis (Schoeman 1999). Clinical information regarding ATE in dogs is less thoroughly documented compared to that in cats in the current literature. In cats, ATE is characterised by an acute clinical manifestation and recurrence is relatively common (Smith et al. 2003). In contrast, approximately half of the dogs of the previous reports showed a chronic clinical manifestation with a low recurrence rate

(Boswood et al. 2000; Lake-Bakaar et al. 2012). Both the acute and chronic onset of the disease has been reported, and clinical signs include absent femoral pulses, cold extremities, signs of pain, exercise intolerance, and hind limb paresis (Van Winkle et al. 1993). In dogs, ATE has been associated with predisposing conditions, including cardiac disease, hyperadrenocorticism, protein-losing nephropathy and enteropathy, and neoplasia (Van Winkle et al. 1993; Carter and Van Heerden 1994; Felix et al. 2008; Winter et al. 2012). Aortic thromboembolism may

arise following the presence of one or more of the following three factors: a decrease in blood flow, an endothelial injury reduction, and a change in the systemic balance of prothrombotic and anticoagulant factors (Rosenberg and Aird 1999).

The aim of this study was to document the clinical presentation and treatment of ATE in dogs with varying predisposing diseases.

Case descriptions

CASE 1

A nine-year-old, neutered, male Schnauzer (weight: 5.8 kg) presented with anorexia, vomiting, and melena. The haematological results were normal. On the biochemical analysis, the blood urea nitrogen (BUN) (56.8 mmol/l; reference range: 2.9–10.7 mmol/l) and creatinine (433.2 μ mol/l; reference range: 44.2–132.6 μ mol/l) were severely increased. A urinalysis showed a specific gravity of 1.012 with evidence of proteinuria (a urine protein: creatinine ratio of 5.25). The increased echogenicity of the kidneys was noted using an abdominal ultrasonography. Chronic kidney disease (CKD) and protein losing nephropathy (PLN) were diagnosed, and the patient was hospitalised for intravenous fluid therapy. One day later, the patient developed lameness in the left pelvic limb, although femoral pulses were still present. The femoral pulses were absent and the left leg was cold after three days. An abdominal ultrasonography revealed the presence of a thrombus in the left external iliac artery.

Hydromorphone (0.05 mg/kg, *i.v.*, t.i.d.) was injected for pain management. Treatment of the thrombosis was attempted with an intravenous infusion of a tissue plasminogen activator (t-PA) (Actilyse; Boehringer Ingelheim) four times at a dose of 0.5 mg/kg at 120-minute intervals, followed by the subcutaneous injection of dalteparin (Fragmin, 100 IU/kg, *s.c.*, t.i.d.). Because the dog showed haematemesis, the infusion of the t-PA was discontinued. Despite treatment, the thrombi did not disappear and no significant improvement was observed in the hind limb perfusion. The pre-existing CKD became more severe and necrosis of the skin and soft tissue of the left pelvic limb developed. The dog eventually died one week after the diagnosis.

CASE 2

A fourteen-year-old neutered female Shih Tzu (weight: 4.25 kg) presented with hyperadrenocorticism (HAC) and cardiac disease (mitral and tricuspid valve regurgitation), and treated with trilostane (3.5 mg/kg, *p.o.*, b.i.d.), benazepril (0.25 mg/kg, *p.o.*, b.i.d.), furosemide (3 mg/kg, *p.o.*, b.i.d.) and pimobendan (0.3 mg/kg, *p.o.*, b.i.d.). Ten months after the diagnosis, an acute onset of signs of pain and left pelvic limb paralysis presented. The extremities were hypothermic, and no pulse was palpable on the left pelvic limb. The haematology was normal. On the biochemical analysis, the creatine kinase (CK) was elevated at 24.95 μ kat/l (reference range: 0.13–3.61 μ kat/l), although the AST was normal. The D-dimer was elevated at 3.83 nmol/l (reference range: < 1.37 nmol/l) and the antithrombin-III (AT-III) activity was normal at 101% (reference range: 80–120%). An abdominal ultrasonography revealed the presence of thrombi in the bilateral external and internal iliac arteries (Figure 1A).

The analgesic hydromorphone (0.05 mg/kg, t.i.d.) was intravenously administered for pain management. Treatment of the thrombosis was attempted with an intravenous infusion of t-PA three times at a dose of 1 mg/kg at 120-minute intervals, followed by the subcutaneous injection of dalteparin (100 IU/kg, *s.c.*, t.i.d.). The following day, the legs became warm and the femoral pulse was palpable. The dog regained full use of its hind limbs. Two days after the treatment, an abdominal ultrasound examination showed that the thrombi in the iliac arteries had completely disappeared (Figure 1B) and the patient was discharged. The dog died six months after the diagnosis of ATE due to the severe worsening of the pre-existing heart disease.

CASE 3

A thirteen-year-old, intact, male Shiba Inu (weight: 11.6 kg) presented with weight loss and partial anorexia. Two months prior, the dog had been presented to another veterinarian with a two-month history of inappetence and weight loss. The dog was presumptively diagnosed with an abdominal mass by ultrasonography at the local hospital. The blood tests revealed mild leukocytosis ($29.49 \times 10^9/l$; reference range, $5\text{--}17 \times 10^9/l$), anaemia (packed cell volume, 34.3%), low albumin (19.6 g/l; reference range, 28–45 g/l) and hypocalcaemia (1.83 mmol/l;

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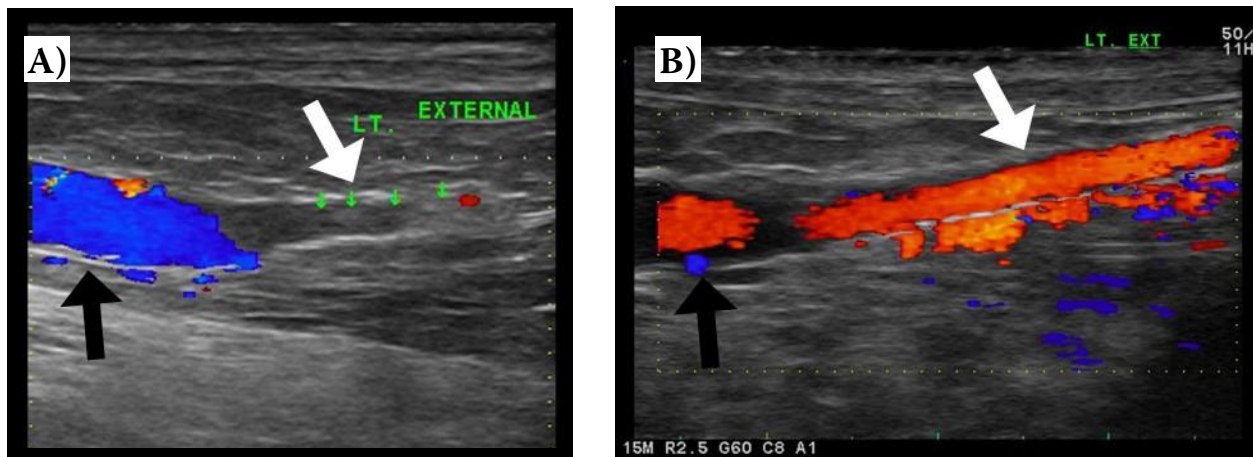


Figure 1. Case 2: The two-dimensional ultrasonographic image of the left external iliac artery of a dog with an aortic thrombosis (AT). (A) This is a Doppler flow ultrasonographic image of the left external iliac artery at the first presentation. The green arrows outline the intramural thrombi. The blood flow (blue) within the aorta is diminished at the location of the thrombi. (B) This is from ultrasonography 2 days after the t-PA injection. The thrombi in the left external iliac artery had completely disappeared. The white arrows indicate the left external iliac arteries. The black arrows indicate the caudal aortas

reference range, 2.25–2.95 mmol/l). A urinalysis showed a specific gravity of 1.025 with no evidence of proteinuria. The radiography, ultrasonography, and computed tomography revealed intestinal and splenic masses. The cytology of the masses by fine needle aspiration in the intestine and spleen suggested a mesenchymal cell tumour with low malignancy and a fibrohistiocytic nodule, respectively.

Surgery was planned for the intestinal and splenic mass, but the dog subsequently showed additional signs of exercise intolerance and lameness. The extremities were not cold and the femoral pulse was palpable. An abdominal ultrasonography revealed the presence of a thrombus in the aortic bifurcation. Dalteparin was injected subcutaneously at 100 IU/kg to prevent a new thrombus formation. The owner declined surgery and further therapy. The dog eventually died 10 days after the diagnosis of ATE due to the severe worsening of the pre-existing disease.

CASE 4

An eleven-year-old, neutered, male Maltese (weight: 3.79 kg) presented with a cough, respiratory distress, and an abdominal distension. On the physical examination, the dog showed mild tachypnoea (42 breaths/min) with shallow breathing, but normal heart sounds. The heart rate (136 beats per minute) and blood pressure (systolic blood pressure, 100 mmHg) were normal. A blood

test demonstrated the decreased total protein (48.5 g/l; reference range, 5–75 g/l) and hypoalbuminaemia (25.2 g/l; reference range, 28–45 g/l). A urinalysis showed a specific gravity of 1.027 with no evidence of proteinuria. The radiography and ultrasonography revealed pleural and peritoneal effusions, which were classified as transudates (total nucleated cell counts, $1 \times 10^9/l$; total protein, 22 g/l). We did not find the cause of the pleural and peritoneal effusions during the first visit.

An acute onset of signs of pain and pelvic limb paralysis occurred ten days after their first visit. The extremities were hypothermic, and no pulse was palpable on the pelvic limb. A second abdominal ultrasound examination was performed and revealed the presence of thrombi in the bilateral external and internal iliac arteries. The blood test at that time revealed an elevated CK ($> 33.4 \mu\text{kat/l}$; reference range, 0.13–3.61 $\mu\text{kat/l}$) and AST (7.5 $\mu\text{kat/l}$; reference range, 0.3–0.85 $\mu\text{kat/l}$). The D-dimer and AT-III activity were normal at 0.55 nmol/l (reference range, $< 1.37 \text{ nmol/l}$) and 85% (reference range, 80–120%), respectively. The bile acid, coagulation profile, serum ammonia level, and adrenocorticotropic hormone (ACTH) stimulation tests were normal. The serum total T4 concentration ($< 6.4 \text{ nmol/l}$; reference range, 12.9–51.5 nmol/l) and free T4 concentration ($< 3.9 \text{ pmol/l}$; reference range, 9.9–44.9 pmol/l) were low, but the thyroid-stimulating hormone (TSH) concentration was normal (0.17 ng/ml; reference range, 0.05–0.42 ng/ml).

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The electrocardiography and echocardiography were also normal.

Hydromorphone (0.05 mg/kg, t.i.d.) was intravenously administered for the pain management. The thrombosis treatment was attempted with an intravenous infusion of t-PA three times at a dose of 1 mg/kg at 120 minute-intervals, followed by the subcutaneous injection of dalteparin (100 IU/kg, s.c., t.i.d.). Over the next 3 days, the dog was ambulatory, but had moderate weight-bearing lameness of the hind leg. Over the next 8 days, the dog continued to improve, and regained full use of its hind limbs. An abdominal ultrasound examination showed that the thrombi in the iliac arteries had completely disappeared and the dog was discharged. Two months later, the patient had a second episode of an aortic thromboembolism. The patient developed lameness in the pelvic limb, although the femoral pulses were still present in this episode. The thrombolytic therapy with t-PA was not performed at the owner's request. The dog was treated with warfarin (0.05–0.1 mg/kg, p.o., s.i.d.) for 20 days. Because the warfarin therapy did not change the thrombus size, the dog went on to be chronically treated with dalteparin (150 IU/kg, s.c., t.i.d.). The thrombi did not disappear on the ultrasonography, but improvement was observed in the hind limb function. The dog was eventually euthanised 17 months after the first diagnosis of AT due to the recurrence of the pleural and peritoneal effusion and the aortic thrombosis.

DISCUSSION AND CONCLUSIONS

In our series, each case had a unique combination of predisposing diseases. Our first case was diagnosed with CKD and PLN. The causes of the thrombosis in renal disease are multifactorial. Furthermore, a deficiency of antithrombin III, secondary to the urinary excretion of this protein, is a major factor in promoting thromboembolism (Carter and Van Heerden 1994). Case 2 had evidence of HAC and mitral insufficiency. The exact mechanism whereby HAC predisposes to thrombosis is not known; however, various possibility pathogeneses have been proposed (Boswood et al. 2000). These include increased concentrations of a plasminogen activator inhibitor, increased concentrations of clotting factors, and an indication of antithrombin III loss in the urine. Cardiac disease can also predispose to thrombosis through

the stasis of the blood in the congested veins and atria, and interference with the normal endothelial integrity (Boswood et al. 2000). However, HAC would be considered much more likely to develop a thrombus in this case because the mitral insufficiency may not have been related to the development of a mural thrombus in dogs (Boswood et al. 2000). A previous study demonstrated that a severe mitral insufficiency with a ruptured chordae tendineae was associated with aortic thromboembolism in the post-mortem study (Van Winkle et al. 1993). Case 3 had intestinal neoplasia, which can predispose to thrombosis in numerous ways, including increased coagulation due to the platelet activation. No underlying disease process was determined in the fourth case.

Aortic thromboembolism in dogs is an uncommon condition that usually arises secondary to a predisposing disease process. Clinical signs of neuromuscular dysfunction were present in varying degrees in each dog in our series. The dogs with an acute onset of clinical signs were more severely affected, exhibiting neurological deficits; dogs with a chronic onset of the disease predominantly presented with exercise intolerance and lameness. In cats, ATE is a disease characterised by an acute clinical manifestation and recurrence is common (Smith et al. 2003). The initial clinical features of the dogs described above are notably different from those reported in cats with a feline aortic thromboembolism. In cases 1 and 3, the clinical signs had been present for more than four days and four weeks before diagnosis, respectively, without a recognisable acute onset. The prolonged duration of the clinical signs prior to the diagnosis has been reported in other dogs (Van Winkle et al. 1993; Boswood et al. 2000).

Medical treatment aimed at thromboembolic diseases consists of dissolving existing thrombi using thrombolytic drugs or preventing the formation of a new thrombus (Smith 2012). Three dogs received thrombolytic therapy using t-PA. Two of these dogs had severe ambulatory dysfunction before the t-PA treatment and became ambulatory after the treatment. Two dogs died shortly after the initial onset of the clinical signs due to the severe worsening of the pre-existing disease (Table 1).

The underlying predisposing causes should be thoroughly evaluated in dogs with aortic thrombosis at the time of the initial examination. Particular emphasis should be placed on diagnosing the sub-

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Table 1. The Summary of the Clinical Cases

	Case 1	Case 2	Case 3	Case 4
Duration of pelvic limb signs before diagnosis	4 days	acute onset	chronic	acute onset
Clinical signs	lameness	paresis/paralysis	weakness exercise intolerance	paresis/paralysis
Muscle enzymes	AST 6.41 µkat/l CK NA	AST 0.84 µkat/l CK 24.95 µkat/l	AST NA CK NA	AST 7.5 µkat/l CK >33.4 µkat/l
Treatment	t-PA Dalteparin	t-PA Dalteparin	Dalteparin	t-PA Warfarin Dalteparin
Survival after diagnosis	7 days	6 months	10 days	17 months
Probable underlying cause	protein losing nephropathy	HAC heart disease	neoplasia	unknown

AST = aspartate aminotransferase; CK = creatine kinase; HAC = hyperadrenocorticism; NA = not assessed; t-PA = tissue plasminogen activator

clinical cardiac disease, the renal disease, or the presence of concurrent underlying neoplastic lesions (Lake-Bakaar et al. 2012). The presence of ATE should be regarded as an important differential diagnosis for dogs with acute and chronic progressive pelvic limb dysfunction.

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