doi: 10.17221/8388-VETMED

Canine mammary anaplastic carcinoma with concurrent aorto-iliac thrombosis in a dog: a case report

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ABSTRACT: An 11-year-old, 6.75 kg, spayed female Maltese dog was referred for evaluation of a recurrent mammary gland tumour (MGT) after recent lumpectomies. We performed a regional mastectomy, and the mammary gland tumour was diagnosed as a mammary anaplastic carcinoma. On the 11th postoperative day, the dog presented with a one-day history of lethargy and left hind limb weakness. Increased D-dimer level and two-dimensional and Doppler ultrasonography revealed a unilateral aorto-iliac thrombus. Although prompt thrombolytic drug administration by intravenous infusion was recommended, the owner did not consent to further examination and treatment due to the side effects, and the patient died 24 h after it was diagnosed with arterial thrombosis (AT). This is the first report of a canine mammary anaplastic carcinoma with concurrent arterial thrombosis in a dog. These results suggest that cancer malignancy-induced hypercoagulability should be considered in the differential diagnosis of arterial thrombosis.

Keywords: arterial thrombosis; D-dimer; hypercoagulability; malignant; mammary gland tumour; dog

Mammary gland tumours (MGT) are among the most commonly diagnosed tumours in female dogs (Philibert et al. 2003). Epithelial tumours, which are the most commonly diagnosed histologic type of neoplasia affecting the mammary gland, constitute more than 90% of all tumours of the mammary gland (Gilbertson et al. 1983). Approximately 50% of all of these tumours are malignant, and, of these, 50% express the metastatic phenotype (Brodey et al. 1983; Gilbertson et al. 1983). Anaplastic carcinoma is the most malignant tumour of the epithelial type, and it is not classifiable on predominance as an adenocarcinoma, solid carcinoma, squamous cell carcinoma, or mucinous carcinoma (Misdorp et al. 1973; Hampe and Misdorp 1974). Anaplastic carcinoma in dogs is characterised by diffuse infiltration and extensive metastasis (Misdorp et al. 1973). In cancer patients, the correct prognostic information is important as it increases the possibility of adequate treatment. Generally, prognostic factors of canine mammary tumours have been limited to histopathological information, including the tumour type, stage, and metastatic lymph node size (Hellmén et al. 1993; Benjamin et al. 1999). However, several reports have demonstrated that hypercoagulability is also considered a prognostic factor (Madewall et al. 1980; Auger et al. 1987). Coagulation abnormalities in humans and dogs with mammary carcinoma are well-recognised paraneoplastic syndromes that are frequently associated with a short survival time (Belt et al. 1978; Goodnough et al. 1984; Madewall et al. 1980; Auger et al. 1987). In human patients, there is evidence that these subclinical haemostatic abnormalities can progress into clinically apparent thrombotic or haemorrhagic complications (Colman and Rubin 1990), and patients with adenocarcinoma have a higher incidence of thrombosis (Blom et al. 2005; Blom et al. 2006). In veterinary medicine, a retrospective study reported that canines with mammary carcinoma have a higher frequency and intensity risk of coagulatory abnormalities as the tumour progressed. However, evidence of thrombosis was not demonstrated (Stockhaus et al. 1999).

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Recently, a single case report demonstrated canine arterial thrombosis (AT) that was complicated by mammary gland adenocarcinoma (Kim and Park 2012). However, no reports have described AT in mammary anaplastic carcinoma, which is the most malignant canine mammary carcinoma. In this report, we describe for the first time the presentation, diagnosis, management, and outcome of mammary anaplastic carcinoma with concurrent AT in a Maltese dog.

Case description

An 11-year-old spayed female Maltese dog was referred to the Veterinary Medical Teaching Hospital of Konkuk University (KU-VMTH) for an evaluation of recurrent MGT after three mammary gland lumpectomies in the previous year for several newly formed MGTs that were histopathologically diagnosed as carcinoma. The dog presented two weeks after the last lumpectomy and had a recurrently formed MGT that was greater than 4 cm in diameter (Figure 1A). Fine needle aspiration of the MGT revealed a few clusters of epithelial cells with anisocytosis, anisokaryosis, and an increased nucleus-to-cytoplasm ratio that was consistent with mammary carcinoma (Figure 1B). Evidence of local metastases to regional lymph nodes and epithelial neoplastic cells were demonstrated (Figure 1C). A physical examination detected a soft systolic murmur (grade III/VI) that was localised at the left heart apex. Blood pressure was normal (systolic blood pressure, 126 mmHg). Nothing remarkable was found with electrocardiography. Thoracic radiography showed normal cardiac size (vertebral heart score, 9.4). Two-dimensional echocardiography disclosed that the anterior leaflet of the mitral valve was thickened and elongated. On spectral Doppler echocardiography, mitral regurgitant jet velocity (peak velocity, 3.5 m/s) with low density was detected. Abdominal ultrasound revealed no remarkable findings. Blood work including D-dimer (0.2 µg/ml, reference range [RR]: less than 0.5 µg/ml) was unremarkable. Based on the diagnosis of myxomatous mitral valve disease with asymptomatic congestive heart failure ACVIM stage B1, the patient was managed with furosemide (Lasix; Handok Pharmaceuticals Co., Ltd., Seoul, Korea), 1 mg/kg twice daily by mouth (per os), and ramipril (Vasotop; Intervet Korea Co., Ltd, Seoul, Korea), 0.125 mg/kg once daily *per os*. In order to assess distance metastasis, thoracic computed tomography was performed, and several contrast-enhancing nodules within the lung lobes confirmed metastasis. The clinical stage based upon the modified World Health Organization classification system was stage V (T2N2M1). The owner agreed to surgical excision of the mammary tumour. Before the surgery, a complete blood count and routine haemostatic profile were determined in order to detect haemostatic abnormalities, and all of the values were within the normal reference ranges : platelet count, 497 × 109 cells/l (RR: 200–500 × 10^9 cells/l); prothrombin time, 11.6 s (RR: 11–17 s); activated partial thromboplastic time, 9.6 s (RR, 7.2–10.2 s).

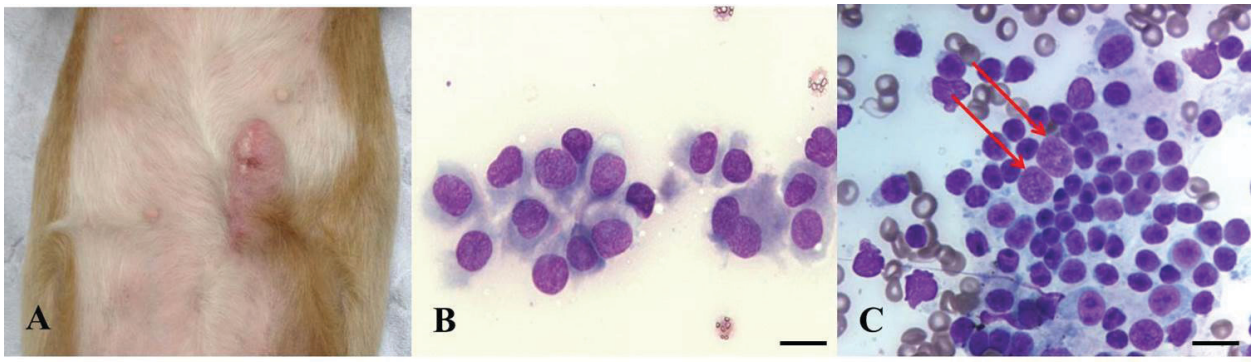

Figure 1. (**A**) Gross findings during the physical examination. The patient exhibited a recurrently formed mammary gland tumour (4.6 cm × 2.3 cm in size). (**B**) Fine needle aspiration (FNA) of the mammary gland tumour revealed mammary carcinoma with an increased nucleus:cytoplasm ratio, anisocytosis, and anisokaryosis (Diff-Quik, × 1000, scale bar = 14 µm). (**C**) FNA of a prescapular lymph node revealed neoplastic epithelial cells (arrows) within the lymph node, indicating local metastasis to the regional lymph node (Diff-Quik, × 1000, scale bar = 14 µm)

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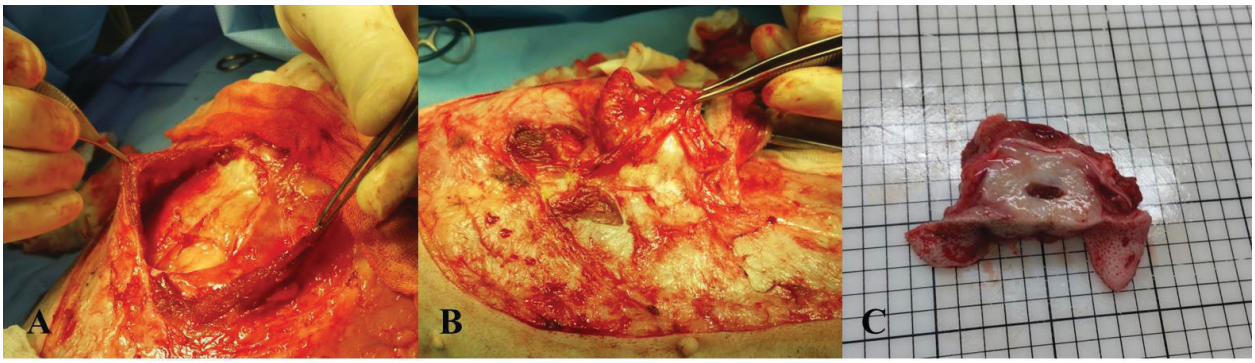

Figure 2. (**A**) The tumour appeared attached to the fascia of the external abdominal wall. (**B**) Tumour removal was performed with a deep margin of one fascial plane, including the external abdominal wall. (**C**) Macroscopic examination revealed that the tumour appeared to have large amounts of collagen fibres with necrotic tissues in the central region

A skin incision was made with a minimum of a 2-cm lateral margin from the MGT. The incision continued through subcutaneous tissue to the fascia of the external abdominal wall, and the tumour appeared to be attached to the fascia (Figure 2A). Tumour removal was performed with a deep margin of one fascial plane, including the external abdominal wall (Figure 2B). The defect was closed with 3-0 polyglycolic acid (Dexon II®; Covidien Animal Health and Dental Division, Mansfield, MA, USA) in a simple continuous pattern. The subcutaneous tissues and skin were closed routinely. Macroscopically, the tumour appeared to have large amounts of collagen fibres with necrotic tissues in the central region (Figure 2C). The excised tumour was fixed by immersion in neutral buffered 10% formalin for microscopic evaluation. The histopathological examination revealed that the tumour tissue was comprised of exceedingly invasive and scattered individualised or small grouped cancer cells that had a round, oval, or polygonal shape and showed anisocytosis (Figure 3A). The majority of cancer cells had lost their junctional properties that are typically observed in cells of epithelial origin. The nuclei of cancer cells are generally huge and round or oval. However, they are highly pleomorphic and exhibit anisokaryosis. They sometimes have multiple nucleoli and several multinucleated cells. In addition, many mitotic figures are seen (mitotic index: 15 mitotic figures/10 high-power fields). Furthermore, desmoplasia was observed around the cancer cells. Because cancer cells are very anaplastic, precisely distinguishing between an epithelial or mesenchymal origin was difficult. Therefore, immunohistochemistry was performed with antibodies against cytokeratin and vimentin, which are expressed in epithelial cells and mesenchymal cells, respectively. These results revealed

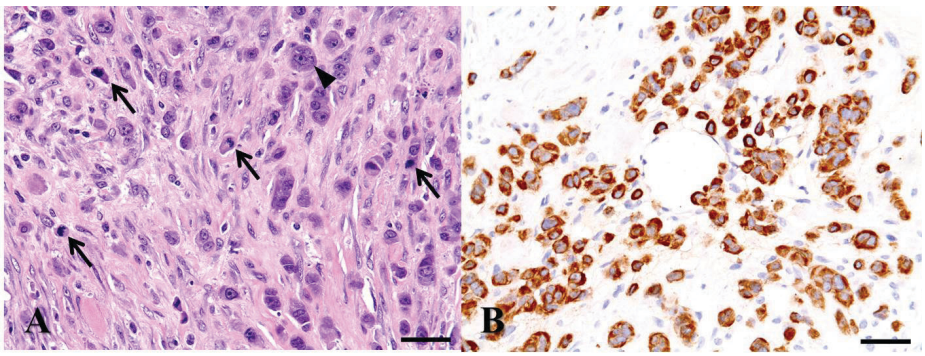

Figure 3. (**A**) Histopathology of the mammary gland tumour shows a diffusely infiltrating neoplasm composed of large pleomorphic cells, an increased nucleus : cytoplasm ratio, anisokaryosis, multiple nucleoli, and rich chromatin; some cells were multinucleated (arrowhead). Note that many mitoses were found (arrows). Haematoxylin and eosin staining, × 400, scale bar = 35 μm. (**B**) The tumour cells are immunolabelled with cytokeratin AE1/AE3 in the cytoplasm. Immunohistochemical staining (Gill's haematoxylin counterstain, scale bar = 35 μm)

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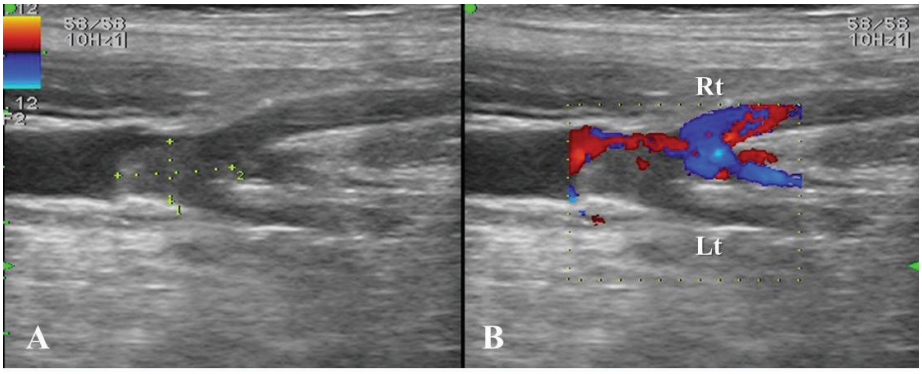

Figure 4. (**A**) Two-dimensional ultrasonography showed saddle thrombus at the aorto-iliac junction of the dog. Note that the left iliac artery contained echogenic luminal material (5.4 mm × 9.4 mm). (**B**) On colour Doppler examination, no signal could be obtained from the left iliac artery

the cytoplasmic staining of cytokeratin in cancer cells (Figure 3B). Positivity of vimentin staining was detected in the surrounding mesenchymal cells but not in the cancer cells. These results indicated that the tumour had an epithelial origin.

On the 11th postoperative day, the dog presented with a one-day history of lethargy and left hind limb weakness with absence of a femoral pulse. With assistance, the dog could stand on its forelimbs and briefly support itself on the right hind limb, but the left hind limb was flaccid and not weight-bearing. The D-dimer levels were markedly increased (2.3 µg/ml, RR: less than 0.5 µg/ml) from the normal value that was obtained preoperatively. A neurological examination revealed paralysis in the left hind limb with weak postural reactions and significantly decreased deep pain. Radiographic and orthopaedic examinations disclosed no abnormalities. Doppler ultrasound of the terminal abdominal aorta was performed. The right and left iliac arteries were visualised, and the left iliac artery contained echogenic luminal material (5.4 mm × 9.4 mm in size) (Figure 4A). The arterial blood appeared stagnant in real time, and slight oscillating movement was noted only in the lumen of the right iliac artery. No pulsed Doppler waveforms or colour Doppler signals could be obtained from the left iliac artery (Figure 4B). AT was suspected based on the results of the laboratory and imaging tests. Although the administration of a thrombolytic agent was recommended, the owner declined because of the side effects and for financial reasons. Therefore, we subcutaneously injected low-molecular heparin (Enoxaparin; JW Pharmaceutical, Seoul, Korea), at 100 IU/kg quater in die as an antithrombotic agent. Thereafter, oral clopidogrel (Clopidogrel hydrogen sulphate; Jin Yang Pharm Co., Ltd., Seoul, Korea) was administered at 10 mg/kg semel in die, and subsequent a daily dose of 4 mg/kg was maintained to prevent further thrombosis. Twelve hours after discharge, the dog deteriorated and was presented to our emergency unit. Blood tests revealed neutrophilic leukocytosis (white blood cells, 40 × 109 cells/l, RR: 6–17 × 10^9 cells/l), azotemia (blood urea nitrogen, 78 mg/dl, RR: 8–31 mg/dl; creatinine, 2.3 mg/dl, RR: 0.8–1.6 mg/dl), and increased levels of aspartate transaminase (152 IU/l, RR: 15–43 IU /l) and creatine kinase (1761 IU /l, RR: 46–320 IU /l). Doppler ultrasonography did not detect further arterial flow below the level of the left kidney. The owner did not consent to further examination and treatment, and the patient died 24 h after it was diagnosed with AT. Unfortunately, necropsy was not performed because of the client's refusal.

DISCUSSION AND CONCLUSIONS

Canine AT is an uncommon secondary condition that generally results from underlying abnormalities of blood flow, vessel integrity, fibrinolysis, or coagulation (Boswood et al. 2000). The high occurrence of coagulation abnormalities in human and dogs with neoplastic disease, especially MGT, has been demonstrated in several studies (Madewall et al. 1980; Auger et al. 1987). In a retrospective study, the incidence of coagulation parameter abnormalities in dogs with mammary tumours increased by 67% (Stockhaus et al. 1999). However, whether the

doi: 10.17221/8388-VETMED

subclinical haemostatic abnormalities in dogs with tumours could progress into clinically apparent thrombotic or haemorrhagic complications was not demonstrated.

Mammary anaplastic carcinoma is the most malignant canine mammary carcinoma. It is generally firm and ill-defined, and it invades the skin and underlying tissues, which are often oedematous. In many dogs, several adjacent glands of one or both mammary chains are affected (Misdorp et al. 1973). The diagnostic microscopic features of malignant anaplastic carcinoma consist of a diffusely infiltrating neoplasm that is composed of large pleomorphic cells, which often have bizarre nuclei that are rich in chromatin; some cells are multinucleated and exhibit an abundant fibrous reaction around the neoplastic cells (Hampe and Misdorp 1974). Many mitoses are found, which was also evident in this case. The cytoplasm is eosinophilic, and vacuoles are not uncommon. In contrast to most other types of canine mammary carcinomas, the anaplastic type is highly invasive, and it exhibits extensive amounts of collagen fibres (scirrhous carcinoma), which is not typical of human anaplastic carcinomas (Misdorp et al. 1973). Some extreme anaplastic carcinomas that are composed of large pleomorphic cells that are embedded in fibrous stroma are similar to anaplastic sarcomas and are very hard to recognise as epithelial tumours, as was shown in this case. In the present case, we also performed immunohistochemistry with vimentin and cytokeratin in order to confirm the origin. We confirmed that the origin was epithelial based on the immunohistochemical positivity for cytokeratin and negativity for vimentin. Carcinomas of this type are difficult to treat with surgery alone because of their early and extensive infiltration into the surrounding tissues and lymphatics. The regional lymph nodes and lungs are the organs that are most frequently affected by metastases (Misdorp et al. 1973). The lungs, when affected, are usually extensively involved and appear firm and compact with multiple small nodules, as shown in this case. Although canine mammary anaplastic carcinomas establish their malignant nature by metastasising, their relationship with hypercoagulability is unknown (Misdorp et al. 1973). In one report of 64 metastasised canine malignant mammary tumours, the anaplastic carcinomas were very malignant and caused death in a short time. The postsurgical survival times in 31 dogs with anaplastic carcinoma ranged from one week to 18 months (average, seven months); in that study of 31 dogs, four had dyspnoea, and four had walking difficulties (total, 8; 26%). However, the relationship with coagulability was not defined. Therefore, this case report provides the first evidence that supports a relationship between hypercoagulability and anaplastic adenocarcinoma in dogs.

In this case, the patient exhibited acute paralytic, pulseless, and cold extremities, which were consistent with AT (Schoeman 1999). Ultrasonography is a simple and non-invasive method that can be used to diagnose a thromboembolism by detecting areas of decreased blood flow. In the present dog, aorto-iliac thrombosis was identified using ultrasonography. Other potential diagnostic tests for aortic thrombosis include selective angiography (Carter and Van Heerden 1994) and radionuclide angiography (Ramsey et al. 1996), and thermography (Kim and Park 2012) has also been advocated when thromboembolic disease is suspected. However, these tests are very invasive or expensive.

In human and veterinary medicine, D-dimers are laboratory markers that are used clinically to detect early thromboembolism (TE) (Nelson and Andreasen 2003; Owaidah et al. 2014). Other laboratory markers of coagulation activation, such as fibrinopeptides A and B, fibrinogen degradation products, prothrombin fragments 1 and 2, and thrombin-antithrombin complexes, have been proposed and used for TE diagnosis, however, only the D-dimer assay has been shown to have clinical utility in people (Bounameaux 1996). In a recent prospective study of dogs with thromboembolic disease, no difference was found between the frequencies of abnormalities of prothrombin time or activated partial thromboplastic time in the TE group versus the control group, and fibrinogen degradation products were not abnormal in any TE patient (Nelson and Andreasen 2003). The human literature focuses on imaging modalities and D-dimers as a laboratory marker. In this case, Doppler ultrasonography revealed no blood flow below the suggested AT site, and the D-dimer levels were markedly increased after the hind limb paralysis. Additionally, the blood abnormalities in this case, including azotemia, leukocytosis, elevated aspartate transaminase and creatine kinase, could be considered a result of local ischaemia and skeletal muscle inflammation from the AT because the results of the preoperative routine blood tests were within normal limits and no remarkable abnormalities were detected in

doi: 10.17221/8388-VETMED

the kidneys with the urinalysis and ultrasonographic assessments. After the hind limb paralysis, arterial flow was not detected, especially below the level of the left kidney on Doppler ultrasonography, and this suggested renal ischaemic damage.

In this case, occlusion of the distal aorta and left iliac artery was found, which suggested complex aetiology. Neoplasia can predispose to thrombosis in numerous ways, including increased coagulation due to platelet activation, thromboplastin release from tumour cells, and the production of factor X activator, as well as reduced clotting factor clearance, reduced clotting factor neutralisation, and decreased fibrinolysis, as previously described (O'Keefe and Couto 1988). In addition, in this case, the metastatic neoplastic cells might have eroded into or arisen from the blood vessels, which would directly result in a disruption of the endothelial integrity and disturbed flow. Second, cardiac disease can predispose to thrombosis through the stasis of blood in congested veins and atria and interfere with normal endothelial integrity (Boswood et al. 2000). The present dog had mitral insufficiency, but there was no evidence of left ventricular or atrial dilatation. Mitral insufficiency is a common incidental finding in aging dogs, and it therefore might not have been related to the development of the mural thrombus. In human patients, severe mitral insufficiency is associated with a moderately high incidence of thrombosis (Fuster and Verstraete 1997). The incidence is lower with mild insufficiency and when atrial fibrillation is not present (Fuster and Verstraete 1997). The present case presented with both a neoplasia and cardiac disease, and, thus, it is uncertain which disease was the principal cause of the thrombosis. Each condition may have predisposed to thrombosis, and the combination of the factors might then have been sufficient for this to occur. However, this patient did not show cardiomegaly, hypertension, or non-tumour related abnormalities, and the D-dimer levels were normal before the acute signs of AT. Therefore, the malignant mammary tumour was the most likely cause of the hypercoagulability and AT in the present case.

Although aorto-iliac thromboses in dogs commonly cause marked morbidity and mortality, several studies have reported that systemic thrombolytic therapy can manage this syndrome in humans and other veterinary species (Clare and Kraje 1998; Kim and Park 2012). Early recognition of this clinical condition and the administration of thrombolytic therapy may be beneficial. Successful thrombolytic therapy with streptokinase (Ramsey et al. 1996) and recombinant tissue plasminogen activator (Clare and Kraje 1998) has been reported in cases of canine aortic thromboembolism. Nonetheless, severe hyperkalaemia can develop as a reperfusion injury after thrombolytic therapy in dogs and cats with AT (Schoeman 1999; Lunsford and Mackin 2007). In the present case, initial thrombotic management was recommended, but the owner declined because of side effects and for financial reasons. Therefore, in order to minimise the risk of any potential future thrombosis, we administered clopidogrel in combination with low-molecular weight heparin as antithrombotic agents. Recent studies in dogs and cats have reported that clopidogrel therapy has antiplatelet effects and no adverse effects in these species that are unable to tolerate aspirin therapy (Hogan 2004; Mellett et al. 2011). Patients suffering from AT often recover with supportive therapy, but severely affected patients may experience ischaemic acidosis and muscle inflammation, which can be life threatening. In this case, the patient deteriorated and died 24 h after the diagnosis of AT. This is the first known description of a fatal AT that was induced by a mammary anaplastic carcinoma in a dog.

In conclusion, canine patients with malignancy could have a higher risk of developing postoperative thromboembolic complications, as is seen in human medicine (Blom et al. 2005; Prandoni et al. 2005). We suggest that the prophylactic management of thromboembolism in canine patients with malignant mammary gland tumours is necessary, and cancer malignancy-induced hypercoagulability should be considered in the differential diagnosis of AT. Additionally, in veterinary medicine, when a malignant mammary tumour is suspected, it is important that veterinarians assess the serial D-dimer levels and perform abdominal ultrasonography in order to improve the therapeutic prognosis.

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Received: 2015–01–15
Accepted after corrections: 2015–07–02

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