DOI: 10.5433/1679-0359.2020v41n2p717

Arterial thromboembolism of non-cardiogenic origin in a domestic feline with ischemia and reperfusion syndrome

Tromboembolismo arterial de origem não cardiogênica em um felino doméstico com síndrome de isquemia e reperfusão

Gabriela da Cruz Schaefer[1*]; Tayná Mayer Veronezi[2]; Camila Gonçalves da Luz[3]; Letícia Gutierrez de Gutierrez[4]; Simone Scherer[3]; Saulo Petinatti Pavarini[5]; Fernanda Vieira Amorim da Costa[6]

Highlights:
Arterial thromboembolism associated with pulmonary adenocarcinoma is uncommon.
The reestablishment of blood flow results in tissue injury due to reperfusion.
The prognosis is from reserved to poor and the survival rate is low.

Abstract

Arterial thromboembolism (ATE) is an acute and severe clinical condition resulting from the formation of a thrombus and its accommodation in an artery, impairing the perfusion of tissues irrigated by it. In felines, it is often related to hypertrophic cardiomyopathy, but there are reports of its association with neoplasms. Ischemia and reperfusion syndrome may occur secondary to ATE and result in difficult to correct electrolyte and acid-base imbalances. The aim of the present study is to describe a case of ATE, including its clinical and laboratory findings and electrolyte and acid-base changes compatible with ischemia and reperfusion syndrome. A 14-year-old crossbreed female feline with sudden pelvic limb paralysis was treated at the Feline Medicine Service of the Federal University of Rio Grande do Sul. Clinical and laboratory alterations included hypothermia, hypotension, bradycardia, azotemia, metabolic acidosis, and hyperkalemia. The electrocardiogram indicated sinoventricular rhythm, and echocardiogram evaluation showed no alterations. Thorax radiographic evaluation revealed areas of higher radiopacity in the pulmonary fields. We opted for abdominal aorta arteriotomy as an emergency treatment for thrombus removal. The feline died in the postoperative period, and histopathological examination of lungs, mediastinal lymph nodes, and heart were performed, being compatible with pulmonary adenocarcinoma with lymph node metastasis. This study deals with a case of ATE of possible neoplastic origin, which is uncommon in cats. In this case, the patient had difficult-to-manage hemodynamic impairment, as well as electrolyte and acid-base balance disorders severe and refractory to therapy, culminating in death. The time to start treatment from the presentation of clinical signs may be determinant in therapeutic success, reducing the possible effects of reperfusion syndrome.
Key words: Pulmonary adenocarcinoma. Thromboembolic disease. Cat. Acute paralysis.

[1] Discente de Doutorado do Programa de Pós-Graduação em Ciências Veterinárias, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brasil, Prof. Auxiliar, Centro Universitário Ritter dos Reis, UniRitter, Porto Alegre, RS, Brasil. E-mail: gabrielacschaefer@gmail.com
[2] Discente de Mestrado do Programa de Pós-graduação em Ciências Veterinárias, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brasil. E-mail: tayna_v@msn.com
[3] Médicas Veterinárias Autônomas. E-mail: caca_luz@hotmail.com; simones.vet@gmail.com
[4] Profª Titular, Centro Universitário CESMAC, Maceió, AL, Brasil. E-mail: leticia.gutierrez@cesmac.edu.br
[5] Prof. Adjunto IV, Departamento de Patologia Clínica Veterinária, Setor de Patologia Veterinária, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brasil. E-mail: sauloppvet@yahoo.com.br
[6] Profª Adjunto IV, Serviço de Medicina Felina, Departamento de Medicina Animal, UFRGS, Porto Alegre, RS, Brasil. E-mail: fernanda.amorim@ufrgs.br
[*] Author for correpondence

Received: July 01, 2019 - Approved: Oct. 28, 2019

Resumo

O tromboembolismo arterial (TEA) é uma condição clínica aguda e grave decorrente da formação de um trombo e seu alojamento em uma artéria, prejudicando a perfusão dos tecidos irrigados por ela. Em felinos, está frequentemente relacionado com a cardiomiopatia hipertrófica, porém existem relatos da sua associação com neoplasias. A síndrome de isquemia e reperfusão pode ocorrer secundária ao TEA e resultar em desequilíbrios eletrolíticos e ácido-base de difícil correção. O objetivo do presente trabalho é descrever um caso de TEA, incluindo seus achados clínico-laboratoriais e as alterações eletrolíticas e acidobásicas compatíveis com a síndrome de isquemia e reperfusão. Foi atendido no Serviço de Medicina de Felinos da Universidade Federal do Rio Grande do Sul um felino, sem raça definida (S.R.D.), fêmea, de 14 anos de idade, com paralisia súbita dos membros pélvicos. As alterações clínicas e laboratoriais incluíram hipotermia, hipotensão, bradicardia, azotemia, acidose metabólica e hipercalemia. O eletrocardiograma indicou ritmo sinoventricular e a avaliação do ecocardiograma não mostrou alterações. A avaliação radiográfica do tórax revelou áreas de maior radiopacidade nos campos pulmonares. Optou-se pela arteriotomia da aorta abdominal como tratamento emergencial para a retirada do trombo. O felino veio a óbito no pós-operatório e foi realizado exame histopatológico dos pulmões, linfonodos mediastinais e do coração, que foi compatível com adenocarcinoma pulmonar com metástase para o linfonodo. O presente trabalho trata de um caso de TEA de possível origem neoplásica, o que é pouco comum em gatos. Neste caso, o paciente apresentou comprometimento hemodinâmico de difícil manejo, além de desordens eletrolíticas e do equilíbrio ácido-base graves e refratárias a terapia, culminando em óbito. O tempo do início do tratamento a partir da apresentação dos sinais clínicos pode ser determinante no sucesso terapêutico, reduzindo os possíveis efeitos da síndrome de reperfusão.

Palavras-chave: Adenocarcinoma pulmonar. Doença tromboembólica. Gato. Paralisia aguda.

Introduction

Arterial thromboembolism (ATE) is an acute and potentially fatal clinical condition that occurs when a thrombus detaches from its original site and is carried through the systemic circulation until it lodges in an artery. The resulting embolism may totally or partially obstruct blood flow and initiate a cascade of events, leading to collateral vessel constriction (Smith & Tobias, 2004). In 90% of affected cats, the emboli lodge in the abdominal aortic bifurcation (Hogan, 2016). Usually, ATE is associated with heart diseases, especially hypertrophic cardiomyopathy (Smith & Tobias, 2004). ATE associated with neoplasm is uncommon, and lung neoplasms are the most commonly reported (Fuentes, 2012).

Clinical signs include paresis of the affected limbs, pain, tachypnea, hypothermia, pallor or cyanosis of the footpads, and weak or absent pulse. Patients often have inadequate systemic perfusion, circulatory shock (Smith & Tobias, 2004), stress hyperglycemia, azotemia, hyperphosphatemia (Fuentes, 2012), metabolic acidosis, and increased serum activity of alanine aminotransferase (ALT) and serum concentration of lactate (Smith & Tobias, 2004). Hyperkalemia is an important and potentially fatal complication that can develop due to ischemia and reperfusion syndrome (Fuentes, 2012).

The prognosis is from reserved to severe and depends on early diagnosis, duration, and site of arterial occlusion. The long-term prognosis is also reserved, as many cats die from underlying disease manifestations or have recurrence of ATE (Smith, Tobias, Jacob, Fine, & Grumbles, 2003). Treatment aims to provide analgesia, treat the underlying cause, stimulate collateral circulation and reduce continued thrombus formation, as well as prevent the formation of new thrombi (Hogan, 2016). The aim of the present study is to report a case of feline arterial thromboembolism of non-cardiogenic origin (neoplastic origin) and its clinical and laboratory findings compatible with ischemia and reperfusion syndrome.

Case Report

A crossbreed female cat aged 14 years was seen at the Feline Medicine Service of the Veterinary Clinics Hospital of the Federal University of Rio Grande do Sul presenting sudden pelvic limb paralysis with 24-hour clinical evolution. On physical examination, the animal was apathetic, hypothermic (34.9 °C), with pelvic limb paralysis and absence of a bilateral femoral pulse. There were no alterations in the breast palpation examination. Blood count showed neutrophilic leukocytosis, lymphopenia, and hyperproteinemia. The patient also had azotemia (creatinine = 259.8 umol L^{-1} and urea = 20.6 mmol L^{-1}), and increased serum activity of ALT (472 U L^{-1}) and serum concentration of lactate (5.1 mmol L^{-1}). The electrocardiogram showed sinoventricular rhythm, while echocardiogram evaluation showed no alterations. Thorax radiographic evaluation revealed areas of higher heterogeneous radiopacity scattered throughout the pulmonary fields. Doppler ultrasonography evidenced a cranial aortic thrombus at the bifurcation of iliac arteries. The presumptive diagnosis was arterial thromboembolism of non-cardiogenic origin. The patient was hospitalized for clinical stabilization. Fluid therapy with lactated Ringer's solution was instituted and the prescribed medications were tramadol (4 mg kg^{-1} SC BID), dipyrone (25 mg kg^{-1} SC BID), acepromazine (0.03 mg kg^{-1} SC TID), heparin (200 U kg^{-1} IV SID and after SC TID), and clopidogrel (18.75 mg PO SID). Urine output was normal. We opted for abdominal aorta arteriotomy for thrombus removal. Blood count was repeated one day after surgery, and normochromic normocytic anemia (hematocrit = 20%), left-shifted neutrophilic leukocytosis, presence of toxic neutrophils, and hypoproteinemia were observed. Azotemia had worsened (creatinine = 396.6 umol L^{-1}). The serum activity of ALT was still elevated (184 U L^{-1}), and lactate was 2.3 mmol L^{-1}.

Four sequential venous blood gas analyses were performed during the hospitalization period, one on the first day, two on the second day (postoperative), and one on the third day. The first examination showed metabolic acidosis (pH = 7.25) and hyperkalemia (K = 6.7 mmol L^{-1}). On the second examination, metabolic acidosis became more pronounced (pH = 7.182), as did hyperkalemia (K = 8.6 mmol L^{-1}). A correction was performed with sodium bicarbonate, regular insulin with glucose, and calcium gluconate. In the third test, performed after correction, the pH normalized (7.298) and hyperkalemia persisted, but less marked (K = 7.9 mmol L^{-1}). The fourth examination, on the following day, showed again metabolic and respiratory acidosis (pH = 7.219) and hyperkalemia aggravation (K = 8.1 mmol L^{-1}). Hyponatremia was observed in all examinations, with sodium ranging from 132 to 136 mmol L^{-1}, and hypocalcemia, with calcium ranging from 0.91 to 0.99 mmol L^{-1} (Table 1).

Table 1
Sequential blood gas analysis of a feline with arterial thromboembolism and ischemia and reperfusion syndrome

Parameters	*Unit*	*Reference values*	*Day 1*	*Day 2*	*Day 2 (after correction)*	*Day 3*
pH		7.277–7.409	7.250	7.182	7.298	7.219
pCO_2	mmHg	32.7–44.7	42.5	41.6	40.3	45.9
HCO_3	mm L^{-1}	18–23	18.8	15.6	19.7	18.7
K	mmol L^{-1}	3.6–5.5	6.7	8.6	7.9	8.1
Na	mmol L^{-1}	145–157	133	132	133	136
iCa	mmol L^{-1}	1.07–1.5	0.99	0.91	0.97	0.97

pCO_2 – partial pressure of carbon dioxide; HCO_3 – bicarbonate; K – potassium; Na – sodium; iCa – ionized calcium. *Values obtained with the i-STAT EG7+ automated pH, gas, and blood electrolyte analyzer (Abbott Laboratories, Chicago, USA).

The feline died the day after surgery, and the cardiorespiratory tract was removed and macroscopically analyzed and, subsequently, packaged in 10% formalin solution. Lung, heart, and mediastinal lymph node fragments were routinely processed for histological analysis and stained by the hematoxylin and eosin (HE) technique. Macroscopically, there were multiple firm, whitish nodules with yellowish areas ranging from 2 to 0.5 cm in diameter with random distribution in the pulmonary lobes (Figure 1A). The mediastinal lymph nodes were enlarged (2 cm), firm, and white. No macroscopic alterations were observed in the heart. Histologically, lung showed malignant neoplastic proliferation of epithelial cells with arrangement from papillary (Figure 1B) to solid (Figure 1C) in a multifocal random distribution in the parenchyma. Cells range from cuboidal to rounded, with abundant and well-defined eosinophilic cytoplasm and oval nuclei with often multiple evident nucleoli of magenta coloration and coarse granular chromatin. Moderate anisocytosis and anisokaryosis with occasional binucleated neoplastic cells and an average of three mitotic figures per field of higher magnification (400x). Extensive areas of intratumoral necrosis and neoplastic cells with squamous differentiation were also observed. There was also multifocal thrombosis with the presence of neoplastic cells interspersed with fibrin (Figure 1D). The mediastinal lymph nodes were almost entirely replaced by neoplastic cells identical to those described in the lung. No histological alterations were observed in the cardiac parenchyma. These findings led to the diagnosis of primary lung adenocarcinoma with lymph node metastasis.

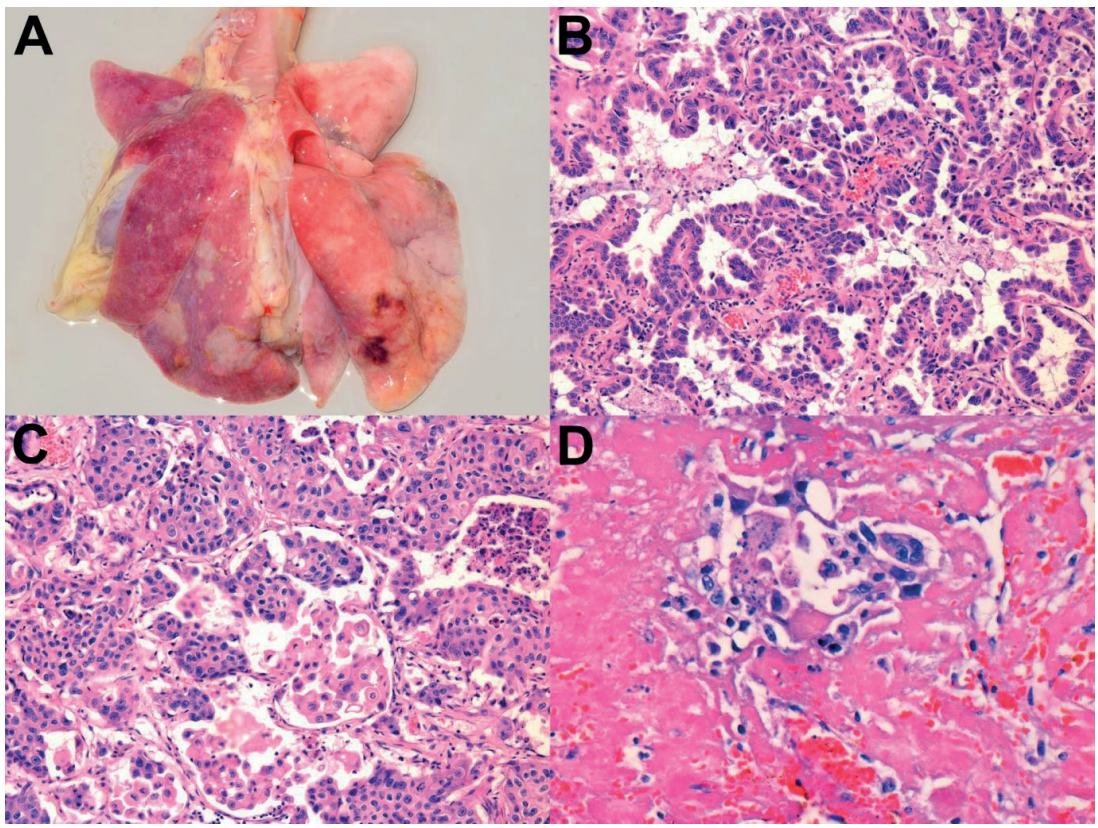

Figure 1. Primary pulmonary adenocarcinoma in a feline with arterial thromboembolism and ischemia and reperfusion syndrome. A. Whitish nodules with yellowish areas, ranging from 2 to 0.5 cm in diameter, with random distribution in the pulmonary lobes. B. Lung. Epithelial neoplastic cells with a papillary arrangement. HE, 200x. C. Lung. Epithelial neoplastic cells with solid arrangement and squamous differentiation. HE, 200x. D. Lung. Fibrin thrombus inside an artery with epithelial neoplastic cells. HE, 400x.

Discussion

Arterial thromboembolism is commonly observed in felines with hypertrophic cardiomyopathy, and it is estimated that up to 50% of cats with this condition may develop ATE (Moore, Morris, Dhupa, Murtaugh, & Rusch, 2000). The non-cardiac causes of ATE most commonly found in cats are metastatic malignant neoplasms (Smith et al., 2003). In a study carried out with 127 cats with ATE, neoplasms were related to ATE in six cases, and, among them, two were pulmonary carcinoma (Smith et al., 2003), similar to this case report.

The mechanisms involved in the onset of thrombotic phenomena associated with neoplasm are of three types: state of hypercoagulability, which may involve veins or arteries, reduction of fibrinolytic activity, and finally, mechanical factors such as venous compression with or without tumor invasion, causing secondary venous stasis (Sequeira, Gomes, Gonzalez, & Sarmento, 1990).

At the time of medical care, the patient presented sudden and total pelvic limb paralysis and absence of bilateral femoral pulse with a clinical evolution of 24h00. Cats with ATE usually have a sudden onset of pain and discomfort. The most commonly reported site of thrombus or embolus occlusion is the terminal aorta, with bilateral pelvic limb infarction occurring in about 60% of cases (Smith et al., 2003; Hogan et al., 2015). In some cases, one pelvic limb is more severely affected than the other is (Fuentes, 2012). Embolic occlusion of the terminal aorta results in ischemic neuromyopathy of pelvic limbs, which causes paresis or paralysis with no segmental reflexes, firm and painful muscles, cold and absent femoral arterial pulse, and cyanotic nail bed (Hogan et al., 2015). Pain management is extremely important in ATE cases, and the use of opioids such as fentanyl, methadone, and buprenorphine is indicated (Fuentes, 2012). In the present report, tramadol was used associated with dipyrone, with good response.

Another clinical sign was severe hypothermia, besides presenting hypotension and bradycardia after hospitalization. These findings are common and result from poor tissue perfusion and circulatory shock (Smith & Tobias, 2004). Studies have already shown that hypothermia and bradycardia are correlated with low survival rates (Moore et al., 2000; Smith et al., 2003). Rectal temperature was considered the best prognostic indicator in one study, with hypothermia associated with higher mortality (Smith et al., 2003).

One of the feline screening tests performed in this report was a thorax X-ray to investigate alterations in the pulmonary fields, which might indicate neoplasia, and to evaluate heart size, seeking some measurement out of the expected pattern. Lister and Buchanan (2000) described the radiographic measurement of the heart using the vertebral heart scale system (VHS) in cats. This method consists in correlating heart size with skeletal structures such as thoracic vertebrae and sternebrae, and thus, determines the absolute and relative value of heart size, being used to assess heart disease progression. According to Fuentes (2012), thorax X-ray may be an alternative means to investigate the presence of congestive heart failure in the absence of audible rales, but should not be performed in cats with dyspnea. Thorax X-rays are also useful for identifying lung neoformations in cats with an underlying neoplastic cause (Fuentes, 2012). In this report, the thoracic radiographic evaluation revealed areas of higher heterogeneous radiopacity scattered throughout the pulmonary fields. There were no noteworthy alterations regarding the cardiac radiographic evaluation.

Laboratory findings of this report corroborate those described in the literature, which have cited the presence of azotemia, increased enzymes associated with muscle injuries, and electrolyte and acid-base balance disorders (Smith et al., 2003). Anaerobic metabolic pathways predominate during ischemia,

and many toxic metabolites are formed. Ischemia favors the formation of reactive oxygen species and oxidative damage through various mechanisms. In addition, depletion of ATP stocks eventually leads to cell membrane pump failure, allowing for potassium release from cells and entry of sodium, calcium, and chloride. This displacement of electrolytes leads to edema and cell death (Fuentes, 2012).

Renal injury, found in this report through increased serum creatinine, may occur due to myoglobinuria nephrotoxicity because serum concentrations of creatine phosphokinase typically increase dramatically due to muscle ischemia and may be aggravated by dehydration, hypotension, acidosis, and presence of free radicals, factors associated with the patient's clinical condition. Azotemia may also be associated with thromboembolism of a renal artery (Smith et al., 2003). As the kidney is an essential organ in homeostasis, compensation mechanisms for electrolyte and acid-base imbalances will be impaired (Takito, Silva, Bueno, Franco, & Burihan, 2005). Metabolic acidosis results from tissue hypoxia and consequent anaerobic metabolism, which produces lactic acid (Dibartola, 2012), which, in this case, could be proven by hyperlactatemia.

Hyponatremia tends to occur due to a deficiency in the sodium-potassium pump. Due to the ischemia and predominance of anaerobic metabolism, energy production is deficient, preventing the action of this pump. Consequently, sodium intake into the intracellular environment is favored and hyponatremia sets in (Dibartola, 2012). Hypocalcemia was observed in 20% of cases in a given study and can be explained by hyperphosphatemia when phosphorus is released from damaged cells and is associated with free calcium (Smith et al., 2003). In this report, the patient presented persistent hypocalcemia and hyponatremia.

In the present report, arteriotomy was chosen as a therapeutic approach. The reestablishment of blood flow, promoted by arteriotomy and thrombus removal, results in tissue injury due to reperfusion. Reperfusion of these tissues throws metabolites, such as potassium, lactate, myoglobin, and oxygen-free radicals, which are potentially fatal, into the bloodstream. Free radicals react with healthy tissues causing more cell damage (Takito et al., 2005). As the patient underwent surgery, plunger removal occurred abruptly, which promotes rapid tissue reperfusion and the occurrence of this syndrome. Similarly, the use of thrombolytic (or fibrinolytic) agents such as streptokinase has been associated with several adverse effects in feline patients with ATE such as hyperkalemia (35%) and metabolic acidosis due to ischemia and reperfusion syndrome, as well as bleeding (Moore et al., 2000). The frequency of reperfusion injury in cats receiving thrombolytic therapy is from 40 to 70%, with survival rates ranging from 0 to 43%. Cats with infarction in both pelvic limbs seem more likely to develop reperfusion injury, which is probably related to the larger area of ischemia (Moore et al., 2000).

A study of rheolytic thrombectomy found no cases of hyperkalemia, regardless of the time of thrombectomy after the onset of ATE symptoms (Reimer, Kittleson, & Kyles, 2006). On the other hand, Rusch (1998) recommends that thrombolytic therapy should be started within 4h00 of the onset of clinical signs to maximize treatment efficacy and reduce reperfusion effects. In this case, the patient underwent arteriotomy after 24h00 of the clinical event, and the fact that both limbs were affected may have contributed to the severe effects of reperfusion.

Hyperkalemia is an important and potentially fatal complication that can develop due to ischemia and reperfusion syndrome (Fuentes, 2012). Increased plasma concentrations of potassium result from potassium translocation from intracellular to extracellular media due to cell injury and usually occur suddenly as perfusion is restored (Smith et al., 2003; Dibartola, 2012), which is why hyperkalemia in this patient worsened one day after arteriotomy. The effects of hyperkalemia include bradycardia

and cardiac arrhythmias, which are potentially fatal (Dibartola, 2012). In the present report, the findings of the electrocardiogram may be explained by hyperkalemia and the patient was refractory to therapy for its correction.

In the present report, antithrombotic therapy with heparin and clopidogrel was instituted on the day the patient was admitted for stabilization. Antithrombotic therapy may be used in patients at risk or recurrence of developing thromboembolism. Aspirin, unfractionated heparin, and low molecular weight heparin are the drugs of choice (Fuentes, 2012). In a recent study, 16 cats receiving clopidogrel were significantly less likely to recur embolism (49%) when compared to those receiving aspirin (75%). Also, clopidogrel was associated with a longer time to a recurrent embolism event (443 days) when compared to aspirin (192 days) (Hogan et al., 2015).

Thrombolytic therapy and arteriotomy are discouraged by some authors because of the effects of ischemia and reperfusion syndrome, with the need for prolonged anesthesia in critically ill patients with arteriotomy, especially in cases of cardiogenic ATE (Alwood, 2010; Ferasin, 2013). The patient should be monitored after treatment is instituted in a veterinary intensive care unit (ICU) to determine a better prognosis, considering the proven risks of these therapies. In addition, antithrombotic treatment should be instituted to reduce the risk of rethrombosis (Fuentes, 2012).

Conclusion

Neoplastic thromboembolism should be included as a differential diagnosis of cardiogenic thromboembolism, being usually caused by pulmonary neoplasms. The prognosis is from reserved to poor and the survival rate is low, thus showing the importance of identifying or suspecting the problem.

References

Alwood, A. J. (2010). Management of thromboembolic disease secondary to heart disease. In K. J. Drobatz, & M. F. Costello (Eds.), *Feline emergency and critical care medicine* (pp. 191-197). Ames: Wiley-Blackwell.

Dibartola, S. P. (2012). *Fluid, electrolyte and acid-base disorders in small animal practice*. 4nd ed. St Louis: Elsevier Saunders.

Ferasin, L. (2013). Management of cardiovascular disorders. In A. Harvey, & S. Tasker (Eds.), *BSAVA Manual of feline practice: a foundation manual* (pp. 344-349). Quedgeley: BSAVA.

Fuentes, L. V. (2012). Arterial thromboembolism: risks, realities and a rational first-line approach. *Journal of Feline Medicine and Surgery*, *14*(7), 459-470. doi: 10.1177/1098612X12451547

Hogan, D. F. (2016). Treatment and prevention of feline arterial thromboembolism. In S. E. Little (Ed.), *August's consultations in feline internal medicine.* 7nd ed. (pp. 369-378). St Louis: Elsevier.

Hogan, D. F., Fox, P. R., Jacob, K., Keene, B., Laste, N. J., Rosenthal, S.,… Weng, H. Y. (2015). Secondary prevention of cardiogenic arterial embolism in the cat: the double-blind, randomized, positive-controlled Feline Arterial Thromboembolism; Clopidogrel vs. Aspirin Trial (FAT CAT). *Journal of Veterinary Cardiology*, *17*, S306-S317. doi: 10.1016/j.jvc.2015.10.004

Lister, A. L., & Buchanan, J. W. (2000). Radiographic and echocardiographic measurement of the heart in obeses cat. *Veterinary Radiology & Ultrasound*, *41*(4), 320-325. doi: 10.1111/j.1740-8261.2000.tb2080.x

Moore, K. E., Morris, N., Dhupa, N., Murtaugh, R. J., & Rusch, J. E. (2000). Retrospective study of streptokinase administration in 46 cats with arterial thromboembolism. *Journal of Veterinary Emergency and Critical Care*, *10*(4), 245-257. doi: 10.1111/j1476-4431.2000.tb00010.x

Reimer, S. B., Kittleson, M. D., & Kyles, A. E. (2006). Use of rheolytic thrombectomy in the treatment of feline distal aortic thromboembolism. *Journal of Veterinary Internal Medicine, 20*(2), 290-296. doi: 10.1892/0891-6640(2006)20[290:uortit]2.0.co;2

Rusch, J. E. (1998). Therapy of feline hypertrophic cardiomyopathy. *Veterinary Clinics of North America: Small Animal Practice*, *28*(6), 1459-1479. doi: 10.1016/S0195-5616(98)50132-5

Sequeira, J. F. A., Gomes, R. M., Gonzalez, M. A., & Sarmento, J. L. N. (1990). Hipercoagulabilidade neoplásica a propósito de dois casos com síndrome de Trousseau. *Acta Médica Portuguesa*, *3*(3), 179-183.

Smith, S. A., & Tobias, A. H. (2004). Feline arterial thromboembolism: an update. *Veterinary Clinics of North America: Small Animal Practice*, *34*(5), 1245-1271. doi: 10.1016/j.cvsm.2004.05.006

Smith, S. A., Tobias, A. H., Jacob, K. A., Fine, D. M., & Grumbles, P. L. (2003). Arterial thromboembolism in cats: acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases. *Journal of Veterinary Internal Medicine*, *17*(1), 73-83. doi:10.1892/0891-6640(2003)017<0073:aticac>2.3.co;2

Takito, A. M., Silva, J. C. C. B., Bueno, V., Franco, M., & Burihan, W. (2005). Ischemic and reperfusion syndrome of hind limbs: functional and histological renal changes in rats. *Medicina (Riberão Preto. Online), 38*(3/4), 294-300.