Ciência Rural, Santa Maria, v.54:04, e20220494, 2024
http://doi.org/10.1590/0103-8478cr20220494
ISSNe 1678-4596
PATHOLOGY

Sudden death caused by pulmonary tumor embolism in a dog

Ariel de Aguiar[1] Valentina Berté Marcus[1] Paula Nitiana Campus Gonçalves[1] Pedro Henrique Salini Butelli[1] Glaucia Denise Kommers[1] Mariana Martins Flores[1*]

[1]Programa de Pós-graduação em Medicina Veterinária (PPGMV), Centro de Ciências Rurais (CCR), Universidade Federal de Santa Maria (UFSM), 97105-900, Santa Maria, RS, Brasil. E-mail: marianamflores@yahoo.com.br. *Corresponding author.

ABSTRACT: Tumor embolization is a well-described cause of unexpected death in human oncologic patients; however, it is poorly explored in veterinary medicine. We report a case of pulmonary tumor embolization in a dog with sudden death. During necropsy, a neoplastic mass was observed replacing the left adrenal gland and forming an intravascular thrombus within the central adrenal vein. A large embolus occluded the left pulmonary artery. The adrenal mass was histologically confirmed as a pheochromocytoma, and the embolus was constituted of neoplastic cells. Multiple smaller neoplastic emboli were observed within the pulmonary artery branches. Tumor embolization should be considered as a possible cause of sudden death in dogs, particularly in oncologic patients.
Key words: embolus, embolism, neoplastic, obstructive shock, pulmonary artery.

Morte súbita causada por embolismo tumoral em um cão

RESUMO: Embolismo tumoral é uma causa bem descrita de morte súbita em pacientes oncológicos humanos, entretanto, é pobremente explorado em medicina veterinária. Descreve-se um caso de embolização pulmonar neoplásica em um cão com morte súbita. Na necropsia, uma massa neoplásica foi observada substituindo a adrenal esquerda e formando um trombo intravascular na veia central da adrenal. Um êmbolo foi observado ocluindo a artéria pulmonar esquerda. A massa da adrenal foi histologicamente confirmada como um feocromocitoma, e o êmbolo era constituído de células neoplásicas. Múltiplos êmbolos neoplásicos menores foram observados histologicamente nas ramificações da artéria pulmonar. O Embolismo tumoral deve ser considerado como possível causa de morte súbita em cães, particularmente em pacientes oncológicos.
Palavras-chave: êmbolo, embolismo, neoplásico, choque obstrutivo, artéria pulmonar.

INTRODUCTION

Tumor embolization (TE) is an uncommon and often fatal complication of neoplastic disease in humans characterized by the movement of a tumor embolus within the vascular system (HE et al., 2021). Tumor emboli can obstruct the pulmonary artery and/or its branches, often leading to patient collapse (FUKUDA et al., 2019; HE et al., 2021). Despite the growing incidence of cancer-related mortality in veterinary medicine, TE is poorly described in animals (WINKLE et al., 1993). This article reported a case of pulmonary tumor embolization leading to pulmonary artery obstruction and sudden death in a dog.

MATERIALS AND METHODS

A dog with a history of sudden death was submitted to a complete necropsy in the Laboratório de Patologia Veterinária of the Universidade Federal de Santa Maria. Small fragments of different tissues were collected, fixed in 10% buffered formalin, routinely processed and stained with Hematoxylin and Eosin for histopathology. Sections of the primary adrenal tumor were submitted to immunohistochemistry using anti-synaptophysin (Dako, clone DAK-SYNAP), anti-cytokeratin (Dako, clone AE1/AE3) and anti-vimentin (Santa Cruz Biothecnology, clone V9) antibodies. Antigen retrieval was performed by microwaving in TRIS EDTA buffer (pH 9,0, microwaving for 10 minutes) for cytokeratin and vimentin antibodies; and by an automated system (BOND-MAX, Leica Biosystems®) using BOND Epitope Retrieval Solution 2 (pH 9,0, 100°C for 20 min) for synaptophysin antibody. Sections were incubated with the primary antibodies diluted in phosphate-buffered saline Tween 20, except for synaptophysin, which was ready to use. Vimentin

Received 09.04.22 Approved 07.10.23 Returned by the author 09.04.23
CR-2022-0494.R1
Editors: Rudi Weiblen Felisbina Queiroga

(1:100) and cytokeratin (1:200) were incubated for 1 h at 37, synaptophysin was incubated for 30 min at 25 C. A polymer-HRP system (Easypath, São Paulo, Brazil) was used, followed by substrate development with 3,30 diaminobenzidine (DAB; Easypath).

RESULTS

A 13-year-old male shih-tzu collapsed during a sidewalk, presenting pale mucous membranes, pedaling, opisthotonos and cardiorespiratory arrest. The dog was immediately taken to a veterinary emergency service and submitted to a resuscitation protocol, with no response. It had been previously healthy and never had any clinical signs indicative of heart disease or any other life-threatening conditions. A complete autopsy was performed.

The dog had severely pale mucous membranes. A 6.5 x 4.5 x 3.5 cm multilobulated, encapsulated mass had replaced the left adrenal gland. It invaded the capsule and the central adrenal vein wall, forming a 3.0 x 0.8 x 0.8 cm tan and firm thrombus within the vascular lumen of this latter vessel that extended itself into the vena cava (Figure 1A). The adrenal mass was friable and pink red to brownish on cut surface, with red areas of coagulation necrosis. The lungs were diffusely congested. A 1.5 x 0.7 x 0.5 cm red-brown smooth, soft embolus occluded the lumen of the initial portion of the left pulmonary artery (Figure 1B).

The left adrenal tumor was histologically constituted of neoplastic cells arranged in small packets supported by a delicate fibrovascular stroma (Figure 1C). The cells were polyhedral, with a moderate lightly eosinophilic, finely granular cytoplasm (Figure 1D). Moderate nuclear pleomorphism and anisokaryosis was noted. Mitotic figures were absent in a 2.37 mm² area. Large areas of hemorrhage and necrosis were observed within the tumor. The tumor invaded the capsule and extended itself through the wall of the adjacent central adrenal vein, forming an intravascular neoplastic thrombus. The embolus in the left pulmonary artery was histologically constituted of the same neoplastic

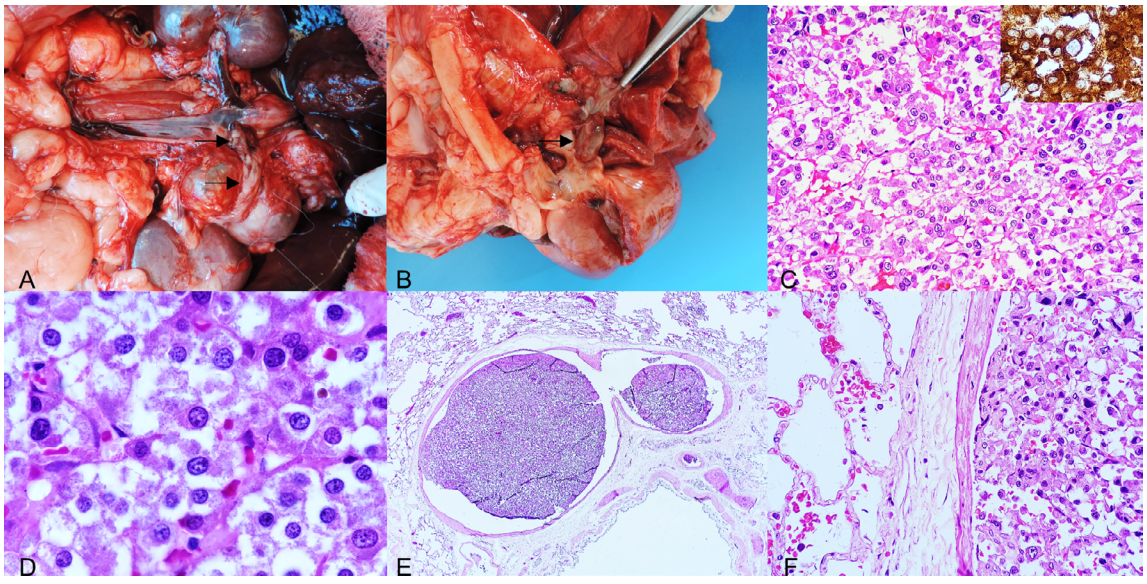

Figure 1 - A- Pheochromocytoma, left adrenal, dog. The adrenal is replaced by a large mass. The central adrenal vein is distended (arrows) by a whitish neoplastic thrombus that extends itself into the caudal vena cava. Figure 1B. Neoplastic embolus in the pulmonary artery. The pulmonary artery is opened (asterisks). A large neoplastic embolus (arrow) occludes the arterial lumen. Figure 1C. Pheochromocytoma, left adrenal, dog. Neoplastic cells are arranged in small packets supported by a delicate fibrovascular stroma. HE. Inset: tumour cells express synaptophysin. Immunohistochemistry. Figure 1D. Pheochromocytoma, left adrenal, dog. The cells are polyhedral, with a finely granular cytoplasm. HE. Figure 1E. Neoplastic embolus in the pulmonary artery branches. The arterial lumen (asterisk) is filled with two neoplastic emboli (arrows). HE. Figure 1F. Neoplastic embolus in the pulmonary artery branches. Cells in the neoplastic embolus show morphological similarities with the ones from the primary neoplasm, showed in figures 1C and 1D. The vascular wall (arrow) separates the embolus from the pulmonary parenchyma. HE.

cells from the left adrenal. Several branches of the pulmonary artery were filled by smaller neoplastic emboli in multiple lung sections (Figures 1E, 1F). The lungs were diffusely congested. The neoplastic cells from the primary adrenal neoplasm showed strong and diffuse cytoplasmic labeling for synaptophysin (Figure 1C, inset) and were negative for cytokeratin and vimentin. A diagnosis of neoplastic pulmonary embolism was established as the cause of sudden death of this dog.

DISCUSSION

TE occurs when a tumor embolus moves within the vascular system (HE et al., 2021). When large enough, emboli may be visible in imaging exams, which can contribute to a clinical suspicion of TE (TAKAHASHI et al., 2008). Probably due to their anatomic proximity to the caudal vena cava, it is not uncommon for canine malignant adrenal tumors to invade the vascular wall and form an intravascular neoplastic thrombus (BARRERA et al., 2013, ROBVEILLE et al., 2020). In a systematic study on dogs undergoing adrenalectomy to treat adrenal gland tumors, approximately 19% of the malignant neoplasms invaded the adjacent vena cava (BARRERA et al., 2013). However, emboli release from these neoplastic thrombi is generally not a feature of these tumors (BARRERA et al., 2013; ROBVEILLE et al., 2020). In fact, some of these neoplasms form neoplastic thrombi large enough to reach the heart, and even in these cases, emboli are not reported (ROBVEILLE et al., 2020). The adrenal tumor described in the present case had large friable areas of coagulation necrosis, which may have contributed to thrombus fragmentation, facilitating emboli release.

Pulmonary embolism is an uncommonly studied phenomenon in dogs. It may be associated with thrombi, fat, gas, parasitic, neoplastic or other types of emboli. Thromboembolism – involving emboli constituted of fragments from one or more thrombi – is a consequence of hypercoagulability, endothelial injury, or stasis of blood flow. The most common causes are malignant neoplastic diseases, sepsis and immune-mediated hemolytic anemia (JOHNSON et al., 1999; EPSTEIN, et al. 2013). Parasitic emboli are a feature in dogs with heart worms submitted to long-term treatment with ivermectin, and in this case, the emboli are formed by the dead heart worms (TAKAHASHI et al., 2008). Fat and gas embolism are rare in veterinary medicine and can be observed in dogs undergoing certain types of surgery, as in total hip replacement procedures (LISKA & POTEET 2003). Neoplastic emboli, as mentioned above, are constituted of groups of neoplastic cells originating from a primary malignant neoplasm (HE et al., 2021).

TE is among the causes of sudden death in human oncologic patients (FUKUDA et al., 2019; HE et al., 2021). It has been associated with different malignant tumors, including most commonly carcinomas (FUKUDA et al., 2019; HE et al., 2021; BOIS et al., 2022, CHAN et al., 2022), among urothelial and breast carcinomas the most common subtypes (HE et al., 2021). Interestingly, TE can also be associated with benign tumors: cardiac myxomas develop within the cardiac lumen and are occasionally associated with embolization of neoplastic cells (BOIS et al., 2022). It is important to emphasize that thromboembolism is also an important consequence of malignancy in human patients (DURMUŞOĞLU et al., 2020). Although, clinical consequences are similar to TE, as mentioned above, the pathogenesis is different, and involves thromboemboli, rather than neoplastic emboli.

Regardless of their size, neoplastic and non-neoplastic emboli may cause severe clinicopathologic consequences, even leading to sudden death in humans and animals (BOIS et al., 2014; FAKUDA et al., 2019). These emboli may loge in various sites, depending on their size and on vascular anatomic features. Some of the sites of embolus lodgement in humans and in animals include the aortic trifurcation, and the femoral, brachial, mesenteric, coronary, cerebral and pulmonary arteries (WINKLE et al., 1993; BOIS et al., 2014; FAKUDA et al., 2019; HE et al., 2021). Clinicopathologic presentations are variable according to the affected site. For instance, dogs and cats with emboli lodged in the limbs may present an acute onset of lameness and limb paralysis (WINKLE et al., 1993). Emboli lodged in the cerebral or coronary arteries, conversely, may lead to cerebrovascular/cardiac stroke (BOIS et al., 2014). Pulmonary embolism may lead to obstructive shock and sudden death (FAKUDA et al., 2019; HE et al., 2021). Common clinical signs in human patients with pulmonary TE include chest pain and shortness of breath followed by death within 3-17 days (HE et al., 2021). On the other hand, if emboli are not too large or numerous, affected animals or humans might recover, sometimes without even presenting clinical signs (LISKA & POTEET 2003). In this case, vascular recanalization takes place, re-establishing the blood flow (TAKAHASHI et al., 2008).

This case was a diagnostic challenge because the dog was clinically healthy before the collapse, and the adrenal pheochromocytoma was only discovered

during autopsy. A similar report has described a case of TE in a clinically healthy five-year-old girl, who died unexpectedly (FUKUDA et al., 2019). Autopsy revealed a renal nephroblastoma invading the vena cava, with TE and pulmonary artery obstruction by a large tumor embolus. The primary tumor had not been diagnosed before autopsy. In another report, a man with hepatocellular carcinoma developed hepatic vein/vena cava invasion by the tumor, with secondary TE, obstruction of the pulmonary trunk and sudden death (CHAN et al., 2000).

Pheochromocytomas are the most common neoplasms in the adrenal medulla of dogs, and generally develop on middle-aged to older animals, with no apparent gender or breed predisposition (ROSOL & MEUTEN, 2017). Many of them are clinically silent; however, these neoplasms may be associated with clinical signs, either due to vena cava invasion/metastases or due to hormonal production (ROSOL & MEUTEN, 2017; ROBVEILLE et al., 2020). If severe enough to occlude the vena cava, invasive tumors may lead to impaired venous return, which can contribute to hindlimb edema or even obstructive shock (BARRERA et al., 2013; ROBVEILLE et al., 2020). Most pheochromocytomas are easily diagnosed with histopathology, mainly to the granular appearance of the neoplastic cells and their arrangement in packets sustained by a scarce fibrovascular stroma (ROSOL & MEUTEN, 2017). In some instances, immunohistochemistry may help confirming these tumors as well. Most canine pheochromocytomas are synaptophysin and chromogranin A-positive, and cytokeratin and vimentin-negative. The tumor from this dog was easily recognized on histologic sections, and immunohistochemistry was solely performed to further characterize the neoplastic cells, which showed synaptophysin expression and did not label for cytokeratin and vimentin.

If diagnosed previously to TE, surgical excision would have been the treatment of choice for the tumor in this dog (BARRERA et al., 2013; ROSOL & MEUTEN, 2017). Adrenalectomy, even in cases with tumor invasion of the caudal vena cava, is a viable option in dogs nowadays (BARRERA et al., 2013). Conversely, diagnosing pulmonary TE is much more challenging, and treatment is still limited, even for human patients (HE al., 2021). An interesting prophylactic choice for human patients with inferior vena cava invasion by renal carcinoma is the placement of a filter in the suprarenal vena cava, which prevents the pulmonary TE development (BRENNER et al., 1992). Apparently, this treatment choice has not been explored in animal medicine. The major causes of sudden death in dogs include cardiac anomalies, gastric dilation/volvulus, hemorrhage from ruptured splenic hemangiosarcoma, hypoadrenocorticism, parvoviral infection and pulmonary arterial thrombosis (MAXIE & MILLER, 2016). Despite being well established in human oncologic patients, TE associated with sudden death is not frequently mentioned in dogs and other domestic animals. It should be considered as a possible cause of unexpected death in oncologic patients.

ACKNOWLEDGEMENTS

This article was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brasil - Finance code 001. Dr. Aguiar and Dr. Marcus have a CAPES scholarship. Ms. Gonçalves had a scholarship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Mr. Buttelli had a scholarship from Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) during the time this research was conducted.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Conceptualization: MMF and AA. Data acquisition: MMF, AA, VBM, PNCG, PHSB, GDK. Design of methodology and data analysis: MMF, AA. MMF, AA, VBM, PNCG and PHSB prepared the draft of the manuscript. All authors critically revised the manuscript and approved of the final version.

REFERENCES

BARRERA, J. S. et al. Evaluation of risk factors for outcome associated with adrenal gland tumors with or without invasion of the caudal vena cava and treated via adrenalectomy in dogs: 86 cases (1993–2009). **Journal of the Veterinary Medical Association**, v.242, p.1715-1721, 2013. Available from: <https://avmajournals.avma.org/view/journals/javma/242/12/javma.242.12.1715.xml?tab_body=fulltext>. Accessed: Feb. 7, 2023. doi: 10.2460/javma.242.12.1715.

BOIS, M. C. et al. Neoplastic embolization to systemic and pulmonary arteries. **J Vasc Surg,** v.68, n.1, p.204-212, 2018. Available from: <https://www.sciencedirect.com/science/article/pii/S0741521417325090>. Accessed: Aug. 30, 2022. doi: 10.1016/j.jvs.2017.09.045.

BRENNER, D. W. et al. Suprarenal greenfield filter placement to prevent pulmonary embolus in patients with vena caval tumor thrombi. **Journal of Urology**, v.147, p.19-23. 1992. Available from: <https://www.auajournals.org/doi/10.1016/S0022-5347%2817%2937122-7>. Accessed: Feb. 14, 2023. doi: 10.1016/S0022-5347(17)37122-7.

CHAN, G. S. W. et al. Sudden death from massive pulmonary tumor embolism due to hepatocellular carcinoma. **Forensic Science**

International, v.108, p.215-221, 2000. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0379073899002121?casa_token=jUohM_K7tN4AAAAA:rppvJ_ej7z4xOHJHfAf8LFUBXrtf_tAvgmjxS4tp8lSXZp_FY51-ZzDpi9L42jnn7Al3iSOlfapp>. Accessed: Aug. 20, 2022. doi: 10.1016/S0379-0738(99)00212-1.

DURMUŞOĞLU, J. et al. Venous thromboembolism in patients with adrenocortical carcinoma after surgery. **Endocrine Connections**, v.9, p.874-881, 2020. Available from: <https://ec.bioscientifica.com/view/journals/ec/9/9/EC-20-0299.xml>. Accessed: Feb. 14, 2023. doi: 10.1530/EC-20-0299.

EPSTEIN, S. E. et al. Diagnostic utility of d-dimer concentrations in dogs with pulmonary embolism. **Journal of Veterinary Internal Medicine**, v.27, p.1646-1649, 2013. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/jvim.12177>. Accessed: Feb. 7, 2023. doi: 10.1111/jvim.12177.

FAKUDA, A. et al. T. Lessons from a patient with a cardiac arrest due to massive pulmonary embolism as the initial presentation of Wilms tumor: a case report and literature review. **BMC Pediatrics**, v.19, p.39-43, 2019. Available from: <https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-019-1413-y>. Accessed: Aug. 20, 2022. doi: 10.1186/s12887-019-1413-y.

HE, X. et al. Pulmonary tumor embolism: A retrospective study over a 30-year period. **Plos one**, v.16, p.e0255917, 2021. Available from: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0255917>. Accessed: Aug. 20, 2022. doi: 10.1371/journal.pone.0255917.

JOHNSON, L. et al. Pulmonary thromboembolism in 29 dogs: 1985-1995. **Journal of Veterinary Internal Medicine**, v.13, p.338-345, 1999. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1939-1676.1999.tb02192.x>. Accessed: Feb. 7, 2023. doi: 10.1111/j.1939-1676.1999.tb02192.x.

LISKA, W. D.; POTEET, B. A. Pulmonary embolism associated with canine total hip replacement. **Veterinary Surgery**, v.32, p.178-186, 2003. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1053/jvet.2003.50016>. Accessed: Feb. 7, 2023. doi: 10.1053/jvet.2003.50016

MAXIE, M. G.; MILLER, M. A. Introduction to the Diagnostic Process. In: Maxie, GM; Maxie, MG, ed. Jubb, **Kennedy and Palmer's Pathology of Domestic Animals**. 6th ed. 1 V. St Louis: Elsevier. 2016, p.4-5.

ROBVEILLE, C. et al. Obstructive shock caused by right atrial thrombosis secondary to malignant pheochromocytoma in a dog. **Australian Veterinary Journal**, v.98, p.462-466, 2020. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/avj.12992>. Accessed: Aug. 20, 2022. doi: 10.1111/avj.12992.

TAKAHASHI, A. et al. Computed Tomography (CT) observation of pulmonary emboli caused by long-term administration of ivermectin in dogs experimentally infected with heartworms. **Veterinary Parasitology**, v.155, p.242-248, 2008. Available from: <https://www.sciencedirect.com/science/article/pii/S0304401708002549>. Accessed: Feb. 7, 2023. doi: 10.1016/j.vetpar.2008.04.027.

WINKLE, T. J. V. et al. clinical and pathological features of aortic thromboembolism in 36 dogs. **Vet Emer Crit Care**, v.3, p.13-21, 1993. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1476-4431.1993.tb00099.x>. Accessed: Aug. 30, 2022. doi: 10.1111/j.1476-4431.1993.tb00099.x.