BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Case Report

Intravascular lymphoma in a dog: case report

Rafael R. M. E. Costa[1*], Paulo E. B. Martinelli[2], Isabela F. S. Perossi[2], Leticia Bonato[2], João Victor B. Silva[3], Bruna R. I. Nascimento[3], Paulo H. L. Bertolo[4], Gabriela P. Lima[4], Rosemeri O. Vasconcelos[5]

[1]Discente do curso de graduação em Medicina Veterinária, Faculdade de Ciências Agrárias e Veterinárias (FCAV-Unesp Jaboticabal), Jaboticabal, SP, Brasil.
[2]Residente do Programa de Residência Profissional na área da Saúde – Medicina Veterinária e Saúde, FCAV- UNESP, Jaboticabal, SP, Brasil.
[3]Discente do Centro Universitário Moura Lacerda, Ribeirão Preto, SP, Brasil
[4]Discente do Programa de Pós-graduação em Medicina Veterinária, FCAV- UNESP, Jaboticabal, SP, Brasil.
[5]Docente do Departamento de Patologia Veterinária, FCAV – Unesp Jaboticabal, Jaboticabal, SP, Brasil
[*]**Corresponding author:** E-mail: rrmedc@hotmail.com

Submitted June, 25th 2019, Accepted March, 27th 2020

Abstract

Intravascular lymphoma is characterized by being a malignant neoplasm of extranodal T or B lymphocytes with exclusive proliferation within the vascular lumen, particularly of small vessels. The clinical signs vary due to the involvement of several organs, mainly the central nervous system. The diagnosis is difficult because many of the tests performed are not conclusive and, therefore, necropsy is the most efficient way to identify this tumor. This case report aims to describe the anatomopathological findings of a case of intravascular lymphoma in a mixed breed, 8 years old dog who presented neurological signs and was submitted to a necroscopic examination with clinical suspicion of granulomatous meningoencephalitis. The necropsy findings were not specific, but the presence of intravascular neoplastic lymphocytes in the brain, spleen, adrenal gland and stomach was verified by microscopy. These cells were positive for the CD3 antibody by immunohistochemistry, confirming the T lymphocyte phenotype. This neoplasm should be considered in the diagnosis of encephalopathies in dogs.

Key words: encephalopathy, lymphoid neoplasm, immunohistochemistry.

Introduction

Lymphomas comprise a set of extramedullary lymphoid neoplasms and are characterized by the clonal proliferation of malignant lymphocytes, being the main hematopoietic neoplasia in dogs (4). According to Daleck and De Nardi (2), their annual incidence is 6 to 30 new cases per 100,000 dogs born.

This neoplasm can be classified in three ways: anatomical distribution, morphology and cell appearance, and immunophenotyping (19). The extranodal manifestation is rare and one of them is the intravascular lymphoma (2).

Intravascular lymphoma (IL) is characterized by the absence of leukemia and solid masses, evidenced by the proliferation of neoplastic lymphocytes confined to the lumen of blood vessels (12) and they are mainly present in the central nervous system, and may or may not be distributed in other organs (9).

Nervous system disorders such as loss of proprioception, seizures and blindness are associated with intravascular lymphoma. Other clinical signs are still commonly observed, such as diarrhea, anorexia, hair loss and lethargy (12). Histopathological examination shows neoplastic lymphocytes in the vessel lumen, but the endothelium is still distinguishable, and the muscular layer remains healthy. These vessels may be distended or occluded and may be associated with infarcted tissues (19).

Although it is a rare and difficult diagnosis, it is necessary to include this neoplasm as a differential diagnosis of other encephalopathies in dogs and cats (7-10).

The present report describes the histopathological findings of an intravascular T-cell lymphoma in the brain, spleen, adrenal and stomach of a dog.

Case report

An 8-year-old male, 33 kg mixed breed dog went to a veterinary clinic for routine checkup. A slight increase in serum urea and thrombocytopenia were seen. Antibiotic therapy was initiated and discontinued after a negative cPCR result for *Erlichia* spp., which is endemic in this region. In the meantime, the dog had seizures.

The animal had undergone abdominal ultrasonography, computed tomography with contrast and cytological examination of cerebral spinal fluid (CSF). These tests were inconclusive and, in the cytology, neutrophilic pleocytosis was diagnosed. The clinical suspicion was of granulomatous meningoencephalitis.

Then, a therapy associating corticosteroids, antibiotics and a cerebral vasodilator was prescribed for a week. The drugs were not effective, and the patient had nonspecific neurological clinical signs (convulsions, nystagmus, pedal movements and head-pressing). Due to the worsening of its clinical condition, the dog was euthanized.

The animal was referred for necropsy at Unesp São Paulo State University, Jaboticabal, SP, Brazil. Grossly the liver showed an accentuated lobular pattern, and the renal capsule had nodulations. The gastric mucosa was diffusely reddish. The brain did not present any gross alterations. For the microscopic analysis, samples of all organs were collected, fixed in 10% formalin solution, buffered with phosphates (pH 7.2), for 48 hours. Subsequently, the tissues were cleaved and processed routinely and embedded in paraffin wax. The samples were cut to 3 μm thick sections, stained with hematoxylin and eosin, and the lesions were observed under light microscopy.

Aggregates of tumor cells were observed obstructing small and large blood vessels of the stomach (Fig. 1A), adrenal, spleen, in the meningeal vessels (Fig. 1B) and the neuropil. In the latter, interstitial edema, neuronophagia, and focal areas of infarction due to vascular obstruction of neoplastic cells associated with hemorrhage were also noted. Individually, the cells presented marked atypia, with high nuclear-cytoplasmic ratio, with scarce and eosinophilic cytoplasm. The nuclei were predominantly rounded, with finely clustered nuclear chromatin and with unique and evident nucleoli. Moderate anisocytosis, anisokaryosis and karyomegaly were also observed, as well as 20 mitotic figures were observed in 10 high power fields (40x objective lens).

In the immunohistochemical analysis of the samples, a positive staining of tumor cells for the CD3 antibody was observed in 90% of cells in the brain (Fig. 1C), splenic tissue (Fig. 1D), adrenal and stomach. Some CD3 positive cells were also observed in the neuropil, near blood vessels. The CD79a antibody was negative for the analyzed samples.

Discussion

The animal presented nonspecific nervous signs, consistent with the reports of IL (1, 9, 15, 17, 18.). The lack of specific clinical signs, the absence of mass formation in organs, and the difficulty of routine tests in detecting neoplastic cells, such as the blood smear, make the diagnosis of this neoplasm difficult (17). The diagnosis of this tumor is predominantly postmortem, with few cases previously detected by biopsy (1, 12).

The lesions caused in the different organs are associated with vascular occlusions caused by the tumor resulting in thrombi and infarcts (10, 18). Macroscopic lesions are uncommon, but when present, involve the central nervous system (12). Macroscopic lesions associated with IL were not observed in this report. In the microscopic analysis of the samples, the presence of tumor cells in the brain and other organs is in accordance with the described in the literature (9, 12). In this case, the clinical signs were related only to the involvement of the nervous system, but the observation of the lesions in other organs shows the systemic distribution of the neoplastic cells. Mazaro et al. reported one case in which IV affected only the kidneys in a dog (11). In humans, it is also reported a higher frequency of involvement of the encephalon by the tumor, but other clinical findings are reported when other organs are affected, such as fever, hemophagocytic syndrome, hepatosplenomegaly and invasion of the bone marrow (13).

The presence of CD3-positive lymphocytes in the perivascular space and the adjacent neuropil suggests a rupture of the blood-brain barrier due to a possible vascular damage secondary to IL (19) or the breakdown of local immunotolerance by activation of glial cells, as described in viral encephalitis (6). However, in human IL it was reported that the vascular endothelium associated with the tumor was intact, by expressing CD29 and CD54, molecules involved in the leukocyte trafficking. These markers were not expressed in the tumor, confirming their pattern restricted to the vascular lumen (16). Report on the intravascular lymphoma of large B cells in people emphasizes that the tumor can interact or release substances that causes endothelial injury resulting in the formation of thrombi. In this case, perivascular reactive lymphocytes were also observed by hematoxylin and eosin (5).

In the present report, the clinical suspicion of an inflammatory process of the encephalon associated with inconclusive results of the imaging exams, as well as of the cytological analysis showed the difficulty of arriving at a definitive diagnosis. In comparison with the literature, it was evident that histopathological examination is the gold standard for the conclusion of the neoplastic origin of the clinical signs (12).

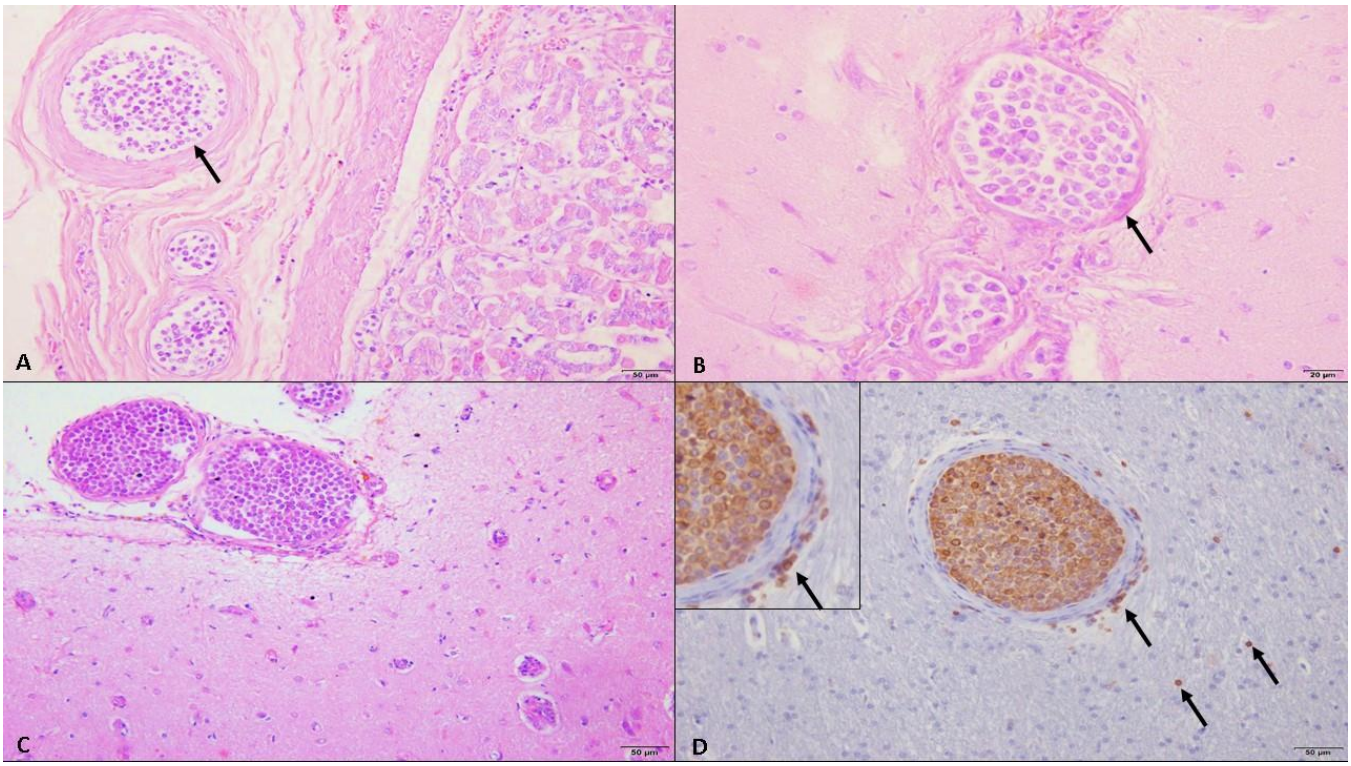

Figure 1. Photomicrography of an intravascular lymphoma in a dog. **A.** Population of neoplastic lymphocytes in the lumen of the vessels of the gastric submucosa (arrow; Hematoxylin and eosin, bar = 50 µm). **B.** Intravascular neoplastic lymphocytes in the meninges (arrow); Hematoxylin and eosin, bar = 20 µm). **C.** Lymphocytes inside vessels in the neuropil (Hematoxylin and eosin, bar = 50 µm). **D.** T lymphocytes strongly labeled for CD3 antibody in vessels of the encephalon perivascular space (detail of D, arrow). Peroxidase-bound polymers complex, bar = 50µm.

The neutrophilic pleocytosis observed in the cytology of CSF could be associated to trauma, post myelography reaction, necrotizing vasculitis, hemorrhage, neoplasms, bacterial or fungal infections (3).

Immunophenotyping of lymphomas by immunohistochemistry is essential for determining the biological behavior of the tumor as well as its response to therapy (19). In the present report, the predominant cellular profile was neoplastic T lymphocytes, according to the veterinary literature (1, 7, 10, 12, 19). In contrast, in humans, ILs are predominantly derived from B lymphocytes, with rare cases of ILs of T lymphocytes (14).

The diagnosis was based on its histological features, which were atypical small lymphocytes that were obstructing vessels of different calibers, with a pattern that was not compatible with any inflammatory process. CSF analysis was not useful to this neoplasm diagnosis.

Thus, IL is an aggressive lymphoid tumor and can cause vascular damage and clinical signs that may vary according to the affected organ, mainly in the nervous system. Therefore, this tumor should be considered in the differential diagnosis of encephalopathies in dogs.

References

1. Bush W, Thoop JL, Mcmanus PM, Kapatkin AS, Vite CH, Van Winkle TJ. Intravascular lymphoma involving the central and peripheral nervous systems in a dog. J Am Anim Hosp Assoc. 2003;39(1): 90–6.
2. Calazans SG, Daleck CR, de Nardi AB. Linfomas in Daleck CR, de Nardi AB Oncologia em cães e gatos. 2nd ed. Rio de Janeiro: Roca; 2016.49:633-648.
3. De Lorenzi, D, Mandara, MT. The Central Nervous System. In: Raskin RE, Meyer DJ. Canine and Feline Cytology: a color atlas and interpretation guide. St Louis: Saunders; 2012. p.325-365.
4. Fighera RA, Graça DL, Sistema Hematopoético. In: Santos RLS, Alessi AC. Patologia veterinária. 2nd ed. Rio de Janeiro: Roca; 2017. p.311-406.
5. Fischer M, Iglseder S, Grams A, Matosevic B, Moser P, Stockhammer G, Pfausler B. Intravascular large B-cell lymphoma mimicking central nervous system vasculitis. Hum Pathol: Case Rep. 2017;8:3-8.
6. Griffin DE. Immune responses to RNA-virus infections of the CNS. Nat Rev Immunol. 2003;3:493-502.
7. Henrich M, Huisinga M, Bauer N, Reinacher M. A case of intravascular lymphoma with mixed lineage

antigen expression in a cat. J Vet Med A Physiol Pathol Clin Med. 2007;54:575-8.

8. Lane LV, Allison RW, Rizzi TR, Stern AW, Snider TA, Moore PF, Vernau W. Canine intravascular lymphoma with overt leukemia. Vet Clin Path. 2012, 41:84-91
9. Lapointe JM, Higgins RJ, Kortz GD, Bailey CS, Moore PF. Intravascular malignant T-cell lymphoma (malignant angioendotheliomatosis) in a cat. Vet Pathol. 1997;34: 247-50
10. Machado GF, Castro MB, Melo GD, Ferreira WL, Aylon EG, Alessi AC. Intravascular Lymphomatosis in the Central Nervous System of Dogs: Immunohistochemical Investigation in Two Cases. Braz J Vet Pathol. 2011;4(1):47-51.
11. Mazaro RD, Fighera RA, Luz FS, Herbichi AP. Renal intravascular lymphoma in a dog. Cienc Rural. 2019;49:1-4.
12. McDonough SP, Van Winkle TJ, Valentine BA. Clinicopathological and immunophenotypical features of canine intravascular lymphoma (malignant angioendotheliomatosis). J Comp Pathol. 2002;126:277-88
13. Murase T, Nakamura S, Kawauchi K, Matsuzaki H, Sakai C, Inaba T, Nasu K, Tashiro K, Suchi T, Saito H. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol. 2000;111(3):826-34.
14. Nizamutdinov D, Patel NP, Huang JH, Fonkem E. Intravascular Lymphoma in the CNS: Options for Treatment. Curr Treat Options Neurol. 2017;19(10):1-8.
15. Oliveira L, Nóbrega J, Amorim R, Sant'ana F, Reis Junior J. Linfoma intravascular de células T em cão. Vet Zootec. 2015;22(4):575-9.
16. Ponzoni M, Campo E, Ferreri AJ. Intravascular lymphoma occurring in patients with other non-Hodgkin lymphomas. Clin Adv Hematol Oncol. 2010;8(9):641-2.
17. Ridge L, Swinney G. Angiotrophic intravascular lymphosarcoma presenting as bi-cavity effusion in a dog. Aust Vet J. 2004;82:616-8.
18. Sanchez L, Beckmann K, Dominguez E, Di Palma S, Shea A. Recurrent cerebrovascular accidents caused by intravascular lymphoma in a dog. Vet Rec. 2018;6(3):e000667.
19. Valli VE, Bienzle D, Meuten DJ. Tumors of the hemolymphatic system. In: Meuten DJ, editor. Tumors in domestic animals. 5th ed. Iowa: John Wiley & Sons Inc; 2017. p.203-321.