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Case Report

Canine large t-cell intravascular lymphoma – report of two cases

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Abstract
Intravascular lymphoma is rare in all species and is characterized by the intravascular proliferation of neoplastic lymphocytes, with the central nervous system being the most affected site. The aim was to report two cases of dogs diagnosed with large T-cell intravascular lymphoma. Both dogs showed neurological signs, including ataxia, seizures, and difficulty walking. Macroscopically, malacia in the brain were noted. Microscopically, there was a predominance of large neoplastic lymphocytes within the vasculature, with CD3 positive and negative to CD20, CD79a, PAX-5 immunohistochemical staining, confirming large T-cell intravascular lymphoma. The complexity of this neoplasm highlights the importance of interdisciplinary collaboration among veterinarians for differential diagnosis of central nervous system diseases.

Keywords: Brain, endothelium, lymphoproliferative disorder, dog, T lymphocyte.

Introduction

Canine lymphomas are characterized by the uncontrolled clonal proliferation of lymphoid cells and can be classified according to four characteristics: anatomical, cytomorphological, histomorphological, and immunophenotypic (16). Intravascular lymphomas (IVL), on the other hand, are considered rare, with few reports in veterinary and human literature, which raises significant interest due to their complexity and challenges (6, 16). They are characterized by the intense proliferation of neoplastic lymphoid cells within the vessels and are considered an extranodal presentation, potentially affecting the subendothelium but not the parenchyma. Unlike leukemia, neoplastic cells present in IVL are not commonly observed in blood smears (4); however, in humans, approximately 5% of reported cases show cells in peripheral blood (10, 17).

The clinical signs directly depend on the affected organ, with the central nervous system being the most commonly involved, showing macroscopic focal to multifocal areas of malacia (4, 5). As a result, animals may exhibit blindness, lethargy, seizures, and proprioceptive disturbances (5, 8, 15). When other organs are affected, findings such as hepatopathies, dyspnea, cardiomyopathy, nephropathy, among others, may be observed (4, 7, 12).

The diagnosis is made based on the association of clinical signs and complementary tests such as histopathology, where the presence of intravascular neoplastic lymphoid cells is observed, and confirmed by immunohistochemistry using antibodies such as anti-CD3, anti-CD79a, anti-CD20, and PAX5 (12). The immunophenotype commonly associated with canine IVL is that of T cells; however, in humans, there is a higher frequency of B cells. Nevertheless, regardless of the phenotype, complications related to the central nervous system always carry an unfavorable prognosis for the patient (4, 5, 8). Thus, the aim was to report the anatomopathological and immunohistochemical aspects of two dogs diagnosed with T-cell IVL.

Case description

Two canine carcasses, namely: a male Akita (Case 1) and a female Rhodesian Ridgeback (Case 2), aged 4 and 10 years, respectivelysent, were sent for necroscopic examination at a veterinary pathology anatomy laboratory located in the city of Recife, PE, with the authorization of the responsible parties. According to the owners, the animals had previously been treated at private veterinary clinics, following contemporary treatment standards, with clinical signs of the ataxia, seizures, vocalization, circling behavior, and difficulty in movement, no history of previous neoplasms. The duration of the disease until death was 7 days after the first neurological signs in both animals.

The necropsy, the following macroscopic findings were observed in both animals: the brain showed focal areas of malacia, with Case 1 having these areas in the frontal region of the left hemisphere (Fig. 1A), in Case 2, focal areas of malacia were observed in the brainstem and corpus callosum (Fig. 1B). Samples were collected for histopathological examination of the lungs, liver, kidneys, brain, gastrointestinal tract, heart, and spleen, preserved in 10% buffered formalin for routine histological processing and staining with hematoxylin and eosin.

Microscopically, large neoplastic lymphocytes were found in all organs, obstructing the vascular lumen of venules and arterioles. The neoplastic cells were pleomorphic, varying from round to polygonal, with distinct borders and variable nucleus-to-cytoplasm ratios. The nuclei were vesicular and round, featuring coarsely aggregated chromatin and indistinct nucleoli. Moderate anisocytosis and anisokaryosis were observed, along with atypical mitotic figures and binucleated cells. Hemorrhagic infarcts due to multifocal venous thrombosis were noted, consisting of fibrin, neoplastic lymphocytes, and erythrocytes in both cases (Fig. 2A,B). Based on these findings, a histopathological diagnosis of intravascular large cell lymphoma was proposed and confirmed through immunophenotyping.

For the immunohistochemical panel examination, antibodies were used anti-CD3 (Clone: nan, AbboMax; San Jose, California, USA), anti-CD20 (#PA5-16701, Thermo Fisher Scientific, Rockford, Illinois, USA), anti-CD79a (Clone: IGA/1790R, Thermo Fisher Scientific, Rockford, Illinois, USA) and anti-PAX-5 (Clone: 3977R, Thermo Fisher Scientific, Rockford, Illinois, USA) at a 1:400 dilution for everyone. Briefly, were used on tissue sections 4µm thick, deparaffinized, and subjected to antigen retrieval with EDTA buffer pH 8.5 (Recovery EDTA, EasyPath, São Paulo, São Paulo, BR) in a Pascal pressure cooker for 20 minutes.

For blocking peroxidase, protein blocking, post-primary (labeling amplifier), polymer, and DAB, the Novolink Polymer Detection System (Leica Biosystems Newcastle Ltd, Newcastle Upon Tyne, UK) was utilized according to the manufacturer's instructions, and the incubation of the primary antibodies was performed overday (1 hour). The slides were then counterstained with Harris Hematoxylin, dehydrated, and mounted.Microscopic evaluation in both cases revealed strong monoclonal labeling for anti-CD3 in more than 80%

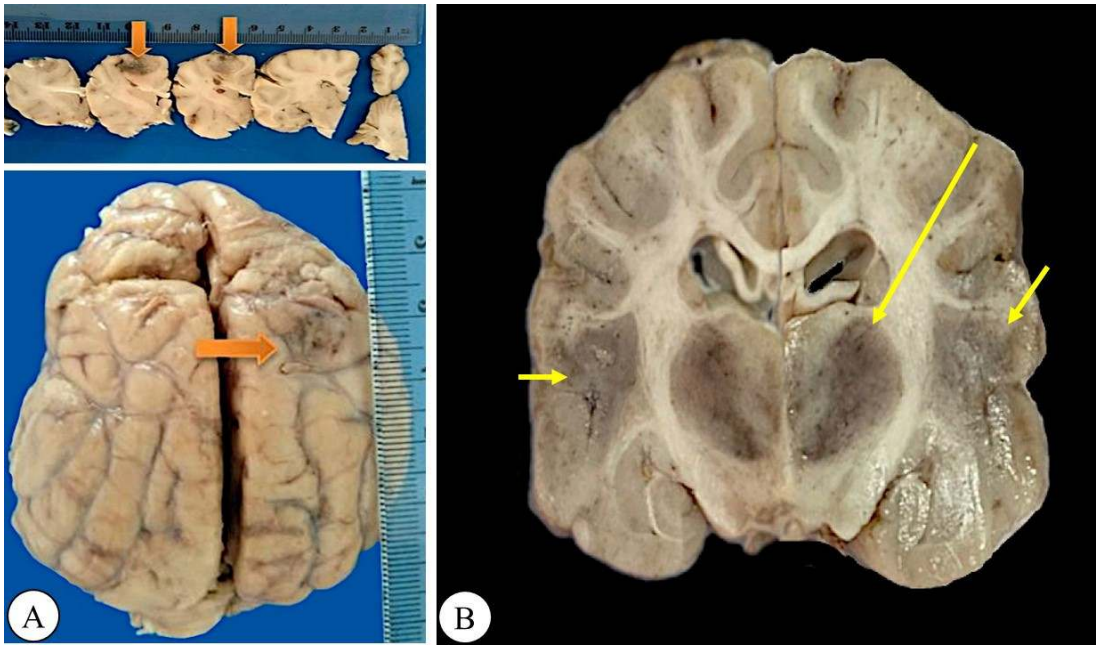

Figure 1. Macroscopy, brain, canine intravascular lymphoma. A – Case 1, brain, telencephalon, focal area of the right hemisphere demonstrating parenchymal depression and malacia (arrow). Upper image, Telencephalon, parietal cortex, cross-section, focal area of malacia, brownish (arrow). B – Case 2, brain, cross-section, thalamus, focal area of brownish malacia and multifocal hemorrhagic spots (large arrow); this process is similar in the parietal cortex of both the right and left hemispheres (smaller arrow).

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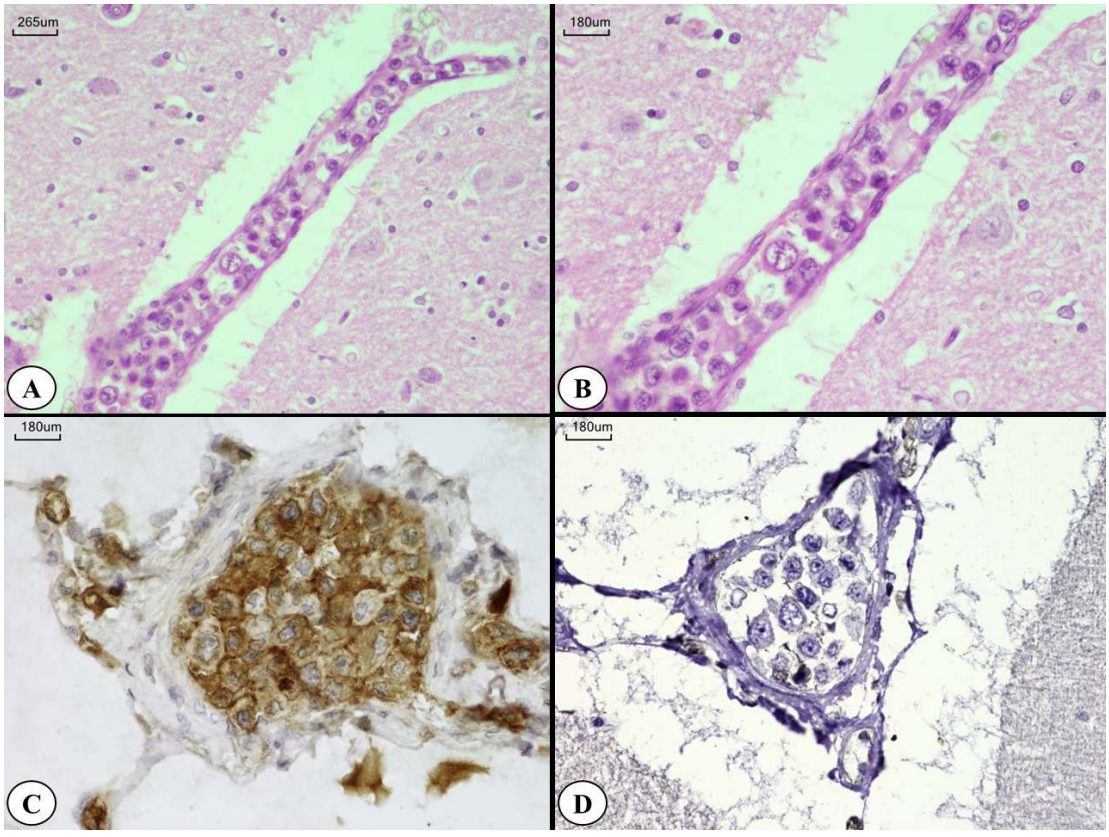

Figure 2. Photomicrography, intravascular lymphoma, cases 1 and 2, canine. A, B 1 - Brain, canine, cerebellum and brainstem, multifocal areas of thrombi with presence of neoplastic lymphocytes intravascularly (H&E, 100x objective, scale bar 200µm). C - Brain, canine, immunohistochemistry. Cerebellum, showing large intravascular lymphocytes positive for anti-CD3 with strong brown staining in the membrane and cytoplasm. (Immunohistochemistry, counterstained with Harris Hematoxylin). D – Brain, negative for anti-CD20, anti-CD79a and anti-PAX-5 (Immunohistochemistry, counterstained with Harris Hematoxylin).

of the intravascular neoplastic cells (Fig. 2C), as well as the absence of immunoexpression for anti-CD20, anti-CD79a, and anti-PAX-5 in the neoplastic cells, (Fig. 2D). According to the anatomopathological findings we confirmed the diagnosis of Intravascular Large T-Cell Lymphoma.

Discussion

In the study in question, the ages of the animals showed a difference in parity, with one being four years old and the other ten years old. The literature is scarce regarding the age of animals affected by Intravascular Lymphoma (LIV), as it is rare; it generally describes an average age of 8 years (2, 5, 7, 10, 12, 13). Animals younger than 8 years old are rarely observed with lymphoid brain afflictions (11), thus confirming the scarcity of reports involving animals of this age compared to other non-Hodgkin lymphomas (2, 16). In humans, this entity typically affects elderly individuals with an average age of 70 years (14).

There is no sexual preference for the occurrence of canine Intravascular Lymphoma (LIV) according to the literature. Although this study evaluated only two animals, both sexes were affected. The breeds are diverse, with reports showing a higher frequency in Rottweilers and mixed breeds (11, 12). However, there is currently no available information regarding the Rhodesian Ridgeback breed.

The clinical findings reported in the animals' history included ataxia, vocalization, circling, motor incoordination, and seizures. These findings are commonly observed in animals and humans affected by LIV (1, 4, 5, 17, 15). The clinical signs result from obstruction and endothelial lesions due to thrombus formation in the cerebral vascular endothelium. This process leads to decreased blood flow, consequently causing ischemia, degeneration, and neuronal necrosis. It is known that these cells are highly sensitive to any changes in blood supply, particularly in the more cortical regions of the telencephalon and in the basal nuclei (9), which are the areas affected in the animals of this study.

The observed brain lesions are the primary causes of death and the most common site of this neoplasia. Magnetic resonance imaging findings that assess lesions secondary to the proliferation of malignant lymphocytes intravascularly in the central nervous system (CNS)

demonstrate a mixed pattern with a predominance of multifocal affected areas, primarily in the telencephalon, and there may be thickening of the meninges (3, 8; 11). This was observed in case 2, where more vascularized regions of the brain and greater impairments due to vascular infarcts were noted. Other studies on canine intravascular lymphoma (LIV) have demonstrated a pattern of malacia in the frontal region, near the ophthalmic nerve extending toward the occipital lobes, similar to those found in case 1. These findings are also common in humans, particularly regarding the multifocal distribution (1, 8, 11).

The microscopic findings were similar for both cases, which exhibited numerous large lymphocytes, predominantly intravascularly in the brain, causing necrosis, the presence of red neurons (ischemia), and the formation of fibrin thrombi due to the disturbance of laminar flow caused by the cells. These changes extended to the liver, spleen, and, particularly in case 1, to the kidneys and bladder, expressed as multifocal nephritis and hemorrhagic cystitis due to the obliteration of blood vessels by neoplastic cells. These findings have also been observed in the literature, reported as an uncommon site in cases of intravascular lymphoma (9, 11, 12, 15). In immunohistochemistry, there was positivity for CD3 in both animals, confirming that it is an intravascular lymphoma of large T cells. In dogs, T cell phenotyping in LIV is common (2, 7, 10), unlike what is observed in humans, where B cells predominately express markers for PAX-5, CD79a, CD203, (17). The behavior of these cells and the genetic lineage factor are not well understood, even in human medicine, necessitating further studies, as there is a scarcity of research depicting this neoplasia (14).

The clinical-anatomopathological findings were essential, along with immunohistochemical analysis, in obtaining the diagnosis of intravascular lymphoma of large T cells in both cases, thus highlighting the important contribution of the veterinary pathologist in assisting with the diagnosis, working in an interdisciplinary manner, especially in cases that are rarely observed in veterinary medical practice. Immunohistochemistry is a valuable tool for diagnosing intravascular lymphoma of large T cells in dogs, providing differentiation of neoplastic cells and decisively contributing to the immunophenotypic profile of the neoplasia, aiding in therapeutic planning and prognosis.

Conflict of Interest

The authors declare no competing interests.

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