PESQUISA VETERINÁRIA BRASILEIRA
Brazilian Journal of Veterinary Research

ISSN 0100-736X (Print)
ISSN 1678-5150 (Online)

Pesq. Vet. Bras. 39(6):393-401, June 2019
DOI: 10.1590/1678-5150-PVB-6295

Original Article
Small Animal Diseases

Feline lymphoma in the nervous system: pathological, immunohistochemical, and etiological aspects in 16 cats[1]

Lauren S. Mello[2], Ronaldo V. Leite-Filho[2], Welden Panziera[2], Marcele B. Bandinelli[2], Luciana Sonne[2], David Driemeier[2] and Saulo P. Pavarini[2]*

ABSTRACT.- Mello L.S., Leite-Filho R.V., Panziera W., Bandinelli M.B., Sonne L., Driemeier D. & Pavarini S.P. 2019. **Feline lymphoma in the nervous system: pathological, immunohistochemical, and etiological aspects in 16 cats.** *Pesquisa Veterinária Brasileira 39(6):393-401*. Setor de Patologia Veterinária, Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves 9090, Prédio 42505, Porto Alegre, RS 91540-000, Brazil. E-mail: saulo.pavarini@ufrgs.br

The pathological, immunohistochemical (IHC), and etiological features of lymphoma involving the nervous system (NS) in cats were analyzed through a retrospective study (2004-2017) in Rio Grande do Sul State, Brazil. The NS involvement was observed in 16 (12.2%) of 125 felines with lymphoma. Young cats were mainly affected, with a median of 24 months old. Most cases were secondary central NS lymphoma, whereas in three cats, the NS involvement was primary. IHC revealed 14 (87.5%) FeLV-positive, six FIV-positive, and one FeLV/FIV-negative cats. Distribution of feline lymphoma in the NS was 8/16 in the spinal cord, 7/16 in the brain, and 1/16 in the paravertebral nerves and ganglia (neurolymphomatosis). The lymphoma pattern in the spinal cord was exclusively extradural, often focal (6/8), and located in the lumbar (3/6), sacral (1/6), thoracic (1/6), and cervical segments (1/6). Brain neuroanatomical patterns were: leptomeningeal lymphomatosis (4/7), lymphomatous choroiditis (2/7), and intradural lymphoma (1/7). The feline with primary neurolymphomatosis presented a marked thickening of paravertebral nerves and ganglia from the sacral region. B-cell lymphoma (75%) was often diagnosed, and diffuse large B-cell lymphoma (DLBCL) (11/16) was the main subtype. T-cell lymphoma (25%) was less commonly observed and was classified as peripheral T-cell lymphoma (PTCL) (3/16) and T-cell lymphoblastic lymphoma (T-LBL) (1/16).

INDEX TERMS: Feline, lymphoma, nervous system, immunohistochemistry, etiology, cats, neuropathology, FeLV, extradural lymphoma, leptomeningeal lymphomatosis, lymphomatous choroiditis, neurolymphomatosis, pathology.

RESUMO.- [**Linfoma no sistema nervoso de felinos: aspectos patológicos, imuno-histoquímicos e etiológicos em 16 gatos.**] Os aspectos patológicos, imuno-histoquímicos (IHQ) e etiológicos do linfoma envolvendo o sistema nervoso de felinos foram analisados através de um estudo retrospectivo (período de 2004-2017) no Estado do Rio Grande do Sul, Brasil. O envolvimento do sistema nervoso foi observado em 16 (12,2%) dos 125 felinos com linfoma desse estudo e afetou principalmente, jovens com idade mediana de 24 meses. A grande maioria dos casos o linfoma era secundário no sistema nervoso central e somente em três gatos o linfoma foi primário do sistema nervoso. Na IHQ, 14 (87,5%) casos foram positivos para FeLV, seis (37,5%) para FIV, e um foi negativo para ambos. A distribuição do linfoma no sistema nervoso foi em 8/16 felinos na medula espinhal, 7/16 no encéfalo e em 1/16 em nervos e gânglios paravertebrais (neurolinfomatose). Na medula espinhal, o padrão do linfoma foi exclusivamente extradural e frequentemente focal (6/8), localizadas nos segmentos lombares (3/6), sacrais (1/6), torácicos (1/6) e cervicais (1/6). No encéfalo, os padrões neuroanatômicos observados foram: linfomatose leptomeningeal (4/7), coroidite linfomatosa (2/7), linfoma intradural (1/7).

[1] Received on February 13, 2019.
Accepted for publication on February 25, 2019.
[2] Departamento de Patologia Clínica Veterinária, Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul (UFRGS), Av. Bento Gonçalves 9090, Porto Alegre, RS 91540-000, Brazil. *Corresponding author: saulo.pavarini@ufrgs.br

No felino diagnosticado com neurolinfomatose primária, foi observado acentuado espessamento dos nervos e gânglios paravertebrais da região sacral. Os linfomas de células de células B (75%) foram os mais frequentes e o principal tipo foi o linfoma difuso de grandes células B (11/16). Os linfomas de células T (25%), menos observados, foram classificados como linfomas de células T periférico inespecífico (3/16) e linfoma linfoblástico T (1/16).

TERMOS DE INDEXAÇÃO: Linfoma, sistema nervoso, felinos, imuno-histoquímica, etiologia, gatos, neuropatologia, FeLV, linfoma extradural, linfomatose leptomeningeal, coroidite linfomatosa, neurolinfomatose, patologia.

INTRODUCTION

Lymphoma is one of the most common neoplasms in cats and typically young cats are affected, accounting for up to 90% of the hematopoietic tumors (Hardy 1981, Schmidt et al. 2010).

Lymphoma mainly arises from lymph nodes and less commonly from other sites, such as the spleen, liver, tonsils, gastrointestinal tract, and nasal cavity (Valli et al. 2017). Anatomically, multicentric, and alimentary lymphomas are the most common form of lymphoma (Reinacher 1989, Sato et al. 2014, Valli et al. 2016).

The main current classification used for lymphomas was formulated by the World Health Organization (WHO), adapted for animals and applied for the classification of feline lymphomas (Vezzali et al. 2010, Valli et al. 2016). The main purpose of this classification system is to correlate histotypes (phenotypic and immunophenotypic) and biological behavior (Vezzali et al. 2010, Valli et al. 2017). Lymphoma is a common CNS neoplasm in cats affecting the spinal cord more than the brain (Troxel et al. 2003, Tomek et al. 2006, Marioni-Henry et al. 2008).

Nervous system (NS) involvement occurs in approximately 12% of cats with lymphoma and usually as part of a generalized disease (Lane et al. 1994, Marioni-Henry et al. 2008). Lymphoma has a wide range of distribution patterns in the feline NS. However, there are limited papers that classify feline lymphoma in the NS, especially those that correlate different patterns and types of lymphoma (Mandara et al. 2016). Thus, the objectives of this study were to determine the epidemiological and anatomopathological aspects of feline lymphomas in the nervous system, in addition to classifying this neoplasm according to WHO, aiming to associate it with lymphoma distribution patterns in the NS.

MATERIALS AND METHODS

All post-mortem records of cats diagnosed with lymphoma were reviewed from January 2004 to January 2017, and cases with nervous system (NS) involvement were selected. All cats studied were from the metropolitan area of Porto Alegre, State of Rio Grande do Sul, Brazil. All data containing information were grouped, registered, and categorized according to age, breed, and sex. Additionally, gross distribution of lymphoma in the NS and extraneural sites were evaluated. The anatomic form was classified according to Gabor et al. (1998).

The anatomic distribution patterns of lymphoma in the central and peripheral NS were evaluated using histological slides stained with hematoxylin and eosin (HE) and characterized according to Mandara et al. (2016).

The classification of lymphoid neoplasms was carried out according to the system adopted by WHO as applied for use in animals (Valli et al. 2016). The NS tissue with neoplastic infiltrate were subjected to immunohistochemistry (IHC) for immunophenotypic analysis of neoplastic lymphocytes by applying primary antibodies CD79α (B-cell marker) and CD3 (T-cell marker). Additionally, FeLV and FIV IHC tests were carried out for the same tissues. The IHC technique was performed on tissue sections mounted on positively charged glass slides previously deparaffinized and dehydrated. The positive controls for IHC consisted of cat normal lymph node and spleen for lymphocyte markers (CD3 and CD79α) and previously tested lymph nodes from cats infected with the FeLV and FIV virus. Negative control sections were incubated with tris-buffered saline (TBS) in place of specific antibodies. Immunohistochemistry sections were counterstained with Harris hematoxylin. The data regarding techniques performed and antibodies employed is shown in Table 1.

RESULTS

Out of 125 cases of lymphoma, 16 (12.8%) exhibited NS involvement. Of the 16 cats, there were 9 females (56.3%) and 7 males (43.7%), 15 mixed breed (93.75%) and one Siamese. The ages ranged from 6 to 156 months, with a median of 24 months. According to anatomical forms, the feline lymphomas were classified into mixed (6/16), atypical (6/16), mediastinal (3/16), and abdominal (1/16). The immunostaining was positive in 14 (87.5%) cases for the FeLV antigen, 6 (37.5%) cases for the FIV antigen, and 1 was negative to both.

From the 16 cases of NS lymphoma, three were considered primary NS lymphoma and 13 secondary NS lymphoma (multicentric-form derived). The distribution of feline lymphoma in the NS was: spinal cord (8/16), brain (7/16), spinal nerves and paravertebral ganglia (1/16). Immunohistochemical

Table 1. Antibodies and immunohistochemistry procedures

Antibody	Antigen retrieval	Dilution	Detection method	Chromongen
Mouse antifeline leukemia virus gp 70[a]	40 min/100°C Tris EDTA buffer pH 9.0	1:500	MACH 4	AEC
Mouse antifeline immunodeficiency virus p24gag[a]	40 min/100°C Citrate buffer pH 6.0	1:200	MACH 4	AEC
Mouse antihumam CD79αcy[b]	20 min/100°C Tris EDTA buffer pH 9.0	1:100	MACH 4	DAB
Polyclonal rabbit antihuman CD3[b]	15 min/RT Protease XIV	Ready-to-use	MACH 4	AEC

[a] Bio-rad®, [b] Dako®; MACH 4 = Universal HRP-Polymer (Biocare®), AEC = 3-amino-9-ethylcarbazole (Dako), DAB = 3,3'Diaminobenzidine (Dako®), RT = room temperature.

analysis revealed that 75% of the cases (12/16) had immunostaining for CD79α (B cell lineage), whereas 25% (4/16) had immunostaining for CD3 (T cell lineage). All CD79α$^+$ cases were mature (peripheral) B-cell neoplasms, which were classified as diffuse large B-cell lymphoma (DLBCL, 11/16) and Burkitt's-like lymphoma (BLL-1/16). The 11 DLBCLs were further subtyped as immunoblastic (DLBCL-I, 7/11), centroblastic (DLBCL-C, 2/11), and T-cell rich (2/11). The four CD3$^+$ cases were classified as peripheral T-cell lymphoma unspecified (3/4, PTCLI, mature peripheral T-cell neoplasms) and T-lymphoblastic lymphoma (1/4, T-LBL, precursor T-cell neoplasm).

Spinal cord lymphoma (SCL)

All eight cases of SCL were positive for the FeLV antigen by IHC, of which, one was also positive for FIV. The ages ranged from 6 to 96 months with a mean with median of 38.5 and 24 months, respectively. The primary CNS lymphomas were identified in two cats (12 and 48 months) owing to the exclusive presentation on the spinal cord. Both the cats were FeLV positive and one was also FIV positive by IHC. The remaining six cases were secondary lymphomas with NS presentation only in the spinal cord, except in one case, which was also observed in the encephalic leptomeninges. The abdominal lymph nodes (5/6) were the most frequently affected in secondary lymphomas.

Feline SCL was predominantly located extradurally in the epidural space and associated with the epidural fat. Grossly, the neoplastic masses varied in size, were irregular, soft, and with white or yellow coloration. Focal distribution was identified in six of the eight cats (Fig.1A) and often involved the lumbar segments (3/6), followed by sacral (1/6), thoracic (1/6), and cervical (1/6) segments. The two remaining cats presented a multifocal spinal cord involvement observed in all spinal regions (Fig.1B).

Three cases (two cases of primary NS lymphoma) presented progressive hemorrhagic myelomalacia and affected the lumbosacral segments (Fig.1C). The grey matter was mainly affected, involving the dorsal and ventral horns. Gross lesions in these cases were characterized by bleeding and soft areas, in addition to occasional cavitation.

Histology showed a diffuse neoplastic infiltrate distributed extradurally and without infiltration in the meninges and spinal cord (Fig.1D). The eight SCLs were divided into B-cell lymphoma (6/8) and T-cell lymphoma (2/8), classified as: BLL (1/8), PTCLI (2/8), and DLBCL-I (5/8). Spinal cord injuries secondary to epidural lymphoma compression occurred in 50% of the SCLs. The main injury was progressive hemorrhagic myelomalacia (3/8) affecting the lumbosacral portion and extended until the thoracic segments. This lesion was found predominantly in grey matter and characterized by extensive hemorrhagic areas, neutrophilic vasculitis,

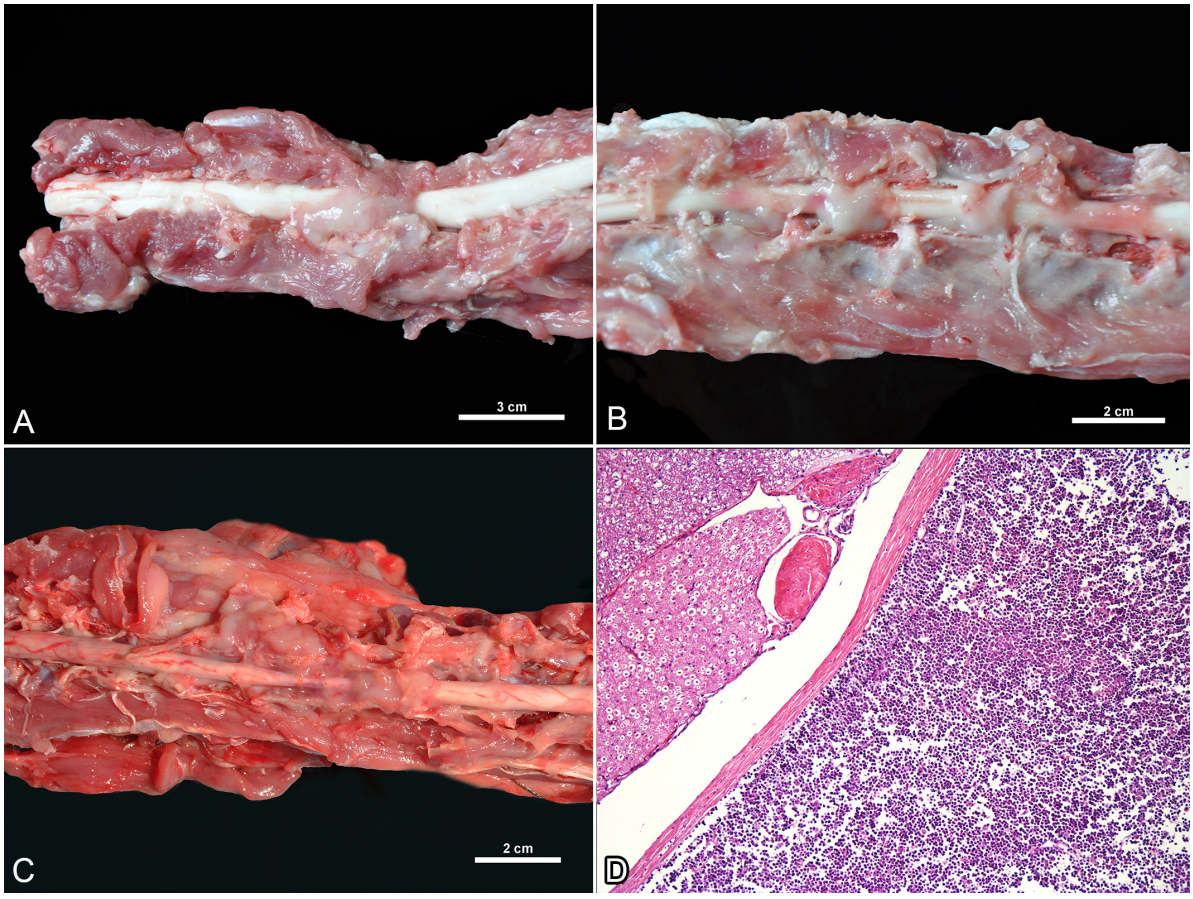

Fig.1. Feline lymphoma in the spinal cord. (**A**) Lymphoma in the cervical epidural space with focal distribution. (**B**) Lymphoma in the lumbar epidural space with multifocal distribution. (**C**) Extradural lymphoma extending to vertebral bodies and skeletal muscle. Hemorrhagic myelomalacia cranial to the tumor mass. (**D**) Extradural pattern of feline lymphoma in the spinal cord. HE, obj.10x.

gitter cell infiltrate, and malacia. Necrotic neurons showed retraction, a hypereosinophilic cytoplasm, and pyknotic nuclei. In the remaining white matter, axonal spheroids, Wallerian degeneration, and neutrophil infiltration were observed.

Brain lymphoma

Brain lymphoma affected six cats with ages ranging from 18 to 156 months with a mean and median of 41 and 24 months, respectively. Four cats were FeLV positive (Fig.2F), two were FIV/FeLV positive, one was FIV positive, and one was negative to both viral agents by IHC.

Grossly, brain lymphoma lesions were absent in most cases, except for a feline that presented a rough and thickened dura mater (Fig.2A). The brain lymphoma presented as a secondary form (multicentric presentation of the disease) in all seven cases, also affecting the liver (6/7), intestines (4/7), kidney (4/7), and lymph nodes (4/7).

The three neuroanatomic patterns found in the brain were characterized by the distribution of neoplastic infiltrates in the leptomeninges (leptomeningeal lymphomatosis, 4/7), choroid plexus (lymphomatous choroiditis, 2/7), and dura mater (intradural, 1/7).

The lymphomas in the leptomeningeal lymphomatosis pattern were classified as: DLBCL-I (2/4), PTCLI (1/4), and T-LBL (1/4). The neoplastic lymphocytes were widespread through the leptomeningeal space (Fig.2B) and expanded

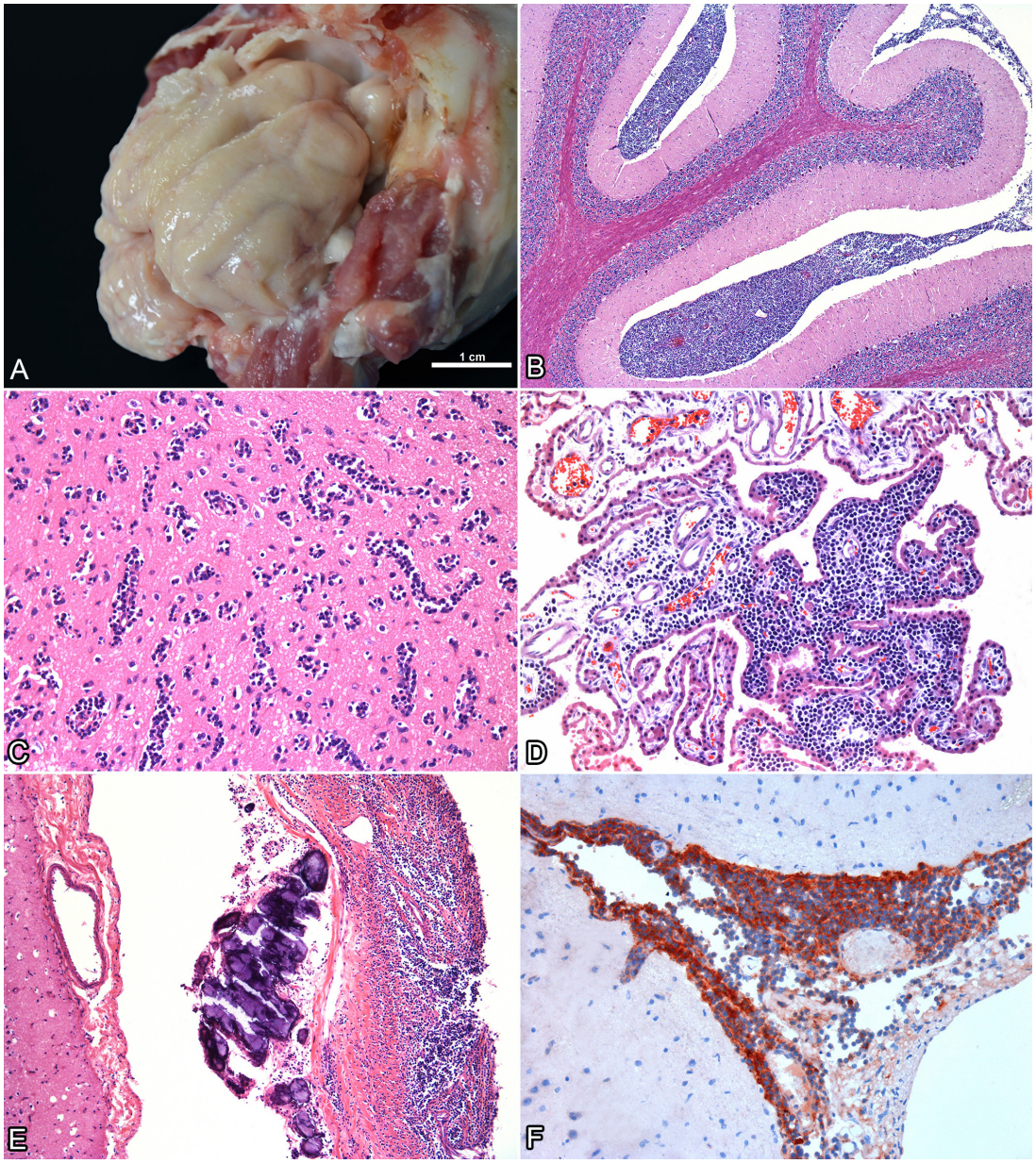

Fig.2. Brain feline lymphoma. (**A**) Brain with irregular and thickened dura mater. (**B**) Leptomeningeal lymphomatosis. Widespread leptomeningeal infiltration by neoplastic cells. HE, obj.4x. (**C**) Neoplastic lymphocyte infiltrating perivascular space of brain parenchyma in association with leptomeningeal lymphomatosis. HE, obj.20x. (**D**) Lymphomatous choroiditis. Diffuse infiltration of the choroid plexuses by neoplastic cells. HE, obj.20x. (**E**) Intradural lymphoma. Dura mater infiltrated by neoplastic lymphocytes and associated with multifocal mineralization. HE, obj.10x. (**F**) Brain leptomeninges, cytoplasmic immunostaining in lymphocytes. IHC for FeLV, obj.20x.

to perivascular spaces of the adjacent parenchyma (Fig.2C). Neoplastic cells were also found in the choroid plexus in one case of leptomeningeal lymphomatosis classified as DLBCL-I. In lymphomatous choroiditis cases, the choroid plexus of the fourth ventricle and lateral ventricles were diffusely infiltrated by neoplastic lymphoid cells classified as DLBCL-C (2/2) (Fig.2D). Additionally, congestion of choroid plexus vessels associated with proteinaceous effusion and exudation of cells into the ventricular lumen was observed. Intradural lymphoma was characterized by diffuse infiltration of DLBCL T-cells exclusively into the dura mater associated with multifocal calcification of the pachymeninges (Fig.2E). This presentation was responsible for the only case with alteration detected grossly in the brain.

Neurolymphomatosis

Neurolymphomatosis occurred in a 72-month-old, mixed breed, male cat that was FeLV positive by IHC and confined to the peripheral NS (primary NS lymphoma). Grossly, the sacral spinal nerves and paravertebral ganglia were bilaterally thickened with a soft consistency and yellowish coloration (Fig.3A). The malignant lymphoid cells classified as DLBCL T-cells were widespread along the sacral spinal roots, nerves, and ganglia and were associated to Wallerian degeneration with formation of axonal spheroids and digestion chambers (Fig.3B-D). The neoplastic cells were diffusely distributed in the leptomeningeal and perivascular spaces of the spinal cord segment adjacent to affected nerves.

DISCUSSION

Lymphoma is the most common neoplasm in cats, presenting a higher incidence in cats than other species, such as humans and dogs (Jarrett et al. 1966, Hardy 1981, Vail & Macewen 2000). Feline lymphoma occurs spontaneously and by viral oncogenic action. FeLV is the main viral agent implicated in lymphoma development. In studies conducted up to the 1990s, more than 80% of leukemias and lymphomas in cats were related to FeLV (Cotter et al. 1975, Francis et al. 1977, Francis et al. 1979, Hardy 1981, Reinacher 1989, Shelton et al. 1990). The prevalence of lymphoma associated with FeLV has been declining over the years in several parts of the world, possibly owing to the implementation of elimination and vaccination programs (Louwerens et al. 2005, Hartmann 2012, Meichner et al. 2012). Nevertheless, the high rate of cats infected with FeLV in the present study remains similar to proportions presented in studies published prior to the 1990s, when the prevalence of FeLV infection in cats with lymphoma was higher (Hardy 1981, Lane et al. 1994,

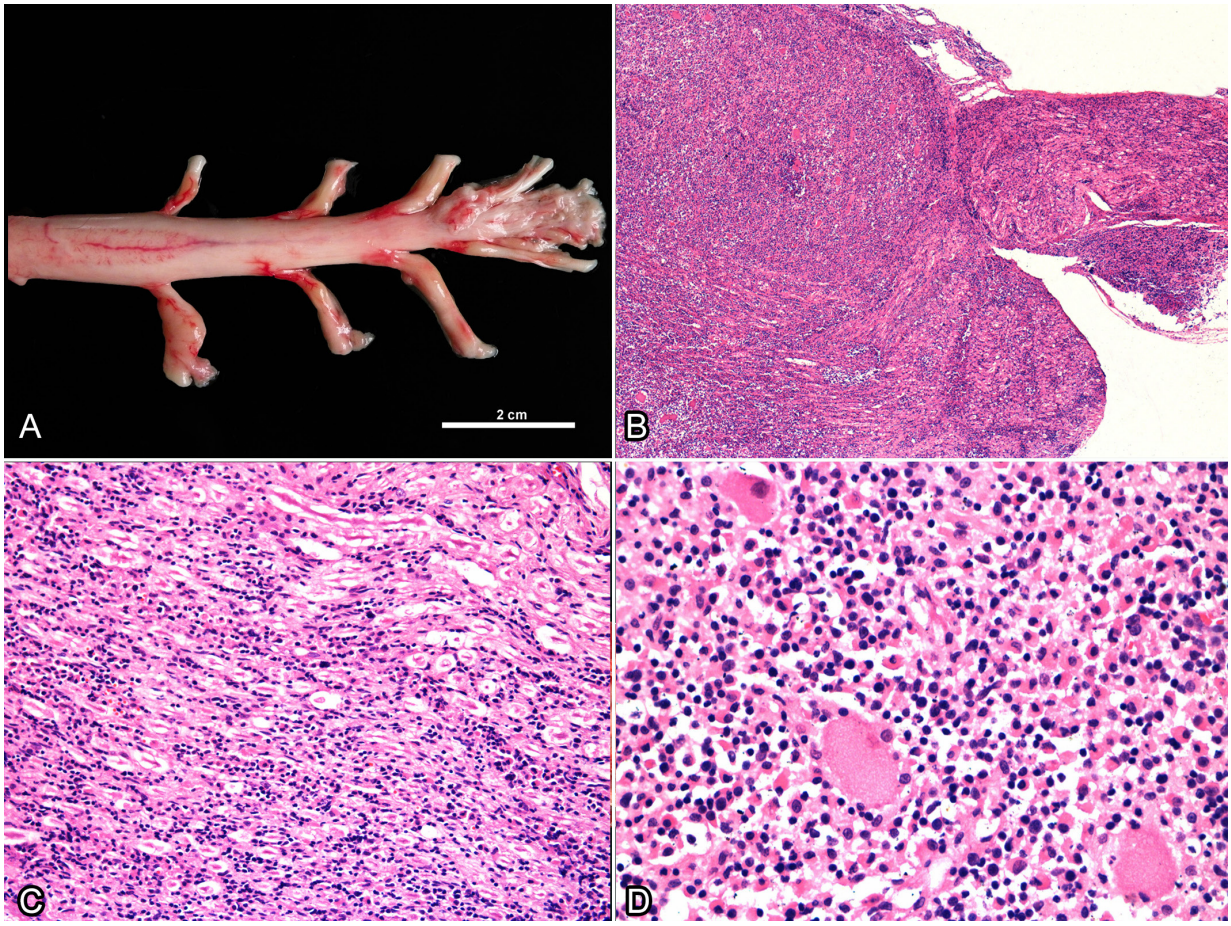

Fig.3. Neurolymphomatosis. (**A**) Bilateral thickened of spinal nerves (sacral region) presenting soft consistency and yellowish coloration. (**B**) Marked thickening of the nerve and paraspinal ganglia by neoplastic lymphocytic infiltrate. HE, obj.4x. (**C**) Neoplastic cells infiltration in the paravertebral ganglia. HE, obj.40x. (**D**) Lymphocytic neoplastic infiltrate along the spinal nerve associated with axonal spheroids, Wallerian degeneration. HE, obj.20x.

Meichner et al. 2012). These data suggest that the regional prevalence of infected cats is possibly still high.

The relationship between FeLV and lymphoma was particularly important in the present study since approximately 87.5% of the cats were infected by this virus. FeLV infected cats were approximately 62 times more likely to develop lymphoma, whereas concurrent FeLV/FIV infection confers approximately 80 times the risk for lymphoma development in relation to negative cats (Shelton et al. 1990, Hartmann 2012). The infection by FIV in the present study occurred in co-infection with FeLV, except for one cat only positive to FIV. Despite the indirect role of FIV in feline lymphoma development, this virus can exert a direct oncogenic role although less frequently (Diehl & Hoover 1992, Beatty et al. 1998, Beatty et al. 2002) with the peak in young cats allegedly attributable to FeLV infection.

Feline lymphoma generally has a bimodal age distribution. The first group more often seen in the present study affected young cats usually under 3 years and widely associated with FeLV infection (Hardy 1981, Lane et al. 1994, Gabor et al. 1998, Schmidt et al. 2010). The second group comprised older cats generally with FeLV infection absent, as seen in the two only FeLV-negative cats that were older than 8 years of age (Hardy 1981, Gabor et al. 1998, Louwerens et al. 2005). Although the incidence of lymphoma may be particularly higher or lower in certain breeds, indicating a probable genetic predisposition, these factors could not be evaluated in the present study owing to the high prevalence of mixed breeds (Gabor et al. 1998, Lyons 2010).

Lymphoma is a common CNS neoplasm in cats and occurs more frequently in the spinal cord than in the brain (Bradshaw et al. 2004). Predominantly, CNS lymphomas are a secondary manifestation of disease that are also presented by other organs (Lane et al. 1994, Tomek et al. 2006, Marioni-Henry et al. 2008). Primary CNS lymphoma (PCNSL) is originated and confined to the CNS and unlike the secondary form is rare in cats (Valli et al. 2017). Despite all the PCNSL cases in the present study being FeLV-positive, this viral relationship is not considered relevant to the frequency of this type of lymphoma (Valli et al. 2016). Unlike cats, the majority of PCNSLs in humans occur in immunocompromised patients by HIV infection (Rubenstein et al. 2008). These lymphomas are often identified as B-cell in both humans and cats (Ferracini et al. 1993, Vernau et al. 2001, Haldorsen et al. 2008, Nakamoto et al. 2009), and rarely as T-cells (Fondevila et al. 1998, Morita et al. 2009).

Feline lymphoma is the most frequent spinal cord neoplasm and the second most common disease of the spinal cord (Lane et al. 1994, Bradshaw et al. 2004, Marioni-Henry et al. 2004, Bradshaw et al. 2004, Marioni-Henry et al. 2008). Lymphoma is predominantly situated extradurally to the spinal cord and this presentation is frequently associated with young FeLV-positive cats (Zaki & Hurvitz 1976, Northington & Juliana 1978, Spodnick et al. 1992, Lane et al. 1994, Bradshaw et al. 2004, Marioni-Henry et al. 2008). Lymphoma involved in all regions of the spinal cord in the studied cats and, as described in the literature, exhibited predilection for lumbar segments (Marioni-Henry et al. 2004). Similarly to those described by Spodnick et al. (1992) and Lane et al. (1994), the epidural masses were often focal. The extension to vertebral bodies or underlying skeletal muscle has been reported in extradural lymphomas (Spodnick et al. 1992, Lane et al. 1994). Lymphoma establishments in the spinal cord possibly develops through direct expansion from the paravertebral region to the epidural space through the vertebral foramen, despite also being possible through hematogenous spread via the epidural venous system (Harrington 1986, Maccauro et al. 2011). Hemorrhagic myelomalacia, described in three cases, is a neurovascular disorder from a secondary compressive medullar injury related to extradural masses (De Lahunta & Glass 2009). In cats this lesion associated with extradural lymphoma has been poorly reported (Laisse et al. 2017).

Lymphoma is the second most common intracranial neoplasm in cats (Troxel et al. 2003, Bradshaw et al. 2004). Leptomeningeal lymphomatosis or lymphomatous meningitis was the most frequent anatomical distribution of lymphoma in the brain. The neoplastic infiltration in leptomeninges could occur through the direct spread of primary or metastatic tumors from the parenchyma, or by hematogenous spread through arachnoid vessels (Grossman & Krabak 1999). This pattern has also been described in humans and is strongly associated with HIV (Levitt et al. 1980, Mamidi et al. 2002). Leptomeningeal lymphomatosis, as seen in cats studied with this pattern, usually cannot be perceived grossly, appearing sometimes as a mild leptomeningeal thickening (Mandara et al. 2016). The lymphomatous choroiditis was the less frequent pattern found. Grossly, in these cats, mass formation was not observed, unlike in the case reported by Zaki & Hurvitz (1976). DLBCL was the main lymphoma type found in leptomeningeal lymphomatosis and lymphomatous choroiditis. DLBCL also was described in dogs as the main type in leptomeninges and choroid plexus (Sisó et al. 2016). However, intradural lymphoma is poorly described in veterinary medicine. The presentation restricted to pachymeninges in CNS is also rarely described in humans (Matmati et al. 2010). The intradural lymphoma was the only case in the brain grossly detected owing to mineralized areas in the dura mater. The dural calcification related to lymphoma in young cats has rarely been reported (Mandara 2003). Calcifications of brain pachymeninges have been reported in humans related both to primary CNS lymphoma and chemotherapeutic treatment (Jenkins & Colquhoun 1998, Apter et al. 2002). However, the cat from the present case had no previous history of chemotherapy treatment. Meninge calcification has also been reported in FIV-infected cats and this association could also possibly be a cause of this lesion in the present study (Hurtrel et al. 1992). Similar aspects have been observed in the human SNC with metastatic lung carcinoma (Inomata et al. 2012). Although not fully known, the calcification mechanism involved in these cases possibly occurs owing to: calcified scar tissue; dystrophic calcification in areas of tumor necrosis; metastatic calcification owing to the high production of calcium phosphate; and deposition of calcium as a result of the tumor secretory function (Mahoney et al. 1990).

Primary neurolymphomatosis, presented by one cat, is the term referred to diffuse infiltration of neoplastic lymphocytes along the peripheral nervous system (PNS) (Grisariu et al. 2010). The gross findings often diverge from the common lymphoma presentation in other organs (Linzmann et al. 2009). Lymphoma is the main secondary tumor in the feline CNS and neurolymphomatosis is a rare condition in cats, other animals, and humans (Allen & Amis 1975, Hankenson et al. 1998,

Kuntzer et al. 2000, Mellanby et al. 2003, Higgins et al. 2008, Choi et al. 2013, Shree et al. 2016). The neoplastic infiltration in leptomeninges (leptomeningeal lymphomatosis) and perivascular space from medullar parenchyma, as observed in the present study, is a common consequence relative to spinal nerve neurolymphomatosis (Lane et al. 1994, Schaffer et al. 2012, Mandrioli et al. 2012, Rupp et al. 2014, Sakurai et al. 2016). The unusual feature of this condition can lead to confusion with other neurological conditions, such as vasculitis and mononeuritis (Mandrioli et al. 2012). PNS lymphoma in humans and animals is often identified as B-cell (Higgins et al. 2008).

DLBCL is the main type classified in dogs and humans (Friedberg & Fisher 2008, Vezzali et al. 2010). FeLV-related lymphomas are mainly T-cell lymphomas, and more precisely, lymphoblastic, and occur as a mediastinal form (Valli et al. 2017). In a study performed on FeLV-positive cats, approximately 30% of the lymphomas originated from B lymphocytes (Jackson et al. 1996). Lymphomas in cats infected with FIV and FIV/FeLV coinfection are often from a mature B-cell lineage, as in that observed in the felines analyzed in the present study (English et al. 1994, Callanan et al. 1992, Terry et al. 1995, Callanan et al. 1996, Hartmann 2012, Beatty et al. 2002). In addition, B-cell lymphoma has been linked to FIV pro-viral DNA even in the absence of antigen detection, which may justify the high frequency of this type of neoplasm in the present study despite the frequency of 35% FIV-positive cats (Beatty et al. 1998). As observed in dogs, most of the lymphomas observed in the CNS of cats analyzed in the present study were B cells, classified predominantly as DLBCLs (Sisó et al. 2016).

CONCLUSIONS

The nervous system (NS) involvement was observed in 12.8% of cats with lymphoma and mainly young cats with a median age of 24 months were affected.

Lymphomas occurred more frequently in the spinal cord than in the brain.

Secondary lymphomas were the predominant form that affected the NS.

The NS primary lymphomas were restricted to the spinal cord.

All spinal cord lymphomas were FeLV positive and B-cell lymphomas were the most common.

Acknowledgments.- The authors acknowledge the National Council for Scientific and Technological Development for financial support (CNPq Proc. 40619/2016-7) and the Coordination of Improvement in Higher Education Personal (CAPES) for awarding scholarship.

Conflict of interest statement.- The authors declare no conflict of interest with respect to the publication of this paper.

REFERENCES

Allen J.G. & Amis T. 1975. Lymphosarcoma involving cranial nerves in a cat. Aust. Vet. J. 51(3):155-158. <http://dx.doi.org/10.1111/j.1751-0813.1975.tb09443.x> <PMid:1174313>

Apter S., Avigdor A., Gayer G., Portnoy O., Zissin R. & Hertz M. 2002. Calcification in lymphoma occurring before therapy. Am. J. Roentgenol. 178(4):935-938. <http://dx.doi.org/10.2214/ajr.178.4.1780935> <PMid:11906877>

Beatty J.A., Callanan J.J., Terry A., Jarrett O. & Neil J.C. 1998. Immunophenotypical characterization of a feline immunodeficiency virus (FIV)-associated lymphoma: A direct role for FIV in B-lymphocyte transformation? J. Virol. 72(1):767-771. <PMid:9420284>

Beatty J.A., Terry A., MacDonald J., Gault E., Cevario S., O'Brien S.J., Cameron E. & Neil J.C. 2002. Feline immunodeficiency virus integration in B-cell lymphoma identifies a candidate tumor suppressor gene on human chromosome 15q15. Cancer Res. 62(24):7175-7180. <PMid:12499253>

Bradshaw J.M., Pearson G.R. & Gruffydd-Jones T.J. 2004. A retrospective study of 286 cases of neurological disorders of the cat. J. Comp. Pathol. 131(2/3):112-120. <http://dx.doi.org/10.1016/j.jcpa.2004.01.010> <PMid:15276850>

Callanan J.J., Thompson H., Toth S.R., O'Neil B., Lawrence C.E., Willett B. & Jarrett O. 1992. Clinical and pathological findings in feline immunodeficiency virus experimental infection. Vet. Immunol. Immunopathol. 35(1/2):3-13. <http://dx.doi.org/10.1016/0165-2427(92)90116-8> <PMid:1337400>

Callanan J.J., Jones B.A., Irvine J., Willett B.J., McCandlish I.A. & Jarrett O. 1996. Histologic classification and immunophenotype of lymphosarcomas in cats with naturally and experimentally acquired feline immunodeficiency virus infections. Vet. Pathol. 33(3):264-272. <http://dx.doi.org/10.1177/030098589603300302> <PMid:8740699>

Choi Y.J., Shin J.A., Kim Y.H., Cha S.J., Cho J., Kang S.H., Yi S.Y. & Lee H.R. 2013. Neurolymphomatosis of brachial plexus in patients with non-hodgkin's lymphoma. Case Rep. Oncol. Med. 2013:1-5. <http://dx.doi.org/10.1155/2013/492329> <PMid:24324902>

Cotter S.M., Hardy Junior W.D. & Essex M. 1975. Association of feline leukemia virus with lymphosarcoma and other disorders in the cat. J. Am. Vet. Med. Assoc. 166(5):449-454. <PMid:163223>

De Lahunta A. & Glass E. 2009. Large animal spinal cord diseases, p.285-317. In: Ibid. (Eds), Veterinary Neuroanatomy and Clinical Neurology. 3rd ed. W.B. Saunders, St Louis. <http://dx.doi.org/10.1016/B978-0-7216-6706-5.00011-1>.

Diehl L.J. & Hoover E.A. 1992. Early and progressive helper t-cell dysfunction in feline leukemia virus-induced immunodeficiency. J. Acquir. Immune Defic. Syndr. 5(12):1188-1194. <PMid:1333529>

English R.V., Nelson P., Johnson C.M., Nasisse M., Tompkins W.A. & Tompkins M.B. 1994. Development of clinical disease in cats experimentally infected with feline immunodeficiency virus. J. Infect. Dis. 170(3):543-552. <http://dx.doi.org/10.1093/infdis/170.3.543> <PMid:8077711>

Ferracini R., Nelson P., Johnson C.M., Nasisse M., Tompkins W.A. & Tompkins M.B. 1993. Non-Hodgkin lymphomas of the central nervous system. Pathol. Res. Pract. 189(3):249-260. <http://dx.doi.org/10.1016/S0344-0338(11)80507-8> <PMid:8332570>

Fondevila D., Vilafranca M. & Pumarola M. 1998. Primary central nervous system T-cell lymphoma in a cat. Vet. Pathol. 35(6):550-553. <http://dx.doi.org/10.1177/030098589803500613> <PMid:9823600>

Francis D.P., Essex M. & Hardy W.D. 1977. Excretion of feline leukaemia virus by naturally infected pet cats. Nature 269(5625):252-254. <http://dx.doi.org/10.1038/269252a0> <PMid:201852>

Francis D.P., Cotter S.M., Hardy Junior W.D. & Essex M. 1979. Comparison of virus-positive and virus-negative cases of feline leukemia and lymphoma. Cancer Res. 39(10):3866-3870. <PMid:225010>

Friedberg J.W. & Fisher R.I. 2008. Diffuse large B-cell lymphoma. Hematol. Oncol. Clin. N. Am. 22(5):941-952. <http://dx.doi.org/10.1016/j.hoc.2008.07.002> <PMid:18954744>

Gabor L.J., Malik R. & Canfield P.J. 1998. Clinical and anatomical features of lymphosarcoma in 118 cats. Aust. Vet. J. 76(11):725-732. <http://dx.doi.org/10.1111/j.1751-0813.1998.tb12300.x> <PMid:9862061>

Grisariu S., Avni B., Batchelor T.T., Van Den Bent M.J., Bokstein F., Schiff D., Kuittinen O., Chamberlain M.C., Roth P., Nemets A., Shalom E., Ben-Yehuda D. & Siegal T. 2010. Neurolymphomatosis: an international primary CNS

lymphoma collaborative group report. Blood 115(24):5005-5011. <http://dx.doi.org/10.1182/blood-2009-12-258210> <PMid:20368468>

Grossman S.A. & Krabak M.J. 1999. Leptomeningeal carcinomatosis. Cancer Treat. Rev. 25(2):103-119. <http://dx.doi.org/10.1053/ctrv.1999.0119> <PMid:10395835>

Haldorsen I.S., Kråkenes J., Goplen A.K., Dunlop O., Mella O. & Espeland A. 2008. AIDS-related primary central nervous system lymphoma: a Norwegian national survey 1989-2003. BMC Cancer 8(1):1-8. <http://dx.doi.org/10.1186/1471-2407-8-225> <PMid:18684320>

Hankenson F.C., Birkebak T.A. & Maggio-Price L. 1998. Pelvic limb paresis in a safari cat. J. Am. Assoc. Lab. Anim. Sci. 48(4):325-329. <PMid:10215468>

Hardy W.D. 1981. Hematopoietic tumors of cats. J. Am. Anim. Hosp. Assoc. 7:921-940.

Harrington K.D. 1986. Metastatic disease of the spine. J. Bone Joint Surg. Am. 68(7):1110-1115. <http://dx.doi.org/10.2106/00004623-198668070-00025> <PMid:3745256>

Hartmann K. 2012. Clinical aspects of feline retroviruses: a review. Viruses 4(11):2684-2710. <http://dx.doi.org/10.3390/v4112684> <PMid:23202500>

Higgins M.A., Rossmeisl Junior J.H., Saunders G.K., Hayes S. & Kiupel M. 2008. B-cell lymphoma in the peripheral nerves of a cat. Vet. Pathol. 45(1):54-57. <http://dx.doi.org/10.1354/vp.45-1-54> <PMid:18192576>

Hurtrel M., Ganière J.P., Guelfi J.F., Chakrabarti L., Maire M.A., Gray F., Montagnier L. & Hurtrel B. 1992. Comparison of early and late feline immunodeficiency virus encephalopathies. Aids 6(4):399-406. <http://dx.doi.org/10.1097/00002030-199204000-00007> <PMid:1319717>

Inomata M., Hayashi R., Kambara K., Okazawa S., Imanishi S., Ichikawa T., Suzuki K., Yamada T., Miwa T., Kashii T., Matsui S., Tobe K. & Sasahara M. 2012. Miliary brain metastasis presenting with calcification in a patient with lung cancer: a case report. J. Med. Case Rep. 6(1):2-5. <http://dx.doi.org/10.1186/1752-1947-6-279> <PMid:22947115>

Jackson M.L., Wood S.L., Misra V. & Haines D.M. 1996. Immunohistochemical identification of B and T lymphocytes in formalin-fixed, paraffin-embedded feline lymphosarcomas: relation to feline leukemia virus status, tumor site, and patient age. Can. J. Vet. Res. 60(3):199-204. <PMid:8809383>

Jarrett W., Crighton G. & Dalton R. 1966. Leukaemia and lymphosarcoma in animals and man. I. Lymphosarcoma or leukaemia in the domestic animals. Vet. Rec. 79:693-699.

Jenkins C.N.J. & Colquhoun I.R. 1998. Characterization of primary intracranial lymphoma by computed tomography: an analysis of 36 cases and a review of the literature with particular reference to calcification haemorrhage and cyst formation. Clin. Radiol. 53(6):428-434. <http://dx.doi.org/10.1016/S0009-9260(98)80271-7> <PMid:9651058>

Kuntzer T., Lobrinus J.A., Janzer R.C., Ghika J. & Bogousslavsky J. 2000. Clinicopathological and molecular biological studies in a patient with neurolymphomatosis. Muscle Nerve 23(10):1604-1609. <http://dx.doi.org/10.1002/1097-4598(200010)23:10<1604::AID-MUS21>3.0.CO;2-F> <PMid:11003800>

Laisse C.J.M., Oliveira E.C., Rolim V.M., Negreiros D.O., Driemeier D. & Pavarini S.P. 2017. Haemorrhagic myelomalacia in a cat with extradural T-cell lymphoma. Semina, Ciênc. Agrárias 38:327-334.

Lane S.B., Kornegay J.N., Duncan J.R. & Oliver Junior J.E. 1994. Feline spinal lymphosarcoma: a retrospective evaluation of 23 Cats. J. Vet. Intern. Med. 8(2):99-104. <http://dx.doi.org/10.1111/j.1939-1676.1994.tb03205.x> <PMid:8046683>

Levitt L.J., Dawson D.M., Rosenthal D.S. & Moloney W.C. 1980. CNS involvement in the non-hodgkin's lymphomas. Cancer 45(3):545-552. <http://dx.doi.org/10.1002/1097-0142(19800201)45:3<545::AID-CNCR2820450322>3.0.CO;2-6> <PMid:6986199>

Linzmann H., Brunnberg L., Gruber A.D. & Klopfleisch R. 2009. A neurotropic lymphoma in the brachial plexus of a cat. J. Feline Med. Surg. 11(6):522-524. <http://dx.doi.org/10.1016/j.jfms.2008.09.007> <PMid:19135398>

Louwerens M., London C.A., Pedersen N.C. & Lyons L.A. 2005. Feline lymphoma in the post-feline leukemia virus era. J. Vet. Intern. Med. 19(3):329-335. <PMid:15954547>

Lyons L.A. 2010. Feline genetics: clinical applications and genetic testing. Topics Companion Anim. Med. 25(4):203-212. <http://dx.doi.org/10.1053/j.tcam.2010.09.002> <PMid:21147473>

Maccauro G., Spinelli M.S., Mauro S., Perisano C., Graci C. & Rosa M.A. 2011. Physiopathology of spine metastasis. Int. J. Surg. Oncol. 2011:1-8. <http://dx.doi.org/10.1155/2011/107969>

Mandara M.T. 2003. Meningial blood vessel calcification in the brain of the cat. Acta Neuropathol. 105(3):240-244. <PMid:12557010>

Mandara M.T., Motta L. & Calò P. 2016. Distribution of feline lymphoma in the central and peripheral nervous systems. Vet. J. 216:109-116. <http://dx.doi.org/10.1016/j.tvjl.2016.07.013> <PMid:27687936>

Mandrioli L., Morini M., Biserni R., Gentilini F. & Turba M.E. 2012. A case of feline neurolymphomatosis: pathological and molecular investigations. J. Vet. Diagn. Invest. 24(6):1083-1086. <http://dx.doi.org/10.1177/1040638712460674> <PMid:22964430>

Mahoney M.C., Shipley R.T., Corcoran H.L. & Dickson B.A. 1990. CT demonstration of calcification in carcinoma of the lung. Am. J. Roentgenol. 154(2):255-258. <http://dx.doi.org/10.2214/ajr.154.2.2153329> <PMid:2153329>

Mamidi A., DeSimone J.A. & Pomerantz R.J. 2002. Central nervous system infections in individuals with HIV-1 infection. J. Neurovirol. 8(3):158-167. <http://dx.doi.org/10.1080/13550280290049723> <PMid:12053271>

Marioni-Henry K., Vite C.H., Newton A.L. & Van Winkle T.J. 2004. Prevalence of diseases of the spinal cord of cats. J. Vet. Intern. Med. 18(6):851-858. <http://dx.doi.org/10.1111/j.1939-1676.2004.tb02632.x> <PMid:15638269>

Marioni-Henry K., Van Winkle T.J., Smith S.H. & Vite C.H. 2008. Tumors affecting the spinal cord of cats: 85 cases (1980-2005). J. Am. Vet. Med. Assoc. 232(2):237-243. <http://dx.doi.org/10.2460/javma.232.2.237> <PMid:18275391>

Matmati K., Matmati N., Hannun Y.A., Rumboldt Z., Patel S., Lazarchick J., Stuart R. & Giglio P. 2010. Dural MALT lymphoma with disseminated disease. Hematol. Rep. 2(1):48-53. <http://dx.doi.org/10.4081/hr.2010.e10> <PMid:22184513>

Meichner K., Kruse D.B., Hirschberger J. & Hartmann K. 2012. Changes in prevalence of progressive feline leukaemia virus infection in cats with lymphoma in Germany. Vet. Rec. 171(14):348-348. <http://dx.doi.org/10.1136/vr.100813> <PMid:22915682>

Mellanby R.J., Jeffery N.D., Baines E.A., Woodger N. & Herrtage M.E. 2003. Magnetic resonance imaging in the diagnosis of lymphoma involving the brachial plexus in a cat. Vet. Radiol. 44(5):522-525. <http://dx.doi.org/10.1111/j.1740-8261.2003.tb00500.x> <PMid:14599162>

Morita T., Kondo H., Okamoto M., Park C.H., Sawashima Y. & Shimada A. 2009. Periventricular spread of primary central nervous system T-cell lymphoma in a cat. J. Comp. Pathol. 140(1):54-58. <http://dx.doi.org/10.1016/j.jcpa.2008.09.003> <PMid:19056092>

Nakamoto Y., Ozawa T., Uchida K., Omori K., Hase K. & Nakaichi M. 2009. Primary intra-axial B-cell lymphoma in a cat. J. Vet. Med. Sci. 71(2):207-210. <http://dx.doi.org/10.1292/jvms.71.207> <PMid:19262034>

Northington J.W. & Juliana M.M. 1978. Extradural lymphosarcoma in six cats. J. Small Anim. Pract. 19(7):409-416. <http://dx.doi.org/10.1111/j.1748-5827.1978.tb05515.x> <PMid:581208>

Reinacher M. 1989. Diseases associated with spontaneous feline leukemia virus (FeLV) infection in cats. Vet. Immunol. Immunopathol. 21(1):85-95. <http://dx.doi.org/10.1016/0165-2427(89)90132-3> <PMid:2549696>

Rubenstein J., Ferreri A.J.M. & Pittaluga S. 2008. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. Leuk. Lymphoma 49(Suppl. 1):43-51. <http://dx.doi.org/10.1080/10428190802311441> <PMid:18821432>

Rupp A., Ives E., Rudorf H. & Constantino-Casas F. 2014. Sciatic T-cell neurolymphomatosis in a dog. Vet. Rec. Case Rep. 2(1):1-6. <http://dx.doi.org/10.1136/vetreccr-2014-000050>

Sakurai M., Azuma K., Nagai A., Fujioka T., Sunden Y., Shimada A. & Morita T. 2016. Neurolymphomatosis in a cat. J. Vet. Med. Sci. 78(6):1063-1066. <http://dx.doi.org/10.1292/jvms.15-0553> <PMid:26960326>

Sato H., Fujino Y., Chino J., Takahashi M., Fukushima K., Goto-Koshino Y., Uchida K., Ohno K. & Tsujimoto H. 2014. Prognostic analyses on anatomical and morphological classification of feline lymphoma. J. Vet. Med. Sci. 76(6):807-811. <http://dx.doi.org/10.1292/jvms.13-0260> <PMid:24521793>

Schaffer P.A., Charles J.B., Tzipory L., Ficociello J.E., Marvel S.J., Barrera J., Spraker T.R. & Ehrhart E.J. 2012. Neurolymphomatosis in a dog with B-cell lymphoma. Vet. Pathol. 49(5):771-774. <http://dx.doi.org/10.1177/0300985811419531> <PMid:21900543>

Schmidt J.M., North S.M., Freeman K.P. & Ramiro-Ibañez F. 2010. Feline paediatric oncology: retrospective assessment of 233 tumours from cats up to one year (1993 to 2008). J. Small Anim. Pract. 51(6):306-311. <http://dx.doi.org/10.1111/j.1748-5827.2010.00915.x> <PMid:20492453>

Shelton G.H., Grant C.K., Cotter S.M., Gardner M.B., Hardy Junior W.D. & DiGiacomo R.F. 1990. Feline immunodeficiency virus and feline leukemia virus infections and their relationships to lymphoid malignancies in cats: a retrospective study (1968-1988). J. Acquir. Immune Defic. Syndr. 3(6):623-630. <PMid:2159993>

Shree R., Goyal M.K., Modi M., Gaspar B.L., Radotra B.D., Ahuja C.K., Mittal B.R. & Prakash G. 2016. The diagnostic dilemma of neurolymphomatosis. J. Clin. Neurol. 12(3):274-281. <http://dx.doi.org/10.3988/jcn.2016.12.3.274> <PMid:27449910>

Sisó S., Marco-Salazar P., Moore P.F., Sturges B.K., Vernau W., Wisner E.R., Bollen A.W., Dickinson P.J. & Higgins R.J. 2016. Canine nervous system lymphoma subtypes display characteristic neuroanatomical patterns. Vet. Pathol. 54(1):53-60. <http://dx.doi.org/10.1177/0300985816658101> <PMid:27511313>

Spodnick G.J., Berg J., Moore F.M. & Cotter S.M. 1992. Spinal lymphoma in cats: 21 cases (1976-1989). J. Am. Vet. Med. Assoc. 200(3):373-376. <PMid:1548176>

Terry A., Callanan J.J., Fulton R., Jarrett O. & Neil J.C. 1995. Molecular analysis of tumours from feline immunodeficiency virus (FIV)-infected cats: an indirect role for FIV? Int. J. Cancer 61(2):227-232. <http://dx.doi.org/10.1002/ijc.2910610215> <PMid:7705953>

Tomek A., Cizinauskas S., Doherr M., Gandini G. & Jaggy A. 2006. Intracranial neoplasia in 61 cats: localization, tumour types and seizure patterns. J. Feline Med. Surg. 8(4):243-253. <http://dx.doi.org/10.1016/j.jfms.2006.01.005> <PMid:16600653>

Troxel M.T., Vite C.H., Van Winkle T.J., Newton A.L., Tiches D., Dayrell-Hart B., Kapatkin A.S., Shofer F.S. & Steinberg S.A. 2003. Feline intracranial neoplasia: retrospective review of 160 cases (1985-2001). J. Vet. Intern. Med. 17(6):850-859. <PMid:14658723>

Vail D.M. & Macewen E.G. 2000. Spontaneously occurring tumors of companion animals as models for human cancer. Cancer Invest. 18(8):781-792. <http://dx.doi.org/10.3109/07357900009012210> <PMid:11107448>

Valli V.E., Kiupel M. & Bienzle D. 2016. Hematopoietic system, p.107-324. In: Maxie G.M. (Ed), Jubb, Kennedy and Palmer's Pathology of Domestic Animals. 6th ed. Elsevier, St Louis. <http://dx.doi.org/10.1016/B978-0-7020-5319-1.00013-X>.

Valli V.E., Bienzle D. & Meuten D.J. 2017. Tumors of the hemolymphatic system, p.203-321. In: Meuten D.J. (Ed), Tumors in Domestic Animals. 5th ed. John Wiley and Sons, Iowa.

Vernau K.M., Higgins R.J., Bollen A.W., Jimenez D.F., Anderson J.V., Koblik P.D. & Le Couteur R.A. 2001. Primary canine and feline nervous system tumors: intraoperative diagnosis using the smear technique. Vet. Pathol. 38(1):47-57. <http://dx.doi.org/10.1354/vp.38-1-47> <PMid:11199164>

Vezzali E., Parodi A.L., Marcato P.S. & Bettini G. 2010. Histopathologic classification of 171 cases of canine and feline non-Hodgkin lymphoma according to the WHO. Vet. Comp. Oncol. 8(1):38-49. <http://dx.doi.org/10.1111/j.1476-5829.2009.00201.x> <PMid:20230580>

Zaki F.A. & Hurvitz A.I. 1976. Spontaneous neoplasms of the central nervous system of the cat. J. Small Anim. Pract. 17(12):773-782. <http://dx.doi.org/10.1111/j.1748-5827.1976.tb06943.x> <PMid:1034854>