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Review

Distribution of feline lymphoma in the central and peripheral nervous systems

Maria Teresa Mandara [a,*], Luca Motta [b], Pietro Calò [c]

[a] Department of Veterinary Medicine, Neuropathology Laboratory, University of Perugia, Via S. Costanzo 4, Perugia 06126, Italy
[b] ChesterGates Veterinary Specialists, Gates Lane, Telford Court, Unit E/F, Chester CH1 6LT, United Kingdom
[c] Europa Veterinary Clinic, Via Kassel 18, Firenze 50126, Italy

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ABSTRACT

In cats, lymphoma (lymphosarcoma) is the most common neoplasm affecting the spinal cord and the second most common intracranial tumour. Although lymphoma commonly develops in the spinal cord as a part of a multicentric process, a primary form may occur. Lymphoma can exhibit a wide range of morphological patterns, including intraparenchymal brain mass, lymphomatosis cerebri, intravascular lymphoma, lymphomatous choroiditis and meningitis, extradural, intradural-extramedullary or intramedullary lymphoma in the spinal cord, or neurolymphomatosis in the peripheral nerves. Lymphoma may occur as a paraneoplastic disorder associated with peripheral neuropathies. Magnetic resonance imaging (MRI) and computed tomography (CT) are the techniques of choice for morphological assessment of nervous system lesions in vivo. However, biopsy should be performed to achieve a definitive diagnosis. Knowledge of the different morphological patterns expressed by lymphoma in the nervous system of cats allows veterinary clinicians to suspect lymphoma and to arrange appropriate diagnostic procedures, including immunophenotype and clonality studies, along with therapeutic protocols and prognostic evaluations.

Introduction

Lymphoma (lymphosarcoma) is the most frequent neoplasm in young cats, comprising 22% of tumours in cats less than 1 year of age (Schmidt et al., 2010) and accounting for 50–90% of all haematopoietic tumours in the cat (Hardy, 1981; Couto, 1989). Feline lymphoma is expressed in different anatomical forms, including alimentary/gastrointestinal, nasal, mediastinal, peripheral nodal, laryngeal/tracheal, renal, central nervous system (CNS), cutaneous and hepatic, the most frequent of which is alimentary lymphoma (Vail, 2013). Lymphoma is the most common neoplasm affecting the spinal cord and the second most common intracranial tumour in cats (Troxel et al., 2003; Marioni-Henry et al., 2008). The CNS was involved in 2.5% of the cases of feline lymphoma reported by Meincke et al. (1972), in 12.1% of the cases of feline lymphoma recorded by Lane et al. (1994), in 13% of extranodal forms of lymphoma in cats (Taylor et al., 2009), in 16–31% of intracranial tumours in cats (Troxel et al., 2003; Tomek et al., 2006) and in 39% of spinal cord tumours in cats (Marioni-Henry et al., 2008). Feline CNS lymphoma commonly is part of a multicentric process, frequently with renal or bone marrow involvement (Mooney et al., 1987; Marioni-Henry et al., 2004, 2008). This review focuses on the anatomical distribution of lymphoma in the feline nervous system, including clinical manifestations and diagnosis.

Anatomical patterns of lymphoma in central and peripheral nervous systems

Intracranial lymphoma

After meningioma, lymphoma is the second most common intracranial neoplasm in cats and 35% of cases are considered to be primary intracranial tumours (Troxel et al., 2003). Intracranial lymphoma may affect the brain parenchyma, the leptomeninges or the choroid plexuses, and can be broadly classified as intraparenchymal lymphoma (IPL) and extra-axial lymphoma (EAL).

Intraparenchymal lymphoma

IPL usually presents as a soft grey, poorly defined mass with occasional areas of yellow–white necrosis, although in some cases it forms multiple grey foci within the parenchyma of the brain (Troxel et al., 2003). In the absence of external gross lesions, IPL produces swelling of the affected brain region (Nakamoto et al., 2009). Histologically, IPL is characterised by dense sheets of neoplastic lymphocytes that tend to expand through perivascular spaces associated with concentric bands of reticulin (Fondevila et al., 1998). The cells have large, round to polygonal, densely heterochromatic nuclei, often with a prominent nucleolus, and small amounts of

* Corresponding author.
E-mail address: mandara@unipg.it (M.T. Mandara).

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eosinophilic cytoplasm. The mitotic index can range from low to high (one to seven mitoses per high power field and apoptosis is evident (Fondevila et al., 1998; Morrison and Fales-Williams, 2006). In the absence of clonality studies and based on immunohistochemistry, T and B cell immunophenotypes have been reported in feline IPL (Morrison and Fales-Williams, 2006; Nakamoto et al., 2009). The brain regions most commonly affected by IPL are the olfactory bulb, diencephalon and midbrain (Troxel et al., 2003; Palus et al., 2012).

In about half the cases in cats, lymphoma of the brain can develop as a diffuse parenchymal infiltration in the cerebrum and brainstem (Troxel et al., 2003) or as a subependymal infiltration (Morita et al., 2009). In these cases, it is justified to call the lesion lymphomatosis cerebri, which is reported in humans as an atypical variant of primary CNS lymphoma (Rollins et al., 2005). Lymphomatosis cerebri is characterised by widespread and diffuse infiltration of the deep cerebral white matter by individual lymphoid cells in the absence of a cohesive mass. Lymphomatosis cerebri needs to be differentiated from diffuse non-suppurative meningoencephalitis (Guil-Luna et al., 2013) and lymphomatoid granulomatosis involving the CNS (Katzenstein et al., 1979). The mitotic index is low (one per HPF) and the only one case submitted for immunophenotyping was a T cell lymphoma (Morita et al., 2009).

Angiotropic lymphoma (AL)

Angiotropic lymphoma, formerly known as intravascular lymphoma (IVL), is recognised in human beings (Louis et al., 2007) and domestic animals (Valli et al., 2002), and is characterised histopathologically by the predominantly endovascular–endoluminal presence of neoplastic lymphocytes. However, extravasation and infiltration of nervous tissue can occur in the late stages of the process, producing a mass lesion (Oomura et al., 2014). In human beings, the immunophenotype of AL is most often consistent with a B cell lymphoma, and only exceptionally with T cells or NK cells (Louis et al., 2007), or with lymphoid cells of dual T and B cell lineage (Tomasini and Berti, 2015). All AL immunophenotypes share a multiorgan involvement, with a tendency to involve the CNS (Fredericks et al., 1991). In cats, AL of T cell origin (Lapointe et al., 1997) and of mixed lineage antigen expression (Henrich et al., 2007) has been reported to involve the kidneys, lymph nodes, liver, choroid and spleen in addition to the CNS. The proliferation of neoplastic lymphocytes within the lumen of blood vessels and the secondary thrombosis generally results in an ischaemic lesion simulating brain infarct (Figs. 1a, b). The adventitia and perivascular spaces can be infiltrated by neoplastic cells (Lapointe et al., 1997). The prognosis is guarded (Fredericks et al., 1991; Lapointe et al., 1997; Henrich et al., 2007). To date, clonality studies have not been performed on AL.

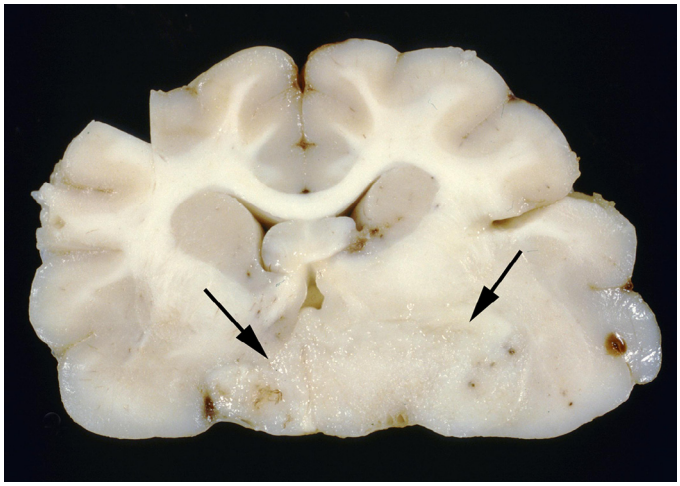

Fig. 2. Extra-axial brain lymphoma. The tumour develops as an extraparenchymal mass at the base of the brain (arrows), with well-defined margins and a soft, granular cut surface.

Extra-axial lymphoma

EAL accounts for 13–50% of intracranial lymphomas in cats (Troxel et al., 2003; Palus et al., 2012). It can develop as a well-defined mass on the leptomeninges, producing a space occupying lesion with effects on the adjacent brain. Macroscopically, EAL is soft and grey–white, with occasional areas of yellow necrosis or haemorrhage (Fig. 2). The cells have typical lymphoid morphology and moderate pleomorphism. The mitotic index can be high. Immunophenotyping and clonality have not been defined for this lymphoma.

Lymphomatous choroiditis (LC)

In the ventricles, EAL develops as 'lymphomatous choroiditis', with diffuse infiltration of the choroid plexuses by neoplastic lymphocytes (Figs. 3a, b). In human beings, this condition may be primary (Yakupoglu et al., 2012) or secondary (Kobayashi et al., 2009). Only one case of feline lymphomatous choroiditis has been reported, affecting the third ventricle of a 2-year-old male domestic short haired cat as a mass associated with subdural and leptomeningeal neoplastic infiltration (Zaki and Hurvitz, 1976). Infiltration of the choroid plexus by neoplastic lymphocytes may resemble feline infectious peritonitis (FIP) (Summers and Delahunta, 1995). The choroid plexuses are hyperaemic and reddened in both lymphomatous choroiditis and FIP. When the choroid plexuses of the fourth ventricle are affected, they can protrude through the lateral apertures,

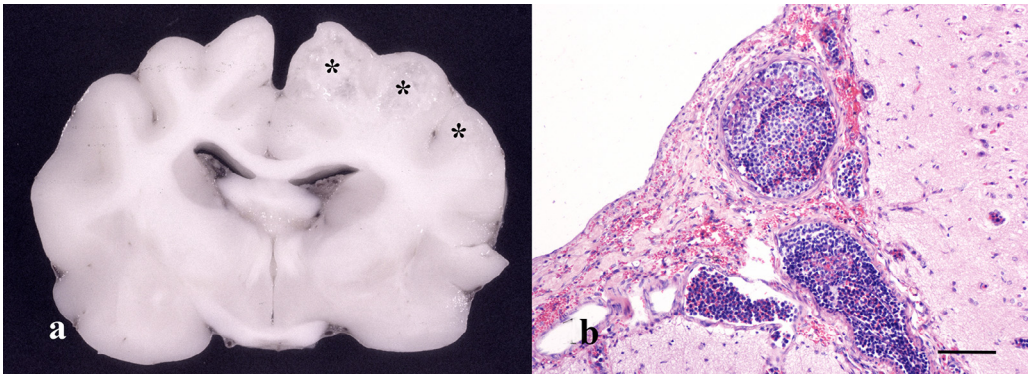

Fig. 1. Intravascular lymphoma. (a) Ischaemic lesion in the right parietal cortex (*) due to ischaemia of the right cerebral artery. (b) The lumina of meningeal veins are blocked by proliferation of neoplastic lymphoid cellular clusters. Scale bar = 150 μm. Haematoxylin and eosin.