Large granular lymphocyte lymphoma with leukemic phase and suspicion of leptomeningeal lymphomatosis in a cat – a case report

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Large granular lymphocyte Lymphom mit leukämischer Phase und Verdacht auf leptomeningealer Lymphomatose bei einer Katze – ein Fallbericht

In diesem Fallbericht wird ein felines Large Granular Lymphocyte (LGL) Lymphom, ein seltener, morphologischer Subtyp eines Lymphoms, bei einer zwölf Jahre alten, weiblich-kastrierten Kurzhaar-Hauskatze vorgestellt, mit Verdacht auf Lymphomatose der Leptomeningen aufgrund der magnetresonanztomographischen- und der Liquor-Befunden. Die Diagnose eines LGL-Lymphoms wurde durch Blutzytologie und Polymerase-Kettenreaktion für Antigenrezeptor-Rearrangements bestätigt.

Schlüsselwörter: Zentrales Nervensystem (ZNS), Liquor, Magnetresonanztomographie (MRI), Leukämie, lymphomatöse Meningitis.

Abstract

In this case report we present a feline large granular lymphocyte (LGL) lymphoma, a rare morphologically distinct subtype of lymphoma, in a twelve-year-old female spayed domestic short hair cat, with high suspicion of leptomeningeal lymphomatosis due to magnetic resonance imaging findings and results of cerebral spinal fluid analyses. Diagnosis of LGL lymphoma was confirmed by means of blood cytology and polymerase chain reaction for antigen receptor rearrangements.

Keywords: central nervous system (CNS), feline, cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), leukemia, lymphomatous meningitis, PARR.

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Introduction

Large granular lymphocyte (LGL) lymphoma is a morphologically distinct and relatively rare subtype lymphoma which arise from a minor population of peripheral blood lymphocytes characterized by intracytoplasmic azurophilic granules. Large granular lymphocytes have a T-cell or natural killer phenotype and share key immunophenotypic similarities with a subset of intestinal intraepithelial lymphocytes.[5,15]

In several studies, LGL lymphoma has been characterized as very aggressive and often chemotherapy-refractory lymphoma with a short mean survival time of few weeks after diagnosis.[2,5,8,15]LGL lymphoma occurs most often in the gastrointestinal tract, mainly in the small intestine, likely originating from the lymphocytes residing in the intestinal epithelium, and spreads very often in the mesenteric lymph nodes, in other abdominal organs, and in the peripheral blood/or bone marrow.[1,2,5,8,14,15,20] Differentiation between LGL lymphoma with leukemic phase from LGL leukemia with bone marrow involvement is seldom performed. This because prognosis described in LGL lymphoma with circulating neoplastic cells is very poor, independently of the origin of these cells.[5]

For LGL lymphoma cytologic evaluation has been reported to be superior to histopathologic examination, which often fail to reveal the characteristic granules of the LGL. Thus, cytology of both affected organs and blood is paramount when LGL lymphoma is suspected.[5,15]

In veterinary medicine, very few studies describe LGL lymphoma/leukemia with involvement of the central nervous system (CNS) in cats[2,11,20], with some more reports in dogs and one in an horse.[11] To the authors knowledge, to date, just two cases of feline leptomeningeal lymphomatosis secondary to LGL lymphoma have been described.[11,20]

In this case report we present the clinical, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings of a confirmed feline LGL lymphoma with high suspicion of leptomeningeal lymphomatosis.

Large granular lymphocyte lymphoma with leukemic phase and suspicion of leptomeningeal lymphomatosis in a cat – a case report

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Case report

A twelve-year-old, female spayed domestic short hair cat was referred to the veterinary diagnostic imaging centre Vetimage Diagnostik AG in Oberentfelden, Switzerland, for an MRI of the head due to acute obtundation and severe generalized ataxia.

Physical examination at the referring veterinarian revealed, in addition to the obtunded state and the ataxia, mild increased rectal temperature of 39,6°C and mild bilateral accumulation of cerumen in the ear canals. Neurologic examination additionally showed abnormal head movements, bilateral mydriasis, bilateral absent menace response, and bilateral absent direct and indirect pupillary light reflexes, indicative for visual loss. Mean systolic blood pressure was between 121 and 147 mmHg initially and, after acclimatization in the hospital, between 100 and 125 mmHg. Fundoscopic examination was reported as unremarkable. Dermatological examination of the ears revealed bilateral mild ear canal inflammation without signs of infection.

A week prior to the presentation in our facility the cat had a similar self-limiting acute onset of ataxia, mild head tilt to the right, and spontaneous horizontal nystagmus. The symptoms improved without any treatment before the acute onset of neurological deterioration at the day of referral.

At this timepoint, neuroanatomical lesion localization was set in the forebrain due to history, clinical, and neurological findings. Visual loss was suspected to be central and originate from a lesion in the region of the optic chiasm, or less likely of a pathology affecting both optic nerves or tracts. A bilateral retinal pathology was considered less likely due to the unremarkable visual ophthalmic evaluation, but could not be excluded. Differential diagnoses for this case included: recurrent forebrain vascular accidents with possible additional central vestibular lesions, inflammatory/infectious meningoencephalitis, neoplastic disease, and otitis media and interna (especially on the right side) with possible associated meningitis/meningoencephalitis.

An initial complete blood count (CBC) performed by the referring veterinarian (Idexx Interlink – ProCyte One) showed mild monocytosis (1,02×10^9/L, Ref: 0,05–0,67×10^9/L) and mild eosinopenia (0,08×10^9/L, Ref: 0,17–1,57×10^9/L). A blood smear was not evaluated. Blood chemistry (Idexx Interlink – Catalyst One) was within normal limits. Feline leukemia virus and feline immunodeficiency virus snap tests (Idexx Interlink – SNAPshot Dx) were negative.

An MRI of the head, including the cranial part of the cervical spine, was performed using a 1,5-Tesla machine (General Electric, Singa 1,5T, GE Medical Systems AG, Glattbrugg, Switzerland) with an 8-channel knee array coil (GE Medical Systems AG, Glattbrugg, Switzerland). MRI images included T2-weighted (W) fast spin echo (FSE) sequences in transverse, and sagittal planes, fluid-attenuated inversion recovery (FLAIR) sequences in transverse and dorsal plane, a T2*-W, T1-W FSE sequence, and diffusion-weighted images (DWI) in transverse, as well as a single-plane pre- and postcontrast T1-W sequences, and a 3D T1-W sequence after intravenous injection of contrast medium (0,2mL/kg gadoteric acid (Clariscan); GE Healthcare AG, Opfikon, Switzerland, 0,5 mmol/mL). The MRI images were reviewed by a board-certified veterinary radiologist.

MRI findings (Figure 1) included generalized moderate leptomeningeal contrast enhancement mostly accentuated in the region of the forebrain and skull base (Figure 1b and d), affecting also the region of the optic chiasm and the initial part of both optic nerves (Figure 1d); severe generalized bilateral contrast enhancement of the sclera, choroid, and retina, right more pronounced than left, without retinal detachment (Figure 1f); complete filling of the lateral compartment and almost complete filling of the medial compartment of the left tympanic bulla with heterogeneous T2- and FLAIR-hyperintense, T1-hypointense, non-contrast enhancing material, as well as mild generalized contrast enhancement of the middle ear epithelium without thickening of the bony part of the left tympanic bulla, and without abnormalities of the regional musculature; similar findings for the right tympanic bulla, but just with very mild filling of the medial compartment; bilateral unremarkable signal of the endo- and perilymph in T2-W sequences with complete suppression in the FLAIR and without contrast enhancement; mild generalized thickening and moderate generalized contrast enhancement of the external ear canals on both sides; and finally, generalized mild to moderate lymphadenomegaly with heterogenous contrast enhancement of the mandibular, medial and lateral retropharyngeal, as well as the parotid lymph nodes; the tonsils were not enlarged.

At this timepoint imaging differentials included: diffuse meningitis of unknown origin with additional bilateral uveitis and regional reactive lymphadenopathy, or leptomeningeal carcinomatosis/lymphomatosis with possible infiltration of the eyes and head lymph nodes. In addition, bilateral otitis externa was confirmed. The bilateral filling of the tympanic bullae was most likely secondary due to a bilateral dysfunction of the tensor veli palatini muscle, an otitis media was considered less likely.

Straight after the MRI examination, CSF was collected from the cerebellomedullary cistern. CSF was macroscopically colourless and clear. Specific gravity (1,006) and total protein (0 g/100mL) were within reference ranges, protein-dipstick and Pandy-test were negative. Leukocyte count was elevated with 310 cells/3µL (Reference: 0–5 cells/3µL). Differential cell count revealed 1 % of neutrophiles, 0 % of

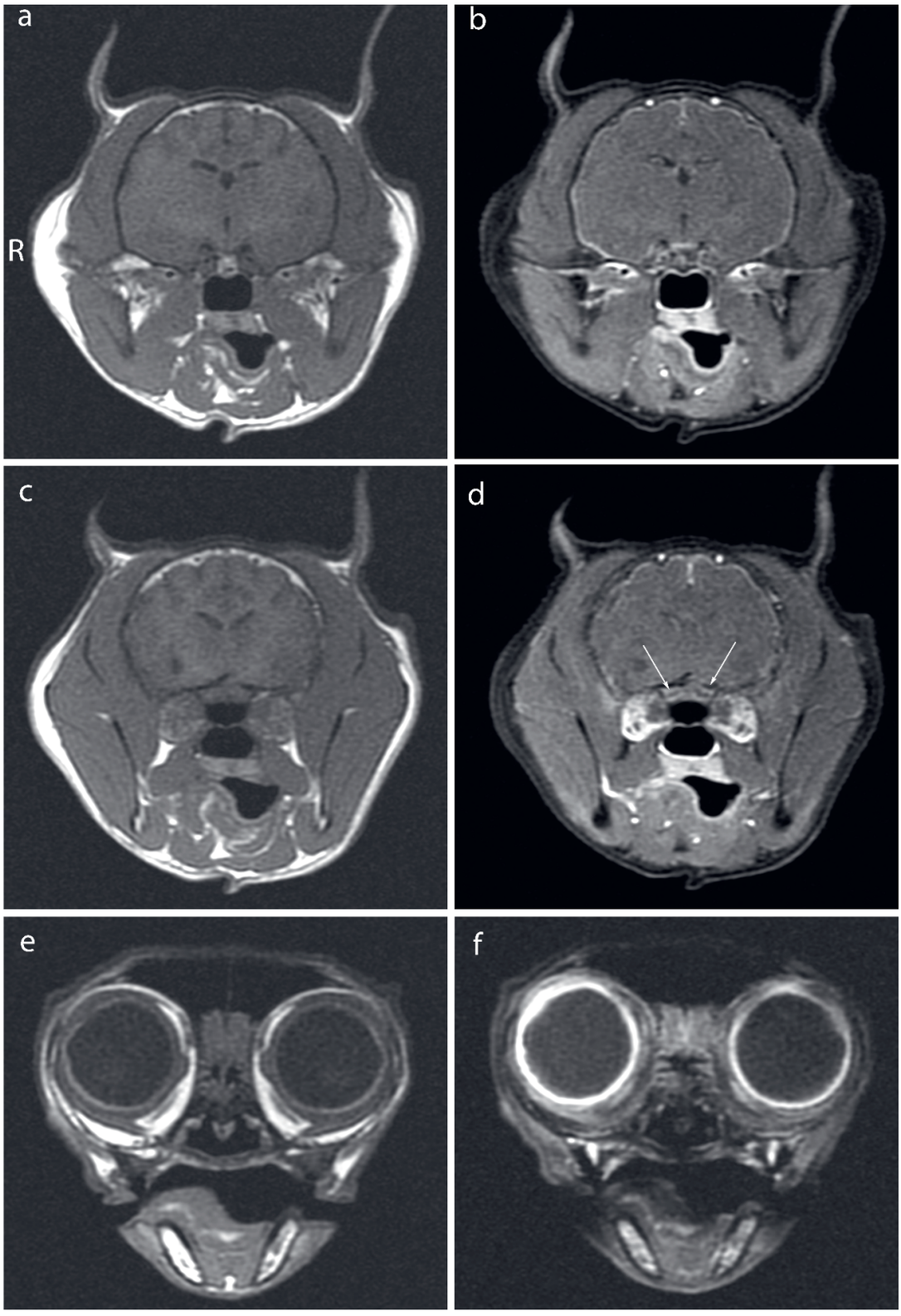

Figure 1: Transverse T1-weighted (W) fast spin echo (FSE) sequences before (a, c, e) and after intravenous contrast medium injection (b, d, f) at the level of the pituitary gland (a, b), in the region of the optic chiasm (c, d), and in the region of the eyes. Right is on the left of the images. Note the moderate generalized leptomeningeal contrast enhancement (b, d), the contrast enhancement in the region of the optic chiasm as well as at the initial part of both optic nerves (arrows in d), and the severe generalized bilateral contrast enhancement of the region of the sclera, choroid, and retina (f).

eosinophiles, 0 % of basophiles, 73 % of monocytes, 26 % of lymphocytes, and multiple atypical medium sized mononuclear cells with azurophilic cytoplasmatic granules consistent with LGL. CSF culture revealed no growth. Polymerase chain reaction (PCR) for *Toxoplasma gondii* and for feline coronavirus were negative.

Due to the presence of LGL in the CSF a CBC was repeated and a blood smear visually evaluated. CBC (Idexx Interlink – ProCyte Dx) revealed similar mild monocytosis (2,09×10^9/L, Ref: 0,05 – 0,67×10^9/L) and mild eosinopenia (0,01×10^9/L, Ref: 0,17 – 1,57×10^9/L) with a warning mark for abnormal non-well differentiable cells. Blood smear evaluation performed by a board-certified pathologist showed 9 % banded neutrophils, 50 % segmented neutrophils, 1 % eosinophils, 0 % basophiles, 2 % small mature lymphocytes with dense nucleus, 7 % monocytes, and 31 % atypical medium sized mononuclear cells, with pale blue cytoplasm and azurophilic cytoplasmatic granules, consistent with LGL. A PCR for antigen receptor rearrangement (PARR) with a DNA concentration of 18,7 ng/µL (minimum of 5 ng/µL) and a DNA-protein-ratio of 1,7 (1,8–2) confirmed a monoclonal T-cell receptor population with a diagnostic sensitivity of 97 %.

The final cytological diagnosis was LGL lymphoma with leukemic phase or LGL leukemia.

The owner opted for a palliative treatment with oral prednisone suspension (1–2 mg/kg, Prednisolon 10 mg/mL, Christoffel-Apotheke, Bern, Switzerland). Further diagnostic procedures were not performed. After discharge, the owner reported a mild and brief improvement of the clinical condition, before the cat suddenly died two weeks later. Necropsy was not performed.

Discussion

Lymphoma in general, is the second most common intracranial tumor after meningioma and the most common spinal neoplasia in cats.[4,10,19] Feline LGL lymphoma subtype is more rare and much less characterized in comparison to other lymphoid neoplasms[5,15], with only few reports of CNS involvement.[2,11,20] Intracranial lymphoma has been broadly classified as intraparenchymal/intra-axial lymphoma with or without lymphomatosis cerebri, extra-axial lymphoma, or angiotrophic lymphoma. Extra-axial lymphomas include also lymphomatous choroiditis affecting the choroid plexuses, and leptomeningeal lymphomatosis.[10] Leptomeningeal lymphomatosis, also known as lymphomatous meningitis or leukemic meningitis, is rare in cats with, to date, just four reported cases in this species.[4,11,19,20] Two of them were confirmed to be LGL lymphoma.[11,20] In a recent study, a wide range of MRI features of lymphomatous nervous system infiltration in cats was published.[4] In this study, one case of leptomeningeal lymphomatosis with additional infiltration of the optic nerves was diagnosed by histopathology. However, similar to a previous case[19], this cat had no visible MRI brain lesion. Most intracranial lymphomas in the study of Durand et al. were classified as both extra- and intra-axial, with more than two-thirds of the cases characterized by a focal lesion, with ill-defined borders, widespread extension, and abnormal meningeal enhancement, most commonly regional/perilesional.[4]

In our case, leptomeningeal enhancement was clearly visible (Figure 1a) and, together with the presence of LGL in the CSF, leptomeningeal lymphomatosis seems very likely. In humans meningeal enhancement in leptomeningeal malignancy, is more common with advanced leptomeningeal involvement, when the CSF cytology is likely to be positive.[6]

As the cat in our study was presented with a LGL leukemic phase or eventually a LGL leukemia, we speculate that leptomeningeal lymphomatosis was advanced and occurred via hematogenous spread with secondary neoplastic cells dissemination into the CSF, as described in the human literature.[6] Because necropsy was not performed, we cannot confirm the suspicion of leptomeningeal lymphomatosis and other differentials, such as inflammatory/infectious meningoencephalitis, cannot be completely excluded, but seem unlikely.

Diagnostic yield of lymphoma through CSF cytology is considered low, as neoplastic and reactive lymphocytes can be difficult to distinguish and low cellularity is frequently present.[3,4,10,11,13,21] However, especially in cases of advanced leptomeningeal lymphomatosis, as in our case, or of lymphomatous choroiditis, CSF can reveal marked lymphoid pleocytosis with abnormal lymphocytes.[3,10] In the present case, identification of abnormal cells in the CSF led to suspicion of LGL lymphoma, which was confirmed per blood cytology and PARR. Very mild blood contamination of our CSF sample cannot be completely excluded. However, this seems unlikely.

Visual loss in our case may be caused by central or retinal blindness, or a combination of both[12] due to suspicion of neoplastic invasion of the region of the optic chiasm and optic nerve, as well as of the sclera, choroid, and retina of both eyes. However, as neither electroretinography nor histopathology were performed, we cannot conclude on a definitive diagnosis.

Filling of the tympanic bullae was suspected to be secondary to a bilateral neurological dysfunction of the tensor veli palatini muscle in our case. This due to the lack of contrast enhancement of the material in the tympanic bullae and the absence of secondary changes such as regional reactive tissue or mass effect. However, a bilateral otitis media cannot be excluded, also considering that a bilateral otitis externa was present. Although bilateral tympanic bulla lym-

phoma with neoplastic infiltration of the leptomeninges and brain parenchyma was described in a post mortem examination in a cat[7], a bilateral neoplasia of the tympanic bullae in our case seems unlikely. Primary tympanic bulla neoplasia is very rare with few cases of carcinoma[18], and lymphoma[4,9,17,18] described, and in our case, there were no signs of propagation of a pathology from the bulla into the CNS. In two cats with bilateral squamous cell carcinoma of the external ear canals, leptomeningeal carcinomatosis was described at necropsy with suspicion of hematogenous spread of the neoplastic cells from the ear canals to the meninges.[16] It seems unlikely that in our case an ear canal carcinoma would be present in addition to the diagnosed LGL leukemic phase/leukemia.

Our case report has several limitations. The main one is the lack of histopathology and/or necropsy examination. Several of our conclusion are for this reason tentative. Another limitation is that further diagnostic procedures, such as abdominal ultrasound, were not performed after diagnosis of the LGL leukemic phase/leukemia. Thus, the possible origin of the LGL lymphoma cannot be defined.

In general, prognosis of LGL lymphoma, especially in cases with a leukemic phase or LGL leukemia, has been reported as poor.[2,5,8,15] However, some authors recently described a better prognosis with longer survival times after treatment with diverse chemotherapeutic protocols.[1,14]

In conclusion, we described the MRI features of leptomeningeal lymphomatosis in a cat with LGL lymphoma. Ante-mortem diagnosis was based on cytologically confirmed LGL in the CSF, peripheral blood, and PARR testing. With our publication we hope to raise awareness of this rare subtype of lymphoma, that should be considered as an imaging and clinical differential diagnosis.

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Large granular lymphocyte lymphome avec phase leucémique et suspicion de lymphomatose leptoméningée chez un chat – un rapport de cas

Dans ce rapport de cas, nous présentons un Large Granular Lymphocyte (LGL) lymphome, un sous-type rare de lymphome, chez une chatte domestique à poil court stérilisée de douze ans, avec une forte suspicion de lymphomatose leptoméningée en raison des résultats de l'imagerie par résonance magnétique et de l'analyse du liquide céphalo-rachidien. Le diagnostic de LGL-lymphome a été confirmé par une cytologie sanguine et une réaction en chaîne de la polymérase pour les réarrangements des récepteurs d'antigènes.

Mots clés: Système nerveux central (SNC), félin, liquide céphalorachidien (LCR), imagerie par résonance magnétique (IRM), leucémie, méningite lymphomateuse.

Large granular lymphocyte linfoma con fase leucemica e sospetto di linfomatosi leptomeningea in un gatto – un case report

In questo rapporto vi presentiamo un Large Granular Lymphocyte (LGL) linfoma, un raro sottotipo morfologicamente distinto di linfoma, in una gatta domestica femmina castrata di dodici anni a pelo corto, con un forte sospetto di linfomatosi leptomeningea supportata dei risultati della risonanza magnetica e delle analisi del liquido cerebrospinale. La diagnosi di LGL-linfoma è stata confermata mediante citologia del sangue e reazione a catena della polimerasi per i riarrangiamenti del recettore dell'antigene.

Parole chiave: Sistema nervoso centrale (SNC), felino, liquido cerebrospinale, risonanza magnetica, leucemia, meningite linfomatosa.

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