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CLINICAL CASE

Large granular leukemia with concurrent central nervous system and articular infiltration in a cat ☆

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KEYWORDS

Large granular lymphocyte, Leukemia, CNS, Articular infiltration, Cat.

Summary A 2-year-old female domestic shorthair cat was referred with a 2 month history of lethargy, weight loss, recurrent hyperthermia and polyarthropathy despite prednisolone. Upon physical examination, the cat showed apathy, hyperthermia, multiple appendicular joint pain and swelling. The CBC showed severe macrocytic normochromic non-regenerative anemia and thrombocytopenia. A population of immature large granular lymphocytes (LGL) was noted on blood smear. Abdominal ultrasonography revealed enlarged mesenteric lymph nodes (LNs), hyper echoic liver and splenomegaly. Cytology of fine needle aspirate of synovial fluid, spleen, liver, enlarged abdominal LNs and bone marrow supported a diagnosis of LGL leukemia with concurrent articular infiltration.

Abbreviations: CBC, Complete Blood Count; CNS, Central Nervous System; COP, Cyclophosphamide, Oncovin, Prednisolone; CSF, Cerebrospinal Fluid; FeLV, Feline Leukemia Virus; FIV, Feline Immunodeficiency Virus; FNA, Fine Needle Aspirates; FA, Felty's Syndrome; LGL, Large Granula Lymphocytes; LN, Lymph Node; NK, Natural Killer; PCR, Polymerase Chain Reaction; RA, Rheumatoid Factors; RBC, Red Blood Cells; SAA, Serum Amyloid A; WBC, White Blood Cells.

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A COP-based protocol was initiated with L-asparaginase (400 UI/kg intramuscularly) and prednisolone (1 mg/kg/day orally). However, the cat presented 1 week later with obtundation and paresis, indicating the involvement of the central nervous system (CNS). LGL were also observed on cerebrospinal fluid analysis. Histologic examination noted LGL in the spleen, liver and LNs. Immunohistochemistry (IHC) yielded negative results for both B- and T-cells thus suggesting NK-cells. The diagnosis was LGL leukemia with concurrent articular and CNS involvement. Articular infiltration with LGL is rarely reported in small animals, whereas CNS involvement was previously only suspected in a cat at necropsy.

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Introduction

Large Granular Lymphocyte (LGL) leukemia is an aggressive malignant hemopathy that carries poor prognosis in cats [1]. Although some reports are available on LGL lymphoma [2–4], there is little information on feline LGL leukemia. Major clinical signs are not specific and include lethargy, fever, anorexia and weight loss [1–4] whereas anemia, leukopenia or leukocytosis are common hematologic abnormalities encountered [5]. Neoplastic infiltration with LGL does not appear to be associated with positive testing for FeLV and FIV [1–5]. Neoplastic LGL can be found within bone marrow, lymph nodes (LNs), spleen, liver and many other organs [1]. Treatment involves chemotherapy but is often unrewarding [6,7]. Some feline LGL leukemia with concurrent articular involvement have been reported [1–4], as well as some necropsy description of CNS infiltration with LGL [8]. However, there is for now no reported description of feline LGL leukemia with simultaneous infiltration of both compartments. We report a case of LGL leukemia with presumptive concurrent articular and CNS infiltration with LGL in a cat. Some clinicopathological abnormalities were compared to those found in Humans' Felty's Syndrome.

Case Description

A 2-year-old spayed female domestic shorthair was referred to the Small Animal Teaching Hospital, for a 2 month history of lethargy, loss of appetite, weight loss with recurrent hyperthermia and multiple articular pain despite prednisolone administration.

The cat was initially presented to the referring veterinarian for anorexia, weakness and discomfort. The CBC, biochemistry and lateral spine radiography were unremarkable. An indirect fluorescent antibody test did not detect anti-feline coronavirus antibodies. Blood testing for feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibodies were negative. The cat was prescribed prednisolone for 3 weeks at 0.5 mg/kg q24h orally. Despite transient and partial improvement, clinical signs recurred after discontinuation of treatment.

Upon physical examination, the cat remained in lateral recumbency and showed generalized weakness. It

displayed hyperthermia with a rectal temperature of 40.4 °C (104.7 °F), right systolic heart murmur and signs of hypovolemia (pallor, tachycardia, unevaluable capillary refilling time and weak femoral pulses). Gait analysis revealed low head carriage, hunched back, bilateral pelvic limb plantigrade stance without lameness. Joint palpations revealed sudden, sharp and repeatable pain on mobilization of each of the elbows, stifles, carpi and the lumbosacral joint. Swelling around both stifles and elbows was also noted.

CBC findings (Table 1) included severe macrocytic, normochromic, nonregenerative anemia and moderate thrombocytopenia. On blood smear, white blood cell differential count was the following: Neutrophils: 13%, Small lymphocytes: 53%, Large Granular lymphocytes (LGL): 27%, Monocytes: 4%, Eosinophils: 3%. Abundant population of LGL measuring 30 to 35 µm in diameter with a high nucleocytoplasmic ratio was observed. The cytoplasm was basophilic and contained thin azurophilic granules. The nuclei were round, eccentric and contained a reticular chromatin with 1 or 2 inconspicuous central or paracentral nucleoli (Fig. 1). The biochemistry profile and urinalysis were unremarkable except that the serum amyloid A (SAA) was moderately increased (22.7 mg/L, reference interval 0–10). The serum

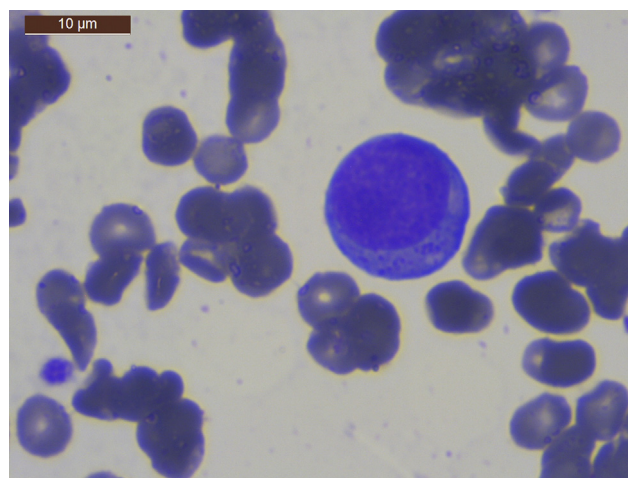


Figure 1. Blood smear showing one large granular lymphocyte. Magnification × 100.

Table 1 Results of the first (CBC₁) and second (CBC₂) Complete Blood Counts. (Sysmex XT 2000 iV, Kobe, Japan). In bold: abnormal value.

Parameter (unit)	CBC1 (day 0)	CBC2 (day 7)	Reference interval
RBC (10 ⁶ /μL)	2.01	1.52	5–10
Hct (%)	12.1	9.2	24–45
Hgb (g/dL)	3.8	2.8	8–15
MCV (μ ³)	60	60.5	39–55
MCH (pg)	18.9	18.4	13–17
MCHC (g/dL)	31.4	30.4	31–36
WBC (10 ³ /μL)	12.2	51.9	5.5–19.5
Granulocytes	1.57	1.38	1.4–9.6
Lymphocytes	10.5	50.3 ^a	1.2–10.4
Eosinophils	0.12	0.21	0.1–1.8
Basophils	0.0	0.0	0.0–0.1
Monocytes	0.0	0.0	0.0–0.8
Platelets (10 ³ /μL)	84 ^b	93 ^b	150–600
Reticulocytes (10 ³ /μL)	0.0	4.56	–

^a Among them 42300 LGLs/μL.

^b Thrombocytopenia confirmed upon cytologic examination of blood smear.

protein electrophoresis showed nonspecific findings (mild increase in α_2 – and β – globulins).

Plain radiography of joints showed mild periarticular soft tissue swelling around the elbows and stifles. Irregular periosteal new bone formation was observed on both distal femoral and humeral diaphysis and metaphysis, associated with an increased opacity of the medulla of these bones, and a coarse trabecular pattern. Meniscal mineralization was identified in both stifles. The carpal joints and thoracic radiographs were unremarkable. Infectious diseases were investigated by polymerase chain reactions (PCR) for feline retroviruses (FeLV, FIV) and *Mycoplasma* spp., performed on bone marrow aspirates and synovial fluid, respectively. An indirect immunofluorescence test to detect antinuclear antibody and direct Coomb's test on whole blood were done. All testing were negative. Abdominal ultrasonound revealed splenomegaly, enlarged and hyperechoic liver, and enlarged hepatic and medial iliac lymph nodes (LNs). Chest radiographs were unremarkable.

Fine needle aspirates (FNA) of synovial fluid (carpi, stifles and elbows), spleen, liver, enlarged LNs and bone marrow aspirates were submitted for cytologic examination. All synovial fluids were cellular (> 1600 cells/μL). The cytologic evaluations revealed similar findings in all joints evaluated: absence of granulocyte, large mononuclear cells (macrophages or synoviocytes), small lymphocytes and numerous (more than 70% of cells) LGL that presented similar features to those observed on a blood smear. Mitotic figures were observed occasionally (Fig. 2A). Cytologic preparations of the spleen and liver were both highly cellular, and those from LNs and bone marrow were moderately cellular. All submitted samples showed the same infiltration with LGL and erythrophagocytosis by lymphocytes was observed within splenic samples (Fig. 2B). Bone marrow was hyperplastic: each spicules observed were occupied by less than 10% of adipocytes and more than 90% of hematopoietic cells, which were nearly 100% composed with LGLs. These showed the same cytological features as those found within

blood compartment. Myeloid to erythroid ratio could not be estimated because of large infiltration with LGLs. In all, bone marrow was more severely infiltrated with LGL than the spleen, liver and LNs, making erythroid and myeloid precursors along with megakaryocytes scarce (Fig. 2C). These findings were consistent with a diagnosis of LGL leukemia with multiple articular involvements.

The cat received supportive care (IV fluid therapy, buprenorphine to address pain at 20 μg/kg q8h IV) and a chemotherapy COP-based protocol with L-asparaginase (400UI/kg given intramuscularly) and prednisolone (2 mg/kg q24h IV then orally). The cat was discharged on prednisolone and tramadol (2.5 mg/kg q8h orally) with a 1 week follow-up.

One week later, symptoms worsened with tetraparesis and obtundation. Neurologic examination revealed bilateral mydriatic pupils without pupillary light reflexes and menace responses, proprioceptive deficits of all limbs along with conserved medullary reflexes. These findings supported an affection of the central nervous system (CNS); in particular diffuse cortical, diencephalic or brainstem disease. The CBC revealed severe anemia, leukocytosis due to a marked lymphocytosis (50.300/μL) with LGL (42.300/μL), mild neutropenia (1380/μL) and moderate thrombocytopenia (93.000/μL). Both SAA and bilirubin were within the reference interval (Table 1). Because of rapid deterioration, the owners declined further investigations, including Magnetic Resonance Imaging and requested euthanasia. Cerebrospinal fluid (CSF) was collected immediately following euthanasia. The sample was translucent on visual inspection and demonstrated a moderate pleocytosis (14 cells/μL, reference interval: 0–5 cells/μL) and mild hemodilution (67 RBC/μL), whereas proteins were within normal values (0.1 g/L, reference interval: 0–0.3 g/L). On cytologic examination, the nucleated cells were mostly composed of large mononucleated cells (17%), small lymphocytes (76%) and non-degenerated neutrophils (2.5%), but LGL (4.5%) were noted (Fig. 2D). Necropsy samples

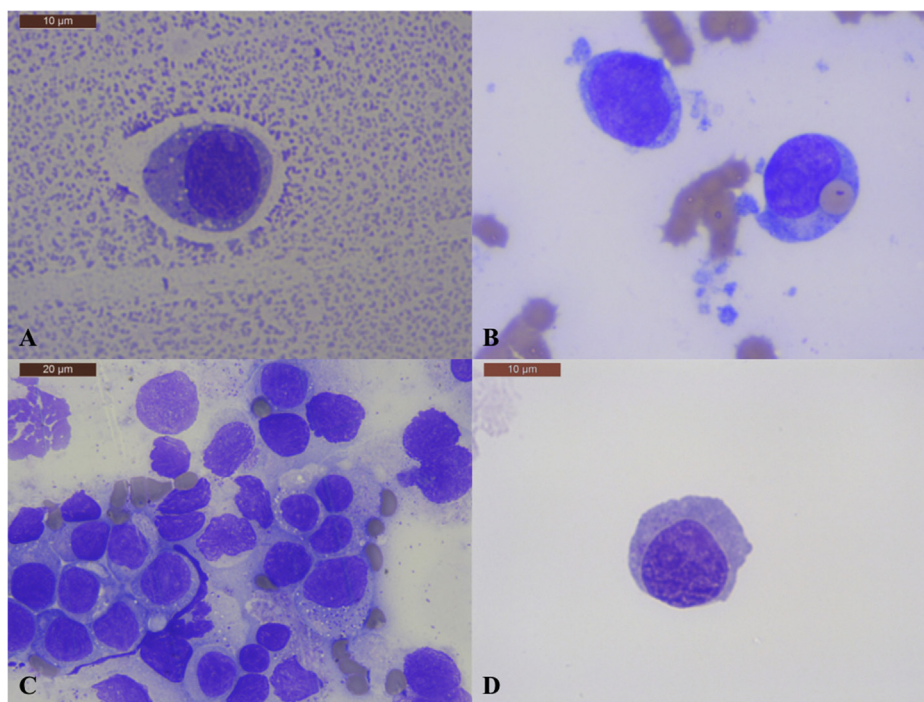


Figure 2. Photomicrographs of cytology. A: Synovial fluid (One LGL and faint mucinous background, $\times 100$). B: Spleen (LGL, note the presence erythrophagocytosis by lymphocyte [arrow], $\times 50$). C: Bone marrow (Large infiltration with LGL, $\times 50$). D: Cerebrospinal fluid (One LGL, $\times 100$).

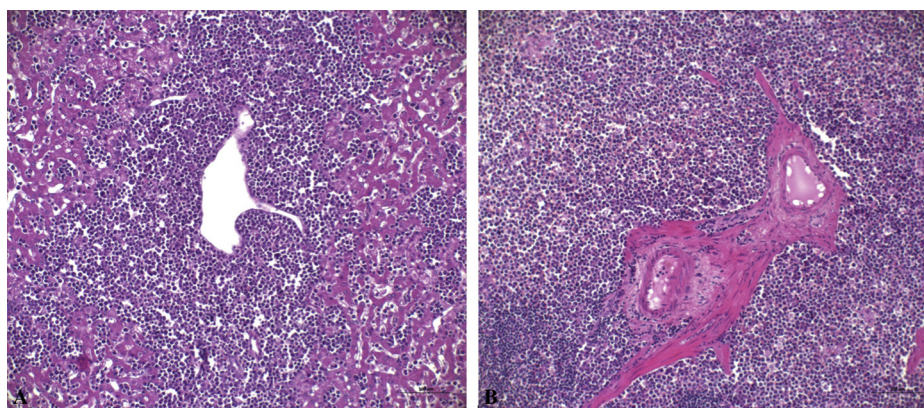


Figure 3. Photomicrographs of histology (massive infiltration with LGL). Hematoxylin and eosine stain, $\times 20$. A: Hepatic necropsy sample. B: Splenic necropsy sample.

from the spleen, liver, enlarged abdominal LNs and synovial membrane were fixed immediately in 10% neutral-buffered formalin for histological examination. The analysis substantiated previous findings and showed the presence of LGL within portal triads, between hepatocytes, within the spleen and abdominal LNs (Fig. 3A and B) but not on synovial membranes submitted for analyses (stifles). Final diagnosis was LGL leukemia with highly presumptive simultaneous articular and CNS involvement. Immunohistochemistry was performed on histological sections of the spleen and liver. Positive controls consisted in splenic and bone marrow samples separately positive for CD3 and Pax-5. The same samples without the application of the primary antibody were used as negative controls. Neoplastic lymphocytes were negative for CD3 and Pax-5. Clonality of lymphocyte

antigen receptor genes, performed on the same tissues as described by Madgen et al. (2013) using markers of T-cell (TCR gene primer), and B-cell differentiation (DP12/17 – DP13/17 genes primers), yielded multiple faint bands (polyclonal pattern). Thereby, NK-cells were highly suspected.

Discussion

This report is the first description of LGL leukemia with presumptive concurrent articular and CNS involvement in a cat.

In cats, articular involvement was documented with myeloproliferative disorders. Indeed, in a previous study [8],

4/31 cats with myeloproliferative disorders had concurrent immune polyarthritides. These cats presented with stiffness, discomfort, pyrexia or anorexia. All cats were shortly euthanized despite prednisolone administration. Necropsy findings included enlarged liver in 1 case and splenomegaly in all cases, as found in our report. Another article detailed an association between myeloproliferative syndrome and erosive polyarthritides in a cat [9]. Although the cat of the present report was diagnosed with a lymphoproliferative instead of a myeloproliferative disorder, we could hypothesize that articular pain was attributable to comparable disease processes, as found in Humans, where studies reported that 4% of people with lymphocytic leukemia had concurrent synovial fluid involvement [10]. This is far more frequent than articular involvement occurring with peripheral lymphoma [11,12]. Additionally, NK-cell leukemia was diagnosed in a patient with a 20-year history of rheumatoid arthritis (RA) that presented both neutropenia and splenomegaly, similar to our description [13]. Interestingly, in another study, a subset of leukemic patients reported former articular pain long before leukemia was diagnosed, raising the question about a potential role of initial arthritis as a triggering factor for subsequent neoplastic infiltration [14]. In the present report, this could be a possible explanation, for the presumed link between articular disorders and the development of LGL leukemia. However, articular involvement could be questionable in our report, as unrelated joint diseases (progressive polyarthropathy or periosteal proliferative polyarthritides) rather than LGL leukemia, might have contributed to non-specific extravasation of LGL into synovial fluid. Interestingly, synovial fluids from all joints sampled were infiltrated with LGLs on cytology but histology of both stifles was normal; this is either due to absence of synovial abnormalities within these joints or far less likely because of early improvement following recent chemotherapy. It remains unknown if synovial membranes of carpi, tarsus or elbows were actually infiltrated with LGLs, as these were not submitted for subsequent histological analysis. Hence, in the present case, we cannot confirm synovitis in any joint. Regardless of the actual explanation, the absence of histologic evidence of synovial abnormality makes leakage of LGL from vascular supply less probable. In this setting, we could speculate that synovial infiltration with LGL was a real feature of the disease that merits further considerations.

The cat in this report also showed neurological signs and cytological findings suggesting CSF infiltration with LGL. To date, the combination of LGL leukemia, CNS and articular infiltration has never been reported in cats [3]. In a small case series of 6 LGL leukemias in cats, focal infiltrates of epidural and subdural spaces of the spinal cord, white matter and spinal nerves were found in one case [1]. However, this cat did not display signs of articular involvement, and it remains unknown whether this cat displayed clinical evidence of neurologic disorders. Although it remains rare, CNS infiltration with neoplastic lymphocytes has been reported with feline lymphoma. Indeed, a large retrospective study reported CNS involvement in 20/602 cases; these cats were significantly younger [15]. A more recent paper describes an infiltration of choroid plexus, leptomeninges, cerebral and cerebellar white matter, as well as medulla oblongata by systemic aggressive LGL lymphoma

in a cat [4]. In dogs, acute lymphocytic leukemia is thought to be the most common leukemia to involve the CNS [16]. For instance, CNS involvement has also been documented in dogs with myeloproliferative disorders, such as acute myelomonocytic leukemias [17–19]. In the present case, neurologic signs could go along with systemic or other CNS disease (metabolic disorder, ischemia, infarction or hemorrhage) rather than infiltration with LGL. Indeed, the CSF cell count was only mildly increased and contained small amount of LGL, which makes the importance of primary LGL infiltration unknown. However, CSF analysis was conducted while facing neurologic signs suggesting CNS disorder. Unfortunately, no CNS imaging or histopathology was done. Therefore, it remains unknown whether the LGL found in the CSF reflected true meningeal infiltration or leakage due to CNS hemorrhage. However, PCR testing and CSF cytology made concurrent inflammatory/infectious or metabolic CNS diseases unlikely, trauma or food poisoning were not reported by the owners, and congenital disorders, degenerative processes or early vascular events (hemorrhage or thromboembolism/ischemia) were not likely while considering history (recent but gradual onset of neurological signs).

This cat actually presented a combination of clinicopathological abnormalities, including articular infiltration with LGL, neutropenia and splenomegaly. In Humans, Felty's Syndrome (FS) is a disorder characterized by the association of RA, neutropenia and splenomegaly that occurs more frequently in females [20–22]. In people, FS may precede LGL leukemia, and these can be a continuum of a unique disease process. Splenomegaly, hepatomegaly and lymphadenomegaly are reported in 100%, 45% and 27% of cases of FS, respectively [20]. Clinicopathological abnormalities associated with RA remain close to those of both FS and LGL leukemia in humans. Thus, the 3 diseases can be considered and studied together [20,22]. In our case report, there are some discrepancies making FS unlikely. First, the pathogenesis of neutropenia in FS might involve survival defects (peripheral destruction) of granulocytes rather than intrinsic bone marrow dysfunction (proliferation or maturation defects) or splenic sequestration and destruction [20]. In the present case, neutropenia and broadly cytopenias, were assumed to follow myelophthisis due to severe LGL infiltration or, less probably, erythrophagocytosis found in splenic specimen, although cytokine suppression of myeloid lineage by proliferating LGL could not be excluded. Second, our cat did not show articular inflammation or erosive lesions based on histology and radiographic findings. These observations make a diagnosis of FS or RA less likely. Unfortunately, rheumatoid factor (RF) antibodies were not assessed. Their accuracy is currently debated as not all individuals with RA have RF [23,24].

The specific cytological features of the neoplastic cells described above along with severe lymphocytosis, and bicytopenia (severe anemia and moderate thrombocytopenia) all support the diagnosis of leukemia. Neutropenia and severe lymphocytosis could make myeloid origin less likely than lymphoid origin. Concurrent bicytopenia might rather be related to bone marrow insufficiency following infiltration with LGLs. Flow cytometry would have ideally allowed us to better characterize the infiltrate. Unfortunately, frozen samples of cell culture medium were not saved for subsequent testing. Additional immunolabelling with

markers of myeloid cells like CD14 or myeloperoxidase would have been highly valuable to completely rule out myeloid origin. Unfortunately, this testing was not available on the paraffin-embedded histological blocks that were saved.

We documented a rapid progression of severe clinical signs despite the use of high doses of prednisolone and L-COP protocol. The efficacy of L-asparaginase has been proven through several studies, and it is part of multi-drug chemotherapy in both humans and small animals particularly with lymphoma and leukemia [6,7,25]. It is still unclear whether this medication contributed to the dramatic clinical deterioration observed, but it seems unlikely. Other chemotherapeutic medications might have been used, such as cytarabine or lomustine that are able to cross the blood-brain barrier and thus are of great interest in treating malignancies involving the CNS [7,26–28].

We described LGL leukemia with unique presumptive features of concurrent articular and CNS involvements. This is a rare occurrence in both humans and might represent the first report in small animals. The association of articular involvement, splenomegaly and neutropenia suggested Humans' FS, although other features refuted this assumption.

Ethics Statement

Not applicable.

Funding

None.

Authors' contribution

TB, DS, LC and FP were responsible for the management of the case. TB, DS, JLC and FP contributed to acquisition, analysis and interpretation of data. TB and JLC were responsible for the first draft of the manuscript. BR performed the cytological analyses of all samples. ES performed radiographs and ultrasounds, as well as fine needle aspirates. SB performed the histological analyses. LC, FP and BR critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Consent to publish

Not applicable.

Availability of data

The data presented within is available for everybody who wants further information. Please request the first author (Tarek Bouzouraa) for additional material (including slides, PARR results).

Disclosure of interest

The author declares that he has no competing interest.

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