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Primary angiocentric/angioinvasive T-cell lymphoma of the tympanic bulla in a feline leukaemia virus-positive cat

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Abstract

Case summary A 5-year-old neutered female feline leukaemia virus (FeLV)-positive domestic shorthair cat with a 5 month history of otitis media was referred for head tilt, stertor and dyspnoea. Computed tomography scan revealed soft tissue opacities inside the right tympanic bulla, with bone remodelling, and concurrent nasopharyngeal and intracranial invasion. Endoscopically guided bioptic samples were collected from the nasopharynx and middle ear. Histology revealed dense sheets of round, large, neoplastic cells, often surrounding or invading vascular walls. Neoplastic cells expressed CD3, FeLV p27 and gp70 antigens. A middle ear angiocentric/angioinvasive T-cell lymphoma was diagnosed. After improvement of clinical conditions following radiation therapy, the cat died unexpectedly. At necropsy, hepatic and splenic spread was detected.

Relevance and novel information Primary middle ear tumours are rare and their diagnosis is often delayed as clinical signs mimic more common otological conditions. Multiple bioptic specimens are pivotal for a definitive diagnosis. The young age of the cat, serology and immunohistochemistry revealed a possible transforming role of FeLV.

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Introduction

Lymphoma is considered the most common neoplasm in cat.[1] Before the introduction of feline leukaemia virus (FeLV) testing and vaccination, primary mediastinal and multicentric forms were reported,[2] while a shift towards intestinal and extranodal lymphoma subtypes is currently being observed.[1] While nasopharyngeal polyps are common and well documented in juvenile cats,[3,4] neoplasms arising from the middle ear are considered rare,[5] and only three cases of feline primary middle ear lymphoma have been reported.[6–8] This report details a cat affected by otitis media developing neurological signs caused by the presence of a middle ear and nasopharyngeal lymphoma.

Case description

A 5-year-old, spayed female, FeLV-positive, domestic shorthair cat with a previous 5 month history of otitis media not responsive to the pharmacological therapy with dexamethasone (0.5 mg/kg q24h) and amoxiclavulanic acid (25 mg/kg q12h), was referred to the University of Milan for persistent clinical signs, which included anysocoria, right head tilt, stertor and dyspnoea.

On physical examination, major clinical signs also included dysphagia, dysphonia and gagging. Myosis of the right pupil was present. A brownish, dense material oozed from the external ear canal. Body temperature,

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pulse and respiration were within normal limits. No clinically relevant alterations of some parameters were recorded by complete cell blood count (CBC) and serum biochemistry (Table 1). Serology with a commercially available enzyme-linked immunosorbent assay test (SNAP FeLV test; IDEXX) was repeated and FeLV was confirmed. A computerised tomography (CT) scan of the tympanic bullae and nasal cavities was performed. The tympanic bullae were characterised by complete bilateral loss of the normal air content. Focal soft tissue attenuation within the medial portion of the right external ear canal was recorded. A homogeneously hyperdense soft tissue opacity with enlargement of the ventromedial aspect of the right tympanic bulla, and multifocal bone lysis and remodelling of the tympanic osseous margins were documented, along with focal lysis of the right temporal bone and a local 1.5 mm opacity within the right piriform lobe (Figure 1a). Additionally, loss of the normal choanal air content and of the right ethmoid labyrinth, with deformity of the right nasopharyngeal wall and complete obliteration of the nasopharyngeal lumen caused by a 4.1 mm extension of soft tissue attenuation, were detected. There was a mechanical effect of the mass onto the hyoid apparatus and larynx, without detectable destructive/reactive processes. No anomalies were documented within the maxillary and frontal sinuses, and the sphenoid recesses. A subsequent total body CT scan was negative for thoracic and/or abdominal organ abnormalities.

An endoscopic evaluation of the nasopharynx with a flexible paediatric fibrobronchoscope evidenced total obstruction of the nasopharynx by a pink, smooth, trilobated soft tissue mass located in close contact with the opening of the Eustachian tube.

Otoscopical examination with a rigid scope (2.7 mm in diameter, 19.0 mm in length) evidenced a mass within the horizontal ear canal, emerging from the middle ear and protruding through a perforated tympanum (Figure 1b). Four perendoscopic bioptic specimens of 2–4 mm in diameter were obtained from the nasopharynx and the middle ear, and submitted for cytology and histopathology.

In accordance with diagnostic imaging and endoscopic evaluations, differential diagnoses for the rhinopharyngeal condition included nasopharyngeal polyp, lymphoplasmacytic rhinopharyngitis, neoplasia and cryptococcal granuloma, and a middle ear polyp or a middle ear tumour were considered for the middle ear condition.

Microscopic examination of tissue samples obtained from both anatomical sites revealed the presence of an unencapsulated, poorly demarcated, densely cellular neoplasm composed of sheets of round cells, surrounding and multifocally invading blood vessel walls (angiocentrism) (Figure 1c). The neoplastic cells were large, measuring 25–28 µm in diameter, with distinct cell borders, a moderate amount of pale eosinophilic and finely vacuolated cytoplasm, and large round nuclei (2.0–2.5 times the diameter of an erythrocyte) with occasional central round nucleoli (Figure 1d).

Table 1 Complete blood count (CBC) and serum biochemistry panel

Test	Result	Reference interval
CBC		
RBC ($\times 10^6$/µl)	6.15	5.0–11.20
Haemoglobin (g/dl)	10.0	10.6–15.6
Haematocrit (%)	34.4	31.7–48.0
MCV (fl)	55.9	36.7–55.0
MCH (pg)	16.3	12.3–17.3
MCHC (g/dl)	29.1	30.1–35.6
RDW (%)	18.3	16.7–22.9
Platelets ($\times 10^3$/µl)	323	175–500
WBC ($\times 10^3$/µl)	4.13	4.04–18.70
Automated differential ($\times 10^3$/µl)		
Segmented neutrophils	2.45	2.3–14.0
Band neutrophils	0.00	0.0–0.0
Lymphocytes	0.5	0.8–6.1
Monocytes	0.11	0.0–0.7
Eosinophils	0.00	0.0–1.5
Basophils	0.00	0.0–0.1
Chemistry – Canine/feline standard panel		
Glucose (mg/dl)	135	67–168
BUN (mg/dl)	45.8	15–60
Creatinine (mg/dl)	1.9	1.0–2.0
Sodium (mmol/l)	151.0	146–157
Potassium (mmol/l)	4.8	3.5–4.8
Chloride (mmol/l)	110	116–126
Total protein (g/dl)	6.08	6.0–8.6
ALT (U/l)	15	<80
AST (U/l)	27	<40
ALP (U/l)	45	<145
GGT (U/l)	6	5.19
Total bilirubin (mg/dl)	0.3	0.1–0.8

RBC = red blood cells; MCV = mean cell volume; MCH = mean cell haemoglobin; MCHC = mean cell haemoglobin concentration; RDW = red blood cell distribution width; WBC = white blood cells; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = γ-glutamyl transpeptidase

Mitotic figures ranged from 2 to 4 per high-power field.

Immunohistochemistry was performed with primary antibodies recognising CD3ε (1:20 dilution, rat monoclonal, clone CD3-12 Rat IgG1, human cross-reactive with feline; Serotec), CD20 (1:400 dilution, rabbit polyclonal, human cross-reactive with feline; NeoMarkers), FeLV p27 (1:100 dilution, mouse monoclonal, clone PF12J-10A; Custom Monoclonal International) and FeLV gp85/70 (1:200 dilution, mouse monoclonal, clone C11D8; Custom Monoclonal International).

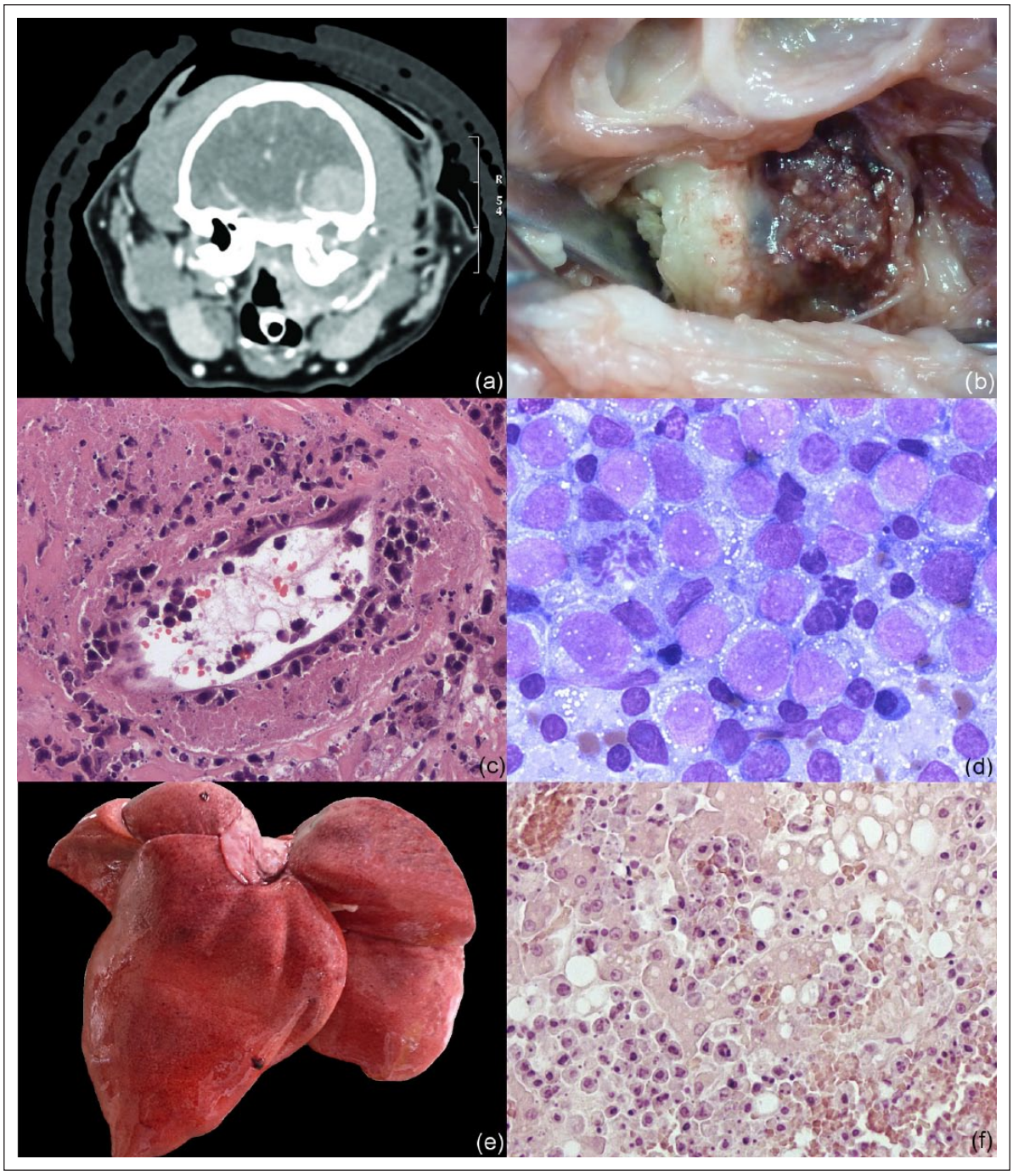

Figure 1 (a) Transverse computed tomography of the head. A soft tissue mass enlarges the medial aspect of the right tympanic bulla, with extension to the external ear canal. There is a concurrent strongly contrast-enhancing extension within the right piriform lobe and retropharyngeal space. (b) Right tympanic bulla. The ventromedial compartment is obliterated by a soft red proliferating mass. There is remodelling of the tympanic osseous margins with lysis and osteophyte formation. (c) Right tympanic bulla, diffuse large cell lymphoma and angiocentric/angioinvasive pattern. Neoplastic cells with irregularly distinct cell boundaries are disrupting and infiltrating a blood vessel. Haematoxylin and eosin (× 40). (d) Right tympanic bulla, diffuse large cell lymphoma and plasmacytoid morphology with brushing. Large, discrete lymphoid cells with scant blue vacuolated cytoplasms, round nuclei and 1–2 prominent nucleoli. Scattered small mature lymphocytes are visible. May Grünwald–Giemsa (× 40). (e) Severe diffuse hepatomegaly. (f) Histological section of the liver. The hepatic parenchyma is obscured and replaced by dense sheets of atypical lymphoid neoplastic cells with severe anisocytosis and nuclear pleomorphism

For all antibodies, antigen retrieval was achieved by heating slides in citrate buffer at pH 6.0 in a commercial pressure cooker Decloaker (Biocare Medical, Walnut Creek, CA, USA) for 10 mins.

Approximately 70% of neoplastic cells were intensely cytoplasmic CD3-positive while CD20 was diffusely negative. Cytoplasmic FeLV gp70 (capsidic glycoprotein) and cytoplasmic p27 (core protein) positivity were observed. A diffuse large cell angiocentric/angioinvasive T-cell lymphoma was diagnosed.

Routine clinical staging results, including chest and abdominal radiographs, serum biochemistry, CBC and abdominal ultrasound, were without clinically relevant alterations, and a stage I lymphoma was confirmed. Given the life-threatening dyspnoea, the cat was submitted for an extensive surgical debulking of the nasopharynx, followed by a radiation protocol of 10 fractions of 3.2 Gy each for the brain and six fractions of 6 Gy each for the middle ear. The cat was irradiated with a 6 MV Varian Linac with MLC (multileaf collimator). A single injection of L-asparaginase was administered after the first half of the radiation protocol. The cat was initially stable but died suddenly 7 days after the last radiation.

A full necropsy was granted by the owners.

At post-mortem examination the nasopharynx was free of disease. There was marked thickening of the right tympanic bone in association with multifocal osteolysis. The ventromedial compartment of the tympanic bulla was obliterated by the neoplastic tissue. A focal central nervous system (CNS) invasion was detected, with compression atrophy of the piriform lobe and adhesion of the neoplastic tissue to the base of the skull. Microscopically, the nasopharyngeal submucosa was variably infiltrated by neutrophils and small lymphocytes. However, following surgical debulking and radiation therapy, no neoplastic cells were evidenced at this time via multiple examined sections. Liver (Figure 1e) and spleen were diffusely pale red, enlarged, with massive infiltration of neoplastic cells with increased cellular pleomorphism (Figure 1f).

Scattered neoplastic cells were also microscopically evidenced in the right piriform lobe.

Death was ascribed to progression of the CNS extension (the cat developed convulsions approximately 1 week after radiation therapy) and multiorgan failure secondary to massive and widespread neoplastic invasion.

Discussion

To our knowledge, a primary tympanic lymphoma extending to the nasopharynx and CNS, followed by internal organ invasion seems not to have been previously reported. The diagnosis of a primary tumour of middle ear origin was derived from the anatomical distribution of the lesions, with concurrent tympanic rupture and the observation of morphologically similar neoplastic cells in both nasopharyngeal and middle ear compartments. In small animals, reports of neoplasia involving middle ear structures are rare.[9] Occasional reports of primary middle ear neoplasia in cats include squamous cell carcinoma (SCC) and rarely carcinomas, lymphomas and fibrosarcomas.[10]

The diagnosis of primary middle ear tumours is not considered straightforward. It is often delayed as clinical signs mimic some more common otological conditions such as inflammatory nasopharyngeal polyps, chronic otitis media, chronic proliferative otitis externa with middle ear involvement and, less frequently, cholesterol granulomas.[4,10,11]

Furthermore, the clinical signs of patients with middle ear tumours are often aspecific and most likely related to vestibular system abnormalities, concurrent otitis media/externa or nasopharyngeal secondary involvement.[12]

In this case, primary origin from the middle ear was confirmed by clinical presentation and anatomical distribution of lesions demonstrated by diagnostic imaging techniques. Indeed, the lesion observed in this cat was confined to the ventromedial compartment of the tympanic bulla, while the dorsolateral compartment of the bulla was devoid of neoplastic lesions. Owing to the characteristic anatomy of the feline middle ear, the ventromedial compartment of the tympanic bulla seems not to be commonly involved in feline auricular diseases.[13–15] This peculiar location, along with the previous clinical history and clinical signs of otitis media, and the onset of respiratory signs only secondarily, were highly suggestive of a primary ongoing process arising from the ventromedial compartment of the middle ear.

Little information regarding clinical signs, FeLV status and phenotype from previous reports of middle ear lymphoma could be retrieved.[6,8] A large T-cell lymphoma with metastasis to the regional lymph nodes has been described to involve the tympanic bulla of a cat.[7] Thus, comparison with other cases was not possible.

This cat had a long history of persistent inflammation, diagnosed by the referring veterinarian. A persistent inflammation has been associated with the subsequent development of a wide range of malignancies, and is accepted as a risk factor for the development of a variety of cancers, including lymphomas, in humans and cats.[16,17]

During chronic inflammation, lymphoid cell proliferation and gene rearrangements of T- and B-cell receptors increase with increasing production of normal but also autoreactive cells or cells with genetic mutations.[18] The relationship between lymphoma and FeLV has also long been studied. Overall, approximately 70% of cats with lymphoma have FeLV antigenaemia.[19] The rate of FeLV serological positivity has been correlated with the anatomical form of lymphoma.[5] However, owing to their rarity, no data are available for nasal or ear lymphomas. This cat was serologically positive for FeLV

and neoplastic cells expressed FeLV proteins. The expression of p27 indicates that viral infection has occurred, and FeLV gp70 expression denotes viral particle assembly confirming viral integration, replication and productive infection.[20] Thus, positivity to FeLV antigens suggested a possible role of FeLV in lymphoma development.

Lymphoid proliferation induced by persistent inflammation favours FeLV reactivation and replication within infected cells, increasing the probability of neoplastic transformation.

Angiocentricity has been described for a subset of subcutaneous lymphomas in cats,[21] where viable lymphoid neoplastic cells formed a rim around functional vessels, as reported in this case. The induction of the expression of specific homing and tethering molecules by vascular cells might have contributed to the angiocentric growth. Additionally, neoplastic lymphoid cells often invaded the vessel's wall, causing necrosis as part of general tissue invasion in our case.

Conclusions

Tumours of the auricular structures are important causes of otic morbidity and mortality, and should be considered in any case of non-responsive otitis. A high index of clinical suspicion along with proper imaging techniques, multiple deep, adequately sized biopsies and immunohistochemistry are usually required for a definitive diagnosis.

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

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