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Clinical features, MRI findings and outcome of a primary extranodal B-cell lymphoma affecting the tympanic bulla treated with chemotherapy alone

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Abstract

Case summary A 2-year-old neutered female feline leukaemia virus (FeLV)-negative domestic shorthair cat was referred with an acute onset of vestibular signs. A clinical examination identified evidence of otitis externa of the right ear and enlargement of the right mandibular lymph node. MRI revealed predominantly T2 and FLAIR hyperintense and contrast-enhancing lesions affecting the right external ear canal, tympanic bulla and nasopharyngeal regions with intracranial extension. Cytology and culture and sensitivity samples collected from the middle ear via myringotomy revealed a population of intermediate to large lymphocytes consistent with lymphoma and mixed *Staphylococcus chromogenes* and *Pasteurella* species infection. PCR for antigen receptor rearrangements on the ear cytology was consistent with a B-cell rearrangement. A primary extranodal B-cell lymphoma affecting the tympanic bulla and other sites with secondary septic otitis media and interna was diagnosed. After the improvement of clinical conditions after corticosteroid, antibiotic and chemotherapy treatment, the cat was alive 22 months after diagnosis without recurrence of clinical signs.

Relevance and novel information This is the first report of a primary extranodal B-cell lymphoma affecting the tympanic bulla with suspected involvement of the nasopharynx and cranial vault treated with chemotherapy alone in the veterinary literature. Although very rare, B-cell lymphoma should be included in the differentials for diseases affecting the inner and/or middle ear and extending intracranially in cats. Chemotherapy represents a non-invasive treatment modality with a survival of up to 22 months appearing possible.

Keywords: Chemotherapy; lymphoma; middle ear; otitis media; nasopharyngeal polyp; skull invasion

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Introduction

Lymphoma is reported to be the most common neoplastic disease in feline patients, with most patients presenting with the alimentary form.[1] Extranodal lymphoma at other sites is less commonly found but considered the second most common lymphoma in cats, with reported sites including the nasal cavity, nasopharynx, larynx and others.[2] Lymphoma with tympanic bulla involvement is rare, with only four previous reports in the veterinary literature.[3–6] In these reports, the outcome was poor, with most cases dying within a few days to a few weeks from diagnosis after receiving surgery alone or surgery and radiotherapy.[3–6] Here we describe the clinical and MRI

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features of a novel case of extranodal lymphoma involving the tympanic bulla, nasopharynx and extending intracranially in a cat treated with chemotherapy alone and surviving for more than 1 year.

Case description

A 2-year-old female spayed domestic shorthair cat was referred due to an acute onset 4-day progressive history of tetra-ataxia. Complete blood count performed at the referring veterinary clinic identified a marked neutrophilia, and biochemistry was unremarkable. General physical examination revealed enlargement of the right mandibular lymph nodes. On neurological examination, mentation was normal, and the cat was tetra-ataxic and hypermetric with drifting to the right and a wide-based thoracic limb stance and a bilateral spontaneous vertical nystagmus. Postural reactions were reduced in the right thoracic and pelvic limbs, and normal on the left. The neuroanatomic localisation was consistent with a multifocal lesion affecting the right central vestibular system and cerebellum.

Serology with a commercially available ELISA (SNAP FIV/FeLV test; IDEXX) was negative for both feline immunodeficiency virus and feline leukaemia virus.

MRI of the head was performed in dorsal recumbency in a 1.5 T unit using a head and neck coil (Ingenia CX; Philips Healthcare). Sagittal plane T2-weighted (T2W), transverse T2W, fluid attenuation inversion recovery (FLAIR), T1-weighted (T1W), spiral three-dimensional T1W turbo field echo (3D T1W), and post-gadolinium administration (ProHance; Bracco; 0.2 ml/kg IV) transverse T1W and 3D T1W sequences were obtained.

The horizontal portion of the right external ear canal was filled with a heterogeneous T2 hyperintense, T1 isointense when compared with grey matter, and markedly contrast-enhancing material, which extended into the tympanic bulla (Figure 1). This material partially obstructed the right side of the nasopharynx and extended through a dilated auditory tube (Figure 2). The medial compartment of the tympanic bulla contained a T2 hyperintense, T1 isointense and contrast-enhancing material coating the luminal surface of its wall and a T2, T1 hypointense and non-contrast-enhancing material centrally. The tympanic bulla was expanded, with an irregularly moderately thickened wall. The contrast-enhancing material within the medial compartment extended into the caudal cranial fossa through a focal large disruption of the petrous part of the temporal bone at the caudodorsal part of the tympanic bulla and through the jugular foramen and tympano-occipital fissure. This material was continuous with a large, extra-axial, T2 and FLAIR hyperintense, T1 isointense and markedly contrast-enhancing mass lesion along the right caudal cranial fossa. The right cerebellar hemisphere was markedly compressed. The cerebellar arbor vitae was markedly T2 hyperintense and the caudal portion of the cerebellum extended through the foramen magnum. The meninges adjacent to the mass were thickened and markedly contrast-enhancing (Figure 3). The endolymph in the right inner ear was not suppressed on FLAIR. The right vestibulocochlear nerve and the lateral aspect of the vestibule of the right inner ear were mildly contrast-enhancing (Figure 1).

Otoscopic evaluation revealed a bulging right tympanic membrane. Samples from the tympanic bulla were collected via myringotomy for cytology and bacterial culture. Cytology revealed a high number of lymphocytes, dominated by intermediate to large forms with a differential count of 43% intermediate forms, 41% large forms and 16% small forms. The large lymphocytes had a round, eccentric nucleus, with coarse clumped chromatin, a single, large, eccentric nucleolus and scant basophilic cytoplasm. Mitotic figures were unevenly distributed, in the range of 0–4 per 50 × high power field. These cytological findings were consistent with lymphoma. Lymphocytic inflammation was considered far less likely; however, it could not be completely ruled out. A septic, neutrophilic inflammation was also present. Bacterial culture grew a mixed population of highly susceptible *Staphylococcus chromogenes* and *Pasteurella* species sensitive to amoxicillin–clavulanic acid. PCR for antigen receptor rearrangements (PARR) from the cytology slide indicated monoclonal B-cell receptor rearrangement. Considering the MRI findings, cytology and PARR results, the cat was diagnosed with a primary extranodal B-cell lymphoma affecting the tympanic bulla, with suspected involvement of the nasopharynx and cranial vault with secondary septic otitis media and interna. Thoracic and abdominal staging was not performed due to financial restrictions. The cat was treated with 0.5 g/kg of mannitol (Mannitol; Fresenius Kabi) intravenously under general anaesthetic due to the suspected increase in intracranial pressure. On recovery, the patient was obtunded. Treatment with 0.2 mg/kg of dexamethasone (Rapidexon; Dechra) q24h and 20 mg/kg amoxicillin-potentiated clavulanic acid (co-amoxiclav; Sandoz) q8h IV was started. The patient gradually improved and was discharged 4 days later with 0.5 mg/kg of prednisolone (Prednisolone; Millpledge Veterinary) q24h, which was continued until the initiation of chemotherapy and 20 mg/kg amoxicillin-potentiated clavulanic acid (Clavaseptin; Vetoquinol) PO q8h for 8 weeks.[7] On discharge, the cat was tetra-ataxic with mild postural reaction deficits in the right thoracic and pelvic limbs. A modified cyclophosphamide, vincristine and prednisolone (COP) chemotherapy protocol, as described by Cotter et al[8] (Table 1), was started 2 weeks after discharge. Reassessment with a clinical and neurological examination and haematology was originally weekly, as per protocol, and then every 3 weeks up to 6 months.

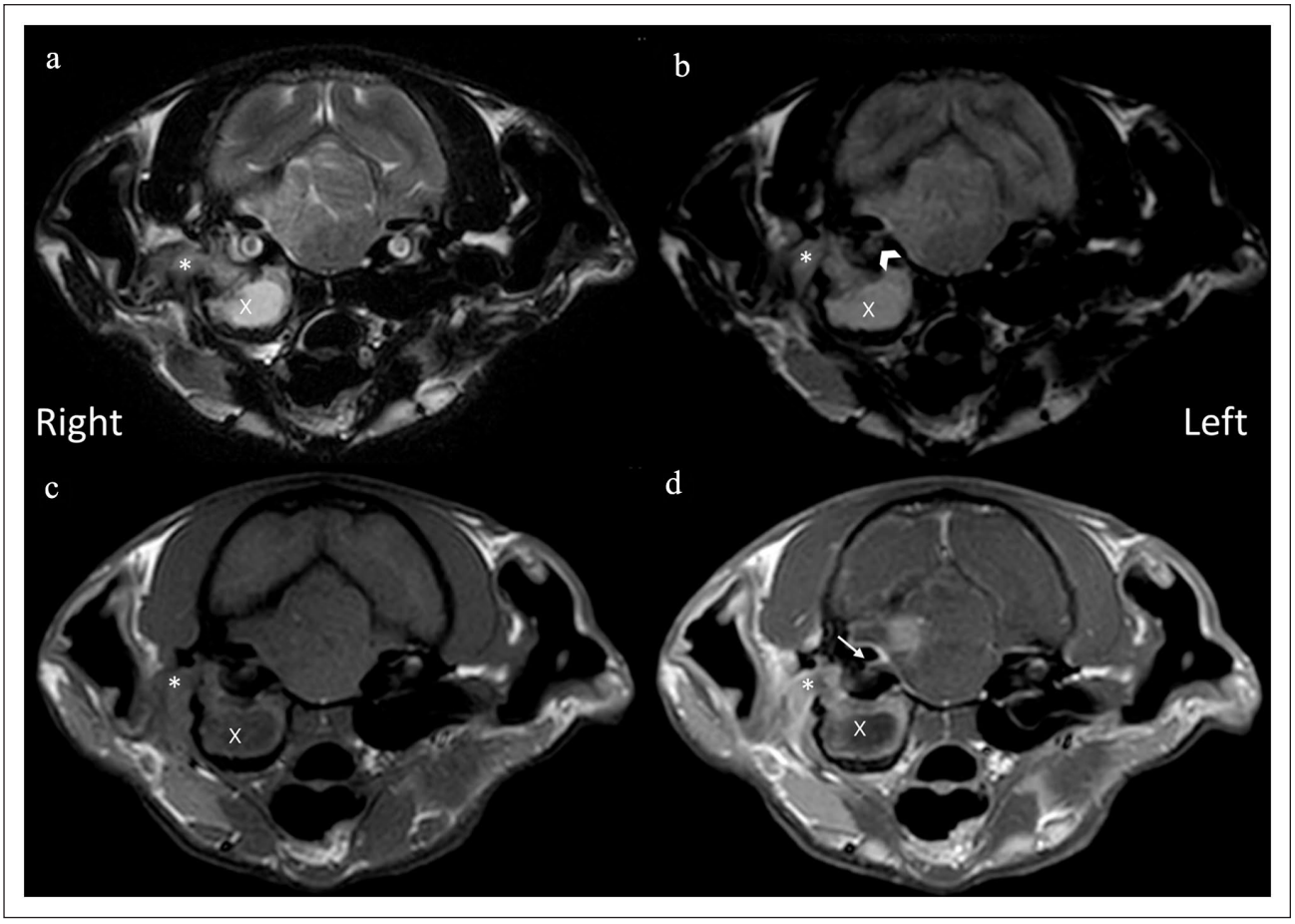

Figure 1 (a) Transverse T2-weighted, (b) fluid attenuation inversion recovery (FLAIR) and (c) T1-weighted pre- and (d) post-contrast images showing T2 hyperintense, T1 and FLAIR isointense and markedly contrast-enhancing material when compared with grey matter in the horizontal portion of the right external ear (asterisks). The tympanic bulla is expanded with a T2 hyperintense and T1 isointense and non–contrast-enhancing material centrally and a T2 and FLAIR hyperintense, T1 iso and contrast-enhancing material peripherally (crosses). Note the lack of signal suppression from the endolymph in the right inner ear (arrowhead) and the contrast enhancement of the right vestibulocochlear nerve (arrow)

After the first chemotherapy injection (vincristine), the cat's ataxia significantly improved. Neurological clinical signs completely resolved 8 weeks after the initiation of chemotherapy. The COP protocol was stopped at 6 months and a clinical reassessment was performed monthly for 3 months and every 3 months thereafter at the referral hospital. The clinical signs never recurred and the last re-assessment was performed at the referral hospital 1 year after the original presentation. A telephone follow-up with the owner and email follow-up with the referring veterinarian at the time of writing revealed the cat was still alive 22 months after the original presentation with no signs of relapse.

This case report was approved by the Animal Welfare and Ethics Review Body of the University of Bristol, reference VIN/23/030.

Discussion

Lymphoma affecting the feline tympanic bulla appears to be rare/under-reported, with only four previously reported cases.[3–6] Immunophenotyping revealed T-cell lymphoma in two cases,[4,5] null-cell lymphoma in another[6] and was not specified in one case.[3] In our case, immunophenotype was consistent with B-cell lymphoma in accordance with previous cases of nasal and nasopharyngeal lymphoma.[9–12] Given the diagnosis of B-cell lymphoma in this cat, it is suspected that the malignant lymphoid population arose from mucosa-associated lymphoid tissue (MALT) of the middle ear, MALT being of a B-cell immunophenotype[13] as has also been described in the middle ears of paediatric patients in human medicine.[14] To our knowledge, this is the first report describing a case of feline primary extranodal B-cell lymphoma

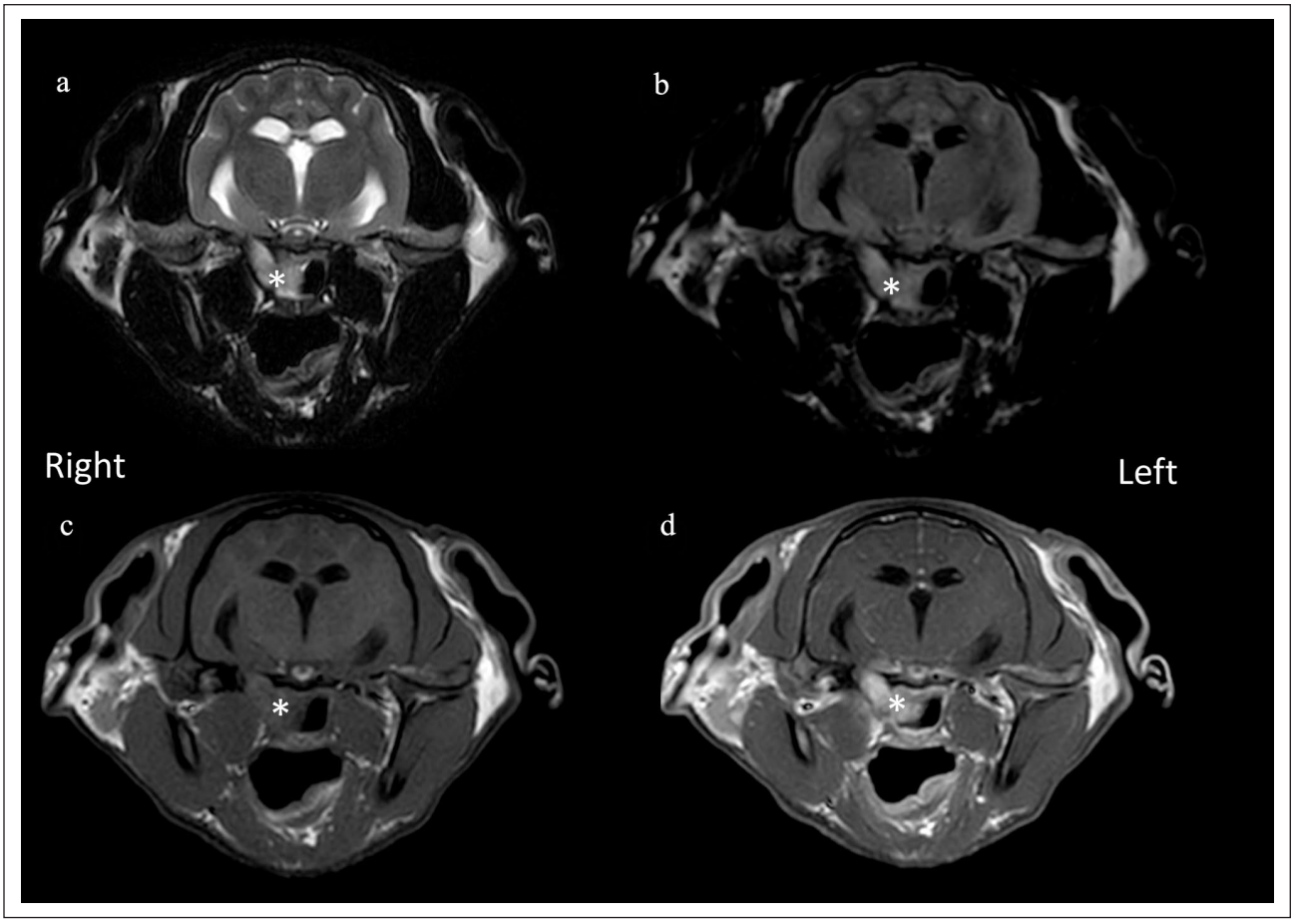

Figure 2 (a) Transverse T2-weighted (T2W), (b) fluid attenuation inversion recovery, (c) T1-weighted (T1W) pre- and (d) post-contrast images showing partial obstruction of the right side of the nasopharynx with a T2 and FLAIR hyperintense, T1 isointense and contrast-enhancing material extending into a markedly dilated right auditory tube (asterisks)

affecting the tympanic bulla with suspected involvement of the nasopharynx and cranial vault treated with chemotherapy alone and surviving more than a few weeks.

In previously reported cases, survival was poor, with all patients dying after general anaesthetic or surgery due to deterioration of clinical signs. In 3/4 cases reported in the literature, ventral bulla osteotomy and surgical debulking was performed.[3–5] In a large case series describing 282 cats treated by ventral bulla osteotomy for a variety of diseases, 68.2% were associated with Horner's syndrome, 30.1% with head tilt, 13.5% with facial nerve paralysis and 6.2% with local disease recurrence.[15] Although the severity of the cats' previously reported clinical signs and/or systemic involvement, as well as possibly more aggressive lymphoma immunophenotypes (T-cell, null-cell), could be responsible for the poor outcomes reported in previous studies, it is reasonable to hypothesise that the deterioration observed could also be secondary to postoperative complications. In our case, the outcome after chemotherapy was extremely positive, surviving 22 months, and in accordance with survival of nasal and nasopharyngeal lymphoma that are normally B-cell in origin.[9–12,16–18] In addition, the good outcome might be due to the complete response to the chemotherapy protocol used and the response to treatment is considered a good prognostic indicator in cats.[10] Our cat was also diagnosed with septic otitis media so the possibility of a false-positive report of PARR was considered. False-positive PARR results are described in non-neoplastic monoclonal lymphoid expansions (ie, benign clonal lymphoid proliferations) and non-lymphoid neoplasms.[19] Benign clonal lymphoid expansions are reported in feline inflammatory bowel disease (IBD) and *Erlichia* species infection.[20,21] Therefore, a marked suppurative process of the tympanic bulla could have caused a benign clonal lymphoid proliferation, as reported in cases of feline IBD. However, this has never been described in the ear. In addition, the specificity of clonality testing in B-cell lymphoma in the literature is reported to be as high as 98%.[22] Therefore, the cytology results coupled with the good response to chemotherapy

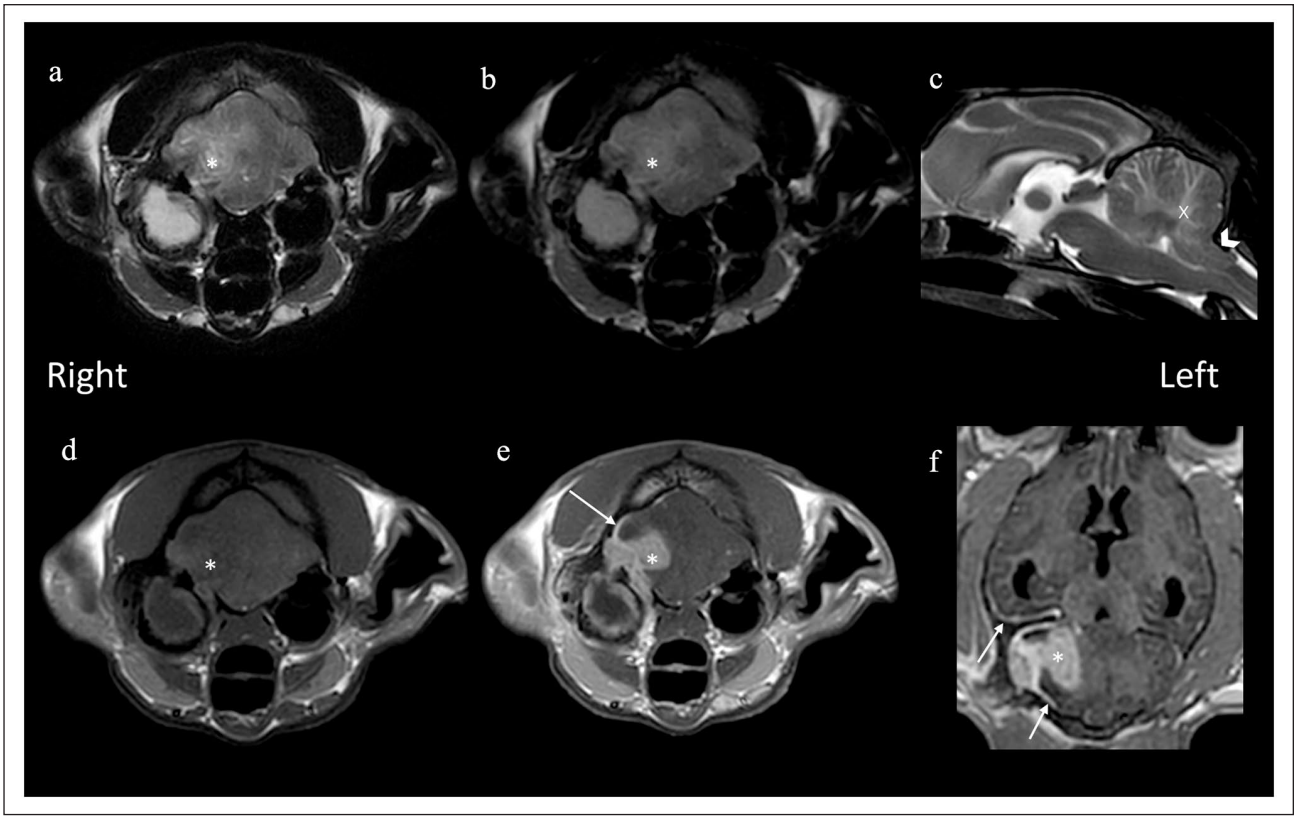

Figure 3 (a) Transverse T2-weighted, (b) fluid attenuation inversion recovery (FLAIR), (c) sagittal T2-weighted (T2W), (d) transverse T1-weighted (T1W) pre-, (e) post- and (f) dorsal post-contrast images showing a large T2 and FLAIR hyperintense, T1 isointense and markedly contrast-enhancing mass lesion in the right side of the caudal fossa, causing marked compression of the right cerebellar hemisphere (asterisks). Note the thickening and marked contrast enhancement of the meninges adjacent to the mass, around the right cerebellar hemisphere and occipital lobe (arrows). The arbor vitae of the cerebellum is markedly T2 hyperintense (cross) and the caudal portion of the cerebellum extends through the foramen magnum (arrowhead)

Table 1 Modified COP protocol

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Vincristine (0.7 mg/m^2 IV)	*	*	*	*	*	*	*			*			*
Cyclophosphamide (250 mg/m^2 IV or PO)	*			*			*			*			*
Prednisolone (reducing dose)	2 mg/kg PO q24h	1 mg/kg PO q24h	1 mg/kg PO q48h	1 mg/kg PO q48h	Taper and stop								

*Week the drugs are given.
COP = cyclophosphamide, vincristine and prednisolone

were highly supportive of lymphoma. The MRI findings were also suggestive of an infiltrative process, with characteristics from both inflammatory and neoplastic disease. The T2 hyperintensity, T1 hypo- to isointensity and contrast enhancement observed are typically seen in inflammatory polyps.[23] However, invasion of the cranial vault is not expected with a polyp without associated otitis media/interna. The intracranial extension and presence of nasopharyngeal changes are consistent with neoplasia such as lymphoma.[24] However, the lesion described in this report was FLAIR hyperintense. This is in contrast with a previous study[25] including one case of lymphoma affecting the middle ear and brain in which the lesion was FLAIR isointense. In this case, the MRI features did not suffice to differentiate between both disease processes; however, cytology and PARR testing revealed a clonal B lymphocyte population.

Unfortunately, complete staging and right mandibular lymph node sampling were not performed in this case due to the client's financial restrictions. These could have

led to the upstage of this disease with the identification of involvement of other organs. Clinical examination, haematology and biochemical analysis were, however, not supportive of multiorgan involvement. Furthermore, feline extranodal nasal and nasopharyngeal lymphoma is commonly presented as stage I (localised disease).[9,10,18,26] Restaging with either MRI or CT was also not performed, for the same reason of the client's financial limitations. Restaging might have been helpful to evaluate the clinical response and early recurrence.

Conclusions

Our findings further support the inclusion of lymphoma in the differentials for diseases affecting the middle and/or inner ear and extending intracranially in cats. Although lymphoma of the middle ear is rare and historically associated with a poor prognosis, a survival time of up to 22 months appears possible with chemotherapy. Chemotherapy should therefore be considered in the treatment of these cases.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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