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TITLE OF CASE ***Do not include "a case report"***
Ependymoma arising from the third ventricle mimicking optic neuritis in a dog
SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***
Neurological examination of a 4.5 year old female neutered Labrador retriever was consistent with a lesion in the subcortical visual pathway (mainly affecting the left retina or optic nerve, and less likely optic chiasm or right optic tract). Ophthalmic examination was unremarkable.

Magnetic resonance imaging (MRI) revealed enlargement of the left optic nerve and optic chiasm. A presumptive diagnosis of immune-mediated optic neuritis was made and immunosuppressive therapy was commenced. The dog represented 14 days later due to progressive deterioration and generalized seizure activity, and was euthanized. Post mortem examination revealed an anaplastic ependymoma extending from the rostral thalamus along the left optic nerve. Ependymoma can therefore mimic an optic neuropathy, such as immune mediated optic neuritis, and should be considered as a differential diagnosis.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Obtaining a definitive diagnosis of optic nerve pathology is challenging given the limited access to the optic nerves and the morbidity associated with biopsy. Advanced imaging provides a vital tool to study structural changes in the optic nerve and so guide clinical decision making. The following case report describes the clinical findings and outcome of an adult Labrador retriever that presented with neurological deficits consistent with a lesion in the subcortical visual pathway (mainly affecting the left retina or optic nerve, and less likely the optic chiasm or right optic tract). MRI findings lead to a provisional diagnosis of left optic neuritis, however progressive clinical deterioration resulted in euthanasia, following which a definitive diagnosis of anaplastic ependymoma was reached via histopathology. To our knowledge, this is the first report of an ependymoma affecting the optic nerve and resulting in a presenting complaint of unilateral blindness.

CASE PRESENTATION ***Presenting features, clinical and environmental history***

A 4.5 year old female neutered Labrador retriever presented for further investigation of a 10-day history of lethargy and possible mild left facial swelling. Improvement of the lethargy was noted after initiation of a course of prednisolone (0.5mg/kg SID), with resolution of the reported mild facial swelling. However, 2 days prior to referral the dog acutely deterioration, with evidence of reduced vision and an anxious demeanour.

On presentation, general physical examination was unremarkable. Neurological and ophthalmic examination revealed mild obtundation with an absent menace response and absent dazzle reflex in the left eye. Pupils were moderately dilated and symmetrical in size in room light, but assessment of the pupillary light reflex (PLR) revealed that shining a bright light in the left eye resulted in constriction of neither pupil, while shining a bright light in the right eye resulted in constriction of both pupils. No other abnormalities (including indirect ophthalmoscopic fundic examination) were noted. These findings were consistent with a lesion in the subcortical visual pathway. As no visible retinal pathology was detected on fundic examination, and focal unilateral optic chiasm or optic tract lesions causing no other neurological deficits are unlikely, an optic nerve lesion was considered most likely. The mild obtundation was suspected to be a result of the anxious demeanour of the dog exacerbated by sudden vision loss, but a central cause could not be excluded.

INVESTIGATIONS ***If relevant***

Haematology was unremarkable, and serum biochemistry revealed a mild elevation of alkaline phosphatase (345 U/L, Reference interval: 19-285) and alanine transferase (240 U/L, RI: 13-88) activity, consistent with recent prednisolone therapy. Serology for *Toxoplasma gondii* and *Neospora caninum* antibodies was negative.

Given the normal fundic examination alongside the unilateral menace response and PLR deficits, electroretinography was felt to have a very low diagnostic yield and it was elected to proceed with advanced imaging of the subcortical visual pathway. The dog was anaesthetised and magnetic resonance imaging (MRI) of the head was performed (Intera 1.5T, Philips Medical Systems, The Netherlands). MRI examination included T2-weighted (T2W) (repetition time, [TR] [ms], echo time [TE], [ms] 4212-6873/110) sagittal, dorsal and transverse images, and T2W fluid attenuated inversion recovery (FLAIR) (TR/TE, 6000/120, inversion time [TI] [ms] 2000) transverse images. Sagittal and transverse T1-weighted (T1W) (TR/TE, 450/15) images were acquired before and after intravenous administration of gadolinium contrast (0.1mmol/kg, gadobutrol, Gadovist, Bayer, UK). Slice thickness was 3.5 mm with an interslice gap of 0.9mm in all planes. The optic chiasm and left optic nerve were markedly thickened (left optic nerve diameter at the level of the optic canal was 7.5mm) and hyperintense on T2W images compared with normal grey matter, isointense on T1W images, extending from the orbit to the cranioventral aspect of the third ventricle, with strong homogenous contrast enhancement (Figure 1). There was enlargement of the left optic canal and slight bulging of the left optic disc. Where the

enlarged optic chiasm impinged on the rostral aspect of the thalamus, there was evidence of mild midline shift. The right optic nerve was unaffected (diameter at the level of the optic canal was 2mm). Analysis of cerebrospinal fluid collected from the cerebellomedullary cistern was non-diagnostic due to blood contamination.

DIFFERENTIAL DIAGNOSIS *If relevant*

Differential diagnoses included an immune-mediated optic neuritis, infectious optic neuritis or neoplasia.

TREATMENT *If relevant*

Given the clinical suspicion of immune-mediated optic neuritis, immunosuppressive therapy was initiated. Cytarabine arabinoside was administered as an intravenous infusion (200mg/m^2 over 12 hours) and prednisolone was administered orally (2mg/kg/day). The dog showed an improvement in demeanour and was discharged from the hospital 2 days later, at which time the menace and direct PLR remained absent in the left eye.

OUTCOME AND FOLLOW-UP

Four days later, a deterioration was noted in the dog's demeanour, which progressed over the subsequent 10 days. A generalized seizure was observed 14 days after hospital discharge and the dog was represented for further evaluation. At this time, the dog was markedly obtunded, non-ambulatory tetraparetic with an absent menace response bilaterally. As previously, shining a bright light in the left eye resulted in constriction of

neither pupil, while shining a bright light in the right eye resulted in constriction of both pupils. These findings were felt to be most consistent with a left optic nerve and diffuse forebrain with brainstem neuroanatomical localisation. Given the severity of the neurological deterioration the owners elected for euthanasia.

Post mortem examination revealed a red-black mass in the ventral part of the thalamus. The mass arose in the midline from the rostral thalamus, just caudal to the optic chiasm and extended cranially along the left rostral cranial fossa (Figure 2A). The mass was approximately 2 cm wide and 1 cm high, extending alongside the left optic nerve and through the left optic canal. Histological analysis revealed the mass to be densely cellular, unencapsulated, infiltrative and bi-lobed (Figure 2B). The cells were highly pleomorphic and small (approximately 8μm diameter) with a scant to moderate amount of stippled eosinophilic cytoplasm. The nuclei were pleomorphic and hyperchromatic with indistinct nucleoli. There was extensive anisocytosis and anisokaryosis, with frequent bizarre mitotic figures (Figure 2C). There was evidence of necrosis, apoptosis and invasion into the surrounding parenchyma, and occasional pseudorosettes were noted around necrotic material. Neoplastic cells were found widely in the subarachnoid space (Figure 2B), being detectable as far caudally as the cerebellum. Nests of neoplastic cells were visible bilaterally in the subarachnoid space of both optic nerves (Figure 2D). The sections of examined optic nerve were otherwise normal. The histopathological diagnosis was an anaplastic ependymoma.

DISCUSSION ***Include a very brief review of similar published cases***

Ependymomas are tumours arising from the ependymal cells lining the ventricular system. They are reported to account for less than 2% of all canine primary brain tumours and most commonly develop as expansile masses within the ventricles (1, 2). Ependymomas typically appear isointense or hypointense to normal grey matter on T1W MRI images, hyperintense on T2W images and with marked, homogenous contrast enhancement, as reported in the current case (1, 3, 4). Secondary obstructive hydrocephalus may occur depending on the size and location of the mass (4, 5). The anaplastic ependymoma in the current report showed an unusual distribution, arising from the rostral aspect of the third ventricle and, rather than expanding out into the ventricular lumen as might be expected, it extended around the left aspect of the optic chiasm and along the left optic nerve.

Macroscopically, ependymomas tend to be large, soft, tan, intraventricular masses. Histologically, they are highly cellular and well vascularized (6), with three main histological subtypes recognised in the dog; papillary, cellular and clear cell (1, 7). The tumour cells have round to oral nuclei, and form characteristic periventricular pseudorosettes embedded in a gliofibrillary stroma (1, 4, 7). Anaplastic ependymomas have been documented in the dog, with features including nuclear atypia, numerous mitotic figures and multifocal areas of necrosis, as found in the current case (4-6, 8).

Limited data exists in the literature regarding treatment response and

prognosis associated with ependymomas. Surgical debulking, radiotherapy and palliative care have been reported (3, 7, 9) but the available case reports typically describe progressive neurological deterioration despite treatment, leading to the decision for euthanasia (3-5, 7, 8).

Neoplastic diseases that have previously been reported to infiltrate or arise from the optic nerve include meningioma, glioma, histiocytic sarcoma and lymphoma (17-19). The human medical literature documents reports of misdiagnosis of optic nerve neoplasia and optic neuritis, resulting in delayed or inappropriate treatment and the potential for poor clinical outcomes (20-22). This emphasizes the importance of optimizing diagnostic interventions and advanced imaging protocols to maximize the likelihood of a correct diagnosis.

Optic neuritis is typically associated with a sudden onset visual field deficit or total loss of vision in one or both eyes (10, 11). Neurological examination findings include reduced to absent menace response and PLR in the affected eye(s). The most common cause of optic neuritis in the dog is granulomatous meningoencephalitis; an immune mediated disease characterised by perivascular mononuclear cell infiltrations (10, 11, 13). Other reported causes include infectious encephalomyelitis or toxic processes (10, 11, 12, 14). MRI findings reported for immune mediated optic neuritis include enlargement of the optic nerve(s) and chiasm, T2W hyperintensity of the optic nerve(s) and chiasm compared with normal grey matter, variable degrees of contrast enhancement and swelling or

bulging of the optic disc (10, 15).

Intracranial neoplasia can affect vision by direct compression or destruction of the nervous tissue of the visual pathway. Such tumours can also affect the function of the visual pathway by indirect compression due to the development of focal cerebral oedema, by disturbance of cerebrospinal fluid circulation, or by secondary vascular effects. In the present case, compression of left optic nerve by the surrounding ependymoma was suspected to be the cause of the unilateral vision loss. Histopathological analysis of the left optic nerve did not reveal structural changes, however the nerve was analysed immediately caudal to the globe, and at the level of the optic chiasm. Analysis of the full length of the optic nerve may have identified structural pathology, and quantitative or ultrastructural analysis may have revealed more subtle abnormalities.

Interestingly, the fundic examination in the current case was unremarkable, while the MRI revealed optic nerve head bulging, suggesting that MRI may be a more sensitive means of detecting optic nerve head changes in some cases. Optic nerve head bulging may represent disturbed CSF dynamics due to physical compression, stasis of axoplasmic flow in the lamina cribrosa of the optic nerve head and/or proliferation of neoplastic cells creating mass effect (16).

The dog in the current case report developed seizure activity 14 days after treatment initiation, consistent with a forebrain neuroanatomical

localisation. At the time of representation it was additionally markedly obtunded and non-ambulatory tetraparetic, raising concern for brainstem involvement. Potentially, the continued growth of the ependymoma exceeded autoregulatory capacity and so resulted in an elevation of intracranial pressure with secondary compression of both forebrain and brainstem structures.

CSF analysis was attempted in the reported case but was non-diagnostic due to the presence of haemorrhage. Neoplastic cells were detected histopathologically in the subarachnoid space and hence cytological evaluation of the CSF may have revealed the presence of exfoliated neoplastic cells and so raised the clinical suspicion of neoplasia. Thoracic and abdominal imaging may rule out systemic involvement but will not facilitate diagnosis in cases of focal inflammation, infection or neoplasia.

This report describes an anaplastic ependymoma extending along the optic nerve and causing visual compromise. MRI findings were consistent with a left optic neuritis, leading to initiation of immunosuppressive therapy. However, marked clinical deterioration prompted euthanasia and histopathology confirmed the diagnosis of an anaplastic ependymoma. Therefore, ependymoma can mimic optic neuritis in regards to the clinical presentation and MRI findings, and should be considered as a rare, but important, differential diagnosis.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- Obtaining a definitive diagnosis of optic nerve pathology can be challenging
- Important differential diagnoses for acute onset, progressive optic nerve deficits include immune mediated optic neuritis, infectious neuritis and neoplasia
- Ependymoma can mimic optic neuritis

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Figure 1: T2W sagittal (A), T2W dorsal (B), T1W post contrast dorsal (C), T2W transverse (D), T1W transverse (E) and T1W post contrast transverse (E) MRI of the head of a Labrador retriever presented with acute onset unilateral blindness. The left optic nerve (indicated by an asterisk on sagittal and transverse views, and by an arrow on dorsal views) was markedly thickened and hyperintense on T2W images compared with normal grey matter, isointense on T1W images with strong homogenous contrast enhancement.

Figure 2: (A) Transverse section of the formalin-fixed brain at the level of the head of the caudate nuclei showing the ependymoma (asterisk) within the rostral thalamus with a necrotic, haemorrhagic centre (arrow). Scale bar =10 mm. (B) Haematoxylin and eosin stained formalin-fixed section of the rostral thalamus showing the densely cellular tumour with large numbers of vessels (white arrows) spreading into and through the subarachnoid space (black arrows). Scale bar = 2 mm. (C) Detail of the pleomorphic neoplastic cells showing hyperchromatic, pleomorphic nuclei and common mitoses (arrows, insert). Scale bar = 100 µm. (D) Left optic nerve (white asterisks) with neoplastic cells in the subarachnoid space

(black asterisks). Scale bar = 100 µm.

OWNER'S PERSPECTIVE *Optional*

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