Presumed primary uveal melanoma with brain extension in a dog

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A 13-year-old, female, mixed, cocker spaniel was examined for a unilateral exophthalmia and protruding mass in episcleral region of the right eye. Mode B ocular ultrasonography revealed a mass extended intraocular from anterior chamber to posterior pole without evidence of extraocular extension. A presumptive diagnosis of melanocytic tumour was made. A complete blood count and chemistry and thoracic radiographs did not show any abnormal changes. The recommended treatment was enucleation, and melanocytic nature of the tumour was confirmed by immunohistochemistry. Three months after surgery, the animal showed a status epilepticus refractory to treatment. Computed tomographic examination of the brain revealed changes compatibles with a tumour. Cerebrospinal fluid analysis was normal. Because of the poor clinical prognosis, the owners elected to have the dog euthanased.

INTRODUCTION

Uveal melanocytic tumours are the most common primary intraocular neoplasms in dogs, and both benign melanocytomas and malignant melanomas have predilection for the anterior uveal tract (Ryan and Diters 1984, Dietz and others 1986, Wilcock and Peiffer 1986, Dubielzig 1990, Collinson and Peiffer 1993, Morgan and Patton 1993, Schoster and others 1993, Miller and Dubielzig 1996, Giuliano and others 1999, Narstrom and Ekestun 1999, Rovesti and others 2001, Hyman and others 2002, Wilcock and others 2002, Miwa and others 2005). Involvement of the choroid is considered to be an extension from the affected iris or ciliary body (Yi and others 2006). Evidence of metastases or extrascleral extension is rarely reported (Dietz and others 1986, Giuliano and others 1999, Narstrom and Ekestun 1999, Miwa and others 2005), although most melanomas have invaded the sclera at the moment of enucleation (Giuliano and others 1999). However, invasion into the brain has not been previously reported.

We present a case of histologically malignant diffuse uveal melanoma in a dog that caused glaucoma and then apparently progressed to cause fatal neurological disease through optic nerve invasion.
After that, the patient was discharged on systemic antibiotics for seven days.

Grossly, an uneven, diffuse enlargement of the uvea with thickening of the base of the iris and ciliary body level was observed. The enucleated eye was fixed in 10 per cent formalin for 24 hours, and selected samples were embedded in paraffin wax. The diagnosis was made on haematoxylin- and eosin-stained tissue sections (Minami and Patnaik 1992). Microscopically, a neoplastic growth was seen occupying both the posterior and the anterior segments and infiltrating retina, sclera and cornea (Fig 2 A). Two populations of tumour cells were observed: (1) large, rounded or polygonal cells with brown pigment in the cytoplasm and (2) small, rounded or elongated cells without pigment (Fig 2B). Atrypia was more marked in the latter neoplastic cell population (Fig 2B). The mitotic count was 7/10 high-power field. The immunohistochemical study was performed using the Abidin-biotin-peroxidase complex technique (ABC method; Vector Lab) and the Melan-A antibody (Dako). This study confirmed the melanocytic nature of the two neoplastic cell populations (Fig 2C), and a diagnosis of malignant primary uveal melanoma was made.

Three months after surgery, the dog was presented to the hospital for an acute onset of seizure activity that progressed rapidly to a status epilepticus refractory to treatment. Over two days, doses of 2 to 3 mg/kg diazepam (Valium; F. Hoffmann-La Roche Ltd) intravenously and 3 mg/kg phenobarbital (Luminal; Kern Pharma) three times a day were used to stop recurrent attacks. Three days after the crisis started, the dog had to be maintained in a sedated status. The owners reported that no abnormal behaviour was observed previous to the crisis. Computed tomography (CT) was performed, and transverse slices of the brain were acquired before and after the administration of an intravenous iodinated contrast medium (iohexol 600 mgI/kg) (Omnitrat 300; Schering Plug). Before contrast medium administration, a heterogeneous diffuse pattern with hyperdense and hypodense zones from olfactory bulb to caudal brainstem was observed (Fig 3). No mass was seen by CT. Cerebrospinal fluid analysis was performed after the CT, obtaining 14 mg/l of protein and no cellular component. All these changes could be compatible with a tumour, and because of poor clinical prognosis, the owners elected to have the dog euthanased.

Post-mortem examination showed a diffuse brown colour of the basal areas of the brain extending from frontal lobe to pons, and medulla with eventual invasion of the parenchyma at the preoptic region was seen (Fig 4). Microscopically, epithelioid and fusiform atypical cells with and without cytoplasmic pigment were observed forming nests within the brain (Fig 5B) and around blood vessels (Fig 5C). These infiltrating cells were also identified as melanocytic because of the expression of Melan-A (Fig 5D) (Ramos-Vara and others 2000). No other lesions were observed at necropsy.

FIG 1. (A) Buphthalmia, exophthalmia and corneal oedema, pigmentation and vascularisation were manifested (B) Intense episcleral injection and protruding mass in the episcleral region were clearly noted in the right eye
DISCUSSION

Unlike in human beings, most primary melanocytic tumours in dogs arise from the anterior uveal tract such as the iris and ciliary body (Ryan and Diters 1984, Wilcock and Peiffer 1986, Dubielzig 1990, Collinson and Peiffer 1993, Morgan and Patton 1993, Schoster and others 1993, Giuliano and others 1999, Narstrom and Ekesten 1999, Rovesti and others 2001, Hyman and others 2002, Yi and others 2006). Thus, some 4 per cent of canine uveal melanomas metastasise (Rovesti and others 2001, Hyman and others 2002), usually by haematogenous route and generally within three months after diagnosis (Hyman and others 2002). In cats with ocular melanomas, the rate of metastasis may be as high as 60 per cent, and it may take years before clinical signs of metastatic disease become evident (Duncan and Peiffer 1991, Rovesti and others 2001, Harris and Dubielzig 2002). In human beings, melanoma is a common primary tumour that metastasises to the brain (Kirsch and others 2005, Naggara and others 2006). Metastasis by the haematogenous route is not the only way to invade other tissues in cases of melanoma, and eventual extraocular extensions with peripapillary scleral infiltration and intracerebral metastases by direct extension through optic nerve have been described (Duffin and others 1981, Jones and others 1988). In dogs, extension of uveal melanomas through the angular plexus into the sclera or even conjunctiva is very common (Narstrom and Ekesten 1999, Hyman and others 2002). Two cases of choroidal melanoma with infiltration into the rostral portions of the optic nerve have been described in dogs (Schoster and others 1993, Miwa and others 2005), while anterior uveal tumours have not been documented to invade the optic nerve. Invasion into the brain seems to be exceedingly rare in dogs, and to the best of author’s knowledge, this is the first published case of such an invasion.

Primary canine uveal melanoma is considered to have a low risk for distant metastasis (Diters and others 1983, Dietz and others 1986, Wilcock and Peiffer 1986, Dubielzig 1990, Minami and Patnaik 1992, Giuliano and others 1999, Narstrom and Ekesten 1999, Rovesti and others 2001, Hyman and others 2002, Yi and others 2006). Therefore, some 4 per cent of canine uveal melanomas metastasise (Rovesti and others 2001, Hyman and others 2002), usually by haematogenous route and generally within three months after diagnosis (Hyman and others 2002). In dogs, extension of uveal melanomas through the angular plexus into the sclera or even conjunctiva is very common (Narstrom and Ekesten 1999, Hyman and others 2002). Two cases of choroidal melanoma with infiltration into the rostral portions of the optic nerve have been described in dogs (Schoster and others 1993, Miwa and others 2005), while anterior uveal tumours have not been documented to invade the optic nerve. Invasion into the brain seems to be exceedingly rare in dogs, and to the best of author’s knowledge, this is the first published case of such an invasion.
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In this case, extraocular muscle, wall of the orbit and optic nerve invasion could not be observed at the moment of enucleation. However, metastatic nodules observed at necropsy from the preoptic region to the hypothalamus (Fig 4) three months after surgery suggest that tumour cells may have invaded the optic nerve before surgery. However, although extension into the brain through the optic nerve or the meninges of the optic nerve seems reasonable, we cannot actually prove this hypothesis because the optic chiasm was not actually examined.

Because of the capability of these tumours to extend into periocular tissues, periodic evaluations, imaging techniques and more aggressive treatment have been accepted as necessary in order to get control in the management of these patients after surgery (Giuliano and others 1999, Hyman and others 2002, Yi and others 2006). These procedures are highly indicated in cases with histopathological parameters suggestive of malignancy (Donaldson and others 2006) because the reported decreased survival in dogs with primary intraocular melanoma is in contrast to the dogma that these tumours are of little clinical significance beyond their effects on the eye (Giuliano and others 1999). Imaging characteristics of the tumours have been described employing magnetic resonance (Kato and others 2005, Miwa and others 2005). In this case, only CT images were obtained when the neurological signs appeared. Perhaps, CT should have been performed at the moment of enucleation to confirm the extraocular extension of the mass and the involvement of the adjacent structures.

In human beings, brain metastases of melanomas are particularly unresponsive to conventional therapies, and many patients will die of cerebral lesions rather than of systemic disease within months. Antiangiogenic therapy has been proposed to keep metastatic disease dormant; however, the clinical applicability of these factors remains speculative (Kirsch and others 2005). There are no available data on whether enucleation increases or decreases the risk of metastasis in eyes with these types of tumours. It is still controversial to do enucleation for a dog with normotensive and non-inflamed, globe-containing choroidal melanoma, and close control to re-evaluate the growth of the neoplasm may be indicated (Wilcock and Peiffer 1986, Miwa and others 2005). However, in this case, as in other cases described in the literature, the globe was initially enucleated because of manifest ocular findings.

Uveal melanomas are classified as benign or malignant based on the basis of several criteria including morphological features of the neoplastic cells (Dubielzig 1990, Collinson and Peiffer 1993, Narstrom and Ekestun 1999), primary site of tumour origin, breed predilection, extent of ocular infiltration, mitotic index (Ryan and Diters 1984, Giuliano and others 1999), amount of cellular pleomorphism, degree of nuclear anaplasia, presence of tumour necrosis and prominent nucleoli (Hyman and others 2002). Reports show that mitotic index is the best criterion for histopathological classification of ocular melanomas of high metastatic potential (Wilcock and Peiffer 1986, Collinson and Peiffer 1993, Rovesti and others 2001). It has been suggested that a mitotic index greater than 4 is indicative of potential malignant biological behaviour (Diters and others 1983, Ryan and Diters 1984, Wilcock and Peiffer 1986, Rovesti and others 2001). However, in a retrospective study, it was concluded that tumour size, degree of local invasion and the mitotic index were found to be no reliable predictors of survival of the patients (Giuliano and others 1999). In this case, indicators of malignancy were cellular atypia and

![FIG 4. Sagittal sections of the encephalon. Melanocytic tumour infiltration from the frontal lobe and diencephalic region to the pons and medulla oblongata can be observed](image-url)
cellular pleomorphism, with two different cell population identified as melanocytic by the expression of Melan-A (Ramos-Vara and others 2000).

The previous diagnosis of glaucoma in cases of ocular melanocytic tumour may be normal as showed in some publications (Hyman and others 2002, Kato and others 2005). Clinical presentation includes glaucoma, hyphema, anterior uveitis and retinal detachment in addition to the presence of a proliferative lesion. The clinical findings of this dog were secondary changes associated with tumour and similar to previous reports (Collinson and Peiffer 1993, Narstrom and Ekestuen 1999, Rovesti and others 2001, Yi and others 2006).

More cases of ocular melanomas need to be reported and followed to determine the potential for malignancy, distant metastasis and invasion of periocular structures in the dog. A long-term follow-up evaluation of these tumours seems to be necessary.

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References


