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CASE REPORT

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Metastatic extradural melanoma of the lumbar spine in a cat

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Abstract

A 7-year-old neutered male Domestic shorthair cat, with a 1.5-year history of left eye enucleation secondary to a diffuse iris malignant melanoma, was evaluated for progressive onset of pelvic limb paresis and ataxia with severe thoracolumbar hyperaesthesia and dysorexia. Neurological examination localised a lesion to the T3–L3 spinal cord segments. Magnetic resonance imaging of the thoracolumbar spine showed a well-defined extradural T1-weighted hyperintense non-contrast-enhancing mass, initially suggesting a potential haemorrhagic component. Exploratory surgery revealed a brownish extradural lumbar mass. Histologic examination concluded to a melanoma, most probably metastatic given the animal's previous medical history. This report highlights the importance of collecting a complete medical history, which can help in obtaining a preliminary differential diagnosis in cats with clinical signs of myelopathy. Although the location of this metastasis is particularly unusual both in human and veterinary medicine, making optimal treatment challenging for neurosurgeon, our increased understanding of immune and tumour cell biology during the past decade is likely to improve the future treatments of feline melanoma and its metastases.

KEYWORDS
extradural, feline, immune cell biology, lumbar spine, melanoma, metastatic

1 | INTRODUCTION

Diffuse iris melanoma is the most common primary intraocular neoplasm in cats (Sandmeyer et al., 2017). Many factors are involved in the pathogenesis of melanoma, including environmental, genetic and immunological factors (Calado et al., 2014), which can make the biological behaviour of feline ocular melanoma variable. Despite this variability and uncertainty, various macroscopic and histological criteria for this type of melanoma have been developed in an attempt to provide some prognostic value (Wiggans et al., 2016).

Metastases of diffuse iris melanoma to the central nervous system have been very uncommonly reported in cats and exclusively in the brain. In human medicine, metastases most often involve the brain through optic nerve invasion; when they involve the spinal cord, they are mostly located in the vertebra, intradural space or intramedullary region (Gokaslan et al., 2000; Ishii et al., 2010; Sun et al., 2013). Epidural metastases are extremely rare (Peters et al., 2015). Consequently, the optimal management of such a metastasis is challenging.

The present report describes a case of a delayed metastatic extradural melanoma of the lumbar spine in a cat, which is a very rarely expected location, both in human and veterinary medicine. To the best of our knowledge, this is the first report of such diffuse iris melanoma metastasis and its management in a cat.

2 | CASE HISTORY

A 7-year-old castrated male Domestic shorthair cat was presented to the neurology department for evaluation of a 3-week history of progressive pelvic limb ataxia and paraparesis with severe thoracolumbar

spinal pain. The cat was inappetent over the previous few days. He was kept indoors and had no history of trauma. Before referral, the cat was treated with prednisolone and cefalexin, which provided transient improvement. No abnormalities were observed in blood analysis (biochemistry and complete blood count) or in survey radiographs of the spine.

One and a half years earlier, the cat had the left eye enucleated following the development 1 year earlier of freckles on the iris of this eye complicated by a glaucoma. On histological analysis, the iris was thickened up to 3 mm by a circumferential, non-encapsulated and poorly defined tumour proliferation, which infiltrates and replaces the ciliary bodies and extends into the sclera in the limbus region. Some groups of tumour cells came into close contact with the wall of the capillaries of the sclera. Cell density was high, with tumour cells ranging from fusiform to rounded, with granular, pale eosinophilic cytoplasm, containing brownish to blackish granules in more than 80% of cytoplasm. Anisocytosis and anisokaryosis were moderate, but the mitotic index was high: there were up to 6 mitoses per field and more than 20 mitoses in 10 consecutive high-power (×400 magnification) fields. A few atypia characterised by plurinucleation, karyomegaly and nuclear indentation are noted. These findings confirmed the diagnosis of diffuse iris malignant melanoma, with histological grade qualified as advanced according to the classification of Kalishman et al. (1998). Staging work-up which included thoracic radiographs was negative for metastasis at that time.

At the time of presentation to our hospital, physical examination revealed a rectal temperature of 102.6°F. Other vital parameters were within normal limits. No micturition disorder was reported. The urinary bladder was small and flexible on abdominal palpation. Neurological examination revealed a mild pelvic limb ataxia associated with an ambulatory paraparesis. Postural responses in the pelvic limbs were decreased, but the patellar reflex, cranial tibial reflex and withdrawal reflex were normal in both limbs. Severe spinal hyperpathia in the thoracolumbar area was noted. The remainder of the neurological examination, including cranial nerves assessment, thoracic limbs postural responses and myotatic reflexes, was within normal limits. Based upon these findings, the lesion was localised to the T3–L3 spinal cord segments. Differential diagnoses included inflammatory (infectious and non-infectious), neoplastic, vascular and less likely traumatic or degenerative spinal cord diseases.

Further imaging of the spinal cord using magnetic resonance (MRI, Vantage Orian, 1.5T; Canon Medical Systems) was performed under general anaesthesia. Imaging included T2-weighted (T2W), T1-weighted (T1W), and short tau inversion recovery (STIR) sequences in all three planes, then repeated T1W sequences following contrast administration (Gadoteridol [Pro Hance, Bracco] 0.5 mmol/mL, intravenous injection of 0.2 mL/kg). A relatively well-defined mass, which appears moderately T2W heterogenously hypointense (Figure 1a,b) and T1W hyperintense without contrast enhancement (Figure 1c,d), was identified in the dorsal portion of the vertebral canal. The mass had a wide base of contact with the vertebral laminae surrounding the L3–L4 disc space, consistent with an extradural compressive lesion of the spinal cord. The mass occupied approximately 60% of the vertebral canal cross-section causing attenuation of the epidural fat and subarachnoid space and deformation/compression of the spinal cord. It focally extended into the left L3–L4 foramen (Figure 1c). No concomitant modification of bony structures in contact with the lesion or extension of the lesion from the adjacent paravertebral musculature was observed. The distal aspect of the nerve root appeared to be symmetrically thickened compared to the contralateral one. Primary interpretation of the magnetic resonance findings included a haematoma or a neoplastic process with a haemorrhagic component (angioma, hamartoma, metastasis, less likely meningioma or peripheral nerve sheath tumour).

Lumbar cerebrospinal fluid (CSF) tap revealed a slight elevation of total nucleated cell count (19 leukocytes/μL, reference <5 leukocytes/μL) characterised by a predominance of mononuclear cells, especially lymphocytes, and a protein concentration of 51 mg/dL (reference <45 mg/dL). No tumour cells were identified in the CSF sample.

The day after diagnosis, a left hemilaminectomy at the third and fourth lumbar vertebrae was performed to remove the compressive lesion (Figure 2). The cat was premedicated with midazolam (0.2 mg/kg intravenous [IV]), induced with propofol (3 mg/kg IV), and was intubated and maintained on isoflurane with oxygen. Morphine (0.2 mg/kg IV) was administered for intraoperative analgesia, and amoxicillin/clavulanic acid (20 mg/kg IV) was administered for perioperative antibiotic therapy. Hemilaminectomy revealed a brown, friable material located in the dorsolateral aspect of the epidural space compressing the underlying spinal cord and infiltrating the adjacent laminae and pedicles of the third and fourth lumbar vertebrae on the left side. As much material as possible was removed. The spinal cord had a normal macroscopic appearance following removal of the mass.

Postoperative medical treatment consisted of pain medication (buprenorphine [Buprecare, Axience] 20 μg/kg IV every 8 h for 1 day and gabapentin 10 mg/kg orally every 8 h), non-steroidal anti-inflammatory drugs (meloxicam [Metacam, Boehringer] 0.1 mg/kg PO once a day for 5 days), antibiotic therapy (amoxicillin/clavulanic acid [Synulox, Zoetis] 12.5 mg/kg orally every 12 h for 10 days) and physiotherapy three times a day. The cat was ambulatory with a persistence of mild back pain on the fourth postoperative day and was discharged from the hospital.

Tissues from the mass were submitted for histopathological examination and bacteriology. Histological evaluation revealed a dense malignant tumoral proliferation with no sign of healthy tissue. The cells were round to spindle shaped and formed lobules and bundles (Figure 3). Cytonuclear atypia (plurinuceate, peripheral chromatin reinforcement, karyomegaly, nuclear indentation) and an abundant eosinophilic cytoplasm occasionally containing a small amount of globular brown to black pigment (melanin) were characteristic cellular features observed (Figure 4). The mitotic index was 2 per field (×40 magnification) and anisocytosis and anisokaryosis were moderate. No anaerobic or aerobic bacterial growth was detected in the culture.

Histologic findings confirmed a spinal cord compression at the level of the third and fourth lumbar vertebrae secondary to an extradural malignant melanoma, most likely consistent with metastasis of the previous diffuse iris malignant melanoma given the animal's history, the

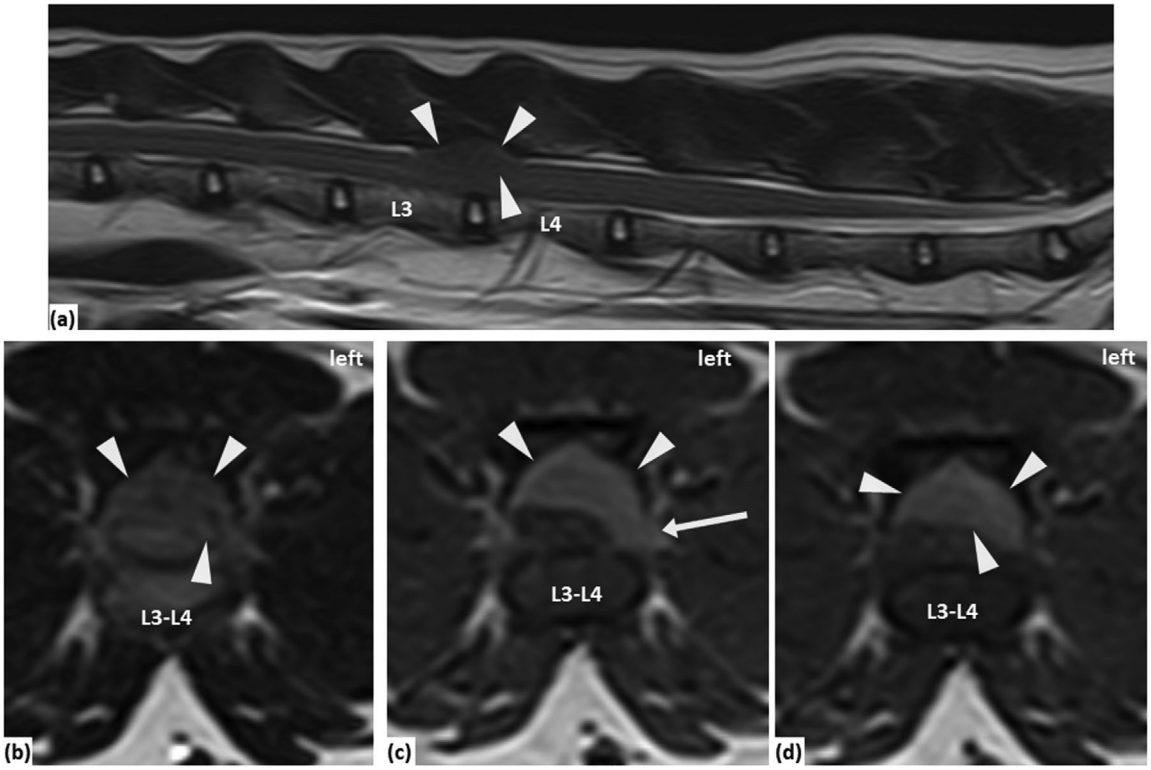

FIGURE 1 Sagittal T2-weighted image of the cat's lumbar spinal cord showing slightly hypointense and heterogeneous mass (arrowheads) in the dorsal portion of the vertebral canal at the level of the L3–L4 intervertebral space (a). Transverse T2-weighted image at the level of the L3–L4 intervertebral disc showing the moderately heterogenous hypointense extradural mass (b). Transverse T1-weighted image at the level of the L3–L4 intervertebral disc showing the hyperintense mass extending within the left L3–L4 foramen (arrow); there is no modification of the vertebral laminae in contact with this mass (c). Transverse T1-weighted images showing no significant contrast enhancement after injection of contrast product (d).

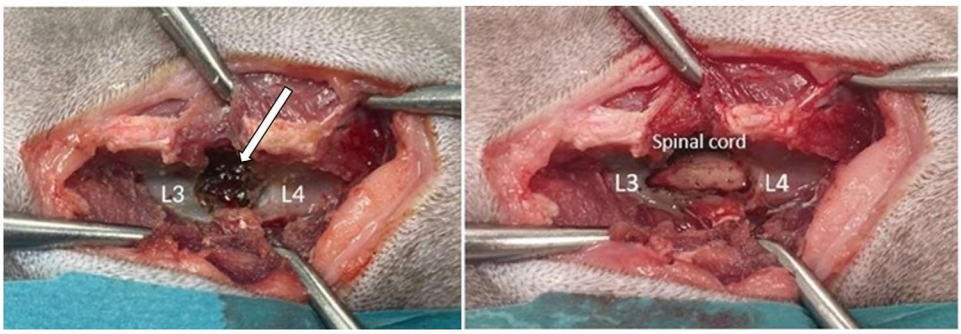

FIGURE 2 Surgical decompression, before (left) and after (right) mass removing. Note the brownish appearance of the mass (white arrow).

high metastatic risk of the primary tumour, the unusual tumour site and less differentiated appearance of the metastasis compared with the primary tumour site with decrease in cell pigmentation.

The cat was in good general condition with resolution of clinical signs until 3 months after surgery, when he started again to develop episodes of back pain, which transiently improved with administration of analgesics.

Six months after the surgery, the cat was presented with respiratory difficulties due to extensive numerous pulmonary metastases detected on thoracic radiography. No further treatment was performed and the owner humanely elected euthanasia.

3 | DISCUSSION

Diffuse iris melanoma is by far the most common primary intraocular neoplasm in cats (Kayes et al., 2022; Sandmeyer et al., 2017). It is known to be locally infiltrative with high metastatic rates (19%–63%) with a preference for distant organs such as the liver, lungs, spleen, lymph nodes and kidneys (Dubielzig, 2016; Ionascu et al., 2012; Pigatto et al. 2010; Planellas et al., 2010; Wiggans et al., 2016), in addition with unusual locations including radial head and proximal diaphysis (Planellas et al., 2010) and wider dissemination throughout multiple organs suggesting cavitary, lymphatic and haematogenous spread

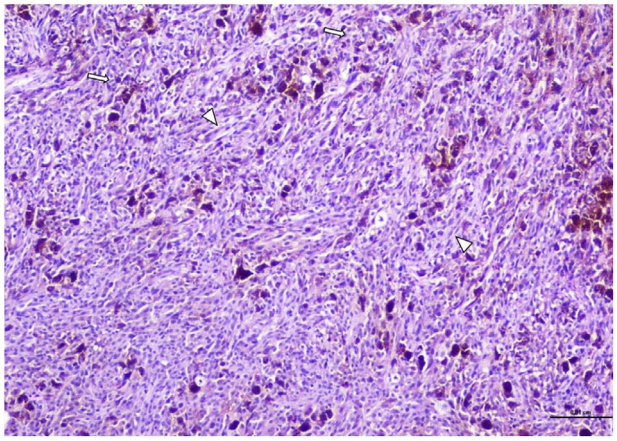

FIGURE 3 Histological section of the extradural mass revealing a dense malignant tumoral proliferation resting on a thin fibrovascular stroma, with cells organised in lobules (arrows) and bundles (arrowheads) (haematoxylin and eosin staining ×100).

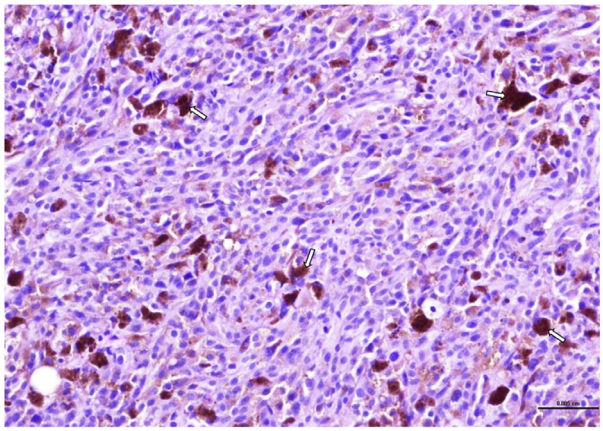

FIGURE 4 Histological section of the extradural mass showing round to spindle-shaped cells, with an abundant eosinophilic cytoplasm rarely containing a small amount of globular brown to black pigment consistent with melanin (arrows) (haematoxylin and eosin staining ×200).

(Calado et al., 2014). However, it may take 3 years before clinical signs of metastatic disease become evident (Kalishman et al., 1998; Stiles 2013).

Various macroscopic and histological criteria of the primary diffuse iris melanoma provide some prognostic value. The presence of a secondary glaucoma (Kalishman et al., 1998), local tumour invasion such as extrascleral or choroidal extension, necrosis within the neoplasm (Gelatt et al.,2021) or high mitotic index with a cut-off value given as >7 mitoses in 10 high-power (×400) fields (Wiggans et al., 2016) were found to be associated with an increased rate of metastasis (Kayes et al., 2022). However, contrasting with previous reports, a recent study of 47 enucleated eyes with a diagnosis of feline diffuse iris melanoma (Wiggans et al., 2016) did not show an association between scleral venous plexus penetration and metastatic rate. In our case, although the choroid did not appear to be invaded and no tumour necrosis was visualised, the secondary glaucoma and the high mitotic index suggested a high risk of metastasis.

Metastasis of iris melanoma to the central nervous system has uncommonly been reported in cats, and only very rarely reported in the brain through optic nerve invasion (Dubielzig et al., 2010; Gelatt et al., 2021). In human medicine, metastasis of uveal melanoma to the central nervous system is rare and most often involves the brain (Abdellatief et al., 2016; Lindegaard et al., 2006). The precise rate has not been documented yet. The prevalence of spinal melanoma metastases from any primary cause is estimated by clinical studies to be 2.4% (Patchell et al., 2005; Spiegel et al., 1995). Human spinal melanoma metastases are most commonly located in the vertebra, intradural space or intramedullary region (Gokaslan et al., 2000; Ishii et al., 2010; Sun et al., 2013). Epidural metastases are extremely rare (Peters et al., 2015), which makes this case report particularly interesting, showing a location of iris melanoma metastasis in a cat already very rarely expected in human medicine. In a retrospective study of 53 dogs with a diagnosis of malignant melanoma, 20 showed metastases involving the central nervous system, with 75% to the cerebrum and 15% to the spinal cord (Razmara et al., 2022).

MRI is the preferred imaging method for the diagnosis of spinal tumours, due to its high soft-tissue resolution capabilities allowing classification of these tumours as extradural, intradural-extramedullary or intramedullary, which is very useful for their characterisation (Besalti et al., 2016). MRI of melanocytic tumours does not consistently show a homogeneous pattern. The MRI T1W signal depends on the presence of melanin, acute or chronic intratumoral haemorrhages and fat deposits (Sun et al., 2013). Hyperintensity on T1W nervous system images is not specific for haemorrhage and may also be seen with melanin, high protein, flow artefacts or paramagnetic effects (e.g., due to manganese) (Mai, 2018). The expected signal pattern for melanoma metastasis is T1W hyperintense, T2W hypointense, associated with signal void on T2*W images because of the combined paramagnetic effects of melanin and haemorrhagic changes commonly present with these lesions (Mai, 2018). The percentage of melanin-containing cells correlates with signal intensity (Atlas et al., 1987).

Once spinal melanoma metastases are diagnosed, median overall survival ranges between 2.9 and 5.9 months in human medicine (Sellin et al., 2015; Spiegel et al., 1995; Stewart et al. 1978). Regarding the poor prognosis, palliation is the primary treatment objective. Surgical resection and radiotherapy are mainstays of treatment and indicated to preserve neurological function. Even though the existing literature on the role of surgery for spinal melanoma metastasis is limited in human medicine and even more so in veterinary medicine where the animals are mostly euthanised (Besalti et al., 2016), some prognostic factors have been developed for human patients who underwent spinal surgery for metastatic melanoma. Diagnosis of spinal metastasis after prior diagnosis of systemic metastasis, presence of progressive systemic disease at the moment of spine surgery or a total spinal disease burden of ≥3 vertebral levels were factors significantly associated with worse overall survival (Sellin et al., 2015). Our patient had positive prognostic factors with a single site of spinal metastasis, not following an old site of metastases; however, an extension work-up at the time of surgery is missing and could have been interesting to give us a more precise idea of the future prognosis.

Even though optimal treatment remains under debate and no single treatment modality has proven fully effective for the management of spinal metastatic melanoma (Caruso et al., 2015; Zheng et al., 2023), recent advances of immunotherapy and targeted therapies over the past two decades offer encouraging results. The majority of human metastatic melanomas were described to harbour the $BRAF^{V600}$ mutation, making the use of antibodies and BRAF-kinase inhibitors, such as vemurafenib, dabrafenib and trametinib, a novel therapeutic strategy for metastatic melanoma (Bollag et al., 2012; Kaufman et al., 2013; Kim & Cohen, 2016). In BRAF mutation-negative metastatic melanoma, a KIT mutation testing should be performed because the probability of a KIT mutation is higher in these subgroups (Lyle & Long, 2013). The use of cytotoxic T-lymphocyte antigen-4 inhibitors such as ipilimumab or tyrosine kinase inhibitors such as imatinib in KIT mutation-positive human patients has shown some efficacy (Lawrence et al., 2012; Lyle & Long, 2013; O'Day et al., 2010). However, the benefit of these therapeutic advances in the metastatic spinal melanoma population is unclear (Davies et al. 2017; Goldberg et al., 2016; Margolin et al., 2012; Zheng et al., 2023). The best treatment approach appears to require combined therapies with aggressive surgical and medical management to maximise median survival (Caruso et al., 2015; Ralli et al. 2020; Rustagi et al., 2019).

A recent study of mutation analysis and gene expression profiling of ocular melanomas in cats (O'Day et al., 2010) demonstrates that common mutations found in human melanomas are not present in feline tumours. Gene expression analysis revealed, for example, a significant upregulation of KIT as well as a downregulation of BRAF in feline ocular melanomas, which highlights the potential of KIT as target for adjunctive therapy in feline ocular melanomas as it seems to harbour a potential target gene as in human patients (Rushton et al., 2017). The use of imatinib in KIT mutation tumours, like in mast cell tumours, has shown favourable clinical responses with tolerable toxicity in dogs and cats (Bonkobara, 2015), which may provide to this molecule a promising therapeutic option in the treatment of feline melanoma with a KIT mutation; further clinical studies are needed, more specifically regarding gene expression in feline metastatic melanoma.

4 | CONCLUSION

Due to the late onset of clinical signs in relation to the initial appearance of the ocular melanoma and the epidural location of the lesion on MRI images, a metastatic melanoma was not initially suspected in the present case. The atypical and uncertain biological behaviour of melanoma should lead us to consider melanoma metastases in the differential diagnosis of acute and/or chronic myelopathies in cats even several years after enucleation for treatment of diffuse iris malignant melanoma, especially when the initial histopathologic characteristics suggest a high metastatic risk.

Even though no single treatment modality has proven fully effective for melanomas and its metastasis and the prognosis is still poor, our increased understanding of immune and tumour cell biology during the past decade is likely to improve our future treatments of this condition in cats.

AUTHOR CONTRIBUTIONS

Sabrina Fert: Conceptualisation; investigation; writing—original draft. **Pablo Rivier**: Supervision; writing—review and editing. **Laura Bondonny**: Investigation; writing—review and editing. **Laurent Cauzinille**: Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

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ETHICS STATEMENT

All relevant legal and ethical requirements have been met regarding the human treatment of the animal. Owners' consent and confidentiality were respected.

DATA AVAILABILITY STATEMENT

The data that support this case report are available from the corresponding author upon request.

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PEER REVIEW

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