CASE REPORT

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Rare primary choroidal melanoma in a dog, with optic nerve infiltration

Raro melanoma primário de coroide em cão, com infiltração no nervo óptico

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ABSTRACT

Intraocular melanocytic neoplasms are common in dogs. However, the choroidal location of these neoplasms and their infiltration into the optic nerve are unusual. This paper reports a case of primary choroidal melanoma in a 12-year-old male Dachshund. On the first examination, the animal presented left eye blepharospasm, protrusion of the nictitating membrane, conjunctival hyperemia, moderate congestion, hyphema, and intraocular hypertension. Opacity hindered the performance of fundoscopy in the affected eye. The ocular ultrasound examination revealed a cupuliform mass in the choroid. Due to suspected intraocular neoplasia, an exenteration was performed. Histopathological examination revealed primary choroidal melanoma with scleral and optic nerve invasion.

Keywords: Choroidal melanoma. Dog eye. Ocular neoplasm. Optic nerve infiltration.

RESUMO

Neoplasias melanocíticas intraoculares são comuns em cães, contudo, a localização destas neoplasias na coroide e a infiltração delas no nervo óptico são pouco frequentes. O presente trabalho relata um caso de melanoma de coroide primário em um cão da raça Dachshund, com 12 anos de idade. O animal ao primeiro exame apresentou blefaropasmo no olho esquerdo, protrusão da terceira pálpebra, hiperemia conjuntival, congestão moderada, hifema e pressão intraocular elevada. Opacidade de meios transparentes impediu a realização de fundoscopia no olho acometido. O exame ultrassonográfico ocular revelou massa cupuliforme na coroide. Em razão da suspeita de neoplasia intraocular foi realizada exenteração. No exame histopatológico foi diagnosticado melanoma primário em coroide com invasão escleral e do nervo óptico.

Palavras-chave: Melanoma de coroide. Olho do cão. Neoplasia ocular. Infiltração no nervo óptico.

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Melanocytic tumors are the most common intraocular neoplasms in dogs. These neoplasms are mostly benign melanocytomas, but the classification of melanocytic lesions is inconsistent. Even with benign histological features, a melanocytic neoplasm can cause secondary glaucoma and be locally invasive, showing necrotic areas, with local malignant features, but without the ability to metastasize. Whatever the classification, the malignancy will always be suspected. On histopathological examination, areas with melanocytoma typical cells can be found in melanomas, thus suggesting malignant transformation (Perlmann, 2010). Choroidal melanomas are rare in dogs, representing 5% of cases. Dog melanoma, unlike human melanoma, appears in the iris and ciliary body, not in the choroid (Maggs et al., 2015). Optic nerve invasion and metastases are not common. However, in a 2020 study carried out at Cornell University, Badanes and co-authors identified optic nerve invasion in half of the 14 eyes analyzed, affected with choroidal melanoma. Cases of choroidal melanoma with optic nerve infiltration have been previously reported (Dubielzig et al., 1985; Galán et al., 2009; Miwa et al., 2005; Schoster et al., 1993). In human medicine, 90% of intraocular melanomas are choroidal (van der Weyden et al., 2020).

Benign melanocytic neoplasms affect both males and females. Concerning melanomas, males are more affected (1:4 ratio). Middle-aged animals, between nine and 10 years old, are more likely to develop benign, or malignant, melanocytic neoplasms. Black-coated dogs are more susceptible to melanomas (Gillard et al., 2014; Prouteau & André, 2019). Oculodermal melanocytosis (*Nevus of Ota*), an irregular distribution of pigments along the ophthalmic nerve, indicates a high risk for melanoma, both in dogs and humans (Malho et al., 2018).

In dogs, sun exposure does not seem to be a determinant for the development of melanomas, as some are seen in regions not exposed to ultraviolet radiation (Gillard et al., 2014; Nishiya et al., 2016), which leads to a suspected genetic predisposition. Imperceptible mutations can occur from embryogenesis. There are genes, such as MITF (melanocyte-inducing transcription factor), which are responsible for cell differentiation into melanocytes, migration, and formation of melanocytic lesions, being important for the understanding of melanoma (Ma et al., 2019) and MicroRNAs identified in humans, homologous to dogs and other species, conserved in evolution, involved in uveal melanomas metastases (Starkey et al., 2018).

This paper reports a case of choroidal melanoma, with optic nerve invasion, as seen at E+ Veterinary Specialties (São Paulo – Brazil). A 12-year-old male Dachshund with no previous eye diseases was referred to the ophthalmology service with apparent discomfort and red eye for 20 days, and protrusion of the nictitating membrane for two days.

On ophthalmic examination, regarding the affected eye, the dog presented blepharospasm and lack of response to menace reflex test, movement test (throwing of a small ball of cotton wool), and dazzle reflex test. The patient also presented a negative response to the pupillary light reflex (PLR) test, direct and consensual. Protrusion of the nictitating membrane, hyperemia, and episcleral congestion was observed. A portable slit lamp biomicroscope revealed corneal edema and anterior chamber hyphema. Fundoscopy could not be performed due to opacity. The measured intraocular pressure was 46 mmHg (TonoVet® - iCare). The contralateral eye-right was within the normal range. Fluorescein dye was used to check tear film stability (TBUT), which was normal in both eyes, and to detect corneal erosions. Paracentral impregnation was observed in the left eye, suggesting keratoconjunctivitis sicca (KCS) due to qualitative disorders.

Given the clinical manifestations presented and the differential diagnoses for hyphema, including trauma, congenital causes, systemic arterial hypertension, parasitic diseases, neoplasms, and coagulopathies (Maggs et al., 2015), the diagnostic conclusion required blood tests and an eye ultrasound to investigate posterior segment diseases.

Due to the increased PIO and dry eye condition, the patient was medicated with an association of 2% dorzolamide and 0.5% timolol (Drusolol®, 3 times a day), plus lacrimomimetic (0.15% sodium hyaluronate, Hyabak®). A follow-up visit was requested after the complementary exams.

Twenty-two days later, buphthalmia and worsening of the left eye condition were observed, presenting mucous

secretion, accentuated conjunctival hyperemia and episcleral vessels congestion, as well as corneal edema and persistent hyphema (Figure 1).

Ocular ultrasound (Vupad – Sonomed® 12 MHz) indicated the presence of a posterior wall lesion, in the peripapillary region with a solid, cupuliform, homogeneous aspect, of high echogenicity, measuring 13.98 mm at the base and 12.55 mm at the apex, suggesting an invasion of adjacent tissues. Partial retinal detachment and vitreous hemorrhage process were observed. No orbital changes were reported (Figure 2).

After performing preoperative tests, including electrocardiogram, Doppler echocardiogram, and blood tests, all with normal results, exenteration was performed on day 37, due to suspicion of intraocular neoplasia. During the surgery, three layers of the suture were performed with 4-0 nylon thread, using Hemospon®, although there was little bleeding. For the postoperative period, amoxicillin with potassium clavulanate (Agemoxi CL® 25 mg/kg, every 12 h for seven days), tramadol hydrochloride (Cronidor® 4 mg/kg, every eight hours for five days), and dipyrone (Novalgina® 25 mg/kg, every six hours for three days) were prescribed.

The eye globe was sent for histopathological analysis. The animal did not return for follow-up. As reported by the owner, it died on day 140, supposedly from pancreatitis. As a necropsy was not performed, no evidence of metastatic melanoma could be confirmed.

Macroscopically, a mass of solid consistency and blackened color was observed in the choroid, covering part of the vitreous cavity. Histopathological examination revealed characteristics compatible with choroidal melanoma. No changes in the anterior uvea were observed. Microscopic findings under hematoxylin-eosin staining indicated epithelioid neoplastic cell proliferation, with a round nucleus, evident nucleolus, and broad eosinophilic cytoplasm, with melanin pigmentation. Five mitotic figures were observed in 10 high magnification fields. A high degree of atypia and pleomorphism was observed. Neoplastic cells were located in the choroid and part of the vitreous cavity, invading the sclera and extending to the optic nerve (Figure 3).

Intraocular, premalignant melanocytic lesions, in both dogs and humans, are difficult to diagnose. They can remain unnoticed for a long time, without ocular manifestations, which makes diagnosis difficult and, more often than not, late. The existence of amelanotic melanomas also complicates the diagnosis even further. In such cases, the immunohistochemical test is useful for the histogenesis definition (Perlmann, 2015).

Clinically differentiating intraocular melanocytic lesions is a challenge. The differentiation between melanocytoma and melanoma is only determined after the material is submitted to histopathological examination, after biopsy or enucleation. Besides, a univocal criterion for differentiating malignant and benign neoplasms is not functional in terms of prognosis. In melanocytoma, there is the possibility of invasion of adjacent structures and necrosis. An evolution from melanocytoma to melanoma is also possible. Melanocytic lesions can even be concomitant at different stages. The transformation of premalignant lesions into uveal melanoma is not well known. The diagnosis of a pre-melanoma lesion would be ideal for treatment purposes (Lemetayer et al., 2017; Miwa et al., 2005; Perlmann, 2010, 2015).

Clinical manifestations frequently precede the diagnosis of choroidal melanoma. Asymmetric, unilateral glaucoma

Figure 1 – (A) Left eye showing mucous secretion, hyperemia and congestion, corneal opacity, and hyphema in the anterior chamber; (B) Left eye showing buphthalmia. Photography: Carinne Liesse Brunato.

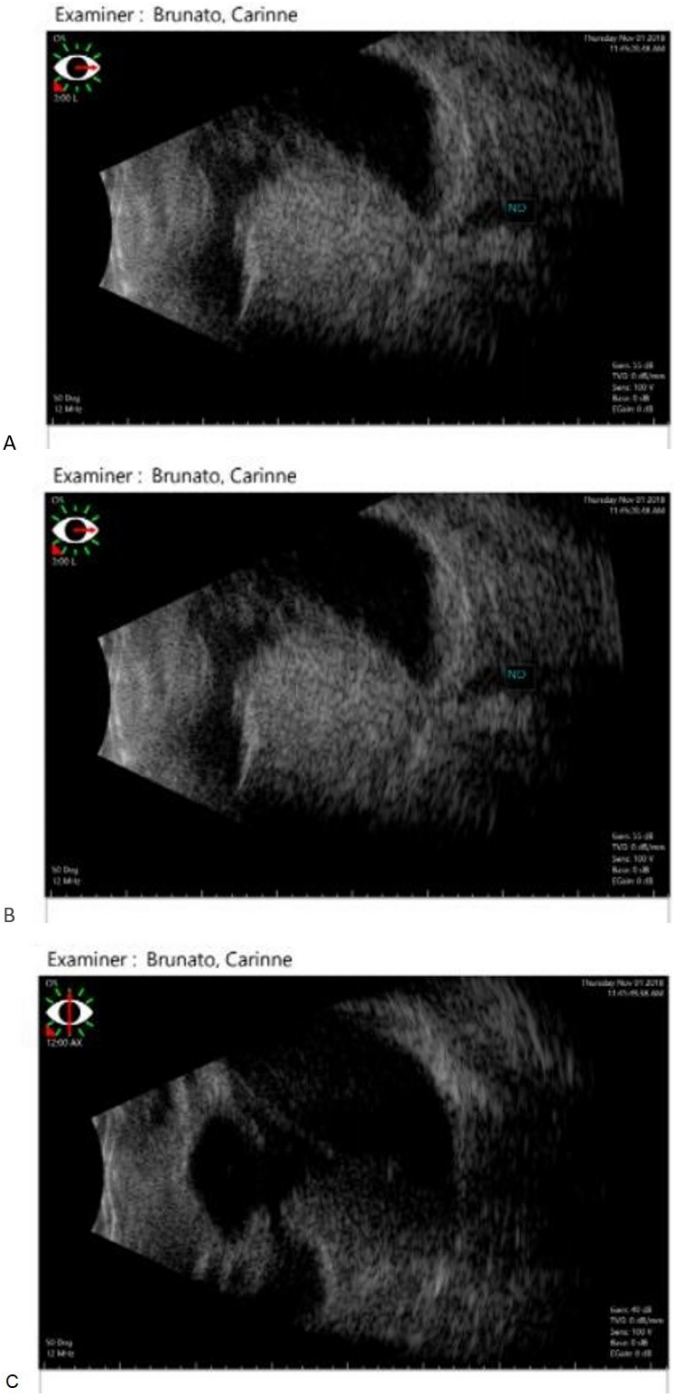

Figure 2 – Left eye ultrasonography. (A) High echogenicity and cupuliform mass in the peripapillary region. Hyperechogenic membrane, adjacent to the apex of the lesion, suggestive of peripheral retinal detachment; (B) The optic nerve in the papillary region is not shown. Assessment of the posterior portion only, with a sinuous path and normal appearance; (C) Punctate echoes in vitreous are suggestive of a hemorrhagic and/or inflammatory process. Iris and ciliary body are unaltered.

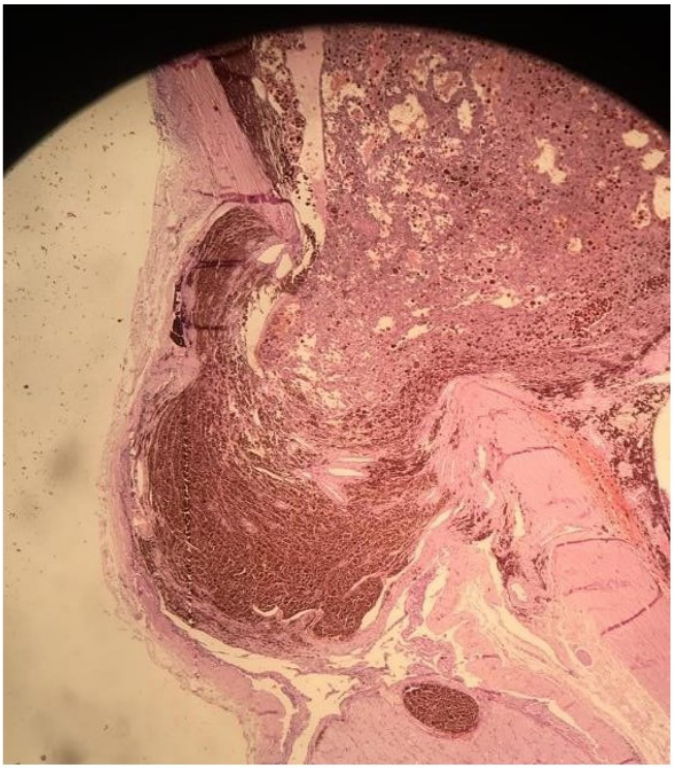

Figure 3 – Histological section stained with Hematoxylin-Eosin showing neoplastic tissue invasion to the sclera, orbit and part of the optic nerve (10X objective lens). Fotography: Eduardo Perlmann.

can foreshadow the existence of a neoformation. To better clarify, the most common cause of secondary glaucoma, as established from neoplastic formation, is the "ocular ischemic syndrome", characterized by ischemia, necrosis, and hypoxia of retinal cells, mechanisms that are caused by neoplastic growth and mediated by a vascular endothelial growth factor (VEGF), causing the formation of cell debris, a proliferation of fibrovascular tissue in the iridocorneal angle and neovascularization around the iris, which interferes with the dynamics of aqueous humor drainage and causes intraocular hypertension (Hase et al., 2021; Sahu et al., 2019). Concomitant events like uveitis, endophthalmitis, corneal stromal edema, hyphema, secondary glaucoma, and retinal detachment are almost always present (Badanes et al., 2020; Maggs et al., 2015).

The mushroom-shaped (cupuliform) ocular ultrasound image is particularly important in the characterization of choroidal melanoma (Wang & Kern, 2015). However, many choroidal neoplasms rupture Bruch's membrane, having the same shape (Perlmann, 2010).

The classification of melanocytic lesions, which is not standardized in either human or veterinary medicine, complicates both diagnosis and prognosis (Zoroquiain et al., 2016). The mitotic index predominates as a malignancy criterion in veterinary medicine (presence of more than 4 mitotic figures, in 10 consecutive fields, as observed under high magnification microscopy). The invasion of structures adjacent to the neoplasm is considered a malignancy factor in human medicine. Thus, a neoplasm described as benign can be comprised of a malignant neoplastic process.

Therefore, the use of the nomenclature "melanocytoma" (benign melanocytic lesion) is insufficient to portray borderline situations, in which clinical manifestations have not yet occurred.

Early treatment with anti-MicroRNAs therapies involved in melanoma is a feasible treatment alternative in human medicine, thus preventing radiotherapy, enucleation, and future metastases. The most common treatment in humans is the brachytherapy plate placement with iodine-125, after transscleral biopsy and diagnosis. In veterinary medicine, the use of radiotherapy for intraocular melanoma is still under investigation. Incipient studies are seeking less invasive treatments, which would preserve vision (Badanes et al., 2020).

Choroidal melanomas are rare in dogs and difficult to diagnose. Invasion of the optic nerve is even rarer. Corroborating data from the literature, it was found that the diagnosis was incidental after manifestations of glaucoma, corneal edema, hyperemia, hyphema, and buphthalmia, which indicates that in elderly animals with such clinical manifestations the presence of ocular neoplasia should always be investigated. In the present case, it can be said that choroidal melanoma was malignant, both by the invasiveness criterion of human medicine and by the histopathological criterion of veterinary medicine.

Choroidal melanoma is usually detected by fundoscopy. However, the alteration in the normal transparency of the cornea and the tendency to bleedings into the subretinal and vitreous spaces, often prevent neoformation detection. Thus, the ultrasound exam is an auxiliary diagnostic method of great importance for eyes with a loss of transparency of cornea, lens, and vitreous. Ocular ultrasound helps diagnosis by revealing typical characteristics of choroidal melanoma that differentiate it from other neoformations, such as shape, location, and echogenicity (Perlmann, 2010). In the present report, the clinical treatment was established at the first signs of ocular discomfort (pain, hyphema, hyperemia, and high intraocular pressure). Ocular manifestations were refractory to drug treatment. The opacity made fundoscopy and visualization of pigmented neoformation (suggestive of melanoma) unfeasible so the ocular ultrasound was essential to detect the neoformation and substantiate the need for exenteration, to prevent extraocular invasion and metastasis. Histopathological examination evinced the whole procedure. In dogs, metastases of choroidal melanoma, though rare, are possible and almost always undetectable at the time of diagnosis. Every melanocytic neoplasm should be investigated, considering the possible evolution to glaucoma, with consequent loss of vision, and further differentiation into melanoma.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

Since this manuscript is a clinical case report, it was not necessary the approve of any animal ethics committee.

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