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Case Report

# Retinoblastoma-Like Tumor with Brain Metastasis in a Border Collie

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**Abstract**

In this report, we described the clinical, ultrasound, contrast-enhanced T2-weighted brain magnetic resonance imaging (MRI), and histopathological findings of a retinoblastoma-like tumor with brain metastasis in a 3-year-old male Border Collie. Ophthalmoscopic and ultrasonographic examination revealed leukocoria associated with a solid mass of retinal origin in the left eye. Simultaneous contrast-enhanced T2-weighted brain MRI evaluation revealed solid masses at three different locations: the first one at the levels of the suprasellar cistern, third ventricle and chiasma opticum; the second one in the medulla oblongata adjacent to the caudal cranial fossa; and the third one in the left intraocular region. Histopathological examination of the extracted mass in the globe revealed a retinoblastoma-like tumor. The patient died before receiving radiotherapy treatment. In conclusion: this report highlights the importance of early diagnosis through ophthalmoscopic and ultrasonographic examinations. Emphasizing the brain as a potential secondary metastatic site, the report underscores the critical need to create a window for timely radiotherapy. Furthermore, the recommendation is made to evaluate dogs with leukocoria during ophthalmoscopic examination for both retinoblastoma and potential brain metastasis.

**Keywords:** Dog, Embryonal tumors with multilayered rosettes (ETMR), Ocular neoplasia, Primary neuroectodermal tumors (PNET), Retinoblastoma-like tumor

## Introduction

The most common intraocular tumors in dogs are primary melanocytic and iridociliary neoplasms. The canine eye is usually the primary neoplastic focus [1,2]. However, it has also been reported that the anterior uvea of the eye is a secondary metastatic focus for tumors such as transmissible venereal tumor, lymphosarcoma, and hemangiosarcoma [1,3]. Primary neuroectodermal tumor (PNET) is a general term used to classify all embryonal neoplasms arising from the germinal neuroepithelium of the neural tube (neuroectoderm), and these tumors occur rarely in dogs [2]. PNETs have recently been terminologically designated as embryonal tumors with multilayered rosettes (ETMR) [4]. In humans, the majority of PNETs are observed in the pediatric population and recognized commonly as retinoblastoma arising from the primitive neuroepithelium of the retina and medulloepitheliomas arising from the primitive medullary epithelium of the ciliary body [5]. There are two types of retinoblastomas in humans; genetic and sporadic. Genetic retinoblastoma originates from retinal neurons in multiple locations in both eyes and is observed in infants under the age of 1 year [6].

In this report, ophthalmoscopic, ultrasonographic, contrast-enhanced brain MRI (CMRI), and histopathological findings of retinoblastoma-like tumor with brain metastasis in a dog were described. The importance of ophthalmoscopy and ultrasonography (USG) for early diagnosis of the patient and buying time to benefit from radiotherapy by considering the brain as a secondary metastatic site as well as the need to consider retinoblastoma in patients with leukocoria were emphasized.

## Case History

For this case report, informed consent was obtained from the patient owner.

A 3-year-old male Border Collie was admitted to VetAmerikan Animal Hospital (İstanbul-Türkiye) with

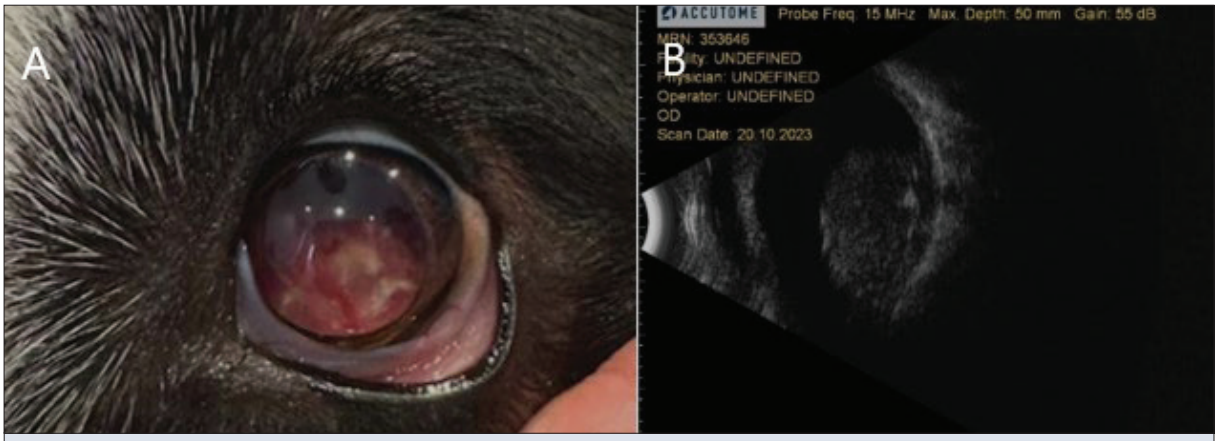


**Fig 1.** Ophthalmoscopic and ultrasonographic examination. **A.** Neoplastic mass enlarged into the posterior chamber and corpus vitreous, and leukocoria in the left eye internal angle, **B.** In the sonogram of the left eye, transversal sections showed an echogenic solid mass of retinal origin extending to the vitreous independent of papilla nervi opticus

complaints of loss of appetite and vision. Hematologic and biochemical parameters were within normal limits. Ophthalmoscopic examination revealed that cotton ball test, menace response, and obstacle test were negative in both eyes. Direct and indirect pupillary light reflexes were positive in the right eye and negative and fixed mydriatic in the left eye, indicating N. oculomotorius damage. In the direct and indirect ophthalmoscopic examination, the fundus of the right eye was normal, and the leukocoria in the left eye was due to the presence of a solid intraocular mass, which was considered to be originating from the retina *(Fig. 1-A)*. Intraocular pressure (IOP) values were determined to be 21 mmHg in the right eye and 27 mmHg in the left eye. Background USG with a 15 MH probe in the left eye (Ophthalmic, Accutome, B-Scan Plus, Canada) suggested that the solitary mass of retinal origin was found to be independent of N. opticus *(Fig. 1-B)*.

Simultaneous T2 sagittal weighted evaluation of the patient with Contrast-enhanced brain MRI (1.5 Tesla, Siemens, Magnetom Sempra, Germany) revealed solid masses of 13.4 x 9.mm intraocular in the left bulbus oculi *(Fig. 2-A)*, 19.1 x 18.4 mm at the suprasellar cistern, third ventricle and chiasma opticum levels of the brain, and 4.0 x 6.7 mm adjacent to the caudal cranial fossa in the medulla oblongata *(Fig. 2-B)*. Contrast-enhanced computed tomography (CT) scan of the thorax and abdomen (Somatom go, Germany) showed no pathologic findings.

Enucleation of the left eye was performed with standard anesthesia and surgical protocol followed by histopathologic evaluation. The eyeball was cut sagittal. A partially solid mass of 13x9 mm in size, originating from the retina and expanding into the vitreous, with no connection to the lens, was found close to the nasal angle of the eye *(Fig. 3)*.

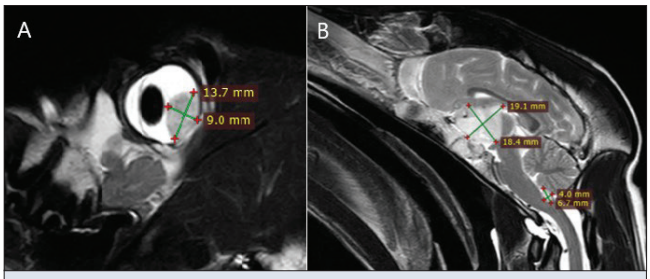


**Fig 2.** Contrast-enhanced brain MRI evaluation. **A.** Intraocular mass on T2-weighted sagittal plane in left bulbus oculi at the size of 13.7 x 9.0 mm, **B.** Solid masses on the T2-weighted sagittal plane at the suprasellar cistern, third ventricle and chiasma opticum levels of the brain (19.1 x 18.4 mm) and in the medulla oblongata adjacent to the caudal cranial fossa (4.0 x 6.7 mm)

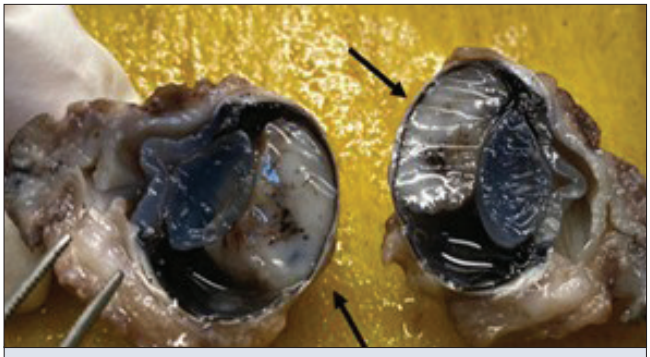

**Fig 3.** Nodular neoplastic tissue in the bulbus oculi (arrows)

The sagittal sectioned eyeball was completely cassetted and subjected to the usual routine procedures. The section surface and the tumoral mass were embedded in liquid paraffin, suitable for dissection. The prepared blocks were cut at a size of 4-5 micron thin with a rotary microtome and stained with hematoxylin and eosin (H&E) to be examined under a light microscope. The mass consisted of neoplastic cells originating from retina and expanding into the vitreous and attached to the retina at large areas *(Fig. 4-A)*. The mass had no connection with the lens and

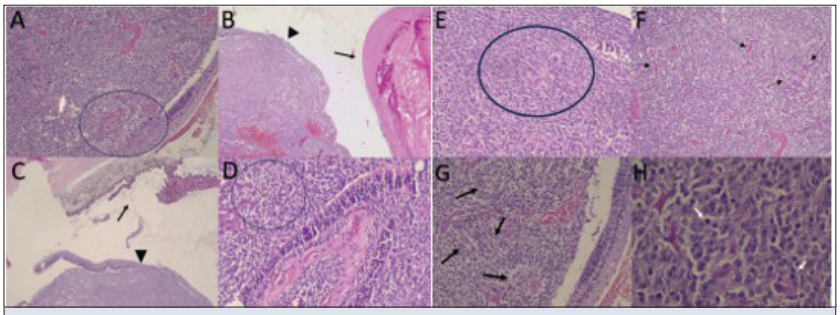


**Fig 4. A.** Neoplastic mass of retinal origin *(circled area)* HE x10, **B.** Lack of connection between neoplastic tissue *(arrowhead)* and the lens *(arrow)* HE x4, **C.** Lack of connection between neoplastic tissue *(arrowhead)* and the ciliary body *(arrow)* HE x 4, **D.** Atypical cells in neoplastic retinal tissue, some with vacuolated cytoplasm *(circled area)* HE x 20, **E.** Atypical neuroepithelial cells forming the neoplastic tissue *(circled area and its surroundings)* HE x 20, **F.** Atypical neuroepithelial cells forming neoplastic tissue with fibrovascular stroma *(arrows)* HE x 10, **G.** Imaginary rosette-like structures in neoplastic tissue *(arrows)* HE x20, **H.** Oval polygonal neuroepithelial cells forming the neoplastic tissue and mitotic structures *(arrows)* HE x40

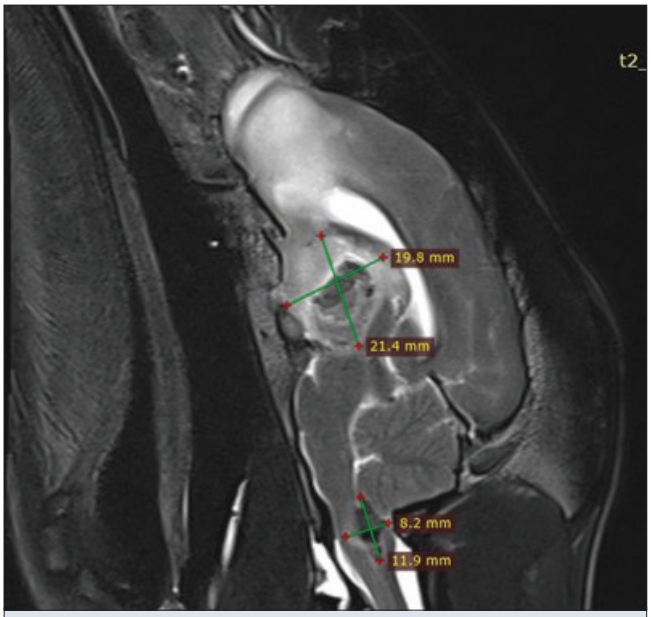


**Fig 5.** In the CMRI evaluation of the patient, on the T2-weighted sagittal plane, expansion of the mass in the suprasellar cistern, third ventricle and chiasma opticum levels of the brain to a size of 19.8 x 21.4 mm and the mass in the caudal cranial fossa adjacent to the medulla oblongata to a size of 8.2 x 11.9 mm

ciliar body *(Fig. 4-B,C)* in serial sections and there were atypical cells in the mass, some with vacuolated cytoplasm *(Fig. 4-D)*. Atypical cells were oval, spindle or polygonal shaped cells of different sizes with hyperchromatic nuclei and little cytoplasm. These cells were similar to immature neuroepithelial cells of the retina *(Fig. 4-E)*. In different areas of the neoplastic tissue, the majority of atypical cells formed rosette like structures (Flexner-Wintersteiner) with based on imaginary appearance *(Fig. 4-F,G)* and 2-4 mitotic figure on average at x40 objective were observed in different areas of oval polygonal neuroepithelial cells forming the neoplastic tissue *(Fig. 4-G,H)*. Moreover, a focus of calcification within an area of atypical neoplastic cells was also detected. Histopathologic findings confirmed that the neoplastic tissue was a retinoblastoma-like tissue. Treatment was suggested as planning tomography followed by intensity-modulated external-beam radiation therapy (Trilogy /Varian Medical Systems, Palo Alto, CA) for both lesions in the brain. The patient died due to development of unconsciousness and pressure on the respiratory center because of rapid expansion of the tumor during intermittent follow-ups.

Contrast-enhanced brain MRI evaluation following death of the patient showed that the mass at the suprasellar cistern, third ventricle and chiasma opticum levels of the brain was enlarged to 19.5 x 21.4 mm, and the mass adjacent to the caudal cranial fossa of the medulla oblongata to 8.2 x 11.9 mm on the T2-weighted sagittal plane *(Fig. 5)*.

## Discussion

Neuroblastoma, ependymoblastoma, retinoblastoma, and medulloepithelioma, which are classified in the PNET or ETMR classes, are observed in both humans and animal species, and they have been reported to occur in the peripheral and central nervous system or in the bulbus oculi [7-9]. The common feature of these tumors is that they have multilayered rosettes in histopathologic terms. Flexner-Wintersteiner rosettes are actual wheel-shaped rosettes in histopathologic evaluation and are known to be specific to retinoblastoma-like tumors and certain PNETs [10,11].

Syed NA found that the tumor contained areas of retinal photoreceptor and glial differentiation, unlike other tumors examined including Flexner-Wintersteiner rosettes, and the histopathological findings and differential staining characteristics of the retinal tumor were consistent with retinoblastoma, and they presented the first documented case of spontaneous retinoblastoma in an animal.

More recently, Regan et al.[9] diagnosed retinoblastoma-like tumors in 4 out of 8 dogs with PNET and interestingly reported that these tumors were frequently observed in dogs ≤2 years of age, which was consistent with the clinical age presentation in humans, while the more common medulloepitheliomas occurred in dogs >7 years of age. They indicated that the characteristics of retinoblastoma include predominantly hyperchromatic small neuroepithelial cells, nuclei, scanty cytoplasm, and low mitotic index with smaller sized rosette formation, often characterized by a single row, as well as radially arranged neoplastic cells.

In the histopathological evaluation of our case, considering that imaginary rosette formation was observed, the tumors surrounded a central lumen containing small cytoplasmic extensions and were characteristic for retinoblastoma, and the fact that the tumor developed in a single eye and at a young age, the findings were remarkable, and the authors agreed on the diagnosis of spontaneous retinoblastoma-like tumor.

Retinoblastomas are malignant tumors arising from the primitive neuroepithelium of the retina while medulloepitheliomas arise from the primitive medullary epithelium of the ciliary body [5]. In our case, microscopic examination clearly showed that the neoplastic tissue originated from the retina, and the neoplasm was of retinal origin.

In a 10-year-old Golden Retriever, ETMR was considered in the histopathologic examination of a retrobulbar mass that pushed the globe to the dorsotemporal region and caused distortion. It has been reported that ETMRs are generally aggressive malignant tumors in both humans and animals, and no systemic metastasis of retrobulbar ETMRs has been reported [12].

In our case, MRI evaluation revealed solid mass metastatic areas of 19.1 x 18.4 mm in the suprasellar cistern, third ventricle and chiasma opticum levels of the brain and of 4.0 x 6.7 mm adjacent to the caudal cranial fossa in the medulla oblongata.

It has been emphasized that detailed ophthalmoscopic/background sonographic examination should be performed in the differential diagnosis of retinoblastoma; retinoblastoma should be differentiated from persistent hyperplastic primary vitreous, cataract, vitreous hemorrhage, retinal detachment, and meduloepithelioma, and that background USG is necessary to recognize the type of retinoblastoma tumor in the differential diagnosis. USG diagnosis of retinoblastoma is based on demonstrating calcifications within the lesion, which produce bright signals with high reflectivity and cause shadowing [13]. Similar reflections were observed on sonography performed with B-Scan mode and 15 MH probe, and a calcified focus was detected on histopathologic examination.

While most ophthalmic tumors are locally invasive and cause distortion of the globe, retinoblastoma has been rarely associated with pain and uveitis attack. In children with retinoblastoma, leukocoria (loss of normal fundus reflex) is related to the tumor filling the globe and is the most important clinical finding [14].

Unlike ciliary - uveal melanomas which may cause elevated intraocular pressure (IOP), uveitis, pain, and globe disorientation; in the present case, the neoplastic mass expanded into the vitreous inside the eye, and the animal did not develop any distress, pain, or uveitis associated with the globe position until it was visible from the outside. Leukocoria was determined as a typical finding in retinoblastoma.

Early diagnosis of ocular neoplasia is an important aspect of treatment success. It has been reported that retinoblastoma shows local invasion to choroid and sclera in humans and can metastasize hematogenously to the bone, liver, central nervous system, and other organs [14]. In the literature review, no case of brain metastasis associated with retinoblastoma was found in dogs, and our case was believed to be the only known case of brain metastasis associated with retinoblastoma. In addition, no malignant focus outside the brain was detected on CT evaluation. Hemangiosarcoma, mammary carcinoma and melanoma are known to be the most common metastatic intracranial neoplasms in dogs. The incidence rates of metastatic brain tumors and primary brain tumors in dogs are equal [15]. Early diagnosis of retinoblastoma increase survival in humans. Among the treatment options for retinoblastoma, the current approach is enucleation and external-beam therapy in humans [5,16]. The authors recommend examination of the brain with advanced imaging techniques in cases of suspected ocular neoplasia. When the MRI findings were evaluated in the patient that died after eye extirpation before the planned radiotherapy could be performed, it was observed that the first mass in the brain rapidly enlarged by approximately 1.2 $mm^2$, and the other mass by 21.84 $mm^2$ within 1.5 months. In the light of these findings, retinoblastoma should be considered especially in young dogs with unilateral leukocoria regardless of breed. Considering that the secondary metastatic site may be the brain and the primary and secondary foci grow very rapidly, it is believed that survival may improve with early-stage diagnosis and planned anticancer treatment.

## Declarations

**Availability of Data and Materials:** The data used in this article will be provided by the corresponding author (E. Özgencil) upon request.

**Competing Interests:** The authors declared that there is no conflict of interest.

**Author Contributions:** Case examination and evaluation of

clinical findings were done by FEÖ, APG, OÜ and VÇ. FEÖ, ÖK, ND and VÇ performed the operation of the patient and provided postoperative care. EEÇ and EY interpreted MRI and CT images. FEÖ and APG contributed to the discussion. AG and DÖ performed the histopathological examination of the patient. FEÖ made the article writing and ND made the submission of the article. The authors have submitted the paper collectively.

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