INTRODUCTION

A 10-year-old dog was presented with exophthalmos, exotropia, periorbital swelling, and protrusion of the third eyelid of the right eye. Computerized tomography of the head identified a mass ventromedial to the right eye. Histopathology of the mass was suggestive of a retrobulbar embryonal tumor with unusual multiple epithelial differentiation.

Retrobulbar neoplasia is the most common orbital disease in dogs. Primary orbital tumors can originate from any orbital tissue, and secondary neoplasms either invade the orbit from adjacent structures or metastasize to the orbit from distant sites.1 A variety of primary and secondary orbital tumors have been reported in dogs, and orbital neoplasia should be considered in any case of progressive exophthalmos.2

Embryonal tumors with multilayered rosettes (ETMR) are embryonal neoplasms derived from the germinal neuroepithelium of the neural tube (neuroectoderm) that develop in the nervous system.3,5 These tumors were previously classified as primitive neuroectodermal tumors (PNETs); however, following a recent reclassification by the World Health Organization (WHO), the terminology was changed to Embryonal tumor with multilayered rosette (ETMR), and the term PNET has been removed from the diagnostic lexicon.6,7 Embryonal tumors can arise in the brain or spinal cord (central ETMR) or peripherally in bone or soft tissues (peripheral ETMR).5,8 Neuroectodermal neoplasms include neuroblastomas, gliomas, medulloepitheliomas, and retinoblastomas, as well as remarkably undifferentiated primitive neoplasms.8,9 Although uncommon, intraocular ETMRs have been described in several species, including dogs,4,10-13 horses,14-16
llamas,17-19 goldfish,9,20 and a cockatiel.21 In contrast, orbital ETMRs are extremely rare in both humans3,22 and animals. To the authors’ knowledge, the only previous report of retrobulbar ETMR in animals described the tumor in a squirrel monkey.23 In this report, we describe a retrobulbar ETMR in a dog.

2 | CASE REPORT

A 10-year-old intact male golden retriever dog presented to the Ophthalmology Service of the Small Animal Hospital at the University of Florida for evaluation of exophthalmos of the right eye (OD). A mild protrusion of the globe was identified by the owners approximately nine months prior to presentation. At that time, the patient was evaluated by the primary veterinarian and was treated with topical antibiotic and steroid (neomycin, polymyxin b, dexamethasone 0.1% ophthalmic ointment, Bausch & Lomb Pharmaceuticals, Inc, Tampa, FL, USA), without significant improvement. Eight months later, the progression of the exophthalmos motivated the owners to consult with an ophthalmologist. The dog had no history of ocular or systemic health issues and was current on routine preventative care and vaccinations.

2.1 | Initial clinical findings

Complete ophthalmic examination including Schirmer tear test-1 (STT-1) (Schirmer tear test strips® - Merck & Co. Inc, WhiteHouse Station, NJ), slit-lamp biomicroscopy (SL-15 Portable Slit Lamp, Kowa, Torrance, CA, USA), tonometry (Tonovet®, Jorgensen Labs, Loveland, CO, USA), and indirect ophthalmoscopy (Vantage Plus LED Binocular Indirect Ophthalmoscope, Keeler Ophthalmic Instruments, Broomall, PA, USA) was performed on both eyes (OU). STT-1 revealed increased tear production OD (32 mm/minute) and normal tear in the left eye (OS) (22 mm/minute). Menace response, dazzle, and palpebral reflexes were present and within normal limits OU. Pupillary light reflex (PLR) was not able to be elicited OD due to extreme miosis. Exophthalmos, dorsolateral strabismus, and ventral periorbital swelling were observed OD. The third eyelid was protruding and mildly hyperemic OD. There was a 4 mm oval white opacity in the axial cornea OD consistent with corneal dystrophy. There was hyphema filling 1/6 of the anterior chamber and fibrin clot in the anterior chamber OD. Visualization of the lens and fundic structures OD was limited by extreme miosis. Clinical findings OS were limited to one free-floating uveal cyst in the anterior chamber, along with incipient anterior cortical cataract. The remaining structures and intraocular pressures were within normal limits OU. Fluorescein staining (Bio-Glo™ sterile fluorescein strips, HUB pharmaceuticals, Rancho Cucamonga, CA, USA) revealed an intact corneal epithelium OU. General physical examination was unremarkable.

2.2 | Ancillary diagnostics tests

Complete blood cell count and serum biochemistry profile were within normal limits for the species and age. Based on the clinical signs suggestive of retrobulbar mass, ocular ultrasound, computed tomography (CT) of the head, abdominal ultrasound, and thorax radiographs were recommended and performed. For the imaging procedures, the patient was premedicated with intramuscular acepromazine maleate (0.02 mg/Kg—Vedco Inc, Saint Joseph, MO) and butorphanol (0.3 mg/kg—Zoetis, Florham Park, NJ). General anesthesia was induced with intramuscular acepromazine (0.02 mg/Kg—Hospira Inc, Lake Forest, IL) and maintained with inhalant isoflurane (Abbott Laboratories, North Chicago, IL). Ocular ultrasound revealed an oval, mainly hypoechoic retrobulbar mass ventral and nasal to the right eye, measuring 2.2 x 1.8 cm and displacing the right globe dorsotemporally. Exfoliative cytology from fine-needle aspirates of this mass was consistent with spindle cell neoplasia, characterized by a highly cellular aspirate composed of mononuclear, oval, fusiform, or stellate cells with distinct borders. Cells were found individually or formed dense sheets, with high nucleus to cytoplasm ratio and mild anisokaryosis. Abdominal ultrasound revealed a lobulated appearance of the cranial spleen, prostatomegaly, and multiple small testicular nodules. Exfoliative cytology from fine-needle aspirates of the spleen showed reactive lymphoid hyperplasia characterized, consistent with a benign hyperplastic splenic nodule. No neoplastic cells were identified. The 3-view thoracic radiographic study was within normal limits for the species and age. Head CT showed a well-defined 3.3 x 2.8 x 2 cm oval, mildly lobular mass in the right retrobulbar region, with fluid attenuating centrally and soft tissue attenuating peripherally. There were multiple thin curvilinear contrast enhancing regions within the interior of the mass and contrast enhancement limited to the periphery. The mass caused dorsolateral deviation of the right globe, as well as compression of its ventromedial aspects.

2.3 | Surgical management

Based on the clinical and imaging findings, exenteration of the right globe and retrobulbar tissues followed by orchietomy was recommended. The patient was premedicated with intramuscular acepromazine (0.02 mg/Kg) and hydromorphone (0.15 mg/kg—Hospira Inc, Lake Forest, IL). General anesthesia was induced with intravenous (IV) propofol (Abbott Laboratories, North Chicago, IL) and maintained with inhalant isoflurane in oxygen after endotracheal intubation. Exenteration of the right globe was performed
as previously described, following a retrobulbar block.\textsuperscript{1, 24} Briefly, the upper and lower eyelids were apposed with 4-0 nylon (Ethicon, Somerville, NJ) in a simple continuous pattern. Two curvilinear, intersecting incisions were made 5mm around the palpebral fissure using a No. 15 blade (Miltex, Plainsboro, NJ). Dissection of the tissues was performed using curved Metzenbaum scissors, and the extraocular muscles, globe, conjunctiva, nictitating membrane, lacrimal gland, orbital tissues, and the retrobulbar mass were removed. Moderate to severe hemorrhage occurred while removing the deep orbital tissues. Hemostasis was accomplished with manual pressure, hemostatic forceps, and hemoclips (Teleflex Medical, Research Triangle Park, NC). Closure of the deep fascial layers and subcutaneous was performed with 4-0 vicryl (Ethicon, Somerville, NJ) in a simple continuous pattern. The skin was closed with simple interrupted sutures using 4-0 monofilament nylon. Due to the unexpected intraoperative hemorrhage, orchietomy was postponed. Recovery from anesthesia was uneventful. The patient was discharged the day after surgery on medical therapy consisting of carprofen (2.2 mg/kg PO q 12h for 7 days), tramadol (4 mg/kg PO q 8-12 h for 5-7 days—Teva Pharmaceuticals, North Wales, PA), and cephalexin (30 mg/kg PO q 12 h for 10 days—Lupin Pharmaceuticals, Baltimore, MD). Postoperative healing was uneventful, and sutures were removed after 12 days. No recurrence has been reported to date (last follow-up via telephone interview, 14 months after surgery), and the owners have subsequently declined the orchietomy.

2.4 Histopathology and immunohistochemistry

The globe, periorbital structures and retrobulbar mass were immersed in 10% neutral-buffered formalin and routinely processed, sectioned, and embedded in paraffin wax. Samples were stained with hematoxylin and eosin. Gross examination revealed a firm mottled light to dark brown, multilobulated retrobulbar mass ventromedial to the optic nerve. The mass did not infiltrate the optic nerve, sclera, or third eyelid. Histologically, the mass was encapsulated, well circumscribed, and arranged in lobules separated by bands of a fibrovascular stroma. Occasionally, the lobules had regions of necrosis and on occasions formed cysts filled with swirling keratin and mucus (Figure 1).

The lobules were composed of three different cell populations: The predominant population was represented by closely packed cells with indistinct cell borders forming clusters and, multifocally, small Homer-Wright-type rosettes (Figures 1 and 2A). These cells had vacuolated, faintly eosinophilic cytoplasm and round to ovoid, small- to medium-sized hyperchromatic nuclei. Among this cell population, twenty mitotic figures were noted per ten, 400x fields (2.37 mm$^2$). A morphologically similar neoplastic cell population was observed encircling the optic nerve forming small clusters and whorls (Figures 1 and 5B). A second cell population lined multifocal cavities filled with whirling keratin (Figures 1 and 3A). The cells were cohesive and polygonal forming trabeculae, islands and nests. The cells had moderate to abundant eosinophilic cytoplasm which, occasionally, formed prominent intercellular bridges (desmosomes), and contained irregular basophilic trichohyalin granules. In these cells, the nuclei were medium to large, round to ovoid with finely stippled chromatin and up to two nucleoli. Occasionally, there was multinucleation. Mitotic figures were approximately four in ten, 400x fields (2.37 mm$^2$). Variable numbers of viable and degenerate neutrophils, foamy macrophages, and hemorrhage were present admixed with the cystic material (necrotic cell debris, keratin, and mucin). A third population of spindloid cells was arranged in interlacing fascicles and set amidst a mucinous intercellular matrix (Figures 1 and 4A). These cells had indistinct borders, with mild to moderate amounts of eosinophilic cytoplasm which at times contained a pale, basophilic material tinctorially resembling the intercellular mucin. These cells had ovoid, hyperchromatic nuclei. Twelve mitotic figures were noted in ten 400x fields (2.37 mm$^2$). Within the peripheral fibrous connective tissue or tumor stroma, there were ectatic glands filled with basophilic secretory material and lined by attenuated low cuboidal to flattened epithelium (Figures 1 and 5C). Although an anaplastic salivary gland tumor was considered, the well-differentiated glands were
considered to be adjacent, preexisting salivary glands infiltrated by the neoplasm. Histopathology of the globe revealed minimal to small number of lymphocytes and plasma cells infiltrating the iris and ciliary body. No neoplastic cells were present in the intraocular structures. The histopathologic findings of the mass were suggestive of an embryonal tumor with multilayered rosettes (ETMR), with multiple epithelial and mesenchymal differentiation, along with lymphoplasmacytic anterior uveitis in the adjacent eye.

Immunohistochemistry was performed for the following elements: S-100, vimentin, pancytokeratin (CK) AE1/AE3, muscle-specific actin (MSA), neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP) (Biocare Medical, Concord, Ca). Appropriate controls were included and exhibited appropriate staining of positive control and no staining in the negative control slides. Staining of the tumor revealed that in the first population of neoplastic cells (less than 50% of the cells) were positive for cytokeratin, including a number of cells that resembled acini and rosettes (Figure 2B). The same cells were negative for vimentin (Figure 2C), S100 (Figure 2D), GFAP, NSE, and MSA (not shown). Also positive for cytokeratin were the polygonal neoplastic cells in the second aforedescribed cell population (Figure 3B and 3C). These cells were also negative for vimentin (Figure 3C). The third population of neoplastic spindle cells demonstrated...
strong positive staining for vimentin (Figure 4C) but failed to stain with cytokeratin (Figure 4B), S100 (Figure 4D), GFAP, NSE, and MSA (not shown). Although an anaplastic salivary gland tumor was considered as a potential diagnosis, the lack of staining with either CK or MSA of the spindle cell component effectively rules out the presence of myoepithelial cells. The glandular structures at the periphery of the tumor were positive for cytokeratin only (Figure 5C). The neoplastic cells surrounding the optic nerve (Figure 5B) were positive for vimentin (Figure 5D) and NSE (not shown).

3 | DISCUSSION

Embryonal tumors with multilayered rosettes are believed to have a neural histogenesis based on evidence of varying degrees of neuroectodermal differentiation and include a wide array of lesions. Those neoplasms with poorly differentiated cells are generally classified as ETMRs; however, tumors can be further classified based on the origin cell line. Neuroblastoma, medulloepitheliomas, ganglioneuroblastoma, retinoblastoma, and ependymoblastomas are
examples. Primary retrobulbar ETMR is an extremely rare tumor, and only a few reports are available in the human literature. Although primary ocular ETMRs have been previously diagnosed in animals, the majority of the reports describe intraocular neoplasms, while retrobulbar primary ETMRs are rare. To the authors’ knowledge, this is the first report of a retrobulbar primary ETMR in a dog.

In humans, while ETMRs, in general, can be found in any age group with a peak incidence in the adolescents, data collected from retrobulbar ETMR do not suggest any age predilection. In dogs, intracranial retinoblastoma-like tumors are more likely to occur in young patients, while intraocular medulloepithelioma has been reported in older animals. Determination of a specific cell line of the tumor in this 10-year-old dog was not possible due to the extremely primitive stage of development of the tumor cells. Data for dogs with ETMRs in dogs regarding breed or sex predilection, clinical characteristics, treatment options and outcomes, and prognosis are not available due to the rarity of this neoplasm.

Retrobulbar ETMRs are heterogeneous from a clinical, histopathologic, and immunohistochemistry standpoint; however, one common feature seems to be a tendency to arise in the lateral orbit, with only a couple of reports of tumors arising in the inferior orbit in humans. Additionally, bony involvement is not a common feature. There are no comments regarding the specific anatomical location of the tumor or bony involvement in the squirrel monkey case. In the present case, the neoplasm was located in the ventromedial aspect of the orbit, and no bony involvement was noted on CT evaluation.

The microscopic aspects of the neoplasm reported here are consistent with what has been described in the literature. Microscopically, peripheral ETMRs are characterized by small round, polygonal, or spindle-shaped cells resembling primitive neuroepithelium, with hyperchromatic nuclei and high nuclear-cytoplasmic ratio. The presence of a fibrovascular stroma, as observed in the present case, is also a common feature of ETMRs. Embryonal tumors are also characterized by various degrees of neuronal differentiation, beginning with neuron-specific enolase expressivity, followed by Homer-Wright rosettes formation, phenotypic ganglion cell differentiation, and finally neurofilament protein expression. Homer-Wright rosettes, a form of neuronal differentiation, are characterized by a radial arrangement of spindloid cells surrounding a central lumen containing tangles of neurofibrillary material. Although Homer-Wright rosettes may be found in other types of neurological tumors, these structures occur in a restricted number of neoplasms and, in the present case, point toward the presumptive diagnosis of retrobulbar ETMR. The presence of necrosis, as described in the case reported here, has also been reported as a common feature of ETMRs in both humans and dogs.

Available information regarding immunohistochemistry features on ocular and non-ocular ETMRs in humans and animals is scarce and controversial. Table 1 summarizes the findings of some ETMRs case reports in the literature. Immunohistochemical stains selected for this case included S-100 (a neuronal and melanocytic cell marker), vimentin (a mesenchymal cell marker), cytokeratin (an epithelial cell marker), and GFAP (a glial cell marker). Cytokeratin expression was the only reactivity observed, and the marker was particularly positive on cells that resembled rosettes formation. The same feature was also observed on a dog with central (brain) ETMR with ependymal differentiation, and the authors described cells expressing cytokeratin associated with the areas of rosette formation. In the present case, it is possible that the cytokeratin-positive structures were actually acini tubules, instead of rosettes. Based on this feature and the location of the mass, salivary gland adenocarcinoma should be considered as a possible differential. However, one would not expect to see the spectrum of different cell populations as observed in the tumor of our patient. Embryonal tumors may have variable immunoreactivity depending on the species and can differ even between individuals on the same species, and this feature can also be observed on Table 1. It is also possible that the immunohistochemical reactions may be influenced by the degree of cellular differentiation and degree of autolysis or necrosis. Due to the variable immunolabeling pattern of those tumors and scarce documentation of those tumors in the literature, data acquisition and documentation of new cases are important to better categorize this entity in the future.

Although ETMRs are generally aggressive malignant tumors in both humans and animals, fatality has been reported in only one case of retrobulbar ETMR in humans. Additionally, no systemic metastases have been documented in retrobulbar ETMRs. Some authors speculate that the lesser metastatic capabilities of the retrobulbar ETMR compared to other peripheral ETMRs may be due to the absence of intraorbital lymphatic vessels. No systemic metastases have been diagnosed in the present case, and although we have only 14 months of follow-up, the benign clinical course in this patient to date is similar to the majority of retrobulbar ETMRs in humans. Nevertheless, long-term follow-up is recommended in the management of any neuroectodermal tumor as metastasis and recurrence have been reported. Another point to consider is that since orchietomy and histopathology of the testicle were not performed in our patient, it is not possible to determine whether the testicular nodules observed via ultrasonography are benign masses unrelated to the retrobulbar tumor.
**TABLE 1** Immunohistochemistry findings on reported cases of primitive neuroectodermal tumors (++, strongest reaction; -, negative reaction; NA, not available)

| Author          | Tumor                                           | IHC | Marker       | Result |
|-----------------|-------------------------------------------------|-----|--------------|--------|
| Headley et al³  | Central ETMR w/ ependymal differentiation (dog) | Yes | GFAP         | ++     |
|                 |                                                 |     | NSE          | +++    |
|                 |                                                 |     | vimentin     | +      |
|                 |                                                 |     | cytokeratin  | +      |
| Choi et al⁵     | ETMR (brain) (dog)                              | Yes | vimentin     | ±      |
|                 |                                                 |     | cytokeratin  | −      |
|                 |                                                 |     | GFAP         | −      |
|                 |                                                 |     | NSE          | +++    |
|                 |                                                 |     | S-100        | +++    |
| Alyahya et al⁶  | ETMR (orbit) (human)                            | Yes | S-100        | −      |
|                 |                                                 |     | vimentin     | −      |
|                 |                                                 |     | cytokeratin  | −      |
|                 |                                                 |     | NSE          | −      |
|                 |                                                 |     | GFAP         | −      |
| Bartlett et al⁷ | Intraocular neuroectodermal tumor (goldfish)    | Yes | S-100        | +      |
|                 |                                                 |     | vimentin     | −      |
|                 |                                                 |     | NSE          | −      |
| Jensen et al¹⁰  | Neuroepithelial tumor (retina) (dog)            | Yes | S-100        | +      |
|                 |                                                 |     | vimentin     | +      |
|                 |                                                 |     | GFAP         | −      |
|                 |                                                 |     | NSE          | −      |
|                 |                                                 |     | cytokeratin  | −      |
| Aleksandersen et al¹¹ | Teratoid medulloepithelioma (ciliary body, brain, kidney) (dog) | Yes | vimentin     | +      |
|                 |                                                 |     | S-100        | −      |
|                 |                                                 |     | cytokeratin  | −      |
|                 |                                                 |     | NSE          | −      |
|                 |                                                 |     | GFAP         | −      |
| Knottenbelt et al¹³ | Intraocular ETMR (neuroblastoma) (horse)    | Yes | vimentin     | ++     |
|                 |                                                 |     | NFP          | +      |
|                 |                                                 |     | GFAP         | +/−    |
|                 |                                                 |     | S-100        | ±      |
|                 |                                                 |     | Pancytokeratin| −      |
| Leiva et al¹⁴  | Intraocular teratoid medulloepithelioma (horse) | Yes | vimentin     | +      |
|                 |                                                 |     | S-100        | +      |
|                 |                                                 |     | NSE          | +      |
|                 |                                                 |     | GFAP         | −      |
| Hendrix et al¹⁵ | Teratoid Medulloepithelioma (intraocular) (llama) | Yes | vimentin     | +      |
|                 |                                                 |     | NSE          | +      |
|                 |                                                 |     | MSA          | ±      |
|                 |                                                 |     | S-100        | ±      |
|                 |                                                 |     | cytokeratin  | −      |
|                 |                                                 |     | GFAP         | −      |
| Fugaro et al¹⁶  | Retinoblastoma (llama)                          | Yes | GFAP         | −      |

(Continues)
or metastatic lesions from the ETMR. In fact, the possibility of the testicles being the primary site of the ETMR cannot be ruled out either, since spermatocytic seminoma with primitive neuroectodermal tumor has been previously diagnosed in one dog.30 As ETMR embraces the concept of embryonal neoplasms arising from the primitive neuroectodermal progenitor cells, various degrees of neuronal differentiation can be expected under the umbrella of ETMRs.4,5,8 This explains the morphologic variation described in the literature, ranging from the most undifferentiated tumors lacking most of the features of neural differentiation, to the most differentiated neoplasms exhibiting more than one characteristics of neural differentiation.8 Moreover, phenotypic differentiation may occur after the transformation of undifferentiated neuroepithelial cells, resulting in lineage variations.8 This may explain the occurrence of neoplasms without a specific cell differentiation as well as with differentiation in 2 or more cell lines, as observed in the present case.7

The case described in this report is presumed to be poorly differentiated ETMR and is the first retrobulbar ETMR case described in dogs. Although rare, ETMR should be considered in the differential diagnosis of retrobulbar tumors in dogs, regardless of the age of the patient, with the understanding that ancillary tests are required for definitive diagnosis.

**ETHICS STATEMENT**

Verbal consent for publication was obtained from client prior to manuscript preparation.

**ACKNOWLEDGMENTS**

The authors would like to thank the Diagnostic Imaging Service at University of Florida for their help and expertise with the imaging modalities. Published with written consent of the patient.

**CONFLICT OF INTEREST**

None.
AUTHOR CONTRIBUTIONS
Bianca C. Martins and Caryn E. Plummer: involved in case management, and manuscript preparation and revision; Jason Struthers and Jeffrey Abbott: involved in histopathology preparation and analysis, and manuscript preparation and revision.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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