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MRI Findings of Suprasellar Germ Cell Tumors in Two Dogs

Laurie Cook, DACVIM (Neurology), DVM, Michelle Tensley, DACVIM (Neurology), DVM, Wm Tod Drost, DACVR, DVM, Christopher Koivisto, DVM, and Michael Oglesbee, DACVP, DVM, PhD

Department of Veterinary Clinical Sciences (L.C., M.T., W.T.D.) and Department of Veterinary Biosciences (C.K., M.O.), The Ohio State University, Columbus, Ohio

Abstract

A 4 yr old border collie presenting for mydriasis and decreased mentation and a 7 yr old Boston terrier presenting for obtundation, head tilt, and paraparesis were both evaluated using MRI. Findings in both included mass lesions of the thalamus and brainstem that were hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images with regions of hypointensity, and robust contrast enhancement and displacement of adjacent structures. Postmortem histopathology findings, tumor location, and a mixed pattern of epithelial cell differentiation were consistent with germ cell tumor in both cases. Germ cell tumor of the suprasellar region is an infrequently reported neoplasm of dogs and imaging findings in this species have not been well described in the prior literature.

Introduction

Germ cell tumor (GCT) of the suprasellar region is an infrequently reported neoplasm of dogs. Imaging features of these types of neoplasm are available in the human literature but have not been well described in dogs.^{1,2} Histopathologic criteria for diagnosis, including tumor marker evaluation, have been published in the veterinary literature.³ The following report details the clinical history, MRI findings, and histopathology of two dogs diagnosed with GCT.

Case Report

Case 1

A 4 yr old intact male border collie presented for a 2 wk history of mydriasis of the left eye, previously diagnosed as anterior uveitis. Aside from pupil dilation, the initial physical examination was unremarkable. Two weeks later, the dog developed progressive anorexia, lethargy, and disorientation. Physical examination revealed a sinus bradycardia (40 beats per min). The neurological examination revealed depressed mentation, absent left pupillary light reflex and menace response, absent oculocephalic reflexes, and decreased sensation in the right naris. The dog was ambulatory with a normal gait but paced compulsively. The remainder of the neurological examination was recorded as normal. A lesion involving the

thalamocortex rostral to the optic chiasm, the left optic nerve, and brainstem was suspected. The dog was noted to be hypotensive with a systolic blood pressure of 80 mm Hg. Complete blood count, serum biochemistry profile, and thoracic radiographs were unremarkable. Serology was positive for *Borrelia burgdorferi*, but that was attributed to prior vaccination. *Ehrlichia canis*, *Rickettsia rickettsii*, *Anaplasma phagocytophilum*, *Cryptococcus*, and *Brucella canis* serology were negative. Initial treatment pending imaging was intravenous Lactated Ringers solution (2 mL/kg/hr), mannitol (250 mg/kg), doxycycline (11 mg/kg), and clindamycin (8 mg/kg). Neurologic status did not improve with therapy. An MRI was pursued.

MR images were acquired using a 3T magnet^a and a knee coil^b. A 2.5 × 2.5 × 2.1 cm mass was present along the ventral aspect of the brain at the level of the thalamus. This mass had irregular margins and was larger on the left than on the right. On T1-weighted (T1-W) precontrast images, the mass was of mixed intensity, predominantly isointense to brain parenchyma with areas of hypointensity (Figures 1A–C, E). This mixed signal intensity could represent hemorrhage or mineralization. On T2-weighted (T2-W) images, the mass was generally hyperintense relative to the adjacent thalamic white matter and had a hypointense, mottled internal region (Figures 1A, B). Following intravenous paramagnetic contrast medium administration (gadodiamide^c, 0.1 mmol/kg), the mass showed mild contrast enhancement peripherally and had lobular margins. The central aspect of the mass displayed less intense contrast enhancement (Figures 1D, F). On the sagittal plane images, thin, tapering contrast enhancement extended from the caudoventral aspect of the mass; in this region, the mass was broad based and resided adjacent to the calvarium (Figure 1F). The mass caused dorsal displacement of the thalamus and left lateral ventricle. A mild rightward shift of the falx cerebri was present (Figures 1B–D). Perceived thinning of the ventral calvarium (triangle arrow, Figure 1B) with mild contrast enhancement extending outside the calvarium (black arrow, Figure 1D) that may represent extension of the tumor or secondary inflammation was suspected. There was also caudal tentorial herniation. FLAIR and T2* sequences were not obtained.

Analysis of cerebrospinal fluid (CSF) obtained from the cerebellomedullary cistern following MRI was interpreted as albuminocytologic dissociation with mild blood contamination. The protein content was 46 mg/dL (normal <27 mg/dL), with 30 red blood cells per microliter and a total of 50 white blood cells/mL (normal <5 nucleated cells/μL). No abnormal cells or etiologic agents were noted. Differential diagnoses included granular cell tumor, histiocytic sarcoma, primitive neuroectodermal tumor, metastatic neoplasia, lymphoma, or a granuloma. We considered a meningioma and primary pituitary tumor less likely due to thinning of the calvarium and presumed extension through the bone. Radiation therapy and continued medical therapy with steroids were declined, and the patient was euthanized due to poor quality of life. A necropsy was elected.

^aPhilips Achieva 3T; Philips Healthcare, Cleveland, Ohio

^bPhilips SENSE Knee-8 Coil; Philips Healthcare, Cleveland, Ohio

^cOmniscan; GE Healthcare Inc., Princeton, New Jersey

At gross necropsy, a 3×2.5 cm soft, gray-tan mass was identified surrounding the optic chiasm. On sectioning, the mass was poorly demarcated and extended 4 cm into the overlying cerebrum, displacing the midline toward the right. The pituitary gland could not be identified. Histologically, the mass was unencapsulated but compressed and invaded the overlying brain parenchyma as well as the underlying bone. The majority of the mass consisted of densely cellular sheets of polygonal cells separated by cords of variably thick fibrovascular stroma and multifocal regions of necrosis. Neoplastic cells displayed marked anisocytosis and anisokaryosis with oval, centrally placed nuclei containing densely clumped chromatin and a single prominent nucleolus. These cells contained moderate amounts of foamy eosinophilic cytoplasm and often a single large vacuole. Frequent small nests of neoplastic squamouslike epithelium or acinar structures surrounding small amounts of eosinophilic to amphophilic material were noted within the sheets of polygonal cells. Immunohistochemical (IHC) staining for cytokeratin (CK) and alpha fetoprotein (AFP) was performed. There was mild to moderate expression of AFP primarily in the vacuolated polygonal cells and CK expression primarily in the epithelioid cells. Immunohistochemical staining for vimentin and c-kit was negative. It was diagnosed as a GCT; Figure 2).

Case 2

A 7 yr old male castrated Boston terrier was originally presented for trembling and back pain. Neurologic evaluation was consistent with a T3-L3 myelopathy. Spinal radiographs revealed no significant changes. The dog was treated with tramadol (2.5 mg/kg *per os* [PO] every 8 hr), carprofen (2.5 mg/kg PO every 12 hr), and cage rest. The owner reported an initial mild improvement in clinical signs of pain. The dog returned 2 wk later for a recheck examination. On questioning, the owners reported the dog had been having episodes of vocalization, disorientation, and reduced responsiveness suggestive of seizure activity. He also had progressive pelvic limb weakness. Physical examination revealed exophthalmos of the left eye with normal retropulsion. Neurological examination identified obtunded mentation, right-sided head tilt, and thoracic limb hypermetria. A lesion involving the cerebellomedullary angle and possibly the thalamus was suspected. Complete blood count, serum biochemistry profile, and thoracic radiographs were unremarkable. An MRI was recommended.

MR images were acquired using a 3T magnet^a and a neurovascular coil^d. A 2.0×1.9 cm mass was present within the thalamus, compressing the rostral aspect of the brainstem. The mass had smooth, slightly irregular margins. The mass was hyperintense and patchy on T2-W (Figures 3A, B) and FLAIR images (Figure 3H). On the T2-W sagittal image, there was caudal tentorial and foramen magnum herniation with high cervical syringohydromyelia. The mass was hypointense to brain parenchyma on T1-W images (Figures 3C, E). Following intravenous paramagnetic contrast medium administration (gadodiamide^c, 0.1 mmol/kg), relatively homogeneous contrast enhancement was present (Figures 3D, F, G). The peripheral aspect of the mass enhanced more than the central aspect. The mass caused caudal displacement of the brainstem and cerebellum. The cerebellum protruded through the occipital foramen on sagittal images. The lateral and third ventricles were dilated. There was

^dPhilips SENSE NV-16 Coil; Philips Healthcare, Cleveland, Ohio

mild contrast enhancement on T1-W sagittal images and mild hyperintensity on FLAIR images around the peripheral margins of the lateral ventricles. This might have represented edema, possibly interstitial edema (Figure 3H). Differential diagnoses included pituitary tumor, meningioma, granular cell tumor, histiocytic sarcoma, lymphoma, or a granuloma. Pituitary tumor or meningioma was considered more likely in this case because of the absence of bone involvement, as had been suspected in the prior dog.

Therapy after MRI was limited to a single dose of intravenous mannitol (500 mg/kg). CSF analysis was not performed due to cerebellar herniation. Radiation therapy or palliative therapy with corticosteroids were offered but declined by the owner. The dog was euthanized due to poor quality of life. A necropsy was elected.

At necropsy, the vermis of the cerebellum was herniated through the foramen magnum. On the ventral surface of the brain, in the region of the pituitary gland and including the hypothalamus, a 2-cm round, white to pale yellow mass that was firmer than the adjacent cerebral tissue was observed extending 2 cm into the brain parenchyma on sectioning (Figure 4). The pituitary gland was compressed but otherwise grossly unremarkable. Histologically, the mass was densely cellular and unencapsulated with compression and focal invasion into the overlying brain. The mass consisted of sheets of polygonal cells separated by thick cords of loose hypocellular fibrovascular stroma. Neoplastic cells displayed marked anisocytosis and anisokaryosis with frequent mitotic figures were present. Nuclei were oval to irregular shaped, centrally located, and contained finely stippled chromatin and a single, large nucleolus. Occasional multinucleation was noted. Neoplastic cells contained abundant, foamy eosinophilic cytoplasm and often formed acini containing eosinophilic to amphophilic material within the lumen. Occasionally, neoplastic cells contained markedly distended, clear cytoplasm that compressed the nucleus against the plasma membrane. Neoplastic cells forming acini were strongly positive for CK by IHC staining, whereas the remaining neoplastic cells were negative. Immunohistochemical staining for c-kit, vimentin, and AFP were negative. It was diagnosed as a GCT (Figure 2).

Discussion

GCT of the central nervous system (CNS) are uncommon tumors in both humans and animals. They account for approximately 0.4–3.4% of CNS tumors in human pediatric patients, with 90% of cases reported in patients younger than 20 yr of age.¹ These tumors are most often identified in the pineal and suprasellar region of the brain in humans but have been reported in other areas within the cranial vault.^{1,2} Canine CNS GCT are predominately identified within the suprasellar region, with isolated reports of tumors in the eye and spinal cord.^{3–10} There is also a single report of a suprasellar GCT in a young heifer calf.¹¹ Dogs are typically young to middle-aged (reported range 1–6 yr). Although both mixed breed and purebred animals are affected, this is the first report in either a Boston terrier or a border collie.

The diagnostic criteria used for pathologic identification of suprasellar GCT in these dogs were first established by Valentine in 1988 and include three key findings: location, presence of multiple distinct cell types including seminomatous or teratomatous differentiation, and

positive AFP staining in some GCT.³ The absence of AFP staining in case 2 did not preclude making the diagnosis of GCT as the AFP IHC may be negative in some cases. The characteristic pattern of multiple cell types, epithelial cells forming duct-like or acinar structures that were in turn embedded in sheets of small polygonal cells, is enough to confirm the diagnosis histologically.³ Although this histologic classification system has been well described in the available veterinary literature, complete MRI findings have been described in only one prior case report. In that case, the lesion was hyperintense in T2-W images and isointense in T1-W images, with a moderate amount of homogenous contrast enhancement.⁸ With the exception of the homogeneity of contrast enhancement throughout the tumor in the previously described case, the findings in our cases are otherwise similar. MR imaging is considered a sensitive method for identifying suprasellar and pineal tumors in humans, but exact determination of histologic tumor type cannot be made without tumor biopsy or tumor marker evaluation.¹ CNS GCT in humans are classified by the World Health Organization into the broad categories of germinomas and nongerminomatous germ cell tumors (NGGCT). These are then further subdivided into multiple categories. The difference in classification between human and veterinary literature makes direct comparison to imaging findings between species challenging. Germinomas and NGGCT are described as iso- to hypointense on T1-W images and iso- to hyperintense on T2-W images. Germinomas are homogeneously contrast enhancing, whereas NGGCT are heterogeneously enhancing.^{1,2} The heterogeneity of NGGCT has been postulated to be secondary to the heterogeneous cell population and microcystic portions of these tumor types.²

Histology of both cases discussed here revealed that they were composed of a heterogeneous cell population as well as areas of necrosis, thick fibrovascular tissue, and acinar structures. This could explain the low signal intensity within the T1-W images, mottled T2-W signal of the internal region of case 1, and mixed intensity T2-W appearance of case 2. Low T2-W signal is seen with only limited pathologies in masses including mineralization, thick fibrous tissue, and paramagnetic substances. Small areas of T2-W hypointensity that do not contrast enhance are noted in case 1 and could be related to the fibrovascular stroma, as mineralization and hemorrhage were not appreciated postmortem. Gradient echo images would have complemented the imaging evaluation for hemorrhage. In case 2, the foramen magnum herniation, dilation of lateral and third ventricles, and suspected interstitial edema were all thought to be secondary to obstruction and mass effect from the tumor.

An unusual feature of the first case not previously reported in dogs is the presence of invasion into bone with GCT. Thinning of the T1-W intramedullary fat signal in the calvarium adjacent to the mass lesion seen in transverse images (Figures 1B, D) may be indicative of the bone invasion noted during histologic assessment. In addition, the contrast-enhancing material outside the calvarium at that site (Figure 1D) likely represents extension of neoplasia or inflammation. Recognition of this change during imaging influences the differential list toward more aggressive neoplasms. Intracranial metastases presumably due to dissemination through the cerebrospinal fluid have been reported in one prior canine GCT case.³ The irregular margins of the mass seen on MRI were likely due to the invasion into overlying brain parenchyma noted at necropsy as tumor invasion into the brain parenchyma is common. In humans with GCT, extracranial metastases have been reported in the peritoneum and lung.¹²

Other tumors that occur in the sellar region of the canine brain include pituitary tumors, meningioma, lymphoma, and ependymoma.¹³ Radiographic findings that may help suggest meningioma include the presence of a dural tail sign and hyperostosis within the adjacent calvarium.¹³ Lymphoma is reported to have irregular margins in T2-W images and abnormal meninges around the lesion.¹⁴ Diagnosis of lymphoma may be secured through identification of lymphoblasts on CSF cytology.¹⁵

Pituitary macroadenomas and adenocarcinomas have similar imaging characteristics to those described above for GCT. They can be isointense on T1-W images and hyperintense on T2-W images and have uniform contrast enhancement.¹³ Differentiation between these tumor types may be difficult based on imaging alone; the reports of GCT often indicate that the pituitary gland is indistinguishable from tumor tissue histologically, due to obliteration or invasion. The inability to identify the pituitary gland in the first dog was likely due to distortion and replacement of the pituitary gland by neoplastic tissue. However, lack of clinical signs associated with hypopituitarism indicates that adequate residual tissue probably remained. Clinical signs of hyperadrenocorticism are often present in patients with pituitary macroadenomas and may be supportive of that diagnosis. In addition, biochemistry results suggestive of pituitary-dependent hyperadrenocorticism are often present in patients with pituitary macroadenomas. Other intracranial signs can be seen with larger pituitary macroadenomas (16). Clinical signs reported in prior canine GCT included depression, mydriasis, blindness, bradycardia, postural reaction deficits, and circling.³⁻⁸ Diabetes insipidus, hypopituitarism, and signs of increased intracranial pressure have also been reported in humans.¹

There are no reported premortem diagnoses or treatment protocols for canine intracranial GCT. Human antemortem diagnoses are obtained through the use of CSF markers such as AFP and c-kit and biopsy.¹ In theory, CSF markers could help identify these tumors in dogs; however, the logistics of establishing reference ranges is unreasonable because of the small number of affected animals. Stereotactic biopsy has been used in human patients, but carries a risk of morbidity and mortality as well as insufficient tissue for analysis.¹ A transsphenoidal approach, as used in treatment of pituitary tumors, has been mentioned as a potential methodology for antemortem diagnoses.⁸ Transsphenoidal hypophysectomy in dogs has been reported to have a 8% postoperative mortality rate, which is correlated to surgeon experience, and a high incidence of surgery-related keratoconjunctivitis sicca.¹⁷ Also, hypophysectomy has been reported in dogs for pituitary-dependent hyperadrenocorticism and pituitary macroadenomas. The complication rate is not known for biopsy, a potentially less invasive surgical procedure.

Treatment protocols for human CNS GCT have consisted of chemotherapy, radiation, or a combination of both. NGGCT in humans, which are more similar histologically to the GCT reported in dogs, are less radiosensitive, but survival rates up to 74% at 4 yr have been reported when a combined treatment is used.

Learning Points

- MRI features of GCT may be helpful in distinguishing these tumors from other masses in the suprasellar region.

- Germ cell tumors should be considered as a differential diagnosis in dogs with masses present in the sellar region of the brain.
- Affected dogs are often young to middle age.
- Methods for premortem definitive diagnosis warrant further investigation.
- Response to treatment (radiation therapy, chemotherapy) in dogs is not known.

Conclusion

Suprasellar germ cell tumor should be included as a differential diagnosis for any young or middle-aged dog with an extra-axial mass identified by MRI in the sellar region. Clinical signs in conjunction with ancillary testing, such as CSF analysis, may be helpful in distinguishing tumor type. Investigation of methods for premortem diagnosis is warranted, but radiation therapy should be considered as an option for palliative treatment in animals suspected to have GCT.

Glossary

AFP	alpha fetoprotein
CK	cytokeratin
CSF	cerebrospinal fluid
GCT	germ cell tumor
IHC	immunohistochemical
NGGCT	nongerminomatous germ cell tumors
PO	<i>per os</i>
T1-W	T1-weighted
T2-W	T2-weighted

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FIGURE 1.

MR images for case 1. (A) T2-W parasagittal plane. (B) T2-W transverse plane. The mass is present along the ventral aspect of the brain at the level of the thalamus, slightly left sided (*arrows*). The mass is mixed intensity with hyperintensity particularly around the periphery. There is suspected thinning of the bone ventral to the mass (*triangle arrow*). (C) T1-W precontrast transverse plane. (D) T1-W postcontrast transverse plane. (E) T1-W precontrast sagittal plane. (F) T1-W postcontrast sagittal plane. The mass is of mixed intensity on T1-W, primarily isointense, and is causing a mass effect with midline shift to the right. Postcontrast, it is well defined and strongly contrast enhancing with mixed intensity in the

center. There is suspected bone thinning ventral to the mass (*D*, *black arrow*) with contrast-enhancing material outside of the calvarium.

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FIGURE 2.

Histology from case 1 (*A–C*) and case 2 (*D–F*). (*A, D*) H&E stain. (*B, E*) Pan-cytokeratin stain. (*C, F*) α -Fetoprotein stain. Note the raft of cytokeratin-positive epithelial cells (*) surrounded by polygonal cells that variably express α -fetoprotein. Bar = 20 μ m.

FIGURE 3.

MR images for case 2. T2-W transverse plane (*A*) and T2-W sagittal plane (*B*). The mass is moderately hyperintense in the center with a markedly high-intensity signal around the periphery. T1-W precontrast sagittal plane (*C*) and T1-W postcontrast sagittal plane (*D*). T1-W precontrast transverse plane (*E*), T1-W postcontrast transverse plane (*F*), and T1-W postcontrast dorsal plane (*G*). The mass is hypointense on T1-W precontrast. The mass is moderately heterogeneously contrast enhancing with fairly well-defined borders and mixed intensity in the center. It is displacing the thalamus and brainstem caudally and compressing the lateral and third ventricles. (*H*) FLAIR transverse plane. The mass has a high signal intensity compared with the brain tissue and CSF. CSF, cerebrospinal fluid.

FIGURE 4.

Transverse necropsy section of the brain from case 2, a 7 yr old Boston terrier, taken at the level of the thalamus. On the ventral surface of the brain, in the region of the pituitary gland and including the hypothalamus, is a 2-cm round, white to pale yellow mass that was firmer than the adjacent cerebral tissue and extends 2 cm into the brain parenchyma (*arrow*). To the right, a transverse postcontrast T1-W MRI at a similar level from the same dog.