Glioblastoma Multiforme with Hypodipsic Hypernatremia in a Seven-Month-Old Golden Retriever

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ABSTRACT

Primary hypodipsic hypernatremia is a rarely reported disease in dogs. Reported underlying causes associated with this disease in dogs include congenital malformations, encephalitis, intracranial neoplasia, and pressure atrophy of the hypothalamus secondary to hydrocephalus. The dog in this report had an infiltrative neoplastic disorder, likely causing damage to the hypothalamic osmoreceptors responsible for the thirst generation. The neoplastic process was identified histopathologically as glioblastoma multiforme, an unusual tumor to occur in a dog this young. A tumor of the central nervous system causing physical destruction of the osmoreceptors has rarely been reported in dogs and none of the previously reported cases involved a glial cell tumor. (J Am Anim Hosp Assoc 2016; 52:319–324. DOI 10.5326/JAAHA-MS-6382)

Introduction

Primary hypodipsia or adipsia causing secondary hypernatremia has been rarely reported in dogs. Previously reported etiologies include hypothalamic granulomatous meningoencephalitis, pressure atrophy secondary to hydrocephalus, prosencephalic dysplasia, lobar holoprosencephaly, and hypothalamic lymphosarcoma, including one report of B-cell lymphosarcoma in a cat.1–6 Although there is one report in a dog and cat each of intracranial neoplasia causing primary hypodipsia or adipsia, to the authors’ knowledge this is the first report of hypothalamic glioblastoma multiforme (GBM) in a dog causing hypodipsia and hypernatremia. Glioblastoma multiforme is an extremely rare tumor; although it has been previously reported in middle-aged to older dogs, this is the first report in a 7 mo old dog.7 Although GBM, the most malignant type of astrocytoma, is the most common type of primary central nervous system tumors in humans, it is rare in dogs.8 In dogs, astrocytomas have been reported to comprise about 10–15% of all primary nervous system tumors; 5% of astrocytomas are GBM.8,9 Astrocytomas are the most common primary brain tumor reported in children, but they have been infrequently reported in young dogs.10,11 Although there are several reports of young dogs (19 wk to 4 yr) with spontaneously occurring astrocytomas, none of the dogs had the high-grade form.12–14 This report describes an uncommon primary intracranial tumor in a young dog, likely causing the rare clinical disease, hypodipsic hypernatremia secondary to presumed destruction of the hypothalamic osmoreceptors.

Case Report

A 7 mo old castrated male golden retriever was presented to an emergency veterinarian with a 6 wk history of circling and lethargy.
He had intermittent diarrhea and panting and was reportedly found pacing and circling to the left. Two wk prior to presentation, his owners noticed that he was consuming very little water or food. On presentation, he was mildly febrile (103.1°F), had a dull mentation, and was lethargic. His neurological examination revealed intermittent circling (wide circles) to the left, delayed proprioceptive placing, and hopping with the right thoracic limb and right pelvic limb with no obvious ataxia. His neuroanatomic localization was the left-sided prosencephalon. Differential diagnoses for his neurological signs included primary brain disease (infection, inflammation, neoplasia, degenerative, congenital) and secondary brain disease (nutritional, metastatic neoplasia). Differential diagnoses for his fever included neurological disruption of his hypothalamic thermoregulator cells (including infectious disease, neoplasia, inflammatory brain disease), pneumonia, gastrointestinal disease, pain, other systemic inflammation, and/or infection.

His blood pressure was measured using an indirect method, which revealed hypotension (50 mm Hg systolic). A complete blood count and serum biochemistry panel were performed, which revealed severe hypernatremia (>180 mmol/L; reference range, 144–160 mmol/L), hyperchloremia (157 mmol/L; reference range, 109–122 mmol/L), and hypealbuminemia (2.0 g/dL; reference range, 2.3–4.0 g/dL). Urinalysis revealed concentrated urine with a specific gravity greater than 1.040 and an inactive sediment. A basal cortisol level was measured and was not consistent with hypoadrenocorticism (9.3 ug/dL; reference range, 2–6 ug/dL, <2 ug/dL being suggestive of hypoadrenocorticism). Three-view thoracic radiographs were normal. An abdominal ultrasound examination showed an area of suspected abnormal small intestinal bunching and was followed by a complete barium contrast study of the gastrointestinal tract. The barium study was normal, showing no sign of intestinal obstruction. Due to the patient’s history, laboratory results, and neurological signs, chronic hypernatremia was suspected, at which time the dog was hospitalized for further diagnostic tests and therapy. Chronic hypernatremia is defined as a mean sodium level greater than 165 mEq/L, present for more than 2 to 3 days.15 The patient’s free water deficit was calculated prior to the administration of IV fluids, using the following formula:

\[
\text{Water deficit} = \text{weight (kg)} \times \left\{ (\text{current [Na]} / \text{previous [Na]}) - 1 \right\}
\]

The referring veterinarian started IV fluids using 5% dextrose in water at 40 mL/hr and 0.9% saline at 75 mL/hr.

The patient’s electrolytes were checked every 4 hr in an attempt to avoid lowering the serum sodium too rapidly and causing edema. The brain protects against cellular dehydration and shrinkage associated with the change in osmolality with chronic hypernatremia by producing intracellular amino acids, known as idiogenic osmoles.16 In this way the neurons adapt to the high extracellular osmolality, and, therefore, if free water is supplemented too quickly, there is a sudden shift of intravascular water into the neurons, causing them to swell (cytotoxic edema). This, in turn, can cause an increase in intracranial pressure. The goal was to bring this dog’s sodium into the normal range over 48 to 72 hr, not dropping the sodium by more than 0.5 mEq/hr.

Within 24 hr, the sodium decreased to 172 mmol/L and the chloride to 142 mmol/L. At this time, the case was transferred to an internal medicine specialist for ongoing care. Since the sodium remained elevated, a corrected chloride of 132 mmol/L was calculated using the following equation:

\[
\text{corrected chloride} = \left( \frac{\text{normal sodium}}{\text{measured sodium}} \right) \times \text{measured chloride}
\]

Forty-eight hr after instituting IV fluids, the sodium concentration was 156 mmol/L and the chloride concentration was 129 mmol/L (uncorrected chloride, as sodium now within reference range). The sodium reduction at this point was above the target of 0.5 mEq/hr, but since the dog’s mentation was improving, it was decided not to adjust the IV fluids. Although the dog’s overall clinical status improved while in the hospital, he remained adipsic and inappetant. Since a primary neurological disease was suspected for the patient’s persistent hypernatremia, dull mentation, and circling, he was referred to Colorado State University for further workup.

After a several hr drive, the dog presented to the Neurology Service at Colorado State University, at which time the dog’s condition had declined significantly. He was weakly ambulatory, lethargic, and febrile (104.6°F). His neurological examination revealed severe tetraparesis without significant ataxia, delayed postural reactions in the right thoracic and pelvic limbs, and compulsive circling to the left. His menace response was absent on the right and the remainder of his cranial nerve examination was unremarkable. His neurological examination was consistent with the previous neuroanatomic localization of a left-sided prosencephalic lesion. Laboratory results showed an elevated sodium level (158 mEq/L, reference range 140–150 mEq/L), despite being treated for more than 48 hr with IV fluids prior to arrival at Colorado State University. Given the previous test results and rapid decline in his clinical status during the travel period, differential diagnoses were overcorrection of chronic hypernatremia and primary hypothalamic disease, including neoplasia and infectious, inflammatory, and congenital diseases.

Magnetic resonance imaging of the dog’s brain was performed using a 1.5 Tesla magnet. The MRI sequences included T2-
weighted, proton density, fluid attenuated inversion recovery, gradient echo and pre- and postcontrast (Gadolinium® 1.0 mL/4.5kg IV) T1-weighted images. Within the thalamic and hypothalamic regions, there was an asymmetric, predominantly left-sided, ill-defined, mixed T1 intensity, T2 hyperintense, and FLAIR hyperintense lesion (Figure 1A–C). On post-contrast T1-weighted images, the lesion was mildly heterogeneously contrast enhancing with a small focal area of mild rim enhancement in the left aspect of the thalamus and adjacent internal capsule (Figure 1D). Minimal mass effect was present. No signal voids were appreciated on gradient echo, making a hemorrhagic lesion unlikely. There was mild bilateral dilation of the lateral ventricles with no visible septum pellucidum, which was thought to be a normal variant for this dog. MRI differential diagnoses included focal granulomatous meningoencephalitis, infectious encephalitis, non-hemorrhagic ischemia, or neoplasia. After the MRI scan, a cerebrospinal fluid sample was obtained at the level of the cerebellomedullary cistern for analysis, the results of which were normal. Cerebrospinal fluid and whole blood were submitted to the Department of Medicine and Epidemiology at the University of California Davis for polymerase chain reaction infectious disease testing. The dog was negative for all tests, which included Canine Distemper Virus, West Nile Virus, Borrelia burgdorferi, Neospora hughesi and caninum, Toxoplasma gondii, Anaplasma phagocytophilum, and Ehrlichia canis and Rickettsia spp (including Rocky Mountain Spotted Fever).

Over the following 24 hr, the dog remained in the hospital on IV fluids (0.45% NaCl at a rate of 46 mL/hr). The chloride level normalized and, although the sodium level generally remained only mildly elevated (152 mEq/L, reference range 140–150 mEq/L), it quickly increased to 162 mEq/L when the IV fluids were decreased. In addition to the IV fluids, the dog was administered therapies for potential inflammatory brain disease while the cerebrospinal fluid analysis was pending. These included cytosine arabinosideb (617 mg/m² IV constant rate infusion over 24 hr) and dexamethasone SPc (0.02 mg IV q 24 hr). The dog was also administered clindamycinb (12.5 mg/kg IV q 12 hr) pending the results of the infectious disease tests. The dog remained adipsic to hypodipsic,
inappetant, and obtunded. The dog was humanely euthanized after 24 hr at Colorado State University and his body was submitted for a necropsy.

The necropsy did not reveal any grossly apparent lesions through the general systemic examination. Upon sectioning of the fixed brain, there were small, pale tan foci in the diencephalon with multiple pinpoint hemorrhages. Upon microscopic examination, the thalamic and hypothalamic neuropil was locally effaced by two foci of a poorly demarcated tumor composed of pleomorphic, globoïd neoplastic astrocytes with abundant branching reactive fibrous stromal trabeculae and vascular proliferation and necrosis. Neoplastic cells had abundant eosinophilic cytoplasm and interwoven fibrillar cytoplasmic extensions. Large pleomorphic nuclei had coarsely clumped chromatin and one to multiple nucleoli. Mitotic activity was regionally variable with several areas exhibiting one to three mitotic figures per single high-powered (400x) field and frequent atypical mitoses. Dissecting hemorrhage marginated the tumor foci. Additional stains were employed to help further identify this mass. Masson’s trichrome stain differentiated branching fibrovascular trabeculae from the neoplastic astrocytes. Neoplastic cells and the dense network of cytoplasmic extensions were immunopositive for glial fibrillary acidic protein (GFAP). A GBM affecting the diencephalon, specifically the thalamus and hypothalamus, was diagnosed (Figure 2). No histologic lesions were seen in the spleen, liver, kidneys, lungs, heart, and adrenal glands.

Discussion

This case report documents the rare occurrence of a GBM in a young golden retriever, which is suspected to have caused destruction of the hypothalamic osmoreceptors leading to hypodipsia and hypernatremia. Hypernatremia can result from water loss (normovolemia), hypotonic fluid loss (hypovolemia), or

![FIGURE 2](image)

**FIGURE 2** (A) Low-magnification (40x) view of the tumor with a peripheral ring of hemorrhage and anastomosing trabeculae of fibrous stroma containing glomeruloid vascular proliferation hematoxylin and eosin. (Inset) Richly blue-stained fibrous trabeculae are differentiated from red neoplastic cells and matrix (Masson’s Trichrome). (B, C). In these serial sections, large pleomorphic coarsely stippled nuclei with prominent nucleoli (arrow) and mitotic figures (arrowhead) are common. Figure C displays similar nuclear characteristics in cells with strong cytoplasmic GFAP immunoreactivity. Fibrillar cytoplasmic processes blend into the surrounding matrix. Hyperplastic vessels and fibrous stroma lack immunoreactivity hematoxylin and eosin rabbit anti-GFAP pAb. Bar = 10 microns. (D) In normal neuropil, the interwoven meshwork of fine fibrillar GFAP-positive astrocytic processes is more evenly dispersed around perikarya, as compared to the neoplasm. (E) Negative control with no aberrant immunoreactivity (Hematoxylin counterstain).
increased sodium gain (hypervolemia). During the course of the diagnostic workup, hypernatremia secondary to hypotonic fluid loss was ruled out. The dog did not have significant vomiting, diarrhea, peritonitis, or pancreatitis. The biochemistry panel and urinalysis ruled out renal disease and osmotic diuresis (such as from diabetes mellitus). Additionally, the hypernatremia persisted after appropriate fluid administration. With no history of salt ingestion, increased sodium gain was considered unlikely.

Since water was readily available at all times, diabetes insipidus was also considered an unlikely differential. With diabetes insipidus, if the dog has free access to water and an intact thirst mechanism, hypernatremia should not result. Additionally, his urine was appropriately concentrated (specific gravity >1.040), while it is often markedly hypostenuric in cases of diabetes insipidus or psychogenic polydipsia. Given these test results and the history of hypodipsia, a primary defect in the thirst mechanism was suspected. The hypothalamic receptor cell that is critical in the thirst sensation is an osmoreceptor. When the extracellular fluid becomes hyperosmolar, induced most commonly by elevated sodium levels, the thirst mechanism is stimulated. Hypovolemia can also induce the osmoreceptors to stimulate the thirst sensation. Therefore, if the osmoreceptors in the hypothalamus are dysfunctional, the thirst mechanism will not be stimulated and subsequent hypodipsia or adipsia results.

In this case, the dog had an infiltrative condition, diagnosed initially via MRI and, later, by necropsy, affecting the hypothalamus, presumably obliterating the osmoreceptors. The neoplastic disease was diagnosed upon postmortem histopathologic examination as GBM in the region of the hypothalamus. GBM is a rare tumor in dogs, generally affecting older dogs and is considered the highest grade astrocytoma. It most commonly occurs in brachycephalic breeds and seems to have a predilection for the frontal and temporal lobes of the cerebrum. Magnetic resonance characteristics of GBM usually consist of hypointense areas of necrosis on T1-weighted images with heterogeneous hyperintense regions on T2-weighted images. Peritumoral edema is a common finding with canine GBM and contrast enhancement can vary from minimal to uniform to ring patterns. The region of abnormality on this dog’s MRI was mixed intensity on T1- and T2-weighted images with an area of rim enhancement and evidence of peritumoral edema, all of which are consistent with previously reported cases. However, a significant mass effect is often appreciated with GBM, which was lacking in this case.

Histopathologically, GBM features include necrosis with pseudopalisading of cells, vascular proliferation, hypercellularity, and nuclear atypia. The dog in this report had similar microscopic characteristics to those reported. Additionally, the tumor cells stained strongly positive for GFAP, which adds support to the diagnosis of a tumor of astrocytic origin. The GFAP stain is highly specific for cells with astrocytic differentiation, and is, therefore, more commonly expressed in astrocytomas than meningiomas, medulloblastomas, and metastatic carcinomas. Although not all astrocytomas uniformly express GFAP, canine GBM tumors tend to stain strongly positive for GFAP. In one study of GBM tumors in dogs, all tumors stained positively for GFAP.

This report should stress the importance of considering neoplasia in very young dogs. Although none of the tumors were high-grade, three cases of naturally-occurring astrocytomas in young dogs were reported, ranging from 1.4 to 4 yr old. One case of an astrocytoma in an immature dog was published but neither the breed nor the age were reported. An oligodendroglioma in the right cerebral hemisphere of a 15 mo old golden retriever was reported, as well as a brainstem oligodendroglioma in a 5 mo old golden retriever. Recently there was a report of an anaplastic astrocytoma extending from the middle of the thalamus to the level of the pons in a 19 wk old boxer, which is similar in age and tumor type to the dog in this report.

Conclusion

This report describes a case of hypodipsic hypernatremia, likely secondary to the destruction of hypothalamic osmoreceptors by a rare central nervous system tumor, GBM, in a young dog. Although naturally occurring primary brain tumors are uncommon in young dogs, this report illustrates the importance of having neoplasia as a part of the differential diagnosis.

The authors would like to acknowledge and thank Dr. Daniel Gould for sharing his neuropathologic expertise in consultation for this case.

FOOTNOTES

REFERENCES