Diagnostic Exercise
From The Davis-Thompson Foundation*

Case #**248**; Month:**November**; Year:**2024**

Answer sheet

Title: Atypical central nervous system neoplasm in a Goldendoodle

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History: A 5-year-old castrated male Goldendoodle was presented for a week-long history of seizures and lethargy. There were no past health concerns per the owners and the dog was up to date on vaccines and taking monthly preventatives. Due to prognosis and lack of clinical improvement, the patient was euthanized.

Advanced Imaging: Centered within the left frontal lobe there was a large, well-defined, centrally fluid to peripherally soft tissue attenuating, moderately heterogeneously and strongly peripherally contrast-enhancing mass measuring approximately 2.6 cm x 2.1 cm x 4 cm causing a moderate rightward midline shift. A thin rim of normally attenuating brain parenchyma surrounded the caudal aspects of the mass. The mass contacted the rostral meninges and cribriform plate and left aspect of the falx cerebri broadly, and caused mild focal lysis of the cribriform plate. No meningeal thickening or enhancement was noted. There was coning of the cerebellar vermis within the rostral aspect of the foramen magnum, consistent with increased intracranial pressure.

Necropsy findings: A centrally located, tan to white extradural mass was present filling the rostral cranium and was loosely adhered to the dura overlying the right and left frontal lobes. The mass was large, multilobulated and measured approximately 3.2 cm x 2.8 cm x 2.1 cm, and was soft to firm. On cut surface, the mass was tan to white with a small central cavitation that contained scant friable material. Removal of the mass revealed a slight indentation in the forebrain and there was mild flattening of the caudal cerebellum. The spaces between the gyri and sulci were mildly narrowed.

Advanced Imaging (Head CT with contrast):

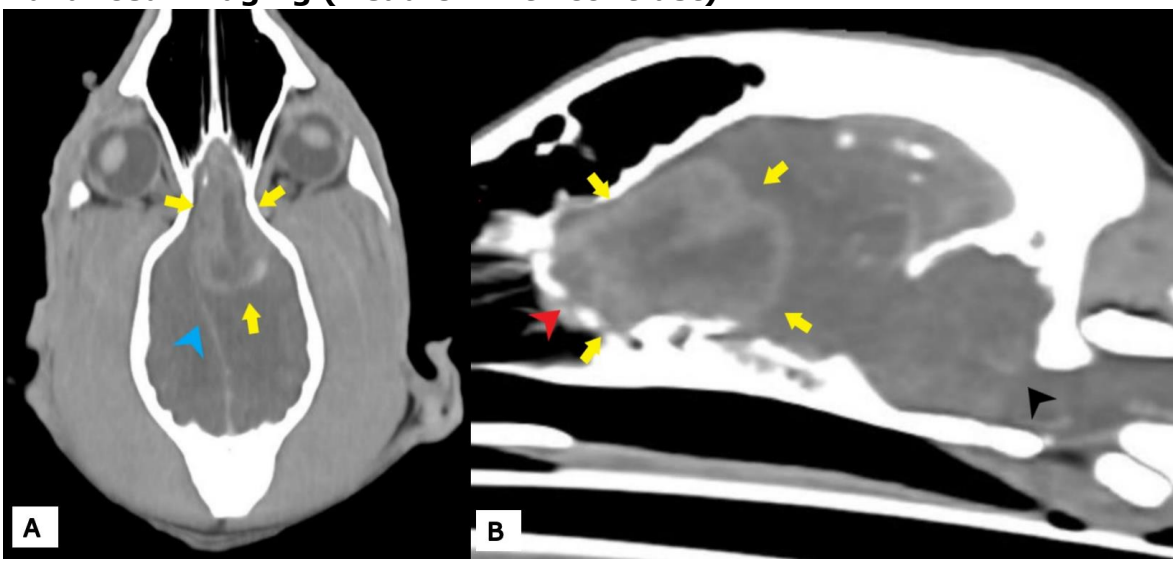

Figure 1. Head CT. **A:** Dorsal plane; the patient's right side is to the left of the image. **B:** Sagittal plane; rostral is to the left of the image. Yellow arrows outline the large, peripherally contrast enhancing, centrally fluid and peripherally soft tissue attenuating mass. The blue arrowhead indicates the rightward midline shift secondary to mass effect. The red arrowhead indicates the focal lysis of the cribriform plate. The black arrowhead indicates coning of the caudal cerebellar vermis.

Gross Findings:

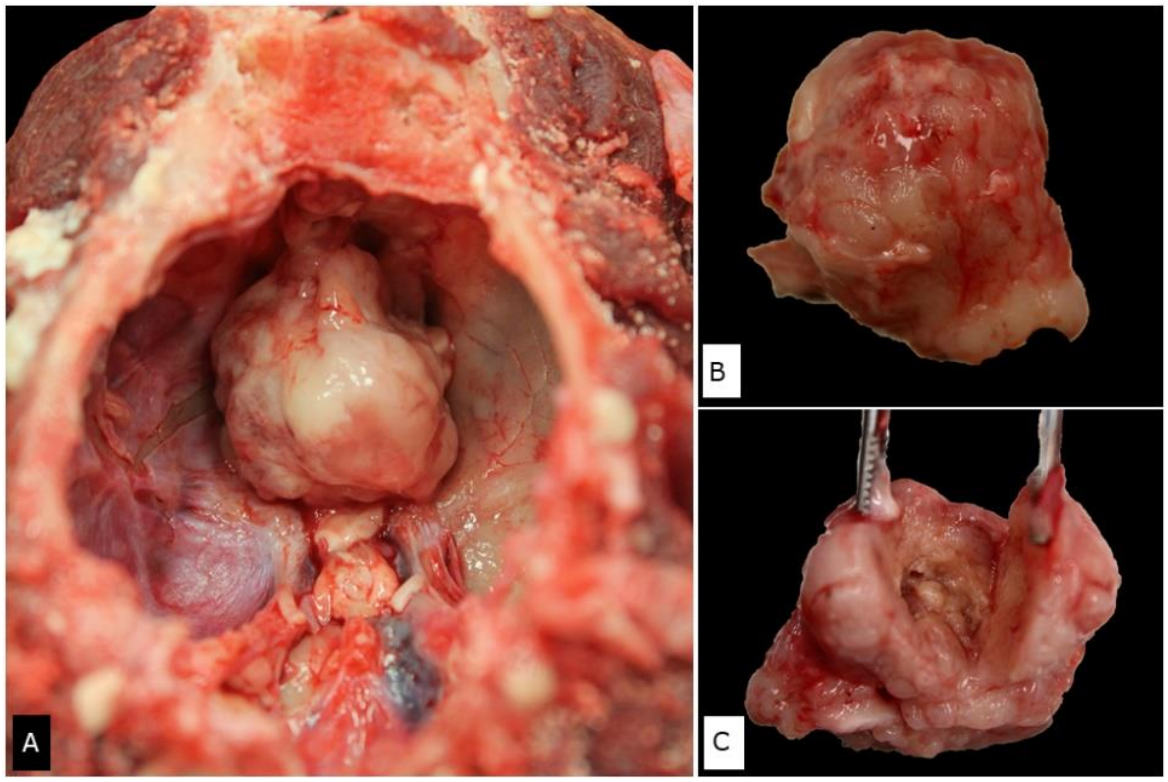

Figure 2. A: A well demarcated, multilobulated mass is present overlying the dura in the rostral cranium that is tan to white and contains scant tan, friable material in the center. **B:** Mass excised. **C:** Mass on cut surface.

Differential Diagnoses:

1. Meningioma
2. Glioma
3. Inflammatory lesion (abscess or granuloma)
4. Olfactory neuroblastoma
5. Round cell tumor

Histological description:

The multilobulated, well-demarcated, unencapsulated, and densely cellular mass was composed of neoplastic cells arranged in streams within preexisting neuroparenchyma (Fig. 3A). Neoplastic cells were oval to elongate with indistinct cell borders, a small to moderate amount of eosinophilic cytoplasm, and contained one round to ovoid nucleus, one nucleolus, and coarsely stippled chromatin. Mitotic figures are 60 in 2.37mm2 (10 FN22/40x fields) and there was moderate anisocytosis and anisokaryosis. The mass contained multiple foci that lacked cellular architecture and were composed of hypereosinophilic cellular debris (necrosis) that coalesced to form serpentine areas that separated the neoplastic cell population into clusters (Fig. 3B, arrows). An increased number of vascular profiles were present at the periphery of the mass and were surrounded by neoplastic cells.

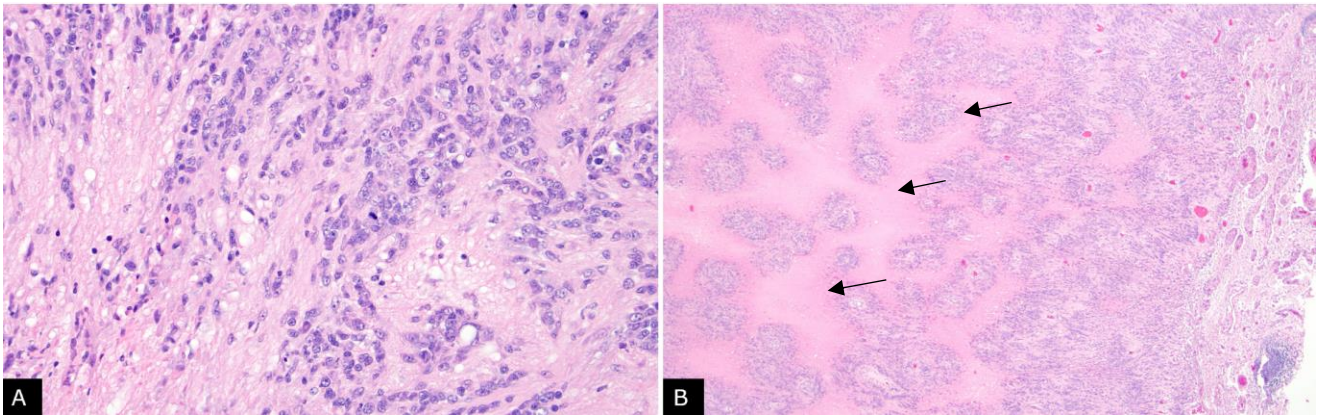

Figure 3. A: H&E, 40x**.** Neoplastic cells within preexisting neuroparenchyma. **B:** H&E, 2x**.** Serpentine necrosis (arrows) with multiple perivascular neoplastic cells at the periphery.

Immunohistochemistry (IHC):
OLIG2, GFAP, MAP-2, E-cadherin, vimentin, pancytokeratin

IHC for OLIG2, GFAP, MAP-2, E-cadherin, vimentin, and pancytokeratin were performed. Neoplastic cells had intracytoplasmic immunoreactivity that were diffusely positive for vimentin (Fig. 4A), multifocally positive for GFAP (Fig. 4B), and diffusely positive for E-cadherin (Fig. 4C). Occasional scattered cells had cell processes with positive intracytoplasmic staining that were positive for MAP-2. Neoplastic cells were negative for OLIG2 and pancytokeratin.

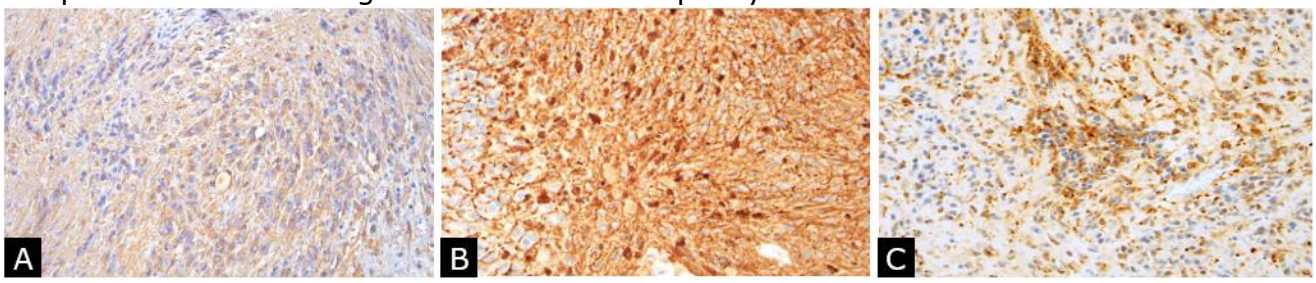

Figure 4. Positive immunohistochemical markers. **A:** Vimentin, 40x. **B:** GFAP, 40x. **C:** E-cadherin, 40x.

Diagnosis: *Atypical central nervous system neoplasm*

Discussion:
This case was an unusual presentation of a central nervous system neoplasm in a dog. On initial postmortem examination, the mass was similar to a meningioma given it was extradural and did not arise from the brain tissue. A glioma or olfactory neuroblastoma was also considered, as the mass could have originated from the olfactory bulbs; however, the extent of invasion past the cribriform plate was not explored during necropsy.

Histologic characterization of the mass was initially suggestive of a high-grade astrocytoma, given the presence of distinct serpentine necrosis, although other features of these tumors - palisading neoplastic cells and glomeruloid neovascularization – were not present (1,2,5). An atypical grade II meningioma or anaplastic grade III meningioma were also considered, as these tumors can also have variable geometric regions of necrosis, moderate to severe cellular atypia, and high mitotic counts (8). While the diagnosis remains open given the atypical histolomorphology, IHC was key in obtaining a working differential list.

IHC in nervous system tumors is beneficial in providing diagnostic confirmation, however in some cases stain uptake can be highly variable as interpretation may be precluded by the degree of artifact, such as tumor necrosis. With high-grade astrocytomas the degree of glial cell differentiation is usually highly variable such that IHC stain uptake can range from 20-50% in the neoplastic cell population (5,7). GFAP, CD133, nestin, and MAP-2 were commonly used for diagnosing astrocytomas, with GFAP being the traditional gold standard (1,7) however more recent literature notes OLIG2 in combination with GFAP, CNPase and Ki67 as being the most beneficial for determining astrocytic versus oligodendrocytic morphology (1). If IHC results are negative, however, one should proceed with caution since OLIG2, GFAP, CNPase, and Ki67 immunoreactivity can be affected by tissue fixation (1). Utility of additional stains such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) have been reported, although expression is variable (2). To rule out a poorly differentiated meningioma, vimentin and E-cadherin can be useful.

In this case, the mass had positive cytoplasmic immunoreactivity for vimentin, GFAP, and E-cadherin which is more consistent with an atypical meningioma although a glial tumor cannot be ruled out. The mass was did not stain with pancytokeratin nor OLIG2, thus ruling out oligodendroglioma. Scattered cells were occasionally MAP-2 positive, however only within the cell processes and thus not diffuse enough to indicate a neoplasm of astrocyte origin. Meningiomas are common central nervous system tumors that arise from the leptomeninges or from cells that form arachnoid granulations (6,8). These tumors, although nonmetastatic, are associated with variable clinical signs depending on tumor size and degree of local compression to the adjacent brain tissue (8). Boxers and brachycephalic dogs (Bulldogs and Boston Terriers) are the most documented breeds with older, castrated male dogs being overrepresented, however, there is no true breed, age, or sex predilection (1,7).

An intra-axial localization of the mass was prioritized based on computed tomographic features (peripheral rim of normal appearing tissue, relatively mild mass effect for tumor size, moderate peripheral contrast enhancement, lack of meningeal thickening). However, extra-axial features were also present (broad contact with the meninges, peripheral location, cribriform plate lysis) (3). A

combination of intra and extra-axial localization features has been reported for high-grade astrocytomas (and other causes of intracranial masses) (4), which is consistent with both imaging findings and gross pathology. Also, while uncommon, invasion of the meninges and cribriform plate lysis is reported with gliomas (6). Magnetic resonance imaging (MRI), which was not pursued in this case, can help strengthen clinical suspicion for high-grade astrocytoma. MRI features consist of "peritumoral edema, sharp borders, ring enhancement, heterogenous T2-weighted signal intensity, iso- to hypointense T1-weighted images, necrosis, and cyst formation" (2,3). Though it is difficult to apply these features across imaging modalities, the mass in the current case displayed both sharp borders and ring enhancement. The central, fluid-attenuating cavitation corresponded to the tan, friable tissue noted at necropsy.

Overall this is an interesting case that still remains an open diagnosis. Grossly, the mass resembles a meningioma and was our primary differential during postmortem evaluation. With the addition of histopathology and IHC, the presence of abundant serpentine necrosis moved high-grade astrocytoma to the top of the differential list however an atypical meningioma or anaplastic tumor of unknown histogenesis could not be ruled out. The gross morphology and incorporation of IHC stains favors a diagnosis of an atypical grade II meningioma however this is not definitive.

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