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Diagnostic Exercise
From the Latin Comparative Pathology Group and the Davis-Thompson Foundation:

Olfactory neuroblastoma in a cat

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History:

An adult, unneutered male, mixed-breed, stray domestic shorthair cat was submitted for postmortem examination at the Veterinary Pathology Service of the Federal University of Rio Grande do Sul (SPV-UFRGS). The cat presented aggression, convulsions, fainting, and drooling. In the subsequent days, the animal developed nasal and rectal bleeding. Despite treatment was performed, the cat died suddenly two days after admission.

Gross findings and cytology:

The cat was in good body condition. The oral and conjunctival mucous membranes were pale. There was bloody nasal discharge. In the paranasal sinuses, there was a significant amount of gelatinous, opaque, mucoid to catarrhal material (Fig. 1A), and a partially delimited and non-encapsulated, soft, tan mass (Fig. 1B). The mass bilaterally obliterated the turbinates and nasal meatus, perforating through the cribriform plate and extending into the frontal lobe of the brain (Fig. 1C;1D). Additional findings included focal red areas of consolidation in the lungs. During the necropsy, touch impressions of the surface of the brain mass were collected and stained with an aqueous Romanowsky stain (Panótico Rápido®) for cytologic examination (Fig. 2). Additionally, samples of several organs were collected for routine histopathology (Fig. 3;4).

Follow-up questions:

- *Morphologic diagnosis.*
- *Cytologic description.*
- *Types of cell arrangements observed in histological sections.*

**The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation (DTF). These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the DTF website: https://davist- hompsonfoundation.org/diagnostic-exercise/*

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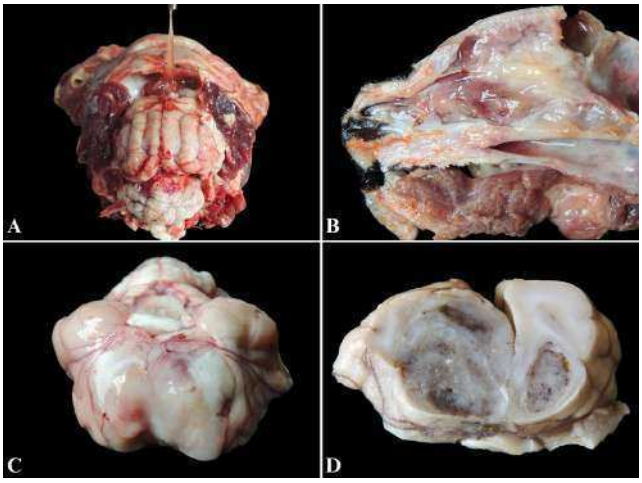


Figure 1. Cat, after the removal of the skullcap. (**A**) A significant amount of gelatinous, opaque slightly red material is observed cranial to the brain. (**B**) Sagittal section of the skull, showing a white, soft, non-encapsulated mass within the nasal cavity. (**C** and **D**) Bilaterally, within the frontal lobe, an irregular, soft, white mass is seen.

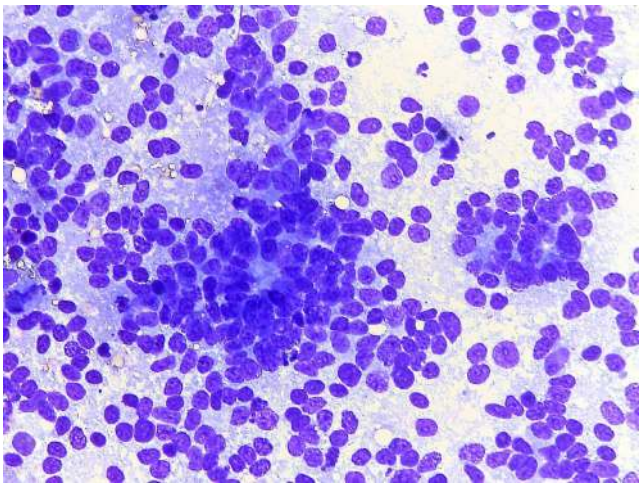


Figure 2. Cat, imprint from the brain mass. Cells arranged in acinar-like structures (arrows). Romanowsky stain.

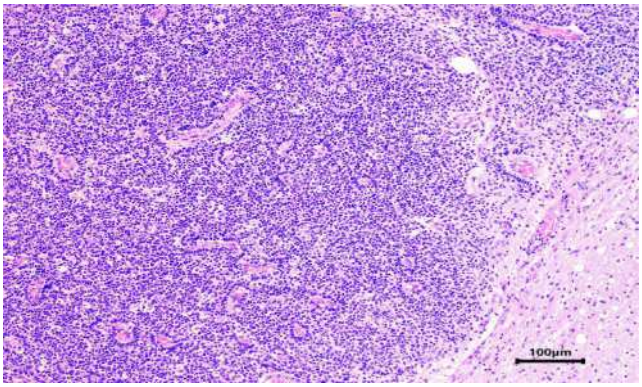


Figure 3. Cat, brain. Non-delimited and non-encapsulated neoplastic proliferation, supported by a sparse fibrovascular stroma. H&E, bar = 200 µm

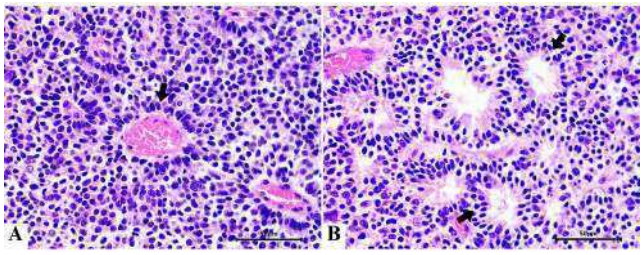


Figure 4. Cat, brain. (**A**) Pseudorosette (arrow). (**B**) Flexner-Wintersteiner rosette (arrows). H&E, bar = 50 µm.

ANSWERS

Morphologic diagnosis:

Brain: Olfactory neuroblastoma.

Cytologic description:

Brain: highly cellular sample composed by predominantly individual scattered cells, with uniform naked nuclei, and occasional small sized clusters exhibiting sporadic acinar-like structures, on a background of slightly basophilic granular material. The intact cells exhibit a round to polygonal shape, with scant, pale blue cytoplasm, with high N:C rate. The nuclei are round, featuring finely stippled chromatin and one to two small, prominent nucleoli. Cells exhibit mild anisocytosis and mild to moderate anisokaryosis. No mitotic figures are observed in the analyzed sample.

Types of cell arrangements observed in histological sections:

- Pseudorosette (Fig. 4A; 5).
- True rosettes:
  - Homer-Wright rosettes (Fig. 5).
  - Flexner-Wintersteiner rosettes (Fig. 4B; 5).

Discussion:

Nasal and sinusal neoplasms are uncommon in cats, lymphoma being the most prevalent, followed by adenocarcinoma and squamous cell carcinoma (7). The olfactory neuroblastoma (ONB) is a rare type of malignant tumor of neuroectodermal origin, which arises from the olfactory neuroepithelium and forms in the upper nasal cavity, near the cribriform plate (1,2,6). The Histological Classification of the Respiratory System of Domestic Animals (3) recognizes nine different types of malignant epithelial tumors of the Nasal and Paranasal Regions: squamous cell (epidermoid) carcinoma; transitional carcinoma; adenocarcinoma, adenosquamous (mucoepidermoid) carcinoma; adenoid cystic carcinoma;

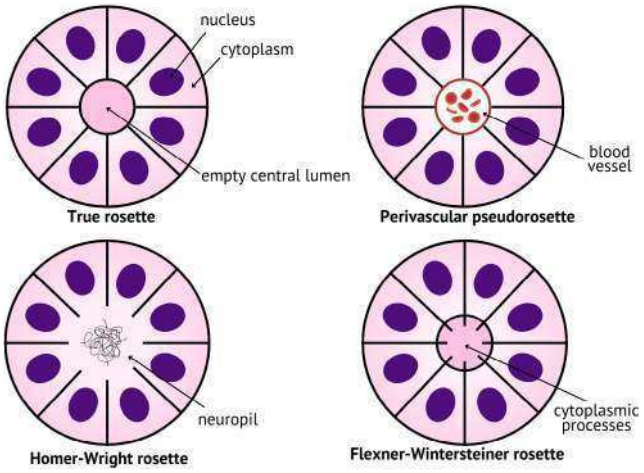


Figure 5. Schematic representation of cell arrangement in neoplasms of neuroblastic or neuroectodermal origin.

acinic cell carcinoma, undifferentiated (anaplastic) carcinoma; neuroendocrine carcinoma; and olfactory neuroblastoma.

Grossly, ONBs are white or brown-grayish, firm and gelatinous masses located within the nasal cavity. The tumors are locally aggressive, which tend to destruction of the nasal turbinates, and extension through the cribriform plate towards the olfactory bulbs (5). As is progresses into the cranial cavity and brain, it causes increased intracranial pressure, resulting in transforaminal and transtentorial herniation (2,5). The ONB's can be associated with signs of unilateral or bilateral serosanguinous or mucopurulent nasal discharge, sneezing, dyspnea, ocular discharge (7), behavioral changes like aggression (1), facial deformity, and exophthalmos (6). In cats, there are reports of metastasis to regional lymph nodes regional lymph nodes, lungs, brain, and bone (8).

Cytologically, ONBs closely resemble neuroendocrine carcinomas, in which most of the cells are lysed, resulting in free-floating nuclei within a cytoplasmic background, with some intact cells appearing in small clusters (7). Samples usually exhibit high cellularity, with cell clusters occasionally forming acinar-like structures on a basophilic background (4). The intact cells are round to oval, showing mild to moderate variation in shape (pleomorphism), and possess scant to moderate amounts of pale basophilic cytoplasm. Many cells lack cytoplasm. The nuclei feature prominent single or multiple nucleoli, and occasional mitotic figures are present (4).

Histological findings of ONBs are diverse and encompasses several subtypes. Well-differentiated ONBs are characterized by delimitated lobules and densely packed trabeculae, and formed pseudorosettes and rosettes, resembling neuroendocrine tumors (5,7) (Fig. 3). In these cases, pleomorphism, necrosis, and high mitotic activity are uncommon (1,7). Neoplastic cells are polygonal, with moderately distinct borders and a moderate amount of eosinophilic finely granular cytoplasm, often containing small clear vacuoles. Nuclei were round with finely granular chromatin and inconspicuous nucleoli (2,5). The types of rosettes are Homer-Wright and Flexner-Wintersteiner. Homer-Wright rosettes are characterized by neoplastic cells encircling a lumen filled with their processes, while Flexner-Wintersteiner rosettes exhibit neoplastic cells forming a predominantly empty lumen with small cytoplasmic extensions protruding. In feline species, rosettes are more commonly reported (1). In poorly differentiated tumors, the lobular architecture is reduced, cells are more pleomorphic, the mitotic rate is high, and there are varying degrees of necrosis (1).

Microscopic differential diagnoses in domestic animals, particularly in poorly differentiated olfactory neuroblastomas (ONBs), encompass tumors originating from epithelial, mesenchymal, and round cell lineages: neuroendocrine carcinoma, undifferentiated nasal cavity carcinoma, rhabdomyosarcoma, extramedullary plasmacytoma, and nasal T cell lymphoma (1,3,6). The absence of rosette formation by tumor cells microscopically distinguishes lymphomas, plasmacytomas, or rhabdomyosarcomas from ONBs (10). Distinguishing between neuroendocrine carcinomas arising from the basal cells of the olfactory epithelium poses a challenge due to overlapping phenotypic characteristics with ONBs, such as rosette formation (3). In such cases, cautious interpretation of immunohistochemistry markers is crucial.

Immunohistochemically, in cats, Neuron Specific Enolase (NSE) consistently labels ONBs, establishing its reliability across species including dogs, horses, and humans (1,6). Microtubule-associated protein 2 (MAP-2) or Class III beta-tubulin also demonstrates labeling in feline ONBs and is deemed more specific than NSE (1,6,7). Conversely, neuroendocrine carcinomas consistently exhibit positivity for markers such as chromogranin A and Synaptophysin, which may also label ONBs but with lesser consistency (1,9).

Epithelial Membrane Antigen (EMA) and Carcinoembryonic Antigen (CEA) show negativity in ONBs (7), which may aid in their differentiation from neuroendocrine carcinomas. These markers, coupled with histological and cytological features, can enhance diagnostic accuracy and aid in determining the neoplastic cell phenotype. However, definitive diagnosis necessitates analysis of highly specific ultrastructural features observable via electron microscopy, such as the presence of electron-dense neurosecretory granules and neurite-like cell processes with neurofilaments and neurotubules (1).

In humans, ONBs are assessed using Haym's grading system and Kadish's clinical staging system (1,5).

Haym's system categorizes tumors into four grades (I–IV) based on various factors including cellular pleomorphism, mitotic index, growth pattern, necrosis, and mineralization. Kadish's system groups ONBs into three grades (A–C) according to tumor extension, correlating with survival likelihood. Despite similarities across species, feline and canine tumors typically exhibit higher mitotic activity and necrosis compared to humans. Brosinski et al. suggest Haym's grading system as a valuable prognostic tool in veterinary medicine, particularly for predicting tumor recurrence (1).

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