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

Canine nasal cryptococcosis

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History:

A 17.8 kg female, spayed, German Shorthaired Pointer with a month-long history of waxing and waning lethargy and obtunded mentation. The patient was treated initially with Doxycycline and Temaril-P and later with Prednisone. The patient's clinical signs were worse when the Prednisone was tapered. There were concerns for multifocal brain and brainstem disease based on physical exam, and because of financial constraints, euthanasia was elected.

Necropsy findings:

In the caudal nasal cavity, there was an approximately 2,5 cm diameter, tan, multinodular, irregular mass compressing the turbinates, perforating through the cribriform plate and extending into the meninges and olfactory bulb of the brain (Fig. 1 and 2). The neuroparenchyma of the left olfactory lobe was soft with multifocal hemorrhages. The cerebellum was slightly herniated through the foramen magnum. In addition, there were multifocal tan nodules approximately 2-3 mm in diameter in the rostral left nasal cavity bordering the nasal septum (Figure 1, arrow). Samples of the nasal septum, caudal nasal cavity, meninges and frontal aspect of the olfactory lobe were collected for histopathology (Figure 3 and 4).

Follow-up Questions:

- *Morphologic diagnosis:*
- *Etiology:*
- *Name the disease:*

**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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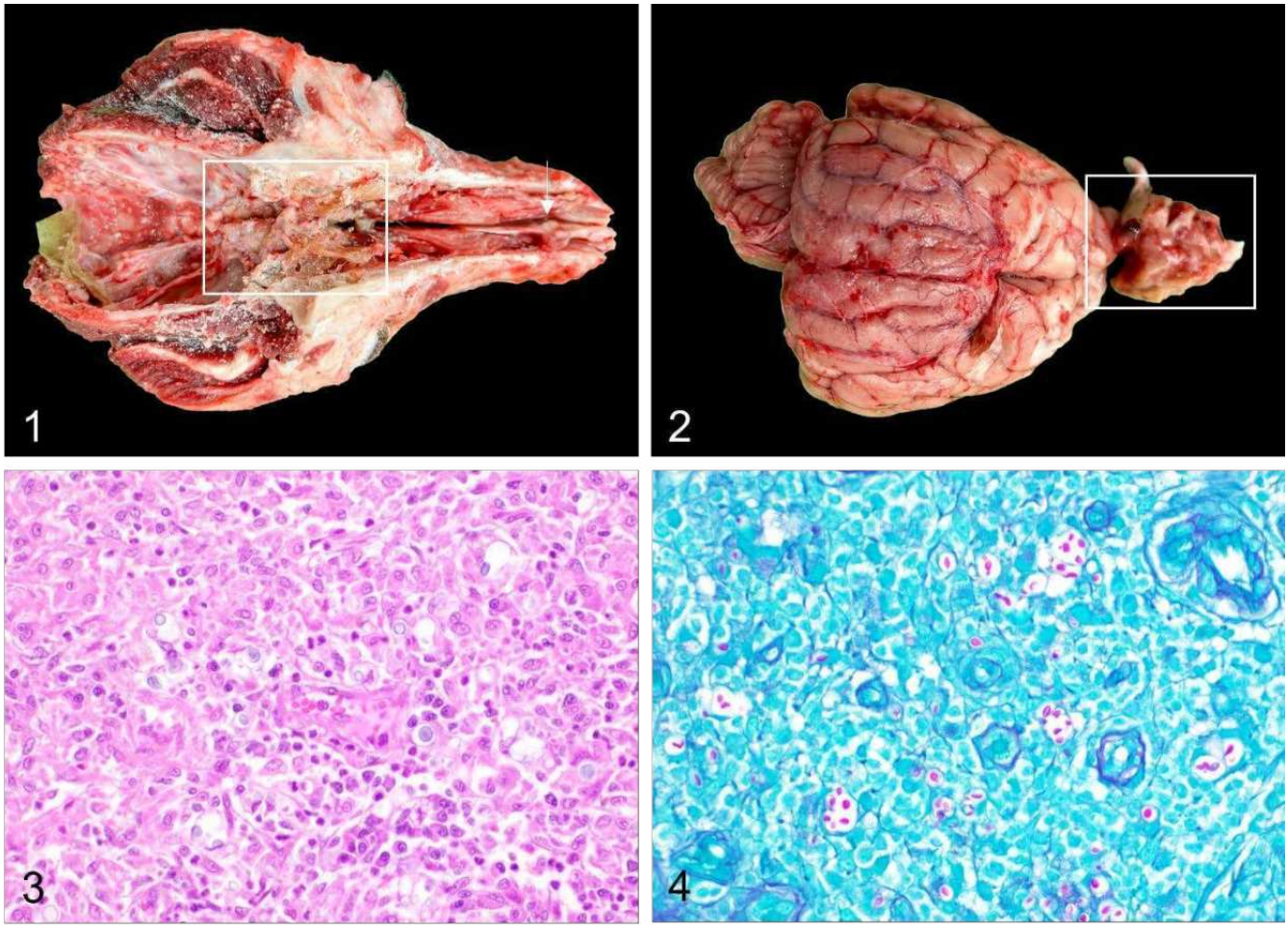


Figure 1 and 2: Nasal and cerebral cavity exposed. Perforating the cribriform plate, a white tan mass was identified (white square). In addition, a few white nodules were noted in the rostral aspect of the left nasal cavity (arrow). **Figure 3:** Histopathology of the mass boxed in figure 2: Pyogranulomatous inflammation, with the presence of numerous yeasts. **Figure 4:** PAS stain of the inflammatory process, highlighting the fungal yeasts.

ANSWERS

Histopathology: Meningeal mass, brain, nasal turbinates and nasal septum (Fig 3): all sections have similar findings. Multifocally infiltrating all these structures, with effacement of the normal histomorphology, there is a dense inflammatory process, composed by large numbers of neutrophils and macrophages, with the presence of numerous round to oval fungal yeast. Individual fungal structures measure approximately 10-15 µm diameter with a central pale basophilic nucleus and a prominent capsule. The inflammatory reaction is sustained in abundant fibrous connective tissue, with multifocal infiltrates of lymphocytes and plasma cells. There are extensive areas of necrosis within the inflammatory mass. Fungal yeasts stain positive with PAS stain (Figure 4) and the capsule is slightly positive with Mucicarnim stain (not shown).

In the brain, inflammation extend through the meninges into the neuroparenchyma, with multifocal areas of degeneration/necrosis, hemorrhages, rarefication of the neuropil and gliosis/astrocytosis.

Molecular results:

Cryptococcus neoformans was detected through PCR and sequencing (University of Florida Veterinary Diagnostic Laboratory).

Morphologic diagnosis:

Rhinitis and meningoencephalitis, pyogranulomatous, severe, multifocal to coalescing, with intralesional fungal yeasts, morphology compatible with *Cryptococcus* spp.

Etiology: *Cryptococcus neoformans*

Name the disease: Nasal cryptococcosis.

Comments:

The clinical signs plus the gross and histopathological findings are consistent with nasal cryptococcosis. Cryptococcosis is a fungal disease caused by a dimorphic encapsulated yeast species from the genus *Cryptococcus* spp. Cats are the most commonly affected species, but dogs, horses, cattle, goats, sheep, birds, ferrets, wildlife, and humans can be infected (1). Cats are five to six times more likely to develop cryptococcosis than dogs (4). The two species associated with infection in domestic animals and people are *Cryptococcus neoformans* and *Cryptococcus gattii*. Dogs are more often infected with *C. neoformans*, whereas cats are more often infected with *C. gattii* (9). Cryptococcosis occurs worldwide, and *C. neoformans* is the most common isolate that causes disease in animals and humans (3). *Cryptococcus* can be isolated from numerous substances depending on the geographic location and the species (10). *C. neoformans* is present throughout the United States and Europe and has been found in pigeon feces, soil enriched by avian feces, milk, fermenting fruit juices, wasp nests, air, dust, insects, and grass (2, 3). Historically, *C. gattii* was thought to only be in tropical and subtropical areas which includes Papua New Guinea, Australia, Southeast Asia, and Central Africa, and in temperate climates in the Pacific Northwest, including Canada, but is now considered to have global distribution (3). The primary ecological niche for *C. gattii* is decayed wood hollows (10). In Australia, *C. gattii* is found in *Eucalyptus* and fig trees and in some fir trees in western Canada (3). People can transport *C. gattii* on shoes and car tires, and the fungus can be dispersed by movement of soil, wood, or water (10). It is believed that infection occurs when basidiospores or desiccated yeast cells are aerosolized and inhaled. Other possible routes of infection include cutaneous inoculation and ingestion, but these occur rarely (3, 5).

Clinical signs are highly variable and depend on the site infected. In dogs, C*ryptococcus* can be localized to the skin, eyes, central nervous system (CNS), and respiratory tract - particularly the nasal cavity and sinuses - or can be multisystemic. Dogs commonly have systemic dissemination of infection with nonspecific signs of lethargy, inappetence, and weight loss (10). Skin lesions can be found anywhere on the body. Ocular manifestations of the disease include anterior uveitis, chorioretinitis, optic neuritis, and detached retina (9). CNS signs are common in dogs, resulting from meningitis or meningoencephalitis, and can be localized anywhere in the CNS and be multifocal (9,10). Neurologic signs include mentation changes, seizures, ataxia, circling, head tilt, blindness, nystagmus, cranial nerve deficits, cervical hyperesthesia, paresis, paraplegia, tetraplegia, and muscle tremors and twitching (8, 10). As the organism is inhaled, the nasal cavity is often affected. Nasal masses commonly form in the caudal nasopharynx due to large accumulations of yeast and can cause no clinical signs or clinical signs associated with chronic nasal disease such as nasal discharge, sneezing, stertor, or open-mouth breathing (10). It is less common for *Cryptococcus* to affect the lungs, and coughing, dyspnea, and tachypnea are infrequent as compared to other mycoses (9). Disease can spread from the nasal cavity into the brain and orbit and organisms gain access to the CNS via hematogenous spread from primary infection sites or through the cribriform plate to the olfactory bulb (10). In this case, both the nasal cavity and CNS were affected, as there were nodules in the rostral left nasal cavity bordering the nasal septum. Further, a multinodular mass was present in the caudal nasal cavity that compressed the turbinates, perforated through the cribriform plate, and extended into the meninges and olfactory bulb. No significant gross or histologic findings were identified in other internal organs.

Differential diagnoses in dogs include other disseminated mycoses (including histoplasmosis, blastomycosis and nasal aspergillosis), mycobacteriosis, actinomycosis and nocardiosis, toxoplasmosis and neosporosis, and neoplasia. Other diseases that can cause chronic nasal disease include nasal foreign body, nasopharyngeal polyp, oronasal fistulas, tooth root abscess, and lymphoplasmacytic rhinitis (7).

A definitive diagnosis requires visualization of cryptococcal organisms by cytologic and/or histologic examination or culture from a normally sterile site (10). Examination of exudates, impression smears, bodily fluids like cerebrospinal fluid (CSF), and nasal exudates and washes can be used for visualization under a light microscope (9). Cytologically, *Cryptococcus* can be differentiated from other mycoses by hematoxylin and eosin (H&E) stain where it appears round to oval with a clear space around the yeast as the capsule is unstained (2). Special stains like Periodic-acid Schiff (PAS) stain can be used to delineate the cell wall, but do not stain the capsule (6). Mucicarmine stain can be used to rule out histoplasmosis and blastomycosis, as *Cryptococcus's* capsule frequently stain intensely pink. The inflammatory response caused by *Cryptococcus* can vary from sparse to granulomatous. Growth on culture media containing canavanine-glycine-bromo methyl blue agar is used to determine which species of *Cryptococcus* is the causative agent and/or PCR and sequencing can be used (10). A sample of the nasal/cerebral mass was submitted for the panfungal PCR to the University of Florida for sequencing, which was 100% identical to *Cryptococcus neoformans.*

The treatment used in this case initially was doxycycline and temaril-P, with prednisone added later. The dog's clinical signs worsened when the prednisone was tapered. Cryptococcosis in dogs is commonly treated with azole antifungals and amphotericin B. There are *Cryptococcus* strains that are resistant to antifungal drugs, especially fluconazole (10). Careful use of glucocorticoids in dogs with CNS signs can temporarily improve the clinical signs, which was observed in this case. Nasal/cerebral cryptococcosis should be included as a differential diagnosis in cases with a clinical history of a nasal mass and the presence of neurologic signs, such as lethargy and obtunded mentation.

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