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Guest Moderator:
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CASE I: L13-2372-2 (JPC 4032973).

Signalment: 4-month-old male BALB/c mouse, *Mus muculus*

History: This mouse received a single bolus of 400 µL PBS containing an unknown concentration of cultured murine trophoblastic cells via tail vein injection. The mouse died immediately and spontaneously after injection.

Gross Pathology: This mouse was presented dead in good body condition and fresh post mortem preservation. All organs and tissues were within normal gross limits.

Histopathologic Description: Multiple sections of lungs are examined, revealing diffusely scattered prominence of pulmonary alveolar capillaries, pulmonary arterioles, and small-caliber pulmonary arteries due to presence of moderate numbers of individually scattered and entrapped, intraluminal, 10-25 µm diameter, polygonal- to amorphously-shaped, deeply amphophilic, coarsely granular cells. The nuclei of these cells (when observable) are large and round- to ovoid-shaped with prominent single nucleoli. Additionally, pulmonary alveolar capillaries, pulmonary arterioles, and small-caliber pulmonary arteries are prominent due to presence of discrete to extensive, amorphous and/or meshwork-like rafts of finely granular, eosinophilic, weakly-PTAH-positive material (interpreted as peracute fibrin thrombi), which may or may not be intimately associated with the aforementioned cells.

Contributor's Morphologic Diagnosis: Lung, trophoblastic pulmonary embolism, disseminated, peracute, moderate with intravascular fibrin thrombi.

Contributor's Comment: An embolus refers to a detached, intravascular mass (solid, liquid, or gaseous) that is carried by and travels within the blood circulation. Embolism occurs when an embolus lodges within the circulation distant from the point of origin of the embolus. Embolism may result in partial or complete blockage of the circulation, and may potentially result in ischemic necrosis (infarction) of distal tissue. Thromboembolism refers to embolism that involves emboli derived from fragments of a thrombus.[6]

Nonthrombotic pulmonary embolism is defined as embolization of the pulmonary circulation by different cell types (adipocytes, hemopoietic, amniotic, trophoblastic, or tumor), bacteria, fungi, foreign material, or gas.[4] The pathogenesis of nonthrombotic pulmonary embolism is more complex and diverse than that associated with pure mechanical obstruction of pulmonary

embolism caused by vascular thrombi, and as such, often results in unusual or peculiar clinical signs.[4] However, many cases of nonthrombotic pulmonary embolism (regardless of cause) are associated with the development of severe peracute/acute inflammatory reactions in the pulmonary circulation, such as acute respiratory distress syndrome.[4]

Trophoblastic pulmonary embolism refers to embolization of the pulmonary circulation by trophoblastic cells derived from placental tissue.[4] Trophoblastic pulmonary embolism has been documented as a spontaneous condition in mammals with hemochorial placentation (where there is direct contact between fetal trophoblastic cells with the maternal circulation), primarily in humans and chinchillas.[3,4] In these species during pregnancy, syncytiotrophoblasts regularly desquamate from the placenta and into the maternal circulation.[3,4] The intravascular trophoblastic cells usually lodge in capillaries of the alveolar septae of the lung. Histologically, they appear as large (>50-100 μm diameter), round to deformable cells with abundant cytoplasm containing multiple, large (>25-50 μm diameter) nuclei.[3,4] The syncytiotrophoblasts are ultimately removed without consequence.[3,4] Trophoblastic pulmonary embolism is only associated with clinical disease is rare cases, and when it does occur, severe respiratory distress is the most common presentation. Positive antemortem clinical diagnosis is difficult. Most cases of trophoblastic pulmonary embolism diagnosed on microscopic examination of lung is usually incidental.[2,3]

In this case, this mouse was part of an experiment studying the interactions of trophoblasts with the circulation. The trophoblasts are smaller than those noted in spontaneous cases in humans or chinchillas. Their morphology is more similar to cytotrophoblasts rather than syncytiotrophoblasts, and might be explained by the cultured history of the cells. Regardless of morphology, the death of the animal immediately post-injection is most suggestive that rapid trophoblastic pulmonary embolism is the cause of death in this animal.

JPC Diagnosis: Lung, pulmonary arterioles and septal capillaries: Trophoblastic emboli, with multifocal fibrin thrombi.

Conference Comment: Conference participants discussed this interesting entity at length, including its correlation to the cause of death in this case. The contributor nicely highlights the different types of emboli and their manifestations in relation to systemic disease, to which trophoblastic emboli are typically described as incidental findings. They have been documented to cause fatalities in people, however.[1] The limited details provided regarding the circumstances of this case left participants to only speculate as to the cause of death in this mouse. The differentials of consideration were anaphylaxis, cerebral embolism, and volume overload. Additional details regarding the timing of death in relation to injection, whether other animals in the study were also affected, and whether similar lesions were observed in other tissues, would help in further elucidating the mystery. Most participants felt the pulmonary lesions were minimal and likely not significant enough to cause the animal's death.

While this condition is most often observed in humans and chinchillas, recently it has been described as a common finding in a colony of cotton rats used to study a variety of infectious agents, indicating the possibility of an alternative model of aberrant trophoblastic deportation in women.[4]

In a developing blastocyst, trophoblasts are the peripheral cells first located at a single pole. They eventually give rise to the embryonic portion of the placenta, by proliferating rapidly into

two distinct cell populations. The inner population is a monolayer of individual cells which are mitotically active and are known as cytotrophoblasts, while the thicker outer layer is composed of continuous multinucleated cells with no cytoplasmic demarcation and are called syncytiotrophoblasts. Cytotrophoblasts continue to proliferate, with the new cells joining the ranks of syncytiotrophoblasts. As syncytiotrophoblasts increase in number, they form vacuoles that coalesce into large spaces known as lacunae. The continued growth of the syncytium erodes the adjacent endometrium and eventually the maternal blood vessels, allowing maternal blood to fill the newly formed lacunae and nourish the developing embryo.[2] With such close association, it follows that syncytiotrophoblasts could be readily introduced into the maternal blood supply causing their embolization as observed in this case.

Contributing institution: Veterinary Service Center, Department of Comparative Medicine, Stanford School of Medicine (http://med.stanford.edu/compmed/)

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CASE II: 13082899 (JPC 4056244).

Signalment: 20-25 week old NOD-SCID (NOD.CB17-Prkdcscid/J) Mice

History: Mice harboring orthotopic xenograft of cancer cell line for oncology research.

Gross Pathology: No gross abnormalities noted at necropsy.

Histopathologic Description: Irregular packets of pleomorphic cells with round to angular, hyperchromatic nuclei diffusely infiltrated the brain parenchyma. Most cells had very little cytoplasm. Few neoplastic cells were large, with abundant eosinophilic cytoplasm and multiple abnormal nuclei. There were several mitotic figures, apoptotic bodies, and degenerate neurons within each high power field (Figure 1). Neoplastic cells infiltrated the cerebral parenchyma without causing significant distortion of normal anatomic structures, hydrocephalus, or extensive necrosis. Capillaries were readily apparent among the neoplastic cells. There was typically bilateral involvement of the cerebral hemispheres and rare extension into the distal brainstem and cerebellum.

Contributor's Morphologic Diagnosis: Brain, gliomatosis cerebri

Contributor's Comment: The engrafted cell line was derived from resection of a human anaplastic oligoastrocytoma (oligoastrocytoma WHO Grade III).[6] The cell line, designated BT142, expresses a mutant form of isocitrate dehydrogenase. Isocitrate dehydrogenase 1 (IDH1) catalyzes the oxidative decarboxylation of isocitrate into α-ketoglutarate within the Krebs cycle. *In vivo,* missense mutations in IDH1 have been identified in a large percentage of gliomas and are thought to play an important role in the biology of these tumors. A loss of IDH1 function leads to inducible levels of hypoxia inducible factor-1 alpha (HIF-1α), an important gene in tumorigenesis. A gain of IDH1 function may also occur, leading to excessive production of 2-hydroxyglutarate.[10] The most common mutation, which is also carried in the BT142 cell line, is R132H, located within the isocitrate binding site.[1,4]

The cell line was orthotopically injected into the right cerebral cortex of the mice with a 30-gauge needle (per protocol approved by the Institutional Animal Care and Use Committee). In the contributor's experience, implantation of other cell lines into the brain by this technique result in a space occupying mass of cells within the cerebrum or adjacent meninges. Cell proliferation typically causes compression of adjacent brain structures and hydrocephalus, which results in clinical signs that can be monitored as a surrogate marker of xenograft growth and progression. The diffuse infiltrative pattern observed in this study, by contrast, failed to produce outward signs of neurologic involvement in the expected timeframe and there was concern that the orthotopic xenograft had failed.

While the pattern of infiltration was unique, the cellular morphology of the implanted BT142 cells were consistent with that described in similar experiments.[6] The diffuse, non-disruptive pattern of infiltration is characteristic of gliomatosis cerebri[3,9] in humans and dogs. This rare disorder is characterized by diffuse and widespread infiltration of the CNS by neoplastic glial cells with relative preservation of the glial architecture. Approximately 42% of cases of gliomatosis cerebri have been found to carry the IDH1 mutation.[2,5,8,10] In humans, IDH1 mutations can be associated with prolonged survival and better outcomes than tumors not positive for the IDH1 mutations.[5]

Gliomatosis cerebri is usually considered to be a malignant lesion corresponding to WHO grade III. These neoplasms are typically of astrocytic and oligodendroglial origin and in some cases positive IHC staining with GFAP is observed. Common symptoms in human cases include corticospinal tract deficits, dementia, headaches, mental and behavioral changes, and seizures. Signs and symptoms begin abruptly or progress slowly for weeks or months, with a long latency period before the development of clinical signs. There is no evidence of sex predisposition and all ages are affected with the peak incidence between 40 and 50 years of age.[9] Similarly, dogs generally present with a variety of clinical signs, including cranial nerve deficits, depression, circling, and reaction deficits.[9]

Human cases are pleomorphic, with cells ranging from well-differentiated protoplastic and fibrillary astrocytes to elongated, more poorly differentiated glial cells. Pleomorphism and anisocytosis are more marked in densely infiltrated areas of the brain, typically the cerebrum and brain stem.[9] White matter is more affected than gray matter and the cerebellum is generally less affected. The morphology of the neoplastic cells in dogs shows ovoid to slender nuclei with indistinct cytoplasm. While the cerebrum is often affected in dogs, the cerebellum is also often

affected, in contrast to human cases.[7] Both humans and dogs show neuronal satellitosis, subpial and subependymal accumlations, perivascular cuffing, and parallel arrangement of neoplastic cells within white matter tracts.[9]

JPC Diagnosis: Brain, cerebrum: Malignant glioma, anaplastic, consistent with xenograft of BT142 anaplastic oligoastrocytoma.

Conference Comment: Our diagnosis was determined following consultation with JPC human physician neuropathologists and evaluation of the immunohistochemical profile. If we were to be consistent with that used in the GORENI (referenced below) classification standard for this case, diffuse malignant astrocytoma would be the most appropriate classification. The morphologic appearance is consistent with the diagnosis provided by the contributor. Also, given the experimental history in this case, another suggested by our consultants (mixed malignant glioma, high grade) may also be appropriate.

Glioblastoma cerebri is a rarely reported neoplasm classified as a neuroepithelial tumor of unknown origin,[3] and the contributor mentions other sources describing it as astrocytic and oligodendroglial origin. Our GFAP stain revealed only reactive astrocytes; neoplastic cells were negative. There is currently not a consistently reliable immunohistochemical marker available for differentiating between astrocytes and oligodendroglial cells, which led some participants to view the diagnosis of the engrafted cell line, anaplastic oligoastrocytoma, with some suspicion though it is recognized in the WHO classification system. The submitted slides from this case represent two different mice, however both from the same study. There is some variation in appearance between a diffusely infiltrative pattern with preservation of normal architecture to some areas with more of a mass effect replacing the neuropil which led to further deliberation on arriving on a name for this tumor. Regardless of nomenclature, the anaplastic features of this neoplasm and extensive involvement through multiple cross sections of the brain indicate a high grade malignant process and many were amazed as to the apparent lack of clinical signs in this animal.

http://www.goreni.org/

Contributing institution: Eli Lilly and Company, Department of Pathology and Toxicology, Indianapolis, IN 46285. www.lilly.com

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CASE III: 13-7233 (JPC 4049289).

Signalment: 22-month-old female Syrian hamster, *Mesocricetus auratus*

History: Control hamster from an experimental study

Gross Pathology: No significant gross lesions were seen.

Laboratory Results: None.

Histopathologic Description: Ovary: The normal ovarian architecture is effaced and compressed by an encapsulated and well differentiated neoplasm. The neoplasm is composed of polygonal neoplastic cells arranged in nests, sheets, and cords supported by moderate fibrovascular stroma. Neoplastic cells have variably distinct cell borders and moderate amounts of foamy to fibrillar eosinophilic cytoplasm. Nuclei are round to oval with finely stippled chromatin and 2-3 distinct nucleoli. Mitotic figures average 1-2 per HPF and neoplastic cells often undergoes individual cell necrosis. Cellular pleomorphism is characterized by mild anisokaryosis. The adjacent stroma, bursa, and adipose tissue are infiltrated by low to moderate numbers of neutrophils, macrophages, lymphocytes and low numbers of mast cells. The lumen of the oviduct and uterus have moderate numbers of neutrophils admixed with epithelial cells, cellular debris and amphophilic fibrillar material.

Contributor's Morphologic Diagnosis: Ovary: Granulosa cell tumor

Contributor's Comment: Granulosa cell tumors are the most common sex-cord stromal tumors reported in domestic animals and have been reported in horses, cows, and dogs, and laboratory animals such as non-human primates, mice, and rats.[15,10,6] They are usually unilateral and benign in mares.[14] Malignant granulosa cell tumors have been reported in cows, dogs, cats, and laboratory mice.[2,5,12,18] Clinical signs associated with granulosa cell tumor in mares include anestrus, stallion-like behavior, and nymphomania. In mares, neoplastic granulosa cells produce

inhibin a peptide hormone that may cause atrophy of the contralateral ovary.[15] Granulosa cell tumors are the most common ovarian tumors of Syrian hamsters.[8,13] Occurrence of both benign and malignant granulosa cell tumors in Syrian hamsters have been reported.[11]

In humans, granulosa cell tumors represent 2-5% of all ovarian tumors and usually have clinical features of hyperestrogenism.[16] Mutations in transcription factor FOXL2 is pathognomonic for adult-type granulosa cell tumors in humans.[17] Further, 17β-estradiol, inhibin, and mullerian inhibiting substance are considered to be reliable diagnostic and prognostic markers in humans.[8] While inhibin-α is a reliable marker in canine granulosa cell tumors[14] calretinin, GATA-4, and neuron-specific enolase are consistently expressed in non-human primate granulosa cell tumors.[3] No such markers have been reported in Syrian hamsters.

JPC Diagnosis: 1. Ovary: Granulosa cell tumor. 2. Oviduct: Salpingitis, suppurative, diffuse, moderate, with ductular ectasia.

Conference Comment: The common occurrence of granulosa cell tumors in hamsters and its histologic difference from those which occur in domestic animals makes this a noteworthy case. The common histologic patterns are follicular (microfollicular and macrofollicular), insular, trabecular, and diffuse. The distinctive microcavities containing eosinophilic material lined by a rosette arrangement of granulosa cells are known as "Call-Exner bodies" and occur most commonly in the microfollicular pattern.[7] This type of arrangement is observed in early stages of bovine neoplasms, but less common in other species.[15] These tumors have a very characteristic gross presentation, especially in the mare, composed of numerous cysts with areas of solid white or yellow content. The cystic cavities are often observed histologically lined by granulosa cells and surrounded by a variable population of thecal cells, and often identified as granulosa-theca cell tumors.[15] In our sections, the neoplasm is a densely cellular population of granulosa cells in nests and packets, with each outlined by a fine fibrous stroma. No cystic cavities or Call-Exner bodies are present in this particular case, which may be indicative of its species-specific differences.

The interesting aspect of sex cord-stromal tumors is their ability to produce a variety of hormones and induce corresponding clinical signs. The contributor mentioned those exhibited by mares, and recent publications have demonstrated increased levels of testosterone and inhibin can be useful in obtaining a presumptive diagnosis.[4] Additionally, anti-Müllerian hormone concentrations are elevated in mares and cows with these neoplasms.[1,4] Estrogen and progesterone may also be secreted, as cystic endometrial hyperplasia and pyometra are common in bitches with sex cord-stromal tumors.[15] In this case, we believe the oviduct and uterus are moderately distended, and there is suppurative inflammation in some sections within the oviduct. The relationship of these inflammatory changes with the ovarian neoplasm is unclear.

Contributing institution: http://web.mit.edu/comp-med

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CASE IV: S12/1884 (JPC 4035414).

Signalment: A male, adult (exact age not known) European hedgehog (*Erinaceus europaeus*) from a wildlife park

History: The hedgehog was found in lateral position with tremors. There was a short improvement of the symptoms with medical treatment (Dexamethasone, Baytril and Levamisol). Euthanasia was performed because of vestibular ataxia four days later.

Gross Pathology: At necropsy, the hedgehog was in poor general body condition. There was severe lung edema and all lung lobes were mottled in dark and light red. There was no macroscopic lesion in the tympanic bullae or the brain.

Laboratory Results: PCR Result: *Cryptococcus neoformans var. gattii*

Histopathologic Description: Brain: Diffusely, the meninges, plexus choroideus, cerebrospinal fluid in the lateral ventricles, Virchow-Robbins space and surrounding brain tissue of the white and grey matter are massively thickened and infiltrated by intra- and extracellular fungal yeasts of 5-20 um in diameter, ovoid to spherical with a 1-2 um basophilic cell wall and a non-staining thick capsule observed as a clear circular halo up to 10 um in thickness. There is rare narrow-based budding. The yeasts are accompanied by a severe infiltrate of macrophages, lymphocytes, plasma cells, fewer eosinophils and neutrophils. Predominantly perivascular located and multifocal pallisading are large numbers of multinucleated giant cells of the foreign body type and Langhans cell type. They contain up to 20 nuclei and intracytoplasmic fungal yeast (phagocytosis). The meningeal and encephalic vessel walls, predominantly of the veins, are severely infiltrated by the above mentioned inflammatory cells, giant cells and yeasts and slightly homogenous and hypereosinophilic (vasculitis and fibrinoid degeneration). Multifocal in the inflammatory areas are moderate numbers of extravasated erythrocytes (hemorrhage). Within the grey and white matter, there is a severe, diffuse increase of glial cells (gliosis) predominantly astrocytes (astrocytosis) which have an elongated or glassy, rounded nuclei (activation), often surrounding neurons (satellitosis). At the white-grey matter junction, the neuropil is loosely arranged and vacuolated, mostly around the affected vessels (edema). Additionally, the epithelium of the ventricle is multifocally thickened and composed of two or three cell layers (hyperplasia).

Contributor's Morphologic Diagnosis:
Brain: granulomatous and lymphoplasmocytic meningoencephalitis and vasculitis, severe, diffuse, chronic with intralesional yeasts consistent with *Cryptococcus* sp.

Contributor's Comment: The disease cryptococcosis is caused by the genus *Cryptcoccus (C.)*, including over 37 species, the majority of which do not cause disease in mammals.[7] The disease-causing *Cryptococcus* sp. are referred to as the *C. neoformans – C. gattii species* complex, which includes *C. neoformans var. neoformans*, *C. neoformans var. grubii* and *C. gattii*.[7] The classification was originally based on serotype, determined by capsular antigens.[3,7] Nowadays, genotyping has replaced serologic typing and divided *Cryptococcus* in two different species, *C. neoformans* and *C. gattii,* and in molecular types VNI and VNII, (*C. neoformans var. grubii*, serotype A), VNIV (*C. neoformans var. neoformans*, serotype D), VNIII (hybrid serotype AD), VGI, VGII, VGIII and VGIV (*C.gatti*, serotype B and C).[3,7]

In our case, the PCR resulted as *Cryptococcus neoformans var. gattii.*

Cryptococcosis is the most common systemic mycotic disease of cats worldwide, but has been described in other domestic species (ferrets, horses, cattle, goats, sheep and llamas) and non-domestic species (parrots, elk, koalas and dolphins).[1,7] The disease is sporadic and the infection is neither contagious nor zoonotic.[1] To our knowledge, *Cryptococcus* has not been described in hedgehogs. This animal was kept in an open wildlife park environment. The immune status was unknown. Similar lesions containing yeasts were also found in the lung and kidney, the infection was considered as systemic. Clinical presentations of cryptococcosis are similar in all described animals; althought *C. gattii* appears to be more virulent and has a greater propensity to infect the CNS.[7] The route of entry is considered by inhalation of basidiospores (yeast cells).[1] CNS penetration is a consequence of the number of organisms inhaled, the virulence of the isolate and the ease of penetration of the nasal and frontal bones and the cribiform plate.[7] It is described that dogs, in comparison to cats, develop a marked inflammatory response, primarily mixed cellular or granulomatous, whereas cats develop a mild, primarily neutrophilic response.[9] In the present case of the hedgehog, there is a moderate to severe granulomatous meningoencephalitis, similar to the described lesions in dogs. Reports of cerebral cryptococcosis without respiratory involvement in domestic animals are scarce, though described in cats[6], horses[2] and in cows.[5]

Recent reports of CNS cryptococcosis include single reports in a bull from Brazil[8] and smaller series of animals as in dogs and cats from California.[9] A special variant of CNS cryptococcosis is the so called cryptococcoma, a single gelatinous pseudocyst in the CNS, often suggested as neoplasia with MRI.[9] The cyst is histologically composed of cryptococcal organisms surrounded by a pyogranulomatous inflammatory reaction and necrosis.[5,6] In people, neurocryptococcosis is linked to immunosuppression, often seen in HIV-infected patients. Whether the same is true in animals remains the subject of debate.[6]

Here, diagnosis was based on H&E histology, supported by special stains and a PCR investigation: The wall of the yeasts stained positive with Periodic acid Schiff (PAS) and Grocott and the capsule stained positive with Mayer's mucicarmine. PCR: *Cryptococcus neoformans var. gattii.*

Histological differential diagnoses based on similar morphology: *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Candida albicans*, *Sporothrix schenkii* and *Prototheca spp*.[5]

JPC Diagnosis: Cerebrum, meninges: Meningoencephalitis, granulomatous, multifocal to coalescing, moderate, with granulomatous ventriculitis and choroiditis, moderate hydrocephalus and numerous intrahistiocytic and extracellular yeasts.

Conference Comment: The contributor introduced recent literature discussing the updated nomenclature of this organism. *Cryptococcus gattii*, identified in this case, occurs in immunocompetent mammals and is thus considered a primary pathogen, while *C. neoformans* var. *neoformans* and *C. neoformans* var. *grubii* are often opportunistic pathogens linked with immunosuppression.[7] Although considered a primary pathogen, the sheer number of organisms present within the meninges and outnumbering the inflammatory cells in this case led conference participants to speculate whether the administration of steroids permitted this organism to proliferate further prior to necropsy. However, glucocorticoid therapy has successfully achieved favorable clinical responses in some cases of cryptococcosis.[9] Contrarily, it may be the yeast

capsule's ability to inhibit leukocyte recognition and chemotaxis that accounts for the lack of inflammation.[1] *Cryptococcus* spp. are readily identifiable by this large negatively-staining but carminophilic capsule, which also aids it in prevention of phagocytosis by macrophages and neutrophils. The organisms also utilize superoxide dismutase and catalase in addition to being one of the many species which produce melanin, all to provide protection from oxidative damage by host mechanisms. Utilizing dopamine as a substrate for melanin production may facilitate its affinity for the CNS.[7]

The thick polysaccharide capsule gives lesions a gross gelatinous appearance, and in the cerebrum these often characteristically develop into cystic spaces as mentioned by the contributor. This is most commonly observed in cats and occurs through a repetitive process of macrophage phagocytosis, cell lysis and subsequent chemotaxis of additional macrophages allowing an expansive accumulation of the polysaccharide capsule.[10] The pathogenesis of this infection is curious, and largely still unexplained as to why the variability in inflammatory responses and lesion development occurs. Findings such as large cryptococcomas being more commonly reported in immunocompetent patients[9], and the lack of increased susceptibility in cats with retrovirus infections[7] seem to be counterintuitive. Overall, cryptococcosis is a disease often associated with a poor prognosis, as median survival time (MST) for all cats was just 19 days in one study despite treatment with antifungal drugs.[9] But when excluding the rapidly deteriorating patients, or those which didn't survive the first three days following diagnosis, the MST is much longer with many cats surviving past the conclusion of the study.[9]

The presentation of *Cryptococcus* in a hedgehog is unique, and conference participants discussed other known diseases within this species as they are becoming increasingly popular as pets. Hedgehogs seem to have a high incidence of neoplasia, with its prevalence at necropsy being as high as 53%.[4] Another condition first described in the mid-1990's is a progressive paralysis called Wobbly hedgehog syndrome with an incidence of 10% in pet hedgehogs in North America.[4] This is characterized histologically as vacuolation of the white matter tracts without an inflammatory infiltrate,[4] similar to degenerative myelopathy which occurs commonly in German Shepherd Dogs.

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