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Case Number: N24-0544

Signalment: 8-year-old, female spayed American Domestic Shorthair cat

History: This cat was managed by the TAMU Neurology Service for seizures since May 2021 and was taking levetiracetam, zonisamide, and prednisolone for seizure management. She presented to the TAMU Emergency Service for an increased frequency of seizures in February 2024. Seizures had increased from one every two weeks to one every 1-2 days, and she frequently injured herself during these episodes. Treatment included an increase in her zonisamide dose, which at first was effective, but then her seizures increased in frequency. She also had chronic urinary tract infections since September 2023. Given the increased seizures, self-injuries, and chronic urinary tract infections, the owners elected euthanasia.

Magnetic Resonance Imaging (MRI) Findings: The right piriform lobe was minimally enlarged and mildly T2 hyperintense with minimal contrast enhancement. Additionally, the rostral aspect of the right hippocampus showed mild enlargement and T2 hyperintensity, with patchy minimal contrast enhancement.

Gross Findings: The ventral hippocampus was slightly decreased in size with a granular texture, and both piriform lobes appeared firm. Urolithiasis and chronic kidney disease were confirmed.

Histologic Findings: Throughout the hippocampus, the dentate gyrus and CA1-CA3 fields have moderate to marked neuronal loss with paucity of the pyramidal neurons. The remaining neurons are often swollen (degeneration) with peripheralized Nissl substance (chromatolysis) or are shrunken with hypereosinophilic cytoplasm and pyknotic nuclei (necrosis). Within the affected areas is a moderate proliferation of glial cells (gliosis). Multifocally in the areas of gliosis within the fimbria and alveus regions, and in the CA2 region to a lesser extent, are numerous round to elongated, 5 to 40 µm in diameter, bright, hypereosinophilic, homogeneous intra-astrocytic accumulations (Rosenthal fibers). GFAP immunohistochemistry reveals strong intracytoplasmic immunolabeling of numerous, haphazardly arranged, astrocytic processes in a superficial rim around the Rosenthal fibers. Within the piriform lobe is a mild increase in glial cells, and rarely, neurons are necrotic.

Histologic Diagnosis: Left hippocampus: Marked, chronic, multifocal, neuronal necrosis and loss with glial scarring and Rosenthal fibers.
Left piriform lobes: Mild gliosis.

Comments: The histologic findings of neuronal necrosis confined to the hippocampus and piriform lobe of this case are consistent with feline hippocampal and piriform lobe necrosis (FHN), which is an uncommon condition in cats. The clinical signs of FHN include acute or recurrent focal seizures, orofacial automatisms, and behavioral abnormalities such as aggression and rapid running. MRI findings that support the diagnosis of FHN include bilateral T2/FLAIR hyperintensity (which was appreciated in this case), T1 hypointensity, and contrast enhancement in the affected regions. However, histopathology remains the gold standard.

The pathogenesis of FHN remains unclear, with no known infectious etiology. Emerging evidence suggests excitotoxicity, which parallels human autoimmune limbic encephalitis (ALE)-induced temporal lobe epilepsy (TLE). In humans, ALE is associated with abnormal voltage-gated potassium channel (VGKC) complex antibody production against neuronal cell membrane antigens that are highly expressed in the limbic system, particularly leucine-rich glioma-inactivated 1 (LGI1). LGI1 is the main component of the VGKC complex antibodies, which are highly expressed in the hippocampal neuropil. Its role includes regulating synaptic functions; therefore, impaired LGI1 function could result in hyperexcitability and excitotoxicity. Excitotoxicity further leads to glial activation, neuronal necrosis, and loss in the cornu ammonis (CA) fields and the dentate gyrus. Hippocampal necrosis proceeding to hippocampal sclerosis (HS) has been observed in patients with ALE and long-standing TLE. Histologically, HS is defined as significant pyramidal cell loss from the hippocampal cell band (CA1–CA4), in combination with reactive astrogliosis. Research indicates that HS is

present in approximately one-third of cats with long-term epilepsy in the CA3 and CA4 regions.

Rosenthal fibers (RFs), which histologically are characterized as deeply eosinophilic, irregularly shaped, elongated to round intra-astrocytic aggregates, indicate chronic gliosis. They are considered one of the hallmark features of Alexander's disease, although they are also present in an array of different diseases that involve chronic gliosis. This case highlights the classic neurologic signs and key histologic features of a chronic case of feline hippocampal necrosis in a cat, with unique formation of Rosenthal fibers.

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