CASE 1 – 07-V6182 (AFIP 3110669)

Signalment: 9-week-old, female, large white pig, porcine (Sus)

History: At a hog grower operation two sheds had been cleaned out and the water turned off from each shed prior to the introduction of a new batch of pigs. On a Thursday, 400 9-week-old grower pigs were introduced into each shed. It was not realized until the following Saturday that drinking water to each shed had not been turned on. The pigs engorged with water on Saturday and Sunday, and by Monday many of the pigs were paddling and had muscle fasciculation, others were blind, and many were having seizures or were down and non-responsive. To confirm the field diagnosis, the attending veterinarian collected and submitted to the laboratory three entire brains fixed in 10% neutral buffered formalin and three meningeal swabs for bacteriology.

Gross Pathology: No significant gross pathological lesions were evident in the brain.

Laboratory Results: On meningeal swabs from three pigs, no bacteria grew on horse blood agar, and haemolysed blood agar plates incubated aerobically for 72 hours.

Histopathologic Description: Lesions varied in severity in each of the three brains. The most consistent findings were as follows: brain, forebrain, in which the leptomeninges, particularly in the sulci are multi-focally and segmentally thickened by increased numbers of well differentiated eosinophils. In the cerebral cortical laminar blood vessels, particularly veins and venules, show thick perivascular cuffs of eosinophils (Fig. 1-1), 1 to 3 cells deep, rarely there are macrophages. Multi-focally blood vessels in the cerebral cortical laminae have prominent and swollen endothelial cells. Segmentally along the cerebral cortical laminae, particularly in the sulci, there is a well delineated multi-focal astrogliosis and microgliosis.

Contributor’s Morphologic Diagnosis: Chronic severe multifocal eosinophilic meningoencephalitis

Contributor’s Comment: This was a case of indirect salt poisoning also known as water deprivation or water intoxication. Of the 800 at risk pigs, 600 died or were euthanized. Only pigs with the mildest of clinical signs survived. It was two weeks before clinical signs ceased in the surviving pigs. Interestingly, the farmer said that one or two pigs started to have seizures before the water supply
was turned on. The attending veterinarian immediately recognized this as a case of indirect salt poisoning (water deprivation) and collected brains for histology to confirm and provide evidence of the clinical diagnosis. Bacterial swabs were collected to exclude the possibility of bacterial meningitis. The farmer was a contract grower for a parent company. The parent company was furious and treated this as a serious breach of animal welfare and a situation that should not have occurred. Furthermore, the company protocol for pigs that have been deprived of water is to turn the overhead sprinklers on and gradually re-introduce water allowing pigs to lick water off the floor. The contributor has only seen one previous case of indirect salt poisoning and that was in pigs delayed in road transport that when they finally arrived engorged on water.

In domestic animals direct salt poisoning occurs in cattle, horses, sheep and pigs with the ingestion of excessive amounts of sodium chloride. Direct salt poisoning can occur in pigs where bore water is used for livestock drinking or diets with excessive salt including salted fish waste, salt whey from cheese factories and excessive salt in baker’s bread dough. Indirect salt poisoning involves a normal intake of sodium chloride, but with limited water intake. The latter is also termed water deprivation or water intoxication. Indirect salt poisoning has only been proven to occur in pigs, with circumstantial evidence in cattle and sheep. Pigs are particularly susceptible to indirect salt poisoning because of the relatively high salt diets. Restriction of water intake to pigs, 4 to 12 weeks of age, fed prepared diets containing 2% salt can result in clinical disease. Poisoning occurs when the animals again have access to unlimited water.

Indirect salt poisoning with decreased water intake, but normal sodium chloride intake results in an accumulation of sodium ions in the brain and other tissues over several days. High sodium accumulation inhibits anaerobic glycolysis, preventing active transport of sodium out of the cerebrospinal fluid. When there is access to water again, water migrates to the tissues to re-establish the salt-water balance. Acute cerebral edema develops and increased intracranial pressure results. Specific to pigs and of diagnostic significance, is that there is an influx of eosinophils into the meninges.

In cases of salt poisoning there are two characteristic changes. The first is eosinophilia of the leptomeninges and Virchow-Robin spaces in the cerebral cortex. The second, develops with increased duration of the lesion, is cerebral cortical necrosis and with advanced lesions cavitating areas of malacia. A mixture of both reactions is most common, but either alone may be encountered.
The differential diagnosis for CNS signs in young pigs includes viral encephalomyelitis, Aujeszky's disease, edema disease, Streptococcal meningitis, Glasser's disease, toxicosis, nutritional deficiencies and Mulberry heart disease. Meningeal and perivascular infiltrates can occur in the brains of pigs with leukomalacia of Mulberry heart disease and other causes of encephalitis. However, the combination of laminar cortical cerebral necrosis and cerebral eosinophilia is pathognomonic for direct or indirect salt poisoning. Histologically, eosinophilic meningoencephalitis can also occur with parasitic infections. In Australia, parasitic encephalitis is rare. In dogs, Angiostrongylus cantonensis occurs infrequently, but has not been observed in pigs.

The importance of this report is that direct or indirect salt poisoning cases often affect many animals and mortalities can be high. In cases of indirect salt poisoning veterinary pathologists should recognize that a restricted water intake is often the cause and this may be due to an underlying animal welfare issue. Veterinary pathologists should recognize that they play an important role in recognizing or confirming animal welfare associated diseases.

AFIP Diagnosis: Brain, cerebrum: Meningoencephalitis, eosinophilic, acute, multifocal, moderate with neuronal necrosis (Fig. 1-2)

Conference Comment: The lesion in this brain had a striking eosinophilic component. Other causes of eosinophilic meningoencephalitis in domestic species include parasitic nematodes and protozoans.

Idiopathic eosinophilic meningoencephalitis has also been reported in dogs and one cat. Severe neurologic signs including recumbency and loss of consciousness have been reported with this syndrome. Eosinophilia and CSF pleocytosis with a predominance of eosinophils are common clinical pathologic findings. Grossly, the meninges often have a green tinge because of the eosinophilic inflammatory infiltrate. Histologic changes include eosinophilic and granulomatous meningoencephalitis of cerebrum and cerebellum with eosinophilic perivascular cuffing. In pigs, Golden Retrievers and Rottweilers are the most commonly affected breeds.

In pigs, salt toxicity can cause laminar cortical necrosis. Several of the submitted slides did have very good examples of neuronal necrosis, while other slides had a dearth of necrotic neurons. Slides submitted for this case were from three different pigs, so that may be the reason for slide variation. In ruminants, differentials for laminar cortical necrosis include lead poisoning, salt toxicity, sulfur toxicity, hypoxia, and thiamine deficiency.

Contributing Institution: Gribbles Veterinary Pathology, 1868 Dandenong Rd Clayton, Melbourne, Victoria, Australia, 3168.

References:
Signalment: Bavarian Warmblood, 11 yrs, female, equine

History: Two week history of fever, depression, gait abnormalities and anorexia. The animal was euthanized after unsuccessful symptomatic treatment.

Gross Pathology: At macroscopic inspection, the brain appeared normal.

Laboratory Results: Brain was positive for Borna disease virus (BDV) antigen by immunohistochemistry and negative for Rabies virus antigen by immunofluorescence test.

Histopathologic Description: Slices of the brain reveal moderate, multifocal, perivascular and parenchymal infiltrating mononuclear immune cells (Fig. 2-1) affecting slightly more gray than white matter with a severe generalized astrogliosis and microglia activation throughout the whole brain. Lesions are most severe in the lateroventral parts of the cerebral cortex, mesencephalon and hippocampal gyrus. Inflammation cells are also infiltrating plexus epithelia and leptomeninges. Moderate neuronal and axonal degeneration (spheroids) can be found and some neurons undergo neuronophagia (Fig. 2-2). No neuronal intranuclear acidophilic inclusion bodies, Cowdry type B, (Joest Degen bodies) are detectable in these slices.

Contributor’s Morphologic Diagnosis: Polioencephalitis, meningitis, plexitis, nonpurulent, multifocal, subacute, moderate

Contributor’s Comment: Borna disease occurs naturally in horses, sheep\(^1\), rarely in cats\(^2, 3\), and other warm-blooded animals\(^1, 4\). Borna disease virus has been classified as the prototype of a new virus family, Bornaviridae (mononegavirales)\(^1, 5\), though the disease has been recognized in Central Europe for more than 250 years and apparently in Asia\(^6, 8\). Because experimental infection of rodents, sheep and horses is achievable by intranasal application of virus, some researches already assume that the natural infection with BDV might occur by the olfactory nerve\(^1, 8, 9\) and several studies indicate wild rodents being a common virus reservoir\(^1, 10\).

The highly neurotropic but noncytolytic virus\(^9\), similar to rabies virus, is transported by retrograde axonal transport from the periphery to the CNS. After infection, BDV causes a persistent infection of the central nervous system and induces an immune-mediated encephalomyelitis. The

2-1. Cerebrum, horse. Expanding Virchow-Robin spaces of the cerebral vasculature are high numbers of lymphocytes, plasma cells, and few histiocytes. (400X)
infiltrating immune cells have been characterized as CD4-positive T-cells, CD8-positive T-cells, macrophages and B cells. The virus can then also spread centrifugally via the peripheral nervous system, resulting in infection of nonneural tissue. A proposed mechanism for the behavioral changes involves protein interference with neurotransmitter function of infected neurons, especially those located in the limbic lobe.

The first evidence that some human psychiatric patients might be infected with BDV, or a BDV-related virus, came from serological studies using immunofluorescence assays. However, several key experiments could not be reproduced by independent laboratories and started a still ongoing, highly controversial, worldwide debate about whether BDV infects humans and causes psychiatric problems. In this case, the detection of viral antigen in fresh brain tissue by immunohistochemistry, the clinical manifestations and the characteristic histopathological changes within the brain all contribute to the diagnosis of Borna disease.

AFIP Diagnosis: Brain, thalamus: Meningoencephalitis, lymphocytic, multifocal, moderate

Conference Comment: Borna disease virus (BDV) is a single-stranded RNA virus and is the sole member of the family Bornaviridae in the order Mononegavirales. It is named after the village Borna in Germany where the first major outbreak of this disease was recognized in the late 1800’s. BDV has a very wide host range, but sheep and horses are the most susceptible species to disease. Borna disease is most prevalent in Europe, but positive titers have been found in the United States. Recently, Borna disease virus has been suggested as a potential cause of proventricular dilatation disease in birds. Research is currently ongoing to prove this link.

Gross lesions are not seen in infections with BDV. Histologic lesions are generally present in the grey matter of the olfactory bulbs, hippocampus, limbic system, basal ganglia, and brain stem. The cerebellum and dorsal aspect of the cerebrum are usually unaffected. Common histologic lesions are a nonsuppurative encephalitis with perivascular cuffing composed of mononuclear cells, gliosis, and neuronophagia. Perivascular cuffing is often pronounced with cells layering upon one another up to seven cells deep. Inclusion bodies (Joest-Degen bodies) are nearly pathognomonic for BDV infection, and, if present, are normally in nuclei and rarely in the cytoplasm. The hippocampus is reported as the best area to find inclusions. This virus is also unique because it replicates in the nucleolus of the host cell.

Dr. Van Winkle discussed the importance of narrowing this particular case down to a list of differentials, and then using the tools available at your particular institution to make a diagnosis. In horses, differentials for this lesion include: West Nile virus, Japanese encephalitis virus, Murray Valley encephalitis, St. Louis encephalitis, Western equine encephalitis, Eastern equine encephalitis, and Venezuelan equine encephalitis. Other potential differentials discussed during the conference included equine protozoal myelitis and equine herpesvirus type 1. Dr. Van Winkle commented that geographic location in many cases of equine encephalitis is a good indicator of what differential should be at the top of the list.

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References:
5. de la Torre JC, Carbone KM, Lipkin WI: Molecular

CASE III – N07-649 (AFIP 3109554)

Signalment: 4-year-old spayed female mixed breed dog (Canis familiaris)

History: 3-week history of seizures, nystagmus, strabismus, lateral recumbency at about weekly intervals. On each occasion, supportive care with intravenous fluid, administered at the referring veterinarian was sufficient to bring about temporary recovery from symptoms. The dog was admitted to the University of Florida Veterinary Medical Center (UF VMC) obtunded with lateral nystagmus, anisocoria, and strabismus. She had patellar hyperreflexia, good palpebral reflexes, miosis of the right pupil, and mydriasis of the left pupil with no pupillary light responses, and good reflexes in all four limbs. Cystic lesions in the brain were diagnosed at the referring veterinarian. The dog began to decline and the owner opted to euthanize.

Gross Pathology: The lateral ventricles in the brain were moderately enlarged. There was a 2cm diameter, poorly-demarcated red focus in the meninges over the right lateral occipital area. One gyrus in this region was expanded and contained an 8x5 mm grey focus.

The kidneys contained numerous irregular depressions on the subcapsular surface that extend into the cortex. The capsule did not peel off easily.

Laboratory Results: Sodium mEq/L = 137 (145-154), potassium = 5.6 mEq/L (4.1-5.3), BUN = 102 mg/dL (8-31), Creatinine = 4.6 mg/dL (0.8-1.6).

Histopathologic Description: Vessels in the meninges are frequently markedly distended with a neoplastic population of round cells (lymphocytes) (Fig. 3-1) which are predominantly confined to the lumina of capillaries, arteries, and veins, but also extend into the perivascular tissue. The lymphocytes are large, have large round to oval nuclei, one to several nucleoli, coarsely clumped chromatin, and small amounts of amphophilic cytoplasm. There is marked anisocytosis and anisokaryosis, and an average of 1-2 mitotic figures per 400X field. There is frequent individual cell necrosis. Frequently, there are scant erythrocytes in the vessels along with the neoplastic lymphocytes. There are thrombi present in a low number of affected vessels. Throughout the parenchyma, in both the gray and white matter, there are a low number of vessels which contain neoplastic lymphocytes. There are several areas in the cerebral cortex which contain increased numbers of small vessels
with prominent endothelial cells and neoplastic cells often present within the vessels. In these foci, there is rarefaction of the neuropil, necrotic neurons and/or loss of neurons, swollen axons, and accumulation of gitter cells (infarcts). Neoplastic lymphocytes rarely extend into the neuropil in these foci.

**Contributor's Morphologic Diagnosis:**
1. Intravascular lymphoma, with thrombosis and subacute to chronic infarction, brain
2. Moderate hydrocephalus

**Contributor's Comment:** Canine intravascular lymphoma is a rare large cell lymphoma in which lymphocytes proliferate within blood vessels in the absence of a primary extravascular mass or leukemia. Blood vessels in nearly all tissues examined contained luminal neoplastic lymphocytes, which often largely filled the vessel lumen. Thrombosis was also identified in numerous tissues, and thrombosis resulted in infarction in the brain, spleen and heart. Infarcts were variably prominent in submitted sections. Multifocal cerebral cortical infarctions were the cause of neurologic clinical signs. The hydrocephalus diagnosed on gross examination was most likely congenital and an incidental finding.

Canine intravascular lymphoma is also known as malignant angioendotheliomatosis. Although most human cases are of B cell origin, canine cases are typically classified as T cell or non-B, non-T cell. Most human cases present with CNS or cutaneous signs. CNS signs are most common in affected dogs.

In a retrospective study of 17 cases of canine intravascular lymphoma, neoplastic lymphocytes rarely extended outside of vessels into the surrounding parenchyma and were not present in lymph nodes or the bone marrow in the 4 cases where these organs were examined. Bone marrow and lymph node involvement were described in an additional canine case report and bone marrow involvement was reported in 4/5 human patients in which neoplastic lymphocytes were also identified in peripheral blood smears. While neoplastic lymphocytes were observed outside of vessels in multiple locations in this case (brain, kidney, pancreas, lung, lymph node, and bone marrow), the overwhelming distribution of neoplastic lymphocytes was within vessels, with comparatively little involvement of the organ parenchyma, suggesting the diagnosis of intravascular lymphoma. Additionally, leukemia was not identified previously while this animal was having neurologic signs, which presumably were due to intravascular lymphoma, thrombosis and infarction. It was uncertain if this animal was leukemic at the time of death, as no bloodwork was done at the UF VMC. The absence of neoplastic lymphocytes in peripheral blood smears in these dogs makes antemortem diagnosis extremely difficult and the diagnosis was made antemortem in a single dog in this study.
AFIP Diagnosis: Brain, cerebrum: Intravascular lymphoma, with fibrin thrombi and multifocal infarcts

Conference Comment: In addition to the diagnosis listed above, some but not all sections contain an interesting well-demarcated focus within an area of rarefaction. This nodular focus is composed of a central core of coagulative necrosis bounded by numerous fibroblasts and glial cells, interpreted as a sequestrum (Fig. 3-2).

The majority of cases of intravascular lymphoma in humans can be placed into four distinct presentations: 1) central nervous system form, 2) cutaneous form, 3) fever of unknown origin, and 4) hemophagocytic form. Most human patients present with neurologic signs, while about 1/3 of human patients present with cutaneous lesions. Cutaneous lesions are not as common in animals with IVL as they are in their human counterparts.

As mentioned by the contributor, most human cases are of B cell origin, while IVL in animals has been shown to be derived primarily from T cells or non-B, non-T lymphocytes with rare cases of B cell tumors. The source of neoplastic cells in IVL is still uncertain, but there is speculation that they may originate from the red pulp of the spleen. The behavior of these neoplasms suggest that initial movement into the bloodstream is possible with subsequent problems related to adhesion and emigration resulting in intravascular accumulations of neoplastic cells as opposed to deposition within organs.

Contributing Institution: University of Florida, College of Veterinary Medicine, Department of Infectious Diseases and Pathology, http://www.vetmed.ufl.edu/college/departments/patho/

References:

CASE IV – 07-2223-6 (AFIP 3106259)

Signalment: 4-year-old, castrated male, Border Collie, (Canis familiaris), canine

History: The dog presented to OSU Small Animal Services for evaluation of progressive neurologic disease of two weeks duration. Initially, the left pupil was dilated and the dog was diagnosed with and treated for anterior uveitis. One and a half weeks later, the dog’s condition rapidly deteriorated with the onset of weakness, lethargy, anorexia, and disorientation.

Gross Pathology: The dog was in good body condition. There were no significant gross lesions of the thoracic, abdominal viscera, or eyes. There was a 3 x 2.5 cm soft, grayish-tan, fixed mass ventral to the thalamus which surrounded the optic chiasm and extended from the ventral temporal lobe rostral to the chiasm to the level of cranial nerve V caudally. Following formalin fixation and sectioning, the mass extended 3-4 cm into the overlying brain parenchyma, involving approximately the ventral third of the brain. The majority of the mass was positioned to the left of midline, causing deviation of normal structures to the right.
Laboratory Results:
- **CBC/Profile:** No abnormalities noted (performed by the referring veterinarian).
- **Borrelia burgdorferi titer:** Positive (performed by an emergency clinic, thought to be due to previous vaccination).
- **Cranial MRI:** Contrast-enhancing extra-axial mass ventral to the thalamus with dorsal displacement of adjacent structures. Meningioma suspected (performed by OSU) (Figs. 4-1, 4-2).
- **Cerebrospinal fluid analysis:** Mildly elevated protein levels and red blood cell count (performed by OSU).

Histopathologic Description: Diencephalon at optic chiasm. There is focally extensive infiltration of the ventral thalamus by a sharply demarcated but unencapsulated, multinodular, hypercellular mass. The mass is an admixture of cells exhibiting three distinct morphologies: 1) small round to polyhedral (“germinal”) cells with scant amphophilic cytoplasm which form dense packets separated by a thin fibrous stroma reminiscent of seminoma (Fig. 4-3), 2) large polygonal (“hepatoid”) cells with abundant brightly eosinophilic cytoplasm which form broad sheets of anastomosing chords and which contain one or more large discrete clear cytoplasmic vacuoles that marginate the ovoid vesicular nuclei of the cells (Fig. 4-4), and 3) large, closely-adherent polygonal (“epithelial”) cells with abundant eosinophilic cytoplasm and central round to ovoid vesicular nuclei which form irregular smaller sheets and chords (Fig. 4-5), and exhibit occasional squamoid differentiation (Fig. 4-6). Neoplastic cells of all three types exhibit a wide range of anisocytosis, anisokaryosis, and nucleoli of variable number and size. The epithelial cells occasionally keratinize and form small concentric whorls of keratin (keratin pearls). There are multifocal areas of coagulation necrosis-characterized by loss of differential staining, pyknosis, and karyorrhexis with accumulation of amorphous cellular and nuclear debris and hemorrhage within the mass. Neoplastic cells, mainly of the hepatoid type, also appear to produce small lakes of homogeneous eosinophilic material (colloid) multifocally (not present in all sections). Mitotic figures are rare (<1 per 40 x field) though they are more common within the germinal neoplastic cell population than elsewhere. Occasional abnormal mitotic figures are noted. Brain tissue immediately adjacent to the mass is markedly compressed and has mild multifocal hemorrhage. There is no evidence of vascular invasion or of ventricular involvement (ventricle not present in all sections).

Regions of the neoplasm comprised of the epithelial and hepatoid cell populations were cytokeratin positive by immunohistochemistry.

Contributor's Morphologic Diagnosis: Diencephalon at optic chiasm: Suprasellar (Perichiasmatic) germ cell tumor with necrosis, hemorrhage, and local tissue invasion and compression.
Contributor's Comment: The diagnosis of suprasellar germ cell tumor was made based upon the location and upon the presence of three diverse neoplastic cell populations within the tumor. Intracranial germ cell tumors can also occur within the pineal gland. Human variants are further classified as seminoma, choriocarcinoma, entodermal sinus tumor, or teratoma based upon additional microscopic features of the tumor. The cell of origin is presumed to be ectopic embryonic germ cells that have failed to migrate from the yolk sac to the developing gonad. The neoplastic germ cells develop three distinct populations based upon morphology and growth pattern which are characteristic for intracranial germ cell tumors: 1) pleomorphic cells which form nests and sheets reminiscent of seminomas (Germinomatous cells) 2) large polygonal cells with abundant cytoplasm which contain lipid vacuoles and form nests (Hepatoid cells), and 3) epithelial cells reminiscent of intestinal or respiratory epithelium which can exhibit acinar, tubular, or squamoid differentiation and frequent keratinization. Epithelial elements are thought to represent teratomatous change within the tumor. Colloid-containing follicles were a minor component in this case and mineralization which is common in intracranial germ cell tumors was not present. The epithelial elements of the tumor in this case were positive for cytokeratin by immunohistochemistry. The neoplastic cells within suprasellar germ cell tumors are also reported to exhibit positive a-fetoprotein staining by immunocytochemistry. Clinically, middle-aged dogs are most commonly affected by this rare tumor, with breed predisposition in Doberman Pinschers. Neurologic signs are acute in nature and are most commonly those of cranial nerve involvement (CN III and IV most frequently exhibit deficits, though CNII – XI may be involved) and/or thalamic compression (lethargy and stupor), both of which were present in this case.

AFIP Diagnosis: Brain, diencephalon at the level of the optic chiasm: Suprasellar germ cell tumor

Conference Comment: Extranongadal germ cell tumors are uncommon in both domestic animals and humans. Due to their location and pattern, suprasellar germ cell tumors must be distinguished from pituitary adenomas and craniopharyngiomas. Germ cell tumors generally arise in either the pineal gland or next to the sella turcica. In man, most tumors occur in the pineal region, in contrast to the predominately suprasellar location in dogs. In humans, in addition to staining for alpha-fetoprotein, these tumors also often stain with human chorionic gonadotropin, and placental alkaline phosphatase.

Grossly, these tumors are usually very large, gray to white, extramedullary masses attached to the ventral aspect and often compressing the diencephalon. Often admixed within the trivariant neoplastic cells are aggregates of lymphocytes that form small accumulations within the neoplasm.

Contributing Institution: Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH, http://vet.osu.edu/
Cerebellum, dog. Suprasellar germ cell tumor, one of three distinct cell populations within the neoplasm. Cords and tubules of closely adherent polygonal (epithelial) cells which have abundant eosinophilic cytoplasm and occasionally undergo squamous differentiation (demonstrated in figure 4-6 below). (HE 400X)
biosciences.htm

References: