CASE I: N761-15 (JPC 4101761).

Signalment: 6-year-old, male, Criollo, Equus caballus, horse.

History: This horse lived in the metropolitan area of Porto Alegre since it was born. It had a nine day history of lethargy, sialorrhea, evolving to neurological signs of ataxia and recumbency. Euthanasia was elected due to the poor prognosis and progression of clinical signs. Two days prior to onset of clinical signs, Trema micrantha branches were pruned, and its leaves were readily available for consumption in the pasture the horse was hold.

Gross Pathology: The brain of this horse was diffusely yellow with grayish to dark-red multifocal do coalescent friable to soft pinpoint foci, mainly involving the pons.

Laboratory results: Fragments of cerebrum, cerebellum and spinal cord were refrigerated and tested by direct fluorescent antibody test (DFAT) for Rabies virus (RABV) in a certified laboratory, following OIE recommendations, and gave negative results.

Microscopic Description: Pons: Approximately one third of the cut section (which corresponds to the pons) presents severe vasculitis and liquefactive necrosis of white and gray matter; these are characterized by multifocal transmural fibrinoid necrosis of blood vessels, which sometimes are occluded by thrombosis and associated with perivascular hemorrhage, in addition to severe vacuolation of myelin (suggestive of intramyelinic edema) and perivascular
edema. There is a moderate multifocal perivascular inflammatory infiltrate consisting predominantly of neutrophils with few lymphocytes and plasma cells. At the periphery of the areas with necrosis of blood vessels, numerous Gitter cells, Wallerian degeneration and multiple axonal spheroids are observed.

**Contributor’s Morphologic Diagnosis:**

**Brain (pons):** Focally extensive, liquefactive necrosis of the white and gray matter, with severe multifocal vasculitis, fibrinoid necrosis, thrombosis, perivascular hemorrhage and intramyelinic edema.

**Condition:** Encephalomalacia due to *Trema micrantha* poisoning

**Contributor’s Comment:** This horse was part of a major study involving 14 horses that were poisoned by *T. micrantha* consumption in different municipalities of Rio Grande do Sul state, Brazil. This condition caused lesions that affected different regions of the CNS, but the most striking lesions were observed in pons.

*T. micrantha* is an arboreal species widely distributed in Brazil, within the Cannabaceae family, occurring in tropical and subtropical areas in almost all tropical and subtropical areas of South, and Central America countries, and in the southern counties of Florida (United States of America). It is a fast growing tree up to 5-20m, that has highly palatable leaves, which are promptly consumed by herbivores, especially when branches with green leaves fall to the ground, either due to pruning or windstorms, becoming readily available for consumption, as in the present case.

The toxic compounds of *T. micrantha* are still unknown, though a toxic compound named trematoxin obtained from *Trema tomentosa* has been described in Australia. This is a hepatotoxic glycoside associated with centrilobular necrosis in cattle, sheep, goats, horses and camels; however hepatic lesions were absent in this horse, as in the majority of the remaining. Neurological abnormalities after *T. micrantha* consumption have been related to hepatic encephalopathy, resulting in Alzheimer type II astrocytes and perivascular edema on histopathology of the CNS from the affected animals. However, lesions of this horse were mainly characterized by malacia, severe fibrinoid

*Presentation, horse.* The horse demonstrated progressive neurologic signs of lethargy, salivation, ataxia, and recumbency. (Photo courtesy of: Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, [http://www.ufrgs.br/patologia/](http://www.ufrgs.br/patologia/))

*Brain, horse.* The brain was diffusely yellow-gray, with numerous areas of hemorrhage and malacia. (Photo courtesy of: Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, [http://www.ufrgs.br/patologia/](http://www.ufrgs.br/patologia/))
degeneration of blood vessels, thrombosis and hemorrhage. The massive necrosis and softening of the brain may be attributed to an ischemic lesion secondary to the fibrinoid necrosis of blood vessels, which resulted in extensive areas of hemorrhage and thrombosis and, consequently, areas of liquefactive necrosis, as previously described. These are not lesions usually related to hepatic encephalopathy. Still, the cause of these lesions is unknown, however it is speculated that it results from the action of an intermediary metabolite formed immediately after *T. micrantha* consumption, which would only occur in equid metabolism.\(^6\)

Differential diagnosis of the present case included parasitic infection by *Trypanosoma evansi* and leukoencephalomalacia due to the prolonged ingestion of corn contaminated with fumonisin B1.\(^7\) This horse did not have access to contaminated corn, and lesions differed from that condition due to the involvement of both gray and white matter. *T. evansi* infection in horses is characterized by a non-suppurative encephalitis and edema,\(^7\) which was not observed in this horse.

In this case, *T. micrantha* consumption caused predominantly a neurological disease, with absent hepatic lesions. Thus, this neurotoxicosis should be considered in the differential diagnosis of CNS diseases in horses.

**JPC Diagnosis:** Brain, pons: Vasculitis, necrotizing, multifocal, marked with thrombosis, edema, and perivascular hemorrhage, Criollo, equine.

**Conference Comment:** This case is an unusual presentation of toxic encephalomalacia caused by *Trema micrantha* ingestion. The contributor provided an excellent review of *Trema micrantha* and *T. tomentosa* poisoning which was mirrored in much of the conference discussion. Conference participants reviewed several differentials, including gram-negative sepsis, purpura hemorrhagica, equine herpesvirus-1, listeriosis, eastern equine encephalitis (EEE), leukoencephalomalacia, *Trypanosoma evansii* and cerebrovascular accidents. Most differentials could be ruled out based on lesion distribution and host inflammatory response. Equine herpesvirus-1 is most common in the white matter of the spinal cord and characteristically results in non-suppurative necrotizing vasculitis and...
thrombosis.\textsuperscript{2} \textit{Listeria monocytogenes}, is common in the brainstem, but is characterized by “microabscesses” composed of small aggregates of neutrophils within the neuroparenchyma.\textsuperscript{2} The equine encephalitides (\textit{Alphaviruses}) produce diffuse lesions in the grey matter with increasing severity in the cerebral cortex consisting of lymphoplasmacytic and neutrophilic necrotizingencephalitis.\textsuperscript{2}

The differentials discussed in-depth include leukoencephalomalacia, purpura hemorrhagica, and cerebrovascular accident, because they are associated with encephalomalacia without significant inflammation of the neuroparenchyma, as is seen in this case.

Leukoencephalomalacia (LEM), also known as moldy corn poisoning, occurs in horses, donkeys, or mules fed corn laced with mycotoxin fumonisin B1 which is produced by \textit{Fusarium verticillioides} or \textit{F. proliferatum}, which grow in warm, moist conditions causing sporadic outbreaks of disease. Fumonisin causes encephalomalacia of the white matter in two ways (1) it damages the microcirculatory system and impairs cardiovascular function, and (2) competitively inhibits sphingosine N-acetyltransferase which leads to the accumulation of sphingosine and blocks the production of spingolipids. In this case, lesions were in both the grey and white matter of the pons. In contrast, LEM produces lesions in the white matter of the cerebrum.\textsuperscript{2,5}

Although often associated with myositis, purpura hemorrhagica can affect many organs as it results in tissue necrosis secondary to vascular injury caused by immune-complex deposition (IgA and streptococcal M protein). In horses, purpura hemorrhagica accompanies \textit{Streptococcus equi} infection and results in fibrinonecrotic vasculitis and hemorrhagic infarcts. Inflammatory infiltrates are rarely seen, but when seen are usually located at the periphery of areas of necrosis and \textit{Streptococcus equi} is isolated from the lymph nodes or guttural pouch.\textsuperscript{3}

Cerebrovascular accidents (CVA) which are increasing in recognition in small animals
due to increasing awareness of their existence as well as sophisticated imaging techniques are often characterized by ring hemorrhage in the absence of significant inflammation. Literature on this problem in large animals is currently lacking.

**Contributing Institution:**
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**References:**
CASE II: 16/545 (JPC 4102434).

Signalment: 6 years old, male, Norwegian lundehund, *Canis familiaris*, dog.

History: The dog had gastrointestinal signs for approximately 5 months. He could be normal for some days, but had recurrent episodes of diarrhea with thin watery and light-colored feces. The appetite was normal, but decreased the last two weeks. At the clinic, a thickened intestinal segment cranial to the pelvis was noted on abdominal palpation. The feces were very light in color, pale brown to almost yellow-white. The consistency was paste-like and it seemed to contain fat. X-ray and ultrasound revealed severely gas-distended and dilated intestines with almost no peristaltic movements. Exploratory laparotomy was performed. The abdominal cavity contained small amounts of yellow clear fluid, and there were no signs of peritonitis. The stomach, duodenum and pancreas were normal. Nearly all of jejunum and ileum, all the way to the ileocecal junction, was characterized by atony and dilation. There were indications of peristaltic movements, but no proper contraction of intestinal wall muscle. The cecum was small and firm and the colon had near normal diameter. No physical obstruction could be detected, and it was possible to press intestinal contents from the ileum to the colon during the explorative laparotomy. The clinical tentative diagnosis was a condition that affected the function of gut motility, a pseudo-obstruction. There were no other signs consistent with dysautonomia. The dog was euthanized.

Gross Pathology: The body condition of the cadaver was below normal. The small intestine was severely dilated with abundant light grey-brown content with a thin porridge-like consistency. The content of the colon was similar in color, but a little firmer. There was no hyperemia in the intestinal mucosa, and the surface of the mucosa was also otherwise normal (the breed is predisposed to intestinal lymphangiectasia).

Laboratory results: None provided.

Microscopic Description: In the inner circular layer of the lamina muscularis of the jejunum there is a multifocal to diffuse loss of smooth muscle cells due to degeneration and necrosis. This layer is affected to a variable degree, but usually the innermost part of the lamina muscularis is better preserved and the outer part, towards the Auerbach’s plexus and the outer longitudinal muscle, was more severely affected. In affected areas, there was a mild multifocal inflammatory cell infiltrate composed of lymphocytes, some plasma cells and histiocytes. In the most severely affected areas, there was near total loss of the inner circular layer of smooth muscle cells, and replacement by mild fibrosis. Except for moderate autolytic changes in the mucosa, the small intestine was otherwise normal. The lamina muscularis in stomach and colon was normal.
Contributor’s Morphologic Diagnosis: Jejunum: Leiomyositis, lymphocytic, chronic with smooth muscle degeneration and necrosis.

Contributor’s Comment: Chronic intestinal pseudo-obstruction (CIPO) is a syndrome characterized by gastrointestinal dilation without any physical occlusion of the lumen. It is a rare condition in humans, and dogs, and single cases are also described in a cat and a horse. Morphologically CIPO may be classified as neuropathy, mesenchymopathy or myopathy, based on predominant involvement of enteric neurons, interstitial cells of Cajal or smooth muscle cells, respectively.

In domestic animals, CIPO may occur in congenital agangliosis, other conditions associated with enteric neuronal loss or ganglioneuritis, the systemic dysautonomias and intrinsic disease of intestinal smooth muscle.

In dogs, CIPO is rare and associated with intestinal leiomyositis. Affected dogs are of variable ages and breeds, they present with acute or chronic signs of vomiting, regurgitation and small bowel diarrhea.

The pathogenesis is unknown, but an autoimmune inflammatory reaction affecting the intestinal lamina muscularis is suspected. Histopathology of small intestine reveals mononuclear inflammation, smooth muscle degeneration and necrosis, and fibrosis centered on areas of myofiber loss. Immunohistochemically, the lymphocytic infiltration is dominated by T lymphocytes.
with fewer B lymphocytes. The intestinal lesions may be segmental in early stages, but in chronic and severe cases, there may be near full thickness loss of smooth muscle cells in the lamina muscularis.⁵

Similar lesions, but milder may also be seen in gastric or colonic wall. In living dogs, a full-thickness intestinal biopsies is required to make a definitive diagnosis.⁵

**JPC Diagnosis:** Small intestine, inner circular layer: Leiomyositis, chronic, lymphocytic, diffuse, severe with smooth muscle loss and fibrosis, Norwegian lundehund, canine.

**Conference Comment:** This is a nice example of chronic intestinal pseudo-obstruction, a rare condition that is described most often in dogs, and results from segmental or diffuse neuromuscular dysfunction leading to a flaccid and dilated section of intestine with no physical obstruction.

In domestic animals, there are two main types of pseudo-obstruction: disorders that affect the ganglia of the myenteric plexi and those that affect the tunica muscularis. In dogs, infiltration of the tunica muscularis with inflammatory cells (predominately T-lymphocytes) and resulting fibrosis is the most common presentation (seen in this case).⁶

With regard to neurpathic entities, in horses, particularly white foals born of parents with “frame overo” color patterns (white on both sides of their bodies), the myenteric plexi of the terminal ileum, cecum, and colon are affected in a congenital condition known as congenital colonic aganglionosis or “lethal white foal syndrome”. Foals with this congenital abnormality are missing the ganglia within those regions of the intestine leading to fatal colic. The gene mutation observed in horses, rodents, and humans with this condition is a loss of function mutation of the endothelin receptor type B gene. This gene functions in timing of the migration of cells of the neural crest. In addition to the myenteric plexus, these foals are also lacking melanocytes in the skin (also derived from the neural crest) which explains their white color. A similar genetic condition of Clydesdale foals is associated with hypoganglionosis of the myenteric plexus resulting in megacolon. The pathogenesis in this unknown, although it does occur in older foals (4-9 months old) indicating an acquired condition.⁶

Dysautonomia or Key-Gaskell syndrome was briefly discussed as a rare entity affecting cats under 3 years of age with an unknown pathogenesis. This syndrome presents as disordered motility, with affected animals that often die due to regurgitation, prolonged starvation, or aspiration pneumonia. Affected neurons in the cranial nerve nuclei III, V, VII, and XII, ventral horns of the spinal cord and dorsal root ganglia appear chromatolytic on light microscopy. Ultrastructurally they have a
characteristic appearance with autophagocytic vacuoles, dilated cisternae, and stacks of smooth endoplasmic membranes in their cytoplasm. Lastly, proventricular dilatation disease (PDD) was reviewed caused by avian bornavirus. PDD causes flaccidity and dilation of any portion of the gastrointestinal tract in parrots, macaws, conures, and cockatoos due to lymphoplasmacytic ganglioneuritis of the myenteric plexi resulting in atrophy of the intestinal wall.

The main differential myopathic condition discussed was canine immune-mediated polymyositis which may involve muscle damage by T-lymphocytes within the alimentary tract, particularly skeletal muscle of the esophagus. Polymyositis is overrepresented in German Shepherd Dogs and Newfoundlands and may occur as part of a spectrum of disease along with systemic lupus erythematosis which is diagnosed by a positive antinuclear antibody (ANA) titer. Testing for serum antibodies to type 2M myosin may aide in diagnosis of polymyositis because most affected dogs lack serum antibodies to 2M myosin. In this case, immune-mediated polymyositis is not likely the cause since it is the smooth muscle in the tunica muscularis that is affected in this dog.
CASE III: CASE 2 (JPC 4101313).

**Signalment:** 8-month-old, heifer, Nelore, *Bos taurus indicus*, Bovine.

**History:** Three sick cows were submitted to the Veterinary Hospital of the Universidade Federal de Minas Gerais (UFMG), as well as samples of the spinal cord of an additional cow from the same farm, collected during a field necropsy. These 4 cows were from a farm in Minas Gerais state, with a herd of 3,000 cattle, where in the past 3 years (2013-2016), 35 cows died after presenting clinical signs characterized by ataxia, paresis and paralysis of the pelvic limbs, emaciation, and sternal recumbency. Two of these cattle were euthanatized due to the severe ataxia, inability to stand, and emaciation. The herd was vaccinated against foot-and-mouth disease twice a year.

**Gross Pathology:** The cow was in poor body condition. Locally extensive areas of the skeletal muscle of the thoracic region (*longissimus dorsi* muscle) were replaced by numerous 0.3-0.8 mm in diameter, yellow and firm coalescent nodules (pyogranulomas) surrounded by moderate amounts of white and firm tissue (fibrous connective tissue). On the cut surface, some nodules contained yellowish and viscous fluid (purulent exudate) or whitish and viscous fluid (similar to the oily adjuvant of the foot-and-mouth disease vaccine). In the medullary canal of the subjacent vertebrae, extending from the intervertebral foramen to

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**References:**

the epidural space and dura mater, there were pyogranulomas identical to those described in the skeletal muscle. The remaining dura mater was thickened and firm (fibrosis).

**Laboratory results:** Laboratory results are pending.

**Microscopic Description:** Meninges: The dura mater is expanded, and partially or completely effaced by extensive areas of pyogranulomatous inflammation with proliferation of fibrous connective tissue. The pyogranulomas are composed by a central clear vacuole of variable sizes (ranging from 30 to 300 µm) (consistent with the space left by the oil adjuvant droplets), surrounded by variable numbers of degenerated and viable neutrophils, with aggregates of necrotic material and mineralization, and, more externally, by large numbers of epithelioid macrophages and fewer multinucleated giant cells, lymphocytes and plasma cells. These structures are further surrounded by a thick layer of dense fibrous connective tissue. Extensive areas of the dura mater are thickened by fibrous connective tissue infiltrated by low to moderate numbers of lymphocytes, plasma cells, and macrophages. Pyogranulomas and fibrous tissues invade or compress the adjacent nerve fibers. In the white matter of the affected sections of the spinal cord, there are numerous well-defined, large and clear vacuoles (dilated periaxonal spaces) containing either swollen axons (spheroids) or foamy macrophages (digestion chambers).

**Contributor’s Morphologic Diagnoses:** 1. Meninges (dura mater): Pachymeningitis, pyogranulomatous and fibrosing, multifocal to coalescent, marked, with intralesional vacuoles (consistent with oil adjuvant droplets). 2. Spinal cord: Wallerian degeneration, multifocal, moderate, with spheroids and digestion chambers.

**Contributor’s Comment:** Clinical signs and gross and histopathological findings, in these four cows, were compatible with compressive myelopathy due to pyogranulomatous reaction to the oily

*FIGURE 1: Spinal cord and dura, ox. The epidural space and dura mater were thickened due to multiple 0.3-0.8 mm in diameter, yellow and firm coalescent nodules (pyogranulomas) surrounded by moderate amounts of white and firm tissue (fibrosis). The remaining dura mater was thickened and firm (fibrosis). (Photo courtesy of: Departamento de Clinica e Cirurgia Veterinarias, Escola de Veterinaria, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, 31270-901. www.vet.ufmg.br)*
adjuvant of a vaccine. The history of previous application of the foot-and-mouth disease vaccine in the thoracic region (site of the muscular pyogranulomas) indicated its involvement with these lesions.

Compressive myelopathies in ruminants have been associated with several causes of space occupying lesions within the medullary canal, including abscesses, granulomas, physical traumas, malformations, and neoplasms\(^1, 2, 3\). While traumas and abscesses are apparently more common in feedlot cattle, calves, and small ruminants; neoplasms, mainly lymphomas, occur more frequently in adult dairy cows\(^3\). Compressive myelopathies due to postvaccinal granulomas are uncommon in cattle and occur mainly in association with foot-and-mouth disease (FMD) vaccine adjuvant\(^2, 3, 4\). Cases of post-vaccinal granulomas have also been related to water-in-oil adjuvant of a vaccine against *Escherichia coli* and *Campylobacter fetus* spp. *veneralis*\(^5\) and of a vaccine against *E. coli* and *Clostridium perfringens* type *C*\(^1\).

Clinical signs of compressive myelopathy related to postvaccinal granulomas include ataxia, paresis and paralysis of pelvic limbs, permanent recumbency, and progressive loss of the muscular tone\(^2, 3, 4, 5\). The beginning of the clinical signs occurs up to 60 days after the vaccination\(^3\). In the reports of the condition in Brazil, the mortality rate ranged from 0.83% to 6.0%\(^2, 3, 4\). Due to the similarity of the clinical signs, this condition must be included as a differential diagnosis of other two important neurological diseases in Brazilian cattle herds, rabies and botulism\(^4\).

An important factor for the development of the medullary lesions was the inappropriate administration of the vaccine in the muscle of a paravertebral area in the thoracic and lumbar regions. According to the orientation from the manufacturers of the vaccine and from the guidelines of the National Program for the Eradication of foot-and-mouth disease\(^6\), this vaccine must be applied subcutaneously or intramuscularly, in the lateral cervical region. Even when applied in the recommended location, subcutaneous and muscular lesions are frequently observed in the sites of application. These lesions are either granulomas or abscesses and are an important source of economic losses due to the cost to trimming the lesion in slaughterhouses\(^1\). According to the owner of these cows, the application of the vaccine in the thoracic region was performed to avoid evident subcutaneous and muscular lesions in the cervical area and to facilitate the procedure when it was performed in a basic cattle handling system with straight race.

The presence of typical intralesional vacuoles (interpreted as the space left by the oily adjuvant of the vaccine, removed during the processing for the histopathological analysis) and the absence of infectious
organisms in special stains (Grocott methenamine silver, Giemsa, or Ziehl-Neelsen acid-fast stains) corroborate the association of the lesions to the adjuvant. Adjuvants are important components of the vaccines and act nonspecifically, increasing the immune response against injected antigens. The adjuvant used in the FMD vaccine, that was responsible for the lesions observed in the cases, is reported as a water-in-oil emulsion. The water-in-oil adjuvant used in a Clostridium perfringens type C–E. coli bacterin-toxoid vaccine and in a Rotavirus and Coronavirus vaccine, was also able to induce muscular lesions, such pyogranulomas, fibrosis, mineralization and necrosis. Occasionally, adjuvants can cause other adverse effects, including, anaphylaxis, lymphoplasmacytic inflammation and neoplasms.

Despite some studies hypothesizing an association between needle insertion into the intervertebral foramen with lesions in the medullary canal, histologic findings indicate a progression of the adjuvant due to constant rupture of the granulomas. This hypothesis is corroborated by the observation of ruptured granulomas, presence of degenerated neutrophils within the granulomas, and occasional free vacuoles among the granulomas. Migration through the tissues is a well-known property of water-in-oil adjuvants.

Vaccination against FMD is one of most important policies for animal health in the beef cattle industry in Brazil. FMD is a highly contagious viral disease affecting cloven-hoofed animals. It has great potential for causing severe economic loss, due its importance for commercial trade, and the requirement for total elimination of the affected herds. Brazil has no outbreaks of FMD since 2005, when outbreaks in two states led to the sacrifice of 39,845 cattle. Currently, the country has 4 zones (corresponding for 76.1% of the national territory) certified as free of the disease with use of vaccination and 1 zone (corresponding for 1.1% of the national territory) as free of the disease without using vaccination.

**JPC Diagnoses:** 1. Spinal cord, epidural space: Pyogranulomas, multiple, with clear vacuoles, Nelore, bovine.
2. Spinal cord: Wallerian degeneration, multifocal, mild with dilated myelin sheaths and swollen axons.

**Conference Comment:** The contributor provided an excellent review of the gross and microscopic lesions associated with tissue migration of water-in-oil adjuvant pyogranulomas.

As mentioned above, adjuvant and associated inflammation can spread into the intervertebral foramina by direct extension through progressive rupture of the pyogranulomas and reformation of the fibrous capsule.

The risk of injection site granulomas appears to be higher in vaccines with bacterial components in them. This is theorized to be due to soft tissue damage from the bacterial endotoxin that abets extension of the inflammation through tissue planes.5

Conference attendees noted Wallerian degeneration (dilated myelin sheaths, swollen axons, Gitter cells in digestion chambers phagocytizing myelin) in the white matter of the spinal cord with grey matter that was relatively unaffected. These changes are characteristic of chronic compression, whereas acute compression predominately affects the grey matter.5

**Contributing Institution:**
Veterinary School
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www.vet.ufmg.br

**References:**


14. Ubiali DG, Cruz RAS, Lana MVC et al. Spinal cord compression in cattle after

CASE IV: CASE #2 (JPC 4101755).

**Signalment:** 11 year old, castrated male, French bulldog, (*Canis lupus familiaris*).

**History:** A veterinarian found a mass at the base of the heart and tried to treat with radiation therapy. Clinically, the dog had severe coughing because of tracheal compression from the mass. A tracheostomy was performed since the larynx had collapsed. The dog was found dead by his owner 17 days after starting radiation therapy.

**Gross Pathology:** Necropsy was done only for the organs in the thoracic cavity. A 7x7x5 cm, reddish-tan to grayish-white, multi-nodular mass was found at the base of the heart involving the aorta, vena cava and trachea. The lungs were mildly edematous and appeared reddish-tan in color.

**Laboratory results:** None provided.

**Microscopic Description:** Heart: The mass is poorly demarcated and invades the right atrium wall. The neoplastic cells are polygonal arranged in cords on a moderate fibrovascular stroma. The nuclei are round to ovoid, with rare distinct nucleoli, and moderate anisokaryosis and anisocytosis.

Mitoses are rare. The cytoplasm is plump with fine eosinophilic granules. Atypical neoplastic cells with giant nuclei are occasionally found especially in the center of the mass. There are multifocal areas of necrosis, and vascular invasion is frequently seen with clusters of neoplastic cells in blood vessels in the less affected area of the heart.

**Contributor’s Morphologic Diagnosis:** Heart: Aortic body carcinoma.
Contributor’s Comment: Aortic body tumor is a type of paraganglioma (chemodectoma) which is derived from cells of the neural crest. In dogs, paragangliomas are predominantly derived from the aortic or the carotid body. Aortic body tumors are more frequent than carotid body tumors in animals, whereas it is opposite in humans. Paragangliomas occur most frequently in dogs with lower incidence in cats and cattle. Brachycephalic breeds such as the Boxer and Boston terrier are highly predisposed, which implies that some genetic predisposition that is aggravated by chronic hypoxia seems to be cause of this tumor. Paraganglioma does not cause functional clinical signs, but it can compress the trachea, aorta and vena cava resulting in cardiac decompensation (hydropericardium, hydrothorax, cyanosis, ascites, edema, and passive congestion of the liver) and/or dyspnea, coughing, or vomiting.7

Aortic body tumors are usually benign but malignant tumors can also occur1,8. Aortic body carcinomas can infiltrate the wall of the pulmonary artery to form papillary projections into the lumen or invade the wall of the left atria. Aortic body carcinomas can metastasize to many organs such as the lung, liver, myocardium, kidney, lymph nodes and adrenal cortex7. A recent report has indicated that 9 out of the 13 dog (69%) cases showed metastasis to other organs9. The authors compared the characteristics of metastatic and non-metastatic aortic body carcinomas and demonstrated that metastasis is correlated with high tumor weight to body weight ratio (g/kg). However, no significant difference was found in malignant features of neoplastic cells such as pleomorphism and presence of giant cells. They concluded that those tumors are generally malignant or potentially malignant. In our case, vascular invasion of neoplastic cells and metastasis to a hilar lymph node were found. Unfortunately, we were prevented from investigating organs outside of the thoracic cavity at the request of the owner.

In humans, genetic mutations of succinate dehydrogenase complex subunit D (SDHD) in familial paraganglioma were first identified in 20002. SDHD protein is one of the subunits consisting succinate dehydrogenase (Complex II of the respiratory chain) integrated in the inner mitochondrial membrane. SDHD forms
dimer with SDHC, another subunit of Complex II. The dimer can be bound to ubiquinone and water during electron transport at Complex II. Genetic mutations of SDHD can decrease the enzymatic activity of Complex II and lead to cellular hypoxia. Although the exact mechanism of tumorigenesis by SDHD mutations is still unclear, hypoxia due to decreasing Complex II activity may be associated with tumorigenesis. Indeed, people living at higher altitudes (e.g. Andes peoples), are subject to paraganglioma and hypoxia-inducible factors (HIF) affect several biological events related to tumorigenesis such as cell proliferation, metabolism and angiogenesis. Mutations of other SDH protein composing Complex II (SDHA, SDHB, SDHC) are also associated with paraganglioma. Specifically, SDHB mutation frequently results in metastatic paraganglioma, whereas SDHD mutation is usually related to benign paraganglioma in the head and neck. In dogs, a study indicated genetic mutations of SDHD and SDHB in some chemodectomas and pheochromocytomas. Canine chemodectomas have the potential to be a model for human paraganglioma but further research is required.

**JPC Diagnosis:** Fibroadipose tissue: Neuroendocrine tumor, French bulldog, canine.

**Conference Comment:** This case provided a beautiful representation of a neuroendocrine tumor in a brachycephalic dog. In the slides provided, there was no myocardium present, and attendees were unable to be more definitive in their diagnoses than neuroendocrine tumor.

Conference participants discussed several stains that could be used to identify this as a neoplasm of neuroendocrine origin. Secretory granules of neuroendocrine cells can be identified with chromogranin A, neuron-specific enolase, synaptophysin, and S100. Churukian-Schenk, a silver-bassed, histochemical stain may also be used to identify granules. Ultrastructurally, secretory granules appear electron-dense and membrane-limited. There are also stellate or sustentacular cells with long cytoplasmic processes present in-between neoplastic cells. These cells are theorized to provide support to the chemoreceptor cells.
Malignant tumors may have decreased secretory granules and sustentacular cells, and some stains (chromogranin A) could potentially be negative.7

Chemoreceptor organs are located at the base of the heart (aortic body) and in the neck (carotid body) and function as sensors of variations in blood carbon dioxide content, pH, and oxygen tension and help to regulate respiration (through parasympathetic nerves) and circulation (through sympathetic nerves) based on detected changes. These organs are small and composed of chemoreceptor cells and sustentacular cells on a fine collagen and reticular fiber stroma. Chemoreceptor cells are of neural crest origin and have intracytoplasmic secretory granules that contain vasoactive factors, dopamine, norepinephrine, enkephalin peptides, and adrenomedullin. In addition to the carotid and aortic bodies, chemoreceptors are located in the nodose ganglion (vagus nerve), ciliary ganglion (orbit), pancreas, below the middle ear on the internal jugular vein, and the glomus jugulare (recurrent branch of the glossopharyngeal nerve).7

Participants were encouraged to read a recent article that outlines the findings in 13 cases of canine aortic body tumors in which 9 dogs had metastases and 4 did not. A recent publication on aortic body tumors in 13 dogs9 identified tradition features of malignancy in these tumors, including pleomorphism, anisokaryosis and anisocytosis, mononuclear giant cells, and local tissue and vascular invasion, but none correlated with metastasis. Hence, these neoplasms should be all considered as potentially malignant.

**Contributing Institution:**
Laboratory of Comparative Pathology
Department of Veterinary Clinical Sciences
Graduate School of Veterinary Medicine

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Heart base, dog. Neoplastic cells are present within the subcapsular sinus of one of the hilar lymph nodes. (Photo courtesy of: Laboratory of Comparative Pathology, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, https://www.vetmed.hokudai.ac.jp/organization/comp-pathol/e/index.html) (HE, 400X)

Hokkaido University
https://www.vetmed.hokudai.ac.jp/organization/comp-pathol/e/index.html

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