



WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #7

8 October 2025

CASE I:

Signalment:

21-year old, female intact, Trakehner horse
(*Equus caballus*)

History:

The mare had a ten-year history of bilateral rear limb suspensory ligament degeneration. She was euthanized due to acute onset of fever and recumbency, which were later attributed to a pheochromocytoma and multifocal myocardial necrosis.

Gross Pathology:

Both rear metacarpophalangeal joints are enlarged with thick, fibrous joint capsules but no effusion. The branches of the rear suspensory ligaments are enlarged to approximately twice the diameter of the front suspensory ligament branches, and they are mottled yellow, tan, and white on cut section.

Laboratory Results:

N/A

Microscopic Description:

Suspensory ligament, right rear branch. Compared to a branch of the clinically normal right front suspensory ligament, collagen fibers are irregular and often form intersecting or divergent bundles. In many areas, there are fewer fibroblasts among collagen fibers than in the normal control. Throughout the tissue, wavy

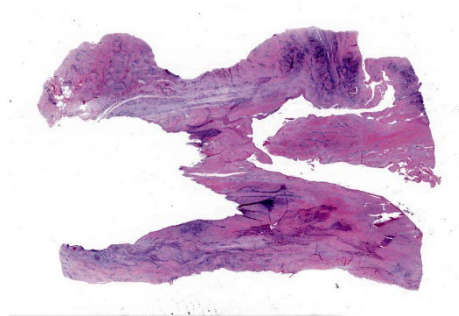


Figure 1-1: Tendon, horse. One section of the suspensory apparatus is submitted for examination and the normal eosinophilic color is interspersed with areas of basophilic ground substance. (HE, 10X)

tendrils of pale basophilic, Alcian blue-positive matrix dissect between collagen bundles. Similar material surrounds increased numbers of variably sized, dilated and tortuous blood vessels. These vessels have thin walls and are lined by plump endothelial cells, and are often surrounded by loosely arranged stellate cells. In other areas, there is chondroid metaplasia, with clustered and individual chondrocyte-like cells in lacunae surrounded by amorphous, pale basophilic matrix, which is sometimes faintly mineralized. There is rare hemorrhage.

Contributor's Morphologic Diagnoses:

Severe chronic extensive suspensory ligament degeneration with chondroid metaplasia and vascular proliferation

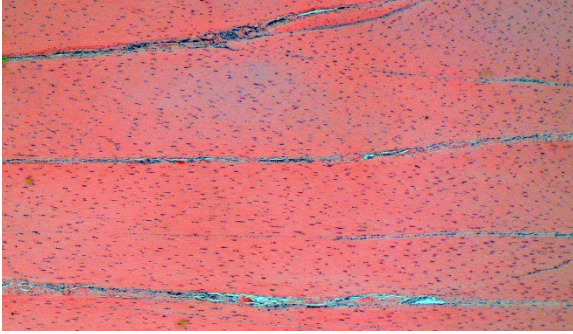


Figure 1-2: Tendon, horse. Histology of a normal equine tendon with eosinophilic collagen fibers arranged linearly and in register, with collagen fibers separated by thin capillaries. (HE,400X) (Photo courtesy of: University of Tennessee College of Veterinary Medicine, <https://vetmed.tennessee.edu/academics/biomedical-and-diagnostic-sciences/>)

Contributor's Comment:

The terms “degenerative suspensory ligament desmitis (DSLSD)” and “suspensory ligament degeneration (SLD)” are used somewhat synonymously, with DSLSD often used to describe horses with a clinical diagnosis of suspensory ligament degeneration, and SLD used to describe histologic findings in the suspensory ligaments of horses that may or may not have a clinical diagnosis of DSLSD. DSLSD causes chronic, progressive multi-limb lameness of variable severity, often recognized by enlarged, hyperextended or “dropped” fetlocks.⁸ The rear limbs are typically more affected.^{3,8} In addition, the terms “suspensory ligament desmitis” or “suspensory ligament desmopathy” may be used to describe any of a variety of clinically or ultrasonographically detected injuries anywhere along the length of the suspensory ligament.³ Histology is rarely performed in these cases, especially in the acute phase, and it is unclear if these injuries are related to degenerative changes.³

Histologic changes in SLD/DSLSD include loss of longitudinal arrangement of collagen fibers, proteoglycan accumulation, presence

of chondrocytes, hemorrhage, vascular proliferation, and widened interstitial connective tissue septa.^{4,6} Despite the use of the term “desmitis,” inflammatory cells are not present.⁴ These changes are reported to be more severe in the branches of the suspensory ligament than in the body or origin of the ligament.^{3,5}

The pathogenesis of SLD/DSLSD is incompletely understood. It has been associated with athletic function, broodmare status, and old age, but strong breed predispositions to DSLSD, particularly in the Peruvian Paso, suggest a hereditary basis in many cases.⁸ In one recent genome-wide association study of single nucleotide polymorphisms in different breeds of horse, several candidate loci were identified among genes which are related to collagen synthesis, tendon aging, mechanotransduction, signaling, and metabolism.⁹ However, a single gene has not been identified as causative, and the disease is assumed to be polygenic and multifactorial.⁹

One avenue of investigation also suggests an association between SLD and pituitary pars intermedia dysfunction (PPID), which may be similar to the Achilles tendinopathy that rarely

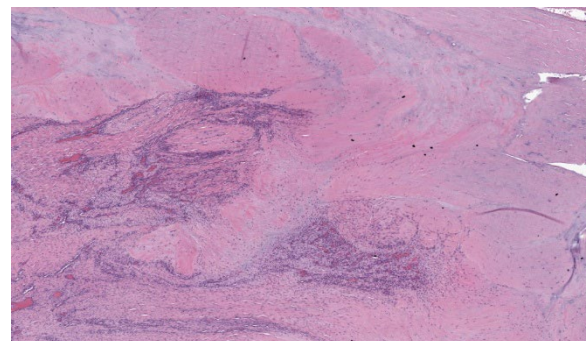


Figure 1-3: Tendon, horse. The normal linear array of collagen bundles within the tendon is lost and there are areas of basophilic ground substance between and within fibers. Collagen bundles are also separated by proliferating and tortuous capillaries. (HE, 33X)

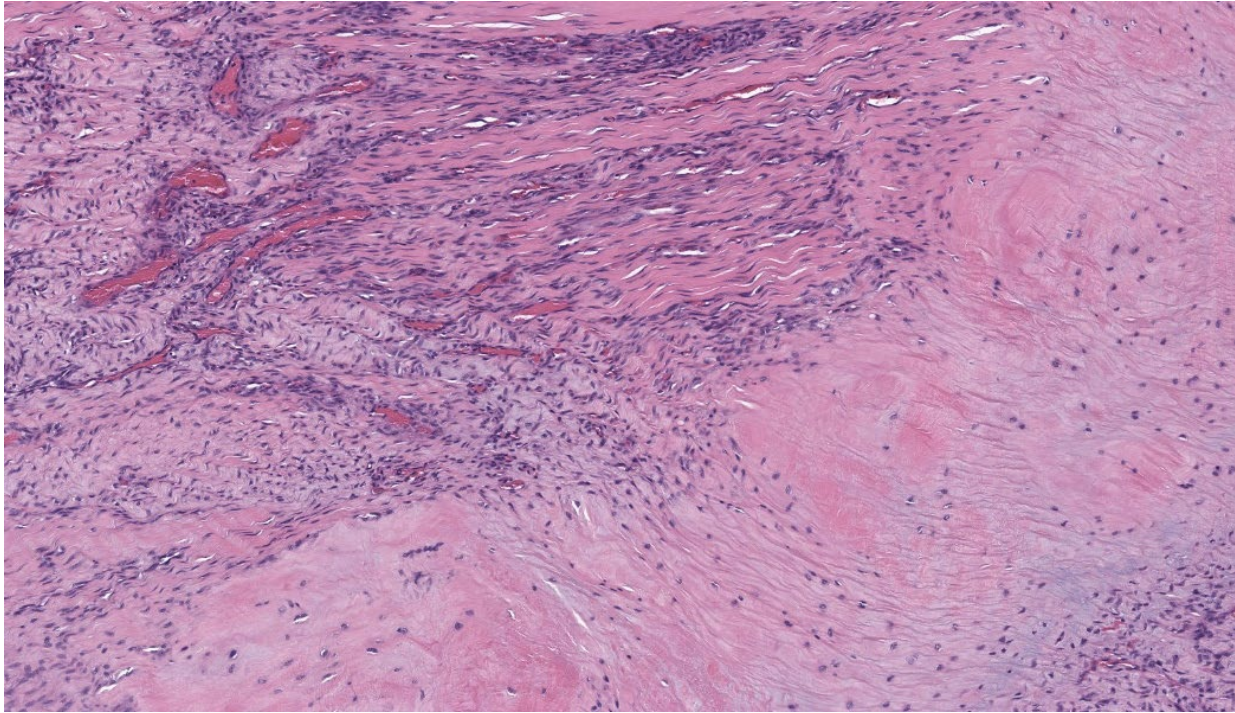


Figure 1-4: Tendon, horse. Collagen bundles are separated by numerous tortuous capillary profiles surrounded by amphophilic ground substance. (HE, 131X)

occurs in humans with Cushing's syndrome.^{1,5,6} Endogenous or exogenous glucocorticoid excess can lead to various changes in collagen, proteoglycans, and matrix metalloproteinases and result in connective tissue weakness.^{1,5,6} The exact mechanisms in affected humans and horses are unknown; however, horses with PPID have increased numbers of glucocorticoid receptors and increased 11 β -hydroxysteroid dehydrogenase type 1 in the suspensory ligament compared to unaffected horses, suggesting a role for abnormal local cortisol metabolism.⁶

Some older studies posit that abnormal proteoglycan deposition and turnover is the primary cause of the functional and structural changes.^{4,7,10} Affected horses have an atypical isoform of the proteoglycan decorin,⁷ and affected ligaments have markedly increased amounts of the proteoglycan aggrecan, as well as increased amounts of aggrecan degradation

products and enzymes.¹⁰ One report suggested that abnormal proteoglycan accumulation may be systemic in affected horses,⁴ but the findings could not be reproduced.¹¹ The cause of the altered proteoglycan milieu is unknown; however, the more recent genome-wide association study failed to identify any alterations in the genes responsible for proteoglycan turnover.⁹

Despite the lack of inflammatory cells in affected ligaments, there are increased levels of inter-alpha-trypsin-inhibitor components, which are associated with multiple inflammatory conditions.¹⁰ In addition, some of the candidate genes identified in the genome-wide association study are associated with inflammatory pathways.⁹ The complete role of inflammatory processes in disease progression is unknown.

Finally, true suspensory ligament desmitis with degeneration has been rarely reported in

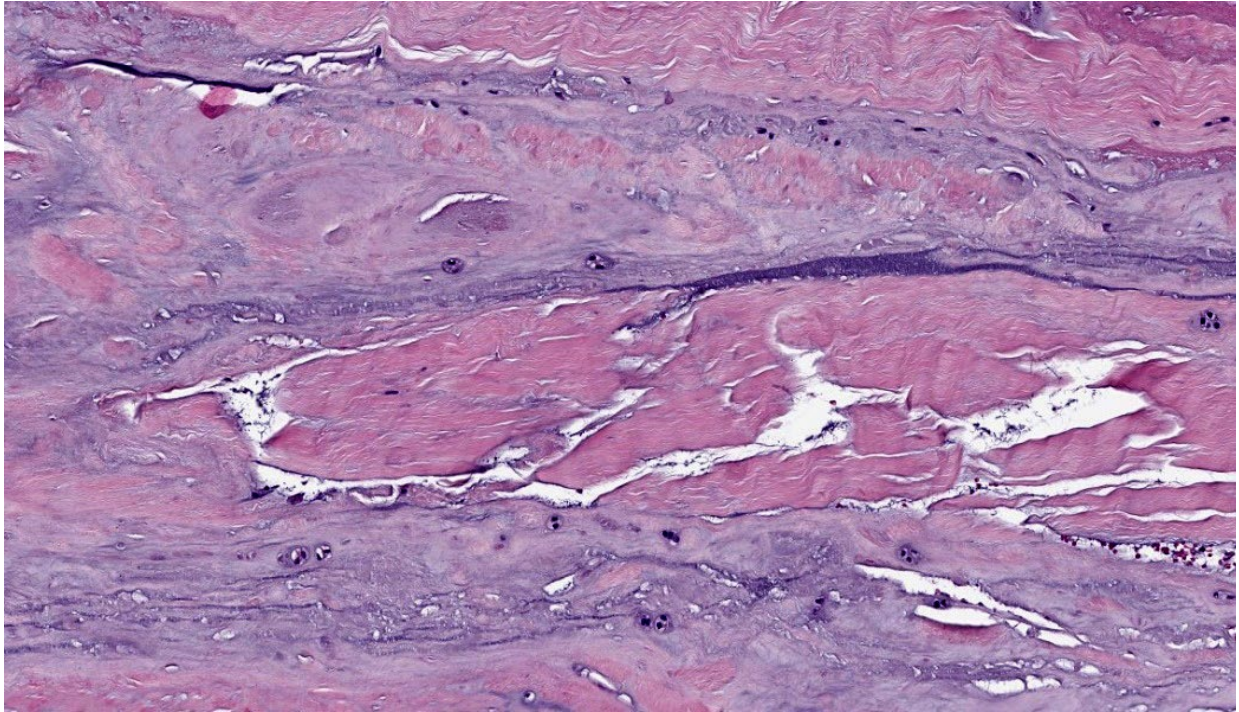


Figure 1-5: Tendon, horse. Collagen bundles are also separated and/or expanded by abundant basophilic ground substance. Within the ground substance, there are foci of cartilaginous metaplasia with individualized chondrocytes within lacunae.

horses and donkeys as a result of onchocerciasis.² Degenerative lesions of the ligament are similar, but they are accompanied by eosinophilic granulomas with encysted nematodes.²

Contributing Institution:

Biomedical and Diagnostic Sciences

University of Tennessee College of Veterinary Medicine

<https://vetmed.tennessee.edu/academics/biomedical-and-diagnostic-sciences/>

JPC Diagnoses:

Ligament: Degeneration, chronic, diffuse, marked, with increased ground substance, vascular proliferation, loss of ligamentocytes, and cartilaginous metaplasia.

JPC Comment:

The JPC's own LTC Erica Barkei moderated this week's conference and chose a variety of fascinating entities, three of which that have never been seen before in the Wednesday

Slide Conference (WSC). She tends to look specifically for cases that are either novel to the WSC, are within residents' 5-year reading windows, or will stimulate great discussion amongst participants. She was certainly successful in that mission this year!

This case, coupled with a well-written and thorough comment from the contributor on this challenging clinical condition, gifted participants with a beautiful slide of an oft-forgotten organ (tendon/ligament) with all the classic features of suspensory ligament degeneration (SLD). The WSC team is grateful to the contributor for this case and the excellent educational value it brought to the conference.

Conference discussion focused on the proposed pathogeneses of this condition (genetic vs. metabolic vs. athletic) in horses and its likely multifactorial origins (see contributor comment). A key feature of SLD/DSLSD is

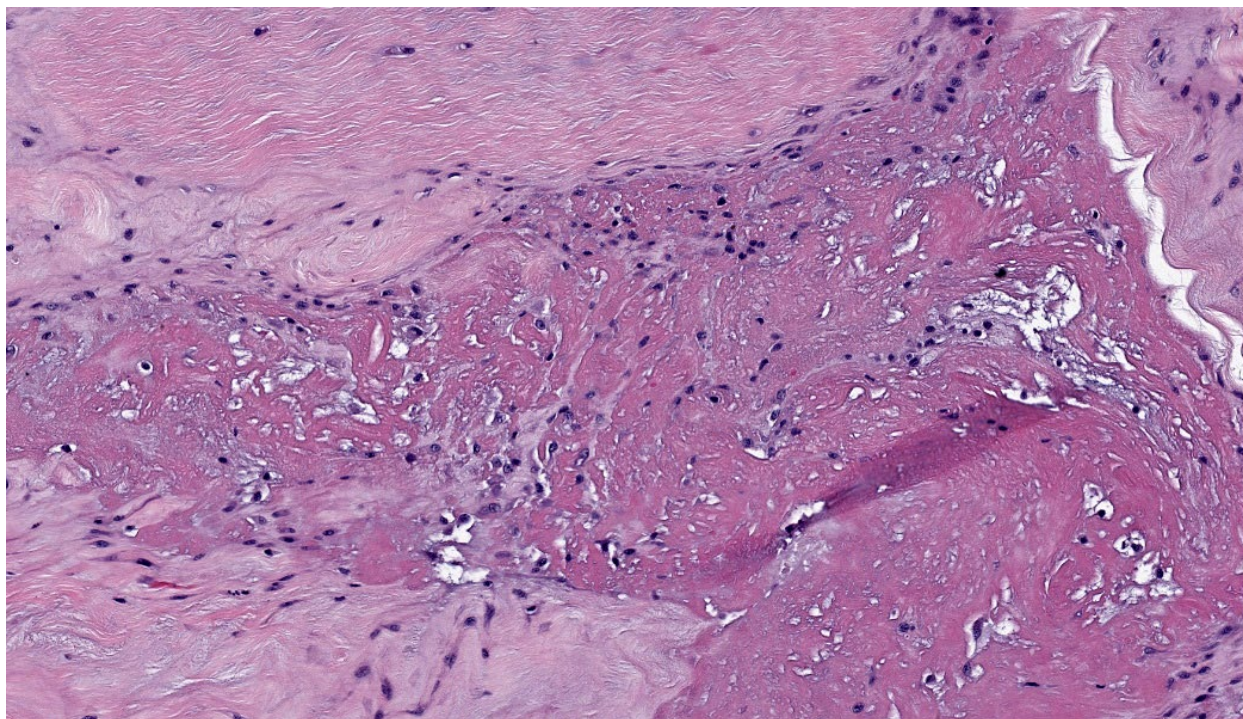


Figure 1-6: Tendon, horse. Collagen bundles are occasionally hypereosinophilic and fragmented.

acellular accumulation of proteoglycans, including decorin and aggrecan, replacing cells and collagen bundles.¹⁰ This suggests a disturbance to matrix homeostasis where the responses of the matrix to mechanical loading are disrupted. As the contributor stated in their comment, there have been numerous genes found to be associated with SLD/DSLD, including those involved in tendon aging (PIN1), mechanotransduction (KANK1, KANK2, JUNB, SEMA7A), collagen synthesis (COL4A1, COL5A2, COL5A3, COL6A5), matrix response to hypoxia (PRDX2), and lipid metabolism (LDLR, VLDLR).^{8,9} These features parallel the changes seen in humans with similar tendinopathies. There are currently conflicting articles within the literature on if the proteoglycan accumulation seen in SLD is systemic or localized, and more research is needed to determine this.^{4,11}

There were a few important “buzzwords” or phrases mentioned during conference that are important to include in a histologic description of an SLD case and include some form of “collagen fiber disorganization” and “loss of tenocytes/ligamentocytes.” (If anyone is wondering, “What the heck are tenocytes and ligamentocytes?”, they are, quite simply, fibroblasts respectively within a tendon or ligament.) The different types of collagens within tendons and ligaments were also reviewed and include: Type I collagen, which is the most prevalent within the normal flexor tendons; Type II collagen, which is found within enthesis insertions and areas where a tendon changes directions around a bony prominence; and, lastly, type III collagen, which is one of the first collagens synthesized within tendons at sites of injury.

The major histologic findings within ligaments suffering from SLD include loss of longitudinal arrangement of collagen fibers (disorganization), proteoglycan accumulation (increased ground substance), presence of chondrocytes (chondroid metaplasia), hemorrhage, vascular proliferation, widened interstitial connective tissue septae, and a lack of inflammatory cells.⁸ As this disease develops, regardless of cause, degenerating collagen fascicles blend together and there is either death of the tenocytes/ligamentocytes or metaplasia of tenocytes/ligamentocytes into chondrocytes. Fibrosis develops within and around the ligament and is usually associated with hypertrophied tenocytes/ligamentocytes. These areas are generally interpreted as failed attempts at repair.

As these changes progress, the suspensory ligament (SL) progressively thickens, weakens, and ultimately ruptures, resulting in the classic dropped fetlocks seen in affected horses.^{8,9} Some horses may also have neurogenic muscular atrophy secondary to either nerve entrapment within areas of fibrosis or due to nerve compression from a thickened and enlarged SL. SLD is typically more evident in the pelvic limbs and is usually bilateral, although some horses have all four limbs affected.^{3,8,9}

The last major discussion point in conference related to the use of the term “desmitis” vs. “degeneration.” In a true SLD/DSLSD case, there should be no inflammatory cells within the tendon/ligament, so conference participants favored “degeneration” over “desmitis.” The exception to this would be in cases of ligamentous Onchocerciasis, where an eosinophilic and granulomatous inflammatory infil-

trate could be expected.² In addition to morphing “degeneration” for this case, a few “withs” were added to the JPC morph to better define the typical findings associated with the degeneration in a case of SLD. Participants thought it was academically pertinent to ensure those were part of the morph for the purposes of resident education and encompass the primary histologic changes of this condition.

References:

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CASE II:

Signalment:

Three-week-old castrated male PIC Camborough ® x PIC 800 ® cross bred pig (*Sus scrofa*).

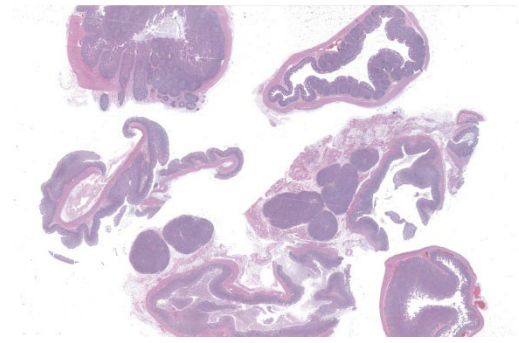


Figure 2-1: Ileum and colon, piglet. Multiple sections of ileum, colon, and attached mesenteric lymph nodes are submitted for examination. (HE, 6X)

History:

Enteric, respiratory, CNS, and systemic signs reported in 3-week-old pigs from a wean-to-finish barn in Iowa.

Gross Pathology:

This pig exhibited significant ataxia and paresis, and would “high-step” if made to walk. It would often become laterally recumbent but typically stayed centrally aware. Eye movement was normal. The piglet was thin and gaunt, with a raised coarse hair coat. All lung lobes were diffusely tan, rubbery, and non-collapsing with multifocal lobules in the cranial and middle lung lobes that were diffusely dark red and firm. Colon content was green-brown and watery, but the associated tissue was grossly unremarkable. The stomach of this animal was full of feed, and no ulcers were apparent. Tracheobronchial and ileac lymph nodes were enlarged.

Laboratory Results:

- PRRSV PCR (lung): Positive (Ct = 11.1)
- IAV PCR (lung): Negative
- PCV 2/3 Differential PCR (spleen): Negative
- TGEV/PEDV/PDCoV Differential PCR: Negative
- PRRSV IHC (intestine/colon): Abundant strong punctate intracytoplasmic staining in mononuclear cells with morphology similar to macrophages in the mediastinal

lymph node, Peyer's patches, and lamina propria.

- Bacterial culture: Low growth from both the intestine and colon of *Salmonella enterica* ssp *enterica* serovar Heidelberg.

Microscopic Description:

Ileum: In several sections, there is moderate multifocal blunting and fusion of villi with a crypt: villus ratio of 1:1. Apical enterocytes are often moderately attenuated with loss of the brush border and reduced apical cytoplasm. In some sections, these cells have a profound number of intracellular but extracytoplasmic 1-2 um circular eosinophilic apicomplexan organisms with 0.5 um basophilic nuclei (*Cryptosporidium* sp.). In other sections, these cells contain numerous larger apicomplexans with varied life-stages apparent including: 10 x 5 um curvilinear binucleate meronts (type I meronts), 4 x 12 um curvilinear uninucleate merozoites (type I merozoites), 9 x 6 um ovoid multinucleate meronts (type II meronts), multiple 3 x 12 um curvilinear uninucleate merozoites joined at their base by a residual body (type II merozoites), a 12um diameter circular lightly basophilic microgamont filled with numerous peripheral uninucleate deeply basophilic microgametes, or a 18 um diameter circular lightly basophilic macrogamont with a 8 um granular circular nucleus (macrogamont) (*Cystoisospora suis*). Rare crypts are ectatic, lined by moderately flattened, attenuated epithelium, and filled with cellular and karyorrhectic debris admixed with rare degenerate neutrophils (crypt abscesses). The associated lamina propria is often infiltrated by numerous eosinophils admixed with a few neutrophils. In one section, there is profound necrosis in Peyer's patches, characterized by abundant karyorrhectic and cellular debris admixed with rare neutrophils, that often obscures typical follicular architecture. Similar changes are occasionally present

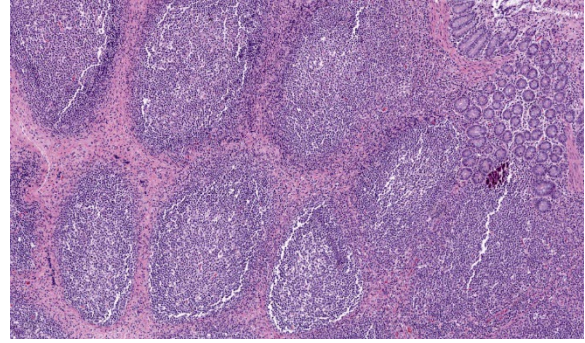


Figure 2-2: Ileum, piglet. Peyer's patches are depleted and lack normal architecture. (HE, 121X)

in the overlying lamina propria, with marked lymphocytolysis and loss of proprial architecture. Vascular structures in all tunics are moderately congested, and macrophages occasionally aggregate around medium-caliber vessels in the submucosa.

Spiral Colon: In both sections, there is moderate multifocal ulceration of the colonic mucosa characterized by loss of apical colonocytes with abundant cellular and karyorrhectic debris admixed with minimal fibrin and extravasated erythrocytes adhered to the exposed lamina propria. Adjacent colonocytes are often flattened, irregularly spaced, with reduced apical cytoplasm (attenuation). The associated lamina propria is often infiltrated by neutrophils and eosinophils admixed with necrotic debris and a few macrophages. Crypts within these areas are often ectatic, lined by mildly attenuated epithelium, and filled with either cellular and karyorrhectic debris admixed with degenerate neutrophils (crypt abscesses) or numerous eosinophils. Several other crypts are filled with up to 15 5 x 7 um pyriform to crescent-shaped protozoa with lightly basophilic cytoplasm and a faint nucleus (Suspect Trichomonads). The colonic lumen contains abundant cellular debris admixed with numerous colonies of basophilic bacteria with morphology ranging from coccoid to bacillary to filamentous, as well as rare 80 um circular flagellated protozoa with a prominent bean-

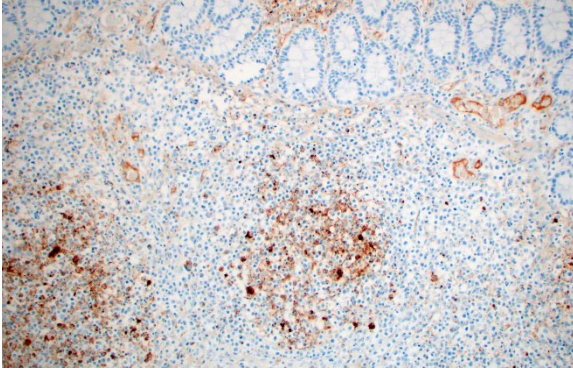


Figure 2-3: Ileum, piglet. Macrophages within Peyer's patches demonstrate strong labeling for PRRSV antigen. (anti-PRRSV, 400X) (Photo courtesy of: Department of Veterinary Pathology, Iowa State University CVM, <https://vet-med.iastate.edu/vpath>)

shaped nucleus and a large cytoplasmic vacuole and abundant phagocytosed cellular debris (Suspect *Balantidium coli*). The submucosa is multifocally infiltrated by numerous macrophages admixed with lymphocytes and a small amount of karyorrhectic debris and these cells often aggregate around medium to large caliber vessels. Multifocally the cortical and medullary architecture of the mesenteric lymph node is effaced by abundant cellular and karyorrhectic debris (lymphocytolysis) admixed with rare infiltrating neutrophils and macrophages.

Contributor's Morphologic Diagnoses:

Ileum and colon (mediastinal lymph node, Peyer's patches, and lamina propria): Lymphoid necrosis, multifocal, profound, subacute.

Ileum: Atrophic enteritis, necrosuppurative and eosinophilic segmental, marked, subacute, with crypt abscesses and numerous intralesional apicomplexans with morphology consistent with *Cryptosporidium spp.* and *Cystoisospora suis*

Colon: Ulcerative colitis, segmental, marked, subacute, with crypt abscesses and numerous intralesional protozoans with morphology

consistent with *Balantidium coli*, and Trichomonads.

Contributor's Comment:

This is great example of a real-world production animal diagnostic case. It's also a great reminder to look for a primary etiology when there are multiple organisms/changes present in a piece of tissue that aren't typically seen together. *Cryptosporidium suis* and *scrofarum* are present in many commercial pigs but typically do not cause clinical disease and are generally not histologically apparent.^{8,13} The presence of such profound quantities of *Cryptosporidium spp.* in this case suggests primary immune suppression. The larger apicomplexan present in this slide has life stages that are morphologically consistent with *Cystoisospora suis*. While this organism can act as a primary enteric pathogen in pigs, it is also present at low levels in many commercial swine post-weaning without causing clinical disease, often with few if any histologically apparent life-stages. The presence of both types of meronts, both types of merozoites, as well as microgamonts and macrogamonts in a single section of tissue is unusual

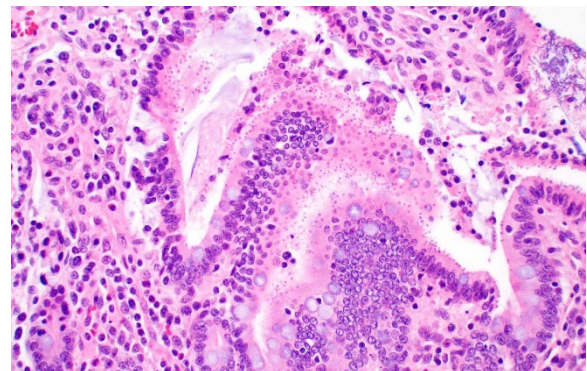


Figure 2-4: Ileum, piglet. Numerous cryptosporidial meronts and gamonts line the attenuated ileal villi. (Photo courtesy of: Department of Veterinary Pathology, Iowa State University CVM, <https://vetmed.iastate.edu/vpath>)

and also suggests that primary immune suppression may be at play. Lindsay *et al.* did a great job describing these life stages in a 1980 *Journal of Parasitology* paper.⁷ The moderate ulcerative colitis in this animal is typical of a *Salmonella* spp. It's also common to have *Balantidium coli* find their way into these colonic lesions, often phagocytosing necrotic debris.^{9,13} The pyriform organisms in the colonic crypts are morphologically consistent with trichomonads. *Tetratrichomonas foetus*, *suis*, *buttrei*, and *Pentatrichomonas hominis* have all been described as inhabitants of the porcine digestive tract. Others are likely present in pigs, and there have been increased efforts, especially in China, to better characterize these organisms.⁶ They are commonly seen in higher numbers in porcine colonic crypts during disease or dysbiosis.

PCV-2 parasitizes lymphocytes and is a common cause of immune suppression in commercial pigs. However, this virus typically causes lymphoid depletion with granulomatous inflammation and rarely intracytoplasmic botryoid inclusion bodies. PCV-2/3 differential PCR was negative in this animal. The massive amount of karyorrhectic debris in the lymphoid tissue is more in line with PRRSV infection, which was detected at a very low CT in lung, and colocalized to the lesioned enteric lymphoid tissue by IHC. PRRSV is a member of the family *Arteriviridae*, which together with *Coronaviridae*, *Roniviridae*, and *Mesonoviridae* form the order *Nidovirales*, a contemporarily relevant viral order that has evolved a unique replication strategy utilizing discontinuous extension and a set of nested subgenomic mRNAs. The economic impact of

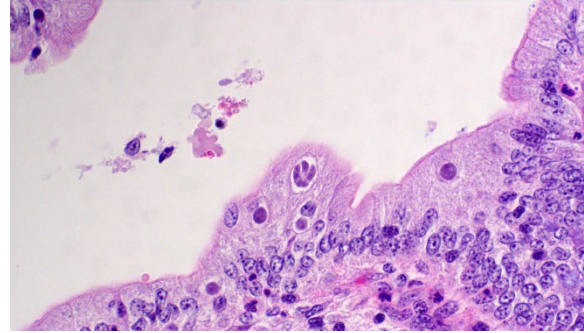


Figure 2-5: Ileum, piglet. Numerous life stages of *Cystoisospora suis* are present within ileal epithelium. This field contains, several primary meronts and a schizont in which merozoites are connected by a residual body. (Photo courtesy of: Department of Veterinary Pathology, Iowa State University CVM, <https://vet-med.iastate.edu/vpath>)

PRRSV in the US is estimated to be \$660 million annually, and a reasonable case could be made that this is the most economically important virus of any domestic species in the US.³ PRRSV replicates in macrophages and, to a lesser extent, dendritic cells. There was much historical controversy about the receptor utilized by this virus for cell entry. In a landmark paper, Prather *et al.* were able to demonstrate complete resistance to the virus by knocking out CD163 in commercial pigs with CRISPR/Cas9 methods.¹¹ CD163 (HbSR) is a hemoglobin scavenger receptor that is expressed in cells of the monocyte-macrophage lineage.¹ Currently, CD163 knock-out pigs are working their way through the federal regulatory system, with the genetics company involved hoping to market a completely PRRSV resistant animal. This may have huge economic implications given the limited success of commercial vaccines against this phylogenetically diverse virus. While this virus is classically associated with interstitial pneumonia with intralesional “necrotic macrophages”, it's a systemic pathogen that can infect macro

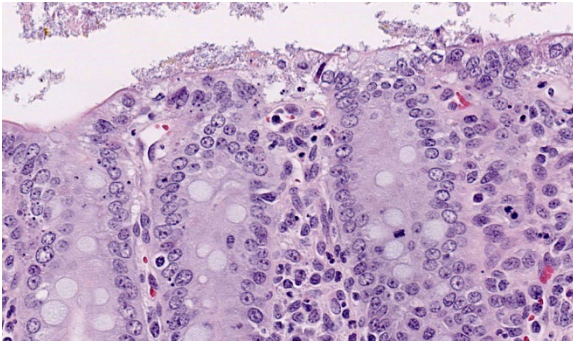


Figure 2-6: Colon, piglet. There is multifocal ulceration of the colonic epithelium with few neutrophils infiltrating the lamina propria. (HE, 455X).

phages in any body system, especially lymphoid tissue. The terms “necrotic macrophages” and “lymphoid necrosis” are somewhat controversial in PRRSV infection. An early paper utilizing tunnel assays, demonstrated widespread apoptosis of noninfected cells in the lung, testes, and lymphoid tissue, giving rise to the idea of “bystander-apoptosis” involvement in the pathogenesis of this virus.¹⁰ Subsequent papers further characterizing the involvement of intrinsic/extrinsic/other apoptotic pathways in infected and uninfected cells are conflicting.² At the very least it can be stated that much of the cell death in a PRRSV infection occurs in uninfected cells, and a significant proportion of those cells are likely apoptotic as opposed to necrotic.

PRRSV-associated lesions and IHC staining were also present in the lung, brain, spleen, and tracheobronchial lymph nodes of this animal (not included on this slide).

In this case, the clinical signs in the population are not the result of a lateral introduction of any of the 4 protozoans described or the *Salmonella* sp. isolated. Rather, all of these organisms were endemic in this population and

caused no clinically apparent disease. The introduction of a new PRRSV strain into the sow farm resulted in significant immune suppression in weaned pigs, disrupting the balance of the enteric ecosystem, culminating in enhanced replication of *Cryptosporidium* spp, *Cystoisospora suis* and several trichomonads.

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JPC Diagnoses:

1. Ileal Peyer’s patches and mesenteric lymph nodes: Lymphoid depletion, chronic, diffuse, marked, with lymphocytolysis.
2. Ileum: Villar blunting, diffuse, marked with numerous intracytoplasmic, extracellular apicomplexan schizonts and gamonts consistent with *Cryptosporidium* sp., and intracytoplasmic, intracellular apicomplexan meronts, schizonts, and gamonts consistent with coccidiosis.
3. Colon: Colitis, ulcerative, multifocal, mild to moderate with crypt abscesses and intraglandular flagellates.

JPC Comment:

The good folks at Iowa State provide a great write-up that touches on some very diagnostically relevant topics and stimulated excellent pathogenesis discussion during conference. The #1 take-home lesson in this case for participants was, “Don’t stop looking just because you found one cause” – a common diagnostic pitfall referred to as “search satisfaction”. As in this case, there were many, many

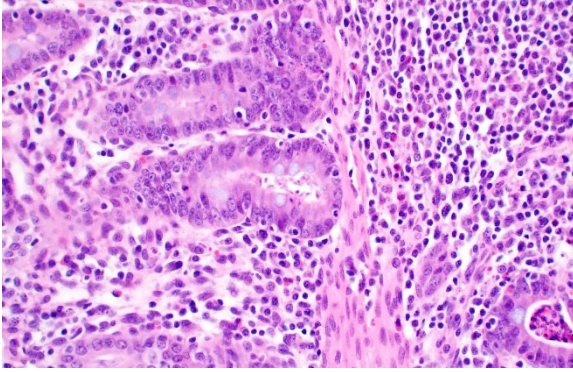


Figure 2-7: Colon, piglet. Occasional colonic glands contain numerous trichomonads. (Photo courtesy of: Department of Veterinary Pathology, Iowa State University CVM, <https://vet-med.iastate.edu/vpath>)

organisms present in far greater numbers than normal as a result of virally-induced immune suppression.

If you see infectious agents, think about how that organism interacts with the host animal. Then, think about if that organism should or should not be present and, if they are expected, are they present in expected numbers? If there are multiple species of agent, and they are in higher numbers than expected, a primary immune suppression should rise to the top of the list. In this case, *Cryptosporidium spp*, *Balan-tidium coli*, and trichomonads are found in many commercial pigs and do not typically cause disease. *Cystoisospora suis* can be a primary enteric pathogen of swine but may also be present in low levels in post-weaning commercial pigs without issue. However, the presence of both types of meronts, both types of merozoites, and both micro- and macrogamonts in one tissue section should raise red flags and make the pathologist look for an underlying cause that might explain the lack of immune regulation of commensals.

Other honorable mentions discussed in conference included the other members of the porcine respiratory disease complex, which are PRRSV, PCV2, *Pasteurella multocida*, swine influenza A, and *Mycoplasma hyopneumoniae*, and a quick mention of other relevant arteriviruses within veterinary species, such as equine Arterivirus (equine viral arteritis), Simian hemorrhagic fever virus in non-human primates, and lactate dehydrogenase-elevating virus in mice (although this one is pretty laid back, all things considered).

This case provides an excellent opportunity to review relevant general pathology of viral infections. One of the most critical players in innate viral defense is type I interferon (IFN-I). The initiation of IFN-I production is dependent on host pathogen recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs), which is where the whole process starts. The body must be able to recognize the “bad guy” before it can mount an appropriate response to handle it.

Certain classes of PRRs, such as the membrane-bound Toll-like receptors (TLR), specifically TLR3, TLR7/8 and TLR9, detect viral PAMPs and foreign nucleic acids within cellular endosomes and help upregulate the production of IFN-1 and pro-inflammatory cytokines. Once one of these endosomal TLRs has bound and recognized a viral PAMP, the TLR recruits the adaptor molecule TIR-containing adaptor-inducing IFN- β (TRIF). TRIF then binds Tumor Necrosis Factor Receptor Associated Factor 6 (TRAF6) and activates transforming growth factor β (TGF- β)-activated kinase-1 (TAK1) and TAK1-binding proteins (TABs).^{4,5} This complicated cascade

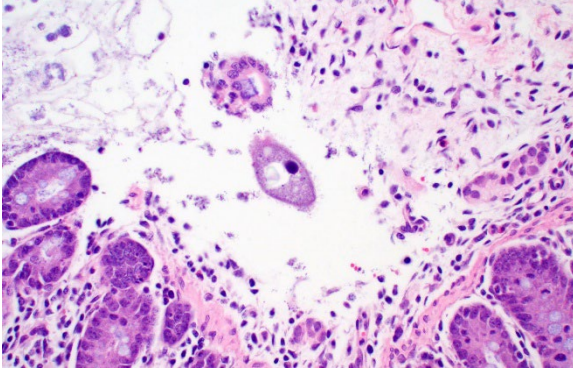


Figure 2-8: Colon, piglet. Rare *Balantidium coli* are present within the colonic lumen. (Photo courtesy of: Department of Veterinary Pathology, Iowa State University CVM, <https://vet-med.iastate.edu/vpath>)

results in the phosphorylation of NF- κ B essential modulator (NEMO) and the activation of an IKK complex. I κ B α , which is bound to and inhibits the transcription factor NF- κ B, is phosphorylated and degraded by the proteasome. Upon release from its inhibitor, NF- κ B translocates to the nucleus and upregulates the expression of IFN- β and inflammatory cytokines.^{4,5,12}

Working in concert with the TLRs are cytoplasmic RIG-I-like receptors (RLRs), another class of PRR that includes retinoic acid-induced gene I (RIG-I) and melanoma differentiation associated gene 5 (MDA5), among others.^{4,5} These RLRs recognize viral nucleic acid in the cytosol of the affected cell. RIG-I and MDA5 both have a feature called the “caspase activation and recruitment domain” (CARD) which, upon activation, interacts with virus-induced signaling adaptor (VISA), the primary (and necessary) signaling adapter protein of the cytosolic RLRs.^{4,5,12} These interactions allow RLRs to relocate to mitochondrial membranes and initiate the formation of the VISA signalosome, which basically functions as a scaffold to which other proteins can stick.⁴ The assembled VISA signalosome recruits

TNF receptor-associated factors (TRAFs) or Fas-associated death domain protein (FADD), which activate caspases 8 and 10.^{4,5} These caspases then stimulate NF- κ B activation. Once activated, NF- κ B translocates to the nucleus to its job of upregulating production of IFN-1 and other cytokines as described above.

Now the body has IFN-1 circulating about. Now what? IFN-I binds to its receptor, appropriately named type I IFN receptor, and initiates the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway, thereby resulting in the expression of numerous IFN-1 stimulated genes that ultimately rev up the anti-viral adaptive immune response.^{4,5} Several arteriviruses, including PRRSV, cleave signaling molecules of IFN-I responses.⁴ A recent study demonstrated that highly pathogenic PRRSV and its nsp4 protein antagonize IFN-1 expression by cleaving VISA and NEMO to block NF- κ B signaling pathways.⁴ (Cue some commentary about evolution being an arms race...)

PRRSV infection occurs primarily through alveolar macrophages in the lung of infected pigs. On top of its anti-IFN-1 actions, PRRSV primarily utilizes a CD163 receptor, especially the scavenger receptor cysteine-rich domain 5 (SRCR5) of the receptor, to infect macrophages.^{1,2,5} The interaction between the PRRSV minor envelope glycoproteins (GP2a and GP4) and the CD163 SRCR5 domain facilitates the release of genetic material from the virus, thereby enabling viral replication within the infected cell.^{1,2,5}

As mentioned by the contributor in their excellent write-up, targeting this interaction by blocking viral binding or removing CD163 from the cell surface is a promising strategy

for controlling PRRSV. Currently, ABS, one of the premier genetics companies for livestock, is developing a CD163-knockout pig strain that is resistant to PRRSV.¹¹ Long story short, no receptor for PRRSV to bind equals no PRRSV infection. This has massive implications for both commercial pig operations and research labs. Research is generally reliant upon smaller, younger pigs. PRRSV has been a challenging confounder of research findings in these pigs, as they are transported in from commercial farms and can develop respiratory disease secondary to transport stress. If a pig has PRRSV and is then utilized for a study, who's to say what lesions are due to PRRSV and what lesions are due to the agent of study interest? Although many institutes are actively looking to reduce the use of animals, some studies are still reliant upon live animal models. Being able to utilize PRRSV-resistant pigs could be a huge leap forward for such studies and would very likely reduce the overall number of animals needed for study completion.

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CASE III:

Signalment:

12-year-old, neutered male, European, cat (*Felis catus*)

History:

The cat was presented to our institution for a right subcutaneous cervical mass that was noticed by the owner 2 months ago. The cat had no general signs and there was no significant clinical history. The cat lived exclusively indoor with no other animals.

Clinical examination revealed an ovoid, 4 x 6 x 6 cm, firm, well-demarcated, non-painful and non-adherent mass in the cranial right ventro-lateral part of neck. Based on location, a right mandibular lymphadenopathy was suspected and a fine-needle aspiration was performed.

Cytological examination revealed a reactive lymphoid population (non-specific hyperplasia) admixed with numerous aggregates of plump and pleomorphic spindle to epithelioid cells that were occasionally separated by a delicate eosinophilic extracellular matrix (Figures 1-3). Atypia were severe with macrokaryosis and irregular macronucleoli but mitoses were not observed. Some siderophages were present. A diagnosis of malignant anaplastic tumor, primary or metastatic, of the right mandibular lymph node was made.

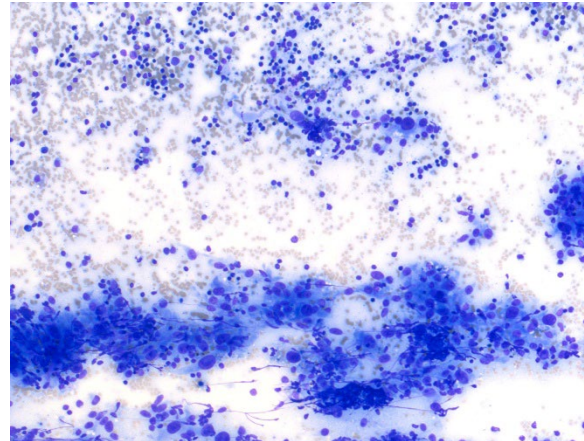


Figure 3-1: Lymph node, cat. Cytologic examination of the cervical mass: mixture of a reactive lymphoid population and atypical spindle to epithelioid cells with malignant features. (May-Grünwald & Giemsa.400X) (Photo courtesy of: Ecole Nationale Vétérinaire d'Alfort, Unité d'Histologie et d'Anatomie Pathologique, www.vet-alfort.fr)

Complete staging, including oral cavity and eyes, did not reveal any other mass and a primary sarcoma of the right lymph node was considered. A needle biopsy was made and revealed a sarcomatous proliferation highly suggestive of hemangiosarcoma. Considering the results of the staging, a primary nodal hemangiosarcoma was considered.

The lymph node was surgically removed and submitted for histopathological examination.

Gross Pathology:

A 4 x 6 x 6 cm lymph node was submitted (Figures 4-6). On cut section (after fixation), the lymphoid tissue was severely compressed and atrophic due to a rather well demarcated, white to dark red, firm to spongy proliferation that occupied 90% of the section. Some cavitory dark foci were present. The proliferation was limited by the nodal capsule and there was no sign of capsular effraction.

Laboratory Results:

Complete blood count revealed a mild macrocytic hypochromic and regenerative anemia with poikilocytosis. Numerous schistocytes



Figure 3-2: Lymph node , cat. This is the fixed section of mandibular lymph node. The nodal parenchyma is atrophic and compressed by a heterogeneous neoplasm with white-tan to dark areas. The neoplasm is well demarcated and encapsulated. Some spongy/cavitary foci are present (Photo courtesy of: Ecole Nationale Vétérinaire d'Alfort, Unité d'Histologie et d'Anatomie Pathologique, www.vet-alfort.fr).

were observed suggesting a mechanical anemia (fragmentation anemia). Thrombocytosis and moderate neutrophilic leukocytosis were also observed.

Microscopic Description:

The remaining nodal tissue was atrophic, congested and severely compressed by a densely cellular, well-demarcated, encapsulated neoplasm composed of compact intermingled bundles of spindle to epithelioid cells associated to a delicate fibrous stroma. Neoplastic cells often delineated vascular lumens filled with red blood cells. They measured 50-100 μm , had distinct cell borders, a moderately abundant eosinophilic cytoplasm and a round vesicular nucleus with a large eosinophilic nucleolus. Some cells contained intracytoplasmic red blood cells.

Pleomorphism and atypical were marked: macrokaryosis, macronucleoli, irregular nuclei, nuclear hyperchromasia etc. Mitotic count was 6 mitoses per HPF (field surface = 0.307 mm^2).

The neoplasm incorporated many remaining lymphoid follicles, some of which were hyperplastic. There was also diffuse lymphocytic and plasmacytic infiltration as well as some siderophages and macrophages showing prominent erythrophagocytosis.

Immunohistochemical staining showed marked positive labelling for vimentin (cytoplasm) and CD31 (membrane) of neoplastic cells. Regarding CD31, normal sinus-lining endothelial cells were also positive.

Contributor's Morphologic Diagnoses:

Right mandibular lymph node: Primary nodal hemangiosarcoma (likely corresponding to malignant transformation of feline plexiform vascularization of cervical lymph nodes).

Contributor's Comment:

There are several descriptions of distinctive vascular lesions in cervical lymph nodes of cats.^{7,8,13,15} They represent a morphologic spectrum ranging from benign lesions (plexiform vasculopathy/vascularization) to clearly malignant neoplasms (hemangiosarcomas).¹³

Feline plexiform vasculopathy/vascularization of lymph nodes (FPVLN) has first been

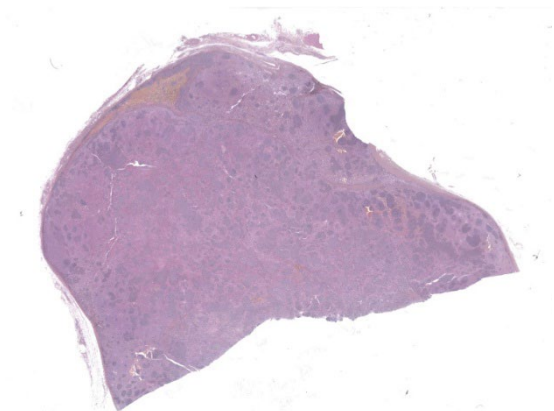


Figure 3-3: Lymph node, cat. A section of lymph node is submitted for examination. At subgross magnification, there is loss of normal nodal architecture. (HE 9X).

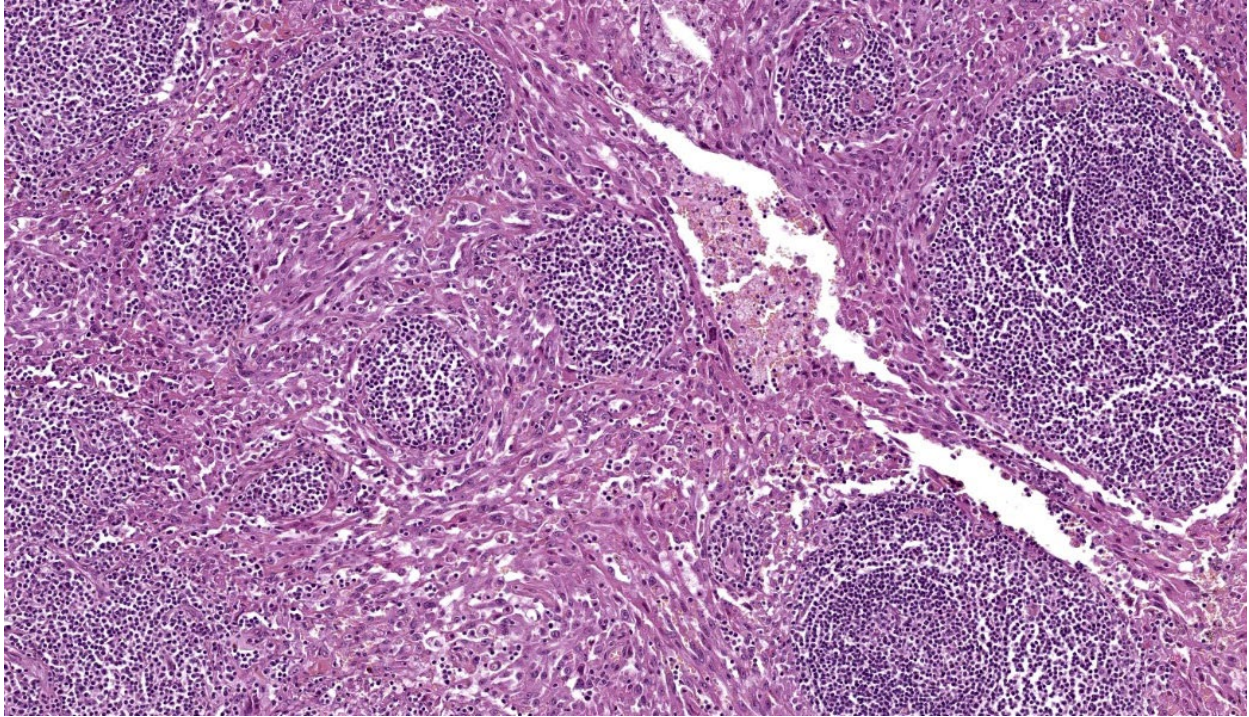


Figure 3-4: Lymph node , cat. Lymph node remnants are separated, surrounded and replaced by neoplastic endothelial cells arranged in sheets and forming small blood-filled spaces. (HE 201X).

described by Lucke *et al.* in 1987 and corresponds to nodal capillary vasoproliferation and lymphoid atrophy.⁸ These lesions have been compared to vascular transformation of lymph node sinuses in humans, a conversion of nodal sinuses to capillary-like channels accompanied by fibrosis.^{8,10,13} Such lesions have also been described in a dog.⁵ In humans, such changes are believed to be secondary to occlusion of efferent lymphatics and/or sluggish venous blood flow due to thrombotic obstruction, heart failure, or other conditions leading to venous stasis.¹⁰ The etiology of FPVLN remains uncertain.

FPVLN has a wide range of age (3 to 16 years old).^{8,13} As in the single canine case, it mostly affects the cervical lymph nodes, which is different from vascular transformation of lymph node sinuses in humans that is predominantly observed in intra-abdominal lymph nodes.^{8,10,13,15} FPVLN involving inguinal

lymph nodes has also been described and other lymph nodes may rarely be affected (axillary lymph node for example).^{8,13} Lesions are most often solitary but may also be multiple/bilateral. Generally, affected cats are otherwise clinically normal and prognosis after complete surgical excision is usually considered to be excellent with no recurrence or progression.^{8,13,15}

Grossly, lymph nodes are enlarged, up to 5-6cm. On cut section, lymph nodes are heterogeneous and appear tan to purple, reflecting follicular structures and congestion respectively.^{8,13} Histologically, there is lymphoid atrophy and a proliferation of capillary-like vessels lined by a single layer of flattened endothelial cells without atypia. The lumen may contain red blood cells or appear empty. Hyperplastic lymphoid follicles may also be observed.^{8,13}

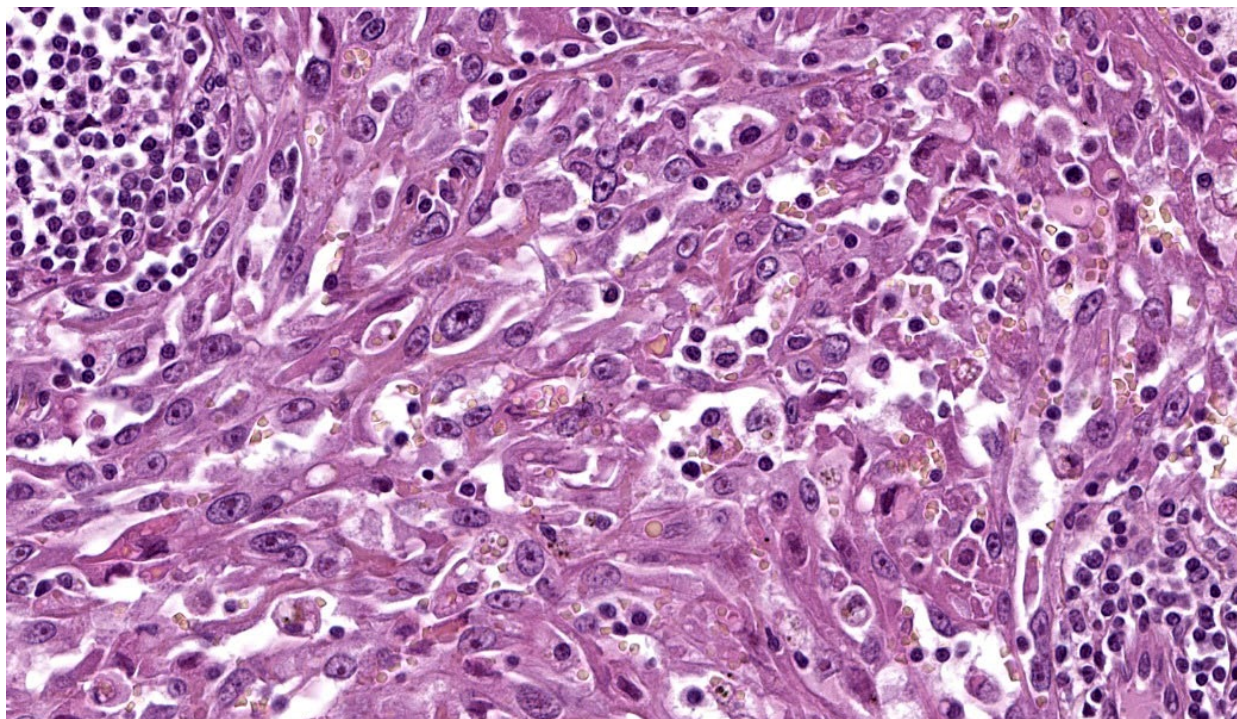


Figure 3-5: Lymph node , cat. Neoplastic endothelial cells demonstrate marked anisokaryosis and nuclear pleomorphism (HE 744X).

Recently, the endothelial cells in FPVLN have been proposed to be of lymphatic origin based on their expression of Prox-1 (nuclear labeling) in addition to CD31 and factor VIII-related antigen, the former being specific of lymphatic endothelial cells. LyVe-1 is another specific marker for the lymphatic endothelium.⁷

In 2015, primary hemangiosarcomas of feline cervical lymph nodes were reported in 12 cats.¹³ Some cats also had typical lesions of FPVLN suggesting that there is a pathogenic and pathologic continuum between FPVLN and primary nodal hemangiosarcomas, similar to the continuum that exists between injection-associated panniculitis and injection site sarcomas in cats.¹³ Clinical and gross findings appear similar to FPVLN, indicating that histopathological examination is essential to distinguish both entities. This is all the more important given that the prognosis of primary

nodal hemangiosarcoma appears different from FPVLN as recurrence and suspected metastases were reported in some animals.¹³

Histologically, the proliferation has the classical appearance of malignant vascular neoplasms.¹³ Although initially considered to be hemangiosarcomas based on the presence of red blood cells within the vascular channels, the recent demonstration that FPVLN arises from lymphatic endothelium suggests that these tumors may actually be lymphangiosarcomas.⁷ The association of red blood cells with lymphatic endothelial proliferation is also found in Kaposi's sarcoma, a distinct low-grade vascular sarcoma in humans associated with human herpesvirus 8 (HHV8). There are several forms of Kaposi sarcoma (classic, African, AIDS-associated and iatrogenic). Interestingly, it has been shown that infection with HHV8 reprograms blood endothelial cells to make them upregulate several

lymphatic-associated genes such as lymphatic vessel endothelial receptor 1 (LYVE1), podoplanin, and vascular endothelial growth factor receptor 3 (VEGFR3), so that, in the end, they resemble lymphatic endothelial cells, at least immunohistochemically (Kaposi's sarcoma is very different histologically from lymphangiosarcoma).¹² This example nicely illustrates that, in oncology, the phenotype of neoplastic cells may not accurately reflect the cell of origin. To date, the cause of FPVLN and FPVLN-associated hemangiosarcomas remains unknown and a viral etiology/contribution may be considered.

So far, FPVLN-associated hemangiosarcomas have not been further characterized immunohistochemically so we do not actually know if they also express markers of lymphatic endothelial cells (in this case, LyVe-1/Prox-1 immunohistochemical labelling was not performed). In such conditions, it might be better, regarding the terminology, pathogenesis and nomenclature, to rather name these distinctive lesions "FPVLN-associated angiosarcomas" or to refer to them as "benign vs. malignant forms of FPVLN".

Other malignant vascular neoplasms in cats include feline ventral abdominal lymphangiosarcoma (a distinctive cutaneous neoplasm previously termed feline ventral abdominal angiosarcoma) and hemangiosarcomas at other sites.^{4,6,9,11,14} Contrary to dogs, hemangiosarcomas are uncommon in cats, accounting for 0.5% of cases at necropsy.¹³ Most feline hemangiosarcomas are cutaneous and subcutaneous, with subcutaneous forms being more aggressive.⁶ Some cutaneous hemangiosarcomas may develop secondary to chronic UV exposure on hypopigmented skin, as in dogs.

Corneal and conjunctival hemangiosarcomas have also been described and appear to be associated with a good prognosis if completely excised.^{11,14} Feline visceral hemangiosarcomas are rare and have a poor prognosis.⁶ Finally, feline reactive systemic angioendotheliomatosis is a rare, multisystemic intravascular proliferative disorder of cats that most commonly affects the heart. Lymph nodes may occasionally be involved.³

This case represents a typical example of primary nodal hemangiosarcoma in the setting of FPVLN (although typical foci of FPVLN may be difficult to demonstrate in this case due to the extent of the hemangiosarcoma). Cytologic diagnosis yielded a diagnosis of malignant neoplasm, prompting for a complete staging in the search of a primary tumor. As no primary tumor was found and the morphology was not typical of lymphoma, FPVLN-associated hemangiosarcoma was suspected and subsequently confirmed by histological examination. Interestingly, hemangiosarcoma could have also been suggested by the finding of regenerative anemia with numerous schistocytes on hematological examination.

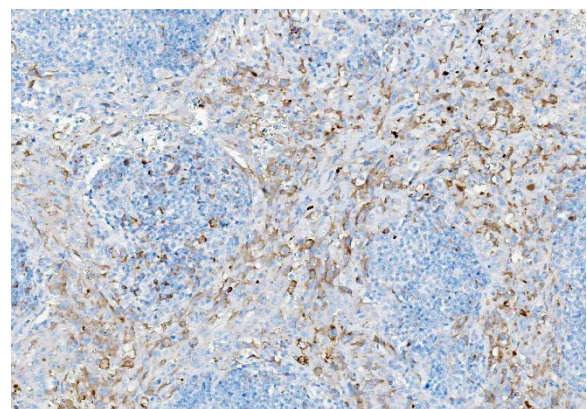


Figure 3-6: Lymph node, cat. Neoplastic endothelial cells demonstrate moderate cytoplasmic immunoreactivity for podoplanin (anti-podoplanin, 175X).

Schistocytes usually result from the fragmentation of red blood cells in abnormal small vessels (fragmentation anemia). They are observed mostly in dogs with disseminated intravascular coagulation, hemangiosarcoma, myelofibrosis, glomerulonephritis etc. They are also described in cats with hepatic disease.² Following the complete excision of the affected lymph node, schistocytes were not found on subsequent blood smears and the animal completely recovered from its anemia.

As a conclusion, differential diagnosis for enlarged cervical lymph nodes in cats should include lymphadenitis, lymphoma (non-Hodgkin and Hodgkin-like), metastases, lymphoid hyperplasia, distinctive peripheral lymph node hyperplasia of young cats, plexiform vascularization and primary (hem)angiosarcoma.¹³

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JPC Diagnoses:

Lymph node: Angiosarcoma.

JPC Comment:

This case proved to be a real diagnostic challenge for participants. Much of the discussion of this entity happened in real-time during conference, as most participants were unclear on the diagnosis in this case. The contributor

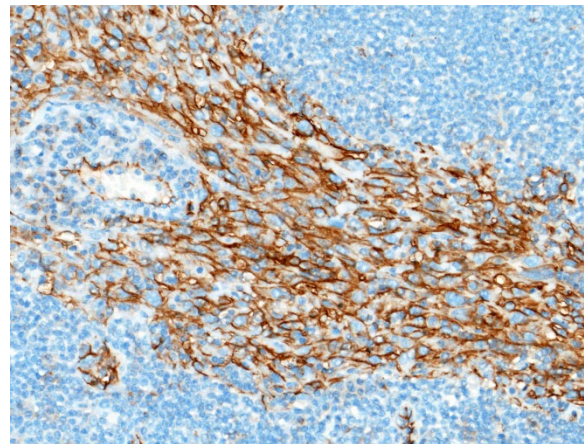


Figure 3-7: Lymph node, cat. Neoplastic endothelial cells demonstrate strong membranous immunoreactivity for CD31) (anti-CD31, 400X). (Photo courtesy of: Ecole Nationale Vétérinaire d'Alfort, Unité d'Histologie et d'Anatomie Pathologique, www.vet-alfort.fr

provided an exceptional write-up on this enigmatic entity and makes numerous excellent points for consideration. Their comment is well worth the read and covers most of what was discussed in conference. Participants were initially unsure on tissue identification given the degree of parenchymal effacement by the neoplasm, with some getting to lymph node, but most thinking spleen. There were a few subtle clues to help participants get to the right organ, the most useful of which is the distribution of the extracapsular adipose tissue. Lymph nodes tend to be embedded in and surrounded by adipose tissue, whereas the spleen has only a strip of adipose tissue along its mesenteric side where vasculature enters the splenic body. In addition to covering much of what was stated by the contributor, differential diagnoses for vascular proliferations in feline patients were discussed and included hemangioma, hemangiosarcoma, lymphangioma, lymphangiosarcoma (especially on the inguinal skin), and systemic reactive angioendotheliomatosis.

As is the nature of science, despite most of the historical literature calling these neoplasms “primary nodal hemangiosarcomas,” there is an increasing body of evidence that the neoplastic cells are immunoreactive for lymphatic endothelial markers (D2-40, Prox-1, LyVe-1).⁷ The most popular arising school of thought regarding this neoplasm in the context of feline plexiform vasculopathy/vascularization of lymph nodes (FPVLN) is that it is most likely of lymphatic endothelial origin and is part of a continuum of FVPLN, where the proliferating benign vasculature undergoes malignant transformation secondary to obstruction of the efferent hilar lymphatics of the lymph node.⁷ There is a similar condition to FPVLN that can occur in the mesenteric lymph nodes of rats, and neoplasms arising from affected lymph nodes in these animals have also been immunoreactive to Prox-1 and VEGF.¹

In an effort to further contribute information to the speculative origins of this neoplasm, a podoplanin was performed in-house at the Joint Pathology Center (JPC) to try and tease out any lymphatic origin in the neoplastic cells in this case (LyVe-1 or Prox-1 are not available for use at the JPC). Approximately 60% of the neoplastic cells had moderate cytoplasmic immunoreactivity to D2-40 (podoplanin) in this case, which correlates with a lymphatic endothelial origin. CD31, Factor VIII, CD20, and CD3 were also performed. The Factor VIII demonstrated diffuse, strong cytoplasmic immunoreactivity within neoplastic cells, while the CD31 had moderate membranous immunoreactivity in approximately 65% of neoplastic cells. Both blood vessel and lymphatic endothelial neoplasms can be immunoreactive to these IHCs. CD3 and CD20 nicely

showed the dispersed follicular architecture of the lymph node, with follicular T-cells and parafollicular B cells demonstrating strong membranous immunoreactivity to CD3 and CD20, respectively. Putting everything in context, conference participants favored the diagnosis of angiosarcoma for this neoplasm.

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CASE IV:

Signalment:

3-year-old male beagle (*Canis lupus familiaris*) dog

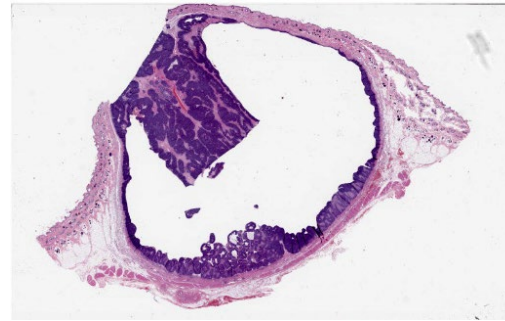


Figure 4-1: Haired skin, dog. A well demarcated cystic neoplasm is present within the dermis. The interaction with the overlying epidermis cannot be assessed based on this section. (HE, 8X)

History:

A 3-year-old male beagle dog was presented to staff veterinarians for the evaluation of a fluctuant mass present on the left caudolateral thorax. A fine needle aspirate was performed; red-tinged fluid was obtained. There was no resolution after 5 weeks. The mass was surgically excised on October 21, 2022, and submitted for histologic evaluation.

All procedures performed on animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional

Animal Care and Use Committee or through an ethical review process.

Gross Pathology:

N/A

Laboratory Results:

N/A

Microscopic Description:

Haired skin: Extending from the dermis deep into the subcutis is an approximately 2 x 2 cm well-demarcated cystic mass lined by neoplastic undifferentiated basaloid epithelial

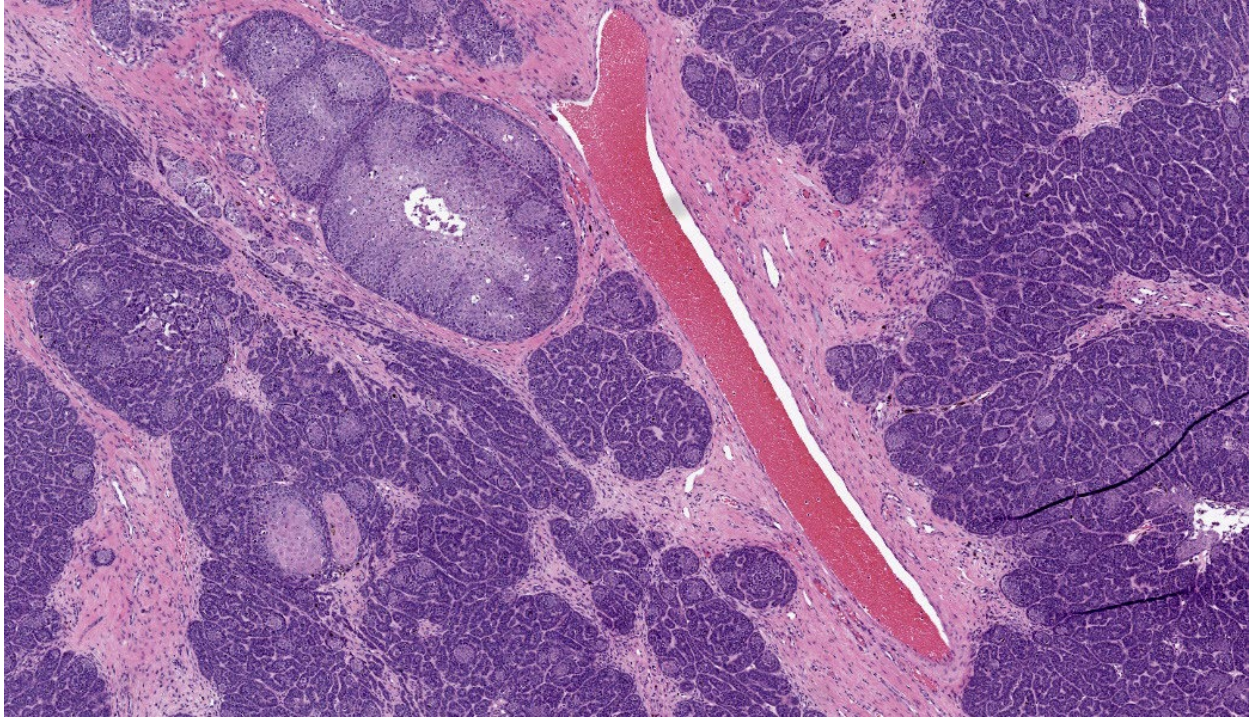


Figure 4-2: Haired skin, dog. Neoplastic basal cells are arranged in variably broad trabeculae and large islands and central areas of islands and trabeculae contain cells undergoing squamous differentiation which basal cells palisade along the outside. (HE, 81X)

cells. The neoplastic cells are arranged in lobules of dense anastomosing and palisading cords or small tightly packed nests, supported by scant fibrovascular stroma. There are multifocal papillary projections of neoplastic lobules into the lumen of the large cystic cavity. Multifocal lobules have smaller central cyst formation. The neoplastic basaloid cells are cuboidal with scant basophilic cytoplasm and round to oval, hyperchromatic nuclei, with two or more prominent nucleoli. There is minimal anisocytosis and moderate anisokaryosis. There is multifocal abrupt squamous differentiation and necrosis and approximately 5 mitotic figures per high power field. Brown granular pigment, most consistent with melanin, is present throughout the periphery of the mass; multifocal melanomacrophages infiltrate neoplastic lobules. Neoplastic cells extend to

within 2mm of the surgical margin; however, there are multifocal foci suspicious for local invasion.

Contributor's Morphologic Diagnoses:

Haired skin: Basosquamous cell carcinoma

Contributor's Comment:

In dogs and cats, cutaneous neoplasms are common. Some of the most common tumor types reported in canine patients include mast cell tumors, lipomas, hair follicular and/or sebaceous gland tumors, histiocytomas, soft tissue sarcomas, and melanocytic tumors.^{2,5,10} However in cats, basal cell tumors, mast cell tumors, squamous cell carcinoma, and fibrosarcomas are the most common skin tumors reported.⁶ Tumors of the epidermis include

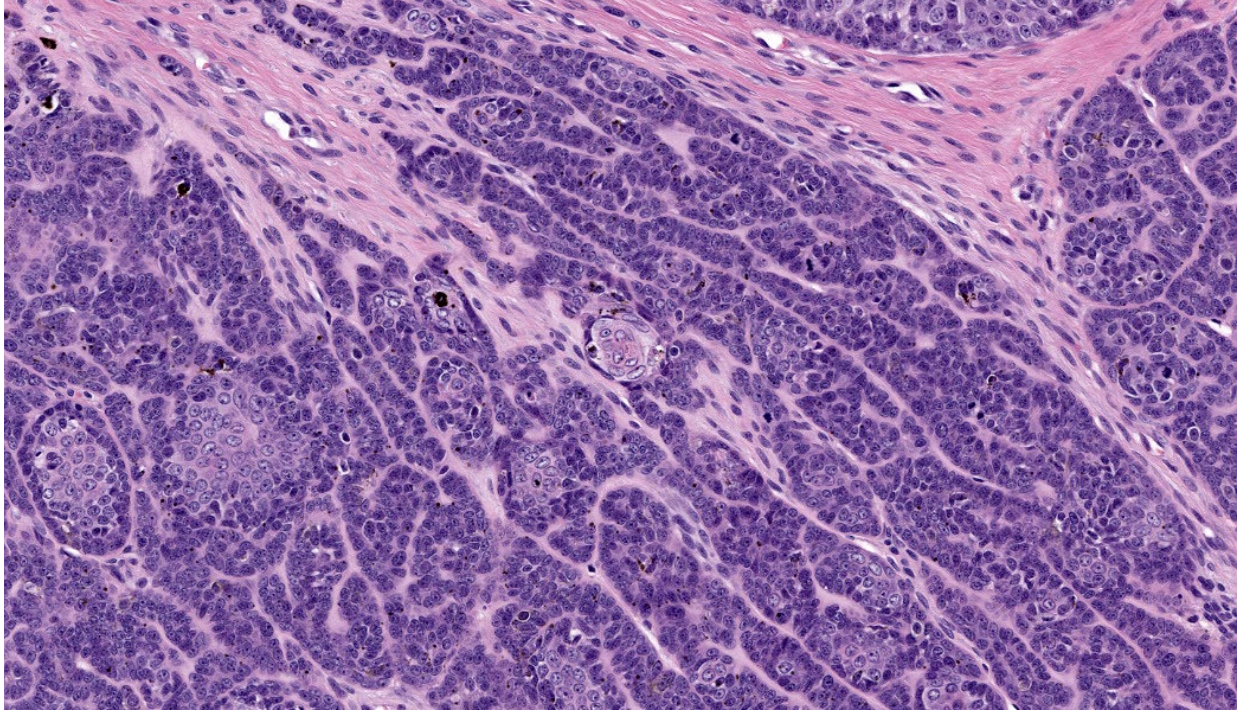


Figure 4-3: Haired skin, dog. Higher magnification of trabeculae of neoplastic epithelial cells. The basal-like cells palisade along the basement membrane, and central areas of trabeculae demonstrate squamous differentiation and keratinization. (HE, 381X)

papillomas and papillomavirus-induced tumors/tumor-like lesions, squamous cell carcinoma, basal cell carcinomas, and basosquamous carcinomas.⁴

Arising from epidermal basal cells, basosquamous carcinomas share features with squamous cell carcinomas and basal cell carcinomas and are considered low-grade malignancies.⁴ Although rare in dogs and cats, along with other domestic animals, these tumors are more commonly reported in dogs.¹ Canine breeds reported to have an increased risk of developing basosquamous carcinomas, include Saint Bernard, bloodhound, Samoyed, and old English sheepdog.¹ These tumors are more likely found on the head, neck, and limbs.¹

Histologically, basosquamous carcinomas are predominately composed of intradermal to subcutaneous lobules of undifferentiated basal

cells with central foci of abrupt squamous differentiation.¹ Keratinocytes at the center of neoplastic lobules have mild “nuclear pleomorphism, mitotic activity and dyskeratosis.”¹ Unlike other epidermal neoplasms, connection to the overlying epidermis is not a consistent diagnostic feature.⁴ However, cyst formation and melanization, as seen in this case, are common and can often be appreciated grossly.^{1,4} Keratinocytes, present in the foci of abrupt and atypical keratinization, that display features of malignancy, along with “the lack differentiation of the follicular isthmus or bulb are features that help differentiate basosquamous carcinomas” from other tumors.⁴

As basosquamous carcinomas share features with squamous cell carcinomas and basal cell carcinomas, these neoplasms represent possible differential diagnoses for basosquamous carcinomas.^{1,4} Adequate surgical excision is

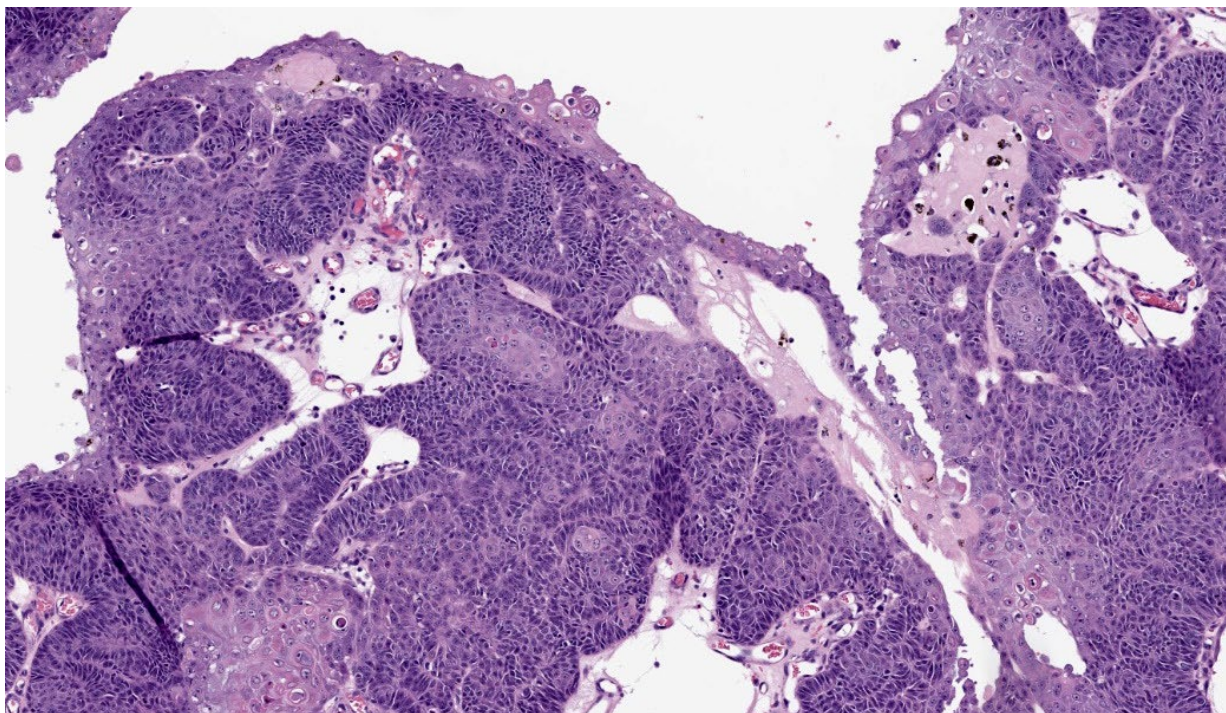


Figure 4-4: Haired skin, dog. Along the central space of this cystic neoplasm, there is more extensive squamous differentiation, and the cystic papillary projections into the central space are lined with several layers of squamous epithelium. (HE, 203X)

usually curative for these slow growing malignancies.¹

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JPC Diagnoses:

Haired skin: Basosquamous carcinoma.

JPC Comment:

Basosquamous carcinoma (BSC) was first described in 1910 by Dr. Henry MacCormac.¹⁰ He called this particular type of growth, which he astutely related to squamous cell carcinoma, a “rodent ulcer”, which was a once-popular term used to describe ulcerative growths that had a “rat bite” appearance. Although this term has long since fallen out of use, BSC remains a controversial entity that has histologic features of both squamous cell

carcinoma (SCC) and basal cell carcinoma (BCC) yet represents its own diagnosis. Whether or not this diagnosis is part of a continuum of changes seen in various stages of either BCC or SCC is currently unclear, and the diagnoses of BSC is highly contested within both human and veterinary medical circles.

In the current academic and clinical environment, BSCs are considered rare cutaneous neoplasms in both humans and veterinary species. While thought of as a low-grade malignancy with low metastatic potential in dogs and cats, this is not the case in humans, where basosquamous carcinomas are considered aggressive with more common metastases and a high rate of recurrence, even with wide surgical margins.³ Behaviorally, BSC is more akin to SCC than to BCC in humans. There are rare reports of metastatic BSC in dogs, as well, but

this incredibly uncommon for this entity in dogs and cats.⁹

In human literature, it is currently believed that the BSC initially arises as a BCC that then undergoes genetic and epigenetic alterations, ultimately leading to squamous differentiation through basal-to-squamous transition (BST). As such, the BSC was classified as a BCC variant by the WHO in 2023.⁷ To further complicate matters, there are also “basaloid SCC” and “keratotic BCC” diagnoses in humans, as well as BCC/SCC collision tumors.⁷ Participants were shown histologic images of what the moderator currently uses to differentiate between a keratinizing BCC, a basaloid SCC, and a BSC. The basaloid SCC is typically described as having comedonecrosis with squamous differentiation at the edges of lobules and is NOT classified as a skin tumor. Rather, it is found in the oral cavity, cervix, lung, etc.⁷ The keratotic BCC variant is composed of horn cysts, parakeratotic cells, and abrupt keratinization.⁷ BSC is identified by abrupt squamous differentiation (not abrupt keratinization) with dyskeratotic squamous cells within the center of lobules of basal cells.⁷ Both the basal cells and keratinocytes have mitotic activity. Considering these factors, a diagnosis of BSC was favored by participants. Ultimately, though, there seems to be substantial disagreement on how to define the BSC in veterinary literature, even between prominent tumor texts and fascicles.

To throw yet another wrench in this entity, it is well-known that papillomaviruses can induce squamous cell neoplasms in numerous species. Common examples include bovine papillomaviruses 1 and 2 causing equine sarcomas, bovine papillomavirus-4 resulting in

squamous neoplasms of the alimentary tract in cattle, and canine papillomavirus-2 causing cutaneous papillomas in dogs.⁴ Any of these can undergo malignant transformation when the right conditions occur. In recent years, *Felis catus* papillomavirus-2 (FcaPV-2) was detected within neoplastic cells of a multicentric cutaneous basosquamous carcinoma in a cat.⁸ Although not generally thought to be associated with a papillomavirus, this was the first case report of a BSC associated with FcaPV-2.⁸ Although better understood in humans, much has yet to be elucidated about this rare neoplasm in veterinary species and its clinical behavior, survivability, and potential correlations to papillomaviruses in certain cases.

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