**Joint Pathology Center**
**Veterinary Pathology Services**

# WEDNESDAY SLIDE CONFERENCE 2024-2025

## Conference #2 21 August 2024

**CASE I:**

**Signalment:**
15 years, castrated male, domestic shorthair cat, *Felis catus,* feline.

**History:**
1-2 days' retching, vomiting, diarrhea.

**Gross Pathology:**
The surgeon noted that the intestinal wall was subjectively thickened and the mesenteric lymph nodes were prominent.

**Microscopic Description:**
Five specimens, per submitter quadrate liver lobe, stomach, jejunum, mesenteric lymph node, and cecum, are bisected and embedded en toto in blocks 1-5, respectively. The major lesions are in the jejunal specimen (submitted slide 3), which has diffuse heavy mucosal infiltration by neoplastic lymphocytes with extension into the submucosa and multifocally along the vasculature into and through the tunica muscularis. A few lymphoid follicles with normal polarity remain in the submucosa. In the mucosa, epitheliotropism is prominent (indicating a T-lymphocyte population) with individual, clusters, and plaques of lymphocytes within the villous epithelium. The neoplastic cells are mostly small to intermediate-sized lymphocytes with a small nucleolus, 0 to 2 mitotic figures per 400x field, and scanty cytoplasm.

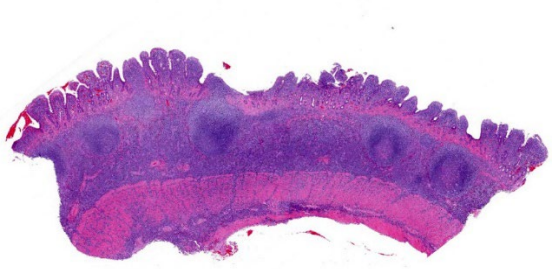

**Figure 1-1. Jejunum, cat. A section of jejunum with markedly blunted villi and a transumural round cell neoplasm is submitted for examination. There are prominent germinal centers scattered along the submucosa. (HE, 22X)**

*The following description is from slides that were not submitted:* Similar neoplastic lymphocytes are found focally in the cecal mucosa and submucosa, but the epitheliotropism is not so obvious in the cecum, and submucosal lymphoid tissue has more organized follicles. The lymph node has only focal expansion of the paracortex by monomorphic small lymphocytes. Only a few sinusoidal clusters of neoplastic lymphocytes are in the liver. Otherwise, the liver has variable centrilobular congestion and degeneration that might account for the dark blotches noted at surgery. The sections of stomach are unremarkable.

**Contributor's Morphologic Diagnosis:**
Epitheliotropic T-cell lymphoma, jejunum.

**Contributor's Comment:**
Despite the reportedly short duration of clinical signs, the histologic findings are typical of feline enteropathy-associated T-cell lymphoma. This alimentary small cell lymphoma

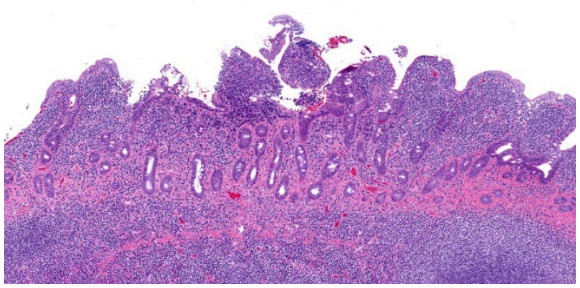

**Figure 1-2. Jejunum cat. There is marked blunting and fusion of villi and loss of crypts within the infiltrated sections of jejunum. (HE, 101X)**

can be difficult to distinguish from inflammatory bowel disease; indeed, there may be a continuum from chronic inflammation to lymphoma.[2,3,6] However, in this case, the clusters and plaques of lymphocytes within the villous epithelium plus the extension into the submucosa and tunica muscularis left little doubt that this is a neoplasm of T lymphocytes.[2,5] Therefore, neither PCR testing for antigen receptor gene rearrangement (PARR) clonality nor immunohistochemical (IHC) phenotyping with T-lymphocyte and B-lymphocyte markers was performed.

Alimentary lymphoma has become the most common form of feline lymphoma and seems to be increasing in prevalence. Most feline small intestinal lymphomas are composed of small cells and confined to the mucosa similar to the human WHO enteropathy-associated T-cell lymphoma type II.[5,8] However, neoplastic lymphocytes extended through the submucosa into the tunica muscularis in this case, making it a transmural T-cell lymphoma (like WHO enteropathy-associated T-cell lymphoma type I). Small cell feline transmural T-cell lymphomas exist, but most are of large granular lymphocyte type.[5] Importantly, transmural T-cell lymphomas have shorter median survival than that of mucosal T-cell lymphomas, but this could reflect the size of the neoplastic cells rather than the depth of invasion.[5]

Duodenal endoscopy is commonly used to assess cats with chronic enteropathy because it is a minimally invasive technique,[1,6] but distinction of transmural lymphoma from mucosal lymphoma requires examination of full-thickness intestinal sections. A lymphoma diagnosed in endoscopic duodenal biopsy specimens would by default be classified as mucosal.[5] In addition, because the jejunum is the most common location of feline intestinal lymphoma, the diagnosis could be missed in a duodenal specimen.[1,5]

The histologic distinction of lymphoma from inflammatory bowel disease, particularly in endoscopic specimens, is greatly facilitated by IHC and PARR.[5,7] In fact, Sabattini et al. reported that for endoscopic duodenal specimens only the diagnosis of lymphoma based on clonality correlated with decreased survival.[7] Nevertheless, clonality results can be mixed, leading authors of a literature review[6] to propose that feline intestinal small cell lymphoma may more closely resemble human indolent digestive T-cell lymphoproliferative disease than enteropathy-associated T-cell lymphoma. In a study of gastric or duodenal endoscopic biopsy specimens of clinically normal adult cats, histologic, IHC, and clonality test results were consistent with small cell lymphoma in 12 of 20 cats.[3] Thus, the authors concluded that the standard criteria for diagnosing chronic enteropathy in cats may need modification.[3]

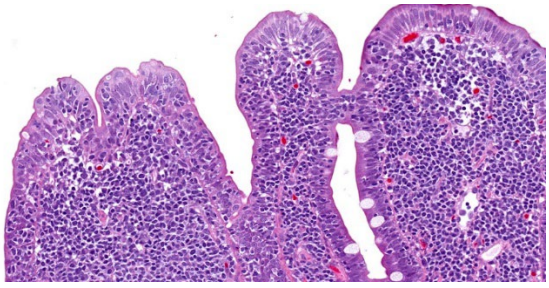

**Figure 1-3. Jejunum, cat. Within the mucosa, neoplastic lymphocytes expand the lamina propria and infiltrate and aggregate within the overlying mucosal epithelium. (HE, 144X)**

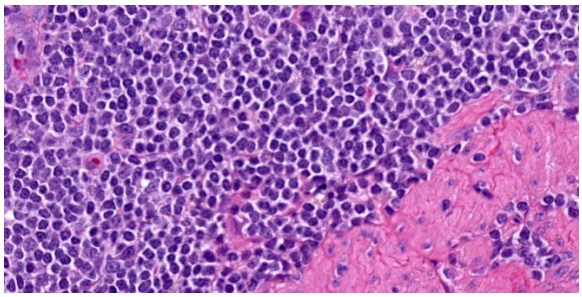

**Figure 1-4. Jejunum, cat. High magnification of neoplastic lymphocytes infiltrating the tunica muscularis (HE,700X)**

**Contributing Institution:**
Purdue University
Animal Disease Diagnostic Laboratory: http://www.addl.purdue.edu/

Department of Comparative Pathobiology: https://vet.purdue.edu/cpb/

**JPC Diagnosis:**
Small intestine: Lymphoma, intermediate to large cell, transmural.

**JPC Comment:**
This week's moderator was the one and only Dr. Bruce Williams who combined his twin loves of unusual pathology and cats to assemble a conference that featured a good amount of both aspects. The first case is a classic enteropathy-associated T-cell lymphoma (EATL) which the contributor nicely describes and generated substantial discussion among conference participants (see below). We performed IHC for CD3, CD20, PAX5, and MUM1 which were diffusely reactive with strong cytomembranous immunoreactivity for CD3 (T-cell marker) in the cells of interest, confirming the diagnosis of T-cell lymphoma (figures 1-5, 1-6). We agree with the contributor that the extension of neoplastic lymphocytes through the submucosa into the tunica muscularis bests fits with an EATL type I interpretation. Interestingly, this case featured large lymphoid follicles that were strongly immunoreactive for CD20 and PAX5 (highlighting B cells) with fewer plasma cells (staining with MUM1) and B cells scattered within the lamina propria. We remarked on a similar finding in Conference 20, Case 4, 2014-2015 – this too probably represents a nexus of chronic intestinal inflammation that has transformed into lymphoma. However, the contribution of a leaky gut (and associated antigen pouring through an incomplete barrier) due to neoplastic lymphocytes disrupting and effacing the enteric mucosa should not be overlooked either in this case.

While the case seemed straightforward, conference participants pointed out several factors that could make this entity more difficult to describe definitively. Foremost, the size of the neoplastic lymphocytes was a point of contention, with some conference participants agreeing with the contributor's description of small to intermediate size while others favored an intermediate to large distribution. Ultimately, the group felt that intermediate to large cells accurately reflected the neoplastic cells based on the more open chromatin pattern and large prominent nucleolus of these cells ('centrocyte-like'). Dr. Williams entertained (and ultimately discarded) the possibility that these cells could reflect a large granular lymphoma (LGL) which is another high-grade large cell T-cell neoplasm, though this diagnosis is often better made on cytology which was not available for this case. Another confounder we considered were the normal population of small lymphocytes within the

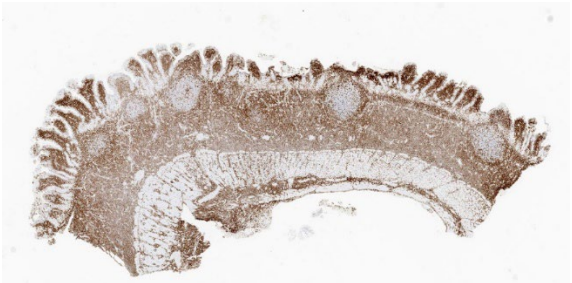

**Figure 1-5. Jejunum, cat. Neoplastic cells stain strongly for CD3, indicating a T-cell origin. (anti-CD3, 22X)**

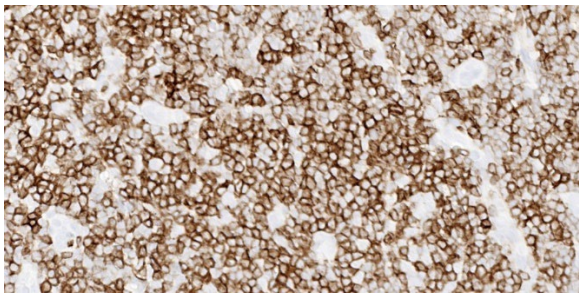

**Figure 1-6. Jejunum, cat. Neoplastic cells demonstrate strong membranous immunopositivity for CD3. (anti-CD3, 459X)**

lamina propria – we focused on the submucosa first and later identified these same cells within the mucosa in making our determination. Participants were also focused on the intraepithelial nests and plaques of lymphocytes which is more classically associated with EATL type 2. There was also spirited discussion of the putative grade of this neoplasm as mitotic figures were rare (1 per 40x hpf) for some participants while others felt that the mitotic rate was at least intermediate (2 per 40x hpf). EATL type 1 tends to fit better with a more high-grade lymphoma which gave us pause. Ultimately, we resolved these points by focusing on the distinction between transmural and mucosal-associated lymphoma and leaving the EATL types aside which is a convention now shared by the ACVIM as discussed in the next section.[4]

Since the submission of case materials to the WSC several years ago, the ACVIM has published new guidance for distinguishing low-grade neoplastic (i.e. EATL type 2) from inflammatory lymphocytic chronic enteropathies in cats.[4] Distinguishing these entities is challenging given the overlap in features. Clinical signs are largely identical for both conditions and current laboratory tests lack appropriate specificity and sensitivity to screen individual cats accurately, though they can help to pare down the differential list (e.g. rule out pancreatitis).[4] Diagnostic imaging is a helpful adjunct for characterizing abnormalities of the intestine and adjacent lymph nodes as well as identifying appropriate regions for biopsy. Histopathology remains the gold standard for diagnosis, though the decision of endoscopic or laparoscopic biopsy, the number of samples to take, and the exact locations to sample remains an active area of discussion among clinicians.[1,4] From a pathologist's perspective, the ideal samples should be cut parallel to the lamina propria of the intestine, facilitating examination of the mucosa and any underlying tissue layers if present.[1,4]

Ancillary diagnostics tests help support the diagnosis of neoplastic or inflammatory enteropathy, but do not make the distinction in a vacuum. The use of IHCs such as CD3, CD20, PAX5, BLA36, CD79a, Granzyme B, CD56, Ki-67 and MAC387/IBA1 is helpful to confirm or refute H&E impressions.[1] In this particular case, the monomorphic population of lymphocytes with transmural infiltration is highly suggestive of EATL on H&E alone before any antibodies are applied. In contrast, mild to moderate cases of lymphoplasmacytic enteritis also feature intraepithelial lymphocytes and increased numbers of lymphocytes within the lamina propria that are similar in appearance to plaques and nests found in emerging EATL.[1] In many cases, the use of PARR could help resolve this debate, though for a subset of cases small biopsy samples with little DNA and/or patchy lesions with few

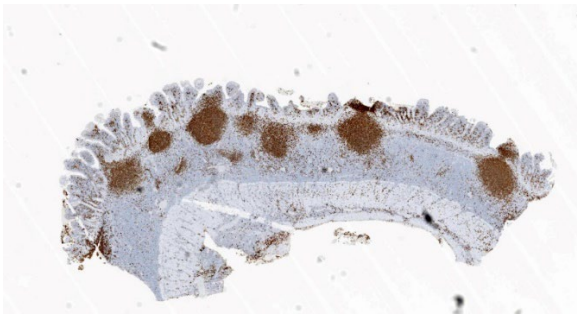

**Figure 1-7. Jejunum cat. Neoplastic cells are immunonegative for CD20, a B-cell marker, but lymphocytes within germinal centers provide a positive internal control. (anti-CD20, 22X)**

T- and/or B-cells present could yield frustrating results.[1] Therefore, clonality should never be considered in a vacuum. It's fair to say that if one enjoys the certainty or confident conclusions often found in WSC proceedings, reading feline intestinal biopsies probably isn't the place to find it.

**References:**


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## CASE II:

**Signalment:**

12.9 year-old FS Yorkshire terrier dog (*Canis lupus familiaris*)

**History:**

The dog has a history of tracheal collapse and coughing. Over the previous 6 months, the owner noted increased respiratory effort and restlessness. Thoracic radiographs indicated a soft tissue opacity in the cranial thorax along with mild cardiomegaly and a mild, diffuse bronchointerstitial pattern in the lungs. An echocardiogram indicated myxomatous mitral valve degeneration and second-degree AV block, as well as confirming a lobulated structure in the cranial mediastinum. Bloodwork was unremarkable. The mass was removed and submitted for histopathology.

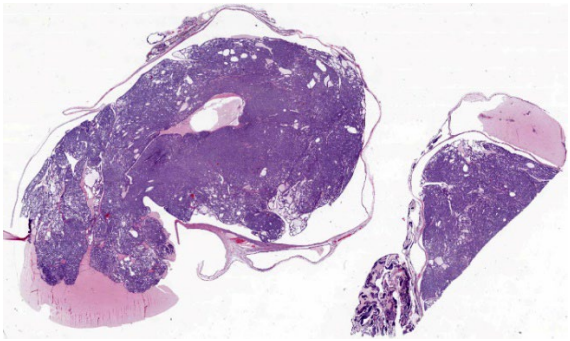

**Figure 2-1. Mediastinum, dog. Two sections of a mass ferom the cranial mediastinum is submitted for examination. (HE, 24X)**

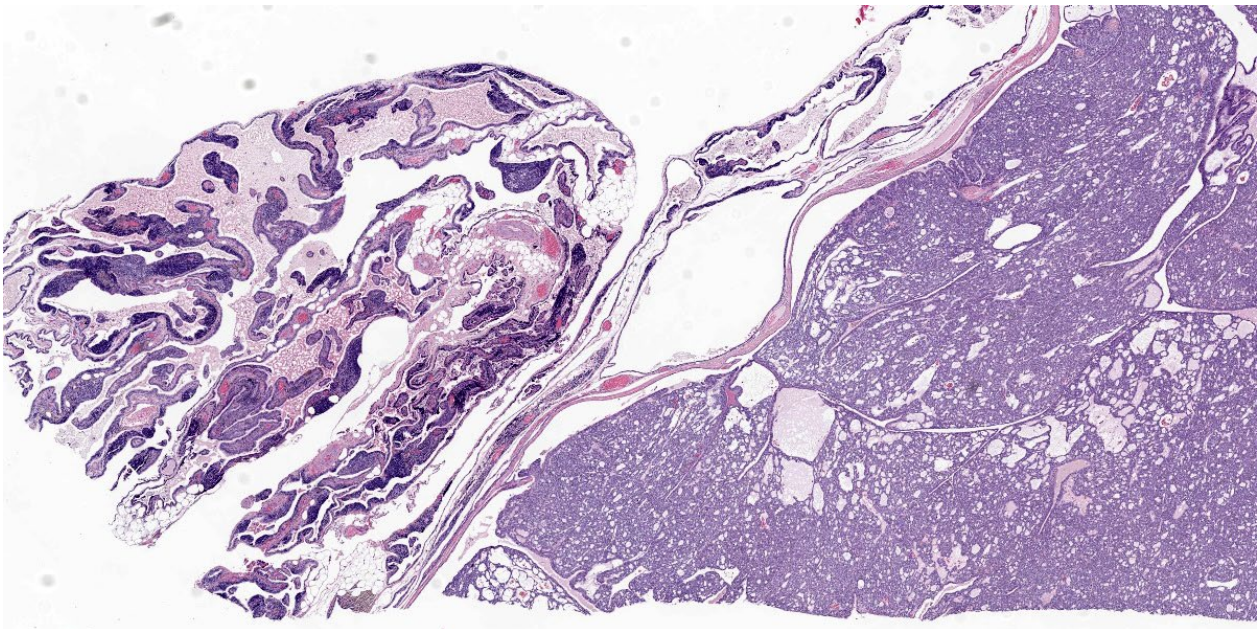

**Figure 2-2. Thymus, dog. The neoplasm arises from the wall of a large, multilocular branchial cyst within the thymic remnant. (HE, 24X)**

**Gross Pathology:**
The mass received measured 3.9 x 2.8 x 1.6 cm and was mottled tan to dark purple, multinodular, and semi-firm to firm.

**Microscopic Description:**
There is minimal residual thymic tissue present, with only minimal lymphoid cells present. There are several, variably sized cysts, containing eosinophilic or clear space and which are lined by ciliated cuboidal epithelium. Within the lumen of several large cysts, with retained cyst lining epithelium, there are mass effects, produced by proliferations of similar epithelial cells to form solid islands, sheets, rare tubules and ducts, some of which contain eosinophilic fluid. The neoplastic cells have moderate amounts of lightly vacuolated cytoplasm, round to ovoid vesicular nuclei, with small to no nucleoli. There is moderate anisokaryosis and anisocytosis. Mitoses are 2 per 10 high power fields (400x).

**Contributor's Morphologic Diagnosis:**
Cranial mediastinal mass: Branchial cysts with transformation to branchial carcinoma

**Contributor's Comment:**
Branchial cysts arise from remnants of pharyngeal (branchial) pouches, which are a series of 4 to 5 bilateral embryonic endodermal evaginations that project laterally between the pharyngeal arches. The pharyngeal pouches and clefts contribute to the formation of the thymus (from the third pharyngeal pouch), parathyroid gland, pharyngeal tonsils, and middle and external ear.[7] Epithelia migrate caudally from the submandibular region, down the neck, and into the cranial mediastinum during development, occasionally leaving remnants at points along this tract that can develop into cysts.[5]

Cervical and mediastinal branchial cysts have been reported in dogs, but there are few reports of thymic branchial cysts in veterinary medicine[2,5] and even fewer reports of neoplastic transformation.[5,8] Some of these

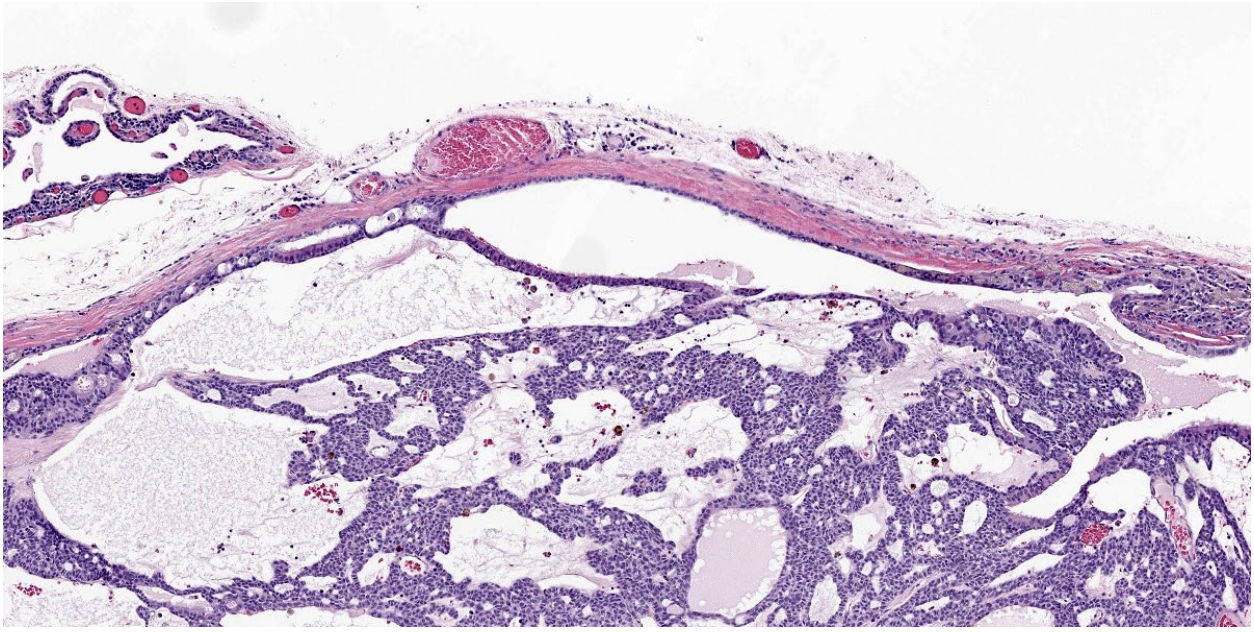

**Figure 2-3. Thymus, dog. A multicystic neoplasm arises from the wall of the branchial cyst. Thymic remnant. (HE, 67X)**

thymic cysts may be attributed to cystic proliferation of thymic reticular cells rather than remnants from the third pharyngeal pouch. Branchial cysts are distinguished by the presence of variably squamous to ciliated lining epithelial cells with no external opening.[9] Thymic branchial cysts are typically benign and more common in older dogs, but can become space-occupying, leading to cranial vena cava syndrome and pleural effusion.[5] In a report of a dog with malignant transformation of a thymic branchial cyst to a carcinoma, pulmonary metastases were present as well.[4]

In humans, suspected malignant transformation of cervical branchial cysts has been reported with a variety of terms, including branchiogenic carcinoma, branchioma or malignant branchioma. The nomenclature and origin of these masses remains under debate. It has been suggested that these masses are metastases to the cyst from an unrecognized primary tumor, most commonly oropharyngeal carcinomas such as tonsillar carcinoma.[3] Overall, these tumors are considered exceptionally rare in humans.[1]

Differential diagnoses for a cranial mediastinal mass in dogs include thymoma, thymic lymphoma, thymic carcinoma, thymofibrolipoma, chemodectoma, ectopic thyroid tumor, schwannoma, thymic hyperplasia, abscess, or granuloma. Given its rarity and a lack of definitive immunohistochemical markers, branchial cyst carcinomas should be considered a diagnosis of exclusion.

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**JPC Diagnosis:**
Thymic remnant: Branchial carcinoma arising in branchial cyst.

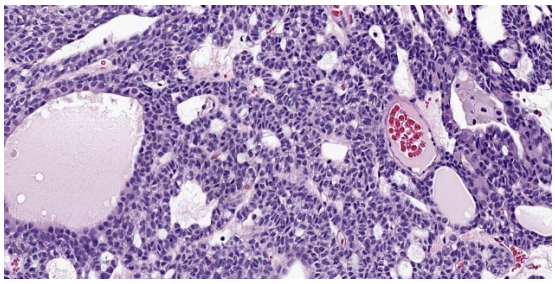

**Figure 2-4. Thymus, dog. Neoplastic cells are columnar and are arranged in anastmosing cords, often lining cystic spaces. (HE, 305X)**

**JPC Comment:**

This particular case is somewhat challenging to recognize the salient features and arrive at an exact diagnosis. The large cystic spaces, the small numbers of lymphocytes, and ciliated cuboidal epithelium are all helpful to note, especially starting from the position shown in figure 2-2. Ciliated epithelium (figure 2-5) is commonly seen in respiratory and reproductive epithelium, though the other two facets don't quite fit with those interpretations. Cilia are also a component of branchial pouch epithelia[8,9] – together with the CD3 positive lymphocytes, the tissue in section most resembles a cyst of branchial pouch origin which is located within the thymic remnant of an older dog. That said, the eosinophilic fluid in the background could easily be mistaken for thyroidal colloid at first glance as well. Conference participants as a whole thought that the tissue was ovarian and that the cystic fluid partially resembled Call-Exner bodies of a granulosa cell tumor (figure 2-4) and explained the ciliated epithelium as part of the oviduct. Though these interpretatoins were not ultimately correct, they were good ruleouts for an exquisitely unusual entity. Although branchial cysts have been reported in veterinary medicine, malignant transformation is rare[4,7] In this case, Dr. Williams felt that there was supporting evidence of transformation of the cyst lining itself into a discrete neoplasm (figure 2-3) within the section presented.

An important differential in this case is multiple thymic cyst and thymic origin neoplasia though we also considered the possibility of a neuroendocrine or thyroid tumor too. The animal in this case reportedly had a mass within the cranial thorax which was localized to the mediastinum via echocardiography. In addition to CD3, we also ran IHCs for pancytokeratin, TTF-1, chromogranin, and synaptophysin. Pancytokeratin was diffusely and strongly cytomembranously immunoreactive while chromogranin, synaptophysin were diffusely negative which was consistent with a cystic epithelial tumor. TTF-1 was not immunoreactive in the cells of interest, which excluded a thyroid tumor. Likewise, the malignant neoplastic cells the contributor describes lack squamous differentiation and a high (>10) mitotic rate that is associated with thymic carcinomas.[9] For these reasons, we favor a branchial cyst carcinoma arising in a thymic remnant for this case. Lastly, branchial cyst remnants were previously (briefly) covered in Conference 7, Case 2, 2017-2018 – we suspect it may be some time before we see this entity again.

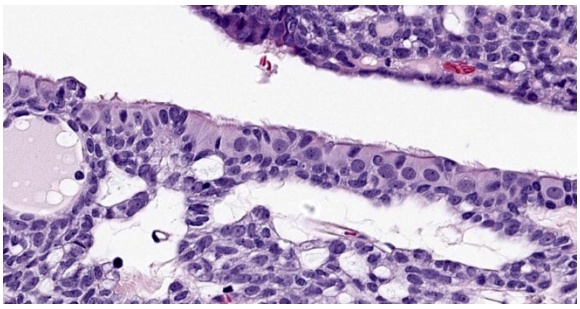

**Figure 2-5. Thymus, dog. Cilia are evident on neoplastic cells lining large cystic spaces (HE, 400X)**

**References:**

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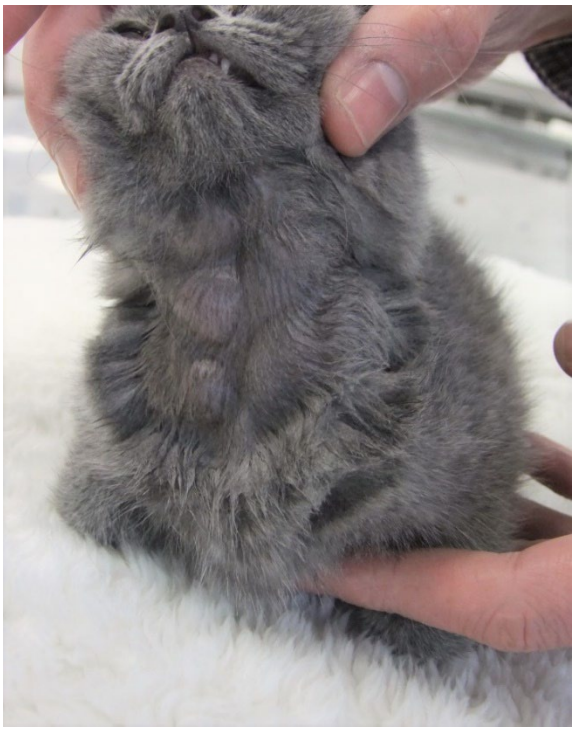

**Figure 3-1. Cervical lymph nodes, kitten. There is marked enlargement of cervical lymph nodes. (*Photo courtesy of:* Massey University, School of Veterinary Science , Palmerston North, New Zealand).**

**CASE III**:

**Signalment:**
Fourteen-week-old, female, British shorthair cat (*Felis catus*).

**History:**
This kitten was one of two in a litter of four British shorthair (BSH) kittens that developed multicentric lymphadenopathy involving all peripheral lymph nodes at 6 weeks of age. Over the following weeks, the lymphadenopathy rapidly progressed to marked but non-painful enlargement of multiple nodes with progressive abdominal distension and lethargy (Figures 1 and 2). Both kittens showed mild regenerative anemia, and blood smears from this kitten showed gross auto-agglutination. Both kittens received immunosuppressive doses of corticosteroids (2.2mg/kg prednisone *per os* sid) for the 2 weeks prior to euthanasia,

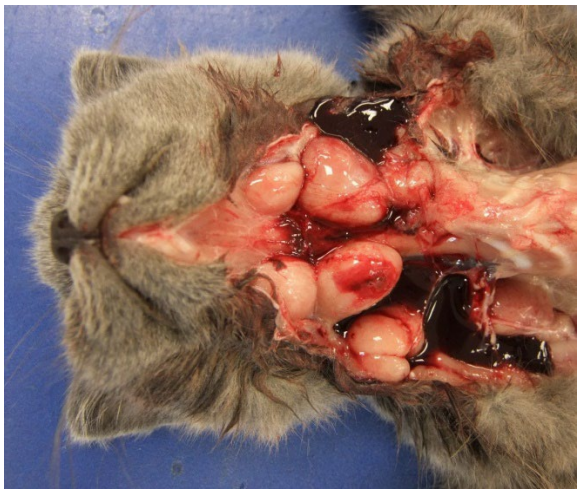

**Figure 3-2. Cervical and mandibular lymph nodes, kitten. There is marked enlargement of mandibular and cervical lymph nodes. (*Photo courtesy of:* Massey University, School of Veterinary Science , Palmerston North, New Zealand).**

but no significant clinical improvement was observed and they were euthanized at 12 and 14 weeks respectively.

**Gross Pathology:**

On necropsy examination, all identifiable peripheral and visceral lymph nodes showed very marked enlargement (Figures 3 and 4) with effacement of corticomedullary architecture when incised (Figure 5). Mild diffuse hepatic enlargement and moderate diffuse splenic enlargement were also present.

**Laboratory Results:**

Blood was negative for the presence of both FeLV antigen and FIV antibody (Snap® Combo FeLV Ag/FIV Ab Test Kit) and was negative on direct Coombs' testing. Immunocytochemistry to assess CD3, CD4 and CD8 expression performed on fine needle aspirates from multiple lymph nodes indicated a CD3+/CD4/CD8- immunophenotype for the majority of cells. Results of molecular clonality PCR amplification of antigen receptor rearrangements (PARR) of both the T-cell receptor gamma (*TCRG*) and immunoglobulin heavy chain (*IGH*) loci on genomic DNA extracted from FFPE lymph node tissue was consistent with a polyclonal and non-neoplastic T-cell proliferation. DNA extracted from fresh-frozen kidney and tested by PCR revealed homozygous Fas-ligand gene (FASLG) variants associated with feline autoimmune lymphoproliferative syndrome (FALPS).

**Microscopic Description:**

Lymph nodes: There is marked expansion of the cortex and medulla of both nodes by a population of round cells consistent with lymphocytes, which effaces or markedly distorts nodal architecture and follicular remnants and expands subcapsular sinuses (Figure 6). Lymphocytes are intermediate to large in size, have generally distinct borders with a scant to moderate amount of eosinophilic cytoplasm, large round nuclei with clumped chromatin and one to two prominent nucleoli. The nuclear diameter of lymphocytes is typically equal to the diameter of approximately 1.5-2 regional erythrocytes. Mitotic figures average 8-10 per 400x high power fields. In some areas, low to

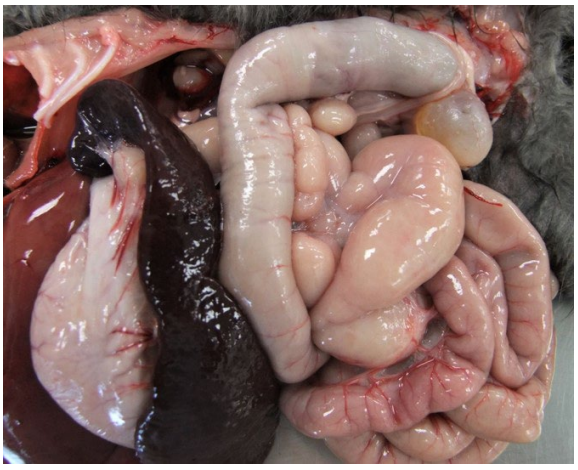

**Figure 3-3. Abdominal lymph nodes, kitten. There is marked enlargement of abdominal lymph nodes. (*Photo courtesy of:* Massey University, School of Veterinary Science , Palmerston North, New Zealand)**

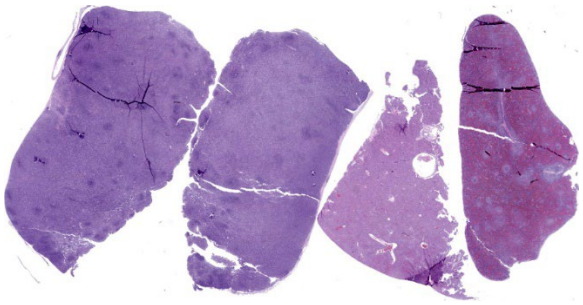

**Figure 3-4. Multiple tissues, kitten. Two sections of lymph node, and one of sliver and spleen are submitted for examination. At this magnification, the architecture of the lymh node is lost. (HE, 6X)**

moderate numbers of small lymphocytes, plasma cells, macrophages and rare neutrophils are also admixed with the lymphocyte population (Figure 7).

Spleen: There is moderate multifocal expansion of the splenic white pulp by a population of lymphocytes similar to those present and described within the lymph nodes.

Liver: There is mild multifocal expansion of periportal areas and more variably, hepatic sinusoids, by a population of cells including both small and large lymphocytes, plasma cells (including Mott cells), and macrophages. Multifocal areas of scattered extramedullary hematopoiesis are present throughout the section and low numbers of Kupffer cells contain intracytoplasmic erythrocytes.

Immunohistochemistry for CD3 and CD20 performed on sections of lymph nodes and spleen confirmed a predominantly CD3+/CD20- cell population consistent with T cells within both tissues (Figure 8), while variable numbers of CD3-/CD20+ B-cells were also present within follicular remnants and subscapular sinuses of some nodes. This staining pattern is consistent with a T-cell proliferation.

**Contributor's Morphologic Diagnosis:**
Lymph nodes, spleen and liver: T-cell lymphoid hyperplasia, severe, diffuse
Liver: Pericholangitis and perivasculitis, mild, multifocal, lymphoplasmacytic with erythrophagocytosis and extramedullary hematopoiesis

**Contributor's Comment:**
This case illustrates typical features of feline autoimmune lymphoproliferative syndrome (FALPS), an unusual autosomal recessive lymphoproliferative disease first seen in multiple related British shorthair kittens in Australia in the 1990s and in New Zealand from 2008.[2] Kittens affected by FALPS appear normal at birth but show failure to thrive, lethargy, regenerative anemia, abdominal distension and generalized lymphadenopathy from 6-10 weeks of age. The disease progresses quickly, has no known effective treatment, and affected kittens usually die or require euthanasia shortly after diagnosis. The disease is easily misdiagnosed as lymphoma, as gross pathology, routine histology and immunohistochemistry results all suggest a diagnosis of a neoplastic (T-cell) proliferation in multiple lymph nodes, spleen and other organs. However, PCR molecular clonality assays (PARR) confirm a polyclonal and non-neoplastic T-cell proliferation within affected nodes indicative of a hyperplastic process and inconsistent with lymphoma.

The genetic basis for FALPS has recently been identified as a monogenic autosomal recessive mutation in the Fas-ligand gene (*FASLG*).[3] Both the *FAS* and *FASLG* genes code for proteins critical in normal cell apoptosis. The mutation in kittens with FALPS involves the insertion of an adenine base in exon 3 of *FASLG*, causing a frameshift mutation and insertion of a premature stop codon, predicted to produce a truncated Fas ligand protein that is unlikely to initiate effective lymphocyte apop-

tosis. Kittens homozygous for the *FASLG* variant allele develop FALPS while heterozygotes are carriers of the defect but phenotypically normal. Genetic testing (buccal swabs or blood) is currently available through Massey University (New Zealand) and Langford Vets (United Kingdom). Recent studies show a relatively high frequency of the variant *FASLG* allele in BSH cats in New Zealand, with 22% of healthy BSH cats from three breeding catteries identified as carriers of the *FASLG* variant.[1] The disease is not currently reported outside Australasia, but as breeding BSH cats from New Zealand and Australia are often exported, it is possible that FALPS may also be seen in BSH and BSH-cross cats in other countries.

The disease in BSH cats is analogous to the inherited disease autoimmune lymphoproliferative syndrome (ALPS) in people.[8] The majority of people with ALPS have inherited *FAS* gene mutations causing defective lymphocyte apoptosis, non-neoplastic lymphoproliferation and variable autoimmunity, although mutations in both *FASLG* and *caspase 10* genes can also cause the disease. In people, most ALPS cases have autosomal dominant inheritance, but the genotype often shows incomplete penetrance with a variable phenotype. Feline autoimmune lymphoproliferative syndrome appears similar to a rare autosomal recessive ALPS variant in people with homozygous *FASLG* mutations which causes a severe and often fatal form of the disease ("ALPS-FASLG") in children.[6] The feline disease also shows similarities to the autosomal recessive "gld" mouse model for ALPS, where mice with homozygous *FASLG* mutations develop severe lymphoproliferative disease early in life.[7]

As this case illustrates, the main gross and histological differential diagnosis for FALPS is multicentric lymphoma, and early cases of FALPS were misdiagnosed as this. Cytology

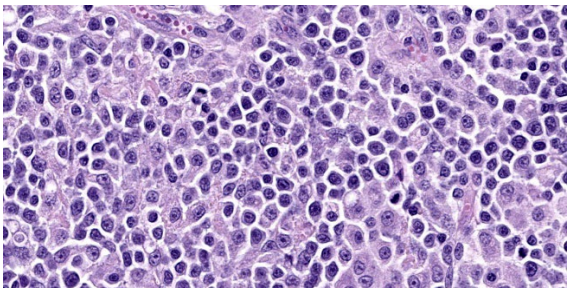

**Figure 3-5. Lymph node, kitten. Nodal architecture is effaced by a proliferation of large lymphocytes with a single prominent nucleoli. (HE, 607X)**

(not shown here) and histology of multiple enlarged lymph nodes in this kitten reveal a monomorphic population of large lymphocytes with a high mitotic rate. Lymphocytes efface or markedly distort normal nodal architecture and fill subcapsular sinuses. These features are strongly suggestive of a neoplastic lymphoid proliferation. In most FALPS cases, as here, low numbers of randomly distributed plasma cells, macrophages and neutrophils also present in some node sections, while other cases show less complete effacement and more obvious retention of cortical architecture. Similar but less dramatic lymphoproliferation is also consistently seen within the spleen (as in this case), and more variably within the liver and gastrointestinal tract in kittens with FALPS. The majority of lymphocytes within lymph nodes and spleen typically show a CD3+ immunophenotype (consistent with T-cells), also suggesting (T-cell) lymphoma. Immunocytochemistry shows these lymphocytes to be an unusual population of "double negative T-cells" (CD3+/CD4-/CD8-), also similar to those seen in people with ALPS.[8] Mild erythrophagocytosis and extramedullary hematopoiesis, possibly secondary to hemolytic anemia, are also seen in the liver in this case; in other FALPS cases these histological features are more marked. The milder erythrophagocytosis and extramedullary hematopoiesis in this case may be related to this kitten's corticosteroid treatment prior to euthanasia; corticosteroids are the first-line of

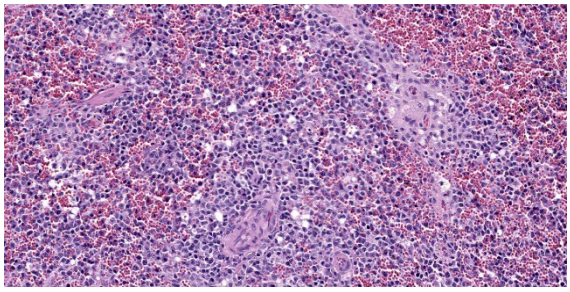

**Figure 3-6. Spleen, kitten. Similar large lymphocytes efface the red pulp of the spleen. (HE, 240X)**

therapy in people to reduce the autoimmune manifestations of ALPS, including anemia.[10]

Despite microscopic features suggesting T-cell lymphoma in this kitten, PARR testing of lymph node samples showed a polyclonal non-neoplastic T-cell proliferation within lymph nodes and other lymphoid tissues, as is characteristic in FALPS-affected kittens. Subsequent genetic testing also confirmed the presence of the homozygous *FASLG* mutations now known to be associated with FALPS.[3] Lymphoma should also be considered an unusual diagnosis in such a young kitten (FALPS-affected kittens are usually less than 5 months of age), particularly where multiple related or sibling kittens are affected by the disease. Although lymphoma has been reported in kittens as young as 9 weeks of age following experimental FeLV infection at birth,[4] lymphoma in kittens under 6 months of age following natural infection appears very rare. FALPS should therefore be considered as a potential differential diagnosis in any BSH or BSH-cross kitten under 5 months of age with enlargement of multiple peripheral lymph nodes, especially where multiple related animals are affected by disease.

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**JPC Diagnosis:**
Lymph nodes, spleen: Atypical lymphoid proliferation, diffuse, severe.

Liver: Extramedullary hematopoiesis, multifocal, mild to moderate.

**JPC Comment:**
In case you thought we lost our minds (we haven't, but thanks for asking!) and put the same entity within the same conference as a separate case, you can be at ease. While this entity may look like lymphoma at first glance, the contributor provides an excellent slide description and summary of FALPS and highlights how a good history and ancillary diagnostics are needed to recognize this entity and spot the differences. That the animal in this case was only 14 weeks old is important – we actually put this detail on the Conference Worksheet to help push participants away from lymphoma and open the door to thinking about other possible diagnoses. Although some conference participants listed FALPS as their associated condition for this case, other rule outs considered were myeloma and FELV-associated lymphoma though the expected time course of these neoplasms do not fit the age of the animal in this case well. The atypical lymphocyte morphology in this case is similar to the lymphocyte morphology in Case 1 with regards to size and chromatin patterns – that these cells were noted in the red and white pulp of the spleen and lymph node led some participants to still favor lymphoma for this case. Although subtle, the low to moderate numbers of inflammatory cells in the background are not an expected feature of lymphoma the same way that they were in the intestine in Case 1. Notably, there are plasma cells and even numerous Mott cells that multiple conference participants pointed out. We ran IHCs for CD3,

CD20, PAX5, MUM1, and IBA1. Lymphocytes did not label with B-cell markers (PAX-5 and CD20) consistent with the contributor's assessment of CD3 reactivity for these cells of interest. IBA1 was not particularly helpful in this case as it labeled the normal existing population of histiocytes within the spleen, liver, and lymph nodes quite well. These findings altogether highlight the validity of PARR to distinguish FALPS from lymphoma as noted by the contributor.

The present entity circles back to general pathology and apoptosis rather nicely. In the extrinsic pathway of apoptosis, plasma membrane receptors (so called 'death receptors') respond to changes in the extracellular environment by trimerizing in response to ligand presentation.[3,5,9] Examples of death receptors include members of the tumor necrosis factor superfamily (e.g.TNFR1) and FS-7-associated surface antigen (FasR) among others.[5] After the ligand-receptor binding interaction, propagation of this signal continues within the cell via continues via associated death domain proteins (FADD/TRADD) which complex with pro caspase-8 to form a death induced signaling complex (DISC).[5,9] The net effect of this interaction is that the death domain protein serves to activate caspase 8 at an appropriate time and initiate a death cascade via downstream 'executioner' caspases with caspase 3 being the most significant. These caspases cleave nuclear and cytoplasmic proteins, leading to disintegration of the nucleus and disruption of the cytoskeleton during apoptosis.[5] Connecting these details back to the case at hand, Fas ligand is normally expressed on a variety of cells including T-lymphocytes – FasL therefore acts as brake of sorts on an excessive immune response. As the contributor points out, a frameshift mutation in the Fas-ligand gene would be expected to disrupt FasL

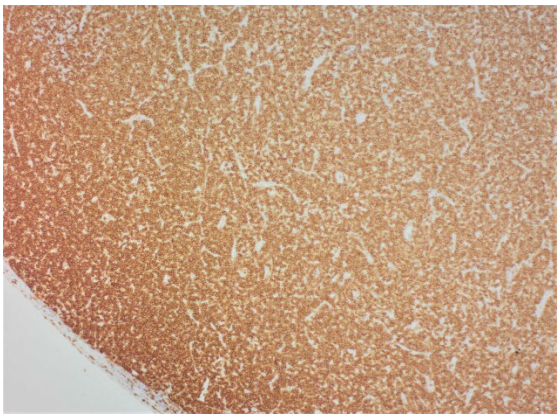

**Figure 3-7. Lymph node kitten: Neoplastic cells stain demonstrate strong diffuse cytoplasmic immunoreactivity for CD-3, a T-cell marker.) (anti-CD3, 400X). (*Photo courtesy of:* Massey University, School of Veterinary Science , Palmerston North, New Zealand).**

and FasR interaction and lead to a non-neoplastic accumulation of lymphocytes due to lack of downstream caspase activity and lack of apoptosis. Conference participants remarked about the presence of tingible body macrophages within lymphoid follicles in this case despite this mutation and felt that alternate death receptors in the TNF superfamily might still be active and allow some lymphocytes to be sufficiently phosphorylated to activate downstream caspases.

Finally, testing for this rare condition has expanded in recent years. In Europe, commercially available testing for FALPS is included with genetic screening for polycystic kidney disease and progressive retinal atrophy in British Short/Longhair cats via Laboklin. As the popularity of British Shorthair cats increases in the United States, demand for such testing may also follow.

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## CASE IV:

**Signalment**:
Cat (*Felis vulgaris*) – 5 months – female castrated

**History**:
Presented with clinical complaints of vomiting and lethargy. Huge amount of fluid in peritoneal cavity (ascites). No abnormalities found on echocardiac examination and blood examination. Laparascopy performed: suspicion of encapsulating peritoneal sclerosis. Died at night.

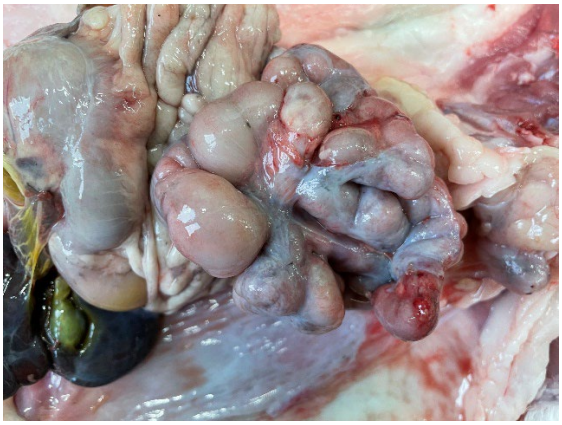

**Figure 4-1. Abdominal viscera, cat. The peritoneum is diffusely thickened, resulting in an opaque appearance. There is a fibrous adhesion between multiple dilated loops of intestine. (*Photo courtesy of:* Department of Pathobiology, Pharmacology and Zoological Medicine, Faculty of Veterinary Medicine, University of Ghent, Salisburylaan 133, 9820 Merelbeke, Belgium https://www.ugent.be/di/di05/nl)**

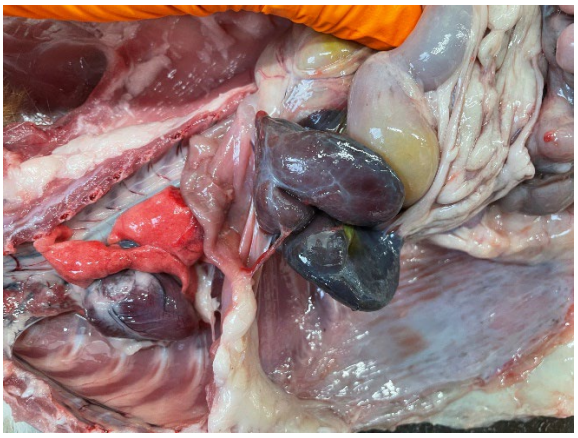

**Figure 4-2. Abdominal viscera, cat: The thickened peritoneum is visible over the liver capsule. (*Photo courtesy of:* Department of Pathobiology, Pharmacology and Zoological Medicine, Faculty of Veterinary Medicine, University of Ghent, Salisburylaan 133, 9820 Merelbeke, Belgium https://www.ugent.be/di/di05/nl)**

**Gross Pathology**:
Most peritoneal organs show an abnormal morphology and are surrounded by a thick, glistening, white layer of peritoneum (figure 1 peritoneal organs *in situ* and figure 2 peritoneal organs removed from body).

- Small intestines are severely attached to each other. Duodenum shows a normal wall thickness but is moderately dilated. Jejunum shows a very tortuous appearance (figures 3 and 4), with a diffusely moderately to severely thickened intestinal wall and a moderate amount of yellow, granular content. The rest of the small intestine does not contain any content.
- Large intestine proximally shows the same appearance as the jejunum, more distally it has a normal appearance and contains a moderate amount of normally formed brown feces. Mucosa of all the intestinal segments is normal. There is no obvious mesentery visible.
- Liver is small with ventrally enlarged rounded edges (figure 5). It has a diffuse dark red black color with multifocal sharply delineated linear grey strikes (fibrosis, figure 6).
- Spleen is severely shrunken with absence of the normal architecture (figure 7). It is surrounded by a thick layer of connective tissue and fat (figure 8).

**Laboratory Results:**
Blood examination normal.

**Microscopic Description**:
Transections of multiple intestinal segments are present. All intestines are clustered together and surrounded by a diffusely severely thickened peritoneal layer, on top of their normal thin peritoneum. The thickened peritoneal layer contains large amounts of linearly arranged collagen fibers. The connective tissue differs in maturity dependent on the location. Multifocal areas have a more mature appearance with accumulation of amorphous eosinophilic material, interspersed with small amounts of spindloid fibroblasts and densely packed connective tissue fibers, while other areas have a less mature appearance with a higher cellularity of more plump fibroblasts, a loose collagenous stroma, and moderate amounts of

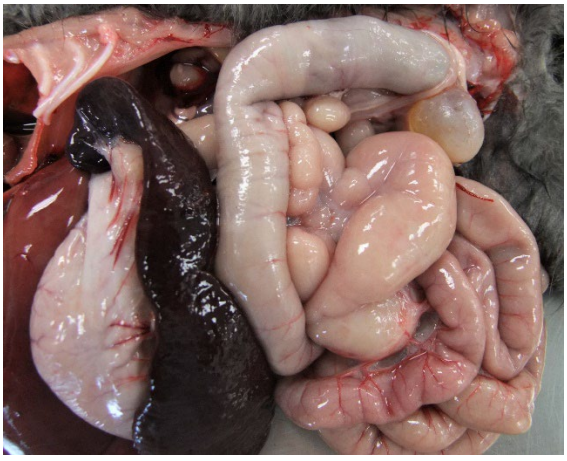

**Figure 4-3. Intestine, cat. Multiple contiguous loops of intestine are submitted for examination. (HE, 6X)**

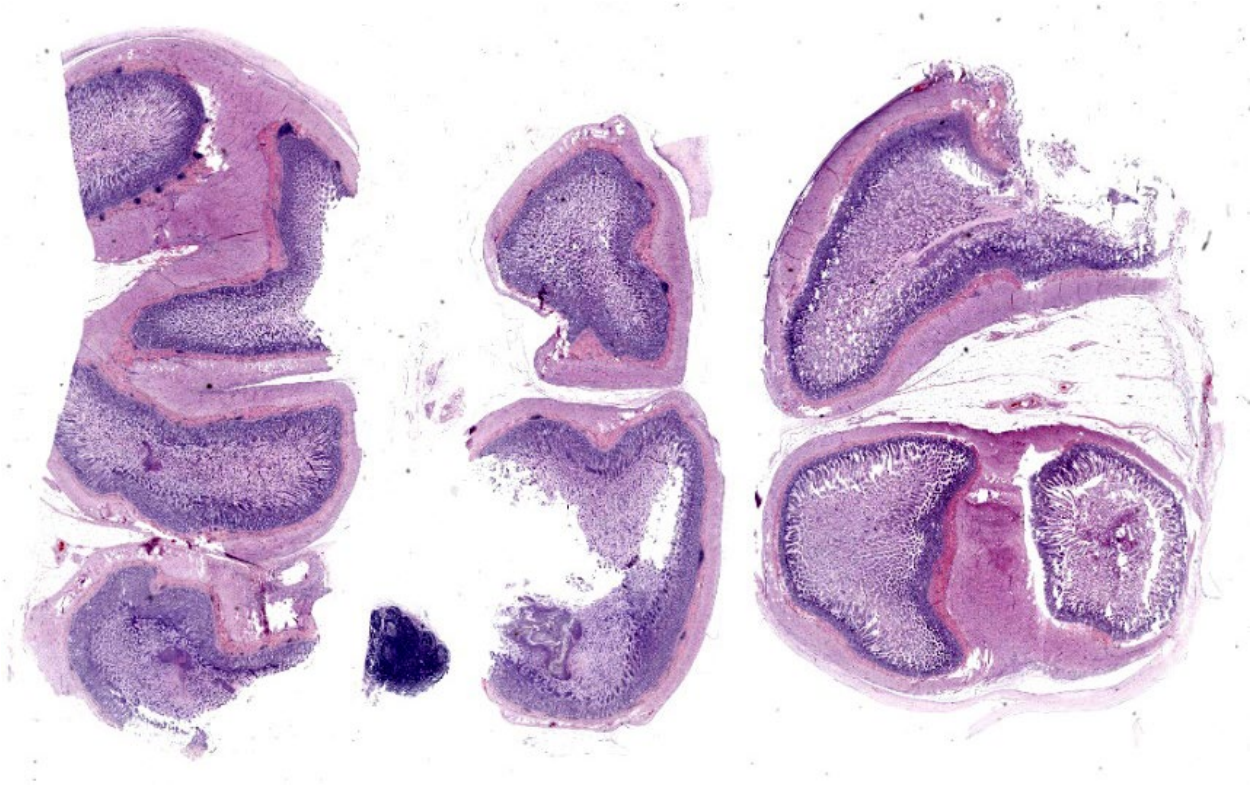

**Figure 4-4. Intestine, cat. Loops of intestine are surrounded by variably dense bands of fibrous connective tissue (arrows) (HE, 6X)**

small tortuous blood vessels lined by plump endothelial cells (granulation tissue). Multifocal there are areas with diffuse linear translucency between the connective tissue fibers (edema). The inner part of the peritoneum shows multifocal mild mixed inflammation, mainly containing neutrophils and lymphocytes, and a mild to moderate amount of small tortuous blood vessels with plump endothelial cells. Mild to moderate lymphoplasmacytic inflammation is also seen in the tunica muscularis, tunica submucosa and the lamina propria of the tunica mucosa.

Trichrome Masson stain performed: severely thickened peritoneum

**Contributor's Morphologic Diagnosis**:
Diffuse severe chronic encapsulating peritoneal sclerosis of the intestines.

**Contributor's Comment**:
Sclerosing encapsulating peritonitis (SEP), also known as 'encapsulating peritoneal sclerosis', is a very rare disease described in humans as well as in animals. Up until 2022, it is described in only 13 canine cases[10] and 2 feline cases.[6,8] It is characterized by a chronic, diffuse, fibrocollagenous thickening of parietal and visceral peritoneum with secondary encapsulation of abdominal organs, mostly small intestines.[1-11,13] In human medicine, it is classified into 4 different types depending on the extent of involved abdominal organs;[2,4,7] type 1 involves small intestines partially, type 2 involves small intestines completely, type 3 involves small intestines and other organs, such as stomach, cecum, colon, liver and/or ovaries, and type 4 involves the entire peritoneal cavity.

Etiopathogenesis remains incompletely understood.[1,2,7] SEP can be divided in primary,

idiopathic forms and secondary forms, which can be caused by lots of different underlying disorders that cause chronic low-grade inflammation of the peritoneum.[1,2,8] In human medicine, peritoneal dialysis is the most common one, while other possible causes are infectious peritonitis, administration of certain medications and intra-abdominal surgery.[2-11,13]

SEP can give a wide variety of vague symptoms in humans, such as intermittent and recurrent, moderate to severe abdominal pain, caused by intestinal obstruction and necrosis.[1,2,3,7,9,11,13] This is mostly in combination with a malnourished appearance, abdominal distention, palpable abdominal mass, nausea and vomiting.[4,6,7,9,11,13]. Common clinical symptoms in canine cases are also vague, and can include vomiting, diarrhea, soft feces, anorexia, depression or lethargy, enlarged abdomen and abdominal pain.[1,3,5,6,10] Chronic cases can show moderate to severe low body condition and low muscle score,[3,5,6] combined with symptoms specific for the underlying etiology.[6] Cats show similar symptoms as seen in dogs: anorexia, intermittent vomiting, rare diarrhea, weight loss, abdominal distention and sensitivity are all described.[6,7]

SEP in humans and animals gives a very typical gross thick collagenous encapsulation of the small intestines with secondary adhesions between the intestinal loops, giving them a very tortuous and mass-like appearance in the central abdomen.[1-3,5-7,9-11,13] Depending on the type of the disease, other organs can be additionally involved, such as stomach, cecum, colon, liver or ovaries.[2,7-9] In humans, an important consequence of SEP is intestinal obstruction with necrosis,[1,2,4,6,13] something that is not described in dogs and cats.[1,5,6] An explanation for this lies in the very active fibrinolytic system of these species.

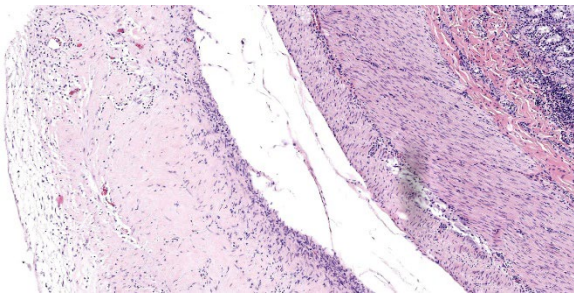

**Figure 4-5. Intestine, cat. In some areas, the fibrous tissue is immature, resembling granulation tissue. (HE, 97X)**

Ascites is seen typically in dogs, while it is not common in humans.[1,3,5,6,10,11,13]

SEP causes very characteristic histopathological lesions: visceral and parietal peritoneum have an uneven, diffusely, moderately to severely thickened appearance.[1,2,5-11,13] Different layers can be seen in the thickened peritoneum of animals. The deepest layer show mature collagenous connective tissue with densely packed collagen fibers, while the more superficial layers are built up of granulation tissue, characterized by loose collagenous stroma with presence of numerous fibroblasts, mixed with abundant, small, tortuous blood vessels lined by plump endothelium (neovascularization), and a mild mucinous deposition.[5,6,8,11] Both in humans and animals, mild to moderate, mostly mononuclear, inflammation can be seen in the thickened peritoneum.[4-6,8-11,13]

Diagnosis of SEP remains difficult due to its vague clinical symptoms, therefore in most of the cases, there is need for a combination of history, pre-existing predisposing factors, clinical symptoms and abdominal imaging before SEP will be suspected.[7] For definitive diagnosis, surgery with histopathology is necessary.

Treatment is not easy, and both surgery, medicinal therapy, nutritional support and treat-

ment of underlying disorders are used. Surgery mostly consists of adhesiolysis with ablation of the fibrous capsule and intestinal adhesions.[1,2,6,9,13] It is very important to realize the dangers of these surgeries, and complicated and fatal results are not uncommon.[1,2,4] Most commonly used medicines are corticosteroids, which work anti-inflammatory and immunosuppressive, and tamoxifen, which has an anti-fibrotic function.[3,4,7-9,11,13]

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**JPC Diagnosis:**
Visceral peritoneum, small intestine: Fibrosis, diffuse, moderate with adhesions and scant granulation tissue.

**JPC Comment:**
Conference 2 concludes with a case of yet another rare entity in a cat. While we suspect some readers may not know of this particular disease, we are confident that a good description of histologic features gets one pretty close (and the search engine of choice does the rest). The large bundles of immature collagen and granulation tissue that encircle the serosal tunic (figures 4-4 and 4-5) and extend between loops of intestine is bizarre yet distinct. For this case, we ran IHCs for desmin and smooth muscle actin (SMA) to delineate fibrosis from muscle as well as special stains (Masson's trichrome, Movat's pentachrome) to highlight tissue architecture overall. Both desmin and SMA are strongly cytoplasmically immunoreactive within the multiple (thick and thin) layers of

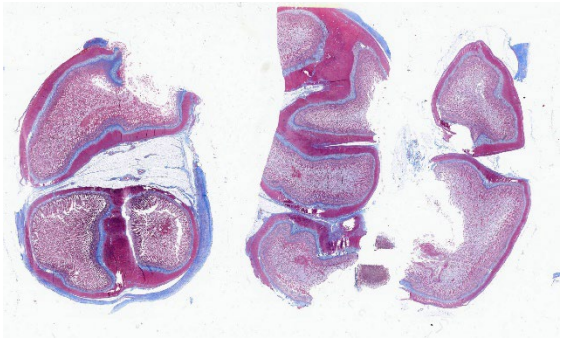

**Figure 4-6. Intestine, cat. A Masson's trichrome demonstrates a sheath of fibrous connective tissue encircling multiple loops of bowel. (Masson's trichrome, 6X)**

smooth muscle that surrounds each loop of intestine, but the chromatic stains are particularly helpful for appreciating the degree of fibrosis and adhesions between adjacent loops of bowel that are not simply a function of cut of the microtome (figures 4-7 and 4-8). Granulation tissue in particular was largely immature collagen (non-polarizing) with fewer small caliber blood vessels, though this aspect may not be consistent between all cases of SEP. Dr. Williams emphasized that the submucosa of this cat, while fairly thick, was likely normal and it was easy to be fooled unless reading feline intestinal biopsies on a consistent basis.

A recent case report from Japan describes a rare successful treatment of SEP in a cat.[12] In that particular case, clinical findings were somewhat similar to the ones described by the contributor, though the cat in conference was only 5 months old at the time of presentation vice being a mature adult as the cat in Japan was. As such, our case may reflect a primary idiopathic cause rather than a chronic inflammatory one. Notably, the cat from Japan also lacked ascites and was intestinally obstructed at the time of presentation. The treatment described for the Japanese cat included multiple surgical adhesiolyses along with tapering courses of prednisolone. During

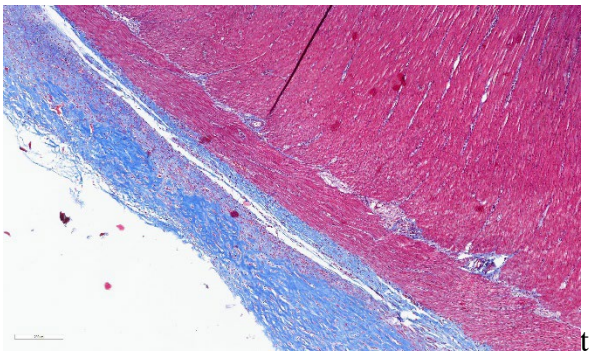 t

**Figure 4-7. Intestine cat. Higher magnification of the trichrome-stained fibrous connective tissue expanding the visceral peritoneum. (HE, 100X)**

surgery, placement of a hyaluronate-carboxymethylcellulose membrane around the intestine was intended to prevent recurrence of adhesions. The authors reported that the cat was symptom-free over 3 years after the second surgery. Possible factors that they considered included prevention of fibrin deposition both chemically (via anti-inflammatory doses of steroids) and physically through the use of a bioresorbable barrier.[12] From a general pathology perspective, this multipronged attempt to thwart conversion of fibrin to collagen by decreasing synthesis and avenues for cross-linking was successful in this case but may prove challenging in severe and/or advanced cases of SEP.

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