Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #14 **4 January 2023**

CASE I:

Signalment:
14 years old, female-neutered, domestic shorthair cat, feline, *Felis catus*

History:
The owner noted a 3 x 4 x 3 cm subcutaneous mass on the left ventral aspect of the mandible and cranial aspect of the neck. On clinical examination, an enlarged mandibular lymph node was diagnosed. The other palpable lymph nodes were normal in size and no other symptoms or lesions were detectable. Laboratory parameters were unremarkable. Serologic tests for FeLV and FIV were negative. The owner opted for surgical removement, and histopathologic examination was initiated.

The postoperative interval was initially unremarkable; there was no evidence of metastasis or recurrence. Three months after surgery, the animal developed deteriorated general condition, inappetence, and vomiting. Multiple cranial lymph nodes were moderately swollen. Radiologically, an intrathoracic mass associated with the trachea was detected, and both kidneys were enlarged. Progression of malignancy was feared. Brief palliative therapy with prednisolone and antibiotics for several days was given. Due to the deteriorating condition, the owner opted for euthanasia. At postmortem examination, multiple lymph nodes on the head and neck were similarly enlarged. A firm white mass 1 x 2 x 1 cm in diameter was noted on the intrathoracic aspect of the trachea. Both kidneys were enlarged and soft, and the cortex was diffusely pale white in color with some hemorrhages.

Histopathologically and immunohistochemically, the enlarged lymph nodes showed the same neoplastic cell population as in the initially removed lymph node, and both kidneys and the tracheal mass showed the same neoplastic infiltration.

Gross Pathology:
A 4.5 x 3.5 x 2 cm firm lymph node was processed, and the cut surfaces were homogeneously yellow-white in color.

Laboratory Results:
See table 1.1

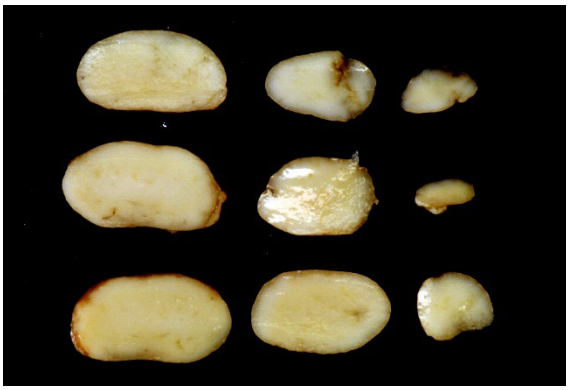

Figure 1-1. Lymph node, cat. The mandibular lymph node is large and there is diffuse loss of nodal architecture. (Photo courtesy of: Institut fuer Veterinaer-Pathologie, Justus-Liebig-Universitaet Giessen, Frankfurter Str. 96, 35392 Giessen, Germany http://www.uni-giessen.de/cms/fbz/fb10/institute_klinikum/institute/pathologie).

Marker	Normal cell type	T7562/21: multinucleated cells (H-RS cells)	T7562/21: monomorphic lymphatic cells (bystander cells)	Other findings
CD3 (polyclonal)	T cells	-	+++	Residual perifollicular cells/T cells ++
CD3 (monoclonal)	T cells	-	+++	Residual perifollicular cells/T cells ++
CD45R (B220)	Feline B cells	-	+	Residual cortical lymphoid follicles/B cells ++
CD20	B cells	-	-	No reactivity
Pax-5	B cells	-	-	Residual cortical lymphoid follicles/B cells ++
BLA.36	B cells	+++	+++	Residual cortical lymphoid follicles/B cells ++
IBA-1	Macrophages, monocytes, histiocytes	-	-	Single dendritic cells +
CD30	H-RS cells	+++	-	No reactivity
CD15	H-RS cells	-	-	No reactivity
Ki-67	Proliferating cells	+	++	30-50 positive nuclei/HPF (0.237 mm^2)

Table 1.1

- negative; + few positive cells; ++ more positive cells; +++abundant positive cells; H-RS cells: Hodgkin and Reed-Sternberg cells.

Microscopic Description:
Lymph node: A densely cellular, poorly demarcated, infiltrative, unencapsulated neoplasm composed of moderate numbers of neoplastic cells on a lymphocytic background and a preexisting fibrovascular stroma effaces the lymph node architecture and compresses the remaining follicles. The neoplastic cells are irregularly polygonal and up to 120 micrometer in diameter with distinct cell borders and abundant eosinophilic cytoplasm. The nuclei define two subtypes of neoplastic cells: Hodgkin cells are mononuclear with a single round to oval nucleus. Reed-Sternberg cells have at least two nuclear lobes or nuclei, but can have up to 5 irregular oval to polygonal (multilobulated) nuclei. The chromatin of both cell types is coarsely stippled to clumped, and the nucleoli are variably visible but often multiple. Rarely, the nucleoli are amphophilic and surrounded by a halo. Multifocally, single neoplastic cells have condensed cytoplasm and pyknotic nuclei ("mummified" Hodgkin cells). There is marked anisocytosis and anisokaryosis, and the mitotic count averages 5 mitoses in 10 high-power fields (2.37 mm^2). Often the mitoses are bizarre.

Contributor's Morphologic Diagnoses:
Mandibular lymph node: Hodgkin-like malignant lymphoma, cat, *Felis catus*

Contributor's Comment:
Lymphomas account for approximately 80% of all hematopoietic neoplasms in domestic animals, and both categorization and classification have been revised and changed several times in the past. Oncologists use different treatment strategies, and follow-up data are often limited.[8,9,10] In addition, diagnoses may vary between pathologists and/or hematopathologists. A still very useful first classification tool is tumor topography. In cats, more than 50% are alimentary forms, whereas in dogs multicentric forms predominate.[11]

The epidemiology of feline lymphomas has changed dramatically in the past due to the successful vaccination campaign against

FeLV.[9,10] Previously, approximately 30% of feline neoplasms were malignant lymphomas and 80% of these were associated with FeLV infection.

In animals, most lymphomas resemble human non-Hodgkin lymphomas, but in some species Hodgkin or Hodgkin-like lymphomas have also been described: for example, a well-characterized case in a ferret.[5]

In 1832, Thomas Hodgkin described a series of seven cases of lymph nodes with unusual changes, now known as Hodgkin lymphoma. In humans, the disease shows a bimodal age distribution with peaks in young adults and the elderly in developed countries. In developing countries, the first peak affects children. Often the disease is localized, with only a few cases being widespread. Overall, this type of lymphoma is considered moderately aggressive but curable in most cases. The typical neoplastic cells are CD30+, usually CD15+, negative for most B-cell markers, typically negative for T-cell markers, negative for immunoglobulin, negative for CD45, and negative for anaplastic lymphoma kinase (ALK). Pax5 is usually expressed by the neoplastic cells.[3]

In veterinary medicine, Hodgkin-like lymphoma appears to be a predominately feline entity manifestating in the upper respiratory and alimentary tract.[7,12] One report described an unusual manifestation of Hodgkin-like

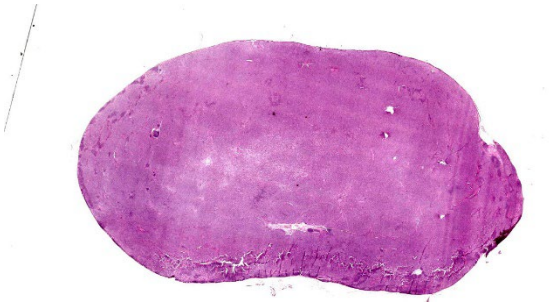

Figure 1-2. Lymph node, cat. There is diffuse loss of nodal architecture. (HE, 7X)

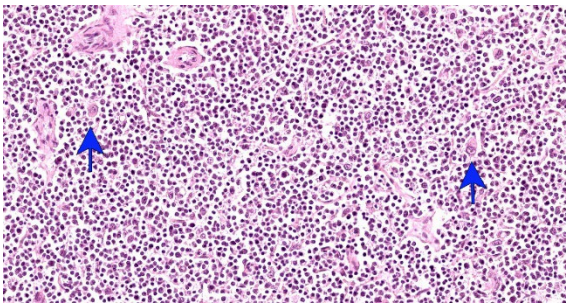

Figure 1-3. Lymph node, cat. Large neoplastic lymphocytes with prominent nucleoli are scattered throughout the section (arrows). (HE, 314X)

lymphoma in the cerebellum of a FeLV-infected cat.[13] Cytologically and histopathologically, the presence of scattered large mononucleated and binucleated to multinucleated cells (Hodgkin and Reed-Sternberg cells, HRS cells) should favor the diagnosis of Hodgkin-like lymphoma. However, immunohistochemistry is required for definitive diagnosis. Many cases appear to be misinterpreted as T-cell-rich B-cell lymphomas.[9,10]

There are some reports of problems with immunohistochemical staining of B cells in cats.[10] CD79-alpha staining, which is well reproducible in dogs, often showed variable results in our laboratory in cats (as did occasionally staining with CD20). Therefore, in the last two decades, the B-cell-specific variant of CD45R (B220) has been preferred by us, as well as by some other laboratories, for B cells in cats. Parallel staining with Pax5 showed reproducible results.[2]

Our case of feline Hodgkin-like lymphoma was well documented clinically, and follow-up examinations including necropsy was performed. Immunohistochemical results (see Table) supported our morphologic diagnosis. The malignant potential in this presented case was obvious.

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JPC Diagnosis:
Lymph node: Lymphoma, large cell, with Hodgkin-like features.

JPC Comment:
Hodgkin lymphoma typically presents as a single enlarged node, or enlargement of multiple contiguous nodes. In humans, these nodes are typically cervical, mediastinal, or para-aortic, and in cats, they are typically mandibular, cervical, or mediastinal.[5,7,12] The neoplasm is thought to arise from germinal or post-germinal center B cells. In humans, neoplastic cells commonly contain increased NF- κB activity, either due to infection by Epstein Barr virus (human herpesvirus 4) or decreased activity of NF-κB suppressors such as IκB.[5] Neoplastic cells produce various cytokines and chemokines which cause influx of a mixed population of leukocytes (lymphocytes, granulocytes, and macrophages); thus neoplastic cells, which are typically giant with abnormal nuclei, account for less than 5% of the cell population within the tumor.[5,12]

The classic neoplastic cell in Hodgkin lymphoma is the Reed-Sternberg cell, as the contributor describes. These cells are up to 45 um in diameter and contain bi-lobed nuclei with large nucleoli up to 7 um in diameter, giving the cell an "owl eye" appearance.[5,12] Mononuclear, multi-nucleated, and lacunar variants of Reed-Sternberg cells also occur. In lacunar variants, the nuclei are folded and surrounded by cytoplasmic clearing due to processing artifact. Reed-Sternberg cells are the predominant neoplastic cell type in classic Hodgkin lymphomas, which can be divided into at four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depletion.[5] These subtypes have similar IHC staining characteristics, but distinct histologic and clinical features.[5]

Another neoplastic cell type, the lymphohistiocytic variant (L&H cell), is seen in a distinct subtype, the nodular lymphocyte-predominance Hodgkin lymphoma. These cells are also known as "popcorn" cells because of

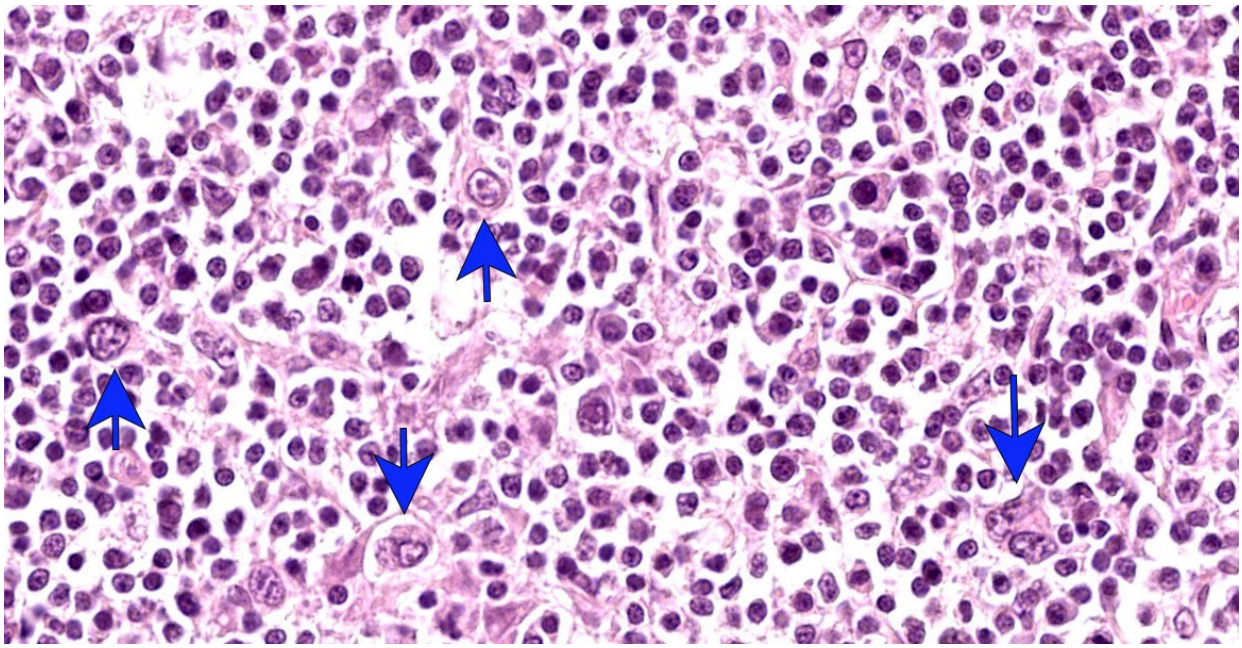

Figure 1-4. Lymph node, cat. Higher magnification of neoplastic cells with large pleomorphic nuclei. (arrows). (HE,750X)

their unique appearance: vesicular, polypoid nuclei with fine chromatin and indistinct nucleoli bear some resemblance to popped popcorn. L&H cells have distinct IHC staining pattern and are generally negative for both CD15 and CD30 and positive for CD20, CD45, and CD79.[5,7]

A report of 20 cases of Hodgkin-like lymphoma in cats provides some insight into this neoplasm, which is uncommon in cats and rare in other veterinary species.[12,14] Unilateral mandibular or cervical lymph node swelling was observed in 18 of 20 cats.[12] Eleven of the cats had classic forms, with nine classified as mixed cellularity and two classified as the nodular sclerosis substype.[12] Nine cats had the lymphocyte-predmoninant Hodgkin lymphoma, with L&H cells predominately surrounded by non-neoplastic small lymphocytes.[12] This study suggested that, as in humans, Hodgkin-like lymphoma is less aggressive than non-Hodgkin lymphoma in cats; however, additional data is needed for statistically significant correlation.[12]

Cases for this week's conference were selected to highlight human-animal correlates in medicine. This week's moderator, Dr. Sarah Cudd, discussed the clinical, pathologic, and historical aspects of the disease in humans. Human MD pathologists at the Joint Pathology center were also consulted on this case, and they favored a diagnosis of malignant B cell lymphoma with Hodgkin-like features, though T-cell/histiocyte-rich large B cell lymphoma could not be ruled out.

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CASE II:

Signalment:
Rabbit – Lionhead *Oryctolagus cuniculus*; Male neutered, 4.4 years old

History:
Two week history of progressive hyperkeratosis/skin crusting/alopecia. Skin scraping negative for mites. The rabbit clinically had severe otitis externa/media, bilateral corneal ulcers, dyspnea, hypothermia, early GI stasis, severe left sided dental disease, suspected tear duct obstruction, severe pododermatitis, severe urine scalding. Euthanized and submitted for postmortem evaluation.

Figure 2-1. Haired skin, rabbit. There is marked hyperkeratosis and crusting of the skin of the neck, face, and periocular areas. (Photo courtesy of: Dept. of Pathobiology, Ontario Veterinary College, University of Guelph, Guelph Ontario, Canada)

Figure 2-2. Haired skin, rabbit. There is marked hyperkeratosis and crusting of the skin of the perioral area. (Photo courtesy of: Dept. of Pathobiology, Ontario Veterinary College, University of Guelph, Guelph Ontario, Canada)

Gross Pathology:
Submitted is the body of a 2.1 kg, white, male neutered Lionhead rabbit. He is in good body condition with ample subcutaneous fat and symmetrical muscling. There is scaling of the skin over the majority of the body surface, most pronounced on the hocks, the dorsal antebrachia, the dorsal surface of the neck and base of the ears extending over the lateral neck on both sides and ventrally to the level of the sternum. Occasionally, there is hair loss associated with this scaling over the antebrachia and the dorsal and lateral neck. There is marked scaling of the skin around the mouth as well as surrounding the eyes with thick accumulations of dry, yellow to brown crusts in these areas. These areas are also alopecic. There is extensive fecal staining of the perianal area and hindlimbs with alopecia of the medial surface of both proximal hindlimbs. Both eyes have an

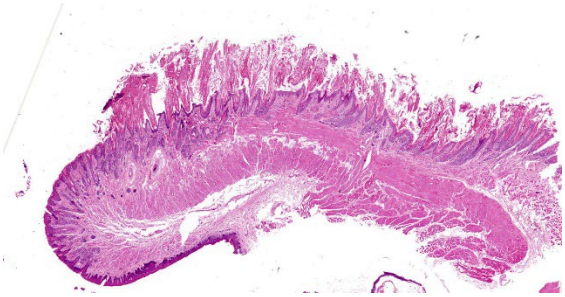

Figure 2-3. Haired skin, rabbit. A section of mucocutaneous junction is submitted for examination. There is a thick 2mm layer of scale over the epidermis. (HE, 10X)

approximately 2.0 mm white opacity centrally on the corneal surface.

There is approximately 2 mL of serosanguineous fluid within the thoracic cavity which contains rare soft, yellow to clear, irregular serous clots. The lungs appear diffusely, mildly atelectatic. The cranial mediastinum is expanded by a dark red to tan, irregular, soft mass measuring approximately 4 cm by 3 cm by 2 cm which displaces the heart caudally and the lungs caudodorsally. This mass is adherent to the ventral thoracic wall and the cranial surface of the pericardial sac. The mass is immediately adjacent to the aorta and cranial vena cava which run over the surface of the mass but are not incorporated into it. On cut section the mass is mottled dark red to tan with multiple cystic spaces containing approximately 1 mL of serosanguineous fluid. There is approximately 1 mL of serosanguineous fluid in the pericardial sac, but the inner surface is intact and there is no association between the mediastinal mass and the heart. The heart appears subjectively enlarged, occupying approximately one quarter of the thoracic cavity. There is subjective dilation of both ventricles but the left: right ventricular ratio is within normal limits. There is an enhanced zonal pattern in the liver which appears diffusely mottled yellow and red. This pattern continues throughout the parenchyma on cut section. The right renal pelvis contains a small amount of red material (rule out hemorrhage vs artifact). The bladder contains a moderate amount of slightly turbid yellow urine. It can be expressed with minimal digital pressure. There are sharp spurs on the lingual aspects of the mandibular cheek teeth and on the buccal aspects of the maxillary cheek teeth, slightly more severe on the left side. There is mild stenosis of the vertical canal of both ears due to thickening and scaling of the skin. There are plugs of white to tan soft exudate within both vertical canals. The tympanic bulla, middle ear, and inner ear appear grossly unremarkable. The nasal sinuses appear grossly unremarkable.

Laboratory Results:
No laboratory results reported.

Microscopic Description:
Individual spinous keratinocytes and basal cells are hypereosinophilic with pyknotic nuclei (cell death) and in some locations there are individual lymphocytes present within the epidermis adjacent to necrotic basal epithelial cells. The epidermis is variably acanthotic (up to 8 cells thick). There is marked, dense compact to basket weave orthokeratotic hyperkeratosis. Occasional nuclei are retained in the some of these keratin layers (parakeratosis). In some sections, there are occasional areas of erosion and thinning of the epidermis with rare areas of complete ulceration extending into the deeper dermis with exposure of the follicular epithelium. These ulcerated areas are covered by an up to 0.7 mm thick serocellular crust with degenerate neutrophils and keratin squames with admixed bacteria.

Lymphocytes are also present within the follicular epithelium (mural folliculitis) and follicles are decreased in size and number and are variably spaced (atrophy/loss). No sebaceous glands are visible in any section.

The superficial dermis has a band of lymphocytes with fewer plasma cells and there is edema of the superficial dermis.

PAS stain: There are rare intracorneal vesicles which contain a pale eosinophilic proteinaceous fluid. No fungal or parasitic organisms are seen in section.

Contributor's Morphologic Diagnoses:
Generalized transepidermal cytotoxic/interface dermatitis, with marked single cell death of epidermis and infundibulum of hair follicles, cell poor lymphocytic dermatitis and mural folliculitis, generalized follicular atrophy, absence of sebaceous glands and marked compact orthokeratotic hyperkeratosis.

Contributor's Comment:
Cytotoxic / interface dermatitis is one of the eight inflammatory reaction patterns in veterinary dermatopathology. It features death of keratinocytes in the epidermis. There are two main subtypes – basal cytotoxic / interface dermatitis (skin manifestation of systemic lupus erythematosus and cutaneous lupus erythematosus) and transepidermal cytoxic / interface dermatitis where all layers are potentially involved – the stratum basale, spinosum and or stratum granulosum. It is called cytotoxic because of death of keratinocytes and the interface terminology is when there is a band of lymphocytes and or plasma cells in the superficial dermis. The primary target of the cytotoxic / interface process is the keratinocyte. The various diseases and syndromes that have the panepidermal or transepidermal pattern of keratinocyte death are either ulcerative or hyperkeratotic. They are ulcerative when the cell death is rapid and severe, and hyperkeratotic (parakeratotic) when the number of dead cells is low.

Transepidermal cytotoxic / interface dermatitis in humans is seen in the syndromes and diseases Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis.[9]

In veterinary medicine, separation of different diseases and syndromes is based on clinical findings including extent of the lesions, location, and progression. Because the lesions are similar on histology, diagnosis of individual diseases should be done by clinicians (including dermatologists). Pathologists recognize the reaction pattern.

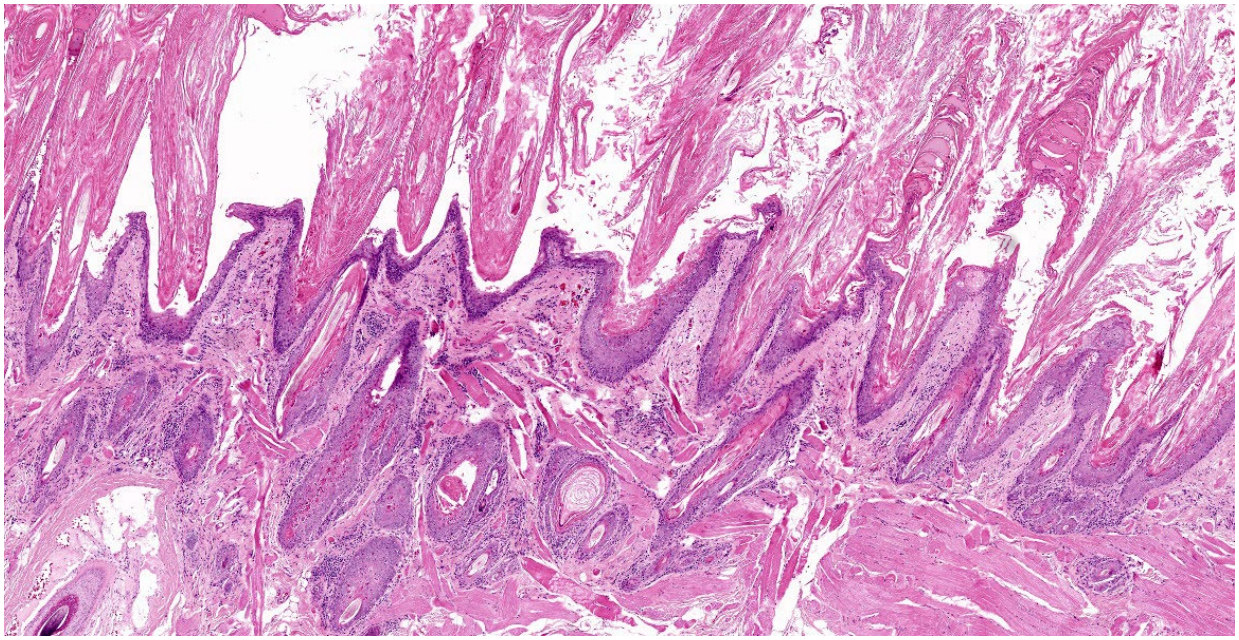

Figure 2-4. Haired skin, rabbit. There is papillary hyperplasia of the epidermis, with a thick layer of orthokeratotic hyperkeratosis. The proliferative and hyperkeratotic change extends into the follicular ostia. (HE, 40X)

This pattern of disease is considered immune-mediated. The trigger is not always identified. In animals, toxic epidermal necrolysis is more likely to be an adverse reaction to a drug; the death of cells is confluent.[9]

This rabbit has a clinically severe scaling or exfoliative dermatitis. The histologic pattern is a transepidermal cytotoxic pattern. The transepidermal pattern is well known in dogs where there are a variety of causes and disease syndromes.[9] This is rare in rabbits, who have a disease profile much like cats. In cats, the diseases are divided into thymoma-associated[7] and non-thymoma-associated exfoliative dermatitis.[4]

The mass in the cranial mediastinum of this rabbit was composed of a mixed population of neoplastic epithelial cells and normal small lymphocytes, thus it was a thymoma. In combination with the scaling dermatitis, the clinical presentation suggests paraneoplastic skin disease that is reported in thymoma in rabbits.[2,6] Overall, studies on exfoliative dermatitis in multiple species both as a paraneoplastic and idiopathic condition provided strong evidence that this is an immune mediated process. There is accumulating evidence that this condition is driven by autoreactive cytotoxic T-cells.

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JPC Diagnosis:
Mucocutaneous junction, lip: Keratinocyte apoptosis, multifocal, moderate, with lymphocytic satellitosis and marked hyperkeratosis.

JPC Comment:
This is the second example of an integumentary paraneoplastic syndrome reviewed this conference year. Case 2 of conference 4 featured paraneoplastic alopecia in a cat due to a carcinoma in the liver, and the contributor and conference comments provide a general review of paraneoplastic skin lesions in veterinary species. In addition to exfoliative dermatitis, thymomas have also been associated with other paraneoplastic syndromes such as

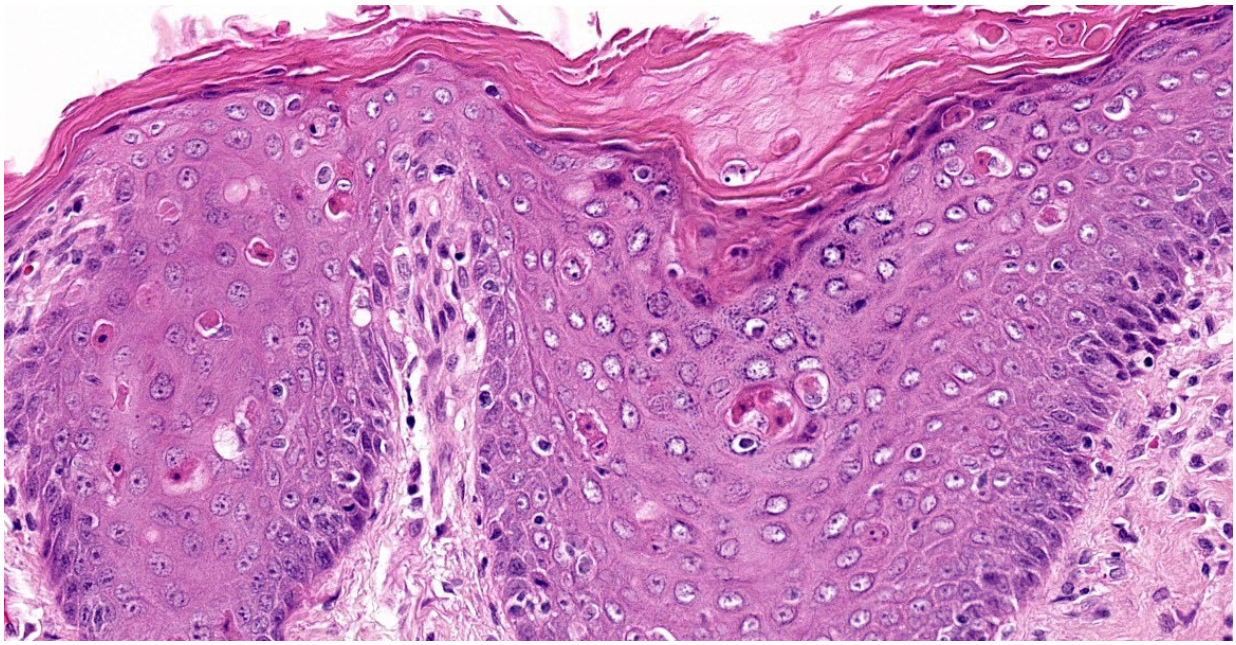

Figure 2-5. Haired skin, rabbit. There are numerous apoptotic keratinocytes within the hyperplastic epidermis. (HE, 381X)

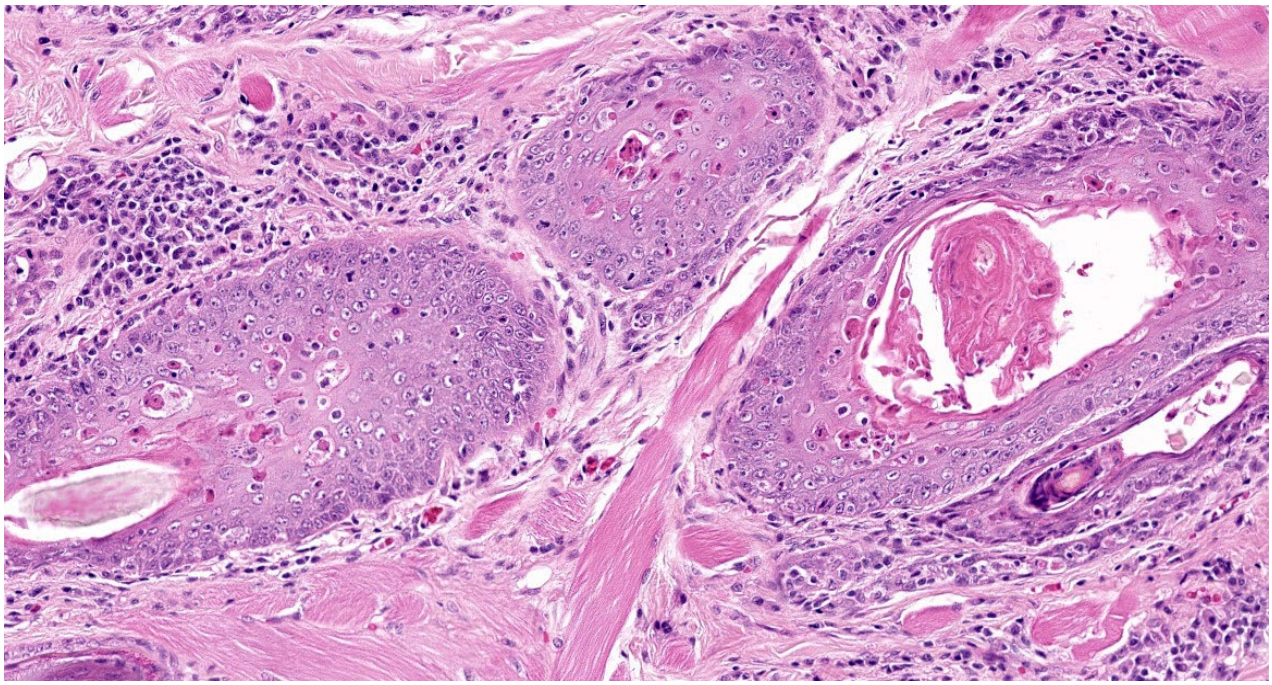

Figure 2-6. Haired skin, rabbit. Similar changes, including epidermal hyperplasia, hyperkeratosis, and keratinocyte apoptosis are present within follicles as well. (HE, 221X)

myasthenia gravis, polymyositis, and granulocytopenia.[1] Additionally, in dogs, thymomas may induce T-cell lymphocytosis, basophilia, or hypercalcemia of malignancy.[8] Exfoliative dermatitis has also recently been reported in a goat with a thymoma.[1]

Thymomas arise from the thymic epithelium and contain variable amounts of lymphocytes. A World Health Organization classification scheme places thymomas in two broad categories based on the histologic appearance of the epithelium. Type B thymomas, the most common type in dogs, have neoplastic cells which are epithelioid in appearance and are further subtyped based on the density of lymphocytes.[5] Type A thymomas have neoplastic cells which are spindloid in shape and accompanied by few lymphocytes.[5] In a study of domestic rabbits, out of 2,970 neoplasms, 48 were thymomas, and the most common subtype was type B1.[5]

In a separate study of thymomas in 13 rabbits, the average age at diagnosis was 6.1 years, and the most common clinical signs were dyspnea, exercise intolerance, and bilateral exophthalmos.[3] These signs were attributed to the mass's space occupying effect in the thorax, and exophthalmos is thought to arise from cranial vena cava syndrome due to decreased venous return to the heart. In some cases, the exophthalmos was transient or accompanied by third eyelid prolapse.[3]

Conference participants discussed two main differential diagnoses in this case: erythema multiforme and exfoliative dermatitis. Given the potentially identical histologic features of these two syndromes, participants could only confidently say exfoliative dermatitis once the clinical history was known. Participants also remarked on the lack of sebaceous glands, a common finding in thymoma-associated exfoliative dermatitis of cats.[7]

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CASE III:

Signalment:
11-month-old male neutered Rottweiler, *Canis lupus familiaris*, canid/domestic dog

History:
An 11-month-old neutered male Rottweiler dog was euthanized 21-days after routine castration under general anesthesia for severe generalized polymyopathy. The dog was reportedly clinically normal prior to the procedure. Ten days following anesthesia the dog presented recumbent, with severe generalized muscle weakness, azotemia, myoglobinuria, and a markedly increased serum creatinine kinase (CK) concentration of 806,080 U/L. With supportive care over the next two weeks the dog's strength and coordination returned, serum CK decreased to 980 U/L, azotemia improved, and myoglobinuria resolved. Twenty-one days post anesthesia/surgery, the dog again became acutely weak and lethargic and was humanely euthanized.

Gross Pathology:
Submitted is the body of a 30 kg brown and black male neutered Rottweiler with adequate fat stores and diffuse decreased symmetrical muscle mass most prominent of the epaxial and gluteal muscles. Mucous membranes are pale pink to white and tacky. There is mild tan/brown tartar on all canines, premolars, and molars. The ventral abdomen from the xiphoid process to the pubis, both antebrachia, the medial aspect of the left and

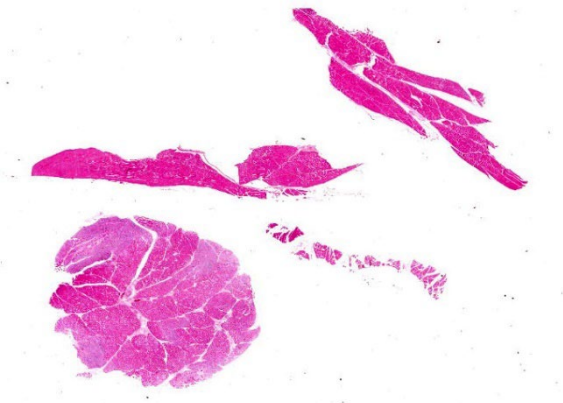

Figure 3-1. Skeletal muscle, dog. Longitudinal and transverse section of skeletal muscle are submitted for examination. (HE, 5X)

right metatarsus, the lateral aspect of the left and right tarsus, and the scrotum have been shaved. There is yellow Vetwrap wrapped circumferentially around the right tarsus. Autolysis is moderate.

External examination:
Paw pad, right forelimb: There is a 3.5 x 0.5-1.0 cm, slightly depressed, well-demarcated, loss of the epidermis with jagged margins that extend the width of the right metacarpal paw pad. The center is mottled tan and pink. There is a similar circular, 1 cm diameter, lesion of the right carpal paw pad. The center is red to brown with serous crusting.

Skin around neck: On either side of the neck there are 2 skin sores that are 4 x 1.5 cm (right-side), and 3.5 x 1 cm (left side). Both sores are well-demarcated with loss of haired skin and a slightly depressed, crusty, pink center. Within the shaved patch of hair on the left antebrachium there is a similar 2.5 x 2.5 cm sore. Scrotum: The skin of the scrotum is light pink. The scrotal incision is intact with little reaction.

Internal Examination:
Skeletal muscle: Throughout the entire body the skeletal muscles are subjectively soft and diffusely pale pink with thin to broad streaks of tan. Most severely affected muscles are within the hindlimbs, epaxial, and serratus muscles, with ~50% of these muscle bundles affected. There are a few small thin streaks of tan in bilateral temporalis muscles, affecting <5% of the tissue. There are a few (~5) tan foci (up to 1 cm in diameter) in bilateral masseter muscles, affecting <5% of the tissue. The diaphragm is diffusely pale and subjectively thickened up to 3 mm.

Heart: In the endocardium of the left atrium there are 4 adjacent raised exophytic nodules. Three of these nodules are small (up to 3 mm), tan to white, firm, with a smooth outer surface. The fourth nodule is larger, ovoid shaped, 8 x 5 mm, 4 mm raised, and red with speckles of tan. It is solid and red on cut section. Surrounding these nodules are multiple (~10) linear to focal, 1-3 mm, hard, raised plaques (suspect jet lesions). Just superior to the pulmonic valve and the aortic valve, there are approximately 2 x 1 cm area that contains multiple previously described hard plaques (suspect jet lesions). The free margins of the right and left atrioventricular valve leaflets are short, white, firm, and mildly thickened. The valve surface remains smooth and glistening.

Kidneys: The kidneys are mottled red/brown to green (suspect autolysis). The cortical surface of both kidneys contains multiple (~50 per kidney) up to 3 mm diameter depressions. On cut section the cortex contains alternating radiating streaks of red/brown and tan.

Spleen: In the capsule at the edge of the head of the spleen there is a dark purple to black 1.0 x 1.0 cm, well demarcated, irregular shaped, depression that is outlined by a 2 mm periphery of tan. This extends slightly into the parenchyma as a tan focus. At the head of the spleen, near the edge, there is also a 0.7 cm x 0.4 cm silver, shiny, plaque adhered to the capsule that does not extend into the parenchyma. Throughout the splenic parenchyma there are hundreds of white foci (0.5 mm to 2 mm in diameter) (suspect lymphoid follicles).

Lungs: The caudal lung lobes are heavy and exude a moderate amount of red-tinged fluid. Subcutaneous tissue: There is a moderate amount of thin light-yellow fluid within the subcutaneous tissues surrounding the hindlimbs.

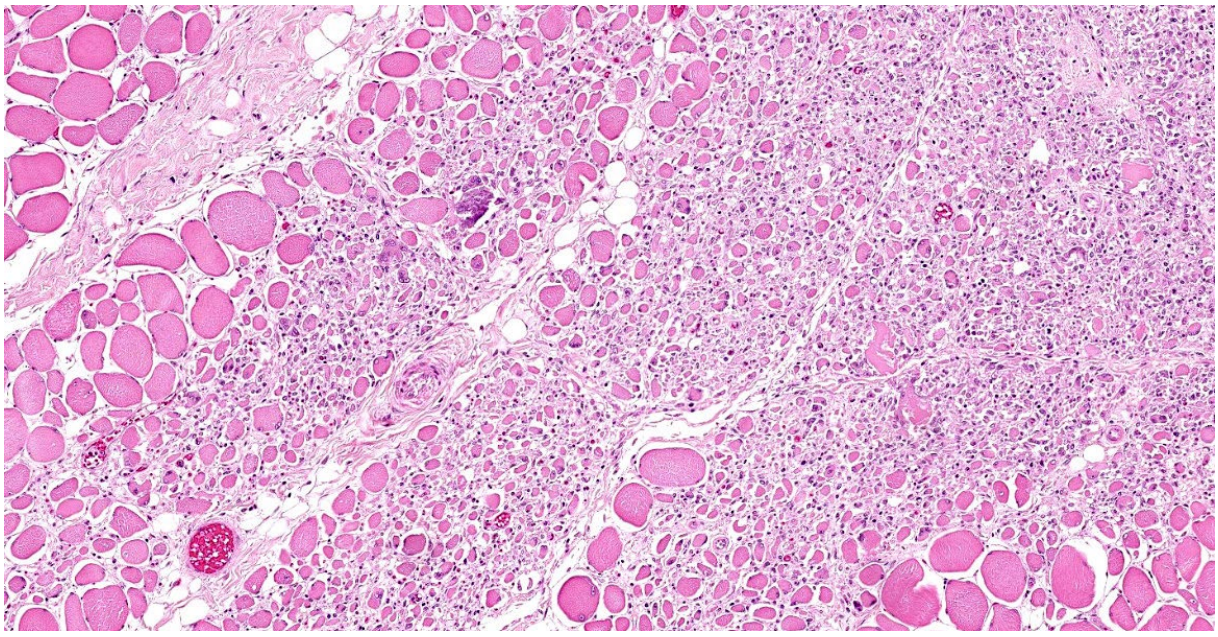

Figure 3-2. Skeletal muscle, dog. There are coalescing areas in which there is marked degenerative changes and atrophy of myofibers. (HE, 129X)

Laboratory Results:
Clinical Pathology:
Day of discharge

Urea 10.6 H mmol/L 3.5-9.0
ALT 317 H U/L 19-107
CK 980 H U/L 40-255
Amylase 1617 H U/L 299-947

Day of readmission before euthanasia Urea: 27.5 mmol/L
ALT 739 U/L
CK 806,080 U/L,
Amylase 1810 U/L

Comparative Neuromuscular Laboratory report:
Cryosection from the epaxial muscle and an archived control muscle were incubated with several polyclonal and monoclonal antibodies against dystrophy associated proteins including the rod and carboxy-terminus of dystrophin, utrophin, spectrin, laminin alpha2 (4F11), dysferlin (hamlet), alpha, beta and delta -sarcoglycans, beta-dystroglycan, caveolin 3, developmental myosin heavy chain (dMHC), MHC-I, collagen VI, emerin, the T cell markers CD3, CD4, and CD8, the B cell marker CD21 and the macrophage/dendritic cell marker CD11c. The staining intensity for rod-domain of dystrophin was normal in appearance. Moderately reduced staining intensity was present with the antibody against the carboxy-terminus of dystrophin and dystrophin associated proteins. Regenerating fibers were highlighted by dMHC staining. Utrophin staining was not increased. Antibody staining for laminin alpha2, dysferlin, caveolin3, collagen VI and emerin were normal in appearance. Several MHC-I and CD11c positive cells were present around necrotic fibers. Sporadic T cells (CD3+, CD4+ & CD8+) were observed. No CD21+ B cells were present. Spectrin2 staining was very weak suggesting partial tissue degradation."
Comment: This may be dystrophin deficient muscular dystrophy with normal staining for rod domain and weak staining for the carboxy terminus. … While I still favor a diagnosis of dystrophin deficient MD, and episode of severe rhabdomyolysis should be ruled out by the clinical history and progression."

Microscopic Description:

Skeletal muscle: All examined skeletal muscles have similar histologic features but vary in severity with up to 50% of myofibers affected. There are large groups of degenerating fibers at different stages of necrosis characterized by: single swollen hypereosinophilic fibers (hypercontraction) with loss of cross-striations, vacuolated cytoplasm and groups of thin, angular fibers with large plump peripheral nuclei. In addition, the cytoplasm of multiple randomly distributed swollen myofibers is replaced by basophilic granular to crystalline matrix (mineral confirmed by Von kossa stain) affecting up to 20% of the affected myofibers in one section (left semimembranosus muscle was most severe). Occasionally there are aggregates of foamy macrophages replacing single myofibers and scattered within the endomysium. Within the large groups of degenerating myofibers there are also single degenerating myofibers characterized by small rounded myofibers with multiple central nuclei (multinucleate muscle giant cells).

Contributor's Morphologic Diagnoses:

Skeletal muscle (generalized): Myonecrosis, degeneration and regeneration, multifocal polyphasic, subacute, severe.

Contributor's Comment:

Differential diagnoses for non-inflammatory canine polymyopathies include, amongst others, congenital or inherited myopathies, rhabdomyolysis, and malignant hyperthermia. Due to the young age of this dog, its breed (Rottweiler), and the gross and histologic findings, an inherited myopathy such as muscular dystrophy was initially suspected.

The most prevalent type of muscular dystrophies are the X-linked dystrophies. Of these, Duchenne's muscular dystrophy (DMD) is the most common followed by Becker muscular dystrophy (BMD. Both dystrophies are caused by a recessive mutation of the large dystrophin gene on the short branch of the X-chromosome encoding the dystrophin protein. Dystrophin is an important protein in stabilization of the myofiber during contraction. Complete loss of dystrophin, as in DMD, or partial loss of dystrophin, as in

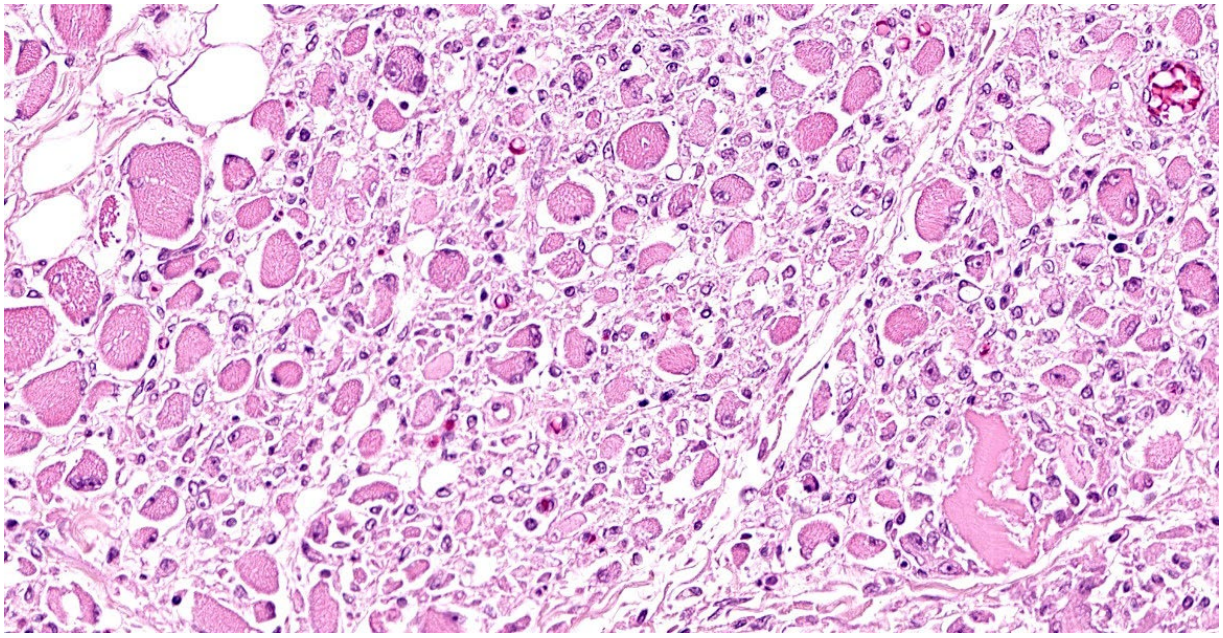

Figure 3-3. Skeletal muscle, dog. Within affected areas, there is marked atrophy of muscle fibers, and fibers display variable signs of degeneration, including loss of cross-striations and vacuolization. Regenerative changes include hypertrophy and internalization of satellite nuclei. A swollen, fragmented necrotic myofiber is at bottom right (arrow). The endomysium is mildly expanded by collagen and fibroblasts. (HE, 349X)

BMD, makes myofibers particularly susceptible to damage. Damaged myofibers leak the muscle-specific enzyme CK which correlates with the often chronically elevated serum CK seen in these cases. Both myofiber necrosis and regeneration within the same muscle is characteristic of the histologic appearance, as a result of repetitive damage.

Canine X-linked muscular dystrophy, specifically DMD, was first described in the Golden retriever in the early 1980s and has since been reported in multiple dog breeds including the Rottweiler. One case of muscular dystrophy resembling BMD in humans was described in a Labrador retriever. In addition, a unique form of muscular dystrophy exists in Rottweilers known as juvenile-onset distal myopathy. This condition has been identified in young dogs with signs of muscle weakness since birth and characterized by skeletal muscle lesions of predominantly the distal limbs. Two dogs in this study had normal immunoreactivity for the dystrophin protein.

Juvenile-onset distal myopathy likely has a different pathogenesis from DMD, and a metabolic defect may play a role. In addition, an inherited non-dystrophin myopathy, known as X-linked myotubular myopathy has also been reported in young Rottweilers, caused by a missense mutation in the MTM1 gene. This inherited condition is characterized by myofibers with central nuclei. Myonecrosis is not a feature.

In this case a diagnosis of muscular dystrophy is supported by the dog's age, breed, gross and histologic findings. However, a defect of the dog's dystrophin protein was not identified by immunohistochemistry and the dog's clinical history is not consistent with past reports of canine muscular dystrophy. Prior to anesthesia/surgery, this dog was reportedly clinically normal with no evidence of muscle weakness.

In addition to muscular dystrophies, a diagnosis of rhabdomyolysis was also considered. Rhabdomyolysis is a condition of acute skeletal muscle necrosis. In dogs it is often associated with painful muscles, limb weakness, markedly increased CK, and myoglobinuria.

Rhabdomyolysis is often attributed to overexertion or trauma but has also been associated with exposure to anesthetic agents, toxin exposure, and drug reaction/overdoses, amongst other things. In this case, a single episode of severe rhabdomyolysis after exposure to inhalant anesthesia is consistent with the myoglobinuria, acute kidney injury, and improved CK. However, rhabdomyolysis does not fit with the histologic findings of multifocal polyphasic myonecrosis and regeneration as rhabdomyolysis is typically characterized by a monophasic pattern of necrosis.

An episode of malignant hyperthermia was also considered. Malignant hyperthermia is an inherited disorder of skeletal muscle characterized by hypermetabolism and contracture and often occurs after exposure to anesthetic agents, exercise, or stress. In humans, pyrexia, hyperkalemia, hypercapnia, systemic acidosis, muscle rigidity, elevated CK levels, and often cardiac arrest are seen. Malignant hyperthermia occurs sporadically in dogs with similar clinical findings. As in humans, canine malignant hyperthermia develops as a result of a mutation of the RYR1 gene, causing uncontrolled calcium-release by skeletal muscles, excessive contraction, and subsequent heat production. Without immediate post-anesthetic bloodwork to support an episode of malignant hyperthermia, evidence of peri-anesthetic pyrexia or cardiac abnormalities, it is difficult to make this diagnosis.

Contributing Institution:

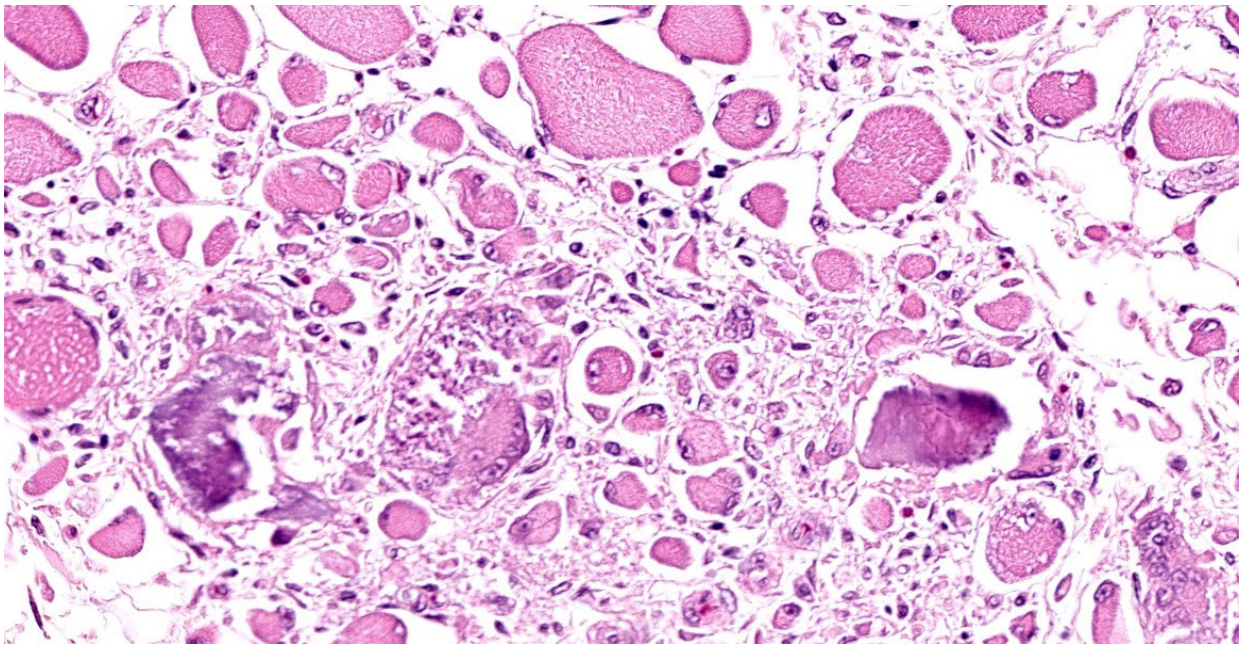

Figure 3-4. Skeletal muscle, dog. There is dystrophic mineralization of necrotic myofibers. (HE, 460X)

Department of Pathobiology, Ontario Veterinary College, University of Guelph https://ovc.uoguelph.ca/pathobiology/

JPC Diagnosis:
Skeletal muscle, myofibers: Degeneration, necrosis, regeneration and loss, polyphasic, multifocal, with mineralization.

JPC Comment:
The contributor provides good differentials for consideration in this case of polyphasic skeletal muscle necrosis. X-linked muscular dystrophy has been reported in the dog, cat, mouse, and pig.[1,2] The disease, which manifests in adolescents, is characterized by progressive muscle atrophy and weakness, though in the cat, mouse, and rat terrier, marked muscular hypertrophy may be seen.[2] Severely affected animals may die shortly after birth. Older animals may develop dyspnea due diaphragmatic fibrosis and contracture, esophageal dysfunction (and potential regurgitation), exercise intolerance, and a stiff gait. The disease also affects the cardiac muscle and in dogs progresses to degenerative cardiomyopathy. Macroglossia is an interesting feature documented in dogs, cats, humans, and, most recently, a pig. In a recent article, Aihara *et al* described macroglossia in a 6-month-old pig caused by Becker muscular dystrophy. The underlying genetic mutation was pseudoexon insertion in the dystrophin gene, and histologically, the skeletal muscle was replaced by abundant adipose and fibrosis, causing gross enlargement of the tongue (pseudohypertrophy).[1]

Cardiomyopathy is now the leading cause of death in young men with Duchenne's muscular dystrophy (DMD).[5] Gross and histologic lesions of the heart were described in a recent study of 26 dogs with golden retriever muscular dystrophy (GRMD), an animal model for DMD.[5] Gross lesions, seen in dogs over 10 months of age, included myocardial pallor and streaking in both ventricles, papillary muscle fibrosis or mineralization, and dilation of one or both ventricles.[5] Histologically, there was significant fatty infiltration and degeneration, most prominently within the subepicardium and also affecting papillary muscles, and lesion severity correlated positively with age.[5] Affected dogs also had arteriolar medial hypertrophy, and 11 of 26 had aortic

mineralization.[5] Acute coagulative myocardial necrosis was seen in many affected dogs.[5] There was no evidence of thrombosis in histologic sections, and semi-quantitative necrosis scores were correlated with the degree of arteriolar hypertrophy.[5] These findings led the authors to suspect that the necrosis was caused by dysregulation of vascular tone causing functional ischemia coupled with increased susceptibility of dystrophin-deficient cardiomyocytes to hypoxia.[5]

The effects of DMD on vascular smooth muscle was the subject of another recent research article, which evaluated dystrophin expression, nitric oxide synthetase (NOS) activity, and endothelial nitric oxide synthetase (eNOS) expression in large arteries of 16 DMD dogs compared to 15 unaffected dogs.[3] Unlike normal dogs, DMD dogs lacked dystrophin in smooth muscle and endothelial cells of the arteries and vena cava.[2] Additionally, DMD had significantly lower endothelial NOS activity and eNOS expression compared to normal dogs.[3] This is attributed to the fact that dystrophin is used to anchor NOS to the sarcolemma; in cells lacking dystrophin, NOS is delocalized and less effective.[3] Affected arteries had both decreased vasoconstriction and decreased vasodilation in response to endogenous signals, and the arteries were also smaller with decreased wall thickness attributed to tunica media atrophy.[3] This conflicts with the findings of Schneider *et al,* in which arteriolar hypertrophy was seen; however, the type of vessel analyzed differed between the two studies (cardiac arteriole versus femoral artery), and both studies agreed that vascular defects may play a role in DMD pathogenesis.[3,5]

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CASE IV:

Signalment:
An adult, male castrated, Golden Retriever, *Canis lupus familiaris*, dog.

History:
The dog presented with reluctance to move and severe pain localized in the cervical spine. Proprioception was decreased in all four legs. MRI showed lytic changes in C2, C7 and T2 vertebral bodies with extension to adjacent musculature and compression of corresponding spinal cord segments. A neoplastic process was suspected and the dog was euthanized due to poor prognosis.

Gross Pathology:
Extending from C2 to T2, the bone marrow of the vertebral bodies, and less frequently the lamina and transverse processes, was gelatinous, dark red to grey-tan and porous with complete effacement of the trabecular bone. Frequently, the process destroyed the cortical bone infiltrating the epaxial and hypaxial muscles and/or protruding into the spinal canal compressing the spinal cord and nerve roots.

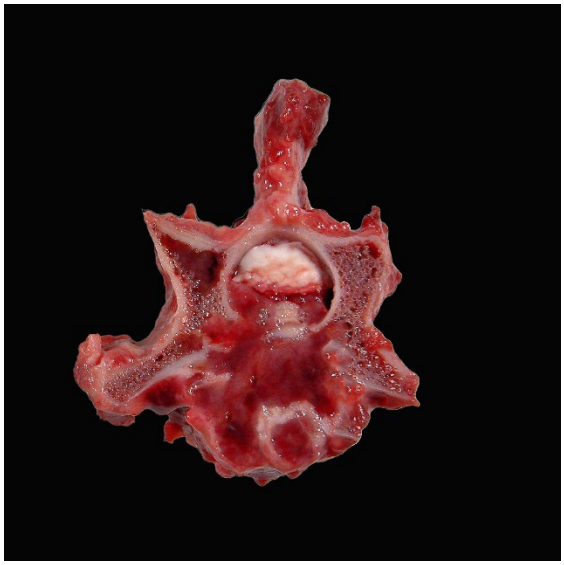

Figure 4-1. 7th cranial vertebra, dog. The bone marrow of the vertebral body, and less affecting the lamina and transverse processes, is multifocally gelatinous, dark red to grey-tan and effacing the adjacent trabecular and cortical bone. The tumor mass is protruding into the spinal canal and compressing the spinal cord. (Photo courtesy of: Department of Veterinary Biosciences, Faculty of Veterinary Medicine, University of Helsinki, https://www.helsinki.fi/en/faculty-veterinary-medicine/research/veterinary-biosciences)

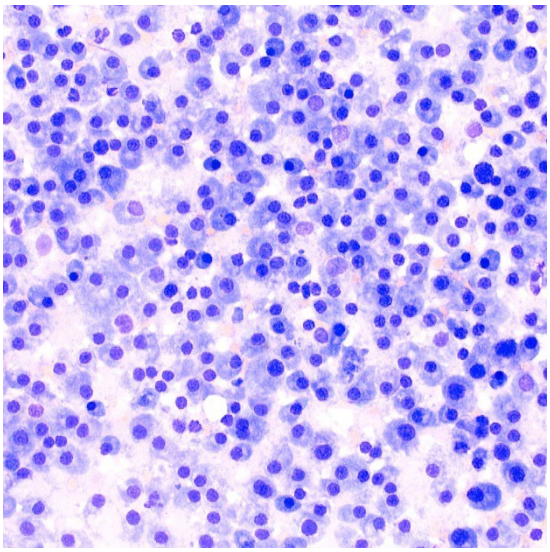

Figure 4-2. Bone marrow (T2 vertebra), dog. Cytologic smear consisting primarily of neoplastic plasma cells with moderate amounts of basophilic cytoplasm, round eccentric nuclei and perinuclear white halo. Neoplastic plasma cells show mild to moderate anisokaryosis and anisocytosis and are occasionally binucleated. (Photo courtesy of: Department of Veterinary Biosciences, Faculty of Veterinary Medicine, University of Helsinki, https://www.helsinki.fi/en/faculty-veterinary-medicine/research/veterinary-biosciences)

Laboratory Results:
Complete blood count revealed mild anemia and serum biochemistry was unremarkable.

Cytologic smear from affected bone marrow of T2: The cytologic smear consists primarily of round cells (neoplastic plasma cells) with moderate amounts of basophilic cytoplasm, round eccentric nuclei and perinuclear white halo. Neoplastic plasma cells show mild to moderate anisokaryosis and anisocytosis and are occasionally binucleated. Mitoses are rare.

Microscopic Description:
Vertebra (T2) and corresponding spinal canal and spinal cord:
Up to 70% of the medullary cavity is effaced by an unencapsulated, poorly demarcated, infiltrative and densely cellular neoplastic process composed of round cells arranged in sheets laying on small amounts of pre-existing fibrovascular stroma. Neoplastic cells have distinct cell borders, moderate amounts of eosinophilic cytoplasm with occasional perinuclear white halo, round to oval, hyperchromatic, eccentric nuclei with up to one basophilic nucleolus. Some cells show large intracytoplasmic pale eosinophilic, homogenous vacuoles pushing the nucleus to the periphery and there are occasional binucleated cells. Mitoses are up to 2 per HPF. Anisocytosis and anisokaryosis are mild to moderate. Necrotic foci composed of eosinophilic cellular debris and karyorrhectic/pyknotic nuclei are observed multifocally. Up to 60 % of trabecular and cortical bone are lytic and/or necrotic and replaced by dense sheets of neoplastic cells and hemorrhages.

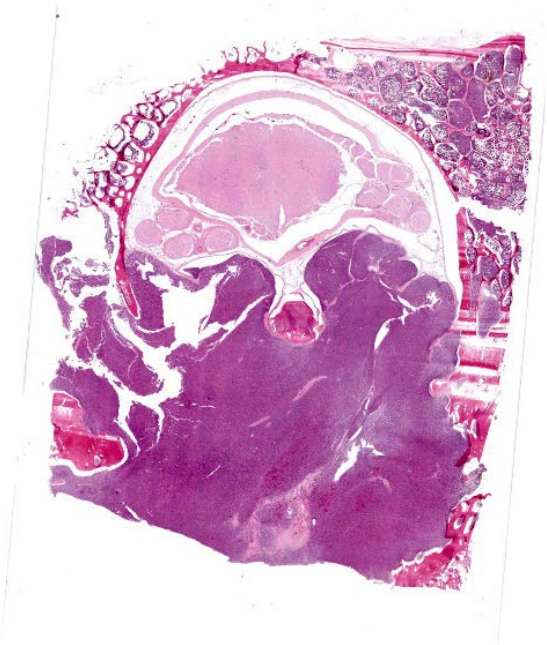

Figure 4-3. 7th cranial vertebra, dog. A multilobular round cell neoplasm has effaced the ventral vertebral body and infiltrated into the spinal canal. (HE, 3X)

Spinal cord (T2): Multifocally, affecting the white matter of the lateral and ventral funiculi, small numbers of axons show evidence of axonal degeneration characterized by dilated myelin sheaths containing glassy, eosinophilic, swollen axons (spheroids) accompanied by increased numbers of activated astrocytes with enlarged, vesicular nucleus (astrocytosis), few astrocytes with large amounts of eosinophilic cytoplasm and large vesicular nucleus (gemistocytes) and activated microglia.

Contributor's Morphologic Diagnoses:
Vertebra (T2): Multiple myeloma with osteolysis and infiltration towards the spinal canal
Spinal cord, T2, white matter: axonal degeneration (ventrolateral funiculi), multifocal, mild, with dilated myelin sheaths and spheroids

Contributor's Comment:
This case represents a classic case of multiple myeloma (MM) affecting the cervical and thoracic vertebrae with multicentric osteolysis and extension towards the spinal canal. MM is a malignant tumor originating from clonal proliferation of plasma cells within the bone marrow. In domestic animals, MM is most commonly reported in dogs, less frequently in cats and occasionally in horses. In dogs, it accounts for approximately 0,5 % of all malignant tumors.[2,11] It is usually diagnosed in middle-aged to old dogs and rarely affects young individuals.[2,11,12] The predilection sites include the vertebrae, ribs, femur, humerus and pelvis, all of which have active hematopoiesis.[2,10,11] The clinical signs are unspecific unless there is tumor-associated bone fracture and spinal cord or nerve roots compression. Generally, affected dogs present with lethargy, weight loss, anorexia, vomiting and fever.[7]

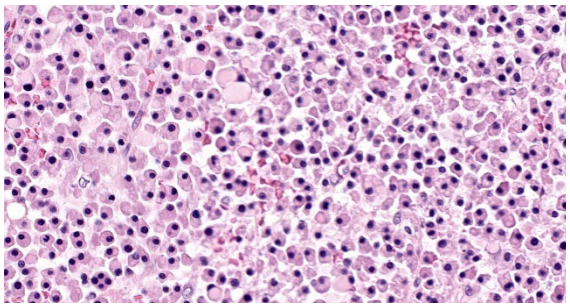

Figure 4-4. 7th cranial vertebra, dog. The neoplasms is composed of sheets of plasma cells. The perivascular hoff that characterizes this cell type occupies almost the entire cytoplasm in some cells. (HE, 589X)

The diagnosis of MM in dogs follows the criteria used for human MM, which is based on detecting ≥2 features including 1) bone marrow with >5 % or >20% of neoplastic plasma cells, 2) lytic bone lesions, 3) presence of clonal immune-globulin paraproteins in the serum (monoclonal gammopathy) and 4) presence of free light-chain immunoglobulins (fLC) in urine (Bence-Jones proteinuria).[5,7,12] Additional clinical findings can include anemia, hyperviscosity syndrome, bleeding disorders and hypercalcemia.[11] Increased numbers of plasma cells in the bone marrow can be also a feature of infectious diseases including ehrlichiosis and leishmaniasis, which should be taken into consideration if other features of MM are not evidenced.[11]

Gross findings in the affected bone are characterized by discrete, irregular, soft to gelatinous, pink-grey foci of tumor tissue replacing trabecular and cortical bone. Secondary pathological fractures may be evidenced.[2,11]

Histologically MM is characterized by dense colonies of well differentiated, monoclonal plasma cells or large, anaplastic plasma cells with high mitotic index, which replace normal hematopoietic and adipose tissue. Multiple myeloma oncogene 1/interferon regulatory factor 4 (MUM1/IRF-4) immunohistochemistry can be used for confirmation of plasma cell tumors in dogs and cats but is often unnecessary due to distinctive histological features of MM.[2,11] Infiltration to the bone with osteolysis is a typical finding mediated by cytokines produced by neoplastic plasma cells leading to decreased numbers of osteoblasts, suppression of their activity and increased numbers of activated osteoclasts. The excess of osteoclastic activity will cause destruction of bone tissue.[1,11]

Metastasis to visceral organs is rarely reported in dogs with the spleen being the most common site. This feature differs from MM in cats, in which metastasis to abdominal organs including spleen, liver, and lymph nodes is frequently observed.[4,6,11] Overall, MM can be additionally accompanied by renal disease or amyloidosis, since light-chain immunoglobulins produced by the neoplastic plasma cells can be deposited in the glomerular membrane resulting in glomerulonephritis, or form amyloid to be deposited in the glomeruli, spleen or liver.[3,4,11] In this case, histological changes observed in the adjacent spinal cord including dilation of the myelin sheaths and spheroid formation are secondary to compression caused by the tumor mass protruding into the spinal canal.

Contributing Institution:
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Faculty of Veterinary Medicine
University of Helsinki

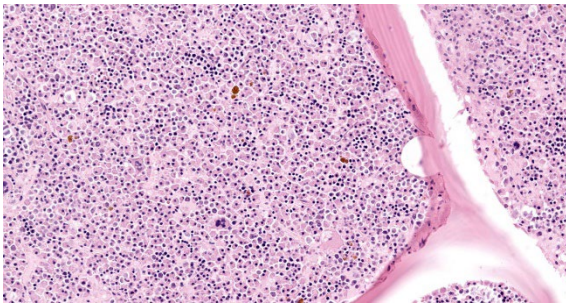

Figure 4-5. 7th cranial vertebra, dog. Neoplastic cells occupy bone marrow spaces in the affected vertebra. (HE, 222X)

https://www.helsinki.fi/en/faculty-veterinary-medicine/research/veterinary-biosciences

JPC Diagnosis:
Vertebra and spinal canal: Myeloma.

JPC Comment:
The contributor provides an excellent review of this classic condition seen in both human and veterinary medicine. All veterinarians and veterinary pathologists are familiar with the condition Bence Jones proteinuria and its neoplastic cause; fewer have knowledge of Dr. Henry Bence Jones and his initial characterization of the phenomenon which bears his name. Dr. Bence Jones was a British physician of the mid-19th century whose initial research focused on chemical chemistry, specifically the analysis of cysteine oxide stones and proteins. He later specialized in the composition of urine in health and disease. Thomas Alexander McBean was a patient afflicted by bone pain and peripheral edema (and who is now known to have suffered from multiple myeloma). His urine contained a protein that produced peculiar results when analyzed using standard laboratory testing at the time. The patient's attending physicians sent a sample to Dr. Bence Jones. After further testing, he dubbed the protein "hydrated deutoxide of albumin" and published the first reports on this unique urinary protein. Bence Jones proteins are now considered to be the first tumor marker discovered, and Dr. Bence Jones the first chemical pathologist.[8]

A recent report described a case of erythrophagocytic multiple myeloma, which is incredibly rare in dogs and cats and slightly more common in humans.[7] A 5 year old female spayed golden retriever dog presented for a severe nonregenerative anemia and thrombocytopenia, and abundant neoplastic plasma cells which occasionally exhibited erythrophagocytosis were observed in the spleen, liver, and bone marrow.[7] Anemia in the patient was likely due to erythrophagia; however, dogs with multiple myeloma commonly have anemia due to erythrocyte destruction in hyperviscosity syndrome, myelophthisis, blood loss, or anemia of chronic disease, so these may have also contributed to the anemia.[7] This week's moderator also explain that anemia is a common presenting complaint in human patients with multiple myeloma.

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