Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #12 7 December 2022

CASE I:

Signalment:
4 years-old, female, goat (*Capra hircus*), unspecified breed.

History:
The sample was submitted by a general practitioner and little information is available regarding the clinical history. This goat was pregnant and was one month away from parturition. Anorexia was reported.

Gross Pathology:
Kidneys are described by the practitioner as pale and swollen, with irregular white foci. Other reported findings are mesenteric lymph nodes with a caseous and mineralized content. Only kidneys were submitted for histopathological analysis.

Laboratory Results:
No findings reported.

Microscopic Description:
Almost all glomeruli are affected by one or more of the following changes:

- Variable thickening of the glomerular capsule with fibroblastic proliferation;
- Marked thickening of glomerular basement membrane with moderate increased in mesangial cellularity (membranoproliferative glomerulonephritis);
- Adhesions between the glomerular tufts and the capsule (glomerular synechiae);
- Extraglomerular proliferation of spindle cells admixed with fibrin around glomerular tufts, resembling glomerular crescents;
- Glomerular congestion and/or hemorrhages;
- Eosinophilic granular materiel (protein exudation) and/or hemorrhages within the urinary space;
- Shrunken and fibrotic glomeruli (global glomerulosclerosis).

These changes affect almost all glomeruli (diffuse changes) and usually the entire glomerular tuft (global changes).

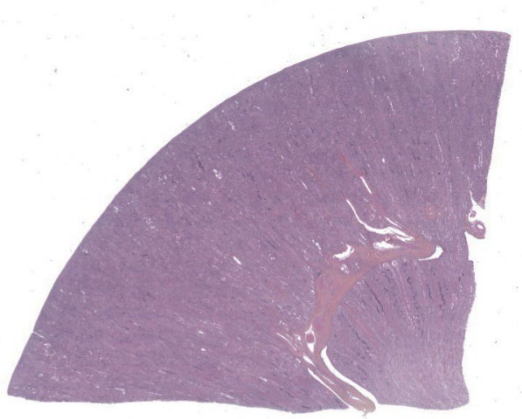

Figure 1-1. Kidney, goat. A single section of kidney is submitted for examination. Tubular dilation and luminal hypercellularity. (HE, 5X)

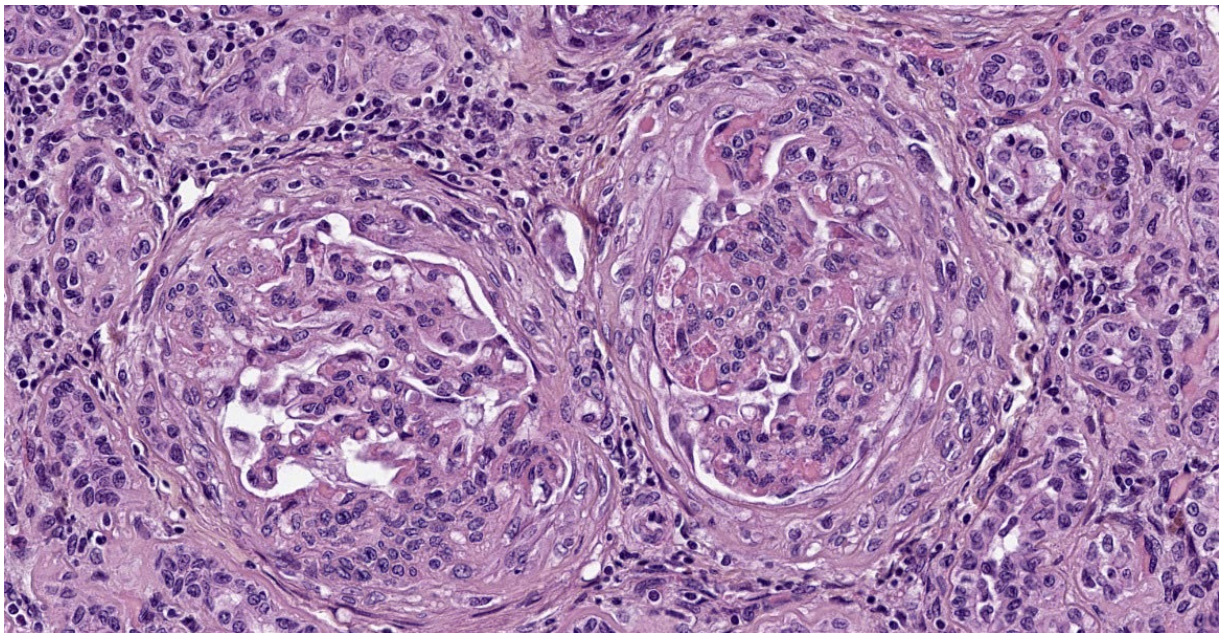

Figure 1-2. Kidney, goat. Glomeruli exhibit expansion of capillary walls and mesangium, mesangial hypercellularity, synechiation, crescent formation, and marked periglomerular fibrosis. The surrounding interstitium is expanded by fibrosis, tubules are mildly atrophic and there is interstitial lymphoplasmacytic inflammation. (HE, 364X)

Also affected are tubules showing a combination of changes: thickened basement membrane; epithelial atrophy; tubular dilation with eosinophilic protein casts, degenerate neutrophils and/or eosinophilic granular debris; mineralization of basement membranes, especially in the medulla; rare crystals (likely calcium oxalate crystals).

The interstitium is moderately expanded by fibrosis and/or infiltration by lymphocytes and plasma cells.

Contributor's Morphologic Diagnoses:
Glomerulonephritis, membranoproliferative, diffuse, global, marked, chronic, with global glomerulosclerosis, lymphoplasmacytic interstitial nephritis, tubular atrophy and tubular casts.

Contributor's Comment:
The case is interesting as it shows a constellation of renal elementary lesions. Glomerulonephritides can be defined as primary glomerular diseases with secondary tubulointerstitial and vascular changes.[2, 4] In this case, the proportion of affected glomeruli (more than 50%), the proportion of the glomerular tuft affected (entire glomerular tuft) and the type of glomerular change (thickening of glomerular basement membrane with mesangial proliferation) favor a diagnosis of diffuse, global, membranoproliferative glomerulonephritis[1]. An interesting feature is the presence of crescent-like structures around glomerular tufts that are reminiscent of crescentic glomerulonephritis in humans. Such crescents have been described in cases of glomerulonephritis in ruminants.[2, 3]

Among glomerular diseases, glomerulonephritis is frequent in veterinary medicine and are the subject of a rather complex nomenclature, based on human renal pathology that can be difficult to apply routinely to veterinary pathology cases especially when additional techniques (immunofluorescence, electron microscopy) are not available. The exact cause is generally unknown but immune-complex deposition secondary to infections is a likely cause in most cases. In ruminants, Maedi-Visna virus and Bovine Viral Diarrhea virus are suspected to initiate immune-mediated glomerulonephritis.[2]

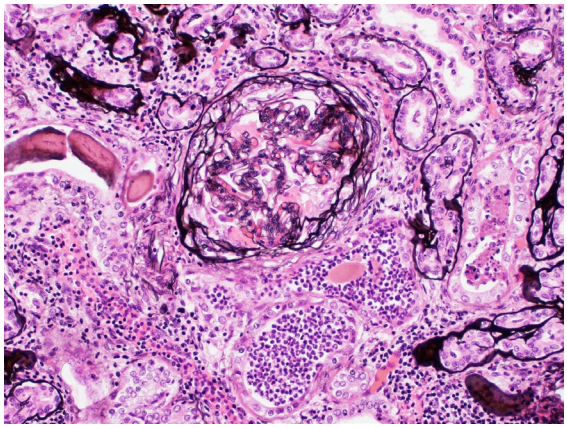

Figure 1-3. Kidney, goat. A periodic acid methenamine silver stain demonstrates the excessive amount of basement membrane within the mesangium, capillary walls and Bowman's capsule crescents. (PAMS, 400X)

Despite showing marked renal changes of glomeruli, tubules and interstitium, there was no clinical sign or gross lesion suggestive of renal failure in this animal. Clinically silent glomerulonephritis appears to be common in ruminants with the exception of the membranoproliferative glomerulonephritis of Finnish landrace sheep that is present at birth and caused by deficiency in complement component C3. Affected lambs die of renal failure around 1-3 months.[2]

Contributing Institution:

Ecole Nationale Vétérinaire d'Alfort
Unité d'Histologie et d'Anatomie Pathologique, BioPôle Alfort
Département des Sciences Biologiques et Pharmaceutiques
7 avenue du Général De Gaulle
94704 Maisons Alfort Cedex
FRANCE
www.vet-alfort.fr

JPC Diagnosis:

1. Kidney: Glomerulonephritis, membranoproliferative, chronic, diffuse, severe with crescent formation and periglomerular and interstitial fibrosis.
2. Kidney: Tubular degeneration and necrosis, multifocal, moderate with numerous tubular casts and intratubular crystals.

JPC Comment:

Immune complex deposition can cause different types of glomerular disease depending on where they are deposited. In general, deposition of immune complexes in the glomerulus leads to complement activation, membrane attack complex formation, mast cell degranulation, and leukocyte chemotaxis.[2] Activated monocytes and neutrophils cause secondary enzymatic and oxidative damage to podocytes, endothelial cells, and the mesangium.[2] Mesangial cells can also produce inflammatory mediators such as IL1 and arachidonic acid metabolites, initiating inflammation and cause self-induced proliferation.[2] The end result is an amplifying loop of inflammation and proliferation.[2]

As the contributor mentions, electron microscopy and/or immunofluorescence are necessary for confirming immune complex deposition and differentiating it from other conditions with similar histologic appearances. Special stains such as silver stains (i.e. Jones methenamine silver), PAS, and Masson's trichrome may be helpful for visualizing glomerular basement membrane changes.[1]

Deposition of immune complexes between podocytes and the glomerular basement

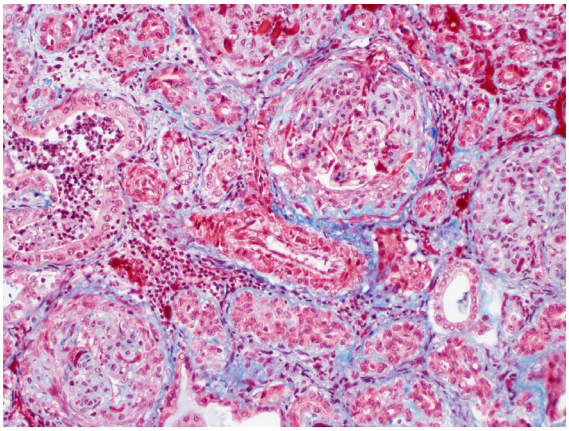

Figure 1-4. Kidney, goat. A Masson's trichrome demonstrates collagen within the glomerular mesangium, capillary walls, crescents, and the surrounding interstitium. (Masson's trichrome, 400X)

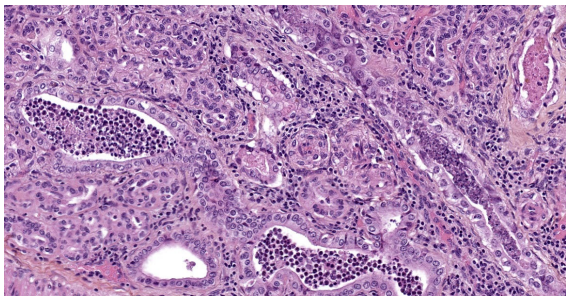

Figure 1-5. Kidney, goat. There is a variety of tubular changes in the midst of interstitial fibrosis and lymphoplasmacytic inflammation, to include ectasia, cellular and protein casts, tubular epithelial degeneration, and tubular atrophy with loss of visible lumina.

membrane leads to membranous glomerulonephropathy.[1] Changes are minimal early in the disease. Later in disease, glomerular basement membranes are thickened, and in advanced stages, there may be secondary glomerulosclerosis.[1] Remodeled glomerular basement membrane features spikes and holes which can be visualized with silver stains such as JMS.[1]

Immune complex deposition on the luminal surface of capillaries leads to membranoproliferative glomerulonephritis.[1] Subsequent endothelial hypertrophy, mesangial hypertrophy, and/or the presence of leukocytes which characteristic hypercellularity of the endocapillary and mesangial compartments.[1] Glomerular basement membranes may be thickened or duplicated, which JMS staining demonstrates in this case.[1] Secondary changes that may occur with membranoproliferative glomerulonephritis include glomerular synechiae and crescents, as seen in this case.[1]

Immune complex deposition within the mesangium leads to mesangioproliferative glomerulonephritis, and resulting hypercellularity is limited to the mesangium.[1]

While low levels of calcium oxalate crystals in the kidney may be an incidental finding in any species, the moderator, Dr. Alicia Moreau, and conference participants remarked about the prevalence of crystals within the section. Ruminants may ingest oxalates in plants such as halogeton, greasewood, rhubarb, and sorrel/dock, or as a mycotoxin in moldy feed.[5] In general, metabolism of oxalate in the rumen makes ruminants resistant to formation of oxalate calculi, but both low magnesium diet and low calcium diets can favor formation of oxalate urolithiasis.[5] Oxalate crystals form in renal vessels and tubules and can cause obstruction, trauma, and necrosis of tubular epithelium, which conference participants suspected in this case.[5] Proximal convoluted tubules are most susceptible to injury due to their high metabolic activity.[5]

References:

1. Cianciolo R, Brown C, Mohr C, et al. *Atlas of Renal Lesions in Proteinuric Dogs*. The Ohio State University; 2018.
2. Cianciolo RE, Mohr FC. Urinary System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol 2. 6th ed. Elsevier, 2017; 401-413, 456-457.
3. Ohnuki T. Crescentic glomerulonephritis induced in the goat by immunization with homologous or heterologous glomerular basement membrane antigen. *Acta Pathol Jpn*. 1975;25(3):319–331.
4. Slauson DO, Lewis RM. Comparative Pathology of Glomerulonephritis in Animals. *Vet Pathol*. 1979;16(2):135–164.
5. Sula M, Lane LV. The Urinary System. In: Zachary JF, ed. *Pathologic Basis of Veterinary Disease.* 7th ed. Elsevier, 2022; 721,734, 736

CASE II:

Signalment:
9-year-old, spayed female, Welsh Corgi dog (*Canis lupus familiaris*)

History:
The patient presented for lethargy, anorexia, and labored breathing with 2 days duration. On physical examination, the submandibular lymph nodes were enlarged and the lungs sounded harsh on auscultation. Radiographs were unremarkable. The patient's condition worsened and the patient passed away overnight.

Gross Pathology:
Necropsy was performed by the rDVM and multiple fixed tissue samples were submitted for diagnostic evaluation (necropsy-in-a-bottle). Gross findings were not provided.

Laboratory Results:
Results from a complete blood count, blood chemistry, and T4 on the day of presentation for clinical signs was provided by the rDVM. The following abnormalities were noted:

Analyte	Result	Reference Range	Units
WBC	14.4	4.0-15.5	10^3/uL
Neutrophils	12096 (high)	2060-10600	/uL
Monocytes	864 (high)	0-840	/uL
ALP	256 (high)	5-131	IU/L
BUN	187 (high)	6-31	mg/dL
Creatinine	11.4 (high)	0.5-1.6	mg/dL
Phosphorus	23.6 (high)	2.5-6.0	mg/dL
Glucose	65 (low)	70-138	mg/dL
Calcium	13.0 (high)	8.9-11.4	mg/dL
Corrected Ca	13.2		
Magnesium	3.3 (high)	1.5-2.5	mEq/L
Sodium	143	139-154	mEq/L
Potassium	7.2 (high)	3.6-5.5	mEq/L
Na/K ratio	20 (low)	27-38	
Amylase	1145 (high)	290-1125	IU/L
PrecisionPSL	364 (high)	24-140	U/L
T4	<0.5 (low)	0.8-3.5	ug/dL

Microscopic Description:
Kidney: The glomeruli are markedly, diffusely, and globally enlarged by pale, smudgy to amorphous, faintly fibrillar, extracellular eosinophilic material expanding the mesangial matrix and obliterating the glomerular tufts. Glomerular capillaries are compressed, and the glomerular architecture is obscured by the extracellular deposits. Bowman's capsule is occasionally and mildly thickened by similar material and rarely surrounded by a few concentric thin bands of eosinophilic fibrous connective tissue (fibrosis). Renal tubules are characterized by various changes, including: 1) lumina distended by clear space and lined by normal epithelium, 2) lumina containing granular debris and lined by markedly flattened (attenuated) epithelium mixed with a few angular and hypereosinophilic epithelial cells, 3) thinned tubules lined by plump epithelial cells with an open nucleus (regeneration), and 4) epithelial cells that are mildly vacuolated and contain numerous small eosinophilic protein droplets. The interstitium is multifocally infiltrated by small to modest numbers of lymphocytes and plasma cells. While less distinct and severe, the medullary interstitium is mildly expanded by similar eosinophilic material described in the glomeruli.

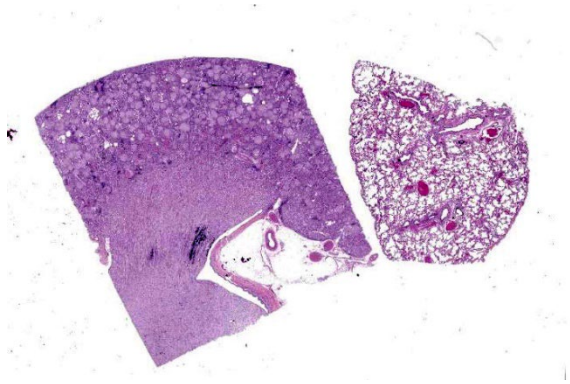

Figure 2-1. Kidney and lung, dog. A section of kidney and lung are submitted for examination. At this magnification, glomeruli and enlarged and hypocellular, and there is a focal area of mineralization within the medulla. There are no discernable lesions in the lung at this magnification. (HE 5X)

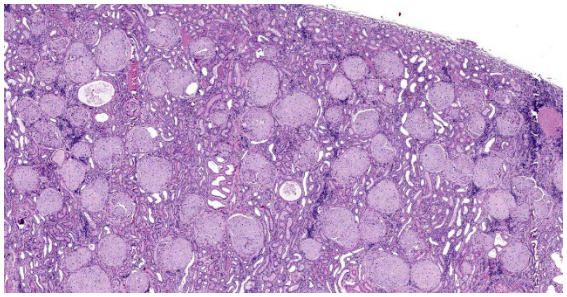

Figure 2-2. Kidney, dog. Glomeruli are markedly enlarged and hypocellular (HE, 33X)

Lung: Alveolar and parenchymal vessels are diffusely congested. The alveolar spaces are often mildly expanded by clear space and contain low numbers of extravasated erythrocytes and fine fibrillary material. In some areas, there is a very faint, thin blue and granular hue to the lining of the alveolar septa (mineralization).

Special staining of the kidney with Congo Red and the lung with von Kossa is performed. Within the kidney, the glomeruli are expanded by orange to red material that rarely exhibits apple-green birefringence under polarized light. The presence of Congophilic material expanding the glomeruli is consistent with amyloid. Within the lung, multifocally lining alveolar septa and partially lining small-caliber parenchymal vessels are thin linear bands of material that stain black, consistent with mineral.

Contributor's Morphologic Diagnoses:
Kidney: Severe glomerular amyloidosis with mild renal tubular degeneration and atrophy, and lymphoplasmacytic interstitial nephritis with fibrosis
Lung: Acute pulmonary congestion with alveolar mineralization and damage

Contributor's Comment:
Amyloidosis is a disease condition that results when amyloid, a proteinaceous material, is deposited intercellularly in a variety of tissues, including the kidneys.[3] Amyloid refers to a group of insoluble, fibrillary proteins with diverse origins but similar structures and properties. [10]

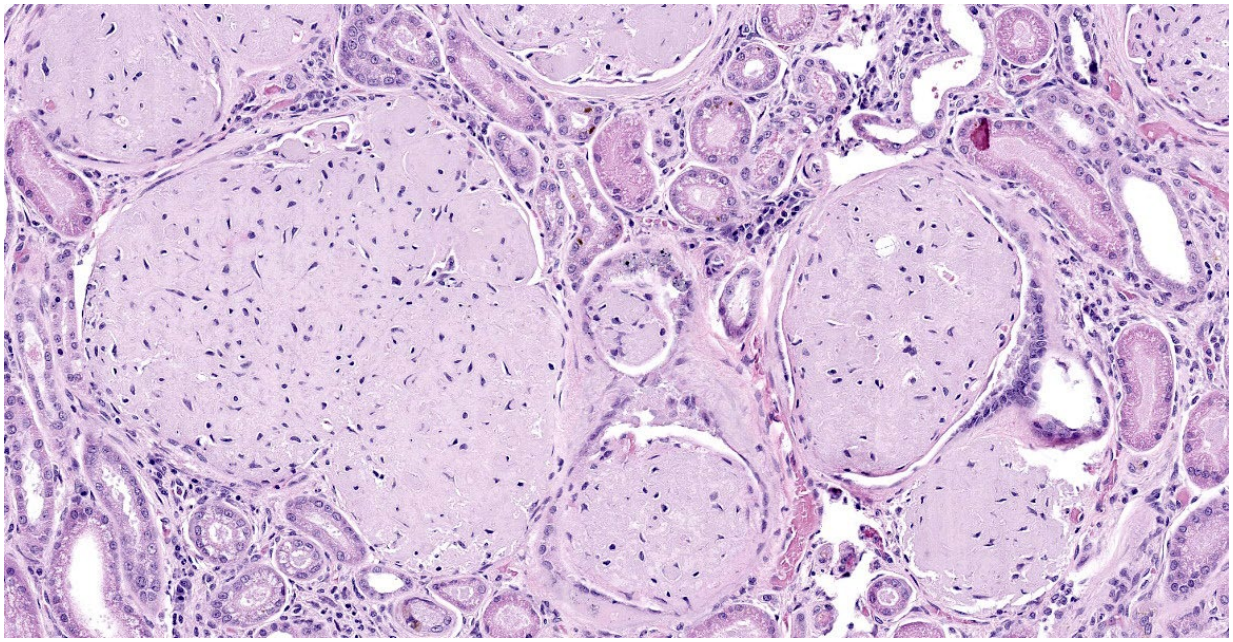

Figure 2-3. Kidney, dog. Higher magnification of glomeruli. Glomerular capillary loops and mesangium are markedly expanded by amyloid, effacing normal architecture. Parietal epithelium is markedly hypertrophic and Bowman's capsule. There is mild fibrosis of the cortical interstitium, tubular degeneration and atrophy, and small aggregates of lymphocytes and plasma cells in the interstitium. (HE, 33X)

Three of the most prominent forms of amyloidosis in animals include reactive, immunoglobulin-derived, and familial amyloidosis. The most common form of amyloidosis is reactive systemic amyloidosis, also called secondary amyloidosis. It results from AA-amyloid being derived from serum amyloid A (SAA), an acute-phase lipoprotein. AA-amyloidosis is often associated with chronic inflammatory disease, persistent infections, or neoplasia. Immunoglobulin-derived amyloidosis, also called primary amyloidosis, is the most common form in humans but less common in domestic animals. It involves AL-amyloid, which is derived from immunoglobulin light chains. [3,10] Familial amyloidosis is another form of amyloidosis that is most commonly seen in Shar Pei dogs and Abyssinian cats.[9]

Amyloidosis occurs when there is misfolding of the progenitor protein. [10] Amyloid proteins are arranged in a β-pleated sheet structure. This renders amyloid insoluble and resistant to proteolysis, allowing it to permanently accumulate in tissues.[7] In the case of AA-amyloidosis, increased SAA due to inflammation coupled with a defect in SAA degradation result in the accumulation of misfolded protein fibrils. [10] Amyloid damages tissues by causing pressure atrophy to adjacent cells. [3] The most common site of amyloid accumulation in dogs is the kidney where it usually affects glomeruli.[9] Amyloid is often also deposited in the liver, spleen, lymph nodes, and adrenal glands. [10]

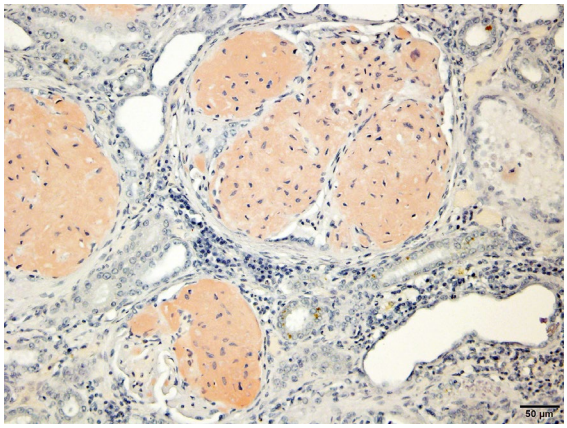

Figure 2-4. Kidney, dog. Glomerular amyloid demonstrates marked congophilia. (Unfortunately, the unstained sections submitted to JPC were too thin to demonstrate birefringence when stained with Congo Red.) (Congo Red, 200X) (Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

Gross changes associated with renal amyloidosis include mild renomegaly, pallor, and a waxy consistency. [3] Microscopically, amyloid is deposited extracellularly.[10] In the kidneys, these deposits are within the mesangial area of the glomerulus.[3] This results in expansion of the mesangium, compressing the adjacent capillary loop.[4] As amyloid accumulates, the glomeruli become enlarged and homogeneous in appearance.[3] In the case of familial amyloidosis in Shar Pei dogs, amyloid often accumulates in the renal medullary interstitium.[9] In order to differentiate amyloid from other extracellular deposits, Congo red stain is used. Congo red stains amyloid deposits orange to red with apple-green birefringence under polarized light.[10]

As renal amyloidosis is irreversible, it often leads to chronic kidney failure. In this case, the dog's serum biochemistry profile indicated severe azotemia, consistent with kidney disease. Additional biochemical findings in this case that are likely attributed to chronic renal failure include hyperkalemia and hyperphosphatemia. Other clinicopathologic abnormalities of renal failure that were either not reported or normal in this case included non-regenerative anemia and metabolic acidosis. Importantly, results of a urinalysis were not provided in this case and so proteinuria, a hallmark of renal amyloidosis, in addition to other common urinalysis findings seen with chronic renal disease cannot be excluded.

A common finding associated with chronic kidney failure and renal azotemia is alveolar

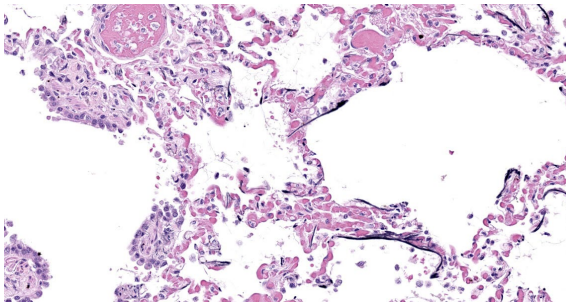

Figure 2-5. Kidney, dog. Alveolar septa are multifocally expanded by deeply basophilic crystalline mineral, mature collagen, and small amounts of edema. There is patchy type II pneumocyte hyperplasia and increased numbers of alveolar macrophages. (HE, 273X)

mineralization within the lungs.[6] Often called uremic pneumonopathy, mineralization occurs within the pulmonary interstitium, specifically the smooth muscle and connective tissue fibers of alveolar septa, veins, and bronchioles.[2] Although uremic mineralization can be multisystemic, mineral deposition often occurs in sites affected by degenerative or necrotic tissue damage. Due to this characteristic and since uremic mineralization can occur regardless of serum calcium concentration, it is most consistent with dystrophic mineralization, as opposed to metastatic mineralization.[1] Other alveolar changes associated with mineralization include pulmonary edema and histiocytosis. Dogs with mineralization of alveoli may or may not exhibit clinical signs of respiratory disease.[2]

Contributing Institution:
University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory
http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/

JPC Diagnosis:
1. Kidney: Amyloidosis, glomerular, global, diffuse, severe, with tubular degeneration, proteinosis, and chronic lymphocytic interstitial nephritis.
2. Lung: Mineralization, subpleural, septal, and vascular, multifocal, moderate.

JPC Comment:
The contributor provides an excellent and succinct comment in this classic condition. Amyloidosis is a subject of frequent research due to its prevalence, diverse presentations, and varied composition in multiple species, including humans. Differentiating the type of amyloid being deposited is critical for understanding the pathogenesis. Traditionally, light-chain amyloidosis (AL) has been differentiated from AA using special stains: AL retains congophilia when pretreated with potassium permanganate, while AA loses congphilia.[5] An additional method to identify AL is immunohistochemical staining for kappa and lambda light chains.[5] Recently, laser microdissection-liquid chromatography-tandem mass spectrometry (LMD-MS) has been used to identify the amyloid precursor proteins in humans, and a study in dogs and cats identified immunoglobulin light chains in 17 of 17 extramedullary plasma cell tumors with amyloid deposition.[5] In the same study, only 12 of 17 cases showed potassium permanganate resistant congophilia, and light chains were only detected in 6 of 17 cases.[5] This study demonstrated that LMD-MS may be more sensitive than traditional methods for identifying light-chain amyloidosis.[5]

Amyloid signature proteins (ASPs) are proteins that are deposited with amyloid fibrils and are likely involved in the pathogenesis of amyloidosis.[8] ASPs studied in man include serum amyloid P component, which protects amyloid fibrils from proteolysis, and various apolipoproteins, including ApoE, which affects the stability and deposition of beta-amyloid.[8] ASPs have yet to be studied thoroughly in veterinary species. Recently, immunohistochemistry and LMD-MS were used to investigate which ASPs are present in three types of amyloidosis in cats; ApoE was identified using both methods in 16 of 16 cases, while SAP was not identified in any cases.[8] In the previously mentioned study of

extramedullary plasma cell tumors, IHC appeared to be more sensitive than LMD-MS, which only identified ASPs in 10 of 15 dogs.[5]

References:

1. Cardoso PGS, Pinto MPR, Moroz LR, et al. Dystrophic Mineralization in Uremic Dogs: An Update. *Pesqisa Veterinária Brasileira*. 2019;**39**: 889-899.
2. Caswell JL, Williams KJ. Respiratory System. In: Maxie MG ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol. 2. 6th ed. Philadelphia, PA: Elsevier Saunders. 2016: 494
3. Cianciolo RE, Mohr FC. Urinary System. In: Maxie MG ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol. 2. 6th ed. Philadelphia, PA: Elsevier Saunders. 2016: 413-415.
4. Cianciolo RE, Mohr FC, Aresu L, et al. World Small Animal Veterinary Association Renal Pathology Initiative: Classification of Glomerular Diseases in Dogs. *Veterinary Pathology.* 2016;**53**: 113-135.
5. Kadota A, Iwaide S, Miyazaki S, et al. Pathology and Proteomics=Based Diagnosis of Localized Light-Chain Amyloidosis in Dogs and Cats. *Vet Pathol.* 2020: 57(5); 658-665.
6. Le Boedec K, Heng HG, Snyder PW, Pressler BM. Pulmonary Abnormalities in Dogs with Renal Azotemia. *J Vet Intern Med.* 2012;**26**: 1099-1106.
7. Mason NJ, Day MJ. Renal Amyloidosis in Related English Foxhounds. *Journal of Small Animal Practice.* 1996;**37**: 255-260.
8. Miyazaki S, Kadota A, Mitsui I, Murakami T. Amyloid Signature Proteins in Feline Amyloidosis. *J Comp Path.* 2020; 117:10-17.
9. Segev G, Cowgill LD, Jessen S, Berkowitz A, Mohr CF, Aroch I. Renal Amyloidosis in Dogs: A Retrospective Study of 91 Cases with Comparison of the Disease between Shar-Pei and Non-Shar-Pei Dogs. *J Vet Intern Med.* 2012;**26**: 259-268.
10. Woldemeskel M. A Concise Review of Amyloidosis in Animals. *Veterinary Medicine International.* 2012; 2012: 427296.

CASE III:

Signalment:
3-month-old castrated male Angus Cross (*Bos taurus*) bovine.

History:
6 out of 30 calves showed acute clinical signs including: bruxism, rapid breathing, dehydration, difficulty rising, and difficulty passing manure. All animals were normothermic (99.5-99.9 F). The herd was pastured in a native grass meadow with oak trees. The area recently received 3 feet of snow, during which the herd sheltered under the oak trees. The submitted animal died shortly after being tubed with fluids. The referring veterinarian submitted kidney, liver and ruminal contents to the diagnostic laboratory for evaluation.

Laboratory Results:
Gallic acid was strongly positive in the submitted rumen contents, confirming exposure to gallotannins.

Microscopic Description:
Kidney: Approximately 30% of the cortical tubular epithelium is necrotic, characterized by loss of cellular detail, rounding of cell borders, separation from the basement membrane, pyknotic nuclei and cytoplasmic hypereosinophilia. Affected tubules are often expanded by brightly eosinophilic granular

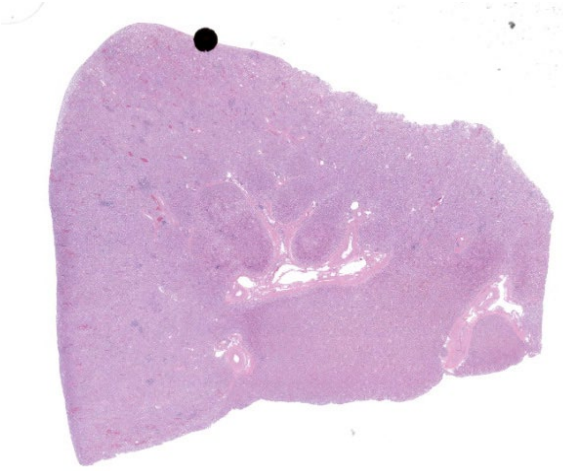

Figure 3-1. Kidney, calf. A wedge-shaped section of kidney is submitted for examination. (HE, 5X)

casts composed of cellular debris and mild amounts of hemorrhage. Occasionally the tubular epithelium is attenuated, mildly vacuolated (degeneration), or hypertrophied with moderate anisokaryosis and rare mitotic figures (regeneration). Few Bowman's spaces and tubules contain high protein fluid. Multifocally the interstitium is expanded by mild fibrosis with infiltration by small aggregates of lymphocytes and plasma cells with fewer neutrophils. The tunica media of large and medium-caliber vessels are mildly vacuolated.

Contributor's Morphologic Diagnoses:
Kidney: Moderate acute/subacute multifocal cortical tubular necrosis.

Contributor's Comment:
The history, histologic lesion, and presence of gallic acid in the rumen are diagnostic for oak toxicosis. Multiple species are potentially susceptible to oak toxicosis including: cattle, sheep, goats, llamas, moose, rabbits, horses, and pigeons.[4, 5, 6, 9, 12, 17, 19] Suspected oak toxicosis has been reported in one dog.[3] Tannins leached from oak leaves that fall into aquatic habitats are known to be toxic to some tadpole species.[10] Pigs appear to be resistant as ingestion increases production of tannin-binding salivary proteins.[17]

Cattle are the most susceptible and most commonly reported species. Cattle develop acute tubular necrosis after ingestion of blossoms, buds, leaves, stems or acorns from oak shrubs and trees (*Quercus spp*) which grow worldwide with case reports in North America, Brazil, Spain, Israel and Africa.[6, 14, 15, 18, 20] Consumption of large quantities of young oak leaves typically occurs in the spring and ingestion of bark or green acorns occurs in the fall. Toxic levels vary between plant species, plant component, and stage of plant maturity.[1] The toxicity of the leaf decreases with maturity, while the opposite occurs with the acorns which are most toxic when mature and freshly fallen.[16] Cattle frequently forage oak components without issue if the oak products represent less than 50% of their diet, therefore feed restriction plays a crucial role, as in this case with snow coverage removing availability of the herd's regular pasture diet.[8] Oak is also not considered to be generally palatable, reinforcing the importance of other feed availability to avoid toxicosis. The toxic substances are metabolites of tannins which are believed to include: tannic acid, gallic acid and pyrogallol.[2,5] Toxicosis is dose-dependent and the exact mechanism of renal tubular damage is unknown. The binding of tannins

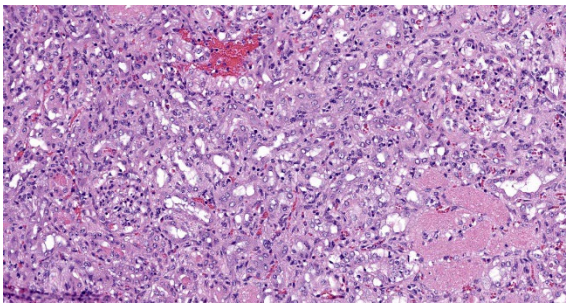

Figure 3-2. Kidney, calf: Due to the numerous and diverse tubular changes, there is loss of normal tubular architecture in the cortex. There is multifocal interstitial hemorrhage and a cluster of tubules containing granular protein casts (lower right). (HE, 228X)

to endothelial cells results in widespread endothelial damage and can lead to perirenal edema, hydrothorax, ascites and disseminated intravascular coagulation.[5]

Clinical signs occur 3-7 days after ingestion and mortality can be as high as 80%.[20] Clinical signs related to endothelial damage and renal failure are typical and can include polyuria, polydipsia, hematuria, dehydration and sternal edema. Animals may also experience abdominal pain, mucoid to hemorrhagic diarrhea, tenesmus, icterus, rumen stasis, anorexia and depression. Malformed calves and abortions have been reported in cows that consume acorns during the second trimester of pregnancy.[11] Clinical pathology findings may include increased BUN and creatinine concentrations, proteinuria, glucosuria, hyperbilirubinuria, hyperphosphatemia, hypocalcemia, and hyposthenuria. Other findings reported include elevated AST, GGT, CK, and lactate dehydrogenase, hypoalbuminemia, hypocalcemia and hypoproteinemia.[2, 5, 6, 14, 16, 20]

Typical gross findings include swollen, pale kidneys with pinpoint hemorrhages on the capsular and cortical surfaces, perirenal edema and hemorrhage, hydrothorax, ascites, and alimentary tract ulceration. Histopathological findings within the kidney are characterized by acute proximal tubular necrosis with casts and intratubular hemorrhage. Chronic cases develop chronic interstitial nephritis with fibrosis, atrophy, thinned cortex and a finely pitted surface. [2, 5, 6, 14, 15, 16, 20]

The diagnosis of oak poisoning is typically based on clinical and gross findings, provided history and histopathological examination of the kidneys. Commercial diagnostic testing for tannin metabolites is available for confirmation. Additional differentials for acute tubular necrosis in cattle include: pigweed (*Amaranthus spp*) toxicity, aminoglycoside antibiotic toxicity, oxalate poisoning, urolithiasis, heavy metal exposure, and ochratoxicosis, yet tubular necrosis with intratubular hemorrhage distinguishes this nephrotoxicity from most other causes.[5]

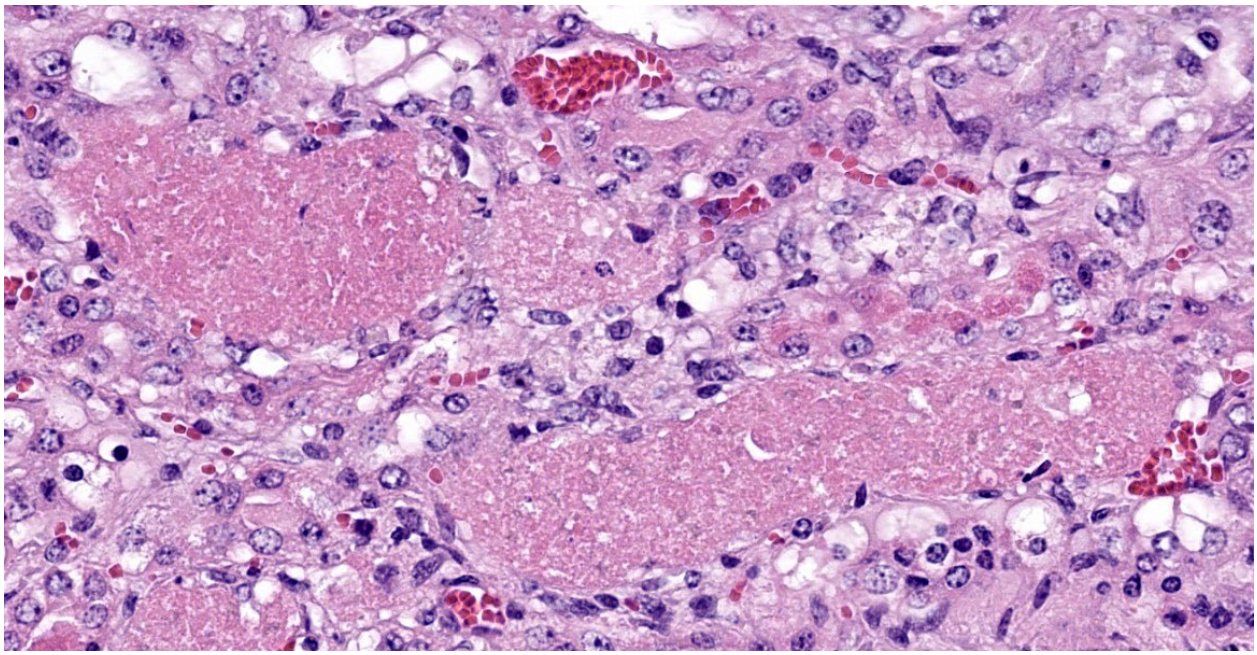

Figure 3-3. Kidney, calf. There is multifocal necrosis and loss of tubular epithelium lining proximal convoluted tubules. Tubular lumina are filled with granular casts. (HE, 560X)

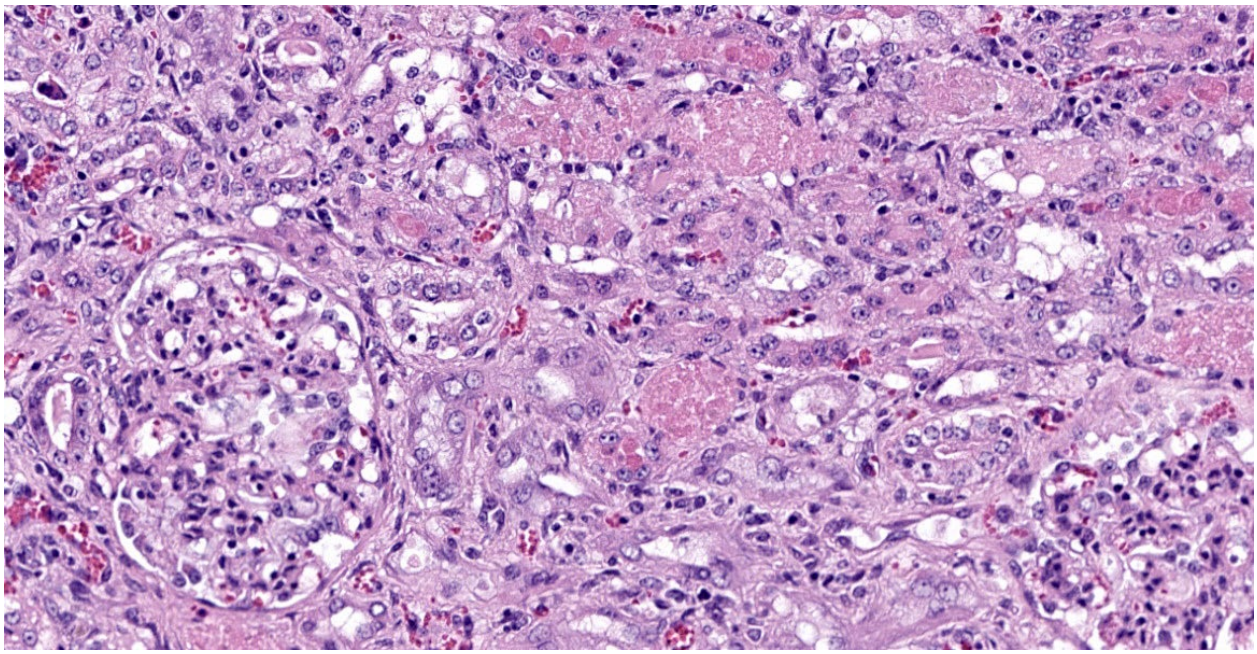

Figure 3-4. Kidney, calf. In additional to necrotic tubules (top center), there are less dramatic changes including numerous regenerating tubular epithelial cells with mildly basophilic cytoplasm and open-faced nuclei, and mildly hypercellular glomeruli. (HE, 350X)

Contributing Institution:
Veterinary Diagnostic Laboratory, Colorado State University Fort Collins, CO, USA
http://csu-cvmbs.colostate.edu/vdl/Pages/default.asp

JPC Diagnosis:
Kidney: Tubular degeneration, necrosis, and regeneration, diffuse, with intratubular granular casts, hemorrhage, and proteinosis.

JPC Comment:
This is a classic case of oak toxicosis. In addition to exogenous toxins so thoroughly described by the contributor, acute tubular injury (ATI) can also be caused by endogenous toxins.[5] Massive release of hemoglobin or myoglobin from hemolysis or rhabdomyolysis can cause pigmentary nephrosis. Tubular injury in these cases may stem from the toxic effects of pigments and secondary factors, such as anemia.[5] Bile is also nephrotoxic in domestic animals.[5] In humans, hepatic cirrhosis causes systemic hypotension and renal hypoperfusion which lead to tubular injury, and bile pigments build up in tubular epithelium and form bile casts in tubules.[5]

Acute tubular injury also occurs as part of renal cortical necrosis; in this condition, all cortical structures, including glomeruli, are damaged. Differentials for renal cortical necrosis include hypoperfusion, ischemia, endotoxemia, disseminated intravascular coagulation, and certain gastrointestinal disease.[5] In some cases, distinguishing ATI and renal cortical necrosis may be difficult as edema may decrease perfusion and cause concurrent ischemia.[5]

The ability to recover from ATI is dependent on preservation of basement membranes.[5] Jones periodic methenamine silver staining and other stains can provide valuable prognostic information in biopsy cases.

References:
1. Basden KW, Dalvi RR. Determination of total phenolics in acorns from different species of oak trees in con-

junction with acorn poisoning in cattle. Veterinary and Human Toxicology. 1987;29.4:305-306.
2. Breshears MA, Confer AW. The urinary system. In: Zachary JF, ed. Pathological Basis of Veterinary Disease. 6th ed. Philadelphia, PA: Mosby Elsevier Inc.; 2017: 672-673.
3. Camacho F, Stewart S, Tinson E. Successful management of suspected acorn (Quercus petraea) toxicity in a dog. The Canadian Veterinary Journal. 2021;62.6: 581.
4. Chamorro MF, Passler T, Joiner K, et al. Acute renal failure in 2 adult llamas after exposure to Oak trees (Quercus spp.). The Canadian Veterinary Journal. 2013; 54.1:61.
5. Cianciolo RE, Mohr FC. Urinary system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals. 6th ed. Vol 2. St. Louis, MO: Elsevier; 2016:439-441.
6. Cortinovis C, Caloni F. Epidemiology of intoxication of domestic animals by plants in Europe. The Veterinary Journal. 2013;197(2):163-8.
7. Díez MT, del Moral PG, Resines JA, et al. Determination of phenolic compounds derived from hydrolysable tannins in biological matrices by RP-HPLC. Journal of separation science. 2008; 31.15:2797-2803.
8. Doce RR, Belenguar A, Toral PG, et al. Effect of the administration of young leaves of Quercus pyrenaica on rumen fermentation in relation to oak tannin toxicosis in cattle. Journal of Animal Physiology and Animal Nutrition. 2013;97.1: 48-57.
9. Dollahite JW, Pigeon RF, Camp, BJ. The toxicity of gallic acid, pyrogallol, tannic acid, and Quercus havardi in the rabbit. American journal of veterinary research. 1962;23:1264-1267.
10. Earl JE, Semlitsch RD. Effects of tannin source and concentration from tree leaves on two species of tadpoles. Environmental toxicology and chemistry. 2015;34.1:120-126.
11. James LF, Nielsen DB, Panter KE. Impact of poisonous plant on the livestock industry. Rangeland Ecology & Management/Journal of Range Management Archives. 1992:45.1: 3-8.
12. Meiser H, Hagedorn HW, Schulz R. Pyrogallol poisoning of pigeons caused by acorns. Avian diseases. 2000:205-209.
13. Meiser H, Hagedorn HW, Schulz R. Pyrogallol concentrations in rumen content, liver and kidney of cows at pasture. Berliner und Munchener Tierarztliche Wochenschrift. 2000;113.3:108-111.
14. Neser JA, Coetzer JAW, Boomker J, Cable H. Oak (Quercus rubor) poisoning in cattle. Journal of the South African Veterinary Association. 1982;53.3:151-155.
15. Pérez V, Doce RR, García-Pariente C, et al. Oak leaf (Quercus pyrenaica) poisoning in cattle. Research in Veterinary Science. 2011;91.2:269-277.
16. Plumlee KH, Johnson B, Galey FD. Comparison of disease in calves dosed orally with oak or commercial tannic acid. Journal of veterinary diagnostic investigation. 1998;10.3:263-267.
17. Smith S, Naylor RJ, Knowles EJ, et al. Suspected acorn toxicity in nine horses. Equine Veterinary Journal. 2015;47(5):568-572.
18. Spier SJ, Smith BP, Seawright AA, Norman BB, Ostrowski S, Oliver MN. Oak toxicosis in cattle in northern California: clinical and pathologic findings. Journal of the American Veterinary Medical Association. 1987;191.8:958-964.

19. Vikøren T, Handeland K, Stuve G, Bratberg B. Toxic nephrosis in moose in Norway. Journal of wildlife diseases. 1999;35(1):130-3.
20. Yeruham I, Avidar Y, Perl S, et al. Probable toxicosis in cattle in Israel caused by the oak Quercus calliprinos. Veterinary and human toxicology. 1998;40(6):336-40.

CASE IV:

Signalment:
A 1.6 year-old, female, domestic short hair, cat (*Felis catus*)

History:
Acute death with no prior clinical signs.

Gross Pathology:
This is the body of a 4.5 kg, reportedly 1.6 year-old female domestic short hair with a body condition score 6/9 and minimal autolysis. The apex of the heart is slightly rounded. Multiple coronary vessels, especially those in the paraconal groove, are segmentally thickened. There are multiple irregular, depressed areas scattered on the renal cortical surfaces (chronic infarctions/tubulointerstitial nephritis). On section, arcuate renal vessels appear up to 3mm thick. There are no other significant findings.

Laboratory Results:

Special stains	Result
GMS staining	Negative
PAS staining	Negative
Acid-fast staining	Negative

Microscopic Description:
Kidney: Multiple small to large sized arteries are circumferentially obliterated, partially to completely occluded and markedly expanded by a moderately cellular proliferation of spindle shaped cells (presumptive smooth muscle cells and fibroblasts cells) within the tunica intima and media admixed with the pale basophilic extracellular matrix. Occasionally, there are also foci of myointimal necrosis. Multiple dense lymphoid aggregations surround within the tunica adventitia of these affected vessels, and there are moderate lymphocytic, histiocytic and neutrophilic infiltrates transmurally. Multifocally, the endothelial lining of the vessels is plump reactive, infrequently sloughed off from the basement membranes, and lost. The vascular lumens also contain numerous lymphocytes, plasma cells, and infrequent basophilic karyorrhectic debris. Multifocally, the inflammatory reactions that surrounded the vessels extent to the renal interstitial spaces. Multifocally, there is a well-delineated regional infarction involving the renal cortex to the renal medulla.

Contributor's Morphologic Diagnoses:
Kidney: Severe, multifocal, chronic, necrotizing and pyogranulomatous vasculitis

Contributor's Comment:
Histopathology has confirmed severe multisystemic vascular disease that is most pronounced in the kidney, heart and a mesenteric artery. Our primary differential is a ster-

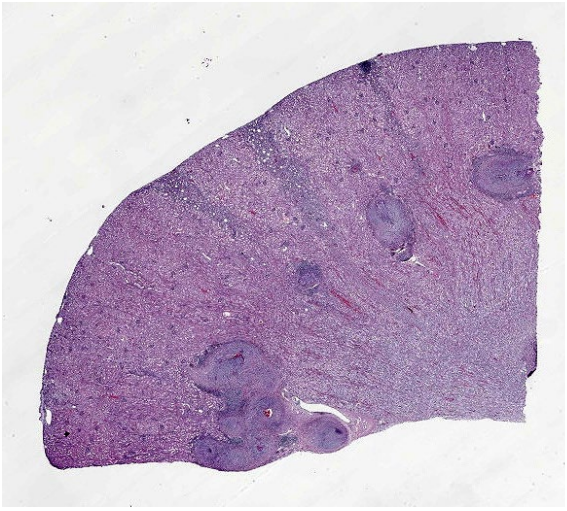

Figure 4-1. Kidney, cat. A wedge-shaped section of kidney is submitted for examination. There is marked increase in the size of the arcuate arteries at the corticomedullary junction. (HE, 5X)

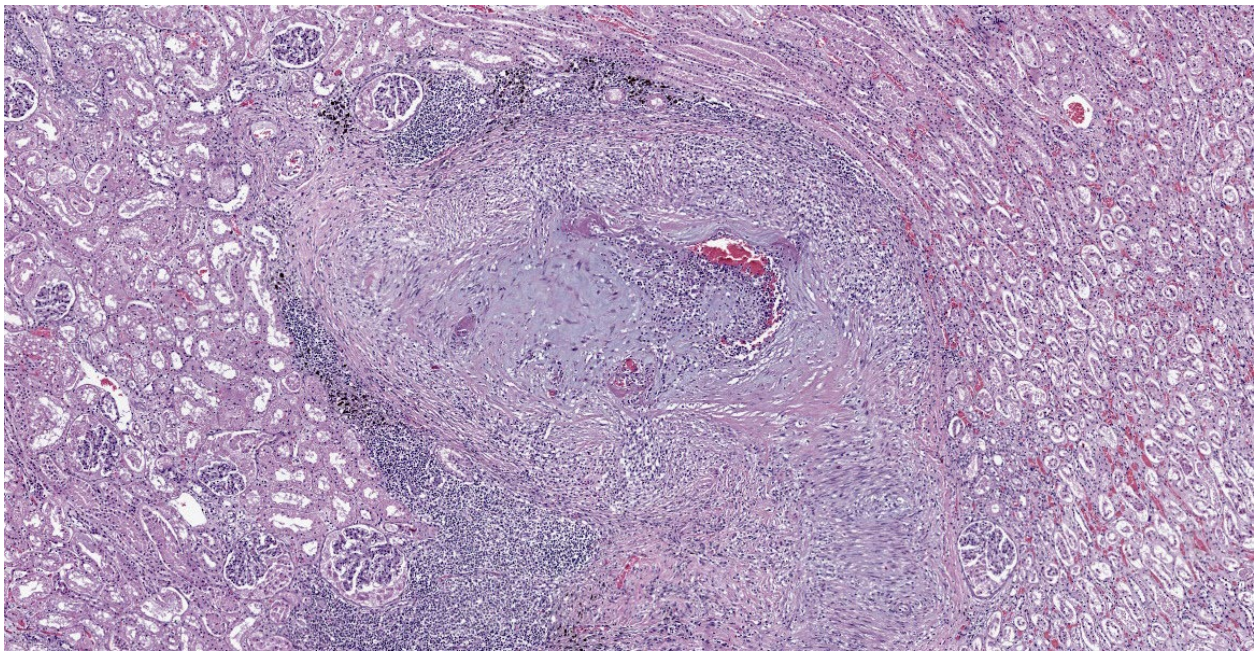

Figure 4-2. Kidney, artery, cat. There is transmural thickening of the wall of an arcuate artery with marked expansion of the tunica intima, media, and adventitia. (HE, 53X

ile/immune mediated arteritis, perhaps resembling polyarteritis nodosa (syn. juvenile polyarteritis) as seen in other species (ie. dogs, cynomolgus macaques, human, rat, others).

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis mainly involving small- and medium-sized muscular arteries of visceral organs.[11, 12] The pathogenesis of PAN is still poorly understood.[11,12] In human, PAN has been associated with some virus infections including hepatitis B and C viruses, human immunodeficiency virus, parvovirus B19 and hairy cell leukemia.[5,6] An immune-mediated vasculopathy is highly suggestive due to the infiltrates of histiocytes and CD4+ T lymphocytes within the vascular walls.[3,5] In veterinary medicine, most cases of PAN have not been associated with infectious agents. However, there are some reports described in many species including blue foxes associated with encephalitozoonosis, in sheep infected with ovine herpesvirus 2 and a streptococcal infection has been suspected in pigs.[7,8,9]

PAN has been recently reported in a cat and in our case, the histopathological findings and gross findings resemble to recently described in the cat which includes systemic necrotizing vasculitis involved the small, medium and large arteries of the heart, kidneys, mesentery.[11] In addition to the recent report, our case demonstrates intense neutrophilic infiltration of the vascular walls.[11]

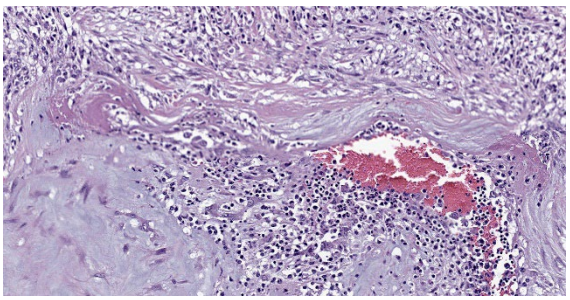

Figure 4-3. Kidney, artery, cat. Higher magnification of the artery in 4-2. There is partial occlusion of the lumen, and at left, pink proteinaceous extruded protein just beneath the remnant endothelium. There is no visible lamina intima, with thickening of the tunica intima by maloriented infiltrating smooth muscle, abundant ground substance, few fibroblasts and collagen and numerous inflammatory cells. The tunica media and adventitia is markedly expanded by fibrosis and inflammatory cells. (HE, 193X)

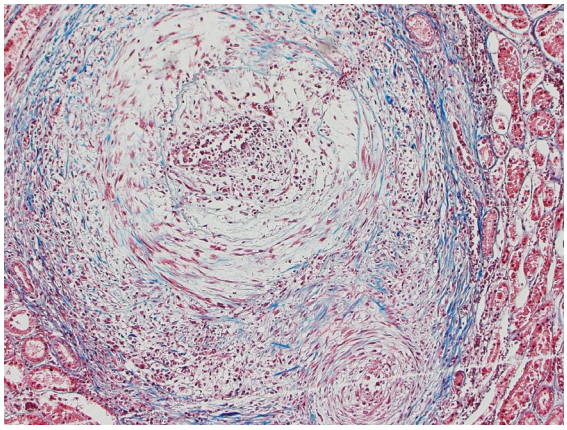

Figure 4-4. Kidney, artery, cat. A Masson's trichrome demonstrates the amount of collagen in the wall of the artery (which should be minimal in the normal state). (Masson's trichrome, 200X)

Some other diagnostic considerations are discussed below. Perhaps the best recognized vasculopathy in the cat is feline infectious peritonitis. Although we have not definitively excluded this pathogen, we suggest that the histologic picture is not entirely typical of this syndrome (ie. morphologic pathology, distribution of lesions). Another possibility might be severe systemic hypertension, but we note that some organs typically affected by hypertension are not involved (ie. meninges, eye).

Contributing Institution:
Oregon State University Magruder Hall Rm. 134 700 SW 30th Street Corvallis, OR 97331
https://vetmed.oregonstate.edu/diagnostic

JPC Diagnosis:
Kidney: Arteritis, proliferative and necrotizing, chronic, diffuse, severe, with cortical infarcts.

JPC Comment:
While relatively uncommon in cats, systemic necrotizing vasculitis is a common background lesion in laboratory species, specifically mice, rats, beagle dogs, and Gottingen minipigs.[1,2,4] In mice, polyarteritis can affect multiple organ systems and tends to occur in strains predisposed to autoimmune diseases, such as MRL and NZB strains. In the kidneys, it can cause segmental infarction, similar to what was seen in this case.[1] Other organs that may be infected include the tongue, pancreas, mesentery, and heart.[1] Polyarteritis may also affect medium sized vessels around the inner and middle ear, causing vestibular signs.[1] Polyarteritis nodosa is a chronic progressive disease of rats and occurs more commonly in rats that are older, male, or Sprague Dawley or spontaneous hypertensive strains.[1,4] Many organ systems can be affected, including the mesentery, kidneys, and testis; however, the lung is spared.[1,4] In beagles, polyarteritis occurs in small to medium caliber arteries of the leptomeninges, cranial mediastinum, and heart and is characterized by lymphoplasmacytic and histiocytic inflammation with fibrinoid necrosis and possible hemorrhage.[2,4] Previously known as beagle pain syndrome for the primary breed affected, this condition is now referred to as steroid responsive meningitis-arteritis and is known to affect other medium and large breeds as well.[2,4] Affected animals have fever and severe spinal pain.[2] Spontaneous polyarteritis also occurs occasionally in Gottingen minipigs, most commonly in small to medium caliber vessels in a single or multiple organs. Affected sites include the heart, reproductive tract (epididymis, oviduct, vagina), kidney, rectum, stomach, urinary

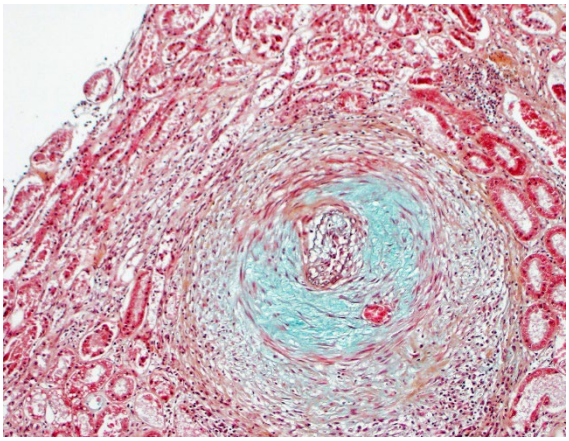

Figure 4-5. Kidney, artery, cat. The internal and external elastic lamina are not visible on a Movat's pentachrome. (Movat, 200X)

bladder, and spinal cord.[4] An important differential to consider in laboratory species used in pre-clinical drug safety studies is drug-induced vasculopathy, which may be induced by vasodilators (minoxidil, endothelin receptor antagonists), bronchodilators (phosphodiesterase inhibitors), and immunomodulatory agents (hydrocortisone, betamethasone).[4]

References:

1. Barthold SW, Griffey SM, Percy DH. *Pathology of Laboratory Rodents and Rabbits.* 4th ed. John Wiley & Sons, Inc: 2016; 98, 99, 156.
2. Cantile C, Youssef S. Nervous System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol 1. 6th ed. Elsevier; 2016: 395.
3. Cid MC, Grau JM, Casademont J, Campo E, Coll-Vinent B, López-Soto A, Ingelmo M, Urbano-Márquez A. Immunohistochemical characterization of inflammatory cells and immunologic activation markers in muscle and nerve biopsy specimens from patients with systemic polyarteritis nodosa. *Arthritis Rheum.* 1994;37(7):1055-1061.
4. Dincer Z, Picciuto V, Walker UJ, Mahl A, McKeag S. Sponatneous and Drug-Induced Arteritis/Polyarteritis in the Gottingen Minipig-Review. *Tox Pathol.* 2018; 46(2):121-130.
5. Forbess L, Bannykh S. Polyarteritis nodosa. *Rheum Dis Clin North Am*. 2015;41(1):33-46.
6. Ishiguro N, Kawashima M. Cutaneous polyarteritis nodosa: a report of 16 cases with clinical and histopathological analysis and a review of the published work. *J Dermatol*. 2010;37(1):85-93.
7. Liu CH, Chiang YH, Chu RM, Pang VF, Lee CC. High incidence of polyarteritis nodosa in the brains of culled sows. *J Vet Med Sci*. 2005;67(1):125-7.
8. Nordstoga K, Westbye K. Polyarteritis nodosa associated with nosematosis in blue foxes. *Acta Pathol Microbiol Scand A*. 1976;84(3):291-6.
9. Pesavento PA, Dange RB, Ferreras MC, et al. Systemic necrotizing vasculitis in sheep is associated with ovine herpesvirus 2. *Vet Pathol*. 2019: 56(1):87-92.
10. Robinson WF, Robinson NA. Cardiovascular System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol 3. 6th ed. Elsevier; 2016.
11. Salvadori C, Vezzosi T, Marchetti V, Cantile C. Polyarteritis Nodosa in a Cat with Involvement of the Central and Peripheral Nervous Systems. *J Comp Path.* 2019;167:6-11.
12. Wessels M, Strugnell B, Woodger N, Peat M, La Rocca SA, Dastjerdi A. Systemic necrotizing polyarteritis in three weaned lambs from one flock. *Jour Vet Diagn Invest.* 2017;29(5):733-7.