Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2018-2019

Conference 4

19 September 2018

Conference Moderator:

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CASE I: N14-111 (JPC 4049562-00).

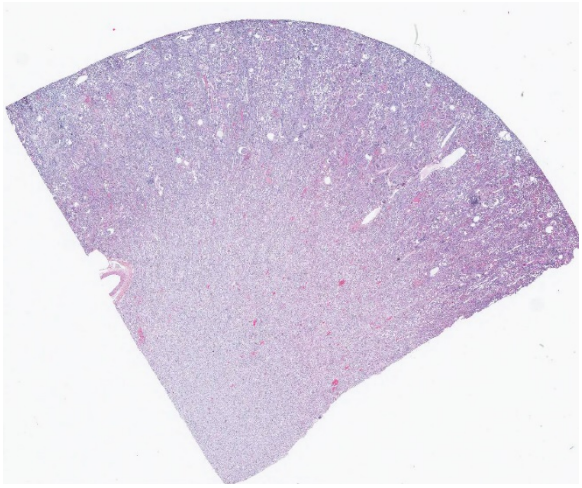
Signalment: Three-year-old castrated male, Scottish terrier cross canine

History: Presented with a history of renal failure and protein-losing nephropathy

Gross Pathology: Enlarged pale kidneys with dozens of red pinpoint foci in the cortex.

Laboratory results: None.

Microscopic Description: Kidney: Diffusely, glomeruli fill Bowman's space and are segmented. They are globally hypercellular with markedly increased mesangial matrix, typically with obliteration of capillary lumina. Synechiae are present multifocally. Tufts occasionally contain karyorrhectic debris, intravascular or intramesangial leukocytes, or exhibit exudation of fibrin and/or proteinaceous fluid

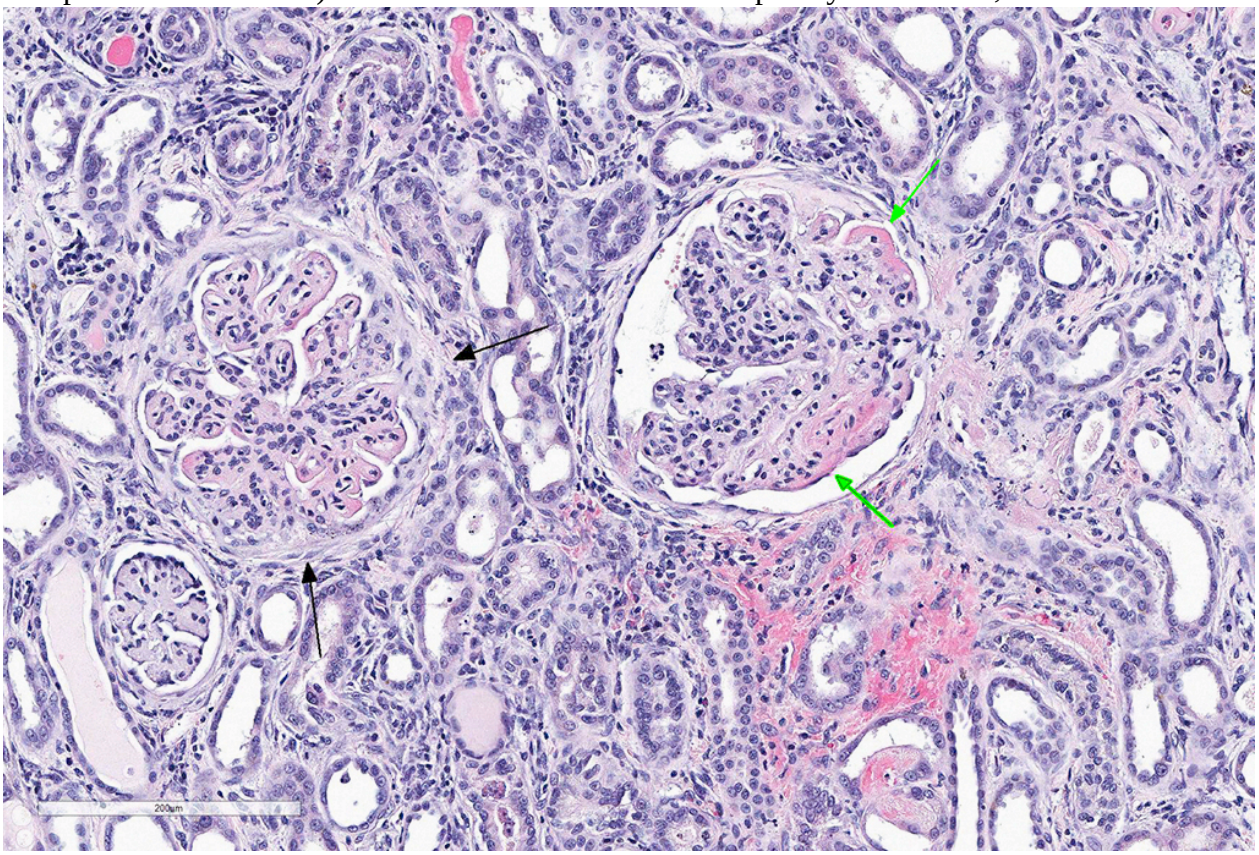


Kidney, dog. A section of kidney is submitted for examination. Tubular ectasia, proteinosis, and cystic glomeruli are evident at low magnification. (HE 6X)

into Bowman's space. Podocytes and parietal epithelial cells are frequently hypertrophied. There is multifocal, mild to moderate periglomerular fibrosis. Diffusely, tubules vary from dilated and lined by attenuated to regenerating epithelium to lined by swollen, vacuolated epithelial cells undergoing hydropic degeneration and necrosis with cytoplasmic hypereosinophilia, nuclear pyknosis, and cellular sloughing. Many tubules contain proteinaceous fluid or casts with fewer containing cellular casts. Occasional tubules are mineralized. The interstitium multifocally contains moderate numbers of lymphocytes and plasma cells with mild interstitial fibrosis. Rare arterioles exhibit fibrinoid necrosis and are surrounded by hemorrhage and fibrin (too infrequent to be a point in these slides).

Contributor's Morphologic Diagnoses: 1. Marked, diffuse, global, membrano-proliferative glomerulonephritis with moderate tubular proteinosis
2. Moderate, multifocal, lymphoplasmacytic, interstitial nephritis
3. Moderate, multifocal, tubular necrosis, degeneration, and regeneration

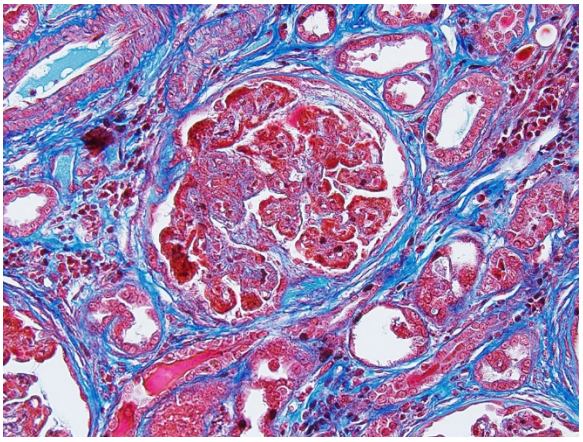
Contributor's Comment: Lyme disease, caused by *Borrelia burgdorferi* is one of the most common tick-borne diseases in the world. The organism is a spirochete, is transmitted by *Ixodes* ticks and lives extracellularly near collagen and fibroblasts usually causing little inflammation in most hosts. Lyme nephritis, which is the most serious form of Lyme disease in dogs is incompletely understood, as recent evidence



Kidney, dog. Glomerular changes include synechia and crescent formation (black arrows), expansion of the glomerular capillary loops by a granular eosinophilic material (green arrows), endocapillary and mesangial hypercellularity, and marked periglomerular fibrosis. (HE, 183X)

has shown that there is no consistent evidence of the presence of *B. burgdorferi* in the renal tissue of dogs with Lyme nephritis. Koch's postulates have not been satisfied and there is no experimental model to study the disease.

As compared with cases of arthritis, fewer dogs (<1-2%) with Lyme-positive status develop severe acute progressive and often fatal protein-losing nephropathy. Labradors, Golden Retrievers and younger dogs are predisposed. Unlike leptospirosis, Lyme nephritis is not due to renal invasion by the spirochete but rather due to immune-mediated glomerulonephritis with Lyme-specific antigen-antibody deposition.[5,7] The microscopic findings of the kidney from Lyme-positive dogs with severe proteinuria, hypoalbuminemia and kidney failure exhibit membranoproliferative glomerulonephritis with subendothelial C3, IgG and IgM deposits, diffuse tubular necrosis/regeneration and lympho-plasmacytic interstitial nephritis.[3] The breed predisposition, younger age of onset and histopathologic findings are different when compared to previously described types of glomerulonephritis. It is thought that the secondary tubular changes may be due to hypertension and efferent arteriole vasoconstriction, tubular hypoxia or toxic proteins in the glomerular filtrate. Very few if any organisms are found by silver stain or PCR in kidneys of dogs with Lyme nephritis. However, Lyme antigen, DNA and occasionally organisms have been found in tubular cells and in urine.[5,7]



Kidney, dog. A trichrome stain demonstrates coalescing brightly eosinophilic immune complexes within subepithelial locations. There is mature collagen within a crescent, as well as periglomerular fibrosis. There is extensive fibrosis of the interstitium as well. (Masson's trichrome, 200X)

JPC Diagnosis: Kidney: Glomerulonephritis, membranoproliferative, diffuse and global, severe, with synechia and crescent formation, tubular epithelial necrosis**,** thrombotic microangiopathy of vascular poles, and moderate lympho-plasmacytic interstitial nephritis.

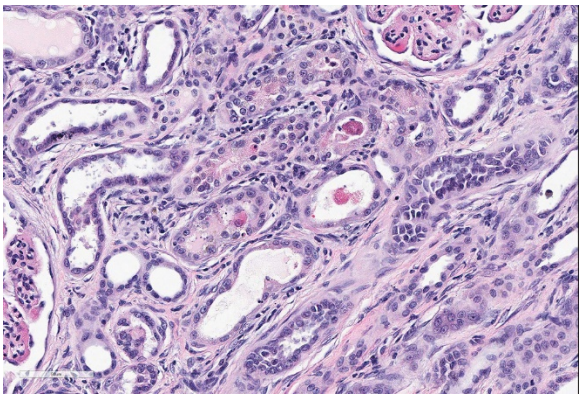
Conference Comment: The contributor provides a concise summary of much as is known about the renal effects of Lyme borreliosis in dogs. Retrievers are predisposed but many breeds are affected in endemic areas.[2] Renal disease has been reported to occur in less than 2% of dogs of serologically positive for Lyme disease; approximately 30% of patients with Lyme disease had concurrent or prior lameness.[2] Antigen-antibody complexes against bacterial outer surface proteins (OSP) OspA, OSpB, and flagellin are thought to be causative for glomerular disease.[2]

Lyme disease and other chronic infectious agents most often result in membrano-proliferative patterns of glomerulonephritis (MPGN) in the dog. From the recent online atlas published by the moderator and other members of the WSAVA study group on renal standardization (https://ohiostate.pressbooks.pub/vetrenalpathatlas/chapter/membranoproliferative-glomerulonephritis/): "…In the MPGN pattern, lesion progression is not straightforward. The lesions are dependent

on the duration/magnitude of immune complex deposition and the severity of the resultant inflammatory response (inflammatory cells and inflammatory mediators). Features that should be assessed include: a) Hypercellularity – this dimension involves the number, location, and types of cells that are present in the glomeruli in excess of what is expected in normal glomeruli, as well as evidence of cellular injury (e.g., pyknotic debris); b) capillary wall remodeling – this dimension invoves the degree and extensiveness of changes in the structures that compose the peripheral capillary wall; namely wall thickening, doule contours of the GBM, cellular interpositioning; and c) sclerosis – this dimension involves the degree and extent of changes that are thought to be irreversible, namely synechia and segmental or global sclerosis."[1]

Equine borreliosis due to *B. burgdorferi* is an emerging disease in many parts of the world. The American College of Veterinary Internal Medicine has recently published a consensus statement about *B. burgdorferi* infection in horses in North America.[4] Documented syndromes in the horse attributed to *B. burgdorferi* infection include neuroborreliosis, uveitis, and cutaneous pseudolymphoma.[4] Although other cases exhibiting lameness and stiffness have been identified in horses, these are often not well documented. Diagnosis of Lyme disease in the horse requires cytology or histopathology of infected fluid or tissue as well as antigen detection.[4]

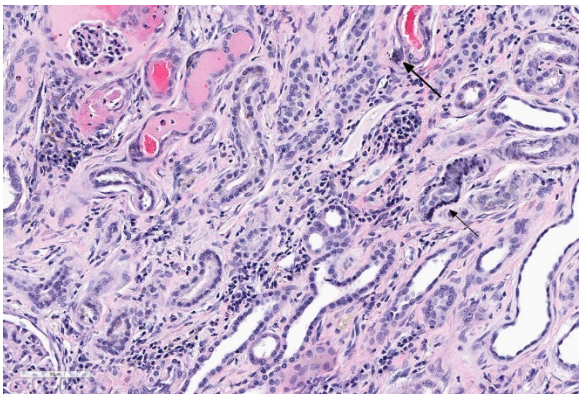
Neuroborreliosis in horses parallels a similar syndrome in humans which generally results in a triad of meningitis, cranial or peripheral neuritis and radiculitis; while clinical signs may be extremely variable, the histologic lesions seen in the horse are unique in equine



Kidney, dog. There is multifocal, often single cell necrosis of tubular epithelium with sloughing into the lumen. Granular and cellular casts are present with many ectatic tubules. (HE, 281X)

neuropathology.[4] Gross lesions are limited to meninges and include opacification, yellowish discoloration, and plaques of hyperemia and edema.[6] Microscopically, horses display variable infiltration of the leptomeninges as well as perivasculitis and segmental vasculitis.[6] Lymphohistiocytic infiltrates predominate but neutrophilic, eosinophilic, and plasmacytic inflammation is also seen inflammatory cells may infiltrate cranial nerves and ganglia resulting in Wallerian degeneration and spheroid formation.[6] Five reports of equine uveitis are present in the veterinary literature.[4] Of these, 3/5 infected horses also displayed neurologic signs and neural inflammation.[4] Organisms were detected within the leptomeninges and vitreous of the eye through the use of Warthin-Starry stains as well as PCR performed on shavings from formalin-fixed paraffin-embedded tissue sections.[4]

Cutaneous pseudolymphoma is a rare condition associated with *B. burgdorferi* infection in the horse, but has also been replicated in experimentally infected colonies.[4] Papular to nodular lesions occurring most often at the site of the tick bite and florid mixed lymphoid hyperplasia are microscopically suggestive of lymphoma in



Kidney, dog. There is multifocal expansion of the interstitium by collagen and loss of tubules. Additional changes include tubular necrosis, proteinosis (with hemorrhage) and mineralization (arrows), and aggregates of lymphocytes and plasma cells. (HE, 281X)

these cases. PCR performed on these lesions will be positive for *B. burgdorferi*.[4]

The moderator discussed a number of potential ruleouts for immune-complex glomerulonephritis in the dog, including *Dirofilaria immitis* infection (which does not always present as a MPGN), tick-borne diseases. The glomerular lesions seen with leishmaniasis are similar to that seen in this case. The moderator identified the wide-spread single cell necrosis in occurring in many tubules as a prominent feature in this particular condition, but also suggested that tubulointerstitial nephritis is not particularly specific for Lyme disease (as has been previously published) and many cases of very active MPGN may result in tubular necrosis resulting from concurrent simultaneous deposition of immune complexes in peritubular capillaries.

The moderator identified the hypercellularity in the glomeruli as being both endocapillary and in the mesangium. A Masson's trichrome run at the JPC on this case highlighted large bright red, often coalescing immune complexes within the subendothelial locations. ("Wire loops" is a term used in human medicine for the appearance of thickened capillary wall due to large coalescing immune complexes.)

The moderator also discussed the changes noted in approximately 20% of the vascular poles, which often display necrosis and intramural protein and erythrocytes (suggestive of possible concurrent hypertension in this patient.) As well as the two potential ways that crescents can form – from rupture of glomerular capillaries or less commonly, due to the rupture of Bowman's capsule.

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CASE II: NA (JPC 4066460-00).

Signalment: Adult (>2.5 years) male cynomolgus monkey, *Macaca fascicularis*

History: This study was conducted in accordance with the current guidelines for animal welfare. All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee. For further information, please see Contributor's Comments.

Gross Pathology: No macroscopic findings

Laboratory results:

Clinical pathology findings:

Increased from pre-study baseline: AST, Urine volume, Urine protein and protein ratio, Urine blood, Urine creatinine, Urine NAG, and Urine microalbumin

Decreased from pre-study baseline: GGT, Total protein, Albumin, Ca

Light microscopic findings:

Glomerulus: Moderate mesangial and podocyte hyperplasia, mild eosinophilic inclusions in podocytes, mild granulocytes in capillary lumens, marked increase in mesangial matrix, moderate synechia, moderate parietal epithelial cell hyperplasia, marked C5b-9 granular staining of capillary walls and podocytes (IHC)

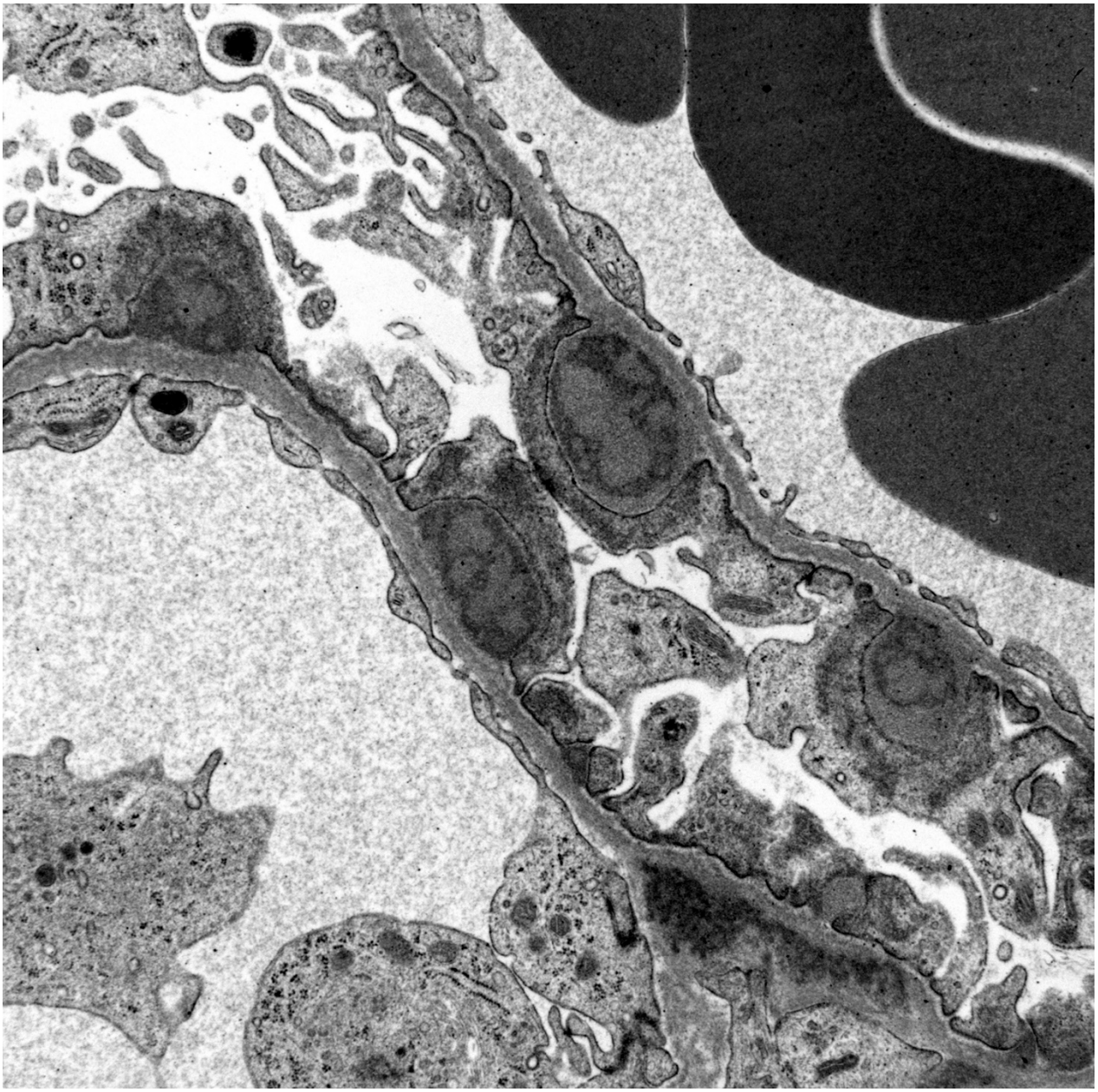
Tubules: Mild distal tubular dilation, minimal distal tubular luminal hyaline casts, moderate erythrocyte casts in proximal and distal tubular lumens

Ureter: Minimal lumenal erythrocytes

Ultrastructural Description: Kidney, portions of two glomerular capillary loops (5,000x original negative magnification) - There are four large generally similar, approximately 500-700 nm diameter, oval-to-spherical, subepithelial, electron dense deposits morphologically consistent with immune complexes. Each consists of an irregular mixture of darker and less dark areas. Facing the capillary lumen, these deposits contact the lamina rara externa of the glomerular basement membranes, and facing the urinary space, deposits contact and are encircled by fused podocyte foot processes (foot process effacement). Podocyte foot process cytoplasm adjacent to these deposits

contains flocculent electron dense material. One smaller subepithelial roughly-triangular dense deposit is also present, and there is also an irregular intramembranous electron dense deposit on one border of the image. Podocyte foot processes adjacent to this intramembranous deposit and in capillary loop sites not adjacent to deposits are also effaced, but less severely so.

There are narrow branching cytoplasmic projections extending from podocytes into the urinary space (podocyte hypertrophy), light accumulations of flocculent material in the urinary space (interpreted as protein



Glomerulus, macaque. The photomicrograph contains cross sections of two capillaries and the intervening uriniferous space. Numerous subepithelial dense deposits are present within the glomerular basement membrane and the overlying podocyte foot processes are effaced.

leakage), and a circular intensely electron dense spherical inclusion in one podocyte pedicle (interpreted as resorbed protein). Glomerular capillary endothelium of one capillary lacks most of its fenestrations, and endothelial cells lining this capillary are enlarged and protruding into the capillary lumen.

Contributor's Morphologic Diagnoses: Kidney: Glomerulopathy, with subepithelial and intramembranous electron dense deposits, podocyte foot process effacement, and podocyte hypertrophy

Contributor's Comment: The overall experimental design employed in this study was adapted from that described by Hebert,[4] In that study, animals administered bovine gamma globulin (BGG) intravenously at 5.5 mg/kg/day (dosed five days per week) developed glomerulopathy beginning as early as after six weeks of dosing. In a previous pilot study conducted by the comtributor, the methods and dose levels outlined below successfully induced immune complex-mediated glomerulopathy. This animal was immunized with, and then dosed with, BGG according to the schedule outlined in the table below.

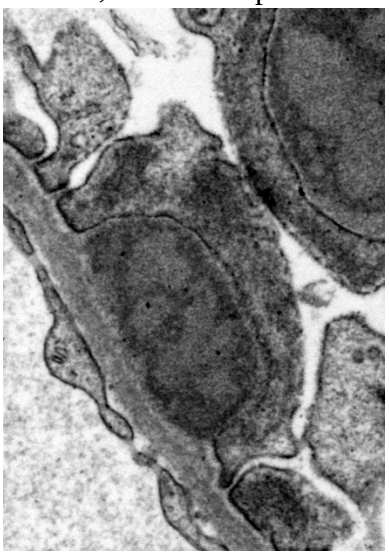
Immunization: On pre-study Day -48, 1.3 mL of Complete Freunds Adjuvant (CFA) at 0.5 mg/mL was combined with 1.3 mL of BGG, reconstituted in PBS, formulated to deliver 1 mg/kg, and administered subcutaneously at 10 different sites along the upper portion of the dorsal thorax. Total volume administered was 2 mL. On pre-study Day -22, 1.3 mL of Incomplete Freunds Adjuvant (IFA) was combined with 1.3 mL of BGG reconstituted in PBS, formulated to deliver 1 mg/kg, and administered subcutaneously at 10 different sites along the upper portion of the dorsal thorax. Total volume administered was 2 mL. All animals were anesthetized with ketamine for CFA and IFA administration and given buprenorphine.

Antigen dosing: BGG was administered once daily over 30 minutes through a vascular access port. On each BGG dosing day, 5 mg/kg of diphenhydramine (DPH) was administered intramuscularly approximately 15-30 minutes prior to BGG administration.

Day 1		**Day 2**	**Day 3**	**Day 4**
5 mg/kg DPH 0.5 mg/kg (0.1		5 mg/kg DPH 0.5 mg/kg (0.1	5 mg/kg DPH 1.0 mg/kg (0.2	5 mg/kg DPH 1.0 mg/kg (0.2
Day 5		**Day 6**	**Day 7**	**Day 8 to Study End**
5 mg/kg DPH 2.0 mg/kg (0.4		5 mg/kg DPH 3.0 mg/kg (0.6	5 mg/kg DPH 4.0 mg/kg (0.8	5 mg/kg DPH 5.5 mg/kg (1.1

BGG immunization followed by daily BGG dosing was tolerated with antihistamine pre-treatment and induced proteinuria and immune complex glomerulopathy in this animal after 8 weeks.

JPC Diagnosis: Kidney: Glomerulonephritis, membranous, diffuse, marked, with subepithelial dense deposits, effacement of podocyte foot processes, and podocyte villar hypertrophy.



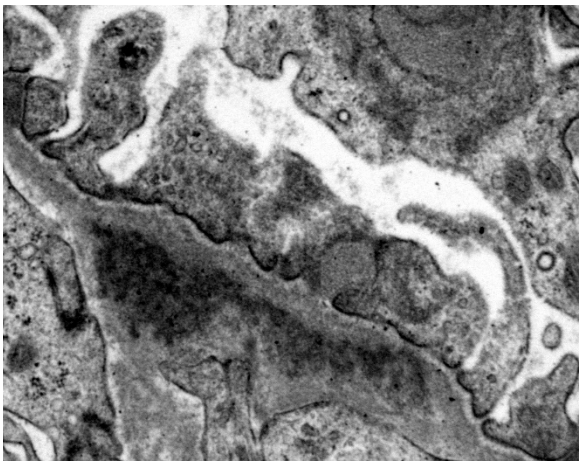
Glomerulus, macaque. Higher magnification of the variegated dense deposits within the glomerular basement membrane. The overlying foot processes of the podocyte are fused (effaced). There is a dark cytoplasmic condensation of actin within podocyte cytoplasmic condensation of actin within podocyte cytoplasm overlying each immune deposit.

Conference Comment: This outstanding electron micrograph excellently demonstrates immune complex deposition in subepithelial areas and effacement of the overlying podocytes. At the bottom corner of the image, a more traditional appearance of dense deposits is seen, which do not result in the bulging of the basement membrane; however podocytes overlying these deposits are similarly effaced. It also demonstrates the uncommon lesion of villous transformation of podocytes, which is usually seen in advanced stages of podocyte effacement.

Immune complex glomerulonephritis (ICGN) is the classic type III hypersensitivity reaction resulting from long-standing inflammation, formation of large amounts of antigen-antibody complexes in circulation, and their deposition within the glomerular basement membrane (GBM). The offending antigen may be that of an infectious organism causing a chronic infection (i.e. *D. immitis*) or may be endogenous in nature (as is seen in systemic lupus erythematosus in humans). [1] Other non–ICGN types of glomerulonephritis include anti-GBM disease as well as those forms which fix complement.[1] This particular model, of periodic injections of bovine serum albumin, mimics the continued antigenemia of infectious disease.

The basic theory of ICGN is somewhat controversial, as many animals with circulating soluble immune complexes may present without glomerulonephritis; others believe that the deposition of immune complexes may be secondary to previous glomerular injury.[1] Additionally other molecules such as C3, capital C1q, and IgM may also adherent to previously injured tissue.[1]

Localization of immune complexes are generally described as subendothelial,

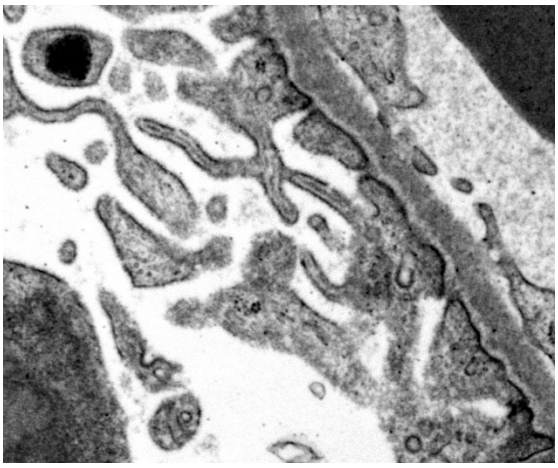


Glomerulus, macaque. Higher magnification of a dense deposits within the glomerular basement membrane.

subepithelial, intramembranous, and mesangial. Their localization within the GBM is predicated on a number of factors including their size, shape, charge, and chemical composition as well as the presence of local mediators of inflammation which may affect transport across endothelium or within the basement membrane.[1] A number of features may also impact the persistence of immune complexes within the basement membrane. Phagocytosis by neutrophils or macrophages, removal of the source of the persistent antigenemia, extracellular degradation by proteases, and even egress from the basement membrane may result in elimination.[1] At the other end of the spectrum, immune complexes may enlarge within the basement membrane through addition of small amounts of antigen or antibody, complement, or by addition of similar immune complexes.[1]

A recently published classification of glomerular disease in the dog[2] identified immune complex-mediated glomerulonephritis as one of the two large categories of glomerular disease, with the other major category characterized by the absence of immune complexes and largely composed of cases of glomerular amyloidosis or focal segmental glomerulosclerosis. When examined only by light microscopy, 22/89 cases were misdiagnosed, emphasizing the importance of additional diagnostic modalities (especially electron microscopy) beyond light microscopy alone.[2]

The WSAVA Classification denotes the characteristic subepithelial location of ICs in cases of membranous glomerulonephritis (as seen in this case), and subendothelial or mesangial locations in cases of membranoproliferative glomerulonephritis. The subepithelial location of the immune complexes results in characteristic glomerular changes. The interposition of



Glomerulus, macaque. "Villar transformation" or hypertrophy of podocytes is seen in cases of severe effacement.

basement membrane between the ICs and the capillary lumen does not engender endocapillary hypercellularity (an increase in the number of leukocytes, endothelial cells and interposed mesangial cells internal to the GBM) which ultimately encroaches or obliterates the lumina of glomerular capillaries.[2] The ability of these subepithelial complexes to fix complement, however, does result in effacement of podocyte foot processes.[2] Conversely, subendothelial locations of ICs results in activation of endothelium and transcapillary recruitment of inflammatory cells and peripheral capillary hypercellularity as previously described.[2]

Interestingly, reports of ICGN in nonhuman primates are relatively scarce within the last decade. Membranoproliferative glomerulonephritis with crescent formation was reported in cynomolgus macaques injected with obinutuzumab, a monoclonal antibody targeted against CD20,[5] exemplary of the immunogenicity of foreign antibodies in primate models. Membranoproliferative glomerulonephritis was also attributed to chronic SHIV infection in a rhesus macaque.[3]

A potential differential on ultrastructure for the immune complexes would in this case would be "hump-like" deposits of complement, as seen in post-infectious glomerulonephritis in humans with a history of recent infectious disease. These "humps' are primarily composed of the third component of complement with little immunoglobulin present.

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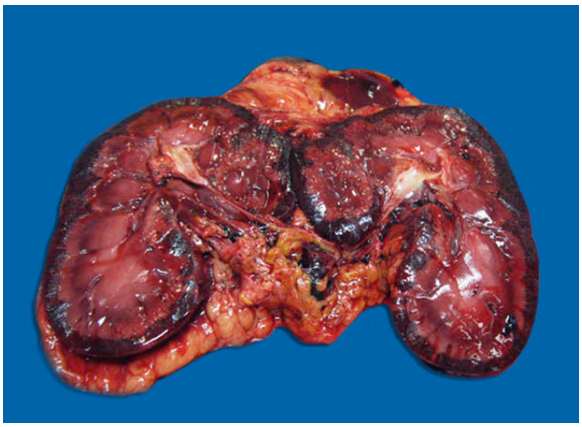
CASE III: P2551-13 (JPC 4048996-00).

Signalment: 3 year-old, female, Standardbred, *Equus caballus*, horse

History: This mare had a history of decreased racing performances of a few weeks duration. A week prior to its last race, an endoscopic examination was performed and revealed excessive tracheal mucus; it was treated with enrofloxacin for a week. The morning after its last race, the horse was anorectic and listless/depressed; it was treated with IV trimethoprim-sulfa, DMSO and electrolytes. The condition rapidly worsened over the next 24 hours, with tachypnea, marked weakness and fever. Clinical biochemistry revealed hyper-creatininemia (800 µmol/L; normal range: 87-150). Tracheobronchial washing results were within normal limits. Acute renal failure was strongly suspected. Due to the poor

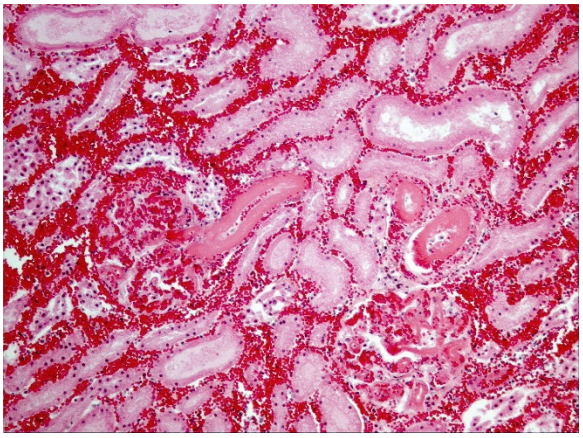


Right kidney; horse. The cortex is diffusely hemorrhagic. (Photo courtesy of: Université de Montréal, Faculty of veterinary medicine, St-Hyacinthe, Quebec, Canada. http://www.medvet.umontreal.ca)

prognosis, the owners elected for euthanasia and a full necropsy was performed.

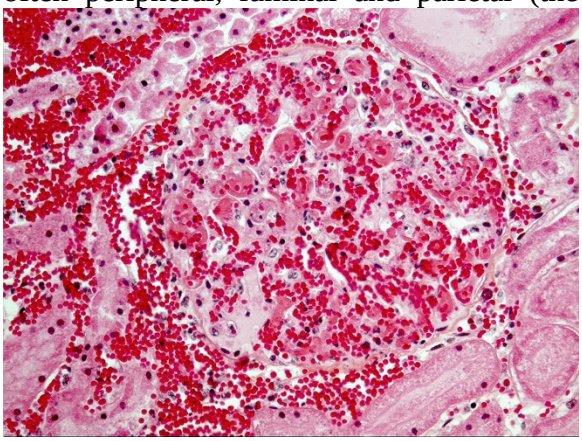
Gross Pathology: There was subcutaneous edema with multifocal petechiation in the dependent portions of the abdomen. Approximately 1.5 L of blood-tinged serous fluid was present in the thoracic cavity. The lungs showed moderate diffuse congestion and edema with a few small (< 1 cm) randomly distributed dark red foci. The liver was pale and appeared slightly yellowish. The cortex of both kidneys was diffusely hemorrhagic. Petechiae were present multifocally on the small intestinal mucosa, sometimes accompanied by mild submucosal edema. Colonic contents were slightly more fluid than normal, without any associated lesions.

Laboratory results: Routine aerobic bacteriology on ileum and colon yielded 4+ of an α-hemolytic *Streptococcus* (not further identified) and 1+ of *E.coli* (negative for *Salmonella*). The latter was negative by PCR for all tested virulence factors including Stx1 and Stx2.



Kidney, horse: There is thrombosis and thickening of vascular walls by fibrinoid material, involving glomerular capillaries, and interlobular and afferent glomerular arterioles. Multifocal acute tubular necrosis is also present. (Hematoxylin-eosin-phloxine-saffron, 400X). (Photo courtesy of: Université de Montréal, Faculty of veterinary medicine, St-Hyacinthe, Quebec, Canada. http://www.medvet.umontreal.ca)

Microscopic Description: On low magnification, the renal cortex has a variegated appearance. There are severe and extensive cortical interstitial hemorrhages associated with vascular lesions involving glomerular capillaries, interlobular and (afferent) glomerular arterioles, and fewer venules. These lesions consist of hyaline thrombi and thickening of vascular walls by fibrinoid material with nuclear debris (fibrinoid necrosis). The fibrinoid material is often peripheral, luminal and parietal (the limit is often blurred), and associated with erythrocytes; the fibrinous nature is supported by its Martius scarlet blue positivity. The fibrinoid vascular material is PAS-positive and Jones' silver-negative. Especially in non-hemorrhagic areas, the capillaries in some glomeruli contain granular material (possible platelets), fragmented erythrocytes and/or thrombi. There is multifocal acute tubular necrosis in the cortex and superficial medulla, the extent of which is hard to evaluate (some post-



Kidney, horse: A glomerulus shows several hyaline thrombi associated with erythrocytes, and thickening of glomerular loops by fibrinoid material and rare nuclear debris. (Hematoxylin-eosin-phloxine-saffron, 400). (Photo courtesy of: Université de Montréal, Faculty of veterinary medicine, St-Hyacinthe, Quebec, Canada. http://www.medvet.umontreal.ca)

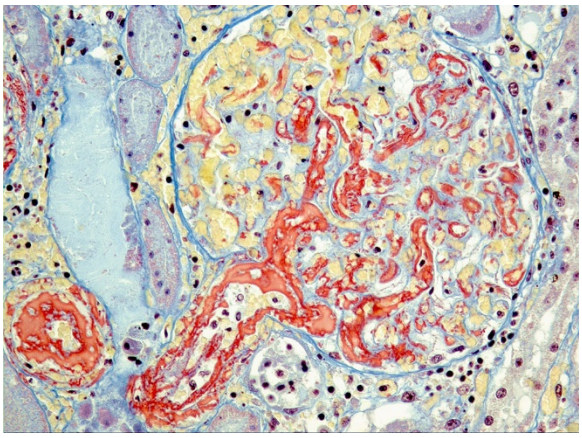
mortem change and very acute), and tubular proteinosis. Inflammation is minimal: occasionally a few interstitial degenerate neutrophils and small lymphocytes.

Contributor's Morphologic Diagnoses: Severe, extensive renal necrotizing vasculopathy with fibrin thrombi (glomerular capillaries, interlobular and afferent glomerular arterioles) and extensive hemorrhage (consistent with hemolytic-uremic syndrome).

Multifocal, acute tubular necrosis (ischemic, secondary to vascular lesions).

Contributor's Comment: Even though hematological data was not available (i.e. to assess microangiopathic hemolytic anemia and thrombocytopenia), hemolytic-uremic syndrome was the final diagnosis, based on the renal lesions associated with acute renal failure. Unfortunately, no cause was found, but only Shiga toxin-producing *E. coli* (STEC) were investigated.

Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are the two best-known thrombotic microangiopathies, which are clinical syndromes characterized by micro-angiopathic hemolytic anemia, thrombocytopenia and dysfunction of one or more organs, the result of microvascular thrombosis and endothelial damage. Both HUS and TTP cause the formation of platelet-rich thrombi in the microcirculation and endothelial swelling, which cause erythrocyte fragmentation (leading to anemia) and excessive platelet consumption (leading to thrombocytopenia).[1,7,10] In their original description, HUS involved mostly or only the kidney, with acute renal failure as a prominent feature, while TTP involved mostly the brain, with mainly neurologic manifestations. However, it is now known



Kidney, horse: Kidney; horse. A Martius scarlet blue stain shows the luminal and parietal distribution of fibrin (red staining) in glomerular capillaries, and interlobular and afferent glomerular arterioles. Martius scarlet blue. (Martius, 400X) Photo courtesy of: Université de Montréal, Faculty of veterinary medicine, St-Hyacinthe, Quebec, Canada. http://www.medvet.umontreal.ca)

that HUS can involve organs other than the kidney, including the brain (and thus cause neurologic dysfunction), and TTP patients often have renal involvement; thus, these two clinical syndromes often overlap.[7,10] Thrombotic microangiopathies in humans are now classified, based on known causes/pathogenesis or associations, as 1) **typical HUS** (epidemic, classic or diarrhea-positive HUS), **atypical HUS** (non-epidemic or diarrhea-negative HUS) and **TTP**. **Typical HUS (tHUS)** is caused by intestinal Shiga toxin-producing bacteria, in most cases *E.coli* producing Stx1 ot Stx2 (STEC), and occasionally other bacteria like *Shigella dysenteriae* type 1; the best known STEC serotype is the O157:H7, which is most often acquired by ingestion of undercooked contaminated ground beef (thus its sometimes epidemic nature). **Atypical HUS (aHUS)** is often associated with a genetic (mutation) or, less commonly, acquired (autoantibodies) deficiency of complement regulatory proteins, mostly factor H (CFH), predisposing to hyperactivation of the alternative complement pathway. **Thrombotic thrombocytopenic purpura**

(TTP) is associated with an acquired (autoantibodies) or, less commonly, a genetic (mutation) deficiency in ADAMTS13, a metalloproteinase which degrades high-molecular-weight multimers of von Willebrand Factor (vWF); subsequent accumulation of ultralarge vWFmultimers (UL-VWF) in plasma promotes platelet aggregation and activation. Triggering conditions or exposures associated with aHUS and TTP include pregnancy, autoimmune diseases and certain drugs (e.g. cyclophosphamide).[1,7,10] The pathogenesis of these syndromes is complex and incompletely understood. The initiating factor in tHUS is endothelial damage by Shiga toxins while it seems to be platelet aggregation in TTP.[1,7,10] In recent years, complement hyperactivation has been proposed as an important common pathogenetic factor, due to its prothrombotic and proinflammatory effects (platelets are activated by complement); the glomerular endothelium, which is targeted in aHUS, is highly susceptible to complement. In tHUS, P-selectin upregulation in endothelial cells by Shiga toxins results in complement deposition on these. Hyperactivation of the alternative complement pathway is central to aHUS pathogenesis. In TTP, the large platelet thrombi may contribute to complement activation. This hypothesis is supported by the clinical efficiency of an anti-C5 antibody in aHUS and some cases of tHUS and TTP.[10]

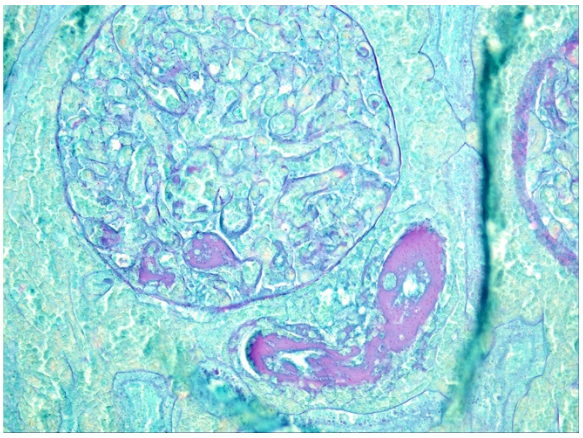
The pathology of tHUS, aHUS and TTP is essentially similar. Microscopic hallmarks of the acute phase of these conditions in the kidney are: 1) occlusion of glomerular capillaries by platelet-rich fibrin thrombi, 2) capillary wall thickening due to endothelial cell swelling and subendothelial cell debris and fibrin deposits, 3) mesangial damage (cells and matrix), and 4) often fibrinoid necrosis of interlobular and afferent glomerular arterioles. These vascular lesions may lead to variably extensive cortical necrosis. Chronic lesions are only seen in aHUS and TTP.[1]

Hemolytic-uremic syndrome is better known in human medicine, but natural cases have been reported in horses and dogs;[2,3,4,6,8,9] the cause was not determined except in one equine case, involving a mare and her foal, in which a 0138:H2 STEC was isolated from the mare's uterus and both animal's gastrointestinal tract.[4]

JPC Diagnosis: Kidney, cortex: Necrosis and hemorrhage, diffuse, severe with fibrinoid vascular necrosis and numerous fibrin thrombi.

Conference Comment: The contributor has provided an excellent review for hemolytic-uremic syndrome in humans. As previously discussed, "typical" hemolytic-uremic syndrome may result from endothelial damage by Shiga toxins produced by several strains of enteropathogenic E. coli (EPEC) This toxin, encoded in the genome of bacteriophages in these strains, binds to the glycolipid receptor globotriaosylcermaide (Gb3) on the surface of endothelial cells.[13] A number of mechanisms result in necrosis of infected cells, including the inhibition of protein synthesis, leading to vascular permeability and cell lysis. The concomitant exposure of endothelial cells to lipopolysaccharides or various inflammatory cytokines (TN F–alpha, IL-1) increases the sensitivity of endothelial cells to the cytotoxic effects of Shiga toxin.

The susceptibility of a particular cell or tissue to the effects of Shiga toxin is directly proportional to the concentration of the Gb3 receptor in a particular tissue. The classic lesions of edema disease in in swine, a



Kidney, horse: Kidney; horse. The fibrin/fibrinoid vascular material is PAS-positive. (Periodic acid-Schiff, 400X). (Photo courtesy of: Université de Montréal, Faculty of veterinary medicine, St-Hyacinthe, Quebec, Canada. http://www.medvet.umontreal.ca)

disease associated with enterohemorrhagic O serotypes of *E., coli* (O138, O139, O140)– edema of the eyelids, gastric wall, mesocolon, larynx, and cerebrum – are directly related to the high concentrations of Gb3 receptors in these tissues.

The most widely recognized Shiga-toxin producing *E. coli* (STEC) is 0157: H7, a major human pathogen, although over 200 other STEC serotypes have been identified.[13] In calves less than four weeks of age, STEC have been associated with ulcerative fibrinohemorrhagic enterocolitis and dysentery. Lesions are most commonly seen in the spiral colon and rectum, although occasionally the ileum and cecum are involved. In a review of outbreaks of human enterohemorrhagic *E. coli* (EHEC), cattle were identified as a natural reservoir of STEC and approximately 75% of outbreaks in humans are limited to the consumption of contaminated beef.[11]

In dogs, STEC have been associated with dysentery and in greyhounds, the syndrome of cutaneous and renal glomerular vasculopathy has been attributed to the consumption of STEC-contaminated beef.[13]

A similar condition of cutaneous and renal glomerular vasculopathy has been recently identified in the UK in dogs, although STEC were not identified in feces from affected dogs.[5]

Another very interesting lesion resembling those caused by STEC has been identified in the mesentery of horses with naturally and experimental endotoxemia. The lesion consists of marked necrosis and loss of medial smooth muscle cells in the mesenteric arterioles with fibrinoid degeneration and intramural hemorrhage.[12]

The moderator discussed thrombotic micro-angiopathy, a term which covers a wide range of conditions (infectious disease, drug reactions, and hypertension among others) in which there is direct damage to endothelial cells. The morphology of renal damage among the disparate forms of TMA does not always target the same vessels in the kidney, as "not all endothelial cells are alike." While the large areas of infarction are the overwhelming feature of this particular slide, careful inspection of will reveal inflammatory cells and cellular debris within the walls of radial arteries (a change referred to in some quarters as "necrotizing arteritis of Weisbrode") as well as the present of occlusive thrombi; thrombi are also present in glomerular tuft capillaries as well. The possibility of purpura hemorrhagica as an etiology (which would cause a lesion more similar to TTP than HUS) was also discussed in this case.

While the clinical picture and lesion morphology is consistent with documented cases of hemolytic-uremic syndrome in the horse, the unavailability of hematologic data, coupled with the inability to identify Shiga toxins (and only a section of kidney to review) may call for a less specific diagnosis than hemolytic-uremia syndrome in this

particular case.

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CASE IV: 13-555-21 (JPC 4034756-00).

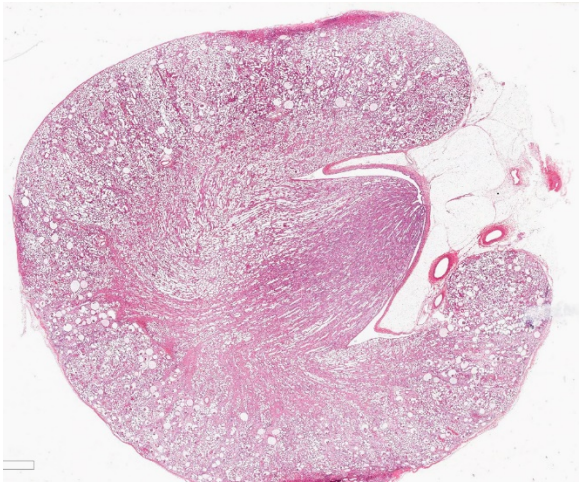
Signalment: 8-month-old, neutered male Airedale, *Canis familiaris*, canine.

History: Presented with depression, vomiting and diarrhea. Significantly raised urea, creatinine, phosphate, sodium, calcium. Did not improve with three days of intravenous fluid therapy and was euthanised. Only the kidneys were sent by the clinician via the surgical biopsy service.

Gross Pathology: Irregularly pitted with an undulating capsular surface.

Laboratory results: None.

Microscopic Description: Kidney. Diffusely, the renal capsule is moderately thickened and multifocally depressed. The subjacent parenchyma consists of irregular foci of loose primitive stroma that contains small caliber vessels, primitive tubules and tubules lined by irregularly tall



Kidney, dog. At subgross magnification, the kidney is characterized by diffuse ectasia of tubules and glomeruli. (HE, 5X)

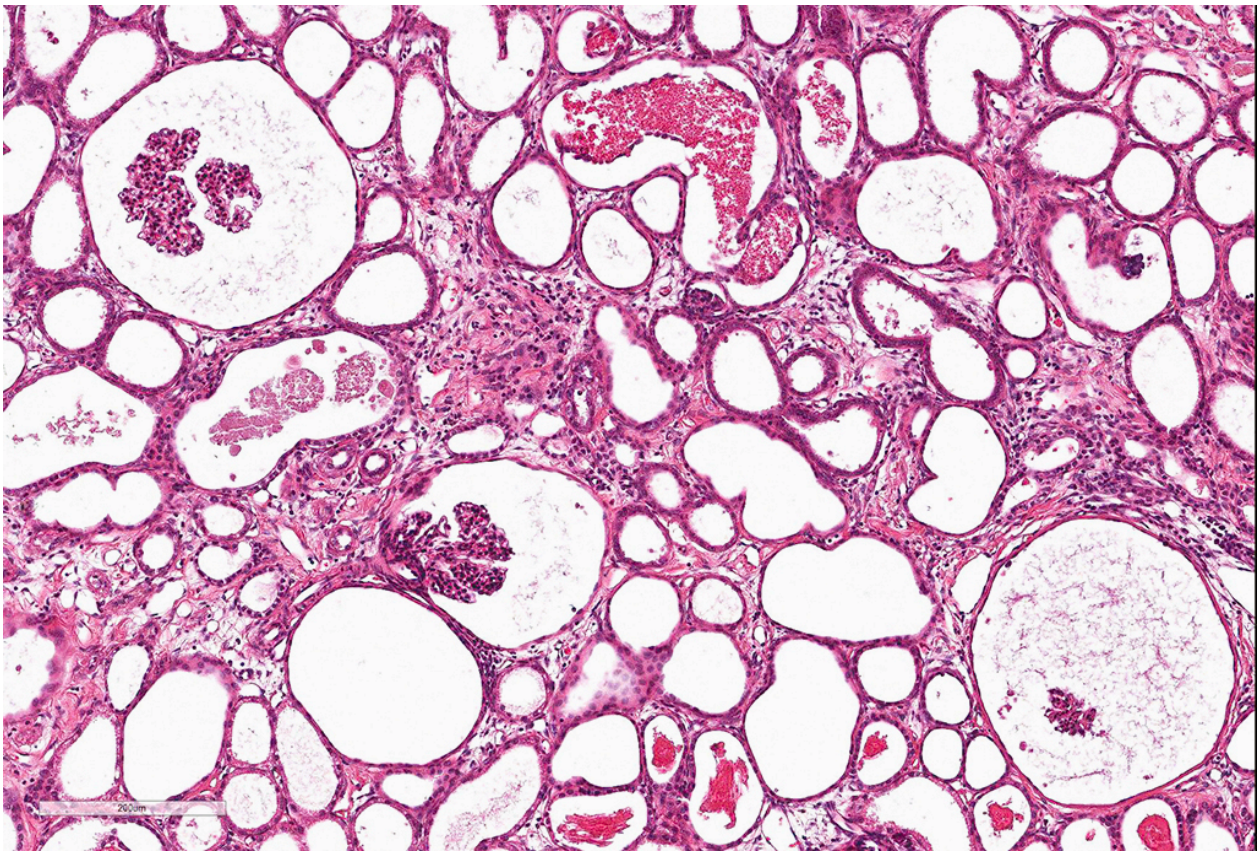
columnar epithelium with basilar nuclear location (persistent metanephric ducts). Extending radially from the outer cortex to the medulla are multifocally extensive areas of loose fibrous stroma (interstitial fibrosis; confirmed with trichrome staining). Predominantly within these areas and affecting over 80% of glomeruli, Bowman's spaces are markedly dilated and multifocally contain a moderately shrunken glomerulus. Multifocally within the superficial cortex glomeruli are small with peripheral nuclei and indistinct capillary tufts (fetal glomeruli). Multifocally Bowman's capsules contain intramural, spherical (2-15µm diameter) basophilic material (mineral; confirmed with von Kossa staining). Diffusely cortical tubules are markedly dilated (up to 120µm in diameter). Tubules are multifocally lined either by plump cuboidal to flattened (attenuated) tubular epithelium or epithelium that is enlarged and hypereosinophilic (tubular degeneration) or multifocally by enlarged, severely vacuolated epithelium with karyorrhexis and karyolysis (tubular necrosis). Multifocally tubules contain amorphous hyaline to granular hypereosinophilic material (protein casts) and tubular epithelium is multifocally replaced or deviated by amorphous basophilic material (mineral; confirmed with Von Kossa staining). Collecting ducts range in diameter from 20 to 140µm and are variously lined by attenuated to plump cuboidal and columnar epithelium, which multifocally partially occludes the lumen (atypical epithelium). Multifocally collecting ducts are surrounded by areas of loose, undifferentiated mesenchyme that is focally infiltrated by low numbers of neutrophils; multifocally lumina contain sloughed pyknotic and karyorrhectic debris (necrosis). The cortical interstitium is infiltrated by low numbers of lymphocytes and plasma cells.

Contributor's Morphologic Diagnoses: 1. Kidney; dysplasia with fetal glomeruli, persistent metanephric ducts, primitive mesenchyme and atypical tubular epithelium.

2. Kidney; marked diffuse tubular and Bowman's space ectasia with multifocal tubular degeneration, necrosis and mineralization and moderate interstitial fibrosis

Contributor's Comment:
Canine renal dysplasia is usually congenital and often thought to be hereditary resulting in disorganized development of renal parenchyma due to anomalous differentiation.[4] It has been reported in many breeds including the Golden Retriever, Beagle, Dutch Kookier, Miniature Schnauzer, Shih Tzu, Lhasa Apso, Great Dane, Samoyed, Alaskan Malamute, Cavalier King Charles Spaniel and Bulldog.[1,2,3,5,9,11]

Disease in the early neonatal period may also cause renal dysplasia by affecting incompletely differentiated renal tissue. This has been reported in puppies that survived intraperitoneal infection with canine herpesvirus at 2 days of age and were



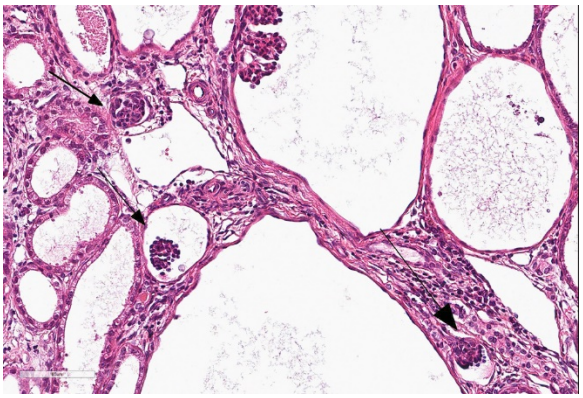
Kidney, dog. Higher magnification shows a marked dilation of Bowman's space and atrophy of glomerular tufts. There is diffuse loss of tubules, ectasia of many remaining tubules with attenuated epithelium, marked interstitial fibrosis, and mild interstitial lymphocytic interstitial inflammation. (HE, 130X)

sacrificed at 11 and 16 days post infection.[8] Similarly renal dysplasia has been reported in calves and kittens following infection with bovine pestivirus and feline parvovirus, respectively.[4]

The kidney develops from successive structures, which overlap in their formation. Renal malformation can therefore occur in many patterns. The developing structures include the pronephros, mesonephros and ultimately, the metanephros. The pronephros and mesonephros degenerate to vestigial remnants but are crucial in the correct formation of the metanephros. The metanephros or 'definitive kidney' forms from complex interaction of the ureteral bud and metanephric blastema. This may explain why malformations of the kidney are often accompanied by ureteral anomalies in man, although this is not commonly reported in dogs.[4, 10]

The clinical presentation and the age at which signs develop are variable. Renal dysplasia in neonates has been associated with reduced appetite, intermittent vomiting, dullness, poor growth and polyuria/polydipsia. Puppies may not survive to weaning; longer survival (over 4 months) results in clinical signs that can be attributed to uremia such as vomiting, diarrhea, anemia, nervous signs and fibrous osteodystrophy ("rubber jaw").[6]

Renal dysplasia may be uni- or bilateral. Grossly, affected kidneys may be small and therefore potentially they could be mis-diagnosed as hypoplastic. They may also be



Kidney, dog. Glomeruli near the capsular surface have a fetal appearance without glomerular capillaries, and a peripheral rim of primitive podocytes with hyperchromatic nuclei. (HE, 183X)

misshapen, lobulated, contain an irregularly thin cortex or thick walled cysts and they may be associated with dilated tortuous ureters.[4,9] They can be indistinguishable from end stage renal lesions in old dogs.[9] Alternatively, they may appear grossly normal, and therefore histopathological examination is required for diagnosis.[4]

In the largest case series available, 45 dogs of various breeds were diagnosed with renal dysplasia. Histological features were described as primary, compensatory and degenerative or inflammatory. At least one of the following primary features was identified in each case:

1) Asynchronous differentiation of nephrons, defined by the presence of fetal or immature glomeruli and/or tubules (40/45 cases).
2) Persistent mesenchyme: a loose stroma found in the medulla, which is alcian blue positive and trichrome stain negative (25/45 cases).
3) Atypical tubular epithelium reported as adenomatoid cuboidal or clusters of squamous epithelial cells (7/45 cases).
4) Persistent metanephric ducts, which are ducts in the outer medulla lined by tall pseudostratified columnar epithelium and often dilated (6/45 cases).
5) Dysontogenic metaplasia: represented as cartilaginous or osseous metaplasia (2/45 cases).[7]

There is disagreement between authors on the features required for a diagnosis of renal dysplasia. Some authors believe juvenile nephropathy or juvenile renal disease is a more appropriate term for cases of renal dysplasia which do not exhibit primitive ducts or dysontogenic metaplasia. Dysontogenic metaplasia and primitive metanephric ducts are the least commonly observed features in 'renal dysplasia', therefore making the classification restrictive and excluding many cases where fetal glomeruli alone are observed. Juvenile nephropathy is a general term that includes non-inflammatory, degenerative, developmental and chronic renal disease of unknown pathogenesis and is therefore non-specific. However this may be a more appropriate term for cases whereby the pathogenesis of the dysplasia is unknown or unclear. Further increasing the confusion, 'familial renal disease' has been used interchangeably with renal dysplasia in the literature. [4,5,9]

Compensatory features were described in 20/45 cases and included enlarged glomeruli with mesangial hyperplasia and cortical tubular dilation with hypertrophic and hyperplastic cuboidal epithelial lining. Degeneration and inflammatory changes may be severe and therefore obscure primary features required for diagnosis.

Degenerative/inflammatory features were present in all cases and predominantly included interstitial fibrosis, which was often segmental and within areas of fetal glomeruli. The appearance of tubulointerstitial nephritis and pyelonephritis was in parallel with the severity of fibrosis. Other changes observed included dystrophic mineralization, cystic glomerular atrophy, microcystic tubules, retention cysts and glomerular lipidosis.[8]

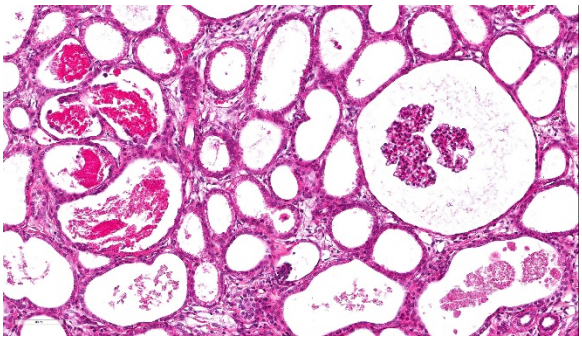
JPC Diagnosis: 1. Kidney: Asynchronous maturation, diffuse, marked, with glomerulocystic atrophy, fetal glomeruli, marked tubular ectasia, and mild chronic interstitial nephritis.
2. Kidney: Tubular loss, diffuse, moderate, with granular cast formation and rare epithelial necrosis.

Conference Comment: The contributor has provided a concise but relatively thorough discussion of renal dysplasia in the dog.

A slightly more detailed review of renal embryogenesis may help in understanding its development. During fetal development, the ureteric bud, an evagination of the mesonephric duct, develops into the metanephros. The ureteric bud extends cranial dorsally into the overlying metanephric blastema whereupon successive divisions of the ureteric bud result in formation of the collecting ducts. Interaction with mesenchymal cells within the metanephric blastoma results of the formation of the remainder of the nephron, including glomeruli and tubules. The structures initially form at the cortical medullary junction, but as the collecting ducts elongate, or subsequently formed in the superior aspects of the cortex. The first few weeks of life see additional development of renal structures.[9]

As the importance of the ureteric bud in the overall development of the kidney now becomes clear, it can be understood how ureteral abnormalities during development have such a profound impact on the developing kidney. Abnormal placement of the ureters during development as well as lower urinary tract obstruction have both been identified as major contributors to renal dysplasia in humans.[7, 10] Such extra-renal abnormalities are not commonly reported in dogs, but this may be the result of incomplete autopsy examination of the entire urinary tract.[9]

As renal dysplasia is a complex, multifactorial disease, obviously there are many other contributors than simply the placement of the ureteric bud. Regulation of "renal branching morphogenesis" is controlled by a wide range of transcription factors, growth factors, and cell surface signaling peptides which, if deficient, results in improper induction of the metanephric blastema and ultimately, renal dysplasia.[4] Subsequent to the observation that cyclooxygenase-2 (Cox-2) deficient mice exhibit renal changes similar to renal dysplasia in dogs, the Cox-2 genes of Lhasa Apso affected with familiar renal dysplasia were sequenced and compared to that of



Kidney, dog. The presence of granular and cellular casts within dilated tubules is not common in canine juvenile nephropathy, and suggests a superimposed second insult to the abnormal renal development in this case. (HE, 285X)

normal dogs.[12] Small insertions and the deletions of GC boxes upstream of the ATG translation start site (which are putative SP1 transcription factor binding sites) were found upstream of the A translation start site in affected animals.[12]

During the slide description, the moderator commented on the difficulty on the precise identification of primitive mesenchyme and metanephric tubules in cases of juvenile nephropathy, as well as the spirited discussions that it often engenders among experts in renal disease. Without precise definitions for these terms even among experts, their identification in many cases is often quite subjective and fraught with peril. In this particular case, after some discussion, the "primitive mesenchyme" identified by some attendees was determined to be edematous mature collagen, and immature tubules more likely to be the result of interesting sectioning of collecting ducts.

The moderator also commented on the amount of debris within tubules which is uncommon in cases of juvenile dysplasia. In this case, this cellular debris is more suggestive of a second, more recent tubular insult, resulting in this animal's acute uremic presentation. The developmental abnormalities seen in this kidney, although dramatic, likely would not have resulted in a death at 8 months on their own. She also commented on the profound ectasia of Bowman's capsules in this case, strongly suggesting downstream obstruction (which is corroborated by the marked tubular ectasia also seen in this case.)

The term "renal dysplasia" itself appears to be falling from favor today among pathologists and clinicians, with other terms such as "juvenile nephropathy" and "renal maldevelopment" gaining favor.

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