Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2011-2012

Conference 2

14 September 2011

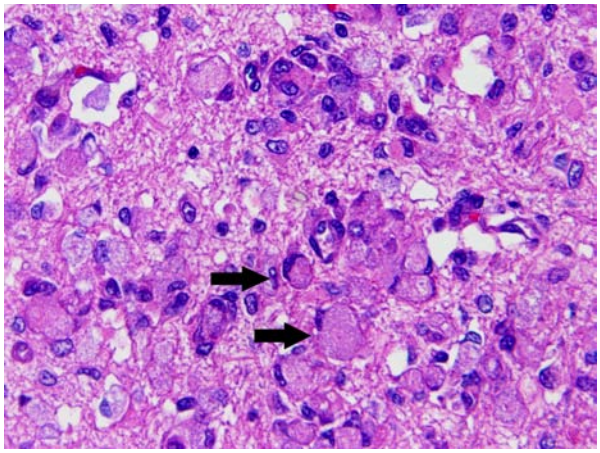
CASE I: 10-5005 (JPC 4003270).

Signalment: 7-week-old male intact mixed breed dog (*Canis familiaris*).

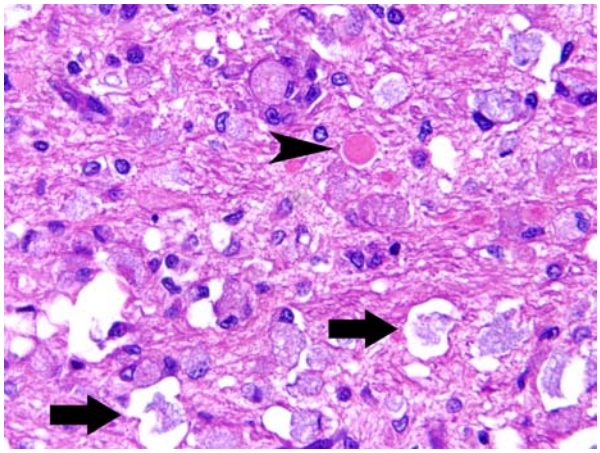
History: The dog was part of a research colony affected with globoid cell leukodystrophy.

Gross Pathology: None provided.

Histopathologic Description: Brain, cerebrum: The white matter is multifocally expanded by large numbers of plump macrophages, which often surround blood vessels or infiltrate myelin sheaths. These cells contain abundant amounts of amphophilic to eosinophilic, fibrillar to flocculent cytoplasm, which often peripheralizes and compresses the nucleus (globoid cells). Multifocally, there are similar cells in the leptomeninges. Multifocally within the white matter, there are numerous dilated axons (spheroids) surrounded by dilated myelin sheaths. Capillaries are lined by plump reactive endothelial cells. There are multifocal aggregates of glial cells, predominantly at the grey-white matter junction.



1-1. Cerebrum, dog. White matter is infiltrated by numerous "globoid cells" with abundant cytoplasm and crescentic nuclei.. (HE 400X)



1-2. Cerebrum, dog. In affectedd white matter, globoid cells surround dilated axons (spheroids – arrowhead) and dlated empty myelin sheaths contain Gitter cells (arrows). (HE 400X)

Contributor's Morphologic Diagnosis: Cerebrum, white matter and leptomeninges: Histiocytosis, perivascular, moderate, multifocal, with abundant intracytoplasmic fibrillar material, and gliosis, mixed breed, canine.

Contributor's Comment: Similar histologic lesions are present in the cerebellum, medulla oblongata, and spinal cord. These lesions are consistent with globoid cell leukodystrophy (Krabbe's disease).

Globoid cell leukodystrophy, also known as galactocerebrosidosis, is an autosomal recessive disease caused by deficiency in the activity of lysosomal galactocerebrosidase (GALC).[1,2] Globoid cell leukodystrophy is part of the sphingolipidosis group of lysosomal storage diseases. The enzymatic deficit blocks the catabolism of galactocerebroside (galactosylceramide), a major component of myelin, and therefore the metabolic function of oligodendrocytes and Schwann cells is affected. The enzyme is also involved in the breakdown of other metabolites, including galactosylsphingosine (psychosine), normally synthesized by oligodendrocytes. This latter substance is cytotoxic to oligodendrocytes. Psychosine accumulation leads to oligodendrocyte degeneration and death, ceasing of myelination and degeneration of formed myelin.[1] Psychosine was sufficient to induce axonal defects and cell death in cultures of acutely isolated neurons in twitcher mice, a murine model of globoid cell leukodystrophy. Axonopathy in young twitcher mice occurred in the absence of demyelination and of neuronal apoptosis.[3]

Macrophages accumulate to ingest the degenerating myelin, but are unable to degrade galactocerebroside, and give rise to the distinctive, swollen, PAS positive "globoid cells". The cells are centered around blood vessels in the white matter, leptomeninges, and endoneurium of peripheral nerves. At the end stage of the disease there is diffuse demyelination, axonal loss, and dense astrogliosis.[1] On electron microscopy, cytoplasmic contents include myelin membranes in various states of degeneration, and aggregates of straight or arched tubules of galactosylceramide bound by a membrane.

Neurological signs in dogs typically appear in young animals (often between 3 and 6 months of age). Clinical signs associated with this disease are variable and may reflect the multifocal distribution of lesions.[2] Clinical signs include ataxia, hypermetria, tremors, and proprioceptive deficits. Progression leads to blindness, anorexia, muscular atrophy, and paraplegia. Death may occur before one year of age. The disease has been reported in a variety of canine breeds including: Cairn terrier, West Highland white terrier, miniature poodle, bluetick hound, basset hound, beagle[1], Pomeranian, Australian kelpie[4], Irish setter[5] and others. In addition to dogs, the disease is reported in domestic cats, polled Dorset sheep, rhesus macaques, and humans. There is a study model for the disease based on the twitcher mouse.[3] Up to date there are 33 distinct *GALC* mutant alleles reported in humans.[6]

JPC Diagnosis: Brain, cerebral cortex, white matter: Demyelination, diffuse, marked, with globoid cell infiltrates and axonal degeneration.

Conference Comment: The contributor has provided an excellent, concise review of this disease.

The conference moderator noted that gitter cells can resemble globoid cells on H&E stained sections and that both will have PAS positive cytoplasmic material; however, globoid cells are only found in the white matter and have a distinctly eccentric nucleus. Additionally, the presence of reactive endothelium can help to differentiate true pathologic findings from artifact or autolysis, and they may be the most noticeable pathologic change on subgross examination to indicate the presence of a microscopic lesion.

There was marked variation of anatomic location among the slides of conference participants. This should not detract from the diagnosis, but may reflect a difference in the histologic description compared to contributor slides.

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CASE II: 97-669-3 (JPC 4003037).

Signalment: 5-week-old male Yorkshire crossbred, *Sus scrofa domestica*, pig.

History: Three early-weaned piglets, each weighing approximately 9 kg, were submitted alive with listlessness and mostly hind limb ataxia and paresis of 4 days duration. One had been treated with dexamethasone and penicillin, with no results. Morbidity was qualified as moderate and mortality was not recorded at time of submission. No other clinical signs were reported. All other affected piglets recovered.

Gross Pathology: No significant gross lesions were seen (the whole CNS was examined in all piglets).

Laboratory Results: Enterovirus was isolated from a pool of fresh brainstem and spinal cord samples; it was not serogrouped.

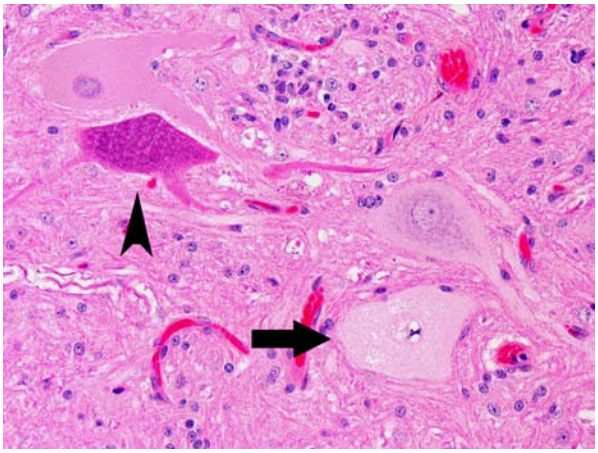
Histopathologic Description: Spinal cord: There is an extensive, moderate nonsuppurative poliomyelitis involving mainly the ventral horns. It is characterized by mild to moderate lymphocytic perivascular cuffing, gliosis mostly in the form of glial nodules, and degeneration/ necrosis in large ventral horn (motor) neurons with neuronal loss and neuronophagia. The necrotic neurons' perikaryon is either swollen, markedly vacuolar and fibrillar or shrunken and hypereosinophilic; nuclei are either absent or pycnotic/ karyorrhectic. Microglial cells/macrophages can be seen around and within necrotic neurons (neuronophagia). Mostly in the dorsal funiculi there is Wallerian degeneration characterized by dilated myelin sheaths with axonal loss and occasional necrotic macrophages (myelinophage). Similar lesions were present in all sections of cervical, thoracic and lumbar spinal cord examined.

Brain (not provided): there were similar but milder lesions with minimal neuronal changes in the brain stem; a mild multifocal nonsuppurative leptomeningitis was also present.

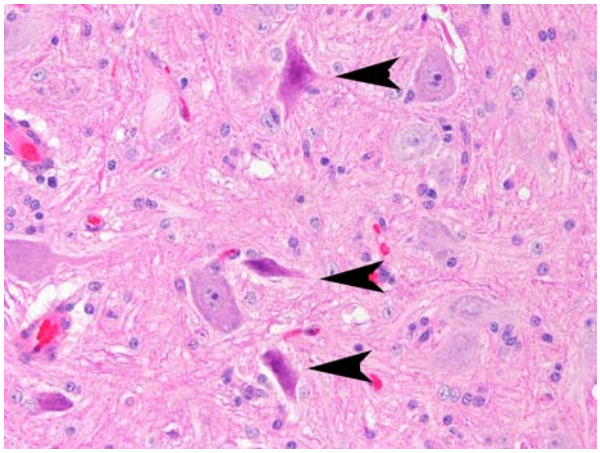
Contributor's Morphologic Diagnosis: Moderate and extensive nonsuppurative poliomyelitis with marked neuronal necrosis and loss, and neuronophagia (ventral horns).

Contributor's Comment: No microscopic lesions were seen in other organs. Based on case history, microscopic lesions and isolation of enterovirus, a diagnosis of enteroviral polioencephalomyelitis, most consistent with Talfan disease, was given. Enteroviruses (genus *Enterovirus*, family Picornaviridae) are found in the enteric tract of humans and animals. Porcine enteroviruses (PEVs) were classified into 13 serotypes (PEV 1–13) that are antigenically related strains with variable virulence. These serotypes have further been grouped into groups I (PEV serotypes 1–7 and 11–13), II (PEV-8), and III (PEVs 9 and 10). Group I is now reclassified as Teschovirus.[7]

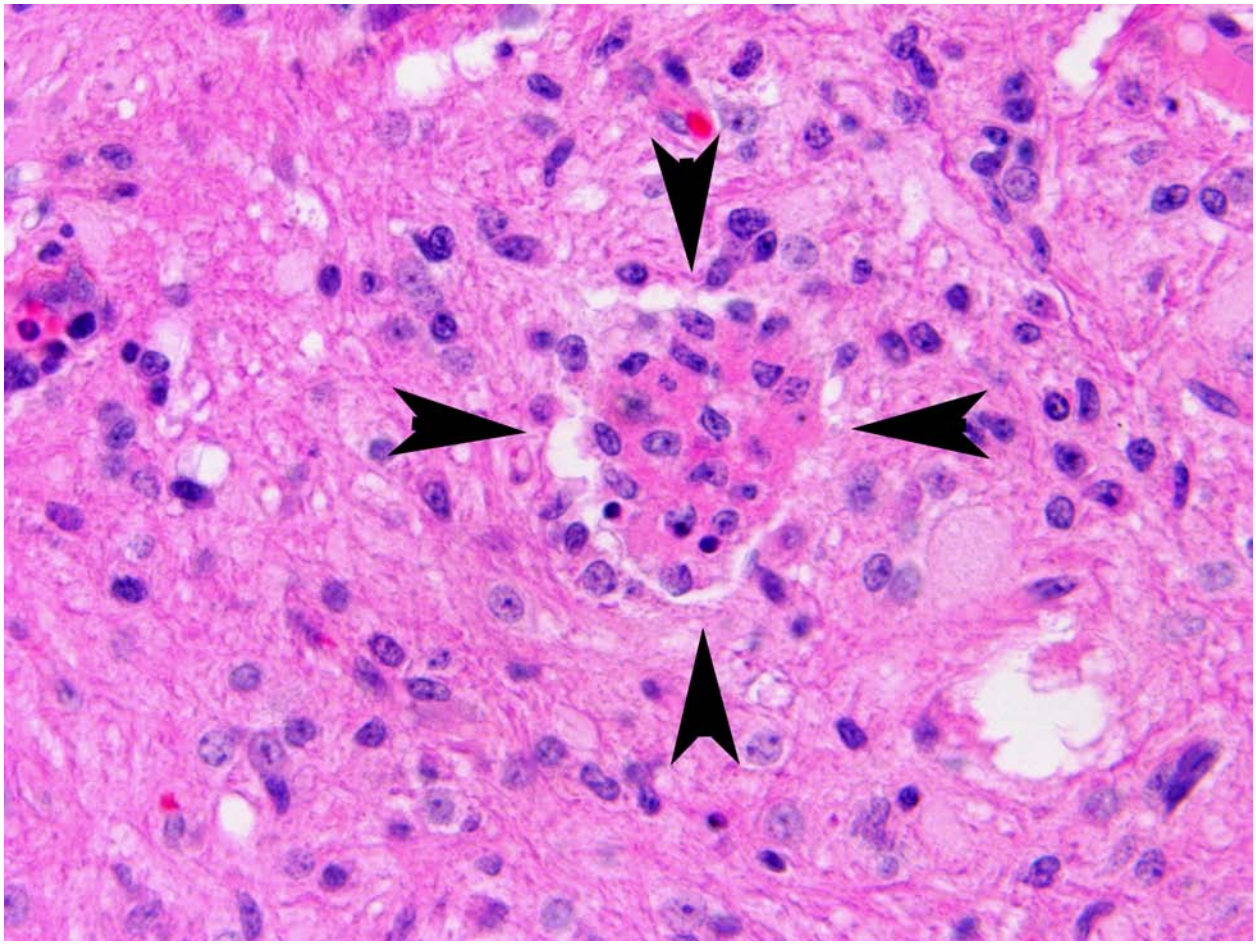
PEVs are ubiquitous and intestinal infection is frequent but most infections are asymptomatic. PEVs undergo local replication in the large intestine and ileum, mucosal lymphoid tissues and lymph nodes, followed by viremia that can lead to the central nervous system infection. The infrequent disease can appear in the postweaning period (generally 6 to 10-week-old pigs) secondary to mixing of pigs from different sources and decreased maternal immunity, and can result in mild to severe neurological disorders.[2] PEV serotype I is highly virulent and the causative agent of Teschen



2-1, Spinal cord, gray matter, pig. Lower motor neurons of the ventral horns show a variety of degenerative changes, including marked cytoplasmic swelling with loss of Nissl substance (arrow) to an angular shape with eosinophilic cytoplasm (arrowhead) (HE 400X)



2.2 Spinal cord, gray matter, pig. Necrotic neurons are angular with dark eosinophilic cytoplasm. (HE, 400X)



2-3. Spinal cord, gray matter, pig Necrotic neurons are occasionally surrounded by numerous glial cells (satellitosis and neuronophagia). (HE 400X)

disease. Clinical signs are acute and include fever, ataxia, seizures, convulsions, opisthotonos, coma and death; mortality is high. Milder infections (also known as Talfan disease, poliomyelitis suum, benign enzootic paresis and Ontario encephalomyelitis) are linked to less virulent strains and clinical signs include ataxia, limb paresis, flaccid paraparesis or paraplegia; mortality is usually low and most pigs can recover.

There are no gross lesions in enteroviral polioencephalomyelitis. Microscopically, lesion distribution depends on the involved strain, but the cerebrospinal axis from the olfactory bulb to the lumbar cord is consistently involved.[3] As described above, there is progressive lymphocytic perivascular cuffing and infiltration of mononuclear cells (nonsuppurative polioencephalomyelitis) into the neuropil secondary to motor neuron degeneration in the ventral gray column. Neuronophagia and glial nodules, characteristic of CNS viral infections, are key features. Gray matter of the spinal cord and adjacent dorsal root ganglia (ganglioneuritis) are more involved than white matter, and changes in the dorsal horn are milder than in the ventral horn.[6] Other changes may be present, such as vacuolation at the periphery of the soma of neurons. There is relative sparing of the cerebral and cerebellar cortices, contrary to the deep substance of the cerebellum that is consistently and severely involved. Lesions can also be found in the pontine nuclei, medulla, thalamus and periaqueductal gray matter.[5] Leptomeningitis may be patchy and sometimes severe in the cerebellum in the older pigs in which the course is prolonged.[3]

Transmission electron microscopic examination reveals separation of ribosomes from the endoplasmic reticulum and loss of Nissl body clusters that provoke a progressive dilation of the endoplasmic reticulum.[5]

Survival is possible sometimes with sequelae. Extraintestinal infections are relatively transient, whereas the virus persists in the large intestine for several weeks.[2]

In this case, differential diagnoses included Teschen disease, Talfan disease and hemagglutinating encephalomyelitis virus (HEV) infection. To our knowledge, Teschen disease is not known to occur in

North America and is associated with high mortality rates. HEV was not isolated and would also have induced higher mortality rates. Porcine reproductive and respiratory syndrome (PRRS) should also be considered in cases with concomitant pulmonary lesions.

PEV are specific and are not zoonotic. Although PEV are different from the human enterovirus (poliovirus) that is responsible for acute flaccid paralysis called "polio", histological lesions induced by poliovirus are quite similar to those described above.[4]

Other enteroviruses are encountered in swine (Swine Vesicular Disease virus) and in mice (Theiler's murine encephalomyelitis virus infection). The virus causing avian encephalomyelitis, formerly classified as an enterovirus, has now been reclassified as a *hepatovirus*.[1]

JPC Diagnosis: Spinal cord, ventral horns: Neuronal necrosis, multifocal, marked, with gliosis, satellitosis, neuronophagia, and dorsal funiculi axonal degeneration.

Conference Comment: The contributor provided the most common examples of viruses that are typical rule outs for this disease. Other viral etiologies considered by conference participants were rabies virus, porcine herpesvirus 1 (pseudorabies), and Japanese encephalitis virus. With rabies virus infection, there is perivascular cuffing, focal gliosis, hemorrhage, neuronal degeneration, vacuolation of neurons and neuropil, and intracytoplasmic Negri bodies.[3] Pseudorabies presents histologically as a nonsuppurative meningoencephalitis with trigeminal ganglioneuritis, with marked neuronal degeneration and necrosis, and eosinophilic intranuclear inclusion bodies can be seen within numerous cells in the CNS.[8] Japanese encephalitis virus is often found in stillborn and neonatal piglets, and is histologically very similar to Teschen/Talfan disease. Gross lesions include hydrocephalus, cerebellar hypoplasia, hypomyelinogenesis, and anasarca.[3]

Another rule out that was regarded by conference participants was toxic poliomyelomalacia caused by selenium; however, this would present as a bilaterally symmetric malacia with distribution in the white and gray matter, with loss of neurons and endothelial and glial proliferation.[3]

This case provides wonderful examples of neuronophagia, neuronal necrosis, and satellitosis, which are characteristic of this and other cases of viral encephalitis. It is difficult to distinguish neurogenic viral etiologies by histology alone, and special diagnostic techniques are usually required.

There was some variation between slides in this case, most notably in the number of spinal nerves, some of which had perivascular inflammatory cells.

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CASE III: 02011 WSC CASE 2 0 0 (JPC 4003028).

Signalment: 10-week-old male Sprague-Dawley rat (*Rattus norvegicus*).

History: Tissue from a rat fed a high salt diet (8% NaCl) and infused with angiotensin II for 14 days.

Gross Pathology: None described.

Laboratory Results: Not available.

Histopathologic Description: Kidney: Multifocal glomeruli globally or segmentally have markedly thickened capillary loops and mesangial matrix expansion by homogeneous eosinophilic material (glomerular hyalinosis and sclerosis) resulting in glomerular tufts 50% to 100% larger than unaffected tufts. Multifocally, cells within affected glomerular tufts contain abundant hypereosinophilic cytoplasm and plump nuclei (hypertrophy) and some affected tufts contain pyknotic cellular debris (glomerulonecrosis). Other tufts contain cells with basophilic or vacuolated cytoplasm. Bowman's capsule parietal epithelium is hyperplastic with prominent, rounded nuclei and abundant slightly basophilic cytoplasm. Frequently, there is adhesion of the expanded glomerular tuft to the parietal epithelium (synechiae). Bowman's capsule basement membrane is variably thickened and surrounded by fibrous connective tissue (periglomerular fibrosis). The tunica media of small caliber vessels, particularly cortical and afferent and efferent juxtaglomerular arterioles and rarely arcuate and interlobar arteries, is multifocally expanded/ replaced by a homogenous, deeply eosinophilic material (fibrinoid necrosis) and occasionally contains basophilic cellular debris. Affected vessels in some areas are surrounded by concentric layers of loose fibrous connective tissue (fibrosis), small to moderate numbers of mononuclear leukocytes, and occasionally, extravasated erythrocytes (hemorrhage). Smooth muscle cells and endothelial cells are hypertrophic. Throughout the cortex are numerous regenerative tubules characterized by crowded tubular epithelial cells with basophilic (occasionally vacuolated) cytoplasm, deeply basophilic nuclei and rare mitotic figures. The tubular alteration is most prominent adjacent to affected glomeruli. Proximal tubules and collecting ducts frequently are ectatic and/or contain hypereosinophilic, homogenous proteinaceous fluid (proteinuria) or sloughed cells (cellular casts) and occasionally are lined by attenuated

Table 1. Selected rat models of systemic hypertension.

Rat Model	Hyper-tension Etiology	Hypertension Mechanism of Action	Age of Onset	Blood Pressure Elevation (Systolic)	Comments
Stroke-prone Spontaneously Hypertensive Rat (SHRSP)[2,9]	Primary, genetic	Renally related -- Transplanting a kidney from SHR to a normotensive Wistar rat increases blood pressure in the recipient	Begins at 6-7 weeks of age	200 mmHg	80% die from stroke
Spontaneously Hypertensive Rat (SHR)[2,9]	Primary, genetic	Renally related -- Transplanting a kidney from SHR to a normotensive Wistar rat increases blood pressure in the recipient	Begins at 5-6 weeks of age, maximal by 12 weeks	180-200 mmHg	30% develop heart failure at 4-5 months of age
Dahl Salt Sensitive Rat[9]	Primary, genetic and dietary	High dietary sodium content increases circulating sodium causing osmotic pull into vasculature, elevating pressure on vessel walls	4-6 weeks of age	Increased even on normal diet; Steeply elevated on high salt diet	30% develop heart failure at 18 months of age
Transgenic TGR(mRen2)27 Rat[4,9]	Primary, genetic	Overexpression of the mouse Ren-2 gene (increased renin activity)	Begins at 5 weeks and maximal by 10 weeks of age	Heterozygous: 240 mmHg; Homozygous: 300 mmHg (high mortality)	Mortality from heart failure at 10 weeks of age
Double Transgenic (dTG) Rat[11]	Primary, genetic	Expresses both human renin and angiotensinogen genes	Early	200-220 mmHg	50% mortality by 7-8 weeks of age
Deoxycorticosterone Acetate (DOCA) + High Salt Diet[2,7,9]	Secondary, endocrine/ dietary	Salt-dependent, mineralocorticoid (DOCA)-induced reabsorption of salt and water resulting in increased blood volume Also increased secretion of vasopressin = vasoconstriction + water retention	Hyper-tension begins 1-2 weeks after start of DOCA and high salt diet	200 mmHg	Mortality from brain, vascular, and renal lesions after 4-8 weeks of treatment
Ang II Infusion and High Salt Diet[10]	Secondary, endocrine	Daily infusion of angiotensin II via osmotic pump and high salt diet	Begins 1 day post infusion	130-200 mmHg	Mortality from renal glomerulosclerosis and vascular necrosis
Goldblatt Method: Two-Kidney One-Clip[2,9]	Secondary, renal	Clip on one renal artery increases circulating renin and angiotensin II	Develops 6 weeks post-surgery	160 - 190 mmHg	Mortality from renal failure and cardiovascular complications
Goldblatt Method: Two-Kidney Two-Clip[2]	Secondary, renal	Partial occlusion of both renal arteries (two stage surgery) increases circulating renin and aldosterone	Develops 4 weeks post-surgery	160 - 190 mmHg	
Godlblatt Method: One-Kidney One Clip[2]	Secondary, renal	Uninephrectomy and clip on renal artery of remaining kidney with rapid salt and water retention; Plasma renin activity is normal	Within hours of surgery	160 - 190 mmHg	
Renal Remnant[12]	Secondary, renal	Uninephrectomy and segmental 2/3 ablation of remaining kidney to 5/6 total renal mass	Within hours of surgery	170-190 mmHg	Mortality from renal failure with cardiovascular complications

epithelium. The interstitium is multifocally expanded by loose fibrous connective tissue and small numbers of mononuclear leukocytes.

Contributor's Morphologic Diagnosis: 1. Glomerulonephropathy, multifocal, chronic with glomerular hyalinosis and sclerosis and tubular degeneration/ regeneration, atrophy, ectasia and proteinuria.
2. Arteriolopathy, proliferative, chronic, multifocal with medial degeneration and fibrinoid necrosis.

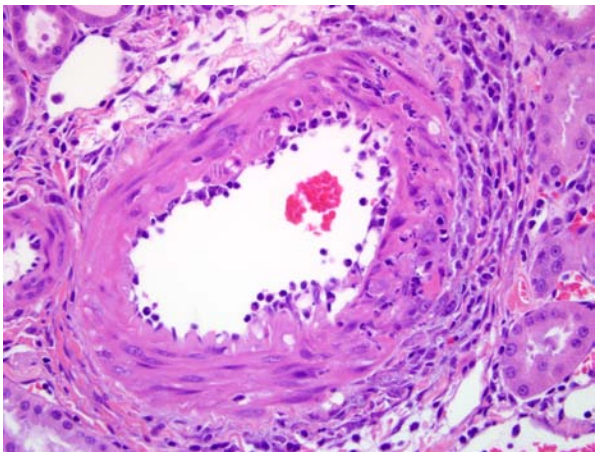
Contributor's Comment: Hypertensive nephropathy is a common sequela to chronic high blood pressure in humans. One quarter of the US population is hypertensive and approximately 6% of affected individuals have chronic kidney disease with the risk of progression to end stage renal disease.[1] The relationship of hypertension and chronic renal disease is complex since hypertension is both a cause and consequence of renal disease.[6] In the human population, risk factors for hypertensive nephrosclerosis include African ancestry, severe and sustained hypertension, family history, microalbuminuria, diabetes mellitus, and left ventricular hypertrophy.[1] The morphological features of human hypertensive nephrosclerosis include vascular wall medial thickening with arteriolar hyaline deposits and intimal fibrosis as well as focal glomerular ischemic changes (retraction, wrinkling, and folding of the capillary walls) with basement membrane thickening, global or even segmental glomerulosclerosis and varying but subtotal foot process effacement (electron microscopy). Tubular atrophy and interstitial fibrosis also occur. This presentation of glomerular changes may be referred to as "focal segmental glomerulosclerosis" (FSGS) and may be attributed to hypertensive renal injury when accompanied by glomerular ischemic changes, periglomerular fibrosis, subtotal foot process effacement and disproportionate vascular sclerosis.[5] When diagnosing the human patient, clinical history is critical and hypertension typically precedes renal insufficiency and proteinuria.[5]

In experimental medicine, rats are the most popular hypertensive model and the spontaneous hypertensive rat (SHR) is the most common model utilized.[9] Impaired endothelium dependent relaxation, cardiac hypertrophy and/or heart failure, cerebral hemorrhage, nephropathy and/or renal failure are features of most models of rat hypertension, mimicking the human spectrum of disease. Hypertension in rats is defined as sustained systolic blood pressure of greater than 150 mmHg.[2] The submitted case illustrates microscopic features that developed after 14 days of hypertension induced by high salt diet and angiotensin II infusion.

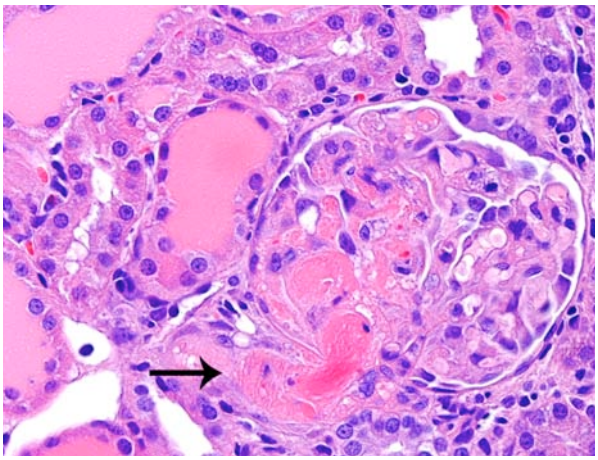
Table 1 on the included chart compares selected systemic hypertensive rat models.

Angiotensin II has a wide array of biological effects including (from Kobori et. al[3]):

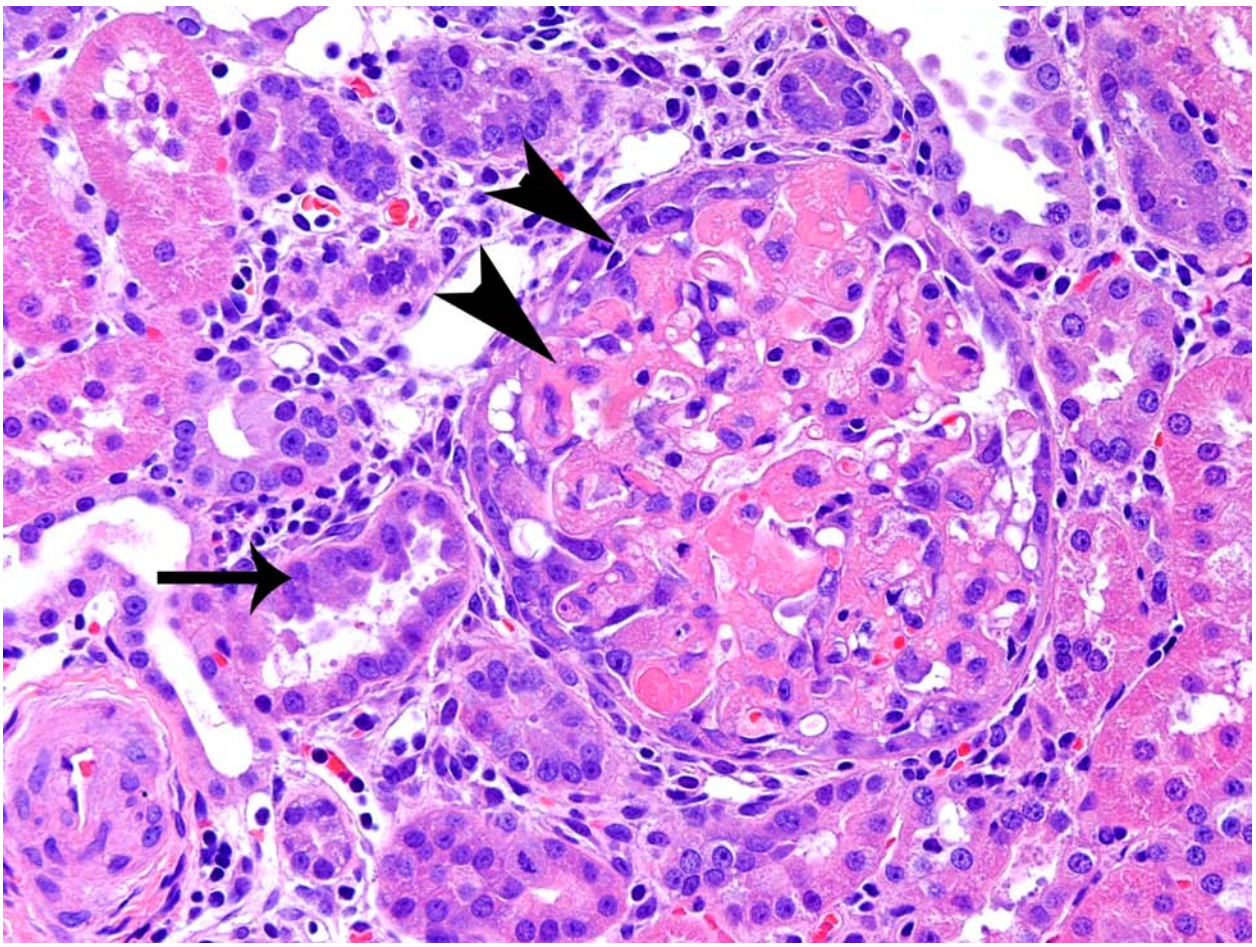
1. Arteriolar vasoconstriction (in the glomerulus, efferent > afferent)
2. Stimulation of aldosterone secretion (zona glomerulosa of the adrenal cortex)
   Acts on distal convoluted tubules and collecting ducts reabsorb sodium and water from urine (exchange for potassium which is excreted in urine) ↑blood volume ↑blood pressure
3. Secretion of anti-diuretic hormone from the pituitary
   a. Vasoconstriction
   b. Reabsorption of water in the kidneys
   c. Stimulation of thirst and salt appetite



3-1. Kidney, Sprague-Dawley rat. The tunica media and adventitia of arterioles are expanded by eosinophilic protein and necrotic cellular debris (fibrinoid necrosis). (HE 400X)



3-2. Kidney, Sprague-Dawley rat. Glomerular tuft with fibrinoid necrosis of the afferent arteriole (arrow) and hyalinosis of the tuft. (HE, 400X)



3-2. Kidney, Sprague-Dawley rat. Glomerular tufts frequently contain hypereosinophilic material (hyalinosis – arrowhead) and there is marked hyperplasia and hypertrophy of parietal epithelium. Tubular epithelium is often basophilic with vesicular nuclei and piling up (regeneration = arrow) (HE 400X)

4. Regulation of sodium transport by renal and intestinal epithelium
   In the kidney, stimulation of Na+/H+ exchange on proximal tubules, thick ascending limb of the loop of Henle, and collecting ducts increased sodium resorption
5. Hypertrophy of renal tubular epithelium
6. Release of prostaglandins counteracts renal vasoconstriction
7. Reduced renal medullary blood flow
8. Increases tubuloglomerular feedback sensitivity lower tubular perfusion (prevents excessive rise in glomerular filtration rate)
9. Other actions
   a. Enhanced cardiomyocyte growth and contractility
   b. Stimulation of release of catecholamines (norepinephrine from adrenal medulla)
   c. Increases sympathetic nervous system activity

JPC Diagnosis: 1. Kidney, arterioles: Arteriopathy, proliferative and necrotizing.
2. Glomerulosclerosis, multifocal, moderate, with tubular degeneration, regeneration, and protein casts.

Conference Comment: Differential diagnoses discussed during conference included chronic progressive nephropathy (CPN) and polyarteritis nodosa (PAN). CPN generally does not include a vascular component centered on small arterioles as in this case, and CPN typically has conspicuous basement membrane thickening, which is absent in this case. Polyarteritis nodosa tends to affect vessels of a larger caliber than is typical with hypertensive nephropathy and to affect vessels more randomly. As the name indicates, CPN becomes progressively more severe with age, and PAN is typically a disease of aged rats.

The contributor has provided an excellent comparative review of hypertensive nephropathy, a condition that is morphological similar in most affected species.

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CASE IV: 08A747 (JPC 3134315).

Signalment: 12.7 yr female Indian rhesus monkey (Macaca mulatta).

History: This animal was inoculated with SIVB670 (clone12) six years prior to necropsy. It had a long history starting 2 years after inoculation of hair plucking that escalated to self-trauma. Epistaxis was noted from time to time. It was sacrificed due to new self-trauma, depression, and anorexia.

Gross Pathology: The surface of the left parietal region of the brain had a 1x2 cm darkened soft depression that extended to the subcortical white matter. Self-trauma to the foot and vegetative valvular endocarditis were noted.

Laboratory Results: Multiple clinical nasal swabs contained beta hemolytic coagulase positive staphylococcus. Bacterial culture of the brain was negative.

In situ hybridization of the kidney and brain demonstrates the presence of SV40 entire genomic nucleic acid (nick translation biotinylated probe, Enzo Life Sciences) in nuclei of renal tubule epithelium and oligodendrocytes.

Terminal CBC: 2.7 RBC, 5.5 Hgb, 19.8 Hct, 3.74 WBC, 65 Seg, 1 Eo, 3 Mno. 31 Lym, 150000 Plt, 6.4 Rtc

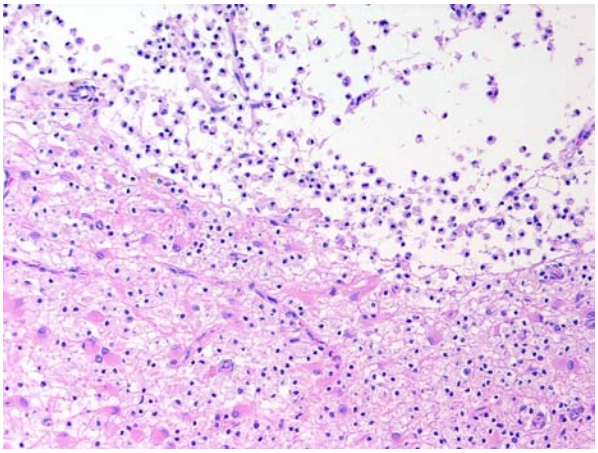
18 months prior CBC: 5.9 RBC, 14.3 Hgb, 43 Hct,3.8 WBC, 58 Seg, 6 Eo, 30.7 Lym
290000 Plt, 0 Rtc

Terminal Chem: 147 Na, 3.4 K, 111 Cl, 5.8 Pro, 2.1 Alb, 3.7 Glob, 0.6 A/G, 30.6 BUN, 85 Glu, 0.56 Crt

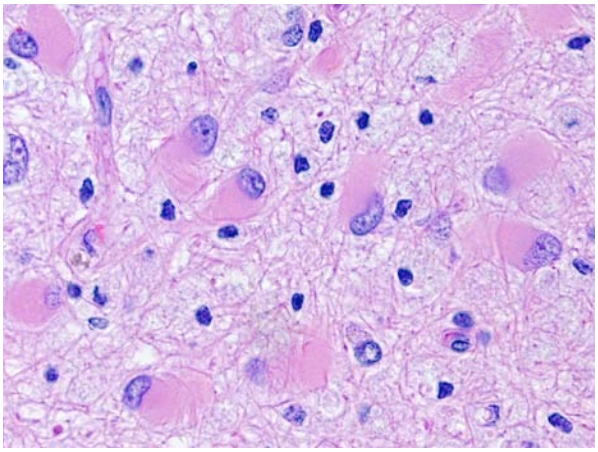
Histopathologic Description: Brain: Multiple zones of malacia and loss of neuropile are present in the cortical grey matter and, in some sections, extend into vacuolated white matter with increased numbers of glial cells. Malacic areas are infiltrated with plump granulated macrophages and smaller numbers of polymorphs. Gemistocytic astrocytes and oligodendrocyte cell bodies are swollen and hyalinized with marginated chromatin and poorly defined to distinct grainy amphophilic intranuclear inclusions. Scattered blood vessels in the surrounding parenchyma have modest cuffs of lymphoid cells or polymorphonuclear leukocytes in malacic areas. Meninges contain mild perivascular lymphoid infiltrates.

Contributor's Morphologic Diagnosis: Brain: Multifocal severe subacute meningoencephalitis with multifocal malacia, demyelination and gliosis, SV40.

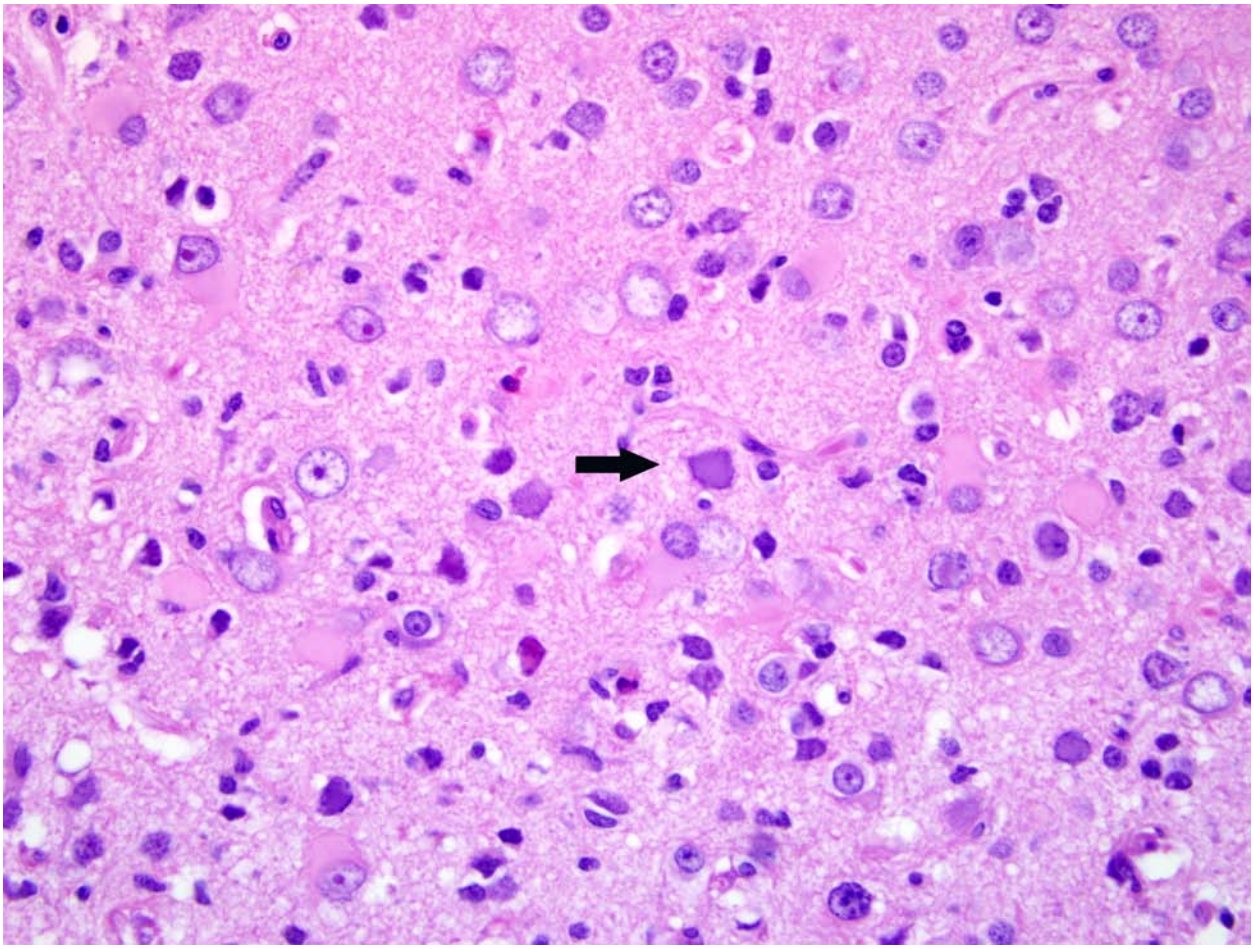
Contributor's Comment: SV40 is an oncogenic DNA virus in the Papova virus family and the polyoma virus subfamily. SV40 produces large and small DNA-binding proteins (T antigens) which serve as DNA molecular chaperones with roles in viral replication (transcription and viron assembly) and tumorigenesis.[7] The rhesus monkey is the natural host, and SV40 persists as a clinically silent renal infection unless immunodeficiency due to Simian Immunodeficiency Virus (SIV) infection allows polyomal viral disease in the kidney, lung or brain. Human polyoma viruses, John Cunningham virus (JVC) and BKV are comparable, and subclinical renal infections can be associated with pregnancy, diabetes, or old age. In immunodeficiency, JVC infects oligodendrocytes and



4-1. Cerebrum, white matter, rhesus macaque. Multifocally, the submeningeal white matter is necrotic, cavitated, and replaced by numerous Gitter cells (top) and adjacent tissue is infiltrated by many glial cells and large gemistocytic astrocytes. (HE 200X)



4-2. Cerebrum, white matter, rhesus macaque. Gemistocytic astrocytes with abundant eosinophilic cytoplasm and eccentric nuclei. (HE 600X)



4-3. Cerebrum, white matter, rhesus macaque. Rarely astrocytes contain large amphophilic intranuclear viral inclusion bodies (arrow). (HE 400X)

causes progressive multifocal leukoencephalopathy (PML) while BKV-infected individuals develop fatal tubulointerstitial nephritis.[3] SIV-infected monkeys have two morphologic presentations of polyoma viral disease in the brain; 1) PML characterized by multifocal demyelination with inflammation and gitter cell accumumation[3] and 2) meningoencephalitis (ME) affecting grey matter without significant demyelination.[5] Both manifestations display gemistocytic astrocytes and swollen oligodendrocytes with intranuclear inclusions, microgliosis, and T lymphocyte infiltration. It has been suggested that, in monkeys, PML is associated with reactivation of a latent SV40 infection while ME is a manifestation of a primary SV40 infection in younger animals.[5] This case has the morphologic lesions of ME and the renal involvement consistent with a primary SV40 infection but the older age of the monkey, the long time duration between SIV inoculation and disease, and presence of demyelination previously linked with PML.

JPC Diagnosis: Brain: Polioencephalitis, necrotizing, multifocal, severe, with gemistocytes, axonal degeneration, and amphophilic intranuclear viral inclusions.

Conference Comment: Simian polyomavirus has historical significance, as it was first identified in 1960 in rhesus macaque renal cell cultures used to manufacture both Sabin and Salk polio vaccine, to which millions of inoculants were exposed. The virus is named for its propensity to produce vacuoles in infected cells, hence the name simian vacuolating virus 40.[2] SV40 suppresses p53 expression through the SV40 Large T-antigen and SV40 Small T-antigen, resulting in loss of transcription initiation.[7] SV40 can also play a role in development of tumors, most commonly sarcomas, and has been used in rats to develop a model for primitive neuroectodermal tumors (PNETs) and medulloblastomas.[1] Additionally, there is ongoing research into the potential of SV40 to cause cancer in humans, as SV40 has been detected in a variety of human cancers, although this topic remains controversial.[3]

Initially, MHC-I molecules cluster in caveolae and bind to SV40. SV40 then enters the host cell via

endocytosis through caveolae, small uncoated invaginations in the host cell plasma membrane important for signal transduction and calcium regulation. Caveolins, membrane bound proteins important to the structure and function of caveolae, associate with the virus membrane, facilitate budding of the virus-containing vesicle into the cell cytoplasm, and the subsequent transfer of virus to the endoplasmic reticulum.[6]

There is some variation among slides and, depending on the section, lesion distribution is either focal or multifocal.

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