Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE
2020-2021

Conference 11

9 December, 2020

Joint Pathology Center
Silver Spring, Maryland

CASE 1: 7950-19 (4137581-00)

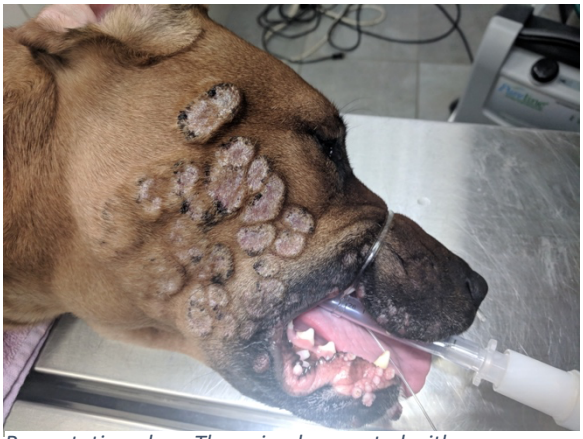
Signalment:
Two-year-old, male, Doberman pinscher mix dog (*Canus lupus familiaris*)

History:
The animal initially presented to the referring veterinarian 90 days prior and over the course of two months was treated with cefdopoxime and clindamycin for suspected folliculitis/ furunculosis. During the two-month treatment period, the animal displayed no clinical signs of systemic illness. Approximately 75 days after initial presentation, the animal presented with acute lethargy, inappetence, and lymphadenomegaly. Numerous skin biopsies of exophytic facial lesions were received for examination as well as lymph node aspirates from the enlarged prescapular and popliteal lymph nodes.

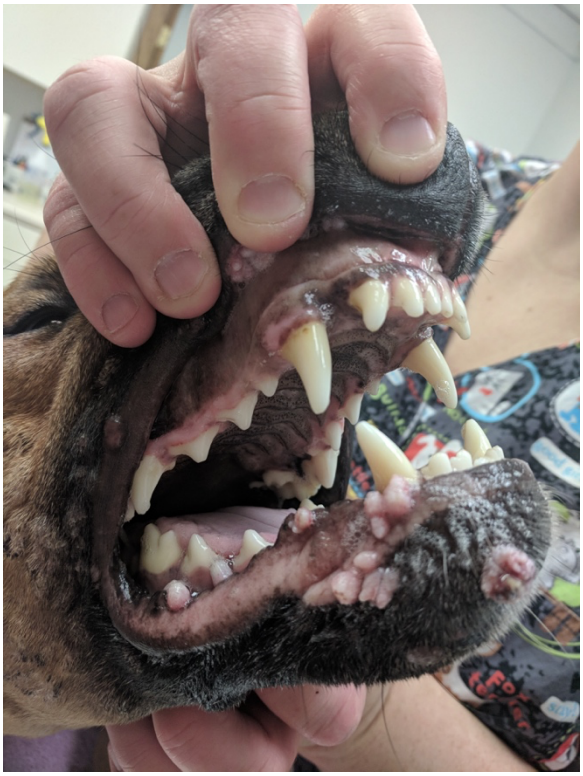
Gross Pathology:
N/A

Laboratory results:
N/A

Microscopic description:
Multiple tissue biopsies are received and evaluated in sixteen sections. Within the sections of haired skin are multiple masses that are predominantly within the superficial to middle dermis, lack a Grenz zone with the epidermis, and in some sections extend deep along pilosebaceous units. The masses consist round cells arranged in sheets which dissect through the dermal collagen. The round cells are large, with distinct cellular margins and moderate to large amounts of finely granular lightly eosinophilic cytoplasm. The nuclei are large and round to oval to reniform with stippled chromatin and 1-3 small nucleoli. Mitotic figures are common and range from 1-5 per high powered field, including a few atypical mitotic figures. There is moderate anisocytosis



Presentation, dog. The animal presented with numerous cutaneous facial masses, predominantly along the right side of the face, at the oral mucocutaneous junction, and within the oral cavity itself. (Photo courtesy of: University of Nebraska – Lincoln, Nebraska Veterinary Diagnostic Center, Lincoln, NE, https://vbms.unl.edu/nvdls)



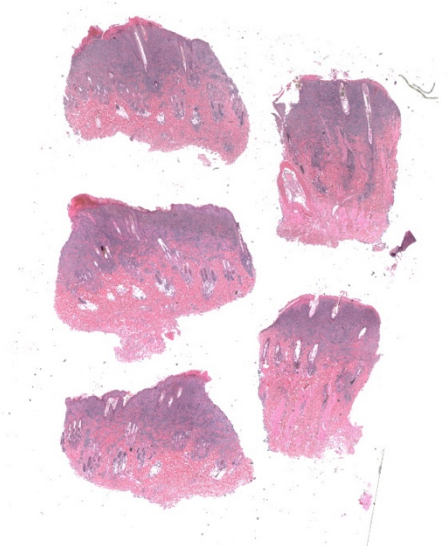
Presentation, dog. Another view of the exophytic masses of the face and oral cavity. (Photo courtesy of: University of Nebraska – Lincoln, Nebraska Veterinary Diagnostic Center, Lincoln, NE, https://vbms.unl.edu/nvdls)

and anisokaryosis. Many lymphocytes are present as are moderate numbers of plasma cells, although they are more prevalent along the periphery and they are more prevalently associated with the adjacent pilosebaceous glands. There is a small amount of scarring in the superficial dermis. The overlying epidermis is hyperplastic and contains a small amount of pseudoepitheliomatous hyperplasia.

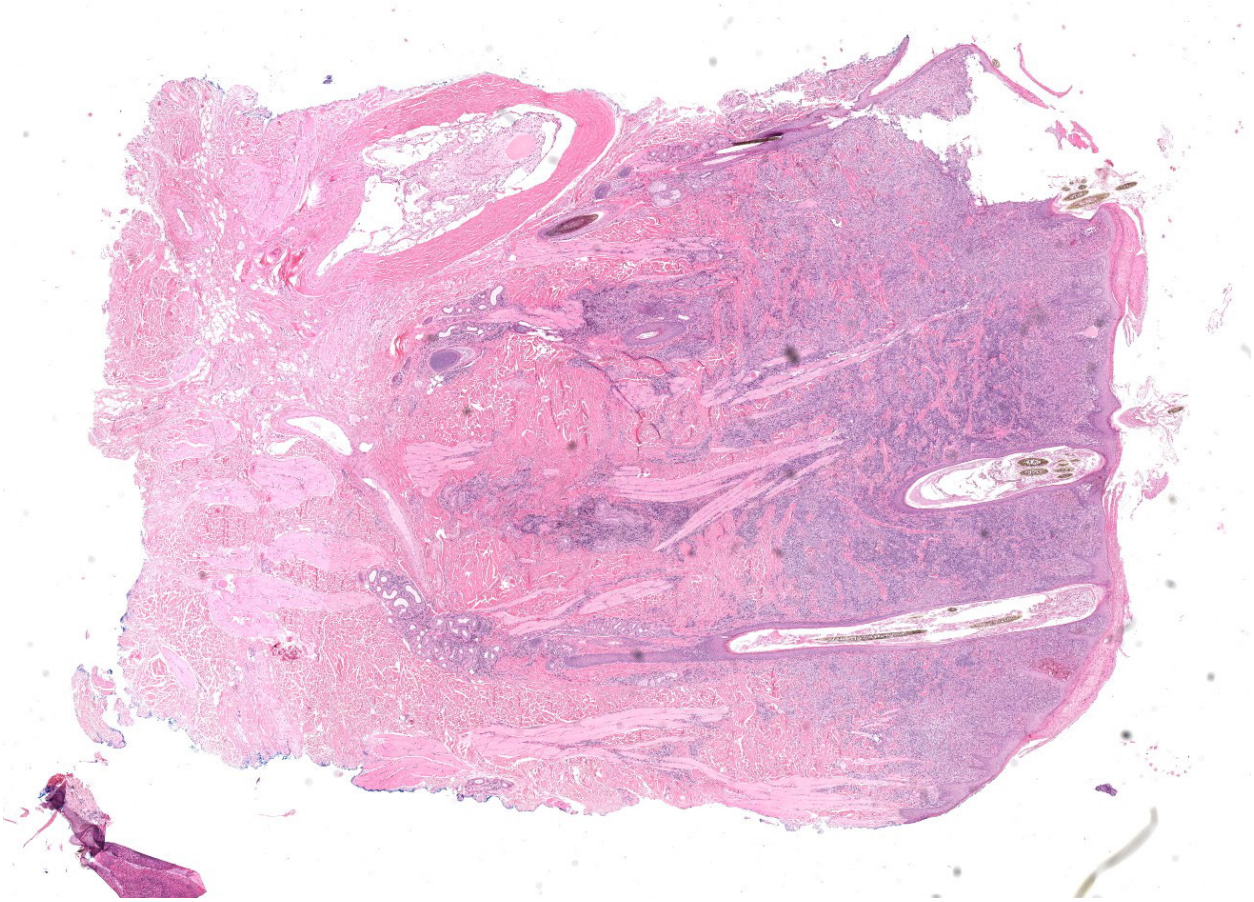
Contributor's morphologic diagnosis:
Langerhans cell histiocytosis

Contributor's comment:
Cutaneous histiocytoma is one of the most frequently diagnosed skin tumors in the dog that commonly occurs in younger dogs with breeds like the boxer, English cocker spaniel, Doberman pinscher, and Scottish terriers (among others) overrepresented in diagnosed cases.[3] Traditionally, histiocytomas are considered a benign lesion that will often spontaneously regress with or without surgical intervention.[2] Langerhans cell histiocytosis (LCH) however, represents a rare malignant form of histiocytic disease in the dog that can mimic histiocytoma grossly, but that often occur as multiple cutaneous lesions and can lead to metastasis of neoplastic cells and a rapid course of disease.[4] The prognosis for LCH with lymph node involvement is poor as the majority of dogs are euthanized due to rapid clinical deterioration associated with metastatic disease.[2]

Histologically, the histiocytoma and LCH can display roughly the same characteristics with LCH tending to exhibit more pronounced anisocytosis and anisokaryosis. Often, as in this case, the clinical history can be very helpful in leading to an accurate diagnosis. It appears likely that if given a single piece of the biopsies submitted without any clinical history pertaining to numerous lesions, even a well-trained diagnostician could mistake these lesions for a routine histiocytoma. The reliable expression of ionized calcium-binding adapter molecule 1 (IBA-1) is well characterized in proliferative histiocytic diseases of dogs and cats.[5] As such, an IBA-1 IHC was performed to confirm the neoplastic cells were of monocyte/macrophage origin and the cells exhibited widespread, intense staining among the neoplastic cells.



Haired skin, dog. Five punch biopsies of the skin are presented for examination. At low magnification, a dense infiltrate in the dermis abuts the multifocally ulcerated epidermis. (HE, 5X)



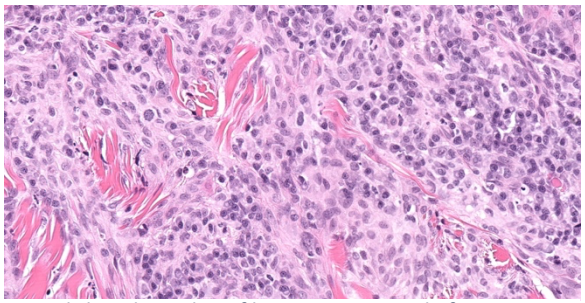
Haired skin, dog. The infiltrate is most dense in the superficial to mid-dermis and tracks downward along the adnexa. (HE, 20X)

A review of histiocytic diseases in dogs and cats describes LCH lesions often observed at mucocutaneous junctions and within the oral cavity.[4] Such lesions were observed in this case. The animal in this case continued to worsen clinically and died on his own within two weeks of the biopsy resection or approximately 105 days after the initial presentation to the referring veterinarian. The referring veterinarian described an easily palpable spleen postmortem, but an autopsy was not performed.

Contributing Institution:
University of Nebraska – Lincoln
Nebraska Veterinary Diagnostic Center
Lincoln, NE
https://vbms.unl.edu/nvdls

JPC diagnosis:
Haired skin, dermis: Langerhans cell histiocytosis, focally extensive, marked.

JPC comment:
In human pathology literature, there is still debate as how to best classify Langerhans cell histiocytosis: inflammatory, or neoplastic? The histologic appearance of the Langerhans cells is benign, the typical accompanying inflammatory infiltrate, and the local and systemic cytokine

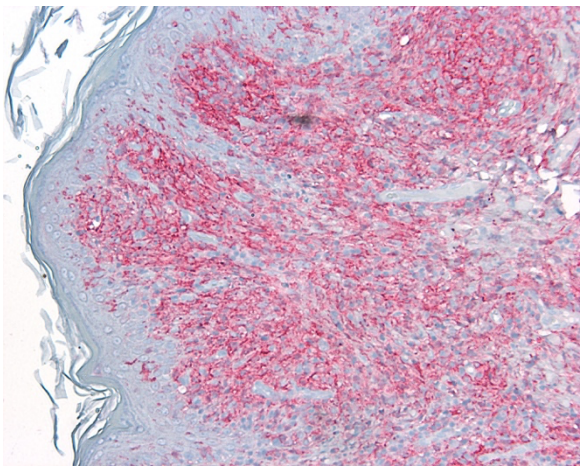


Haired skin, dog. The infiltrate is composed of numerous spindled to polygonal histiocytes with occasional mitotic figures (arrow) with fewer lymphocytes and plasma cells. (HE, 400X)

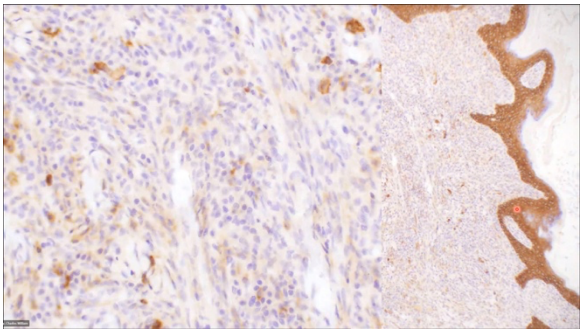
storm are suggestive of an inflammatory disease. Yet there is clonality of the cell population, identified mutations in the MAPK pathway, and some identified mutations shared with hematopoietic precursors provide support for a neoplastic classification. Approximately 57% of human cases of LCH express the *BRAF V600E* mutation, a key kinase in the RAS-RAF-MEK signaling pathway. The *BRAF V600E* mutation forces the MAPK pathway to be constitutively active, leading ultimately to increased expression of downstream transcription targets.[1]

Based on the presence of somatic MAPK mutations in myeloid precursor cells provides the current basis of classification of Langerhans cell histiocytosis as a myeloid neoplastic disorder. While there are differences between human and veterinary species, this classification appears valid until additional research in animals can be pursued.[1]

This case also provides the context to discuss immunohistochemistry to differentiate histiocytic diseases. As the contributor stated, IBA-1 is reliably expressed on histiocytes of all lineages. In addition, Langerhans cells in the dog and cat express CD1a, CD18, and E-cadherin. Crucially, E-cadherin is differentially expressed on Langerhans cells and not on interstitial dendritic cells, the origin of systemic histiocytosis,



Haired skin, dog. Widespread chromogen staining among the neoplastic cells confirming the presence of the histiocytic phenotype marker ionized calcium-binding adapter molecule 1. IHC Iba-1. 200X. (Photo courtesy of: University of Nebraska – Lincoln, Nebraska Veterinary Diagnostic Center, Lincoln, NE, https://vbms.unl.edu/nvdls)



Haired skin, dog. There is patchy but specific positive membranous immunolabeling by anti-E-cadherin antibodies in neoplastic histiocytes. Overlying keratinocytes are diffusely, strongly immunoreactive. IHC E-cadherin. Photo courtesy of: University of Pennsylvania, Philadelphia, PA)

cutaneous histiocytosis, histiocytic sarcoma, feline progressive histiocytosis, and dendritic cell leukemia. Additionally, if available, CD207 (Langerin), would be a specific marker for Langerhans cells, consistent with histiocytoma, cutaneous Langerhans cell histiocytosis, or feline pulmonary Langerhans cell histiocytosis.[4]

References:

1. Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. *The New England Journal of Medicine.* 2018;379:856-68.
2. Gross, T.L., Ihrke, P.J., Walder, E.J., Affolter, V.K. *Skin Diseases of the Dog and Cat*, 2nd ed. 2005; Ames, IA; Blackwell Publishing.
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CASE 2: C-5838-19 (4135141-00)

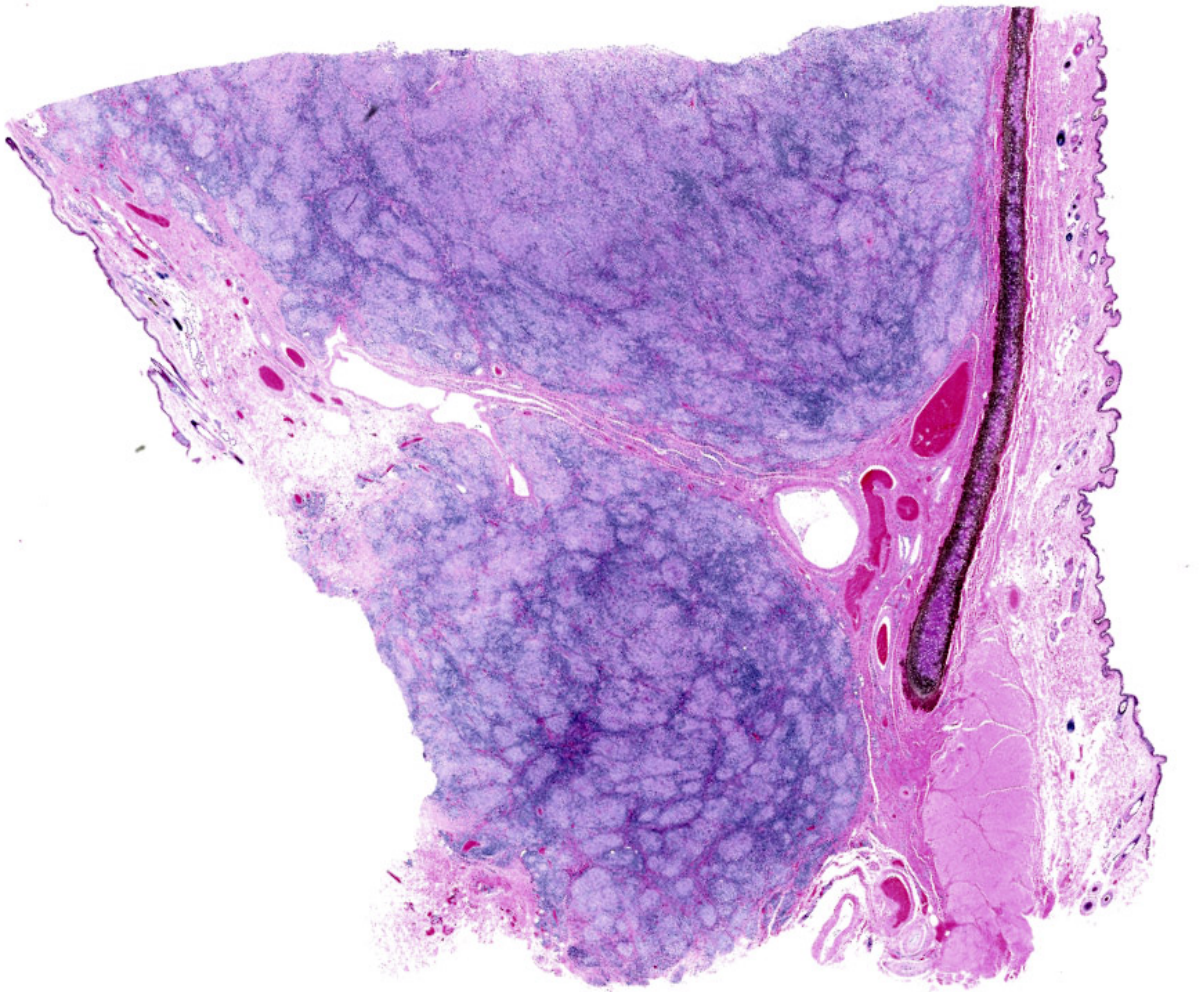
Signalment:
5½-year-old, castrated male, Greyhound, dog (*Canis familiaris*)

History:
Owner noticed small cutaneous lesion on ear a month ago. Since then, the lesion has grown to 2 cm in greatest diameter, and a chain of additional similar masses have developed.

Gross Pathology:
A 2.7 x 2.0 x 1.8 cm irregularly shaped section of haired skin diffusely expanded by an expansile cutaneous mass composed of several raised alopecic nodules labeled as removed from the left pinna is submitted for histopathologic examination.

Laboratory results:
N/A

Microscopic description:
Haired skin left pinna cutaneous mass: The dermis is infiltrated, expanded, and effaced by marked pyogranulomatous inflammation composed of anastomosing nodular pyogranulomas. The inflammation is composed of large numbers of epithelioid macrophages admixed with smaller numbers of multinucleate giant cells, neutrophils, lymphocytes, and plasma cells. Neutrophils are often located centrally and the lymphocytes and plasma cells along the periphery of the pyogranulomatous nodules.

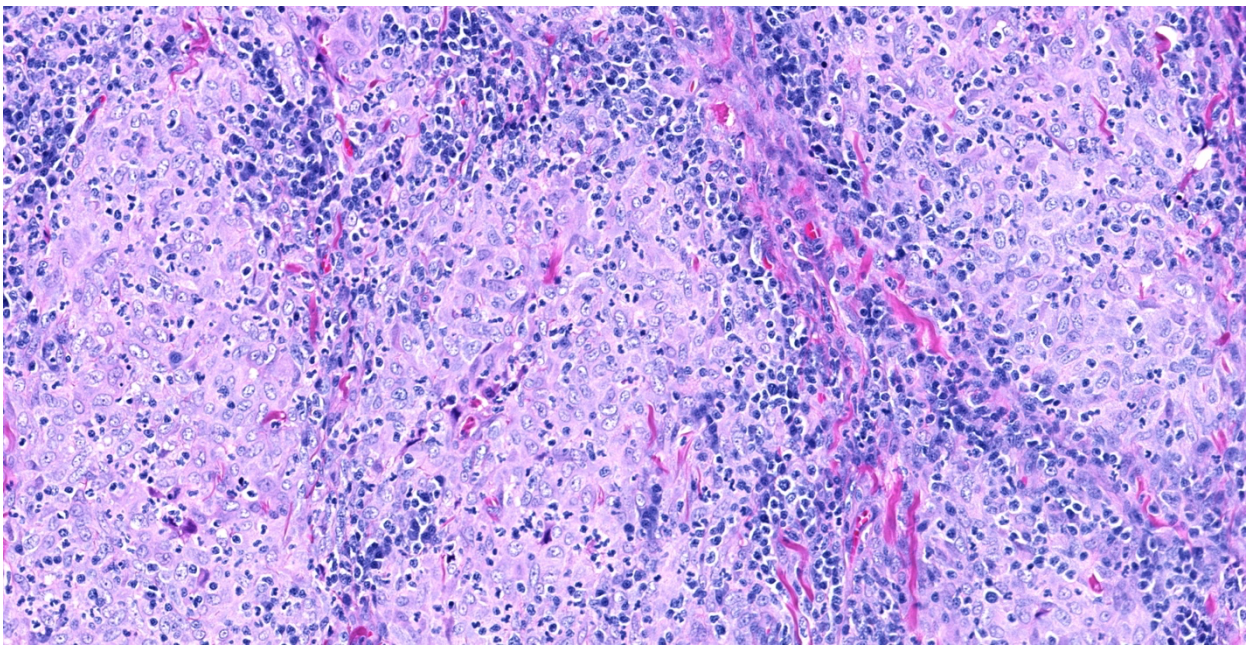


Pinna, dog. The dermis underlying the glabrous skin is markedly expanded by a multilobular, multinodular inflammatory infiltrate. (HE, 5X).

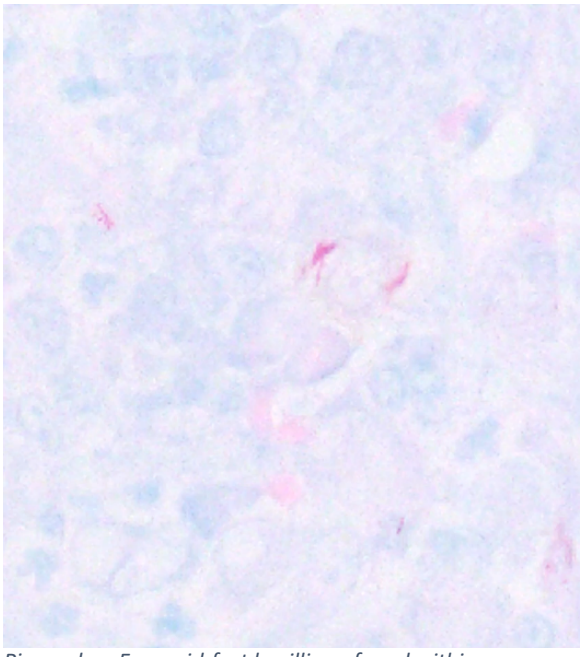
Lymphoplasmacytic cuffs are often also seen around intralesional and perilesional blood vessels. Acid fast and modified acid-fast stains reveal acid-fast bacteria within moderate numbers of individually scattered macrophages; some affected macrophages only have 1 or 2 intracytoplasmic acid-fast bacteria while others contain numerous (>20+) acid-fast bacteria. The acid-fast bacteria are pleomorphic in appearance, ranging from coccoid to rod-shaped to beaded and filamentous. The inflammation extends on both sides of the pinnal cartilage and infiltrates the superficial dermis approaching (but not obscuring) the dermo-epidermal junction. The overlying epidermis is locally extensively thickened due to acanthosis and is covered by small amounts of compact hyperkeratotic to orthokeratotic keratin, with one superficially eroded area with local serohemorrhagic to neutrophilic exudation and crusting.

Contributor's morphologic diagnosis:
Haired skin left pinna: Severe, chronic, locally extensive, pyogranulomatous pinnal dermatitis, with intrahistiocytic acid-fast pleomorphic bacteria (canine leproid granuloma).

Contributor's comment:
Canine leproid granuloma (CLG) is an uncommon (but probably underdiagnosed) nodular mycobacterial disease of the skin.[4,6] The condition usually occurs in short-coated breeds, with Boxer dogs and their crossbreeds remarkably overrepresented; Staffordshire Bull Terriers, Foxhounds, and Doberman Pinschers are also commonly affected. CLG presents clinically as single or multiple, firm, well-circumscribed nodules in the skin or subcutis that range in size from 2 mm to 5 cm; larger skin lesions may be alopecic or ulcerated.[6] The lesions may be non-pruritic and painless, but mild signs of pain or pruritus have been reported in some animals.[2] The dorsal surface of the pinna is a strongly predisposed site.[6] In one large study, the head (including the ears) was affected in 85% of dogs, and the ears were involved in 64%; less commonly the distal extremities (especially the forelegs) may be affected.[6] The great majority of CLG lesions are self-limiting with spontaneous regression of lesions often occurring within 3-6 months.[4,6] Persistence of lesions beyond this time frame may warrant antibiotic treatment; cell-mediated immunity may be compromised in these patients and thus spontaneous regression may not occur.[6] Extension of the infection to lymph nodes or visceral organs has not been reported.[4,6]



Pinna, dog. The inflammatory infiltrate is composed of numerous macrophages throughout which are scattered low numbers of neutrophils. Large numbers of lymphocytes and fewer plasma cells are present at the periphery of the nodules. (HE, 250X)



Pinna, dog. Few acid-fast bacilli are found within macrophages. Fite-Faraco. Photo courtesy of: University of Pennsylvania, Philadelphia, PA)

Cytologically, microscopic examination of fine needle aspirates of CLG syndrome lesions commonly reveals numerous, often spindle-shaped, macrophages admixed with variable numbers of lymphocytes and plasma cells, and fewer neutrophils. Usually few to moderate numbers of medium-length bacilli were detected within macrophages or extracellularly.[1] Histologically, canine leproid granulomas are composed of nodular to diffuse, granulomatous to pyogranulomatous inflammation. Very small, or moderate numbers of acid-fast pleomorphic bacteria are present within small clusters of intralesional macrophages or are within individually scattered macrophages.[1] The bacteria are acid-fast when stained with Ziehl-Neelsen stain and are usually bacilli when viewed in cytologic samples, but the microscopic appearance of the mycobacteria in histologic samples has been reported to be more pleomorphic and may include long, slender filaments in parallel sheaves, short and variably beaded bacilli, and highly beaded to coccoid forms.[1]

The causal agent of CLG is fastidious mycobacterial species which does not grow on synthetic mycobacterial media using standard microbiological methods. The disease has been reported in dogs from southern Africa, Australia, New Zealand, Brazil, and the United States (California, Florida, and the northeastern US).[3,7] Recent publications using molecular techniques have shown genetic uniformity of the mycobacteria found in leproid granulomas from dogs in Australia, Brazil, USA, New Zealand, and Australia.[2,3,5,8] The closest relative of the causative species of mycobacteria has been suggested to be *Mycobacterium simiae*.[5] The mode(s) of transmission of the causative organism remains unknown; percutaneous inoculation has been suggested as a likely route of entry and biting insects have been proposed as potential mechanical vectors.[2,6,8]

Contributing Institution:
Atlantic Veterinary College
University of Prince Edward Island
https://www.upei.ca/avc/

JPC diagnosis:
Haired skin, pinna, ear: Dermatitis, nodular and granulomatous, focally extensive, severe.

JPC comment:
The contributor summarizes the sparse literature on this entity. Other differentials that may be considered include histiocytoma, plasmacytoma, fungal dermatitis, sterile granuloma, and sterile pyogranuloma syndrome.[4]

The hallmarks of histiocytoma, including epithelial hyperplasia, reniform nuclei, moderate mitotic rate, and top-heavy distribution were not present in this case. Plasmacytomas most often have binucleated cells, "helmet" cells, with well differentiated and distinguishable plasma cells at the periphery of the neoplasm. While a fungal infection could result in a similar lesion, the performed GMS stain revealed no fungal hyphae or yeasts. Sterile pyogranuloma syndrome also affects Boxers disproportionately but tend to have a vertical orientation that tracks hair follicles and have a more varied inflammatory cell content. In this case, the acid-fast bacteria provide the etiology for these lesions.

References:

1. Charles J, Martin P, Wigney DI, Malik R, Love DN. Cytology and histopathology of canine leproid granuloma syndrome. Aust Vet J. 1999; 77(12):799-803.
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4. Gross TL, Ihrke PJ, Walder EJ, Affolter VK. Skin diseases of the dog and cat: clinical and histopathologic diagnosis, 2nd ed. pp. 281-283. Blackwell Publishing, Ames, IA, 2005.
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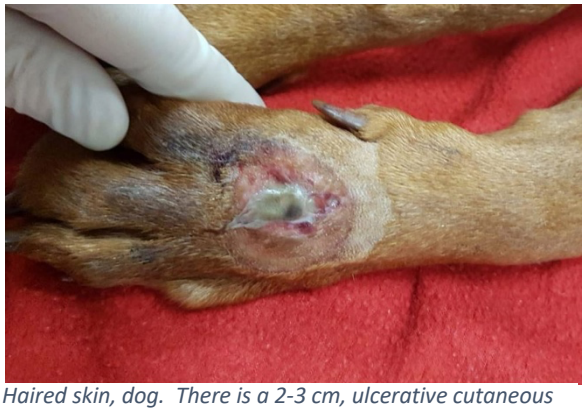
CASE 3: N542/18J (4137397-00)

Signalment:
5 month-old, entire male, Hungarian vizsla, dog (*Canis lupus familiaris*)

History:

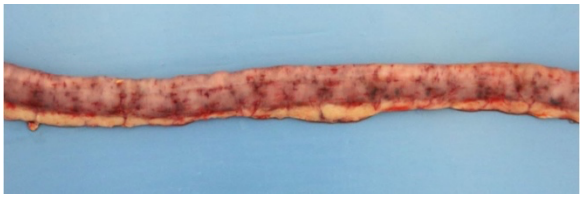


Haired skin, dog. There is a 2-3 cm, ulcerative cutaneous lesion on dorsal aspect of right metacarpus. (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

The dog lived on a farm, had been vaccinated and treated for parasites, had no prior medical history, and had never travelled outside of Ireland. The dog was referred to the UCD veterinary hospital with a 4-day history of a progressively developing well-demarcated, ulcerative and exudative skin lesion on the dorsal aspect of the left metacarpal region. This had been associated with excessive licking, swelling of the left pad, and a mild weight-bearing lameness. Clinical signs of lethargy, anorexia, pyrexia (39.6ºC) and vomiting had followed the onset of the cutaneous lesions.

The dog was managed with intravenous fluid therapy (5 ml/kg/hour, anti-emetic (maropitant 1 mg/kg IV SID), and gastroprotectant (omeprazole 1 mg/kg IV BID) and broad-spectrum antimicrobial therapy (amoxicillin-clavulanate).

On the day of admission, to obtain punch biopsies of the skin lesions, the dog was intravenously sedated with butorphanol 0.3 mg/kg and medetomidine 1 ug/kg. Five minutes later, a short (approximately 30 seconds) but violent episode of generalized tonic-clonic seizure activity associated with autonomic signs occurred. Intravenous diazepam was administered (0.5 mg/kg IV) and the dog was admitted to the intensive care unit to complete this procedure and to monitor the patient. Additional seizure activity, which responded to intravenous diazepam (0.5 mg/kg) followed by levetiracetam (20 mg/kg), was noted 12 hours later. On the third day of hospitalization, repeat hematology, biochemistry



Intestine, dog. There is multifocal serosal hemorrhage along the small and large intestine. (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

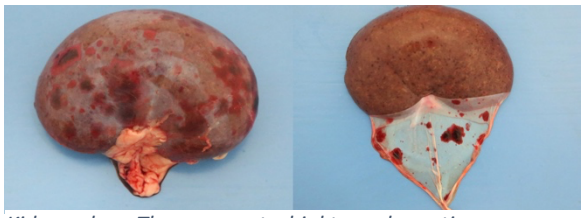
and urinalysis identified moderate thrombocytopenia and severe azotemia and hyperphosphatemia despite the concurrent administration of intravenous fluid therapy. Given the clinical signs and laboratory results (particularly the rapidly progressing azotemia), a tentative diagnosis of cutaneous and renal glomerular vasculopathy (CRGV) was made. Despite the very guarded prognosis the option of intensifying the supportive and monitoring care was offered to the owner. This was declined and humane euthanasia was performed.

Gross Pathology:

2-3 cm, ulcerating, encrusted, red-brown cutaneous lesion on dorsal aspect of right metacarpus extended into the subcutis. Pronounced petechiae and ecchymoses over serosal surfaces (particularly gastric, small and large intestinal serosae). The gastric and small and large intestinal walls were transmurally edematous. Two liters of pale-yellow tinged aqueous fluid was recovered from the peritoneal cavity. Pulmonary congestion/hemorrhage, especially dorsocaudally. Multifocal hemorrhagic infarcts (1-2 mm) scattered throughout cardiac ventricular myocardia. Petechiae over pancreas and bilaterally over renal cortices with cortices diffusely reddened and wet on sectioning. Petechiation within leptomeninges.

Haematology	Day One	Day Three
Platelets (RI 150 – 500 x 10^9/l)	**66**	**24**
Leucocytes (RI 6 – 17 x 10^9/l)	15.96	**27.87**
Neutrophils (RI 3 – 11.5 x 10^9/l)	**11.97**	**20.07**
Band neutrophils	-	**0.56**
Lymphocytes (RI 1 – 3.6 x 10^9/l)	1.92	2.51
Monocytes (RI0 – 1.35 x 10^9/l)	**1.92**	**4.74**
Smear report	Normal morphology of red and white blood cells. 1+ macroplatelets. Manual platelet count 150 x 10^9/L	Leucocytosis with mature neutrophilia, rare band neutrophil and monocytosis. Mild anisocytosis. 1+ macroplatelets. Manual platelet count 75 x 10^9/L

Biochemistry	Day One	Day Three
Total protein (RI 54 – 71g/l)	54.1	**48.7**
Globulin (RI 28 – 42g/l)	**26.3**	**25.3**
Calcium (RI 2.3 – 3mmol/l)	2.96	2.66
Creatinine (RI 20 – 120umol/l)	**179**	**412**
Cholesterol (RI 3.2 – 6.5mmol/l)	**8.16**	**6.82**
Alkaline phosphatase (RI 0 – 82U/L)	**434**	**203**
Total bilirubin (0.9 – 10umol/l)	3.1	0
Phosphorous (RI 0.8 – 1.8mmol/l)	**3.87**	**4.8**
Creatine kinase (RI 0 – 122U/L)	**486**	**8179**
Sodium (RI 137 – 151mmol/l)	144.3	144.5
Chloride (RI 105 – 117mmol/l)	**104.5**	**102.8**
Anion Gap (RI 11 – 26mmol/l)	19.74	22.56
Albumin (RI 25 – 38g/l)	27.8	**23.4**
A:G ratio (RI 0.59 – 1.11)	1.06	0.92
Urea (RI 3.6 – 8.6mmol/l)	**31.1**	**60.6**
Lipase (RI 0 – 130U/L)	33	**299**
Glucose (RI 3 – 6.5mmol/l)	**7.23**	5.58
Triglycerides (RI 0.11 – 1.69mmol/l)	0.51	1.05
Gamma glutamyl transferase (RI 0 – 16U/L)	0	0
Alanine aminotransferase (RI 0 – 36U/L)	**89**	**147**
Glutamate dehydrogenase (RI 0 – 16U/L)	**23.3**	0
Aspartate amino transferase (RI 0 – 37U/L)	**84**	**982**
Potassium (RI 3.7 – 5.8mmol/l)	3.84	4.96

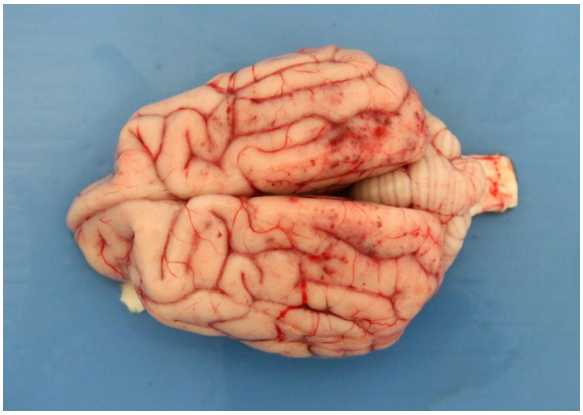


Kidney, dog. There are petechial to ecchymotic hemorrhage on the renal capsule and within the cortex. (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

Urinalysis	Day One	Day Three
Colour	Dark yellow	Red
Odour	Normal	Normal
Turbidity	Cloudy	Cloudy
Specific gravity	> 1.050	**1.018**
RBC	1+	**4+**
WBC	1+	1+
Protein	**3+**	**3+**
Glucose	-	**1-2+**
Casts	**Few granular, waxy and cellular**	-
Urine protein:creatinine ratio (RI <0.5)	**3.2**	
Coagulation testing		
PT (RI 7 – 14s)		9.4
aPTT (RI 12 – 25s)		21.8
D-dimers (RI 0 – 0.5mg/l)		0.2

Laboratory results:
Selected laboratory results on days 1 and 3 of hospitalization (values outside normal ranges highlighted in bold). Key findings: thrombocytopenia, mild hypoalbuminemia and azotemia.

Microscopic description:
Diffusely, glomeruli exhibit extensive segmental to global intravascular coagulation, necrosis, and hemorrhage (thrombotic microangiopathy). Arterioles at the glomerular vascular pole also feature luminal thrombosis, along with transmural and circumferential eosinophilic hyalinized material and karyorrhectic debris (fibrinoid necrosis). Necrotic vessels are surrounded by aggregates of admixed intact and degenerate neutrophils that extend into the adjacent interstitium where there is accompanying marked hyperemia and hemorrhage. Larger caliber cortical arterioles also feature hyalinization of their walls with accompanying karyorrhectic debris. Multifocally, contiguous transverse cross-sections of cortical tubules exhibit epithelial nephrosis and luminal hyaline to more granular casts. Casts in medullary tubules also vary from hyalinized to palely eosinophilic and finely granular in appearance.



Cerebrum, dog. Hemorrhages dot the leptomeninges. (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

Martius scarlet blue staining of renal lesions confirms extensive glomerular intravascular thrombosis and fibrin within necrotic arteriolar walls.

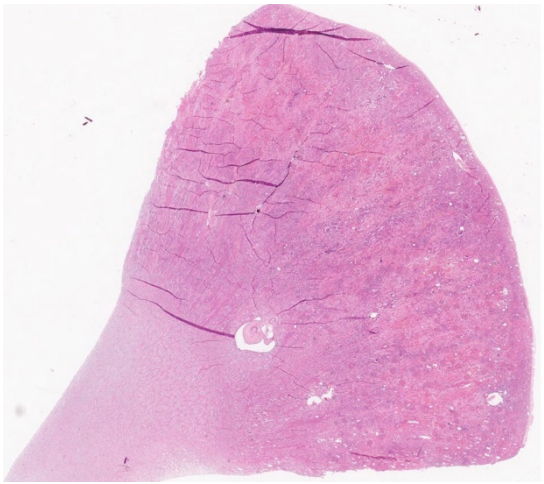
Additional Findings

Skin lesions: extensive deep ulceration with dense fibrinocellular exudate (admixed intact and degenerate neutrophils and macrophages) extending into subjacent fibrovascular tissue, dermis and subcutis with widespread microthrombi.

Heart: multifocal acute severe myocardial necrosis with subtle dystrophic mineralization and mild to moderate associated leucocytic infiltrates.

Small intestine: transmural fibrinoid necrosis and microthrombosis with associated luminal inflammation and hemorrhage, mucosal necrosis/erosion, submucosal edema and smooth muscle necrosis/hemorrhage.

Brain: focally within cerebral grey matter and meninges the walls of small caliber arterioles feature transmural and circumferential eosinophilic hyalinized material and cell debris (fibrinoid necrosis). There is associated edema and mild inflammation in the surrounding parenchyma.



Kidney, dog. A wedge-shaped section of the kidney is submitted for examination at low magnification. Extensive areas of cortical necrosis are evident as areas of hypereosinophilia, most prominent in the inner cortex. (HE, 5X)

Contributor's morphologic diagnosis:
Kidney: glomerular fibrinoid degeneration and microthrombosis (thrombotic microangiopathy), acute, severe with attendant cortical tubular necrosis.

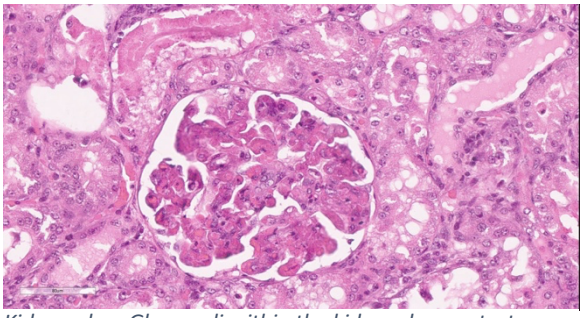
Contributor's comment:
The clinicopathological features of this case are consistent with a diagnosis of cutaneous and renal glomerular vasculopathy (CRGV), an idiopathic vascular disease which causes predominantly cutaneous and renal lesions in dogs. The condition was first described in breeding and racing greyhounds between the ages of 6 months and 6 years in 1988 associated with a specific racetrack in Alabama in the USA and hence given the pseudonym 'Alabama Rot'.[1]

Since 1988, CRGV has been diagnosed in other parts of North America, Germany and the United Kingdom and in breeds of dog other than greyhounds.[1,3,7] Spaciotemporal 'clusters' of dogs with the condition were reported in the UK between 2012 and 2014.[3,8,9] This is the first case to be reported on the island of Ireland.

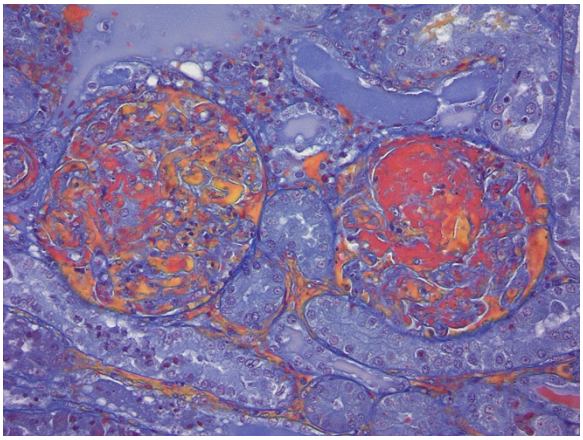
The hallmark of CRGV is renal thrombotic microangiopathy (TMA), a pathologic process that features endothelial damage, thrombosis and red cell shearing.[1,3,6] Thrombosis is also described in dermal, gastric, enteric and colonic arterioles.[1,2,3] TMA particularly targets glomerular capillaries resulting in acute renal glomerular necrosis. Cutaneous lesions feature epidermal necrosis, subcutaneous hemorrhage, fibrinoid necrosis of small arterioles, mixed inflammatory infiltrate and thrombosis.[1,3,6] The current case developed seizure episodes shortly after admission to the UCD veterinary hospital. Such neurological deficits have been described in previously where histopathology found multifocal neuronal necrosis, hemorrhage and edema.[7] Similarly, in the current case, thrombosis with associated necrosis, hemorrhage and inflammation was observed in cerebral grey matter. Ultimately TMA results in consumptive thrombocytopenia, hemolytic anemia and multiorgan failure.[3,6]

Ultrastructural examination suggests glomerular endothelial damage is a central early event in the pathogenesis of CRGV.[2,3] Changes described include: endothelial swelling, detachment, and necrosis; membranous whorl formation; and platelet adhesion and aggregation. This is followed by narrowing of capillary lumens and thickening of capillary walls by the subendothelial accumulation of flocculent, amorphous, variable electron-dense material, along with erythrocytes, cellular processes, and fibrin. Aetiologic agents or electron-dense deposits typical of immune complexes have not been observed.

TMA may be associated with underlying conditions, such as malignant neoplasms,



Kidney, dog. Glomeruli within the kidney demonstrate multifocal thrombosis, segmental to global necrosis and hemorrhage and abundant granular cellular debris. Adjacent tubules exhibit necrosis, or attenuation of epithelium with abundant luminal granular debris or protein. (HE, 400X)



Kidney, dog. A Martius scarlet red stains demonstrates abundant fibrin (red) in necrotic glomeruli. (MSB, 400X). (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

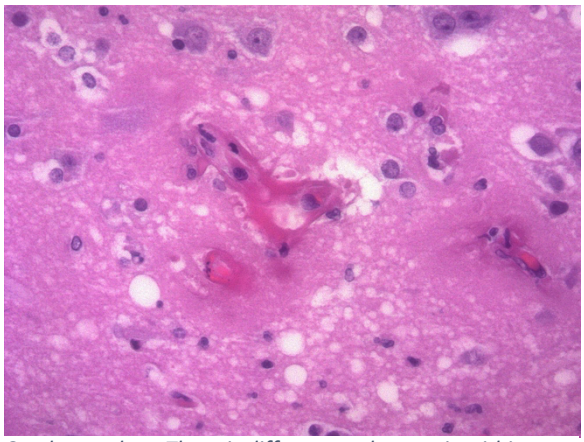
administration of certain chemotherapies and other drugs, transplantation, and sepsis.[6] While the ingestion of bacterial-associated shiga toxin and other factors are suggested etiologies of CRGV, studies have failed to consistently incriminate shiga toxin or indeed particular bacteria or viruses.[1,3] Similar to the situation pertaining at the race-track in Alabama in the 1980s, spatiotemporal clustering of CRGV has occurred in the UK: in the New Forest region between February and March 2013 and between April 2015 - 2017 and in Manchester between February and April 2014.[8,9] Although this 'clustering' may have been a consequence of heightened awareness of the condition in these areas at these times, there remains the possibility of common aetiological factors linked to the local environment or to seasonality: cases were generally associated with woodlands, increasing mean maximum temperatures in winter, spring and autumn, increasing mean rainfall in winter and spring and decreasing cattle and sheep density.[8,9] Two UK Kennel Club breed groups – 'hounds' (odds ratio [OR] 10.68) and 'gun dogs' (OR 9.69) - had the highest risk of a diagnosis of CRGV compared with terriers, while CRGV was not diagnosed in toy breeds.[8] Interestingly, this UK study found that Hungarian vizslas, the breed of dog involved in this case, were one of the breeds that had an increased odds of developing CRGV when compared with crossbreds.

Clinical pathology findings include azotemia, hypoalbuminemia, hyperbilirubinemia, increased alanine transaminase and creatine kinase activities, non-regenerative anemia, thrombocytopenia, presence of schistocytes, burr cells and acanthocytes on blood smears, isosthenuria, hemoglobinuria, myoglobinuria, proteinuria, glucosuria and presence of casts in the urine sediment.[1,3,7] The prognosis is considered guarded for dogs that develop azotemia, and particularly oligoanuric acute kidney injury, as a result of CRVG, although intensive medical intervention has been successful in some cases.[1,3]

Contributing Institution:
Room 012, Veterinary Sciences Centre, School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland
http://www.ucd.ie/vetmed/

JPC diagnosis:
Kidney: Vasculitis, necrotizing, glomerular and arteriolar, diffuse, severe, with thrombosis, extensive tubular necrosis, and proteinosis.

JPC comment:
The contributor provides a concise summary of this case and expands on the background of three cases in Ireland. Of the described cases, two were vizsla dogs, a breed previously reported to experience CRGV at higher rates. Unfortunately, a common etiology was not identified, though the



Cerebrum, dog. There is diffuse mural necrosis within small cerebral arterioles. (Photo courtesy of: School of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland http://www.ucd.ie/vetmed)

cases occurred in similar environments (woodland), and two cases were geographically similar (within 7 miles, 4 years apart).[5]

Cutaneous and renal glomerular vasculopathy (CRGV) falls under the umbrella of thrombotic microangiopathies (TMA), as stated by the contributor. The other reported TMA in animals is hemolytic uremic syndrome (HUS), reported in dogs, cats, rabbits, calves, and horses. Currently, there appear to be a variety of possible initiators of endothelial damage, which start the events leading to microthrombi in small vessels. Some possible causes identified in human TMAs include an ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency, complement dysregulation, disseminated intravascular coagulation (DIC), systemic lupus erythematosus, certain drugs, infectious causes, and others. Given the epidemiology of this disease, which indicates a seasonality, and the fact that it primarily affects dogs with an active outdoor lifestyle in woodland areas, there may be a smaller list of causes for veterinary species. The list of infection associated causes of TMAs in humans include Shiga-toxin, *Campylobacter jejuni, Streptococcus* pneumonia, HIV, cytomegalovirus, Epstein-Barr virus, parvovirus, BK virus (polyomavirus), and influenza. The possibility that there is an infectious agent or toxic cause influenced by the season and environment cannot yet be discounted.[4]

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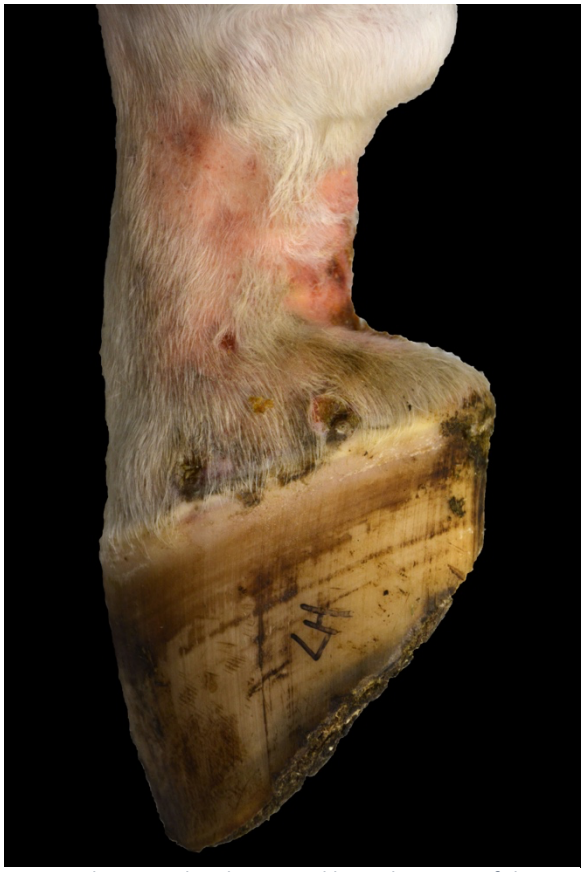
9. Stevens KB, Jepson R, Holm LP, Walker DJ, Cardwell JM. Spatiotemporal patterns and agroecological risk factors for cutaneous and renal glomerular vasculopathy (Alabama rot) in dogs in the UK. Vet Rec **183**(16):502-512, 2018

CASE 4: 18-2823-3 (4138049-00)

Signalment:
15-year-old Thoroughbred gelding

History:
The patient presented to NCSU College of Veterinary Medicine for evaluation by the Equine Orthopedic Surgery Service and Dermatology Service for a 2.5-month history of right hind limb lameness and chronic pastern dermatitis. Based on radiographs and ultrasound of the right hind limb, the referring veterinarian diagnosed annular ligament desmitis, but following treatment with stall rest, hand-walking, trazodone, and acepromazine, the horse showed no improvement and became increasingly difficult to manage on stall rest. The pastern dermatitis was treated chronically with a variety of medications including flunixin meglumine, cetirizine, and enrofloxacin. The swelling in his distal limbs increased while on stall rest. Physical exam identified marked thickening and effusion of the right hind digital flexor tendon sheath and



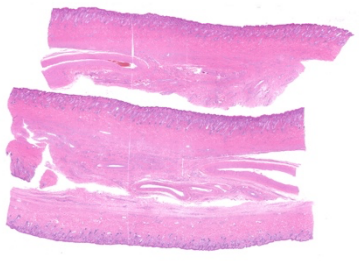
Pastern, horse. The plantar and lateral aspects of the fetlock and pastern (which were circumferentially non-pigmented) show mild to moderate, multifocal, fairly well-demarcated regions of erythema and edema with multifocal areas of alopecia. (Photo courtesy of: NIH Comparative Biomedical Scientist Training Program (CBSTP), https://nih-cbstp.nci.nih.gov/).

annular ligament constriction, as well as evidence of cellulitis with chronic crusting and ulcers over the pastern region of both hind limbs (left > right). Ultrasound of the right hind distal limb identified a tear of the manica flexoria, superficial digital flexor tendon, and possibly deep digital flexor tendon. Surgery to further evaluate the tendon injury was recommended but given the need for aggressive management of the dermatitis prior to surgery and the suspected prolonged rehabilitation time with an uncertain prognosis for recovery, euthanasia was elected.

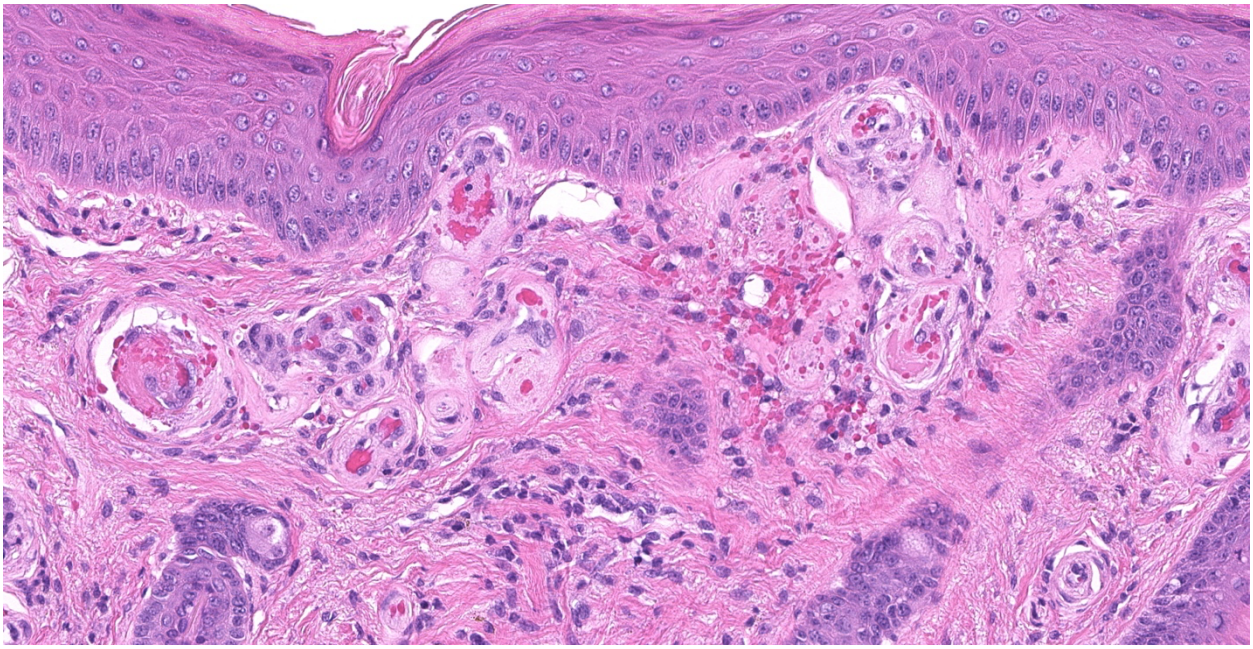
Gross Pathology:
Submitted for autopsy is a 15-year-old Thoroughbred gelding of unreported weight. The body is in good postmortem condition (euthanasia to autopsy interval of approximately 15 hours) with minimal autolysis and dehydration. On both hind limbs, the plantar and lateral aspects of the fetlock and pastern (which were circumferentially non-pigmented) show mild to moderate, multifocal, fairly well-demarcated regions of erythema and edema with multifocal areas of alopecia. Additionally, on both hind limbs just proximal to the coronary band circumferentially are 5-8, multifocal, up to 1.5 cm in diameter ulcers overlain by serous crusts (see gross photo). Just proximal to the fetlock joint, the distal right hind limb has mild, regional thickening of all ligamentous structures, and the overlying soft tissues are expanded by soft tissue swelling and subcutaneous edema. In this region, the lateral manica flexoria has a 4 mm in length tear, and the associated portion of manica flexoria and superficial digital flexor tendon (SDFT) are mildly thickened. Deep to the manica flexoria, the distolateral deep digital flexor tendon (DDFT) is moderately thickened with edema and mild erythema, and along the lateral margin is a roughened, markedly erythematous surface overlain by fibrinous material. Within the flexor tendon sheath there are additional loose coagula of soft, fibrinous material.

Laboratory results:
No additional testing

Microscopic description:
Haired skin (right pastern): The superficial dermis is mildly expanded by increased clear space (edema) and frequently has dilated small caliber vessels that are multifocally increased in number. These superficial small caliber vessels multifocally have walls thickened and replaced by hyalinized eosinophilic material (fibrinoid



Haired skin, horse. Three sections of haired skin are submitted for examination. (HE, 5X)



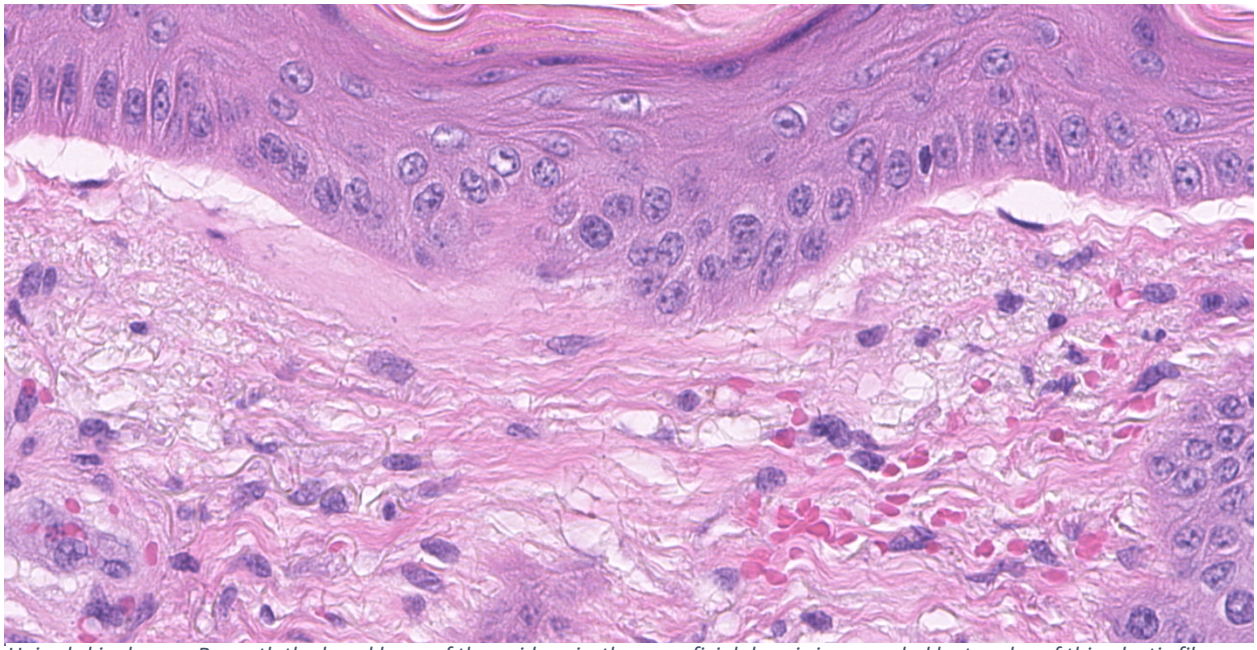
Haired skin, horse. Within the superficial dermis, small vessels are necrotic with acellular walls expanded by abundant brightly eosinophilic protein and hemorrhage (left). (HE, 350X)

vascular necrosis) with an occasional dusting of karyorrhectic cellular debris and rare neutrophils within the vessel wall (leukocytoclastic vasculitis). There are occasional microhemorrhages into the wall and adjacent interstitium. In occasional affected vessels, the lumina are completely occluded by coagula of homogenous eosinophilic material (fibrin microthrombi). In intact vessels, endothelial cells are frequently hypertrophied. Occasionally within superficial and mid-dermal vessels, the vessel wall is pale, eosinophilic and distorted (hyalinosis). The epithelium is mildly thickened with occasional mild orthokeratotic hyperkeratosis. The superficial dermis has minimal, multifocal to coalescing, perivascular to interstitial infiltrates of lymphocytes and plasma cells. There is occasional follicular ectasia. The superficial dermis multifocally has prominent elastin fibers (elastosis).

Contributor's morphologic diagnosis:
Haired skin of the right pastern:

a. Moderate to marked, multifocal, superficial arteriolar fibrinoid vascular necrosis with microhemorrhages, fibrin microthrombi, and hyalinosis
b. Moderate (solar) dermal elastosis

Contributor's comment:
Pastern leukocytoclastic vasculitis, also called photoaggravated vasculitis or photoactivated vasculitis, is a disease of cutaneous vasculitis unique to horses that typically affects nonpigmented skin of the distal limbs and occasionally the muzzle.[2] Gross cutaneous changes include crusts, erosions to ulcerations, and edema, and the condition can be quite painful.[2] Because the pastern is typically affected, other causes of equine pastern dermatitis must be ruled out and include primary irritant or allergic contact dermatitis, pastern folliculitis/pyoderma (due to infection with *Staphylococcus aureus* or *Dermatophilus congolensis*), chorioptic mange, dermatophytosis, Malassezia infection, immune-mediated dermatitis (such as pemphigus foliaceus), and neoplastic conditions (such as sarcoidosis).[1] Pastern leukocytoclastic vasculitis most often affects adult horses, and there does not appear to be a sex predisposition.[5,6] Lesions are typically bilaterally symmetrical but can be confined to just one limb, even if other limbs have non-pigmented regions, and lateral and medial aspects of the distal limbs are most often affected with hind limbs affected more often than the forelimbs.[2,5] Histological findings are similar to those in this case and include dermal edema, vascular dilation and intramural inflammatory



Haired skin, horse. Beneath the basal layer of the epidermis, the superficial dermis is expanded by tangles of thin elastic fibers (solar elastosis). (HE, 586X)

cells, leukocytoclasia with nuclear dust, microhemorrhages, and thickening of the vessel wall of the small superficial, mid, and deep dermal vessels.[5] Secondary bacterial infections are common.[5] Uncommonly, chronic cases can develop marked, papillary epidermal hyperplasia that develops a verrucous appearance.[2]

The pathogenesis of this syndrome is poorly understood, and it is thought to be immune-mediated.[2] Because the changes tend to occur on non-pigmented skin, UV radiation is thought to be involved in inducing vasculitis.[2] However, the support for this is variable among studies with some studies suggesting that UV radiation is likely only a minor contributor.[5,6] Photosensitization has been suggested as the underlying cause, but there is no evidence of hepatic insufficiency nor known exposure to photosensitizing compounds. Additionally, lesions often do not affect the entirety of the nonpigmented skin as other photosensitizing conditions do, and pigmented skin can also be involved though usually to a lesser degree.[5] Other causes of cutaneous vasculitis are not present in these cases because there is no history of trauma nor vasculitis-associated infectious agents such as *Staphylococcus* spp. or dermatophilosis.[2,5] In the present case, the solar elastosis supports the contribution of UV exposure to disease development, and there is evidence (predominantly in other sections not included in the submitted slide) for bacterial infection that was likely secondary rather than causal given the presence of vasculitis in areas without evidence for infection. Thus, the etiology of photoaggravated vasculitis remains unclear, making treatment of the condition challenging and often unsuccessful.[5,6]

Cutaneous vasculitis is most common in the horse and dog and is considered rare in most other species such as cats, pigs, and cattle.[2] Other forms of cutaneous vasculitis in the horse include purpura hemorrhagica (leukocytoclastic vasculitis induced by *Streptococcus equi* subspecies *equi* and leading to hemorrhages and extensive edema) and nodular eosinophilic vasculitis (nodular to linear lesions that are firm and painful on one or more legs).[2,3] In the dog, causes of cutaneous vasculitis are varied and complex and may be associated with hypersensitivity reactions (type I, II, or III), infectious agents, neoplasia, drugs, or toxin exposure.[2] A classic example is infection with the endotheliotropic *Rickettsia rickettsii*. Familial or

inherited forms of vasculitis have also been documented. In pigs, cutaneous vasculitis is most commonly associated with *Erysipelothrix rhusiopathiae*. Additionally, porcine dermatitis and nephropathy syndrome, associated with porcine circovirus 2, results in systemic vasculitis primarily affecting the skin and kidneys.[2]

Contributing Institution:
Submitted by NIH Comparative Biomedical Scientist Training Program (CBSTP)
https://nih-cbstp.nci.nih.gov/

Case materials from: North Carolina State University College of Veterinary Medicine
Department of Population Health and Pathobiology

JPC diagnosis:
Haired skin, superficial dermis: Vasculitis, necrotizing, diffuse, marked, with mild solar elastosis.

JPC comment:
The contributor summarized much of what is currently understood about this disease. While a direct causal link to bacterial infection has not yet been established, in some reported cases, *Staphylococcus intermedius*, coagulase-negative staphylococci, *S. pseudintermedius*, *S. aureus*, *Proteus* spp, and *Pseudomonas aeruginosa* have been isolated at affected sites. In a recently reported case, a multidrug-resistant *Pseudomonas aeruginosa* (MRPA) was cultured from a deep skin biopsy. Following three weeks' treatment with oral enrofloxacin and topical chlorhexidine shampoo cleaning, the skin lesions had healed, and hair was regrowing.[4]

This reported case highlights the dearth of knowledge about pathogenesis of this disease. While it is biologically plausible that certain bacteria cause type III hypersensitivity induced vasculitis, identification of a causative bacterium is inconsistent. It is also difficult to discount the predilection for non-pigmented skin, though there can be less severe manifestations in pigmented skin. From the sparse case data accumulated to date, it seems likely that disease progression is multifactorial, perhaps with both an immune complex vasculitis component, as well as a component of photosensitization.

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