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Source: Journal of Feline Medicine and Surgery Open Reports, 4(2)

Published By: SAGE Publishing

URL: <https://doi.org/10.1177/2055116918812329>



Caroli's-type ductal plate malformation and a portosystemic shunt in a 4-month-old kitten

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Journal of Feline Medicine and Surgery Open Reports
1–5

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DOI: 10.1177/2055116918812329

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Abstract

Case summary A 4-month-old neutered male Russian Blue kitten had a 4 week history of hypersalivation and failure to thrive. In addition, there was a 2 week history of soft tissue swelling on the ventral abdomen, which had failed to improve with antimicrobial therapy. There were no significant physical examination or neurological deficits on examination; however, the cat had a quiet demeanour for its age. Postprandial bile acids were increased (32 $\mu\text{mol/l}$; reference interval $<25 \mu\text{mol/l}$). An abdominal CT scan revealed changes consistent with an extrahepatic portosystemic shunt and inflammation of fat of the ventral abdominal body wall. Surgical biopsy and culture of the subcutaneous swelling identified non-infectious steatitis. Ten weeks following initial presentation, surgical exploration, liver biopsy and ligation of the portosystemic shunt were performed. Liver biopsy was submitted to the Anatomical Pathology Laboratory of Cornell University Animal Health Diagnostic Center, New York, USA. Histopathology revealed a ductal plate malformation (Caroli's type), as well as changes consistent with a portosystemic shunt.

Relevance and novel information Ductal plate malformations are rarely described in the veterinary literature. To our knowledge this is the first reported case of Caroli's-type malformation in a cat. There are no biochemical changes that allow for differentiation of ductal plate malformations from other hepatopathies. Liver biopsy is required for a definitive diagnosis.

Keywords: Liver; feline ductal plate malformation; Caroli's disease; cystic liver disease; portosystemic shunt

Accepted: 15 October 2018

Case description

A 4-month-old neutered male, Russian Blue cat was investigated for a 4 week history of hypersalivation, failure to thrive and a 2 week history of a soft tissue swelling of the ventral abdomen. Haematology and biochemistry performed by the referring veterinarian revealed an inflammatory leukogram with a marked mature neutrophilia and monocytosis ($39.6 \times 10^9/l$ [reference interval (RI) $3.8\text{--}10.1 \times 10^9/l$] and $1.4 \times 10^9/l$ [RI $<0.6 \times 10^9/l$], respectively). There was a mild increase in blood urea nitrogen (11.3 mmol/l; RI 3.6–10.7 mmol/l) and phosphate (3.10 mmol/l; RI 1.10–2.74), attributed to prerenal causes and age-related change, respectively. Postprandial bile acids were increased at 32 $\mu\text{mol/l}$ (RI $<25 \mu\text{mol/l}$). Serological tests for feline leukemia virus/feline immunodeficiency virus were negative. The cat was receiving amoxicillin (12.5 mg/kg PO q12h) for treatment of the ventral abdominal swelling, provisionally diagnosed as a subcutaneous abscess.

On physical examination, the cat was lethargic with hypersalivation with a poor body condition score (3/9). Vital signs were normal. There was a firm nodular thickening on the ventral abdomen. A dual-phase (portal and delayed-venous) abdominal CT scan was performed under general anaesthesia with a six-slice helical unit (Brilliance 6; Philips). The left gastric vein was dilated (5 mm vs 1.5 mm for the main portal vein) and communicated directly with the left phrenic vein, terminating in the caudal vena cava (Figures 1 and 2). Intrahepatic portal vein branches were subjectively small and

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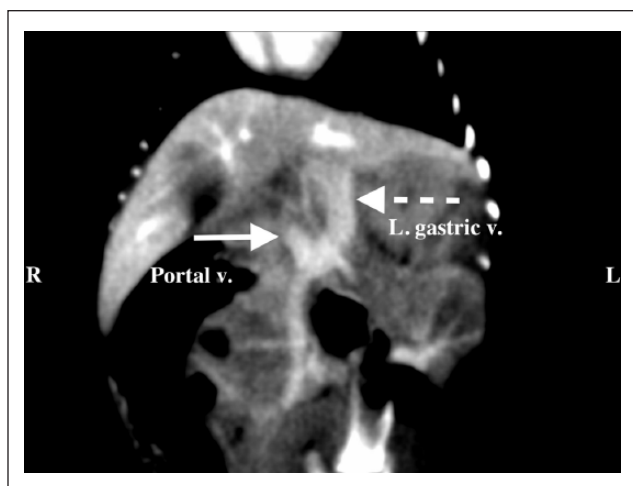


Figure 1 Delayed-phase maximum intensity projection dorsal multiplanar reformat (MPR) CT image in a 4-month-old Russian Blue with a portosystemic shunt. This image shows the venous anomaly in the cranial abdomen. The main portal vein (Portal v.) is identified by the solid arrow. It is much smaller than the dilated left gastric vein (L. gastric v.) identified by the dashed arrow. The liver also has subjectively reduced volume. L = left; R = right

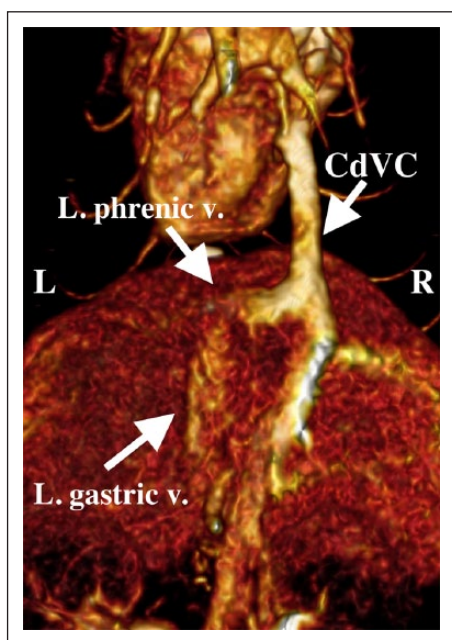


Figure 2 Three-dimensional volume render of the caudal thorax and abdomen of a 4-month-old Russian Blue, viewed from the dorsal side. This image also shows the enlarged left gastric vein (L. gastric v.) and relationship between the phrenic vein (L. phrenic v.), diaphragm and caudal vena cava (CdVC). L = left; R = right

difficult to identify. There was subjective microhepatia. These changes were supportive of an extrahepatic portosystemic shunt. In addition, soft tissue attenuating

streaking of the ventral subcutis was identified, suggestive of steatitis. Surgical tissue biopsies from the ventral abdomen were obtained for histopathology and tissue culture.

The patient was discharged with oral lactulose (0.5 ml PO q12h) for interim medical management of hepatic encephalopathy. Doxycycline (11.1 mg/kg PO q12h [12.5 mg]) was started for possible mycobacterial panniculitis, at the clinician's discretion. Histopathology, including Ziehl–Neelsen staining for mycobacteria of the subcutaneous tissue, identified steatitis with no pathogenic infectious agent identified. There was no microorganism growth on prolonged tissue culture. A lower protein diet was recommended, such as Hill's k/d.

Ten weeks after initial presentation, the patient re-presented for exploratory laparotomy for ligation of a suspected portosystemic shunt. The patient was receiving oral lactulose (0.5 ml PO q12h) and had been commenced on levetiracetam (22 mg/kg PO q8h) 7 days prior as per hospital policy for portosystemic shunt patients. On examination, the patient was alert and responsive but considered quieter than expected given its age. Body condition score had improved (4/9) and vital signs were normal. The steatitis had resolved.

Preanaesthetic haematology and biochemistry indicated a mild hypochromic microcytic non-regenerative anaemia (haematocrit 27.7% [RI: 30.3–52.3%]; mean cell volume 34.4 fl [RI 34.3–35.9 fl]; mean cell haemoglobin 11.5 pg [RI 11.8–17.3]) and moderate lymphocytosis ($7.36 \times 10^9/l$; RI 0.92 – $6.88 \times 10^9/l$). A low creatinine (65 $\mu\text{mol/l}$; RI 71–212 $\mu\text{mol/l}$) and mild hyperphosphataemia (2.72 mmol/l; RI 1.00–2.42 mmol/l) were attributed to suboptimal body condition score and age-related change, respectively. Electrolytes were within normal limits.

Exploratory laparotomy under routine general anaesthesia confirmed the presence of a left gastrophrenic portosystemic shunt, in addition to a double vena cava, which joined at the level of the renal veins. A partial ligation of the portosystemic shunt with cellophane banding was performed. A 6 mm punch biopsy from the quadrate lobe of the liver was obtained. The patient had an unremarkable anaesthetic recovery. Liver biopsy was submitted for external histopathological review to Cornell University Animal Health Diagnostic Center. The patient was discharged 2 days after shunt ligation with phenobarbitone (1.9 mg/kg PO q12h for 2 weeks), levetiracetam (19 mg/kg PO q8h for 2 weeks) and buprenorphine (0.02 mg/kg PO q8h) as required for analgesia. The patient developed upper respiratory tract signs with mucoid nasal discharge and was commenced on doxycycline (9.6 mg/kg PO q12h for 7 days). The previous low-protein diet was advised until liver function was reassessed.

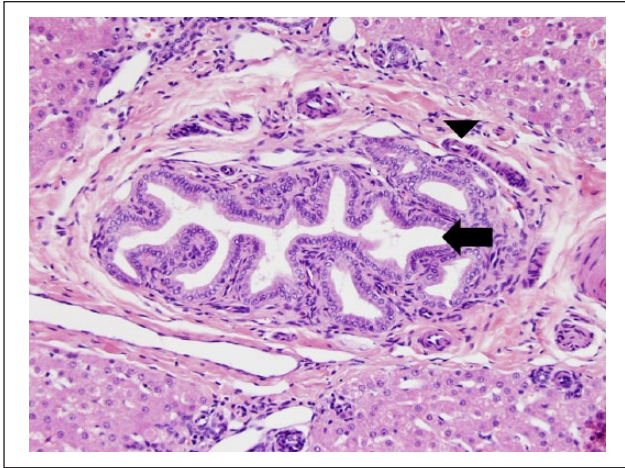


Figure 3 Liver histopathology from a 4-month-old Russian Blue with a portosystemic shunt and ductal plate malformation. This photomicrograph reveals a sacculated bile duct with abnormal contours and multiple sacculations (black arrow). The lymphatics are dilated and arterioles have stout walls (arrowhead). Stained with haematoxylin and eosin at $\times 40$ magnification

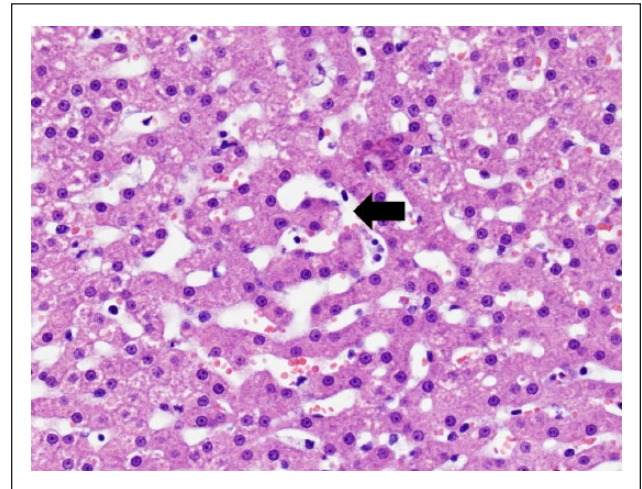


Figure 5 Liver histopathology from a 4-month-old Russian Blue with a portosystemic shunt and ductal plate malformation. This photomicrograph is of hepatic sinusoids. The sinusoids are irregularly branching with occasional hairpin turns identified by the black arrow. They are moderately dilated. Stained with haematoxylin and eosin $\times 40$ magnification

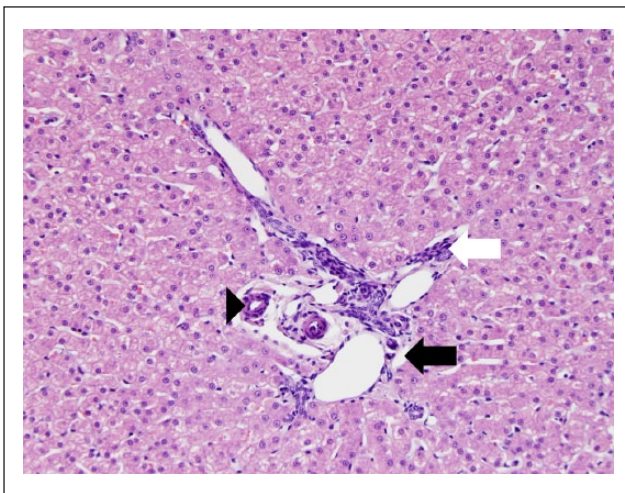


Figure 4 Liver histopathology from a 4-month-old Russian Blue with a portosystemic shunt and ductal plate malformation. This is a photomicrograph of a portal tract. The smaller portal tracts have arteriolar proliferations (white arrow), dilated lymphatics (black arrow) and stout-walled arterioles (arrowhead). Stained with haematoxylin and eosin at $\times 20$ magnification

Histopathology of the liver biopsy revealed large bile ducts with irregular, sacculated contours (Figure 3). There was increased profile of abnormal bile ducts that occasionally breached the limiting plate. The proliferations extended out a short distance blindly into the hepatic parenchyma. Both the small and medium portal tracts contained thick-walled arterioles and mild serpiginous, plexiform proliferations of arterioles. The portal

veins were frequently inconspicuous and portal lymphatics were frequently moderately dilated (Figure 4). The sinusoids were irregularly branching (Figure 5). Portal tracts contained small numbers of lymphocytes and plasma cells primarily around bile ducts. There was portal vein hypoperfusion. These findings are consistent with Caroli's-type ductal plate malformation and congenital portosystemic shunt.

Two months after surgery, the cat was bright and clinically well. Repeat haematology and biochemistry indicated a mild microcytosis and a mild elevation in alkaline phosphatase (72 IU/l; RI 5–50 IU/l). Resting ammonia was 87 $\mu\text{mol/l}$ (RI 0–95 $\mu\text{mol/l}$) and fasting bile acid remained elevated at 18 $\mu\text{mol/l}$ (RI <11 $\mu\text{mol/l}$), attributed to incomplete attenuation of the portosystemic shunt.

Discussion

To our knowledge, this is the first reported case of a Caroli's-type ductal plate malformation (DPM) in a feline patient.

The ductal plate is an embryonic precursor of intrahepatic bile ducts. Initially formed from transformation of hepatoblasts, the plate consists of a double layer of cuboidal biliary-style epithelium that surrounds the developing portal vein.^{1–3} Development and remodelling of the ductal plate is orchestrated by a range of regulatory factors in a time- and context-dependent manner, commencing in a centripetal fashion from the larger portal vein branches at the hilum.³

DPMs represent any malformation, persistence or lack of remodelling of the ductal plate. Varying degrees of cystic dilation of intrahepatic bile ducts are observed in DPMs.^{1,4} The pathomechanisms resulting in DPMs remain elusive, and the associated syndromes in people are genetically and phenotypically heterogeneous. Genetic abnormalities that affect the structure and function of the primary cilia of the biliary epithelium have been identified in people with DPM, leading to the consideration that DPM may be a primary congenital cholangiociliopathy.^{2,5} In veterinary patients, congenital cystic liver disease has been categorised as:⁶ (i) congenital dilation of the large and segmental bile ducts (morphologically identical to Caroli's disease); (ii) juvenile polycystic disease/congenital hepatic fibrosis; and (iii) adult polycystic disease, including Von Meyenburg complexes.

In Caroli's disease, insufficient involution of the ductal structures at the level of the segmental bile duct leads to formation of large, cystic ducts. In the medical literature, concurrent congenital hepatic fibrosis is included with the histopathological description of Caroli's syndrome, which is not included in the World Small Animal Veterinary Association (WSAVA) categorisation.^{5,7}

Only a small number of dogs have been diagnosed with Caroli's-like disease in the veterinary literature. The most recent publication describes the clinical and histological features of ductal plate malformation in 30 Boxer dogs. Of these dogs two had histological change consistent with Caroli's malformation. One of these dogs had concurrent bridging portal fibrosis.¹ A small case series identified hepatic cystic and fibrotic changes in two Golden Retriever littermates.⁵ Clinical signs described in these cases were non-specific and included vomiting, polyuria, polydipsia, anorexia, lethargy and reduced activity.^{1,4,5,8}

A well-documented autosomal dominant polycystic kidney disease in Persian cats is also recognised to have concurrent hepatic cystic changes.^{4,9-11} Cystic disease of the liver and kidney has been described in a range of canine breeds, including Cairn Terriers, Collies, Frisian Stabyhouns, Jack Russell Terriers and a mixed-breed dog.^{5,8} Several case reports suggest that Caroli's disease without cystic kidney disease occurs in both dogs and people, as was also the case in this patient.

In this cat, Caroli's disease was present with an extrahepatic portosystemic shunt with a histopathological diagnosis of portal hypoperfusion and Caroli's disease. In the absence of fibrosis that could contribute to portal hypertension, we propose the portosystemic shunt is most likely congenital in origin.⁹ The medical history and status of the littermates, queen and tom cat is unknown.

There are no clinicopathological abnormalities that allow distinction of DPM from other hepatopathies.¹ Biochemical abnormalities that have been documented in both animals and people include an increase in alanine transaminase, alkaline phosphatase, bilirubin and pre- and postprandial bile acids. In this cat, clinical signs (failure to thrive, hypersalivation) improved after partial ligation of the macroscopic shunt and are therefore more likely attributable to the portosystemic shunt than the Caroli's disease. The patient had an unremarkable anaesthetic recovery at the time of diagnostic investigations, which is not always observed in patients with portovascular or hepatic abnormalities. Owing to the risk of post-ligation seizure activity in cats the patient was commenced on both levetiracetam and phenobarbitone; these were discontinued 2 weeks following surgery, when no seizure activity was appreciated.¹²

Possible sequelae of Caroli's malformation in people include cholestasis, resulting in ascending cholangitis (both acute and chronic), cholelithiasis and secondary hepatic fibrosis.^{1,3,13} This is largely attributed to the ciliopathies associated with DPM. In this cat, there were no histological characteristics suggestive of active inflammation. Clinical signs that could develop in this patient in the future include an acute febrile illness, including vomiting, inappetence, icterus and/or cranial abdominal pain, or non-specific malaise. Haematology and biochemistry may reveal an inflammatory leukogram and a cholestatic hepatopathy, progressive from post-ligation baseline. As the shunt was only partially attenuated, clinical signs and manifestations of altered portal blood flow may become apparent as the patient continues to grow. A bile acid stimulation test and resting ammonia were recommended to be evaluated at 2 weeks and then again at 6 months.

There are case reports of cholangiocarcinoma in humans with Caroli's disease presumed secondary to bile stasis and chronic inflammation.³ In people, treatment of Caroli's disease is largely supportive; however, in instances of unilobar disease (which has been reported) radical liver resection or liver transplantation has been described with reasonable success.¹³ Given the potential sequelae of the partially attenuated portosystemic shunt and Caroli's disease, a proactive approach towards diagnostic investigations and management is therefore encouraged for this patient.

Conclusions

To our knowledge, this is the first case of Caroli's-type DPM in a cat. There are no identified clinicopathological abnormalities that allow for distinction of DPM from other hepatopathies. Therefore, diagnosis requires liver biopsy for histopathology.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

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