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TITLE OF CASE *Do not include "a case report"*

Suspected hepatic hydrothorax secondary to cirrhosis in a dog

SUMMARY *Up to 150 words summarising the case presentation and outcome (this will be freely available online)*

An 8-year-old entire-female Labrador Retriever presented with a two-week history of abdominal distension. Biochemistry identified hepatic dysfunction (elevated hepatobiliary markers, hypocholesterolaemia). Abdominal ultrasonography documented an irregular liver and a large-volume of anechoic peritoneal effusion, which laboratory analysis confirmed as a protein-poor transudate. Thoracic computed-tomography identified a moderate-volume of pleural effusion with a similar composition to the peritoneal fluid. Hepatic histopathology was consistent with cirrhosis secondary to chronic hepatitis and, in the absence of another cause for the pleural effusion, hydrothorax secondary to the hepatic disease was suspected. The patient was started on ciclosporin for treatment of the underlying liver disease but developed signs consistent with disseminated intravascular coagulopathy 24 hours later and was humanely euthanised. As reported in humans, hydrothorax may therefore occur secondary to cirrhosis in dogs and should be considered as a differential diagnosis for pleural effusion in patients with advanced hepatic disease and concurrent peritoneal effusion.

BACKGROUND *Why you think this case is important – why did you write it up?*

This case reports a case of suspected hepatic hydrothorax secondary to cirrhosis in a dog. This condition is well described in the human medical literature as an "accumulation of transudate in the pleural cavity of patients with decompensated cirrhosis but without cardiopulmonary and pleural disease"¹, but reports in the veterinary literature are limited.² This report highlights that thoracic imaging should be considered in patients presenting with cirrhosis and ascites to assess for the presence of pleural effusion and that advanced hepatic disease should be considered as a differential diagnosis for dogs with biventricular effusion.

CASE PRESENTATION *Presenting features, clinical and environmental history*

An 8-year 9-month-old entire female Labrador was referred with a two-week history of abdominal distension. Biochemical assessment prior to referral had documented hypoalbuminaemia (24g/L; R.I. 25-39), decreased serum urea concentration (3.4mmol/L; R.I. 3.5-7.0), hypocholesterolaemia (2.9mmol/L; R.I. 3.8-7.9), elevated resting serum bile acids (89.2µmol/L; R.I. 0-25) and mildly elevated serum bilirubin (11.1µmol/L; R.I. <5.0). Other pertinent medical history included the excision of a well differentiated subcutaneous mast cell tumour from her left-flank three-years prior to presentation.

INVESTIGATIONS *If relevant*

Initial investigations identified elevations in hepatobiliary enzymes (ALT 258 IU/L; R.I. 14-67; AST 115 IU/L; R.I. 12-49; ALP 170 IU/L; R.I. 25-41); mild hypoalbuminaemia (24g/L; R.I. 25-41) and hypocholesterolaemia (2.9mmol/L; R.I. 3.3-6.5). Coagulation testing identified a mildly prolonged one-stage prothrombin time (13.2s; R.I. 7.6-11.6) but normal activated partial thromboplastin time and normal platelet count. Abdominal ultrasonography (performed with a Philips EPIQ Elite ultrasound machine using a curvilinear probe with a frequency of 5-8MHz) revealed moderate amounts of anechoic peritoneal effusion and an enlarged, irregularly hyperechoic liver that contained numerous small-rounded variably sized hypoechoic nodules. Assessment of the portal vasculature and portal flow was precluded by the degree of abdominal distension and the large patient size. Analysis of the peritoneal fluid was consistent with a protein poor transudate (protein <7g/L; nucleated cell count $0.1 \times 10^9/L$) with no evidence of atypical cells or infectious agents, most likely indicative of portal hypertension. Cytological assessment of a mildly enlarged left mandibular lymph node was deemed consistent with metastasis of a mast cell tumour based on previously described criteria.³

The findings of the initial investigations were thought most compatible with a hepatopathy with secondary peritoneal effusion due to portal hypertension. Differential diagnoses for the hepatopathy included chronic hepatitis (e.g. copper-associated, immune-mediated, infectious, toxic, or idiopathic), neoplasia (e.g. hepatocellular carcinoma, cholangiocellular carcinoma, lymphoma or metastatic disease, including mast cell metastasis considering the mandibular lymph node cytology), or less likely vacuolar hepatopathy, nodular hyperplasia or extra-medullary haematopoiesis. Hyperbilirubinaemia in the absence of a pre- or post-hepatic cause indicated liver dysfunction and a bile acid stimulation test was therefore not performed.

Due to its location and the time elapsed since its excision, it was considered unlikely that the previous mast cell tumour on the left flank was related to the mandibular lymph node findings and a computed-tomography (CT) scan of the head, neck, thorax and abdomen was therefore performed pre- and post-contrast (2ml/kg of Omnipaque Injection 300mg I/ml solution; GE HealthCare, United Kingdom) to investigate the possibility of mast cell tumour metastasis from an unidentified primary tumour. This documented no other

evidence of neoplasia, but a moderate volume of pleural effusion (figure 1) was identified mostly within the right hemithorax, with consolidation of the ventral tips of all the lung lobes. This pleural effusion was not detected across the diaphragm during the initial abdominal ultrasound scan. The heart was within normal limits on CT with no evidence of chamber enlargement to suggest congestive heart failure. In the abdomen, the liver was enlarged and irregular containing multiple hypoattenuating and non-contrast enhancing nodules throughout its parenchyma which distorted the capsular margin. There was also a moderate amount of peritoneal effusion. No evidence of acquired portosystemic shunts were seen on CT. CT of the head was unremarkable apart from a mildly enlarged left mandibular lymph node measuring 1.1cm diameter, with no evidence of a primary mast cell tumour. Thoracocentesis was performed under ultrasound guidance, yielding 112mL of clear, yellow pleural fluid with similar composition to the peritoneal fluid (protein 14g/L, nucleated cell count $0.6 \times 10^9/L$), consistent with a low protein transudate (hydrothorax).

In the absence of another obvious aetiology for the bicavitary effusion, the dog subsequently underwent laparoscopic liver biopsy to further characterise the hepatopathy. At laparoscopy the liver was diffusely heterogenous and enlarged with nodules throughout all lobes which were distorting the capsule. Hepatic biopsies were collected from the left lateral, quadrate and right lateral liver lobes using laparoscopic cup forceps. Extirpation of the left mandibular lymph node was planned but was aborted due to anaesthetic instability.

Hepatic histopathology revealed severe, multifocal hepatocyte nodular hyperplasia with moderate portal-to-portal bridging fibrosis (cirrhosis); severe biliary hyperplasia and evidence of moderate-severe chronic, lymphocytic and histiocytic hepatitis (figures 2 & 3). Rhodanine staining for copper revealed grade three copper accumulation with a random distribution, but assessment of the copper distribution was confounded by the degree of fibrosis and distortion of the architecture by hepatic nodular hyperplasia. Copper quantification was not performed prior to initiating treatment due to the urgent requirement to start treatment considering the patients poor clinical condition. Overall, these findings were therefore considered likely indicative of cirrhosis secondary to advanced chronic hepatitis.⁴ Differential diagnoses for the underlying cause of the chronic hepatitis included immune-mediated, copper-associated, infectious, or idiopathic aetiologies.

DIFFERENTIAL DIAGNOSIS *If relevant*

TREATMENT *If relevant*

Whilst awaiting the histopathological results the dog was managed supportively with maropitant (Prevomax, Dechra Veterinary Products; 1mg/kg intravenously q24h) and intravenous fluid therapy with lactated Ringer's solution (Vetivex 11, Dechra Veterinary Products) due to ongoing hyporexia. Once the histopathological results were returned the dog was started on ciclosporin (Atopica, Elanco Animal Health; 5mg/kg per os q12h), as has been previously described for the management of idiopathic chronic hepatitis in dogs.⁵

OUTCOME AND FOLLOW-UP

Unfortunately, spontaneous nasal and oral bleeding was noted after 4 days of treatment at which time severe prolongations in prothrombin time (>100s; R.I. 11-14) and activated-partial thromboplastin time (>350s; R.I. 60-93) with marked thrombocytopenia ($23 \times 10^9/L$; R.I. 148-484) were documented. These findings were most consistent with disseminated intravascular coagulopathy and due to the dog's grave prognosis, she was humanely euthanised.

DISCUSSION *Include a very brief review of similar published cases*

It is believed that hepatic hydrothorax results from the movement of peritoneal fluid, arising secondary to portal hypertension, through small defects in the diaphragm. As these communications are predominantly located on the right side of the diaphragmatic tendon, a right sided pleural effusion is the most common finding in humans, occurring in 85% of cases^{2,6} This unilateral nature of the fluid would be less likely to occur in dogs due to the fenestrated nature of the canine mediastinum, but potentially an increased volume in the right pleural space could be expected.⁷

The case described bears similarity to many of the features of hepatic hydrothorax described in human medicine, particularly the moderate volume, predominantly right-sided pleural effusion with no evidence of cardiopulmonary or pleural space disease in a patient with histologically confirmed cirrhosis. Moreover, the fluid was a low protein transudate and clinicopathologically similar to the peritoneal effusion.⁶ Other differential diagnoses such as hypoalbuminaemia, neoplastic disease (including mast cell tumour), right-sided heart disease and vasculitis were excluded based on the absence of significant hypoalbuminaemia, evidence of cardiac disease or other pathology on clinical examination or thoracic CT, and the results of fluid analysis.

Reports of pleural effusion due to hepatic disease in dogs are very limited with only one case secondary to cirrhosis and one case secondary to chronic active hepatitis reported with limited further clinical information provided.⁸ A case of bicavitary effusion secondary to liver lobe torsion in a dog has been previously described, but fluid analysis in that case was consistent with an exudate and the mechanism was suggested to be related to severe inflammation and subsequent vasculitis.⁹ This mechanism was considered unlikely in this case due to characteristics of the fluid (low-protein transudate) and the lack of evidence of systemic inflammation (Serum Amyloid-A $1.6 \mu g/mL$; R.I. <2.2). C-reactive protein was not measured as serum-amyloid A has previously been shown to have at least equal diagnostic performance.¹⁰

Limitations of this report include the lack of echocardiographic assessment of the dog; the lack of post-mortem assessment to confirm the presence of diaphragmatic rents, definitively exclude microscopic intra-thoracic pathology, and further characterise the mandibular lymph node findings; and the lack of available follow up to determine if resolution of the pleural effusion can be achieved with treatment of the hepatic disease.

In conclusion, the concurrent hydrothorax and ascites in this patient with cirrhosis highlights that advanced hepatic disease should be considered as a differential diagnosis for pleural effusion in dogs. In addition, thoracic imaging should be considered in patients presenting with cirrhosis and ascites to assess for the presence of pleural effusion.

LEARNING POINTS/TAKE HOME MESSAGES *3 to 5 bullet points – this is a required field*

- Pleural effusion can occur due in dogs with cirrhosis and ascites.
- Hepatic histopathology is required to confirm a diagnosis of cirrhosis.
- Hepatic hydrothorax may occur due to the movement of peritoneal effusion through small defects in the diaphragm.
- Lateralisation of hepatic hydrothorax may be explained by the asymmetric distribution of diaphragmatic rents, but bilateral effusion may also occur due to the fenestrated nature of the canine diaphragm

CONFLICT OF INTEREST STATEMENT *Required. A statement should be included even if there are no conflicts of interest to declare (e.g., “The author(s) declare(s) they have no conflicts of interest.”)*

The authors declare they have no conflicts of interests.

ETHICS STATEMENT *Required. A statement explicitly describing the ethical background to this study and any institutional or national ethical committee approval must be included within the manuscript.*

Ethical approval was not required for the present case report; informed consent was obtained and anonymity was maintained.

FUNDING STATEMENT *Required. Please list all funding sources. If no funding was received, please provide a statement to this effect. Authors are responsible for the accuracy of their funder designation.*

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AUTHOR CONTRIBUTION STATEMENT *Required. Please list the contributions of each author (e.g., AA and BB conceived and designed the project, AA, CC and DD acquired the data, AA and CC analysed and interpreted the data, AA and BB wrote the paper).*

The case was primarily managed by Oliver Russell under the direct supervision of Andre Kortum. Diagnostic imaging was performed by Bethany Guy under the supervision of an ECVI diplomat. The hepatic histopathology was reported by Fernando Constantino-Casas. The manuscript was prepared and edited by all authors.

ACKNOWLEDGMENTS *Optional*

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

Figure 1: Thoracic computed-tomography acquired with a Toshiba Aquilion 16-slice helical scanner, soft-tissue window (window width 350, window level 50, 1mm slice

thickness, 120KV, 100MA, pitch of 0.8, rotation time 0.5s) post-contrast demonstrating pleural effusion and consolidation of the ventral lung lobes.

Figure 2: Liver histopathology highlighting the hepatocyte nodular pattern (N) surrounded by collagen fibres (arrows). (Masson's trichrome stain, bar 200µm, magnification x100).

Figure 3: Liver histopathology showing the predominantly lymphocytic inflammatory infiltrate (arrows). (hematoxylin and eosin stain, bar 80µm, magnification x200).

OWNER'S PERSPECTIVE *Optional*

IMAGE QUIZ *Optional (but highly encouraged) – please provide 1 or 2 sentences to describe one of the images in your article. The “Image quiz” will be published with your article if accepted. Don't forget to indicate which image the quiz relates to*

MULTIPLE CHOICE QUESTION *provide one multiple choice question based on the description above (may be “what's the likely diagnosis?”)*

Which of these is a cause of concurrent pleural and peritoneal effusion in a dog?

POSSIBLE ANSWERS TO MULTIPLE CHOICE QUESTION *Max 6*

1. Advanced hepatic disease
2. Lymphoma
3. Concurrent left and right sided congestive heart failure
4. Severe hypoproteinaemia
5. Coagulopathy secondary to rodenticide toxicity (e.g. difenacoum)
6. All of the above

CORRECT ANSWER *With a brief explanation (the answer will also be linked to the published case)*

6. All of the above options can lead to concurrent pleural and peritoneal effusion in dogs. Advanced hepatic disease can lead to hydrothorax as described in the report. Lymphoma can lead to a bicavity neoplastic effusion. Concurrent left and right sided congestive failure can lead to pleural and peritoneal effusion due to increased hydrostatic pressure. Severe hypoproteinaemia can lead to bicavity effusion due to reduced colloid osmotic pressure. Finally, coagulopathy secondary to rodenticide toxicity can lead to haemorrhagic bicavity effusion.

PLEASE SAVE YOUR TEMPLATE WITH THE FOLLOWING FORMAT:

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