NOTE *Clinical Pathology*

A case report of suspected hepatopulmonary syndrome secondary to ductal plate malformation with chronic active hepatitis in a dog

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ABSTRACT. Hepatopulmonary syndrome (HPS) is a respiratory complication of hepatic disease, that is well recognized in humans and defined by the presence of 1) liver disease, 2) hypoxemia and/or high alveolar-arterial oxygen gradient ($AaDO_2$) and 3) intrapulmonary vasodilatation. The present report describes a similar case of HPS in a dog. A six-month-old Papillon was diagnosed with ductal plate malformation with chronic active hepatitis and showed progressive increases in $AaDO_2$ over the course of the following six months. The presence of intrapulmonary vasodilatation was confirmed by agitated saline contrast transthoracic echocardiography. Also, the absence of congenital cardiac defect was confirmed by transthoracic echocardiography. From these results, we suspected that this dog had HPS. This is the first description of suspected canine HPS.

KEY WORDS: agitated saline contrast transthoracic echocardiography, canine, ductal plate malformation, hepatopulmonary syndrome

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Hepatopulmonary syndrome (HPS) is a serious pulmonary vascular complication of liver disease in humans [8, 24]. There is a report indicating that the median survival time was significantly lower in cirrhotic patients with HPS compared with those without HPS [6, 19]. Diagnosis of HPS is made by demonstrating a triad of 1) liver disease, 2) hypoxemia and/or high alveolar-arterial oxygen gradient ($AaDO_2$) and 3) intrapulmonary vasodilatation [8, 22, 24]. $AaDO_2$, the indicator of gas exchange efficiency, was calculated based on the partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$). Pulmonary microvascular dilatation results in ventilation-perfusion mismatch and thus hypoxemia and/or high $AaDO_2$ in the absence of marked intrinsic cardiopulmonary disease, such as congenital heart disease with right-to-left shunt [16, 18, 20]. To the best of our knowledge, HPS has not been reported in dogs, and this case report describes the first suspected case of HPS in a dog.

A six-month-old female intact Papillon, weighing 1.82 kg, was referred to our hospital due to intermittent vomiting, excessive salivation and staggering with a duration of 2 months. At the referring hospital, hematology and serum biochemistry revealed decreased glucose (26 mg/d*l*) and increased fasting ammonia (352 μg/d*l*) and serum bile acid (201.5 μM/*l*), but did not point to specific primary causes. Lethargy, inappetence and vomiting resolved after symptomatic treatment, but ascites developed 10 days before referral.

At the first presentation (Day 0), abnormal physical examination findings included a body condition score of 2/5, moderate dehydration and abdominal distention. The dog's body temperature was 38.5°C, heart rate was 148 beats per min, and respiratory rate was 40 breaths per min (bpm). Heart and lung sounds were normal. At the referring hospital, the patient had been subjected to blood tests 1 week previously (Day −7). Therefore, the dog was subjected to minimal blood tests on Day 0 (Table 1). On Day 0, complete blood cell count (CBC) abnormalities included an elevated white blood cell count and mild anemia. Abnormal biochemical values included increases in ammonia, alkaline phosphatase, gamma glutamyl transferase and C-reactive protein as well as decreases in total protein, albumin, glucose and total cholesterol (Table 1). The dog was not icteric, and the coagulation profile (prothrombin time, activated partial thromboplastin time and fibrinogen) was normal. Abdominal ultrasonography revealed ascites, microhepatia (Fig. 1) and mobile biliary sludge in the gallbladder. No abnormalities were found in the other abdominal organs. Ascites was a pure transudate with low protein (0.7 mg/d*l*), a low specific gravity (1.005) and low nucleated cell counts (400 cells/μ*l*). Based on these findings and signs, ductal plate malformation and portal vein hypoplasia were suspected.

Liver biopsy was performed under general anesthesia. The dog was premedicated with a subcutaneous injection of atropine sulfate (0.04 mg/kg: Atropine sulfate injection, Fuso Pharmaceutical Industries, Osaka, Japan). Thirty

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Table 1. Results of blood tests on Day −7 and Day 0

	Day 0	Reference range		Day −7	Day 0	Reference range
RBC ($\times10^6/\mu l$)	5.1	5.5–8.5	BUN (mg/d*l*)	10	-	9.2–29.2
PCV (%)	30	37–55	Cre (mg/d*l*)	0.5	-	0.4–1.4
Hb (g/d*l*)	9.5	12–18	AST (U/*l*)	85	-	17–44
MCV (f*l*)	59.6	60–77	ALT (U/*l*)	56	-	17–78
MCHC (%)	31.5	32–36	ALP (U/*l*)	2,187	2,130	47–254
Plate ($\times10^3/\mu l$)	476	200–500	γ-GTP (U/*l*)	11.6	19	5–14
WBC (/μl)	32,700	6,000–17,000	TP (g/d*l*)	4.1	4.2	5.0–7.2
Neutrophil (/μl)	2,587	3,000–11,500	ALB (g/d*l*)	1.4	1.8	2.6–4.0
Lymphocyte (/μl)	7,521	1,000–4,800	GLU (mg/d*l*)	32	58	75–128
Monocyte (/μl)	981	150–1,350	NH_3 (μg/d*l*)	-	203	16–75
Eosinophil (/μl)	327	100–1,250	T-CHO (mg/d*l*)	98	-	111–312
			TG (mg/d*l*)	22	-	30–133
			T-Bil (mg/d*l*)	0.1	-	0.1–0.5
			CRP (mg/d*l*)	-	3.4	≤1.0
			SBA (μMl/*l*)	55.9	-	≤25.0

RBC: red blood cell, PCV: packed cell volume, Hb: hemoglobin, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, WBC: white blood cell, BUN: blood urea nitrogen, Cre: creatine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, TP: total protein, ALB: albumin, GLU: glucose, NH: ammonia, T-CHO: total cholesterol, TG: triglyceride, T-Bil: total bilirubin, CRP: C-reactive protein, SBA: serum bile acid, -, No data.

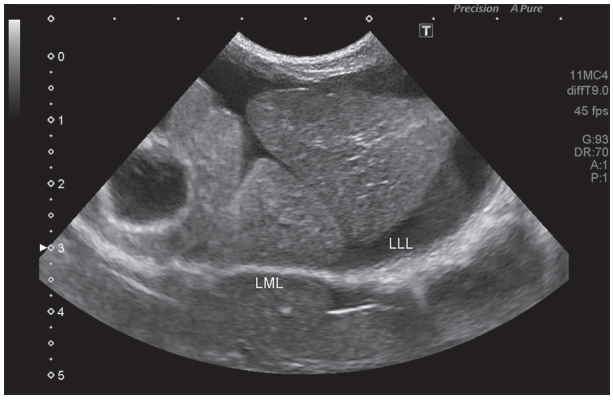

Fig. 1. Ultrasonograph of the liver in the dog with ductal plate malformation. Ascites and microhepatia in the left lateral (LLL) and left medial lobes (LML) were noted. The intrahepatic portal vein was not clearly identified.

minutes later, fentanyl (10 μg/kg; Fentanyl Citrate, Janssen Pharmaceutical, Tokyo, Japan) was injected for sedation, and propofol (approximately 3 mg/kg; Propofol injection, Fuji Pharma, Tokyo, Japan) was administered for tracheal intubation. Anesthesia was maintained with 0.4–1.2% isoflurane (Isoful, DS Pharma Biomedical, Osaka, Japan) delivered with pure oxygen and fentanyl delivered as a continuous rate infusion (42 μg/kg/min). Liver biopsy was performed with particular attention to hemostasis, as ascites was observed. During the laparoscopic biopsy procedure, multiple small nodules suggestive of cirrhosis were visually confirmed in all of the liver lobes (Fig. 2A). Laparoscopy also revealed multiple portosystemic shunts near the caudal vena cava (Fig. 2B). Biopsy specimens were obtained from the left lateral lobe and the quadrate lobe of the liver. The procedure was completed after confirming hemostasis. The histopathological diagnosis was ductal plate malformation with chronic active hepatitis (Fig. 3).

Until the histopathological diagnosis, the dog was placed on symptomatic therapy with 0.5 m*l*/kg lactulose (Piarle Syrup 65%; Takata Pharmaceutical, Tokyo, Japan) orally twice a day, 1 mg/kg furosemide (Furosemide; Teva Pharmaceutical, Tokyo, Japan) orally twice a day, 1 mg/kg spironolactone (Spironolactone; Nichi-Iko Pharmaceutical, Toyama, Japan) orally twice a day, 5 mg/kg polaprezinc (Promac granules 15%; Zeria Pharmaceutical, Tokyo, Japan) orally twice a day, 0.2 g/animal of branched-chain amino acids product (Livact granules; Ajinomoto Pharmaceuticals, Tokyo, Japan) orally twice a day and 0.5 g/animal of a liver support supplement (Vegetable Support Doctor Plus; W.I. System, Tokyo, Japan) orally twice a day. Based on the histopathological diagnosis, tapering doses of prednisolone (Prednisolone; Takeda Pharmaceutical, Osaka, Japan) were added to the regimen (1 mg/kg orally twice a day for 3 days, 1 mg/kg orally once a day for 1 week, 0.5 mg/kg orally once a day for 2 weeks and then 0.5 mg/kg orally every other day). Regular follow-up evaluations were scheduled.

We have previously encountered poor respiratory conditions in patients with hepatic disease. In particular, dogs with chronic hepatitis showed significantly lower PaO_2 and higher $AaDO_2$ than dogs in the control group [9]. The present case did not show serious respiratory signs; however, the respiratory rate increased slightly. Therefore, arterial blood gas analysis was performed regularly. Arterial blood samples were obtained in room air. The dog was placed and rested in lateral recumbency, and blood was drawn from the femoral artery using a 25-gauge needle and a heparinized 1-m*l* syringe (a small amount of heparin sodium was drawn into the syringe to wet the entire syringe and expelled to the

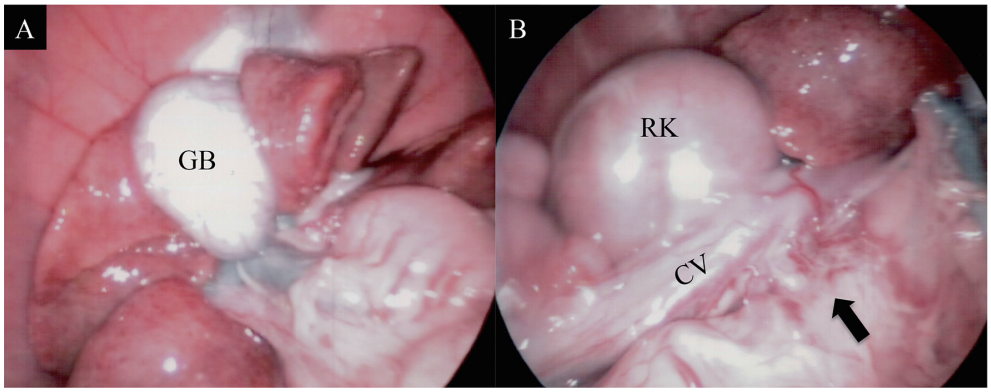

Fig. 2. Laparoscopic image of the liver (A) and multiple portosystemic shunts (B) in the dog with ductal plate malformation. All of the liver lobes were small, and small multiple nodules were visually confirmed (A). Laparoscopy also revealed multiple portosystemic shunts (arrow) near the caudal vena cava (B). GB: gallbladder; RK: right kidney; CV: caudal vena cava.

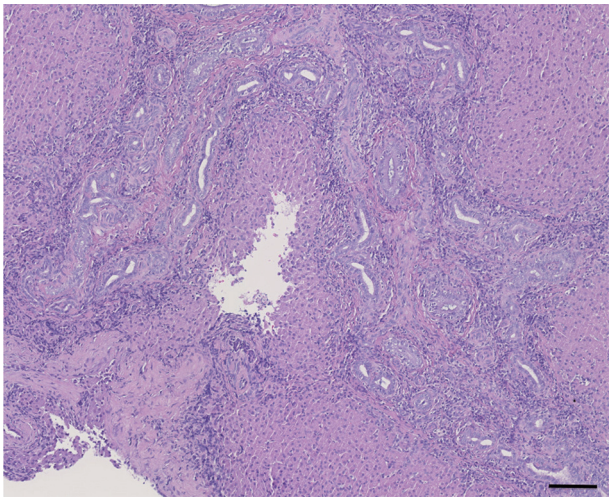

Fig. 3. Photomicrograph of the left lateral lobe of the liver stained with hematoxylin and eosin. Note the poorly defined lobular structure, extensive proliferation of medium-sized interlobular bile ducts and lack of the portal structure. Mild-to-moderate interlobular fibrosis is accompanied by infiltration of numerous lymphocytes, plasma cells and some neutrophils. Ductal plate malformation with lymphoplasmacytic active hepatitis was diagnosed. Bar=100 μm.

fullest extent possible). Arterial blood gas analysis (i-STAT 300F analyzer, Fuso Pharmaceutical Industries, Osaka, Japan, with i-STAT CG4+ cartridges, Abbott Laboratories, Abbott Park, IL, U.S.A.) was performed within one min after sample collection. On Day 29, the dog's respiratory rate was 40 bpm. PaO_2 (reference ranges, 80 to 100 mmHg), $PaCO_2$ (reference range, 35 to 45 mmHg) and $AaDO_2$ (reference range, ≤15 mmHg) were 93 mmHg, 28.8 mmHg and 20.7 mmHg, respectively. On Day 168, the dog was panting. Increased $AaDO_2$ was noted (30.4 mmHg) with a PaO_2 and $PaCO_2$ of 89 and 24.3 mmHg, respectively. Although thoracic radiographs did not show any abnormalities, increased

Table 2. Results of arterial blood gas analysis on Day 29, Day 168 and Day 174

	Day 29	Day 168	Day 174	Reference range
PaO_2 (mmHg)	93	89	85	80–105
$PaCO_2$ (mmHg)	28.8	24.3	28.7	35.0–45.0
$AaDO_2$ (mmHg)	20.7	30.4	28.9	≤15.0

PaO_2: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide, AaDO2: alveolar-arterial oxygen gradient.

$AaDO_2$ indicated possible ventilation-perfusion imbalance, right-to-left shunting or diffusion impairment. On Day 174, the dog's respiratory rate was 52 bpm. $AaDO_2$ was still high (28.9 mmHg) with a PaO_2 of 85 mmHg and $PaCO_2$ of 28.7 mmHg (Table 2).

At this point, we suspected HPS, as the patient satisfied the first two criteria (liver disease and high $AaDO_2$) and $AaDO_2$ had gradually increased. Therefore, we performed agitated saline contrast transthoracic echocardiography (ASC-TTE) to examine intrapulmonary vasodilatation. Routine echocardiography revealed mild mitral regurgitation but ruled out the presence of septal defect or other form of congenital heart malformation. For ASC-TTE, 2 m*l* of saline were mixed with 0.2 m*l* of the patient's blood and air, agitated to generate bubbles and injected into a cephalic vein as a bolus. The bubbles made with agitated saline were detected in the right heart immediately after injection and then in the left heart after the 5th heartbeat (Fig. 4) (Supplementary movie), which is indicative of intrapulmonary vasodilatation. From these results, HPS was strongly suspected, as the dog met all three criteria for HPS. The dog was managed with the same drug regimen and close monitoring. On Day 287, similar results were obtained by ASC-TTE, but the dog's condition was generally favorable with a relatively stable respiratory rate (24 bpm), although hyperammonemia (235 μM/*l*) and elevated liver enzymes persisted.

First reported in 1966 [5], HPS is a well-recognized liver-induced vascular disorder of the lung in humans [8, 24]. It

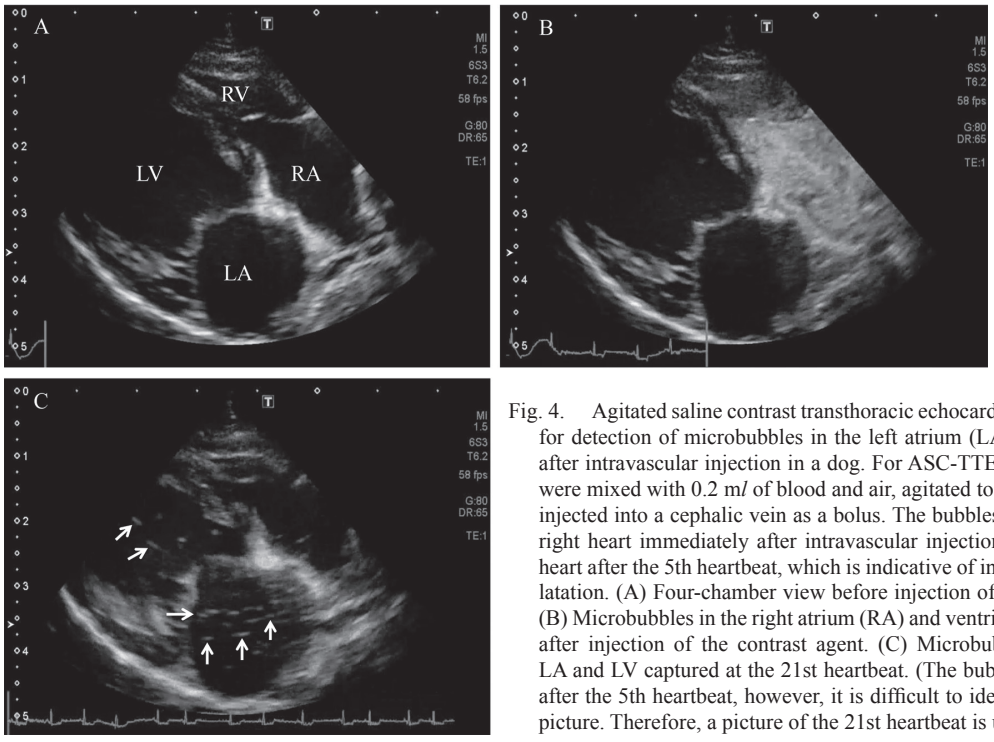

Fig. 4. Agitated saline contrast transthoracic echocardiography (ASC-TTE) for detection of microbubbles in the left atrium (LA) and ventricle (LV) after intravascular injection in a dog. For ASC-TTE, 2 m*l* of 0.9% saline were mixed with 0.2 m*l* of blood and air, agitated to generate bubbles and injected into a cephalic vein as a bolus. The bubbles were detected in the right heart immediately after intravascular injection and then in the left heart after the 5th heartbeat, which is indicative of intrapulmonary vasodilatation. (A) Four-chamber view before injection of saline microbubbles. (B) Microbubbles in the right atrium (RA) and ventricle (RV) immediately after injection of the contrast agent. (C) Microbubbles (arrows) in the LA and LV captured at the 21st heartbeat. (The bubbles started to appear after the 5th heartbeat, however, it is difficult to identify the bubbles in a picture. Therefore, a picture of the 21st heartbeat is used in this figure.)

is more frequently associated with chronic forms of liver disease, occurring in 10 to 30% of cirrhotic patients [8], and known to markedly increase the mortality rate [6, 19]. Currently, liver transplantation is the only option for treatment [8, 22, 24] and is recommended at the earliest possible timing [14]. Although the exact pathophysiological mechanism of HPS is not understood, it appears that intrapulmonary vasodilatation and/or a pulmonary arteriovenous fistula leads to ventilation-perfusion mismatch, resulting in impaired arterial oxygenation [8, 22, 24]. Dilatation of pulmonary microvessels at the gas exchange interface increases the distance that oxygen must travel from the alveolus to equilibrate with red blood cells in the center of the alveolar capillary. This causes a functional diffusional barrier to oxygen exchange [2, 10]. In addition, HPS patients with cirrhosis have been reported to have hyperdynamic circulation [13]. Therefore, this diffusional barrier is exacerbated by rapid blood transit, as alveolar-capillary equilibration for oxygen is influenced by the blood transit time [10]. Also, the pulmonary gas exchange abnormalities of HPS are characterized by hyperventilation [24]. Therefore, dilation of micro-vessels allows PaO_2 and $PaCO_2$ to decrease. $AaDO_2$ was calculated based on PaO_2 and $PaCO_2$ with the a fraction of inspiratory oxygen (FiO_2) of 0.21 (for room air), barometric pressure (P_B) of 765 mmHg, water vapor pressure (P_{H2O}) of 50 mmHg and respiratory exchange ratio (R) of 0.8 using the following formula: $AaDO_2=[FiO_2 \times (P_B - P_{H2O}) - PaCO_2/R] - PaO_2$. Therefore, $AaDO_2$ increases in HPS with intrapulmonary vasodilatation [8, 24]. Patients may also have true anatomical shunting in the form of direct arteriovenous communications, which allow blood to completely bypass alveoli, resulting in mixed venous blood passing into the pulmonary veins [8].

The diagnosis of HPS requires demonstration of the triad of liver disease, abnormal arterial blood gases and intrapulmonary vasodilatation. ASC-TTE is a simple and highly sensitive diagnostic procedure for the detection of intrapulmonary vasodilatation [1, 3, 21]. When a small amount of saline solution, blood and air are agitated and intravenously injected, the bubbles they form are initially detected in the right heart and then move to the pulmonary vascular bed, but they cannot pass the pulmonary capillary circulation because they are larger (≥15 μm) than the diameter of the capillaries (5 to 8 μm in humans and 6.5 μm in dogs) [7]. Generally, bubbles are not observed in the left heart in dogs [12]. Thus, immediate detection of bubbles in the left heart indicates congenital malformation in the heart, such as an atrial septal defect or ventricular septal defect [22, 24]. In dogs, this technology has been used to demonstrate right-to-left shunting [4, 23], but not to demonstrate intrapulmonary vasodilatation. On the other hand, as demonstrated in the present case, if bubbles appear in the left heart about 4 to 6 heartbeats after visualization in the right heart [1, 3, 21], it suggests the presence of intrapulmonary vasodilatation. The present report also demonstrated the usefulness of ASC-TTE for the diagnosis of pulmonary vasodilatation in dogs.

In this case, 1) liver disease (ductal plate malformation with chronic active hepatitis), 2) high $AaDO_2$ without hypoxemia and 3) intrapulmonary vasodilation, as shown by ASC-TTE, were present. Therefore, HPS was strongly suspected, as the dog met all three criteria for. Human HPS patients often report shortness of breath during normal exercise. In this case report, the respiratory rate was slightly

increased, but respiratory signs were not observed. Hypoxemia (PaO_2<80 mmHg) was not observed as well. Thus, it is considered that this case would be classified as mild HPS in humans [15]. However, there is a report that the median survival time was significantly lower in cirrhotic patients with HPS compared with those without HPS [6, 19]. Therefore, detection of gas exchange abnormalities, even if they are mild abnormalities (increased $AaDO_2$, PaO_2>80 mmHg), and diagnose of HPS are important [24]. There are no reports of dogs with HPS yet. It is unclear whether the prognosis evaluation for human could be applied to dogs. However, HPS is typically a progressive pathophysiology [11, 17, 20]. Therefore, dogs with HPS should be closely monitored for respiratory condition.

This is the first report of suspected canine HPS. The present case fulfilled the definitive diagnosis requirements for HPS in humans, but it is considered necessary to perform autopsy in the future. The prevalence of HPS is reported to be from 10 to 30% in human patients with liver cirrhosis [8]. It is possible that dogs with liver disease, especially chronic hepatitis and liver cirrhosis, more or less experience deterioration in gas exchange. Therefore, clinical veterinarians will need to recognize the presence of the disease.

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