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Case Report

Hyperdynamic circulatory state in a dog with leptospirosis : a case report

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Abstract

A hyperdynamic circulatory state is a common consequence of portal vein hypertension. Interestingly, this case report demonstrates acute canine leptospirosis manifesting with abdominal effusion, which it is focused on a hyperdynamic circulatory state, caused by portal hypertension. Severe acute kidney injury caused by leptospirosis in this case was hypothesized to be aggravated by renal hypoperfusion. This condition was noticed to occur in a similar way to hepatorenal syndrome (HRS) in humans. Briefly, a dog with leptospirosis manifesting with abdominal effusion which was diagnosed to be the consequence of hyperdynamic circulatory state caused by hepatopathy and severe acute kidney injury. Peritoneal dialysis was done in the anuric state resulting in a decrease in blood urea nitrogen (BUN) and serum creatinine. However, it was insufficient to improve short-term survival. Regarding the treatment of HRS in humans, vasopressin analogues and alpha-adrenergic agonists have been used for the treatment of HRS and have been seen to reduce mortality. However, the outcome of these drugs for a complicated hyperdynamic circulatory state treatment in dogs remains to be studied further in a large population.

Keywords: hyperdynamic circulatory state, hepatorenal syndrome, leptospirosis, canine

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Introduction

Leptospirosis is an emerging zoonotic infectious disease occurring worldwide (Sykes *et al*., 2011; Klaasen and Adler, 2015). Clinical pictures of canine leptospirosis exhibit varying severities and outcomes, depending on the infecting strain and the host's immune response (Sykes *et al*., 2011; Wilson *et al*., 2013). Diagnosis of canine leptospirosis is based on serological detection and leptospire isolation from blood and urine. The microscopic agglutination test (MAT) is the common test for detecting antibodies against the specific *Leptospira* serovar (Sykes *et al*., 2011). Detection of *Leptospira* specific-IgM is used for a clinical diagnosis of leptospirosis, since an increase in IgM occurs in the first week post-infection (maximum 2-3 weeks). While most dogs receiving leptospira vaccine have been found to have a relatively low *Leptospira*-specific IgM titer, the IgM titers may persist for up to 1-3 month(s) (Bolin, 1996; Lizer *et al*., 2017). Leptospire isolation by cultivation has limitations for clinical diagnosis (Klaasen and Adler, 2015), hence detection of leptospiral deoxyriboneucleic acid (DNA) by polymerase chain reaction (PCR) in blood and urine is an alternative diagnosis (Miotto *et al*., 2018). However, diagnosis of leptospirosis generally involves a combination of the clinical picture, thr history of vaccination and serological detection or leptospire isolation.

Apart from hepatic or kidney injury, manifestations of canine leptospirosis have been reported, such as uveitis, pulmonary hemorrhage syndrome, pancreatitis, petechial hemorrhage, vasculitis and abdominal effusion (Sykes *et al*., 2011; Klaasen and Adler, 2015). Vasculitis may be manifested as peripheral edema and abdominal effusion or mild pleural effusion (Sykes *et al*., 2011). However, pure transudative abdominal effusion in the absence of marked hypoalbuminemia involves portal hypertension. Pathophysiology and therapeutic aspects of abdominal effusion, associated with a hyperdynamic circulatory state owing to portal hypertension, are discussed in this report.

Clinical description

A 4-year-old male, mixed breed dog, weighing 20.6 kg, was presented at the Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Khon Kaen University with a history of jaundice, anorexia, weakness and vomiting for three days. The dog had received the precedent vaccine in a period over three months before presentation.

Clinical examination

Physical examination revealed a capillary refill time (CRT) < 2 sec, 5% dehydration and panting. The body temperature was 101.2°F. The heart rate was 111 bpm, and heart and lung sounds were also normal. Blood pressure was 140/93 mm Hg measured by oscillometry. No evidence of peripheral edema or cutaneous hemorrhage was noted. The initial diagnosis included leptospirosis, hepatobiliary diseases, acute kidney injury and pancreatitis.

Diagnosis workup

The blood profiles, including hematology and serum biochemistry, revealed mild anemia, lymphopenia, thrombocytopenia, marked increased serum creatinine and BUN, mildly increased ALT, markedly increased ALP and hyperbilirubinemia by which increases in total, direct and indirect serum bilirubin were found. Seropositivity to *Leptospira* IgM was detected using the immunochromatographic test (FASTest® Leptospira IgM, Megacor Diagnostik GmbH, Hoerbranz, Australia). Considering the clinical picture and through being seropositive to *Leptospira*-specific IgM, with a history of recent vaccination more than three months before, leptospirosis was the tentative diagnosis. Abdominal ultrasonography was performed on the second day of hospitalization (Figure 1-2). Morphology and the sizes of the liver and pancreas were unremarkable and other hepatobiliary diseases (e.g. hepatic mass) and gall bladder disorders were excluded. A large amount of abdominal effusion and a small amount of retroperitoneal effusion were detected. The abdominal effusion was collected by abdominocentesis under ultrasound guidance to identify the fluid. Abdominal fluid analysis mainly showed 8.22 g/l of protein, 1,000 cells/µl of nucleated cell count and a specific gravity of 1.011, which was consistent with pure transudate (protein <20 g/l and nucleated cell concentration <1,500 cells/µl) (Wray, 2018). The creatinine level of the abdominal fluid was 15.5 mg%. There was no urine leakage from the urinary tract into the abdomen. Arterial blood gases showed mild metabolic acidosis, hyponatremia and hypochloremia. The next day, metabolic acidosis was progressive and an impaired respiratory function which was indicated by an increased in PO_2 (A-a) (>15 mmHg) and a decreased in PO_2 (a/A) was found.

Treatment plan

The treatments included intravenous fluid therapy with acetate ringer's solution and 0.9% saline solution, amoxy-clavulanic acid (8.75 mg/kg SC SID), omeprazole (0.5 mg/kg IV SID) and ondansetron (0.5 mg/kg IV BID). Persistent anuria was detected until the third day of hospitalization. An inability to induce diuresis existed after receiving a diuretic drug with furosemide by IV constant rate infusion at 0.66 mg/kg/h (total 6 mg/kg). Progressive uremia developed (206.69 mg% of BUN and 16.88 mg% of serum creatinine). The antibiotic drug was changed to penicillin G at 25,000 U/kg IV BID. Peritoneal dialysis was performed using warmed in-house dialysate (1.5% dextrose in 0.9% saline solution or acetated ringer's solution). After four cycles of dialysis over 24 hours, BUN and serum creatinine dramatically decreased to 6.8 mg% and 0.40 mg%, respectively. Peritoneal dialysis was done consecutively on the 4th and 5th days. Although peritoneal dialysis resulted in a decrease of both BUN and serum creatinine, abdominal effusion and anuria continued. Progressive kidney injury exacerbated by a hyperdynamic circulatory state was thought to be the main cause of death on the 5th day of treatment.

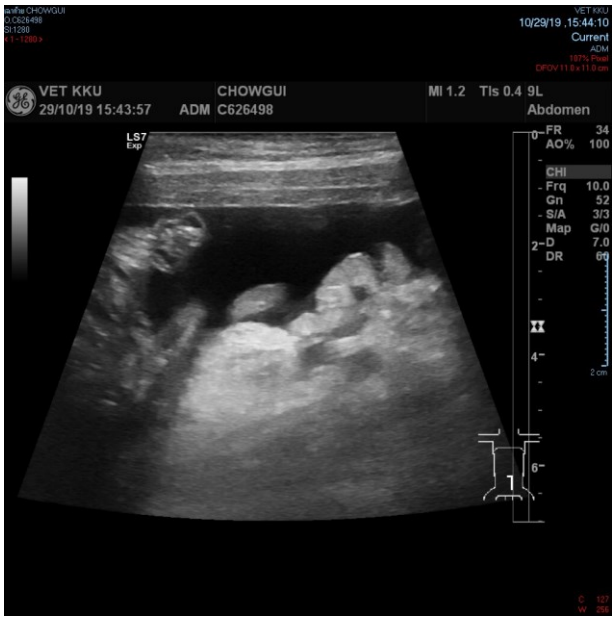

Figure 1 Abdominal ultrasonographic image demonstrating the peritoneal or abdominal effusion in the abdomen.

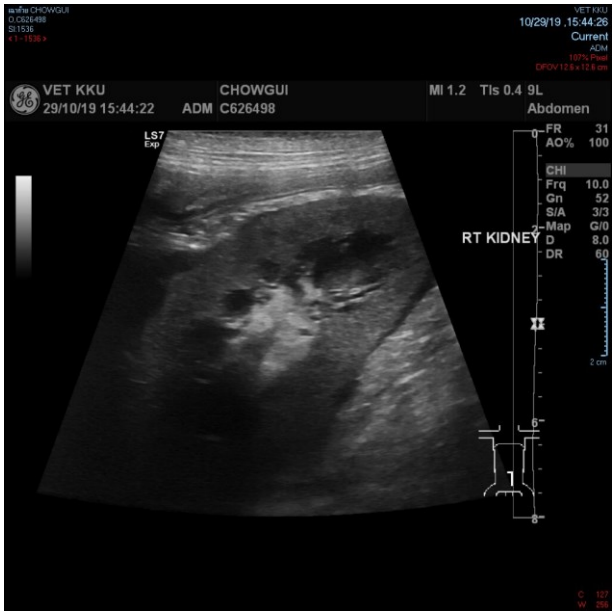

Figure 2 Anechoic appearance at the peri-renal capsule indicates retroperitoneal effusion.

Discussion

In *Leptospira* vaccination, restriction of vaccine-induced immunity depends on serologically related serovars and annual vaccination (Klaasen and Adler, 2015). In addition, vaccination may not prevent infection in the case of a strong *Leptospira* infectious challenge or a highly invasive strain (Klaasen *et al*., 2003; McCallum *et al*., 2019). The sequential investigation for abdominal effusion, including blood profiles, abdominal fluid analysis, abdominal and Doppler ultrasound, and liver and kidney histological examination, would provide the definite conclusion. Because of confinement to both organ biopsy and necropsy in this case for performing the histological study, we have endeavored to investigate the pathogenesis in accordance with rudimentary information. Pure transudative abdominal effusion is usually performed due to marked hypoalbuminemia or portal hypertension (Wray, 2018). Vasculitis induced ascites may be related to the modified transudates or exudates (high total nucleated cells and total protein concentrations) (Bohn, 2017; Wray, 2018). Pure transudative abdominal effusion developing without marked hypoalbuminemia has been reported to be ascribable to portal hypertension in dogs (Hunt *et al*., 1993). In this case, serum albumin was 25 g/l. Consequently, the main cause of pure transudative abdominal effusion focused on portal vein hypertension. Direct measurement of portal venous pressure can be obtained by insertion of a manometer or pressure transducer into the portal vein or its tributaries, while indirect measurement can be obtained by angiographic balloon catheterization. Presently, the clinical consequences of hyperdynamic circulation (e.g. ascites) and assessment of portal vein hemodynamics with Doppler ultrasound may indicate the presence of portal hypertension (Buob *et al*., 2011). We planned to investigate this dog's portal vein

hemodynamics using Doppler ultrasound. Unfortunately, the dog died before the ultrasound could be done.

Portal hypertension arises from either an increase in resistance or an increase in blood flow or both. Increase in hepatic resistance results from structural changes (thrombosis, fibrosis and cell regeneration) and changes in vascular tone in the splanchnic system. An increase in portal venous blood flow arises from a hyperdynamic state and vasodilators (Treiber *et al*., 2005). In this case, the abdominal fluid protein (8.22 g/l) to plasma protein (70 g/l) ratio was calculated and expressed as a percentage. It was 11.74 per cent, indicating a low protein leakage that may be involved with a pre-sinusoidal portal hypertension. This condition may result from portal vein thrombosis, hepatic disease with fibrosis and hepatic arteriovenous fistula (Hunt *et al*., 1993). Unfortunately, the histopathology in this case was not performed. Thus, lack of this result is a limitation of the study. However, a previous study indicated that histopathological changes in the livers of dogs with leptospirosis demonstrated findings of granulomatous hepatitis and portal fibrosis (McCallum *et al*., 2019). It is suggested that hepatopathies which occur in leptospirosis could be related to portal hypertension. However, liver lesions in cases with abdominal effusion require further study.

The predominant consequences of portal hypertension exacerbate haemodynamic alteration, consisting of systemic vasodilatation and fluid retention, leading to secondary involvement of kidneys, which characterize hepatorenal syndrome (HRS) (Treiber *et al*., 2005; Barbano *et al*., 2014). The pathophysiology is illustrated in Figure 3. Retroperitoneal effusion shown at the peri-renal capsule develops into acute kidney injury. This has been found in canine leptospirosis and is suggested to be an ultrafiltrate associated with tubular back-leak into the renal interstitium (Holloway and O'Brien, 2007). In this case, it was thought to result from hyperdynamic circulation.

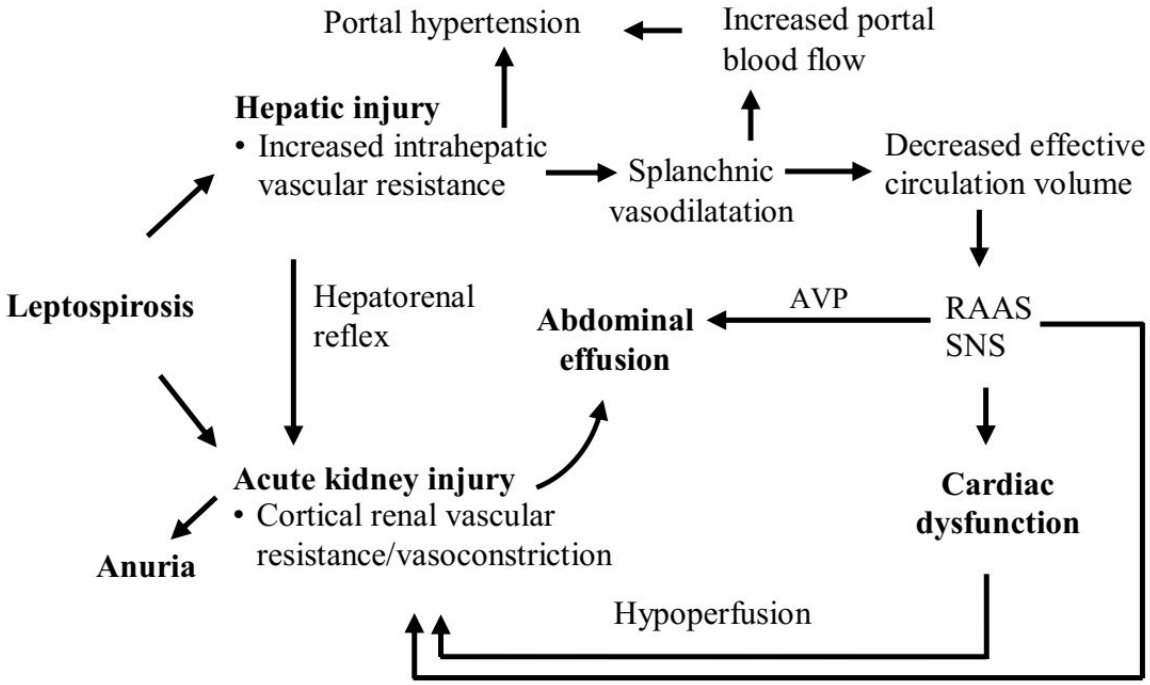

Figure 3 Pathophysiology of a complicated hyperdynamic circulatory state.
Regarding the previous reports, increase in intrahepatic vascular resistance occurs within the liver. Splanchnic circulation undergoes progressive vasodilatation that further increases portal blood flow and portal hypertension. Progressive splanchnic vasodilatation eventually causes circulatory response failure and the development of systemic vasodilatation. Decrease in effective circulatory blood volume stimulates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), and is mainly responsible for a vasoconstriction effect, resulting in cardiac dysfunction, renal hypoperfusion and cortical renal vascular resistance. Additionally, RAAS and arginine vasopressin (AVP) leads to sodium retention and water accumulation, causing fluid overload and abdominal effusion. Furthermore, the hepatorenal reflex (an increase in intrahepatic pressure that affects renal sympathoadrenal activity stimulation to reduce renal blood flow and glomerular filtration rate) and renal hypoperfusion aggravate cortical renal vascular resistance that further progresses to severe kidney injury. This condition is thought to be similar to hepatorenal syndrome (HRS) (applied from Moller and Henriksen, 2004; Buob *et al*., 2011). In this case, concerning the clinical information, leptospirosis caused hepatopathy and acute kidney injury, the manifestation of pure transudative abdominal effusion in the absence of marked hypoalbuminemia was proposed to be involved with portal hypertension. A hyperdynamic circulation resulted from portal blood flow alteration and splanchnic vasodilatation. This change finally caused renal hypoperfusion. Detection of hyponatremia was suggested to be involved with intensive water accumulation rather than sodium retention. The hyperdynamic circulation accompanying with the hepatorenal reflex was thought to convince severe progressive kidney injury and persistent anuria. In turn, this could exacerbate abdominal and retroperitoneal effusion.

Therapeutic interventions for the treatment of hyperdynamic circulation in HRS may improve short-term survival (Minneci *et al*., 2004). Perspectives of pharmacological interventions for the treatment of HRS in dogs are limited, therefore, this situation has been discussed from the literature relating to humans as mentioned earlier. Mainly, vasopressin analogues and alpha-adrenergic agonists have been studied recently for the reversal of spanchnic vasodilatation and for the outcomes of patients with HRS (Guevara *et al*., 1998; Solanki *et al*., 2003; Singh *et al*., 2012[a]; Singh *et al*., 2012[b]).

Arginine vasopressin (AVP) is responsible for the regulation of fluid volume. The antidiuretic effect of AVP acts through the kidney V_2 receptor (V_2R) while the arterial vessel constriction effect acts *via* the vascular V_1 receptor (V_1R) (Holmes *et al*., 2003). Administration of terlipressin, a long-acting vasopressin analog, has been seen to improve kidney function (increased urine output and improved creatinine clearance) and an increase in survival in HRS (Solanki *et al*., 2003). Terlipressin has a relatively higher affinity for V_1R than V_2R, thereby resulting in reduced vascular leakage (Morelli *et al*., 2009). V_1R presents abundantly in mesenteric arteries, therefore vasopressin analogues probably account for the vasoconstrictive effect in the splanchnic circulation (Hirasawa *et al*., 1994). Furthermore, a vasopressin analogue binds to V_1R, which selectively acts on efferent arterioles contractions but not on afferent arterioles (Holmes *et al*., 2003). V_1R selectivity probably accounts for the paradoxical effect of increasing urine output and probably increases glomerular filtration (Eisenman *et al*., 1999; Holmes *et al*., 2001; Holmes *et al*., 2003). However, the side effects of vasopressin analogues include ischemia, abdominal pain and cardiac arrhythmia (Guevara *et al*., 1998; Solanki *et al*., 2003). Besides, alpha-adrenergic agonists (midodrine and noradrenaline) have also been used for HRS treatment (Singh *et al*., 2012[a]; Singh *et al*., 2012[b]; Goyal *et al*., 2016; Obiedallah *et al*., 2017).

In conclusion, a complicated hyperdynamic circulatory state resulting from portal blood flow alteration mainly exacerbates the severity of kidney injury. This state requires instantaneous diagnosis and treatment. Vasopressin analogues and alpha-adrenergic agonists have been reported to be effective in the reversal of HRS. However, the outcomes of these drugs for the treatment of dogs with HRS remains to be studied.

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