Jurnal Veterinar Malaysia

ISSN 0128-2506

Vol. *32* No. *1* (July) *2020*

Veterinary Association Malaysia

J. Vet. Malaysia (2020) 32 (1): 13-18

Case Reports

SEPSIS RELATED NEPHROTIC SYNDROME IN A PUPPY

E. GULERSOY[1*], M.U. AKGUN[1], N. ISMAILOGLU[1], G. AKCAKAVAK[2], M.B. ATES[2], M.K. DURGUT[1], A. NASERI[1] and H. GUZELBEKTES[1]

[1] Selcuk University, Veterinary Faculty, Department of Internal Medicine, 42250, Konya, Turkey,
[2] Selcuk University, Veterinary Faculty, Department of Pathology, 42250, Konya, Turkey

SUMMARY

This case reported a 4-month-old male puppy was admitted to the Small Animal Hospital of Faculty of Veterinary Medicine of Selcuk University with complaints of loss of appetite, stagnation, reluctance to walk, polyuria, polydipsia and abdominal distention. Sepsis and sepsis related nephrotic syndrome was diagnosed by clinical and laboratory examinations. Cardiac complications such as ventricular premature complexes, myocardial injury and calcification were detected by electrocardiographic and echocardiographic examinations. The puppy did not respond to the supportive and anti-proteinuric treatment and due to worsening of the clinical condition, euthanasia was performed. Sepsis related nephrotic syndrome and cardiac complications were confirmed via pathology. It was concluded that nephrotic syndrome is a rare condition in younger dogs which can be predisposed by sepsis leading to severe cardiomyopathy. Biochemical analysis of serum together with ultrasound and electrocardiogram examination are integral components in the diagnosis of nephrotic syndrome and its related complications.

Keywords: Nephrotic syndrome, sepsis, cardiomyopathy, myocardial calcification, puppy

INTRODUCTION

Renal dysfunction in dogs is recognised as glomerulonephritis, renal insufficiency, nephrotic syndrome and/or proteinuria (Devine and Polzin, 2016). Nephrotic syndrome (NS) is defined as the presence of hypoalbuminaemia, proteinuria, extravascular fluid accumulation and hypercholesterolaemia (Klosterman et al. 2011). NS is rare in the first 12 months of life of dogs, with an average prevalence of 0.5%. Mean survival time of dogs with NS-associated glomerular disease is 12.5 days while in non-nephrotic dogs, it is 104.5 days (Klosterman and Pressler, 2011). NS is caused by increased permeability of the damaged basal membrane in the renal glomerulus by infectious agents or thromboembolism. It resulted in an abnormal glomerular permeability which may be a kidney specific disease or secondary to sepsis, diabetes mellitus, systemic lupus erythematosus of congenital (Tapia and Bashir, 2018).

Sepsis is a clinical syndrome associated with the systemic inflammatory response syndrome (SIRS) evoked by invading microorganisms or their toxins in the blood stream. Severe sepsis is defined as the presence of sepsis concomitant with dysfunction of one or more organs (Angus and van der Poll, 2013). During sepsis, one of the most common affected organs is kidney (Poston and Koyner, 2019). This results in kidney injury which contributes the morbidity and mortality following sepsis. Sepsis is associated with 50% of acute kidney injury and 60% patients with sepsis have acute kidney injury (Uchino et al. 2005, Poston and Koyner, 2019). The risk factors and consequences of sepsis for kidney injury are hypovolaemia, nephrotoxic therapies and inflammatory cascade (Poston and Koyner, 2019). Recent studies revealed that renal hypotension and related ischaemia is the primer lesion in sepsis related kidney injury and also inflammation, tubular cell injury, apoptosis and expression of biomarkers such as KIM-1 are playing role in the pathophysiology of sepsis related kidney injury (Maiden et al. 2016; Poston and Koyner, 2019). Studies have reported that there is a 13-fold higher risk of NS-induced sepsis and bacterial infection in humans (Wei et al. 2012, Wu et al. 2012). However, there is little information about kidney injury in dogs with sepsis (Kenny et al. 2010). According to the authors' knowledge, there has been no report of sepsis related NS in dogs. So, the purpose of this case report is to describe a clinical case of a sepsis related nephrotic syndrome in a puppy.

CASE REPORT

A 4-month-old puppy was presented to the Small Animal Hospital of the Faculty of Veterinary Medicine, Selcuk University, with complaints of loss of appetite, stagnation, polyuria, polydipsia and abdominal distention. Upon initial physical examination, dullness and apathetic state of the puppy was remarkable. Physical examination revealed hypothermia (35.8ºC), tachycardia (168 beats/min), tachypnoea (44 breaths/min) and abdominal ballottement. Blood gases analysis showed severe metabolic acidosis (pH=7.15), low bicarbonate (11.7 mmol/L), severe base excess (-17 mmol/L) and hypernatraemia (168 mmol/L). Complete blood count (CBC) revealed severe leukocytosis (44.03 m/mm^3),

Corresponding author: Dr Erdem Gülersoy (E. Gulersoy); Phone No: +905333344042; Email: egulersoy@selcuk.edu.tr

Editorial history
Paper received: 23rd Feb 2020
Accepted for publication: 7th May 2020
Issue Online: July 2020

granulocytosis (33.72 m/mm^3) and anemia (3.73 m/mm^3) (Table 1). In the serum biochemistry, elevated BUN and creatinine levels and hypercholesterolaemia and hypertriglyceridaemia were observed. Severe hypoalbuminaemia was significant (Table 2). Also, a remarkable proteinuria (>3 g/L) was detected by urine dipstick analysis (Table 3).

Table 1. Blood gases and haemogram findings for this case

Acid-base			Reference range	Haemogram		Reference range
pH		7.16	7.35 – 7.45	WBC m/mm^3	48.0↑	5.0 – 19.0
pCO_2	mmHg	33	40 - 45	Lym % (diff.)	14.1	5.0 – 30.0
pO_2	mmHg	39.9	30 - 42	Mon % (diff.)	15.7	2.0 – 6.0
K	mmol/L	3.0	3.4 – 5.6	Gra % (diff.)	70.2	40.0 – 80.0
Na	mmol/L	168	150 - 165	Lym (cells/mL)	6.8	0.2 – 5.7
Ca	mmol/L	0.9	2.0 – 2.7	Mon (cells/mL)	7.5	0.1 – 1.1
Cl	mmol/L	137	104 - 128	Gra (cells/mL)	33.7 ↑	2.0 – 15.2
Glucose	mg/dL	73	64 - 170	RBC M/mm^3	3.7 ↓	4.0 – 9.0
Lactate	mmol/L	0.7	0 - 2	MCV fl	58.8	35.5 – 55.0
Hct %		16	29 - 48	Hct %	21.9	24.0 – 45.0
BE(ecf)	mmol/L	-17	-4 - 4	MCH pg	19.5	16.0 – 24.0
BE (B)	mmol/L	-16	-4 - 4	MCHC g/dl	33.3	28.0 – 40.0
HCO_3(P,st)	mmol/L	12	19 - 24	RDW	11.3	8.0 – 12.0
HCO_3 (P)	mmol/L	12	19 - 24	THR # m/mm^3	97	120 - 500

pH: Hydrogen ion concentration, pCO_2: Partial pressure of carbon dioxide, pO_2: Partial pressure of oxygen K: Potassium, Na: Sodium, Ca: Calcium, Cl: Chloride, Hct: Haematocrit, BE: Base excess, HCO_3: Bicarbonate, WBC: White blood cell, Lym: Lymphocyte, Mon: Monocyte, Gra: Granulocyte, RBC: Red blood cell, MCV: Mean corpuscular haemoglobin, MCH: Mean corpuscular haemoglobin, MCHC: Mean corpuscular haemoglobin concentration, RDW: Red cell distribution width, THR: Thrombocyte, Diff: Differential count. ↑: Increase, ↓: Decrease.

Table 2. Serum biochemistry findings for this case

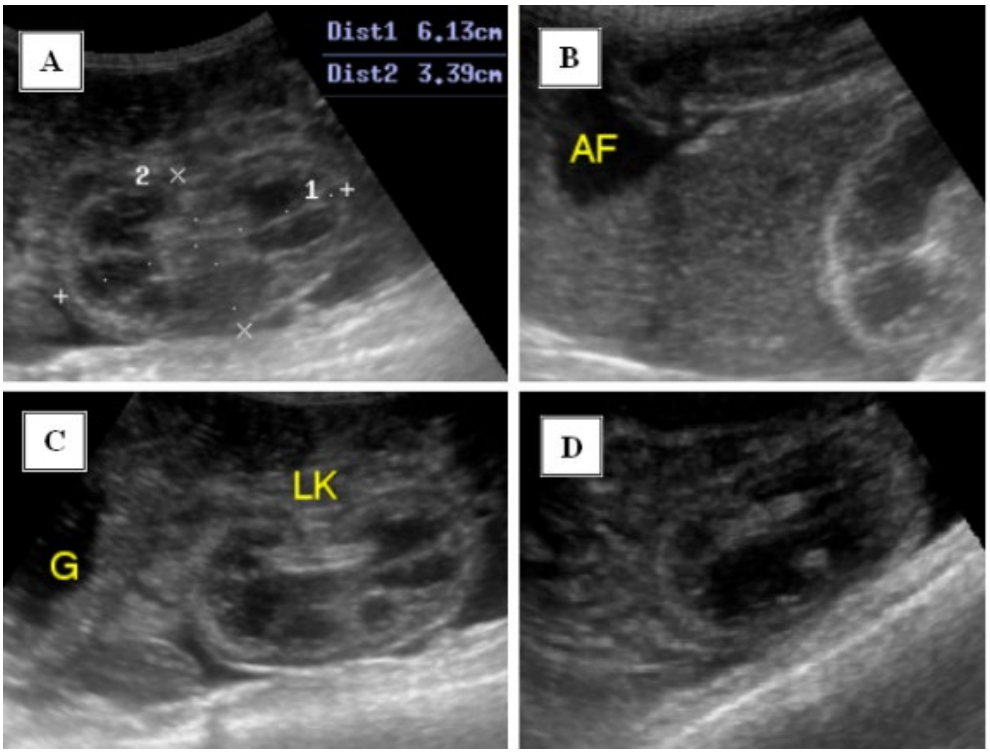
Parameter			Reference ranges
BUN	mg/dL	117↑	14 – 36
Creatinine	mg/dL	5.0 ↑	0.6 – 2.4
AST	U/L	53	10 – 100
ALT	U/L	48	10 – 100
ALP	U/L	534 ↑	6 – 102
Amylase	U/L	1014	100 – 1200
Glucose	mg/dL	77	64 – 170
Magnesium	mg/dL	2.2	1.5 – 2.5
LDH	U/L	350	20 – 500
Total bilirubin	mg/dL	0.6 ↑	0.1 – 0.4
Direct bilirubin	mg/dL	0.3	0 – 0.4
Phosphorus	mg/dL	13.1 ↑	2.4 – 8.2
Cholesterol	mg/dL	355 ↑	75 – 220
Albumin	g/dL	1.3 ↓	2.5 – 3.9
Calcium	mg/dL	9.1	8.2 – 10.8
Triglycerides	mg/dL	199 ↑	25 – 160
GGT	U/L	12 ↑	1 – 10
Protein	g/dL	3.0	5.2 – 8.8

BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase, ↑: Increase, ↓: Decrease.

Leucocyte	0 cell/uL
Ketone	0 mmol/L
Nitrite	-
Glucose	0 mmol/L
Protein	+3 >3 g/L
Specific gravity	1.025
pH	5.0
Blood	0 cell/uL
Microalbumin	>150 mg/L
Calcium	< 1 mmol/L
Creatinine	8.8 mmol/L

Table 3. Urine dipstick findings for this case

For evaluation of kidneys and probable abdominal effusion, an ultrasonography was performed using by 5 MHz probe (Mindray Dc-6, China). Ultrasonographic examination revealed thinning of the renal cortex, dilatation of the medulla and abdominal effusion (Figure 1). Abdominocentesis was performed with a 22 gauge needle from 2-3 cm caudal of the umbilical region and 5 ml content was taken for analysis. The density and total protein of taken fluid were 1.010 and 0 g/L, respectively and conformed to be a transudate (Karkhanis and Joshi, 2012).



AF: Abdominal fluid, G: Gaster, LK: Left kidney

Figure 1. Ultrasonograph of the selected organs A. Hypertrophic kidney. B. Free abdominal fluid C. Free abdominal fluid with hypertrophic kidney D. Dilatation in medulla of kidney

The arterial blood pressure was measured by oscillometric method (Compact 7, Medical Econet, Germany), and showed a systolic blood pressure (SBP) of 172 mmHg. Electrocardiographic examination (derivations I, II and, III, paper speed: 50 mm/s; calibration at 10 mm=1 mV) revealed premature ventricular complexes (Figure 2) (EDAN VE-300, China). Two-dimension (2-D) and M-mode echocardiographic examination using of right parasternal long and short-axis windows was performed by 4 MHz probe (Apogee 3500V, SIUI, China). Hyperechoic areas of the left ventricular posterior wall and, decrease of ejection fraction (EF=50%) were detected (Figure 3).

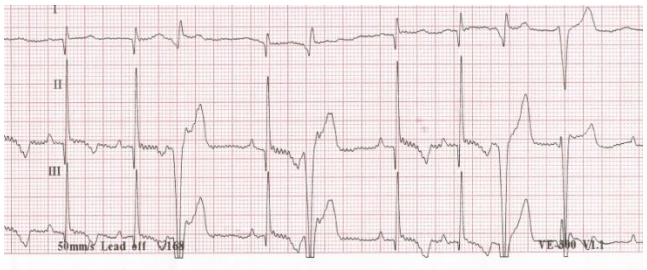


Figure 2. Electrocardiogram showing a premature ventricular complexes

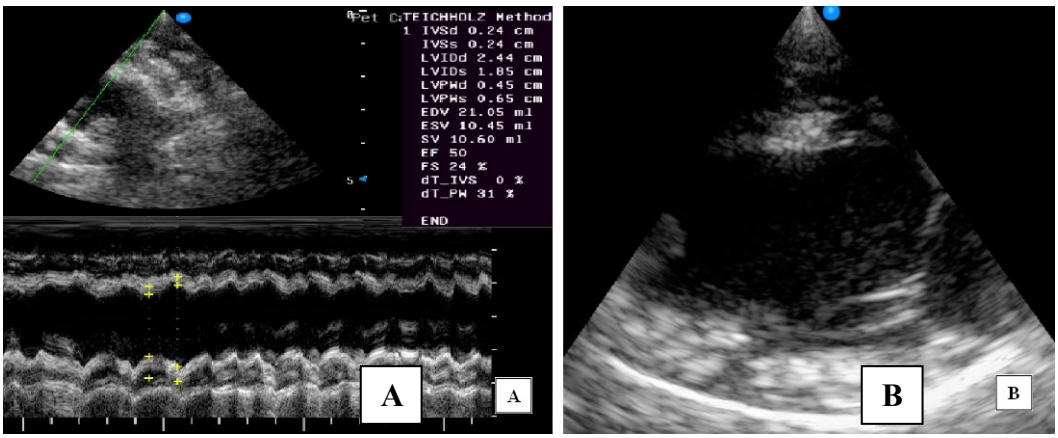


Figure 3. Echocardigraph showing A. Reduction of left ventricle EF (50%) B. Calcified areas on the LV posterior wall in the right parasternal long axis 4 chamber view

Despite the intensive therapy, the puppy's condition deteriorated and euthanasia was done and necropsy performed. Tissue samples taken from various organs for histopathological examination were fixated in 10% formaldehyde for one day and then routine tissue follow-up procedures were performed, the 5µm cut sections were stained with Hematoxylin-Eosin (Luna, 1968) and examined under a light microscope (Olympus BX51, Tokyo, Japan).

At post mortem, ecchymotic hemorrhages in the capsule of the kidneys, paleness and easily degradable structure was noted (Figure 4A). Ecchymotic haemorrhage extending from the cortex to the medulla on the cross section and corticomedullary gravitational white radial extensions were noted in the kidneys (Figure 4B). Grossly, widespread pale areas on the epicardium was observed, which when cut revealed variably-sized (5-10 mm in diameter) mineralized areas on the endocardium and myocardium (Figure 4C-D). Besides the presence of froth in the trachea, a voluminous lung that ooozed transparent fluid upon incision was seen. The edges of the liver were blunt and dark colored blood oozed freely upon incision. Mucoid and catarrhal contents were seen in the lumen of intestines.

Histopathologically, dissociation, atrophy in hepatocytes, enlargement in sinusoids and intrahepatic cholestasis were observed in the liver (Figure 5A). Expansion in the interstitial tissue in the lungs due to mononuclear cell infiltration, and emphysema and edema in alveoli were determined. Intense mineralized areas were seen in the renal cortex, drainage canals and tubule lumens. Necrotic changes such as pyknosis, karyorrhexis and karyolysis were recorded in the proximal tubular epithelial nuclei (Figure 5B-C). Diffuse mineralizations were observed, especially in the subendocardial parts of the heart muscle. Swelling and loss of striation were observed in muscle fibers. The nuclei of cardiomyocytes had pyknosis and karyolysis. (Figure 5D).

DISCUSSION

Sepsis is defined as SIRS combined with infection. Severe sepsis is sepsis complicated with at least one organ dysfunction. Our findings showed that the puppy had criterias for severe sepsis and, metabolic acidosis, azotaemia, high ALP, were the findings of dysfunctional organ systems (Silverstein and Hoper, 2015). Kenney et al. (2010) reported that 89 of the 114 septic dogs (78%) had dysfunction of one or more organ systems. Among the 14 out of 89 septic dogs (16%) the organ that develops dysfunction was the kidney.

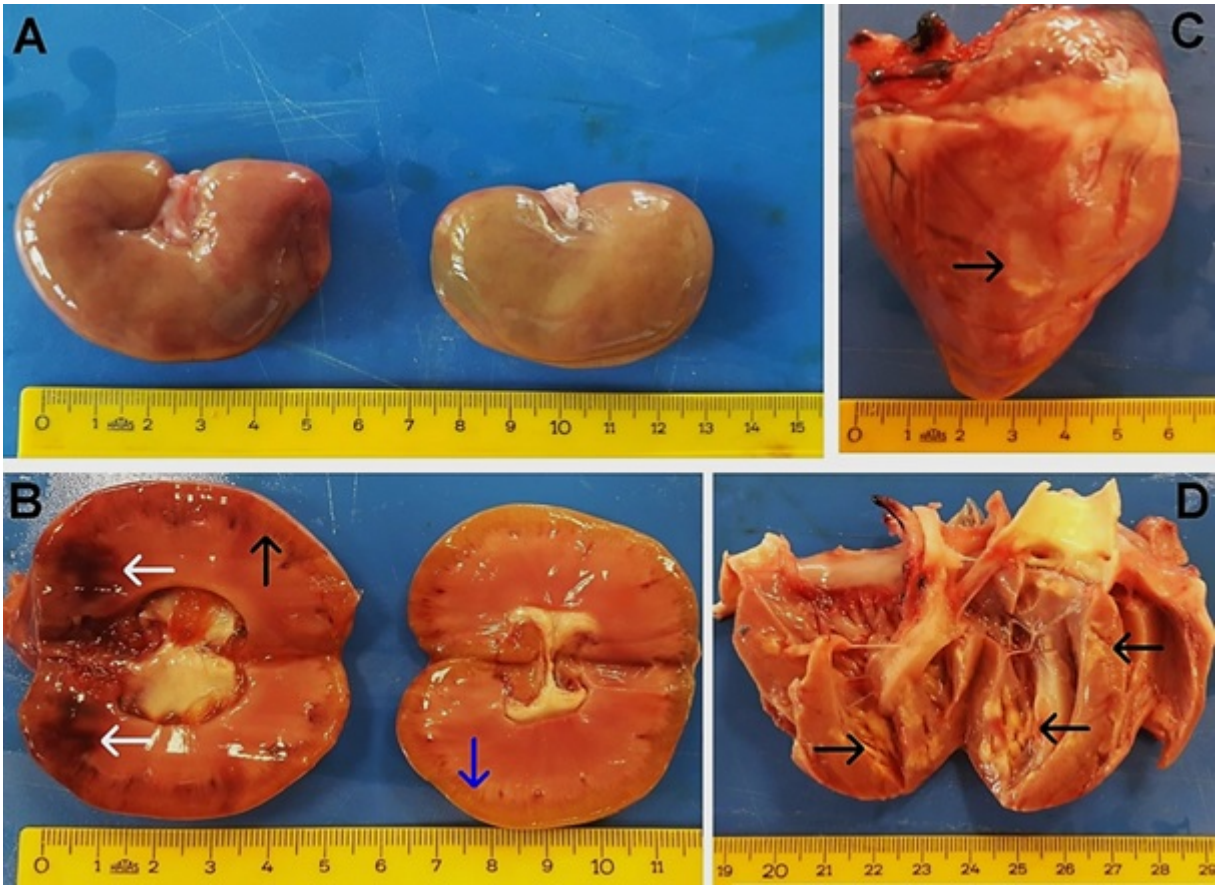


Figure 4. Macroscopic examination photographs of organs. A. Pale and mottled appearance in the kidneys. B. Ecchymotic hemorrhage in the cortex and medulla (white arrow), narrowing of the cortex (black arrow) and white radial extensions (calcification areas) (blue arrow) in the cortex. C. Pale areas of epicardium in heart (black arrow). D. Mineralized areas of 5-10 mm diameter on the endocardium in the heart (black arrow).

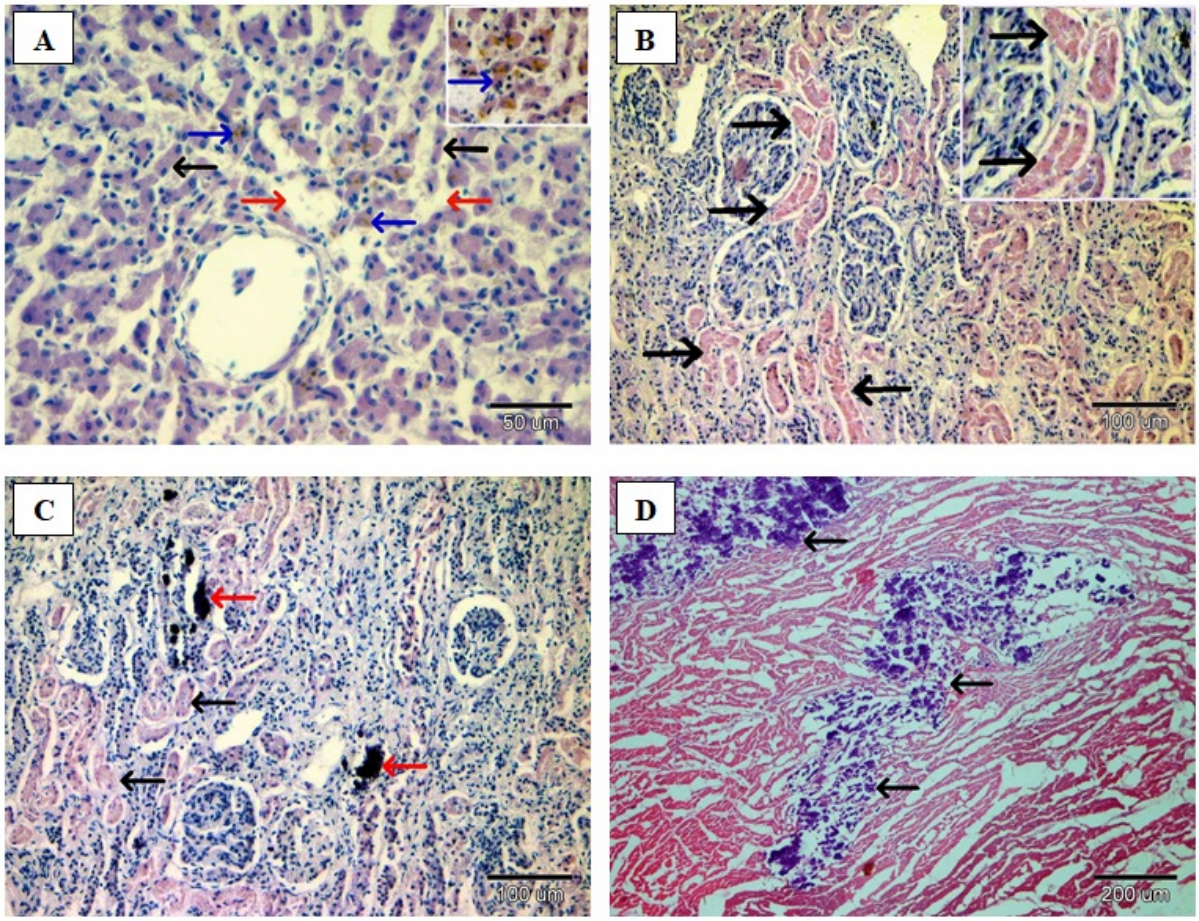


Figure 5. Photomicrograph of selected organs. A. Atrophy in hepatocytes (black arrow), expansion of sinusoids (red arrow) and intrahepatic cholestasis (blue arrow). B. Coagulation necrosis in proximal tubules epithelium C. Necrosis in proximal tubules (black arrow) and mineralized areas in drainage canals (red arrows). D. Diffuse mineralization areas in the heart muscle (black arrow) and myocardial necrosis (pink colored areas).

Nephrotic syndrome is defined as the presence of hypoalbuminaemia, proteinuria, hypercholesterolaemia and extravascular fluid accumulation and may develop secondary to sepsis (Tapia and Bashir, 2018). Our findings showed severe reduction of serum total protein and albumin and increase SBP. Decreasing intravascular oncotic pressure by the low plasma protein level associated with proteinuria (Bockenhauer, 2013). The amount of fluid leaking into the vascular cavity exceeds the reabsorption capacity of the lymphatic system and the resulting hypovolaemia and hypotension stimulate the renin-angiotensin-aldosterone (RAAS) system and sodium retention (Doucet et al. 2007). Therefore, hypertension (SBP>160 mmHg) is common in dogs with NS (de Seigneux and Martin, 2009).

Myocardial depression is one of the complications of sepsis as seen in humans, dogs and calves with sepsis (Nelson and Thompson, 2006, Vieillard-Baron et al. 2008, Naseri et al. 2018, Ince et al. 2019). Studies to elucidate the actual pathophysiology of myocardial dysfunction during sepsis suggest that genetic factors, molecular alterations (calcium channels, nitric oxide, endothelin-1, cytokines and toll-like receptors), metabolic alterations (ischaemia, mitochondrial dysfunction and oxidative stress, autonomic dysregulation) and structural modifications (myocardial infiltration by immune cells, apoptosis and necrosis) are the major causes of myocardial depression during sepsis (Antonucci et al. 2014).

The echocardiographic findings in this case showed that beside the myocardial depression, there were mineralized areas of the heart and widespread VPCs. Septic myocardial calcification is a very rare condition. Maintaining normal serum calcium levels requires a positive calcium balance in most patients with renal failure and nephrotic syndrome, likely contributing to extensive vascular calcification (Goodman et al. 2000). Calcification in cases of renal impairments such as nephrotic syndrome as in our case, with consequent hyperphosphatemia is due to pathogenic dystrophic calcium mechanism, as stated below (McClure et al. 1981). Some factors trigger myocardial calcification in the cases of sepsis and renal failure. Increase in circulating endogenous and exogenous catecholamines can, due to their vasoconstrictive mechanism, cause ischemia with subsequent cardiomyocyte necrosis. Additionally, both the infection and the resulting inflammatory reaction can cause cardiac damage secondary to important release of free oxygen radicals, increase in nitric oxide and inducible nitric oxide synthase production, and microvascular ischemia deriving from the direct flow obstruction of the inflammatory

infiltration site. Two mechanisms of myocardial calcification have been suggested, viz; metastatic and dystrophic. In metastatic mechanism, due to abnormal calcium homeostasis in kidney disease calcium crystals accumulate in the septic myocardium. In the dystrophic mechanism, calcium crystals accumulate in the previously damaged myocardium (Maiese et al. 2019). Presumably, in the present case, sepsis has been triggered the renal dysfunction and release of inflammatory mediators and, abnormal calcium hemostasis leads to the myocardial depression and, septic myocardial calcification.

CONCLUSION

Nephrotic syndrome is rare in young dogs and this is the first report in dogs showing that sepsis can lead to the NS and severe cardiomyopathy. Biochemical analysis and diagnostic imaging techniques are important tools in the diagnosis of cardio-renal deterioration in sepsis.

CONFLICT OF INTEREST

None of the authors of this paper has financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

REFERENCES

Angus, D.C. and van der Poll, T. (2013): Severe sepsis and septic shock. The New England Journal of Medicine, 369: 840-851.

Antonucci, E. Fiaccadori, E. Donadello, K. (2014): Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. Journal of Critical Care, 29:500–511.

Bockenhauer, D. (2013): Over- or underfill: not all nephrotic states are created equal. Pediatric Nephrology, 28:1153–1156.

de Seigneux, S. and Martin, P.Y. (2009): Management of patients with nephrotic syndrome. Swiss Medical Weekly, 139:416-422.

Devine, L. and Polzin, D.J. (2016): Presumed masitinib-induced nephrotic syndrome and azotemia in a dog. The Canadian Veterinary Journal, 7:752-756.

Doucet, A. Favre, G. Deschenes, G. (2007): Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. Pediatric Nephrology, 22:1983-1990.

Goodman, W.G. Goldin, J. Kuizon, B.D. Yoon, C. Gales, B. Sider, D. Wang, Y. Chung, J. Emerick, A. Greaser, L. Elashoff, R.M. Salusky, I.B. (2000): Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. The New England Journal of Medicine, 342: 1478-1483.

Ince, M.E. Turgut, K. Akar, A. Naseri, A. Sen, I. Süleymanoglu, H. Ertan, M. Sagmanligil, V. (2019): Prognostic importance of tissue Doppler imaging of systolic and diastolic functions in dogs with severe sepsis and septic shock. Acta Veterinaria Hungarica, 4:517-528.

Karkhanis, V.S. and Joshi, J.M. (2012): Pleural effusion: diagnosis, treatment, and management. Open Access Emergency Medicine, 4:31-52.

Kenney, E.M. Rozanski, E.A. Rush, J.E. deLaforcade-Buress, A.M. Berg, J.R. Silverstein, D.C. Montealegre, C.D. Jutkowitz, L.A. Adamantos, S. Ovbey, D.H. Boysen, S.R. (2010): Association between outcome and organ system dysfunction in dogs with sepsis: 114 cases (2003–2007). Journal of the American Veterinary Medical Association, 1:83-87.

Klosterman, E.S. and Pressler, B.M. (2011): Nephrotic syndrome in dogs: Clinical features and evidence-based treatment considerations. Topics in Companion Animal Medicine, 26:135–142.

Klosterman, E.S. Moore, G.E. de Brito Galvao, J.F. DiBartola, S.P. Groman, R.P. Whittemore, J.C. Vaden, S.L. Harris, T.L. Byron, J.K. Dowling, S.R. Grant, D.C. Grauer, G.F. Pressler, B.M. (2011): Comparison of signalment, clinicopathologic findings, histologic diagnosis, and prognosis in dogs with glomerular disease with or without nephrotic syndrome. Journal of Veterinary Internal Medicine, 25: 206-2014.

Luna, L.G. (1968): Routine Staining Procedures. In: Manual of Histologic Staining Methods of the Armed Forces Institutie of Pathology Eds, 3. United States of America: McGaw-Hill Book Company. 32-44.

Maiden, M.J. Otto, S. Brealey, J.K. (2016): Structure and Function of the Kidney in Septic Shock. A Prospective Controlled Experimental Study. American Journal of Respiratory and Critical Care Medicine, 194:692-700.

Maiese, A. Manetti, F. La Russa, R. (2019): Septic myocardial calcification: A case report. Journal of Forensic and Legal Medicine, 65:45-47.

McClure, J. Pieterse, A.S. Pounder, D.J. Smith, P.S. (1981): Myocardial fibre calcification. Journal of Clinical Pathology, 34: 1167-1174.

Naseri, A. Turgut, K. Sen, I. Ider, M. Akar, A. (2018): Myocardial depression in a calf with septic shock. Veterinary Record Case Reports, 1:p.e000513.

Nelson, O.L. and Thompson, P.A. (2006): Cardiovascular dysfunction in dogs associated with critical illnesses. Journal of the American Animal Hospital Association, 42:344–349.

Poston, J.T. and Koyner, J.L. (2019): Sepsis associated acute kidney injury. British Medical Journal, 1-17.

Silverstein, D.C. and Hoper, K. (2015): Small Animal Critical Care Medicine 2nd Ed. Elsevier Saunders USA.

Tapia, C. and Bashir, K. (2018): Nephrotic syndrome. StatPearls Publishing, NCBI Bookshelf.

Uchino, S. Kellum, J.A. Bellomo, R. (2005): Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. The Journal of the American Medical Association, 294:813-818.

Vieillard-Baron, A. Caille, V. Charron, C. (2008): Actual incidence of global left ventricular hypokinesia in adult septic shock. Critical Care Medicine, 36:1701–1706.

Wei, C.C. Yu, I.W. Lin, H.W. Tsai, A.C. (2012): Occurrence of infection among children with nephrotic syndrome during hospitalizations. Nephrology (Carlton). 17:681–688.

Wu, H.M. Tang, J.L. Cao, L. Sha, Z.H. Li, Y. (2012): Interventions for preventing infection in nephrotic syndrome. Cochrane. Database. Syst. Rev 4. CD003964.