Animal Diseases

CASE REPORT

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Clinical features of chronic kidney disease in dogs with the serological presence of *Leptospira* spp., *Ehrlichia canis,* and *Anaplasma phagocytophilum*

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Abstract

Chronic kidney disease is commonly diagnosed in dogs, and clinical signs may be aggravated when infected agents are involved. In this case report, 33 dogs with chronic kidney disease were clinically evaluated and serologically tested for *Leptospira* spp., *Ehrlichia canis,* and *Anaplasma phagocytophilum*. The seroprevalence for *Leptospira* spp. was 39.4%. The most frequent serovars found were Pyrogenes, Canicola, Bratislava and Australis, with serological titers between 1:100 to 1:800. Clinical signs included fever, depression, decreased body condition, vomiting and hematuria. Significant laboratory findings were anemia, leukocytosis, thrombocytopenia, increased liver enzymes, urea and creatinine, hyperbilirubinemia and hyperphosphatemia. All leptospira seronegative dogs were positive for one or both monitored homoparasites (i.e., *E. canis* and *A. phagocytophilum*); only three leptospira seropositive dogs were positive for one or both hemoparasites. Findings also suggest that endemic hemoparasites of dogs should be monitored in dogs with a kidney condition for a better clinical picture of the patients and therapeutic approach.

Keywords Anaplasma, Chronic kidney disease, Dog, Ehrlichia, Leptospira

Introduction

In veterinary medicine, renal pathologies are classified as acute kidney injury (AKI) and chronic kidney disease (CKD) (IRIS 2019). Cases of CKD may increase in older dogs with diseases such as leptospirosis (Lizer et al. 2017) and other infectious diseases (Chirek et al. 2018). Dogs are specific hosts for the *Canicola serovar* but are incidental hosts for many others (Reagan and Sykes 2019). Leptospirosis is a risk factor for developing kidney disease due to direct damage to the epithelial cells of the renal tubules (D'Hoore et al. 2015). Sant'Anna found exposure titers in 25% of dogs with CKD and concluded that dogs with CKD are 3 times more likely to be seroreactive and 3.3 times more likely to be infected (Sant'Anna et al. 2019). Other infectious agents may be involved in cases of CKD; for instance, positive *Ehrlichia* spp. antibodies in *E. canis*-endemic regions have been associated with a higher incidence of CKD in dogs (Burton et al. 2020). Although no increased risk for developing CKD was found in dogs when exposed to *Anaplasma* spp., a significant risk increase was observed with exposure to

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other hemoparasites, such as *B. burgdorferi* (Drake et al. 2021).

Evaluation of CKD in dogs positive for *Leptospira* spp., *E. canis,* and *A. phagocytophilum* is important to understand their potential role in clinical value in an endemic region.

Case presentation

Case history

Thirty-three dogs with CKD were evaluated (16 males and 17 females), with a mean age of eight years and no leptospira vaccines or vaccination for more than one year.

As inclusion criteria, kidney disease was considered according to criteria established by the IRIS. For the classification of CKD, the presence of associated factors (susceptibility, triggers, and progression), renal azotemia (creatinine ≥ 1.4 mg/dl), hyperphosphatemia (≥ 0.81 mmol/L), isostenuria (UD of 1,008–1,012) or hypostenuria (UD ≤ 1,008), persistent proteinuria and hypertension for at least one year were considered.

Clinical findings

In the clinical history of patients with kidney disease, the most frequent aspects reported were depression, decreased body condition, vomiting and hematuria. Hyporexia, fever and polyuria-polydipsia syndrome were more frequently seen in dogs positive for Leptospira spp. and hemoparasites (Table 1).

The most frequent alterations in the general physical examination were the depressed state of consciousness, thin body condition, pale mucosa, hyperthermia, abdominal pain, hepatomegaly, and increased prescapular and popliteal lymph nodes. Pleural friction and crepitation were detected in one Leptospira seropositive dog. The specific frequencies of these alterations can be seen in Table 2.

Since most animals were patients from private clinics or hospitals, detailed postevaluation data were not always available. However, follow-up of patients was performed via telephone or email for two months. The mortality rate during the observation period was 9% (3/33). Two dogs died from cardio-respiratory arrest, and one was euthanized at the owners' request due to an advanced kidney disease condition.

Detection of antibodies against *Leptospira* spp.

For detecting antibodies against Leptospira spp., the Microscopic Agglutination Test (MAT) was used, considered the gold standard test for diagnosing leptospirosis. Titters of 1:100 were considered positive and confirmed with a second sample. Titles 1:800 in the first sample were considered confirmatory.

Table 1 Frequency of clinical signs in dogs with kidney disease and positive and negative serology for leptospirosis

Clinical signs	CKD positive for *Leptospira* (*n* = 13)	CKD negative to *Leptospira* (*n* = 20)
Fever	8 (61.5%)	4 (20.0%)
Anorexia	5 (38.4%)	7 (35.0%)
Hyporexia	7 (53.8%)	6 (30.0%)
Vomits	8 (61.5%)	9 (45.0%)
Diarrhea	-	1 (5.0%)
Melena	-	1 (5.0%)
Hematochezia	-	-
Polydipsia	7 (53.8%)	11 (55.0%)
Oral ulcers	4 (30.7%)	4 (20.0%)
Uremic breath	4 (30.7%)	6 (30.0%)
Respiratory distress	3 (23%)	2 (10.0%)
Cough	5 (38.4%)	3 (15.0%)
Hematuria	6 (46.1%)	8 (40.0%)
Polakiuria	1 (7.7%)	2 (10.0%)
Oliguria	-	-
Polyuria	9 (69.2%)	8 (40.0%)
Anuria	-	-
Jaundice	4 (30.7%)	4 (20.0%)
Petechiae	4 (30.7%)	5 (25.0%)
Ecchymosis	-	-
Suffusion	-	-
Decrease in BC	11 (84.6%)	17 (85.0%)
Depression	9 (69.2%)	13 (65.0%)

CKD chronic kidney disease, *BC* body condition

The frequency of *Leptospira* spp. was 39.4% (13/33). The most frequent serovars were Pyrogenes, Canicola, Bratislava, and Australis, detecting serological titers that fluctuated between 1:100 and 1:800. Of the total positive sera, 55.6% (10/18) reacted to more than one serovar. It is worth mentioning that a dog had titters of 1:800 for the Pyrogenes serovar in paired samples, showing only alterations in their laboratory tests without clinical signs (Table 3).

Hemoparasite results

All dogs with CKD and seronegative to *Leptospira* spp. were positive for some of the tested hemoparasites (55.0% against *E. canis*, 5.0% against *A. phagocytophilum* and 40.0% for both hemoparasites) using a commercial snap kit; one leptospira seronegative dog was positive for *E. canis,* and the other was positive for both hemoparasites. None of the control dogs presented serological evidence of *Leptospira* spp. or any tested hemoparasites. To detect hemoparasites, the commercial SNAP kit 4Dx Plus (IDEXX Laboratories) was used, reporting 99.0% sensitivity and 99.3% specificity for *D. immitis*, 94.1% and

Table 2 Frequency of alterations in the general physical examination of dogs with chronic kidney disease that were seropositive and seronegative for *Leptospira* spp

Clinical evaluation	ERC positive for *Leptospira* (*n* = 13)	ERC negative to *Leptospira* (*n* = 20)
Mental status		
Alert	2 (15.4%)	10 (50.0%)
Depressed	11 (84.6%)	10 (50.0%)
Hydratation status		
< 5%	-	-
5–6%	10 (76.9%)	18 (90.0%)
7–8%	3 (23%)	2 (10.0%)
Body condition		
Cachexia	1 (7.7%)	1 (5.0%)
Thin	9 (69.2%)	11 (55.0%)
Normal	3 (23%)	8 (40%)
Hearth rate		
Bradycardia	-	-
Normal	12 (92.3%)	19 (95.0%)
Tachycardia	1 (7.7%)	1 (5.0%)
Respiratory rate		
Bradypnea	-	-
Normal	11 (84.6%)	13 (65.0%)
Tachypnea	2 (15.4%)	7 (35.0%)
Pulso S/F/C	11 (84.6%)	18 (90.0%)
Week pulse	2 (15.4%)	2 (10.0%)
Mucous		
Pink	3 (23%)	6 (30.0%)
Palid	6 (46.2%)	12 (60.0%)
Icteric	4 (30.8%)	2 (10.0%)
CRT		
< 3 seg	13 (100%)	20 (100.0%)
> 3 seg	-	
Cough reflex		
Positive	2 (15.4%)	1 (5.0%)
Negative	11 (84.6%)	19 (95.0%)
Palmopercussion		
Positive	1 (7.7%)	-
Negative	12 (92.3%)	20 (100.0%)
Temperature		
Hypothermia	1 (7.7%)	1 (5.0%)
Normothermia	5 (38.5%)	16 (80.0%)
Hyperthermia	4 (30.8%)	1 (5.0%)
Fever	3 (23%)	2 (10.0%)
Abdominal palpación		
Normal	4 (30.7%)	14 (70.0%)
Pain	3 (23.1%)	3 (15.0%)
Hepatomegaly	6 (46.2%)	3 (15.0%)
Distension	-	-
Lymph nodes		
Normales	4 (30.8%)	14 (70.0%)
Increase size	9 (69.2%)	6 (30.0%)

94.3% specificity for *Anaplasma* spp., 93.4% sensitivity and 96.8 specificity for *Ehrlichia* spp., and 95.5% sensitivity and 96.2% specificity for *B. burgdorferi* (IDEXX 2016).

Complete blood count, clinical chemistry, and urinalysis results

The normal range of values of the CBC, blood chemistry, and urinalysis of the clinically healthy dogs (control dogs) compared with CKD dogs according to the seropositivity toward *Leptospira* spp. and/or hemoparasites are summarized in Table 4. Blood count was significantly higher only for the number of leukocytes and lower in platelets compared to the control group. The liver enzymes ALT and AST, total bilirubin, urea, and creatinine were significantly higher ($P < 0.05$) in the CKD dog groups than in the control groups. However, differences were observed in dogs seropositive for Leptospira spp. and hemoparasites. For instance, increased levels of ALT and AST were more evident in dogs positive for *E. canis* and *A. phagocitophilum* and dogs seropositive for Leptospira spp. Only dogs positive for *E. canis* and *A. phagocitophilum* had a very high number of blood cells in the urine.

Discussion and conclusions

In CKD, a gradual loss of nephrons occurs due to some unrestored primary lesion, which induces compensatory adaptive changes in the remaining nephrons (Ross 2011) and triggers glomerular capillary hypertension and vasoconstriction of the afferent arteriole, which leads to a decrease in the glomerular filtration rate, renal azotemia and inability to concentrate urine (Reynolds and Lefebvre 2013). Affected dogs with CKD in this report had a mean age of 8 years, which may be associated with the gradual decrease in the number of functional nephrons (Bartges 2012), probably due to the presence of diverse chronic inflammatory processes throughout their lives, including infectious diseases (Chirek et al. 2018).

There are no specific clinical signs of CKD. However, as found in this report, hyporexia/anorexia, vomiting, uremic breath, ulcerative stomatitis, polyuria/polydipsia, loss of weight and body mass, and lethargy are common findings (Bartges 2012; O'Neill et al. 2013).

The clinical signs and laboratory alterations observed correspond to those previously described for CKD. However, the presence of fever, pale mucous membranes, abdominal pain, and increased lymph node size, as well

Table 3 Frequency of MAT reactions and titers of *Leptospira interrogans* serovars in 29 dogs with chronic kidney disease from Merida, Yucatan

Serovar	Positive reactions	%	Titters				
			1:100	1:200	1:400	1:600	1:800
Australis	4	12.1	4	-	-	-	-
Bratislava	4	12.1	4	-	-	-	-
Autumnalis	1	3.0	1	-	-	-	-
Canicola	5	15.2	3	2	-	-	-
Gryppotyphosa	-	-	-	-	-	-	-
Icterohaemorragiae	1	3.0	1	-	-	-	-
Panamá	2	6.1	2	-	-	-	-
Pyrogenes	8	24.2	5	2	-	-	1
Pomona	2	6.1	1	-	1	-	-
Hardjo	-	-	-	-	-	-	-
Wolffi	2	6.1	-	2	-	-	-
Total	29	100	21	6	1	-	1

Table 4 Values (mean and standard deviation) of hematological, biochemical, and urinalysis tests of dogs with chronic kidney disease seropositive and seronegative for *Leptospira interrogans*

Analyte	Reference value	Control ($n=10$)	CKD positive for *L. spp* ($n=13$)	CKD negative to *L. spp* ($n=20$)
Blood count				
Erythrocytes (10^9/L)	5.5–8	$6.68 \pm 0.44^{\dagger}$	$5.3 \pm 1.8^{\dagger}$	$5.7 \pm 1.8^{\dagger}$
Hb (gr/dL)	12–18	$15.22 \pm 1.3^{\dagger}$	$14.4 \pm 2.7^{\dagger}$	$22.4 \pm 43.5^{\dagger}$
Hct (%)	35–57	$46.1 \pm 5.4^{\dagger}$	$42.3 \pm 5^{\dagger}$	$40.7 \pm 10.7^{\dagger}$
Leukocytes (10^9/L)	6–16.9	$8.7 \pm 0.7^{\dagger}$	$16.8 \pm 6.5^{\ddagger}$	$13.3 \pm 5.2^{\dagger\ddagger}$
Platelets (10^9/L)	200–500	$348.7 \pm 50.5^{\dagger}$	$147 \pm 39.2^{\ddagger}$	$186.8 \pm 76.6^{\ddagger}$
Clinical chemistry				
ALT (U/L)	10–109	$33.8 \pm 8.4^{\dagger}$	$40.2 \pm 149.3^{\ddagger}$	$111.2 \pm 89.7^{\ddagger}$
AST (U/L)	23–66	$29.18 \pm 4.1^{\dagger}$	$93.5 \pm 91.5^{\ddagger}$	$100.7 \pm 149.3^{\ddagger}$
Total proteins (gr/dL)	5.4–7.5	$6.6 \pm 0.5^{\ddagger}$	$6.8 \pm 0.9^{\dagger}$	$5.8 \pm 1^{\ddagger}$
Albumin (gr/dL)	2.3–3.1	2.66 ± 0.2	2.5 ± 0.5	2.8 ± 0.6
Globulin (gr/dL)	2.7–4.4	$3.3 \pm 0.3^{\ddagger}$	$4.5 \pm 0.9^{\dagger}$	$3.4 \pm 0.7^{\ddagger}$
Ratio A:G	0.59–1.1	0.84 ± 0.06	0.6 ± 0.2	0.86 ± 0.3
Total bilirrubin (mg/dL)	0.0–0.3	$0.08 \pm 0.07^{\dagger}$	$1.9 \pm 2.7^{\ddagger}$	$1.53 \pm 3.7^{\ddagger}$
Urea (mg/dL)	12.8–55.6	$16.8 \pm 3^{\dagger}$	$105.7 \pm 51.7^{\ddagger}$	$81.1 \pm 27.4^{\ddagger}$
Creatinine (mg/dL)	0.5–1.7	$0.7 \pm 0.12^{\dagger}$	$3.2 \pm 1.8^{\ddagger}$	$2.2 \pm 1^{\ddagger}$
Phosphor (mg/dL)	2.9–5.3	$3.5 \pm 0.4^{\dagger}$	$5.9 \pm 2.6^{\ddagger}$	$4.8 \pm 2.9^{\dagger\ddagger}$
Sodium (mEq/L)	142–152	$146.5 \pm 2.5^{\dagger}$	$147 \pm 4.2^{\dagger}$	$144.6 \pm 10.9^{\dagger}$
Potassium (mEq/L)	3.9–5.1	$4.5 \pm 0.4^{\dagger}$	$5 \pm 0.7^{\dagger}$	$4.4 \pm 0.6^{\dagger}$
Urianalysis				
UD	1.03–1.060	$1.033 \pm 0.002^{\dagger}$	$1.014^{\ddagger}$	$1.018^{\ddagger}$
pH	5–8.5	6.4 ± 0.5	5.9	6.3
Blood (cel/µL)	Negative	Negative†	$10 \pm 23.6^{\dagger\ddagger}$	$25.7 \pm 60.2^{\ddagger}$
Proteins (g/L)	Negative	Negative†	$3.08 \pm 5.7^{\ddagger}$	$3.8 \pm 7^{\ddagger}$

CKD chronic kidney disease, *Hb* hemoglobin, *Hct* hematocrit, *ALT* alanine transaminase, *AST* aspartate transaminase, *UD* urinary density

†,‡ different symbols denote statistically significant differences between groups, $P < 0.05$

as the presence of leukocytosis, thrombocytopenia, and even an increase in liver enzymes ALT and AST in the groups of seropositive patients against Leptospira and hemoparasites, may suggest the presence of other concomitant infectious conditions (Chen et al. 2018; Ross 2011).

The MAT is considered the gold standard method for diagnosing leptospirosis, with a sensitivity of 92.6% and specificity of up to 83.6% (Schlichting et al. 2015). In most cases, the serological results found for Leptospira (titters of 1:100) indicate previous exposure and are not necessarily the primary cause of kidney disease. However, an asymptomatic dog had titters of 1:800 in both paired samples for the same serovar (Pyrogenes). The diagnosis of leptospirosis with a clinical course is confirmed if the MAT titer is > 1:800 in unvaccinated patients or with evidence of an increase of up to 4 times in the titer in paired tests (Brown et al. 2015). Therefore, this case was considered a clinical course of the disease and could even be the original cause of kidney failure. In the other seropositive dogs with CKD and with exposure titers, an additive effect could be associated since during the chronic stage, dogs can develop a picture of asymptomatic leptospirosis, being 3 times more likely to be seroreactive and 3.3 times more likely to be infected (Sant' Anna et al. 2019). Due to the presence of various factors, such as prolonged exposure time, exacerbation of the lesions in the renal parenchyma, and even the development of tubular nephritis and renal fibrosis, this results in an inflammatory process initiated by the reaction to the membrane protein of the leptospiras (Carrillo-Larco et al. 2019).

In leptospirosis, laboratory findings are characterized by an increase in white blood cells due to the initial leukocyte response (Gualtieri et al. 2012), highly regenerative anemia as a response to hemolysis processes, loss due to intestinal or pulmonary bleeding, inhibition of hematopoiesis due to inflammation (Knöpfler et al. 2017), thrombocytopenia secondary to platelet activation and aggregation, and even immune-mediated destruction and disseminated intravascular coagulation (Murphy 2018). Renal azotemia may also be present (Knöpfler et al. 2017; Murphy 2018) because of interstitial nephritis with degeneration and tubular necrosis (Matsui et al. 2016). There may also be an increase in ALT and AST enzymes due to liver dysfunction caused by subcellular lesions induced by leptospiral toxins (Gualtieri et al. 2012), hyperbilirubinemia due to liver damage and cholestasis (Murphy 2018), and even hyperglobulinemia due to the presence of proinflammatory agents (Cagliero et al. 2018). However, the clinical and laboratory manifestations presented in dogs with leptospirosis are associated with the tropism of the different serovars to target organs (Siuce et al. 2015). For instance, the serovar Canicola is known to have a special tropism to the kidney, but leptospiral toxins can generate hepatocellular damage in the chronic form, inducing alterations in liver enzymes, hyperbilirubinemia, and jaundice, as occurs with the Pyrogenes serovar (Rissi and Brow 2014). In urinalysis, hematuria associated with an inflammatory process and an increase in capillary vascular permeability (Lizer et al. 2017; Cagliero et al. 2018) and proteinuria due to an increase in glomerular damage (Carrillo-Larco et al. 2019) can be observed.

Although these alterations can also be induced by other infectious diseases, such as those transmitted by vectors in endemic areas, the additive effect on the development of kidney disease is not completely ruled out (Hall et al. 2017; Chirek et al. 2018). Although the results of the SNAP test only indicate previous exposure, positive cases are not necessarily associated with clinical cases. However, the side effects of hemoparasites must be considered; thus, serological evidence of hemoparasites in acute and chronic kidney patients is a relevant finding. The effects of such agents are highly damaging to kidney function because proinflammatory cytokines are released during the infectious process, which induces vasodilation that, together with the presence of anemia due to erythrocyte destruction, generates systemic hypotension and triggers renal ischemia and hypoxia, decreasing the glomerular filtration rate and consequently the manifestation of azotemia and uremia (Kuleš et al. 2018). Tubular and glomerular lesions predispose to the development of chronic kidney disease or complicate it (Kuleš et al. 2018). Burton found a relative risk of 2.12 for the development of CKD in dogs with positive antibody tests against *E. canis* (Burton et al. 2020). Therefore, their presence and leptospirosis contribute to kidney damage and may have been the condition's origin. The presence of such hemoparasites in the study regions is commonly diagnosed in owned dogs from the city, with prevalences of 8.8% (Jimenez-Coello et al. 2009) to 14% (Ortega-Pacheco et al. 2016) of *E. canis* and prevalences of 2% of *D. imitis*, 12.5% of *Anaplasma pahgocytophilum*, and 26.5% of *A. phagocytophilum* + E. canis (Ortega-Pacheco et al. 2016); this is highly relevant when dealing with concomitant diseases such as CKD, as demonstrated in the present study.

In studies related only to kidney disease, a mortality of 45% has been determined for AKI (Legatti et al. 2018) and 10.8% for CKD (Pelander et al. 2015), while in the study by Knöpfler et al. (2017) on CKD and leptospirosis, a mortality of 32% was found. However, in our study, deaths were due to systemic complications, and we cannot associate leptospirosis as the primary cause since the determined serological titers indicated previous

exposure, but it can be considered an added factor in kidney disease, contributing to the mortality of patients.

The findings here indicate that leptospirosis with *E. canis* and *A. phagocytophilum* may be involved in the development and/or complication of kidney disease, so they should be considered in dogs that present alterations in renal functionality for the implementation of specific therapies. However, further studies are still required to determine the specific role of the various Leptospira serovars within CKD and the potential risk of these patients in transmission to humans or other animals.

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Authors' contributions
All authors took part in the development of the study. MFC, MJ, and AO contributed to the design of the experiment. CAV, MFC, and NRP participated in sampling, leptospiral evaluation, and biochemical traits. EG, CAV, and AO analyzed the data. AO and MJ wrote the paper in collaboration with all of the authors. All authors approved the final manuscript.

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Availability of data and materials
The dataset is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The present study was conducted on patients suffering from chronic kidney disease, so sampling was conducted to diagnose and monitor the patient's health status, which does not require a specific bioethical format. However, the owners signed informed consent following the regulations of the internal bioethics committee following permit CB-CCBA-M-2019-011. Participation in the study was completely optional.

Consent for publication
The authors have permission for publication.

Competing interests
All authors declare that they have no conflicts of interest.

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