Salud, Ciencia y Tecnología. 2023; 3:334
doi: 10.56294/saludcyt2023334

BRIEF ORIGINAL

Acute acalculous cholecystitis as a manifestation of Canine Leptospirosis

Colecistitis alitiásica aguda como manifestación de Leptospirosis Canina

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Cite as: Tintel MJ, Rivas J, Marini R. Colecistitis alitiásica aguda como manifestación de Leptospirosis Canina. Salud Cienc. Tecnol. 2023;3:334. https://doi.org/10.56294/saludcyt2023334

Submitted: 15-02-2023 **Revised:** 27-02-2023 **Accepted:** 18-03-2023 **Published:** 21-03-2023

Editor: Lic. Mabel Cecilia Bonardi

ABSTRACT

Introduction: leptospirosis is considered the most widespread zoonosis in the world. It is typically transmitted through direct contact of the skin and mucous membranes with urine, blood, and other organic fluids contaminated by infected animals.
Aim: to present relevant data on dogs with acalculous cholecystitis as a relevant symptom in leptospirosis.
Methods: this study had a retrospective design. The data was collected from various private veterinary clinics in Asunción, Paraguay during the period from August 2022 to January 2023.
Results: the age range of the dogs analyzed ranged from 1 to 7 years. 4/6 were males, being able to adjudicate the predominance by sniffing habits and territorial behavior, which makes it more predisposing. The leukocyte count ranged from 7,900 to 16,200 cells/µl. Leukocytosis is the increase in the number of cells of the white blood series, indicating that there is an intense activity of the defenses against an infection of bacterial origin. In cases of acute leptospirosis, leukocytosis usually occurs in moderate or severe cases. However, in most of the cases that are oligosymptomatic or pictures similar to viral processes, the leukocytes usually have counts within normal limits; Likewise, it is common to see leukopenia in seriously ill patients or in patients with associated comorbidity.
Conclusions: it is important, in canine patients with non-specific symptoms accompanied by AAC symptoms, to include leptospirosis as a differential diagnosis, to implement adequate antibiotic treatment and avoid unnecessary surgical procedures.

Keywords: Leptospirosis; Canine; Acalculous Cholecystitis; Zoonosis.

RESUMEN

Introducción: la leptospirosis es considerada como la zoonosis más extendida en el mundo. Se transmite habitualmente a través del contacto directo de la piel y mucosas con orina, sangre y otros fluidos orgánicos contaminados de animales infectados.
Objetivo: presentar datos relevantes sobre perros con colecistitis alitiásica como síntoma relevante en la leptospirosis.
Métodos: este estudio tuvo un diseño retrospectivo. Los datos se recopilaron en varias clínicas veterinarias privadas de Asunción, Paraguay, durante el período comprendido entre agosto de 2022 y enero de 2023.
Resultados: el rango de edad de los perros analizados osciló entre 1 y 7 años. 4 de 6 eran machos, pudiéndose atribuir la predominancia a hábitos de olfateo y comportamiento territorial, lo que los hace más propensos. El recuento de leucocitos varió de 7,900 a 16,200 células/µl. La leucocitosis es el aumento en el número de células de la serie blanca sanguínea, indicando que hay una intensa actividad de las defensas contra una infección de origen bacteriano. En casos de leptospirosis aguda, la leucocitosis suele ocurrir en casos moderados o graves. Sin embargo, en la mayoría de los casos oligosintomáticos o cuadros similares a procesos virales, los leucocitos suelen tener recuentos dentro de los límites normales; asimismo, es común ver

leucopenia en pacientes gravemente enfermos o en pacientes con comorbilidad asociada.
Conclusiones: es importante en pacientes caninos con síntomas inespecíficos acompañados de síntomas de CAA, incluir la leptospirosis como diagnóstico diferencial, implementar un tratamiento antibiótico adecuado y evitar procedimientos quirúrgicos innecesarios.

Palabras Clave: Leptospirosis; Canino; Colecistitis Alitiásica; Zoonosis.

INTRODUCTION

Leptospirosis is a bacterial zoonotic disease with a worldwide distribution.[1] The genus Leptospira belongs to the family Leptospiraceae and to the order Spirochaetales, which diversified early in the evolution of bacteria. They have traditionally been classified based on their antigenic determinants into two species, most of the pathogenic leptospires were grouped within the "interrogans complex" (later L. interrogans sensu lato), the others were placed in the "biflexa complex" (after L. biflexa sensu lato) that mainly groups the saprophytes.[2]

The transmission of the disease is influenced by the presence of asymptomatic individuals (rodents, canids, cattle) in regions with humid tropical and subtropical climates. Infection occurs by direct contact of mucous membranes or skin lesions with urine, blood, water, or soil contaminated with Leptospira spp.[3,4]

In the case of canids, the infection develops leptospiremia with subsequent invasion of the renal tissue, excreting leptospires in the urine for several months, contaminating the environment where they live.[5,6]

L. interrogans, a multi-organ invasive microorganism, reaches tissues through the skin, mucous membranes, abrasions or wounds, in contact with objects, soil, stagnant or not standing water, or inhalation of contaminated aerosolized water; quickly reaches the bloodstream, invades any tissue, especially muscle, liver, kidney and to a lesser extent CSF, eye or lung. The muscle and CSF invasion stage is usually asymptomatic; subsequently hepatic invasion.[7]

Environments with high temperatures and humidity allow the survival of leptospires on land and in bodies of water for months,[4,5,6,7,8] facilitating a greater spread of the disease.[9] The course of the disease varies depending on the age and immune response of the host, the serovar involved, and the virulence of the strain, among other factors. The course in canines is estimated to last from 1 to 3 weeks.[10]

Acute leptospirosis is extremely heterogeneous in its presentation and can range from a self-limited nonspecific mild febrile illness to organ dysfunction encompassing hepatitis, myocarditis, acute renal failure, or pulmonary hemorrhage.[11]

The disease can have a courseacute, subacute, chronic, or subclinical. Leptospirosis is usually diagnosed by serological tests, particularly the microagglutination test (MAT) is considered the standard test. Other tests used are: ELISA, indirect immunofluorescence (IFI), tube agglutination, immunohistochemistry and other serological methods.[10]

Therefore, it is important to consider leptospirosis in those presenting with a nonspecific febrile illness, with or without organ dysfunction, and to take an appropriate exposure history. In this study, we will present canines with leptospirosis that presented acute acalculous cholecystitis (AAC) as relevant signology, which with better recognition could present as a useful diagnostic sign of leptospirosis.

Aim: to present relevant data on dogs with acalculous cholecystitis as a relevant symptom in leptospirosis.

METHODS

Place of study

This study had a retrospective design. The data was collected from various private veterinary clinics in Asunción, Paraguay during the period from August 2022 to January 2023.

Collection and processing of samples

Blood samples, with and without anticoagulant, were obtained by aseptic puncture of the saphenous or antibrachial cephalic vein. Blood samples obtained with anticoagulant (EDTA) were used to perform complete blood counts and blood chemistry.

The serological diagnosis of leptospirosis was made using the Microscopic Agglutination Test (MAT), internationally recognized as the technique of choice for determining the kinetics of antibodies in this disease. Each sample was tested for the following L. interrogans serovars: Icterohaemorragiae, Canicola, Pyrogenes, Grippotyphosa, Castellonis, Pomona, and Wolffi.

Abdominal Ultrasound

It was performed in all the patients because of abdominal pain as the predominant symptom.

Variables

Vaccinated dogs or dogs without knowledge of their vaccination status were considered positive if they had titers greater than or equal to 1:400. This cut-off point was used taking into account that vaccine titers do not exceed 1:400 and titers due to Leptospira spp infection can exceed 1:1600.[12]

RESULTS AND DISCUSSION

Table 1. Hematological values of the patients

Case	Race	Age	Sex	Leukocytes	Erythrocytes	GPT	GGT	FAL	Albumin	Creatinine
1	Welsh Terrier	4	Female	8,900	7,320,000	134	fifteen	209	3,2	0,41
2	Beagle	5	Male	8,300	6,890,000	106	14	193	2,1	0,34
3	Pitbull	2	Male	16,200	4,610,000	91	3	116	2,42	0,60
4	french bulldog	3	Female	15,400	4,920,000	124	9	203	3,3	0,76
5	schnauzer	1	Male	9,100	5,150,000	210	4	190	3,1	0,45
6	MR. D	7	Male	7,900	8,900,000	198	8	105	2,8	1,1

SRD: no race defined
Reference values: Leukocytes (5-8) x 6/ mm3 Erythrocytes (5-15) x 3/ mm3 GPT (10-70 U/L) GGT (3-10 U/L) FAL (10-200 U/L) Albumin (2,4- 3,9 g/dL) Creatinine (0,3- 1,6 mg/dL).

Table 2. Patient symptoms and MAT results

Case	Fever	Decay	Diarrhea	Anorexy	Jaundice	Abdominal pain	Myositis	Claudication	Conjunctivitis	MAT
1	X	X	X	-	X	X	X	-	X	Canicola1/400 Pomona1/200
2	X	-	-	-	-	X	-	-	-	Icterohaemorragiae1/400 Pomona1/100
3	X	-	-	X	-	X	X	-	-	Grippotyphosa1/200 Pomona1/400 Canicola1/400
4	X	-	X	-	X	X	X	-	X	Icterohaemorragiae1/400 Canicola1/100
5	X	X	-	X	-	X	-	X	X	Grippotyphosa1/200 Pomona1/800
6	X	X	-	-	-	X	-	-	-	Icterohaemorragiae1/200 Canicola1/400

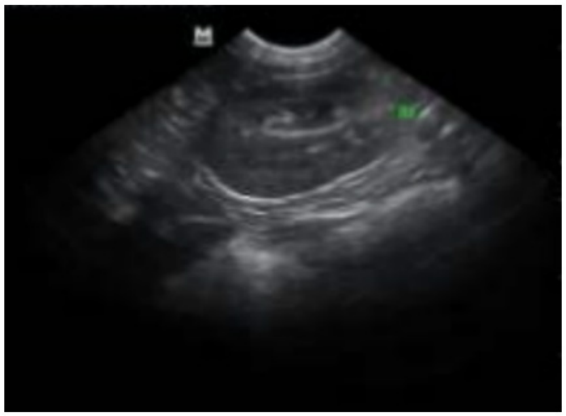

Figure1. Cholecystitis with thickened gallbladder wall without evidence of cholelithiasis

The age range of the dogs analyzed ranged from 1 to 7 years. 4/6 were males, being able to adjudicate the predominance by sniffing habits and territorial behavior, which makes it more predisposing. The leukocyte count ranged from 7,900 to 16,200 cells/µl. Leukocytosis is the increase in the number of cells of the white blood series, indicating that there is an intense activity of the defenses against an infection of bacterial origin. In cases of acute leptospirosis, leukocytosis usually occurs in moderate or severe cases. However, in most of the cases that are oligosymptomatic or pictures similar to viral processes, the leukocytes usually have counts within normal limits; Likewise, it is common to see leukopenia in seriously ill patients or in patients with associated comorbidity. In general terms, what does occur more frequently is a tendency to neutrophilia, regardless of whether the leukocyte count is normal, above, or below normal limits.

The GPT/ALT was reported elevated in all the patients; which is an intracellular cytosolic enzyme, considered specific to the liver. Serum elevation is associated with inflammation or hepatocellular necrosis, as well as alterations in the gallbladder and pancreas.

GGT and alkaline phosphatase values were relatively in range in the patients analyzed. GGT is an enzyme that, in addition to being found in the liver; It is also distributed throughout the body. Likewise, alkaline phosphatase; It is a protein found in all body tissues, with higher amounts in the liver, bile ducts, and bone. For the aforementioned issues; both enzymes are not specific to the liver. To speak of liver failure, it occurs with an affection of 70-80 % of the hepatocytes and is characterized by a high blood concentration of ALT, GGT and alkaline phosphatase.

Related to the symptoms, the predominant common one was fever and abdominal pain. The symptoms reported were non-specific. It should be noted that 90 % of symptomatic patients suffer from the mild and generally anicteric variant of leptospirosis, with or without associated meningitis; 5–10 % of those infected have a severe presentation with profound jaundice.[13]

Typically, leptospirosis presents two phases: acute or leptospiremic and immune or leptospiruric. However, in many cases the two phases are indistinguishable, and in mild cases the second phase is not always present.[14]

Only 2 patients manifested jaundice. It is important to understand that in the disease it is of hepatocellular origin due to injury to hepatocytes and disruption of intracellular junctions between hepatocytes, resulting in loss of bilirubin from the bile canaliculi; intrahepatic obstructive and at the same time sometimes hemolytic, due to the aforementioned action of hemolysins and microangiopathy. This supports the concept that jaundice is not a pathognomonic sign in leptospirosis, although its presence increases suspicion and suggests a high possibility that the condition is caused by Icterohaemorrhagiae.[15]

The six mentioned cases presented seroconversion to more than one leptospirosis serovar. MAT is considered the gold standard, it is important to note that it can cross-react with other serovars. Using the MAT technique, specific antibodies can be detected from the first week after infection, so a negative result before that date is not a reason to rule out the disease and a new evaluation is required a week later. High titers or the presence of agglutination in more than one serovar are indicative of recent disease.[15]

Abdominal ultrasound studies in all cases showed evidently edematous and thickened gallbladder wall, without sludge or stones, which was consistent with acute acalculous cholecystitis. The causes of acalculous cholecystitis are related to bacterial lineage infections (anaerobic and gram negative). However, a relationship has been verified with the use of prolonged parenteral nutrition, as well as extensive burns, abdominal trauma, dehydration and heart disease with this pathology.[16]

Numerous theories have been postulated to explain the pathogenesis of this disease, currently agreeing that it is of multifactorial origin. Despite this, numerous studies emphasize bile stasis as the main trigger factor for acute acalculous cholecystitis, since the thickening of the bile, with an increase in the concentration of bile salts, could obstruct the cystic and the normal components of the bile.

Another proposal has been vascular failure of the gallbladder due to ischemia, which is clinically supported by the association with trauma, sepsis, surgical procedures, causes that can decrease perfusion during periods of hypotension.[17]

Another cause involved has been the presence of tissue necrosis resulting from infections, trauma, or endotoxemia, especially through the activation of inflammatory cascades. Human gallbladder cells stimulated in vitro with lipopolysaccharide secrete eicosanoids and platelet activating factor, when there is a host response to gram-negative bacteremia or ischemia injury, vasoactive mediators play a very important role in the pathogenesis of AAC. In relation to the direct participation of germs, bile cultures are negative in half of the cases, while in others various germs are obtained, particularly disseminated candidiasis or leptospirosis; or during the course of active diarrheal diseases or with tuberculosis, malaria, brucellosis, Q fever and dengue.[18]

CAA secondary to Leptospira infection can appear in isolation,[19,20] or associated with pancreatitis, with elevated serum amylase and lipase along with radiological changes typical of this last.[21]

Villar et al.[22], described the first human report, this is the first report in canines. The pathogenesis of AAC is unknown, although considering leptospirosis as a generalized vasculitis, microvascular involvement could play an important role. Intact bacteria can sometimes be detected in the gallbladder,[19] bile or intra-abdominal

fluid, or by immunohistochemistry for bacterial antigens on the gallbladder wall. Its treatment is controversial, since, although sometimes AC can be resolved only with medical and supportive management, without requiring surgery,[21] human cases of poor evolution have been described after initial stabilization and several days of hospitalization.[19,20,21,22]

In our case, all the patients responded favorably to antibiotic therapy with complete resolution of the associated symptoms without undergoing surgery for cholecystitis.

CONCLUSIONS

It is therefore important, in canine patients with non-specific symptoms accompanied by AAC symptoms, to include leptospirosis as a differential diagnosis, to implement adequate antibiotic treatment and avoid unnecessary surgical procedures.

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FUNDING

No financing.

CONFLICTS OF INTEREST

The authors have no conflicts or competing interests to declare that are relevant to the content of this article.

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