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Scientific Report

First description of reactive arthritis secondary to leptospirosis in a dog

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Abstract

Background: Leptospirosis is a zoonotic bacterial infection that is common worldwide, with a wide spectrum of clinical signs. It commonly infects the kidneys and the liver but can damage a number of organ systems. **Case description:** An 18-month-old boxer dog was referred because of reluctance to walk and sickness. **Findings/treatment and outcome:** His clinical presentation, including swollen and inflamed joints fulfilled the requirements for a diagnosis of immune-mediated polyarthritis (IMPA). Shortly after, unexpected icterus developed and laboratory signs of hepatic and renal failure were observed. A diagnosis of leptospirosis was reached after observing typical clinical signs, along with a positive microagglutination test. Since the diagnostic molecular test for *Leptospira* from joint fluids came back negative and also the localization of *Leptospira* in multiple joints in association with inflammation has never been described in canine patients, an immune-mediated complication seemed most likely. The dog quickly recovered after the administration of ampicillin for 5 days, followed by a two week course of doxycicline. **Conclusion:** In human medicine, this case would be considered as a reactive arthritis (ReA), which is mistakenly cited in the current veterinary literature for cases associated with chronic infections. In humans, ReA is described as inflammatory arthritis not directly caused by culture-proven infection of joint tissue but by infection at another site due to a complex interplay of host antimicrobial factors. This case presentation reports for the very first time, a case of canine leptospirosis mimicking an IMPA and fitting the description of ReA in human medicine.

Key words: Dog, Icterus, Leptospirosis, Polyarthritis, Reactive arthritis

Introduction

Polyarthropathies are characterized by neutrophilic inflammation of multiple joints. Clinical signs include lameness, stiffness, and/or reluctance to walk and some patients display signs of systemic illness. A modern veterinary classification includes infectious causes (direct infection of joints), secondary to distant immunogenic stimulus (infectious or inflammatory or caused by drug therapies, neoplasia or post-vaccinal) and a primary immune-mediated cause (Stone, 2017). In this clinical case, a severe form of polyarthritis preceded a classical form of leptospirosis, with liver and kidney failure.

Case description

An 18-month-old male boxer dog was presented with reluctance to walk for a couple of days, with signs of malaise. Previously the dog had been in perfect health and had received only the first course of vaccination, including bivalent leptospirosis, at 2-3 months of age. During the physical examination the attending clinician found neck pain and stiffness, swollen and painful joints at the distal limbs. The neurological examination was normal. The blood work revealed severe systemic inflammation, as witnessed by the relevant increase of C reactive protein, signs of mild liver involvement and normal kidney function (Table 1). A computed tomography (CT) scan under general anaesthesia was performed in order to evaluate the vertebral column and joints as well as a full body scan to exclude any inflammatory or neoplastic lesions in extra-articular regions. A cerebrospinal fluid (CSF) tap and synovial aspiration from several joints was performed. The CT scan report included signs of intrahepatic bile duct dilatations and diffuse arthropathies (Figs. 1A and B). Cerebrospinal fluid cytology revealed a mild inflammation, mostly neutrophilic and a neutrophilic inflammation was present in the joints exhibiting a severe polyarthritis (Fig. 2). Bacterial culture from CSF and synovia and the molecular biology tests for *Leishmania infantum*, *Ehrlichia canis*, *Borrelia burgdorferi sensu strictu*, *Anaplasma* spp., *Rickettsia conorii*, and *Leptospira* spp. were all negative. Polymerase chain reaction (PCR) for *Leptospira* had been carried out on whole blood and urine and also resulted negative. The clinical condition was rapidly deteriorating and the attending clinician was forced to start an immunosuppressive therapy with prednisolone (Prednicortone, Dechra, Milan, and Italy) 2 mg/kg once a

Table 1: Selected serum biochemistry tests at the day of admission and after 3 days

Test	Day 1	Day 3	Reference ranges	U.M.
Paranaxonase-1	5.21	3.70	2.99-4.84	IU/L
C reactive protein	15.77	8.50	0.01-0.39	mg/dL
Haptoglobin	186	238	1-82	mg/dL
Ferritin	202	228	76-173	ng/ml
Total iron	39	68	88-191	µg/dL
UIBC	292	211	198-282	µg/dL
TIBC	331	279	337-427	µg/dL
Saturation	11.8	24.4	27.2-47.8	%
CK	1091	3254	50-102	IU/L
AST	118	244	19-37	IU/L
ALT	142	228	42-89	IU/L
ALP	497	733	17-77	IU/L
GGT	6.1	25.1	2.1-5.2	IU/L
LDH	42	65	15-45	IU/L
Cholinesterase	3714	3661	3322-5963	IU/L
Total bilirubin	0.62	5.73	0.16-0.29	mg/dL
Fasted biliary acids	49.2	19.3	1-7.9	µmol/L
Total protein	6.4	6.1	6.1-7.1	g/dL
Albumin	2.9	2.7	3-3.4	g/dL
Globulin	3.5	3.4	3-4	g/dL
A/G ratio	0.83	0.79	0.77-1.07	
IgG	387	374	305-775	mg/dL
IgM	136	175	87-167	mg/dL
IgA	10	15	2.32-16.14	mg/dL
Cholesterol	264	264	182-325	mg/dL
Triglycerides	59	66	25-55	mg/dL
Amylase	779	2377	579-1336	IU/L
Lipase	126	679	237-682	IU/L
Lipase (DGGR)	64	656	29 * -143	IU/L
Urea	34	216	22-51	mg/dL
Creatinine	1.14	5.05	0.95-1.3	mg/dL
Glucose	109	106	93-120	mg/dL
Calcium	9.4	8.9	9.9-10.9	mg/dL
Phosphorus	3.7	8.5	3.3-5.5	mg/dL
Ca × P	34.8	75.6	33.7-52.5	mg/dL
Magnesium	0.79	0.97	0.72-0.91	mmol/L
Sodium	145	144	142-149	mEq/L
Potassium	4.3	4.8	4.1-4.8	mEq/L
Na/K ratio	33.7	30.0	30.8-35.7	
Chlorine	114	111	108-116	mEq/L
Lactate	2.7	0.9	1-2.5	mmol/L
HCO_3	23.7	20.4	18.5-25.9	mmol/L
Measured osmolality	298	331	295-309	mOsm/kg

UIBC: Unbound iron binding capacity, TIBC: Total iron binding capacity, CK: Creatine kinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: γ-Glutamyl transferase, LDH: Lactate dehydrogenase, A/G: Albumin-globulin ratio, IgG: Immunoglobulin G, IgM: Immunoglobulin M, IgA: Immunoglobulin A, Lipase DGGR: 1,2-o-dilauryl-rac-glycero glutaric acid-(6'-methylresorufin) ester (DGGR) lipase, Ca × P: Calcium × phosphorus, and Na/K: Sodium-potassium ratio

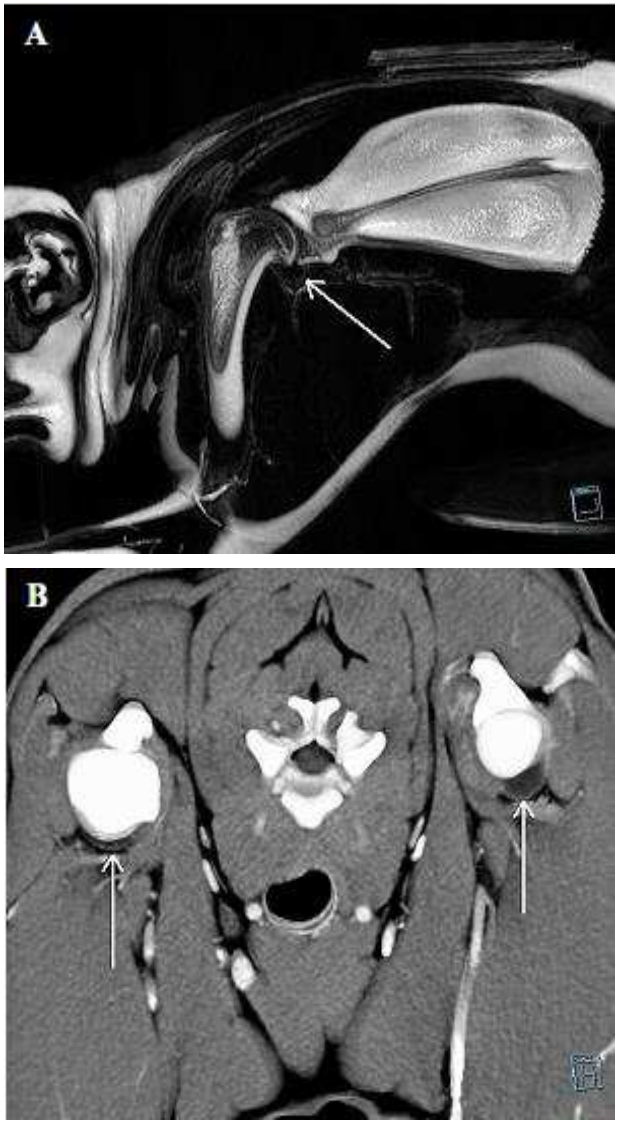

Fig. 1: Volume rendered images, CT-scan Dual Source/Dual Energy SOMATOM Force, Siemens (scanning protocol: before and after contrast medium): Capsular enlargement (arrows) due to an abnormal accumulation of fluid in the articular space of both shoulder joints. (**A**) Sagittal view, and (**B**) transverse view

Table 2: Microagglutination titers at day 3 after the admission and at the day 20 (*Leptospira interrogans*)

Micro-agglutination	Serogroup	Serovar	Antibody titration day 3	Antibody titration day 20
Leptospira kirschneri	*Grippothyphosa*	Grippotyphosa	1:800	1:100
Leptospira interrogans	*Icterohaemorrhagiae*	Copenagheni	1:200	1:200
Leptospira interrogans	*Icterohaemorrhagiae*	Icterohaemerrohagiae	1:200	1:800
Leptospira interrogans	Australis	Bratislava	Negative	Negative
Leptospira interrogans	Canicola	Canicola	Negative	Negative
Leptospira interrogans	Pomona	Pomona	Negative	Negative
Leptospira interrogans	Sejroe	Hardjo	Negative	Negative
Leptospira interrogans	Ballum	Ballum	Negative	Negative

day by mouth. This treatment was also a valid choice of therapy for the diagnosis of immune-mediated polyarthritis (IMPA) (Johnson and Mackin, 2012a). After 48 h of admission, the patient abruptly presented with icteric mucous membranes with signs of hepatic and renal failure (Table 1). A microagglutination test (MAT, carried out accordingly the Office International des Epizooties, Terrestrial Manual, 503-518, 2018) for antibodies against *Leptospira* was submitted and while awaiting the results, ampicillin 20 mg/kg^{-} (Amplital, Pfizer, Latina, Italy) every 8 h intravenously was administered. Corticosteroid therapy was ceased abruptly. The patient responded fairly well to the antimicrobial therapy, with a rapid improvement of neck pain and joint stiffness. Microagglutination test results at day 3 after hospitalization are presented in Table 2. The

seroconversion, executed 17 days after the first test (Table 2), along with the clinical picture, was fully compatible with a diagnosis of leptospirosis (Schuller *et al*., 2015), likely caused by *Leptospira interrogans* serogroup/serovar Icterohaemorrhagiae. After 5 days of therapy with ampicillin the patient was treated with doxycycline 10 mg/kg once a day by mouth (Vibravet, Pfizer, Latina, Italy) for a duration of 2 weeks, as per the current guidelines (Schuller *et al*., 2015). The patient fully recovered thereafter.

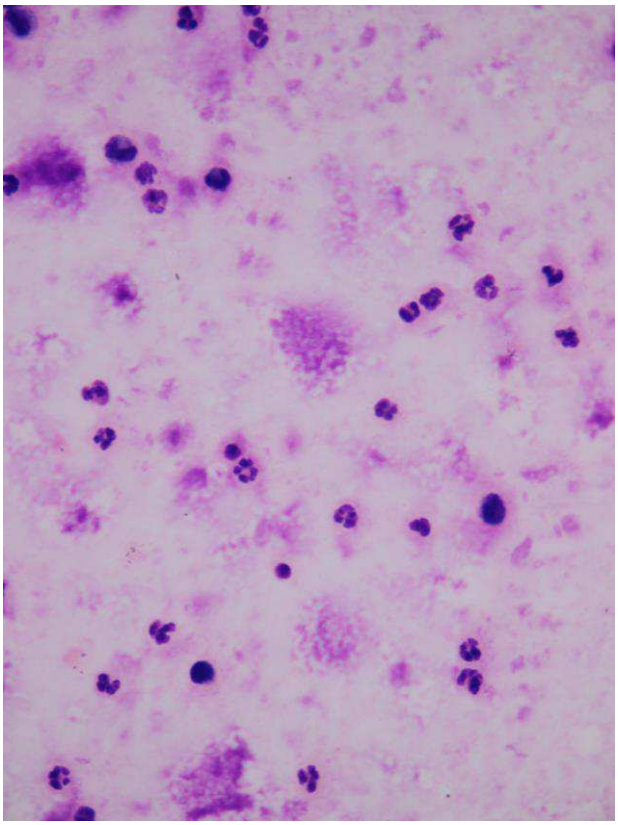

Fig. 2: Synovial fluid from the stifle joint. The cellular count was 6600 cells/ml (normal: <3000). Roughly 90% of cells are mature, nondegenerate neutrophils. Loss of viscosity is witnessed by the chaotic distribution of cells

Discussion

The diagnosis of polyarthritis is relatively straightforward, as it is confirmed by a positive cytology for neutrophilic inflammation of synovial fluids from 2 or more joints. The clinician's next step, after having obtained the diagnosis, is to distinguish between different causes and its pathogenesis as the therapy and prognosis is totally different depending on those two factors. An updated etiological list would include joint infections or secondary to distant immunogenic stimulus ("reactive forms") or primary immune-mediated causes, erosive or non-erosive (Stone, 2017). Older, yet still popular classifications of IMPA, would include the reactive forms according to the classic classification scheme:

Type I: No underlying disease
Type II: Reactive
Type III: Enteropathic
Type IV: Neoplasia-related

Types II-IV are often grouped together and are referred to as reactive polyarthritis (Johnson and Mackin, 2012b). Clearly, it becomes difficult in veterinary medicine to obtain a clear-cut definition of reactive arthritis (ReA), while in human medicine it is a well described condition - an inflammatory arthritis not directly caused by culture-proven infection of joint tissue, but rather after an infection at another site (Schmitt, 2017). Even the pathogenesis is remarkably different because in veterinary medicine, type II polyarthritis is associated with infectious or inflammatory diseases distant from the joints that, in chronic conditions, can produce antigens that combine with antibodies to form immune complexes that accumulate in the joints, activating complement and leading to inflammation (Johnson and Mackin, 2012b). In humans the pathogenesis of ReA is associated in some cases to the positivity to Human leukocyte antigen (HLA) B27, a class I surface antigen encoded by the B locus in the major histocompatibility complex, that can activate an abnormal immune response. Human leukocyte antigen B27 non-associated mechanism is already described including cases of ReA complicated by infections such as Borrelia, Brucella, *Leptospira* and many others (Ferreira *et al*., 2015). In the present case, three different joints tested negative with microbial culture and PCR testing for several infectious agents was also negative. As a consequence, articular infections as a diagnosis was unlikely and that of IMPA was more than acceptable. The sudden onset of typical clinical and laboratory signs of leptospirosis such as icterus, systemic inflammation, hepatic and renal failure, which was later confirmed by serological tests (Schuller *et al*., 2015; Murphy, 2018), obviously ruled out a primary immune-mediated disease. It becomes challenging to associate the veterinary definition of ReA (secondary to a chronic antigenic stimulation driven by a type III hypersensitivity reaction) in such an acute and typical presentation of leptospirosis. The concept of ReA as defined in human medicine is much more adherent to our case, associating acute genitourinary infections, among others, and arthritis in a complex interplay of host antimicrobial factors and not merely after long standing deposition of immune-complexes. It is remarkable that leptospirosis in humans has been specifically associated to ReA (Pappas *et al*., 2003), while, to our knowledge, polyarthritis has never been described in the dog concurrent to acute leptospirosis. The spinal pain elicited in this case may have originated from the meninges or meningeal vasculature, the intervertebral facetal joints or both (Webb *et al*., 2002). The mild inflammation observed in the CSF would suggest a meningeal involvement, supposedly aseptic, accordingly to the negative molecular biology test. Aseptic meningitis has been described in up to 25% of humans affected by leptospirosis, but confirmed reports of meningitis/meningoencephalitis in association with

leptospiral infections in the dog are lacking (Schuller *et al*., 2015).

This case proposes to consider leptospiral infections in any case of IMPA, even in the absence of the typical clinical and laboratory signs. It is strongly suggested to align the classification of polyarthritis in dogs to that applied in human medicine in order to correctly include cases of ReA such as the present one.

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Conflict of interest

The authors declare that there was not any conflict of interest.

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