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CASE REPORT

Companion or pet animals

Mitral endocarditis secondary to *Listeria monocytogenes* in a dog

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Abstract

A Beauceron was evaluated for a 3-week history of unresponsive immune-mediated polyarthritis and meningitis. Physical examination revealed a previously unreported grade III/VI left apical systolic heart murmur. Based on the echocardiographic examination and blood culture, a diagnosis of mitral valve infective endocarditis secondary to *Listeria monocytogenes* was made. Despite extensive workup, no definitive primary focus of infection was identified in this case. The endocarditis was suspected to have triggered secondary immune-mediated polyarthritis and meningitis. The dog was treated with empirical antimicrobial combination therapy and immunosuppressives, and fully recovered from infection. No relapse was documented 5 months after discontinuation of treatment. Cardiomegaly secondary to persistent mitral regurgitation had developed. This is the first description of endocarditis secondary to *L. monocytogenes* in a dog.

BACKGROUND

This case represents the first report of *Listeria monocytogenes*-associated endocarditis in a dog. *Listeria*-associated infective endocarditis is known to carry a worse prognosis than endocarditis due to other pathogens in human medicine, yet the case reported here displayed a favourable outcome. The authors feel this case is a good opportunity to increase knowledge about the pathogenicity of *L. monocytogenes* in dogs.

CASE PRESENTATION

A 6-year-old, castrated, 44 kg Beauceron was referred to the veterinary clinic of Liège University for a month-long history of fever, weakness and lethargy. Three weeks prior to referral, neutrophilic polyarthritis and mixed neutrophilic and macrophagic meningitis had been diagnosed based on joint and cerebrospinal fluid analysis, respectively. Indirect immunofluorescent assays for infectious agent antibodies (*Ehrlichia* spp., *Borrelia* spp. and *Toxoplasma gondii*) were negative and a presumptive diagnosis of idiopathic immune-mediated polyarthritis and meningitis was made. The dog was referred for persisting clinical signs despite immunosuppressive prednisolone (2 mg/kg, PO, every 12 hours) treatment. The day prior to referral, bloodwork revealed moderate hyporegenerative anaemia (haematocrit 27.3 L/L; reference range, 37 to 55 L/L, reticulocyte count 29 $\times$ 10^3 cells/μL; reference range, 10 $\times$ 10^3 to 110 $\times$ 10^3 cells/μL) and severe thrombocytopenia (34 $\times$ 10^3 cells/μL; reference range, 175 $\times$ 10^3 to 500 $\times$ 10^3 cells/μL) with mild neutrophilia (15 $\times$ 10^3 white blood cells [WBC]s/μL; reference range, 2 $\times$ 10^3 to 12 $\times$ 10^3 WBCs/μL) without left shift. Biochemistry and electrolytes measurements revealed increased alkaline phosphatase (1308 U/L; range 23–212 U/L) and alanine transaminase (552 U/L; range 10–125 U/L) concentrations, considered to be secondary to prednisolone administration. The dog was current with vaccination and worming and had no travel history. Upon admission, the dog was obtunded with a rectal temperature of 38.9°C, a heart rate of 128 beats per minute and a respiratory rate of 40 movements per minute. Auscultation revealed a previously unreported grade III/VI left apical systolic heart murmur and an unremarkable lung auscultation. Mucous membranes were pale pink with a capillary refill time of 2 seconds and synchronous adequate femoral pulses. The dog had painful and distended carpal, stifle and tarsal joints compatible with the reported polyarthritis. Cervical manipulation appeared painless, but a pain response was elicited upon palpation of the lumbar area.

INVESTIGATIONS

Three-view thoracic radiographs revealed a moderate bronchial pattern and a normal cardiac silhouette. The bronchial pattern was considered an incidental finding given the lack of respiratory signs. Abdominal ultrasound was performed and did not reveal an underlying cause for the meningitis and polyarthritis. Urinalysis revealed a specific gravity of 1.036 with mild proteinuria on urine dipstick and a negative urine sediment and culture. C-reactive protein was mildly elevated at 30.8 mg/L (reference range, <9 mg/L), compatible with moderate inflammation.

To investigate the heart murmur, full-Doppler echocardiography was performed and showed vegetative lesions on both leaflets of the mitral valve with severe excentric mitral

regurgitation, compatible with mitral endocarditis (Figure 1). Hemodynamic repercussions on the left heart were absent as left atrium and ventricle size and systolic function were normal (left atrial dimension to aortic annulus dimension ratio 1.1; reference range, < 1.5; normalized left ventricular internal dimension at end-diastole 1.45; reference range, < 1.7[1]; fraction shortening 34%; reference range, 25 to 35%). No other abnormalities were noted. In search for a potential primary infectious focus, lumbar radiographs were performed to screen for signs of discospondylitis, compatible with the lumbar pain response. Lumbar radiographs only displayed signs compatible with degenerative lumbo-sacral stenosis.

TREATMENTS

The dog was hospitalized on empirical combination therapy with amoxicillin-clavulanate (20 mg/kg, IV, every 8 hours) and enrofloxacin (5 mg/kg, IV, every 24 hours). This combination was chosen based on current treatment recommendations pending results of blood polymerase chain reaction for *Bartonella henselae* and hemoculture.[2] Mycophenolate mofetil was added (10 mg/kg, PO, every 12 hours) while prednisolone was tapered (0.5 mg/kg, IV, every 12 hours). A second immunosuppressive was added to avoid potential side-effects and complications of prednisolone therapy and due to severe joint pain when prednisolone was tapered, despite opioids analgesics (methadone, 0.2 mg/kg, IV, every 4 hours). Gabapentin (10 mg/kg, PO, every 8 hours) was also prescribed for pain management. After initial improvement, the dog experienced a syncope 4 days after diagnosis. Monomorphic premature ventricular complexes, both isolated, in couplets or in run of idioventricular accelerated rhythm, with right bundle branch block morphology were identified on electrocardiogram. On echocardiography, aortic insufficiency with a mildly thickened aortic leaflet was diagnosed, suggestive of aortic valve endocarditis. Based on these results, enrofloxacin was switched for amikacin (15 mg/kg, IV, every 24 hours) as it is the antibiotic of choice to use if resistance to enrofloxacin is suspected.[2] Monitoring of renal toxicity of amikacin by serial urine sediment analysis revealed no cylindruria, and renal values did not rise during treatment.

Blood polymerase chain reaction for *B. henselae* came back negative but *L. monocytogenes* was diagnosed on haemoculture. No antibiogram was available from the reference laboratory.

OUTCOME AND FOLLOW-UP

Clinical and full-Doppler echocardiographic re-examinations demonstrated gradual reduction of valvular vegetations despite persistent mitral regurgitation and no relapse of polyarthritis and meningitis despite tapering of immunosuppressives. Examinations were performed every other day, the first week after diagnosis and then once a week for the following 5 weeks. After 2 weeks of treatment, amoxicillin-clavulanate was switched from intravenous to oral administration (15 mg/kg, PO, every 12 hours) while amikacin was maintained intravenously for 6 weeks. Arrhythmias were never re-observed during follow-up. Eight weeks after diagnosis, the dog still received oral amoxicillin-clavulanate (15 mg/kg, PO, every 12 hours), prednisolone (0.25 mg/kg, PO, every 24 hours) and mycophenolate mofetil (10 mg/kg, PO, every 12 hours). Echocardiography showed near-complete regression of mitral vegetative lesions, although leaflets remained thickened and hyperechoic with persistent mitral regurgitation. Aortic insufficiency was absent and aortic valves had normal morphology. Left-heart size and systolic function were within normal limits (left atrial dimension to aortic annulus dimension ratio 1.2; reference range, < 1.5; normalized left ventricular internal dimension at end-diastole 1.5; reference range, < 1.7; fraction shortening 35%; reference range, 25 to 35%). The amoxicillin-clavulanate was continued at the same dosage for 3 months and then stopped, while prednisolone and mycophenolate mofetil were tapered and stopped over the same period. Five months after discontinuation of treatments and 9 months after diagnosis, the dog remains clinically well. Echocardiography shows persistent remodelling and thickening of mitral leaflets (Figure 2) with severe excentric mitral regurgitation. Left-heart remodelling is present with mild left atrial (left atrial dimension to aortic annulus dimension ratio 1.7) and left ventricular dilation (normalized left ventricular internal dimension at end-diastole 1.75). Systolic function is within normal limits (fraction shortening 34%, reference range, 25 to 35%). Because the dog developed cardiomegaly, pimobendan 0.25 mg/kg twice daily was prescribed and a re-check is planned in 6 months. At the time of writing, the dog is free of clinical signs.

LEARNING POINTS/TAKE HOME MESSAGES

- *Listeria monocytogenes* is a potential causative agent of infective endocarditis in dogs.
- Although this disease carries a grave prognosis in human medicine, the case reported here displays a favourable outcome.
- Immune-mediated reactive disease is well-described in dogs with infective endocarditis and the auscultation of a newly diagnosed heart murmur should prompt further investigations in a dog with presumed primary immune-mediated polyarthritis or meningitis.

DISCUSSION

Listeria monocytogenes is a facultative intracellular Gram-positive bacterium that is present in food and soils, and in the gastrointestinal tract of ruminants.[3] It is a rare cause of endocarditis in human patients, representing approximately 8% of all listeriosis cases in humans.[3,4] In veterinary medicine, to the authors' knowledge, *L. monocytogenes*-associated endocarditis has only been reported in one alpaca.[5]

In humans, the majority (72%) of reported cases of *L. monocytogenes* endocarditis are associated with prosthetic intracardiac devices, compared with only 28% of endocarditis involving other bacterias.[4,6] Affected human patients are

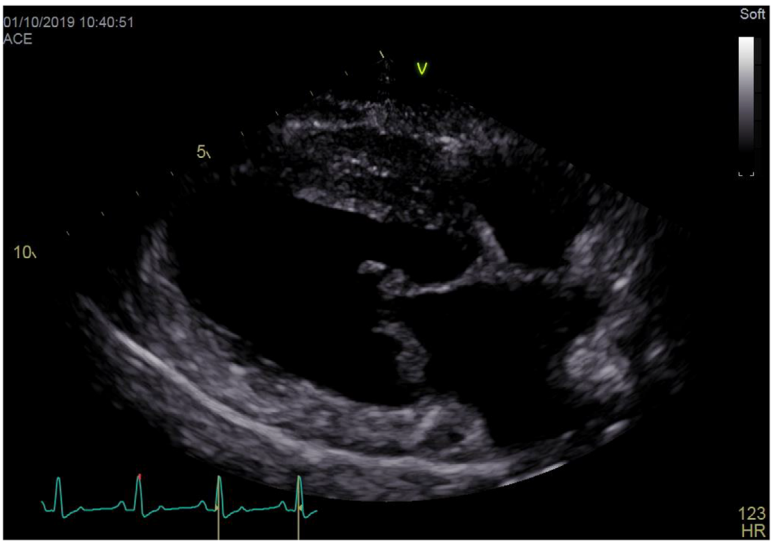

FIGURE 1 Right parasternal long-axis four chambers view at diagnosis, showing vegetative lesions on both leaflets of the mitral valve

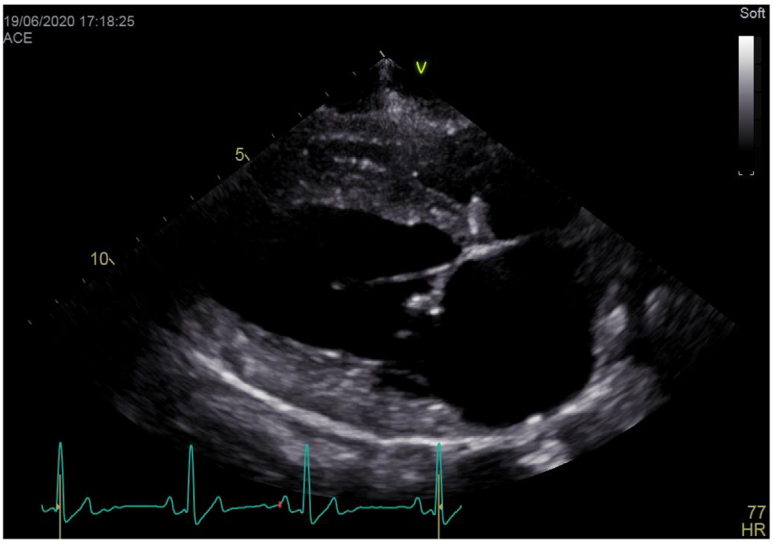

FIGURE 2 Right parasternal long-axis four chambers view 9 months after diagnosis, showing improvement of mitral valve lesions

also older and exhibit a higher rate of immunosuppressive comorbidities.[4,6] Our patient might have had reactive immune-mediated polyarthritis and meningitis secondary to endocarditis, as is described.[7,8] Alternatively, the *L. monocytogenes* endocarditis might be a complication of immunosuppressive prednisolone therapy, as reported in humans.[4,6] In our case, cultures were not performed due to the low clinical suspicion, as septic polyarthritis and meningitis are rare in dogs. Infectious agents were not seen on cytology of joint and cerebrospinal fluid, although cytology is an insensitive method for the detection of infectious agents. Moreover, extensive screening for infectious diseases was not performed due to low prevalence in Belgium, lack of travel history and full vaccination status. For these reasons, it seems more likely that endocarditis was the initial trigger for secondary immune-mediated disease in our case. Because immune-mediated conditions were considered complications of the infective endocarditis, prednisolone was rapidly tapered after the institution of antibiotic therapy. The persisting joint pain warranted the addition of mycophenolate mofetil and opioid analgesics in an effort to limit potential side effects and complications of extensive prednisolone therapy. The lack of improvement can be explained by initial inadequate antibiotics choice for *L. monocytogenes* infection, further illustrated by progressive disease despite initial antibiotic therapy in our case.[4,9] Indeed, the dog started to improve when enrofloxacin was switched for amikacin, which is recommended as a first-line therapy for listeriosis in veterinary patients.[9]

In order for endocarditis to develop, bacteraemia must occur. It can be induced by physical manipulation or traumatization of bacteria-laden mucosal surfaces or disseminating from a primary infectious focus.[10] In our case, despite extensive workup, a primary focus of infection was not identified. Urine culture was negative. Although this does not completely rule out bacterial cystitis, occult urinary tract infection was considered unlikely to be the cause for bacteraemia, because culture would have been expected to be positive, especially in the context of chronic immunosuppression. Moreover, *L. monocytogenes* is not a common cause of bacterial cystitis in dogs.[11] In humans, *L. monocytogenes* is typically a food-borne pathogen, although it is also present in the gastrointestinal tract of healthy ruminants.[5,12] Contamination could have happened through ingestion of contaminated food or ruminants' faeces, but this was not reported by the owner.

Arrhythmias and conduction deficits, in particular, ventricular arrhythmias are commonly diagnosed in dogs with

endocarditis, as observed in our case.[7] The cause of the intermittent ventricular arrhythmia is uncertain as the myocardial injury is poorly correlated with the development of arrhythmias in dogs with infective endocarditis.[7] A plausible trigger for ventricular arrhythmias in our case could be myocardial injury secondary to spreading infection, or a thromboembolic coronary event with subsequent myocardial hypoxia. Thromboembolic complications are common in dogs and humans with infective endocarditis and appear to occur more commonly with mitral valve involvement.[7,13] Similarly, a thromboembolic event could have precipitated the occurrence of a syncope, although other causes, such as ventricular tachycardia or reflex syncope, cannot be excluded. Ideally, a 24-hour ambulatory electrocardiogram should have been placed to determine the origin of syncope but was not performed as a single isolated episode was observed.

In humans, *L. monocytogenes*-associated endocarditis carries a grave prognosis, with mortality rates twice as high as for endocarditis secondary to other pathogens.[4] This may be due to the high incidence of underlying cardiac disease, prosthetic intracardiac devices and non-cardiac comorbidities in these patients.[4] Aortic valve involvement and corticosteroids have been shown to negatively affect prognosis in dogs.[8,10] Moreover, by suppressing lymphocyte activity, mycophenolate mofetil affects cell-mediated immunity which is known to be an important factor to prevent the development of clinical listeriosis.[9] This choice was made before knowing the disease was caused by *L. monocytogenes*, and while this could have negatively affected prognosis in our patient, it was decided to carry on with the same therapy despite haemoculture results because the dog was doing clinically well and cardiac lesions were resolving. Our patient had a favourable outcome, despite aortic involvement and immunosuppressive therapy, but had no pre-existing cardiac disease, which might have contributed to his favourable recovery. That said, the secondary persisting mitral regurgitation will likely result in slow cardiac disease progression.

This case report indicates *L. monocytogenes* is a potential cause of infective endocarditis in dogs.

CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

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