Bartonella henselae Associated Myocarditis in Cats, First Report in Israel

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ABSTRACT

Bartonella spp. are small gram-negative intracellular bacteria infecting mammals worldwide. The most common *Bartonella* species identified in cats include *Bartonella hensellae, Bartonella clarridgeiae* and *Bartonella koehlerae*, all three exist in Israel. The present report represents the first *Bartonella Henselae*-associated myocarditis in cats from Israel. *Bartonella* spp. causing endocarditis and myocarditis have been reported in dogs and human patients in Israel and worldwide. As *B. henselae* is zoonotic with a variety of clinical manifestations, the awareness to bartonellosis should be increased among health workers.

Key words: *Bartonella henselae*; Myocarditis; Feline; Cat; Zoonosis.

INTRODUCTION

Bartonella spp. are small gram-negative intracellular bacteria infecting mammals worldwide. Their primary targets are the vascular epithelium and erythrocytes. The organisms may be transmitted by a variety of vectors including fleas, lice, and sand-flies (1).

Several species of *Bartonella* have been identified in cats including *Bartonella henselae, Bartonella clarridgeiae, Bartonella koehlerae, Bartonella quintana, Bartonella bovis and Bartonella vinsonii* subsp. *Berkhoffii* (2). The first 3 species are the commonly detected species in cats, and *B. henselae* is the primary zoonotic bacteria associated with cats. It is the agent of cat scratch disease (CSD) in humans (3). Most cats naturally infected with *B. henselae* do not present clinical signs (4), however, endocarditis, pyogranulomatous myocarditis and diaphragmatic myositis may occur is rare cases (5, 6). Although anemia, gingivostomatitis, uveitis, neurologic and other conditions have been associated with feline bartonellosis, most case-controlled studies have not proven such an association (7, 8).

In Israel, the occurrence of feline bartonellosis was studied on blood samples collected from 179 stray and 155 domestic cats. Samples were screened for *Bartonella* infection by culture isolation and molecular detection using high-resolution melt (HRM) real-time PCR assay targeting the 16S-23S rRNA internal transcribed spacer (ITS) (9). The prevalence of *Bartonella* spp. infection in the general tested population was 25.1% (84/334). All 3 common feline species (*B. henselae*, *B. clarridgeiae* and *B. koehlerae*) were detected in Israel as well as coinfections with more than one species. A higher prevalence was detected in the stray cats

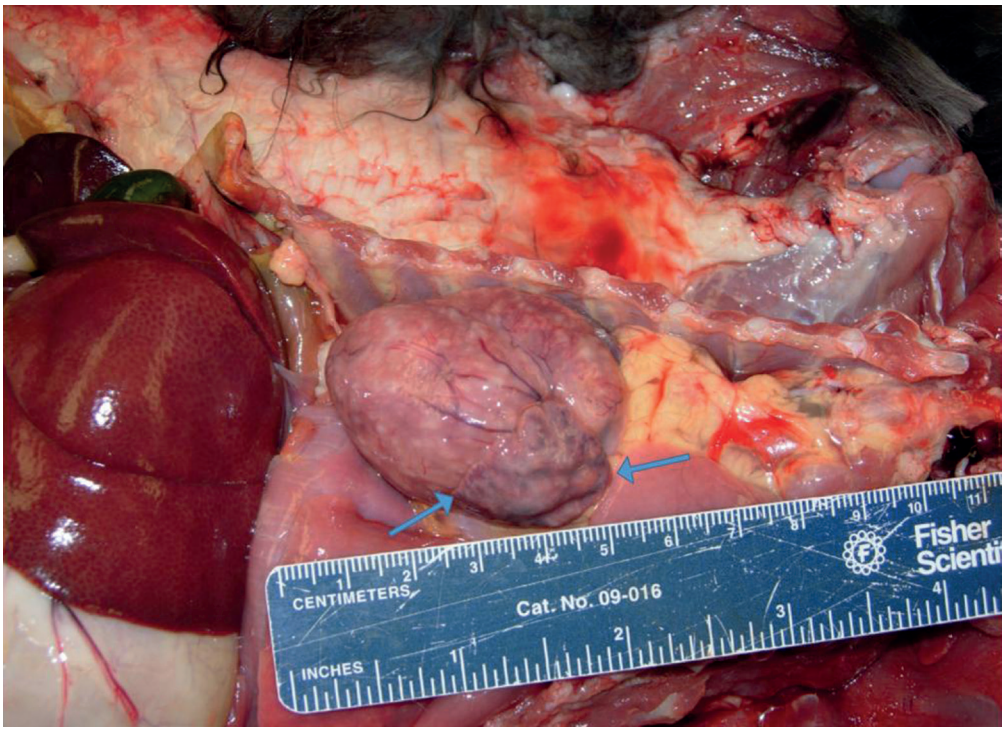

Figure 1: A markedly hypertrophic heart with dilated left atrium (between arrows) mottled with numerous slightly elevated white-creamy nodules (Queen cat #1).

(30.7%; 55/179) than the domestic cats (18.7%; 29/155) (3). Furthermore, another study showed evidence that *B. henselae* was the principal *Bartonella* species responsible for seroreactivity against *B. henselae* and *B. quintana* in naturally exposed cats from Israel (10).

This present publication represents the first reports of clinical *B. henselae* infection with myocarditis in cats from Israel.

CLINICAL HISTORY

Two cats were submitted for necropsy following vague clinical signs and unclear diagnosis. Cat #1 was an allegedly young and healthy queen, submitted for an elective spay in a shelter clinic. It died shortly after completing an uncomplicated surgical procedure. Cat #2 was a tomcat referred by a veterinary clinic to a veterinary teaching hospital of the Hebrew University following signs of malaise and died shortly after admission.

PATHOLOGICAL FINDINGS

On post mortem examination, both cats were moderately infested with fleas. The queen (#1) was in a poor body condition. The tomcat (#2) was in a good body condition. Both cats had moderately enlarged hearts with markedly dilated left atria (Figure 1: arrows). The myocardium, of both left and right ventricles and to a lesser extent the atria, contained numerous multifocal spherical, 1-3 mm discrete, uniform, slightly firm, white-creamy elevated nodules (Figures 1 and 2).

LABORATORY EXAMINATIONS

Histologic examination of the heart revealed marked multifocal pancardiac inflammatory infiltrate composed of large numbers of lymphocytes and histiocytes and rare neutrophils. There was myocardial necrosis and degeneration within the inflammatory foci.

No bacteria or fungal organisms were detected on routine special stains (including PAS, Giemza, Gram and ZN). Immunohistochemistry for corona virus, toxoplasma and neospora were negative. Bacterial and mycotic cultures were negative. Serology for *Leptospira* was negative.

Fresh samples of both hearts were submitted for PCR testing for *Bartonella* at the laboratory of Prof. Shimon Harrus at the Koret School of Veterinary Medicine of the

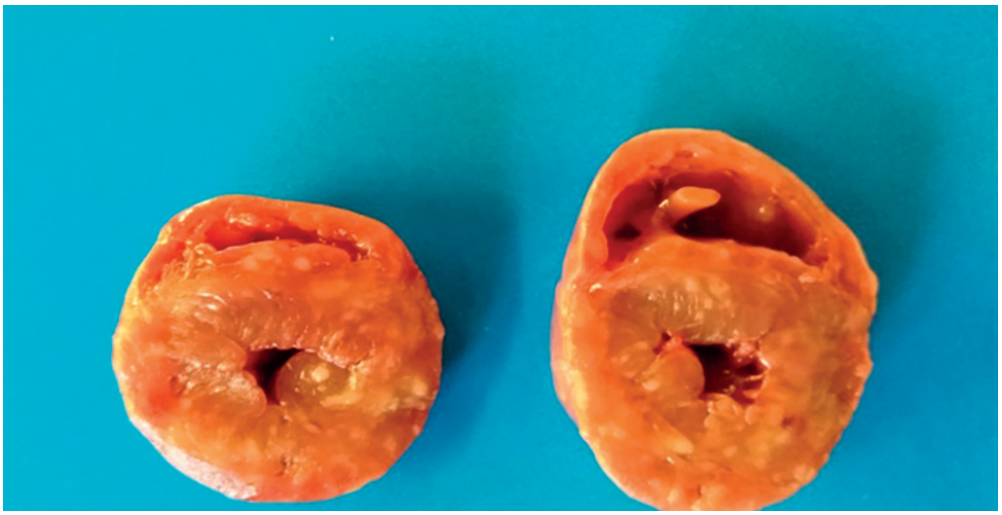

Figure 2: Cross section of the heart of the tomcat (case #2) exhibiting a moderately hypertrophic left myocardium mottled with multiple 1-3 mm white creamy nodules

Hebrew University. DNA was extracted from the left and right chambers, oracles, outside and inside walls of the heart biopsies, using Illustra Tissue & Cells GenomicPrep Mini Spin kit (GE Healthcare, Buckinghamshire, GBR). Samples were tested for the presence of *Bartonella* spp. DNA by real-time polymerase chain reaction (PCR) targeting a 190-bp fragment of the internal transcribed spacer (ITS), as described elsewhere (11). Additionally, a confirmatory conventional PCR was performed targeting a 790-bp long fragment of the citrate synthase gene (*gltA*), following protocols described earlier (12). All positive PCR amplicons were purified with a PCR purification kit (Exo-SAP; New England BioLabs, Inc., Ipswich, MA) and sequenced by the BigDye Terminator cycle sequencing chemistry with the Applied Biosystems ABI 3700 DNA Analyzer and the ABI Data Collection and Sequence Analysis software (ABI, Carlsbad, CA).

PCR sequences were positive for *Bartonella henselae*-DNA from both cat samples. Sequencing results showed 100% identity to GenBank deposited *B. henselae* reference genome (accession number BX897699.1).

DISCUSSION

This study provides molecular evidence for the first clinical cases of *B. henselae*-associated myocarditis in cats from Israel. The two cats presented in this report did not show any prior definitive clinical signs. This differs from the single previous report of 2 cats with pyogranulomatous myocarditis from a North Carolina shelter which died after showing signs of fever, lethargy and watery diarrhea (5).

In natural *Bartonella* infection, clinical signs are rare (1, 3). However, few cats naturally infected with *Bartonella* have exhibited clinical signs. Fever and valvular endocarditis have been reported in few cats naturally infected with *B. henselae* (3).

From a public health point of view, cats are considered carriers of *B. henselae* without exhibiting clinical signs, in most cases (2). They serve as reservoirs and vectors for this bacterium which is believed to be transmitted to humans mainly through contamination of cat scratches with infected flea excrement (2).

Discrepancies in the pathological findings of cats infected with *B. henselae* have been reported. These differences may be related to the virulence of the bacteria and/or the strain and the duration of the infection (6). Experimentally, differences in pathogenicity among *B. henselae* strains have been reported, possibly indicating the presence of virulence factors which affect the disease expression (6). In a study in which healthy cats were experimentally inoculated with *B. henselae*, subsequently euthanized and necropsied 3 to 4 weeks after resolution of fever, no gross pathological lesions were found. However, one cat had multifocal aggregates of lymphocytes in the myocardium, and both cats had evidence of chronic lymphoid stimulation (13).

Bartonella spp. causing endocarditis and myocarditis have been reported in dogs (14, 15, 16) and human patients (17).

Bartonella species are emerging causes of culture-negative endocarditis with more cases currently being diagnosed compared to 2 decades ago when *Bartonella quintana* endocarditis was first described in a patient infected with human immunodeficiency virus (HIV) (17). Despite the disease being increasingly reported, the exact epidemiological features are not clear, with prevalence rates ranging between 2% and 10% of all cases of culture-negative endocarditis (17).

In conclusion, this is the first documented *B. henselae* myocarditis in cats from Israel. As *B. henselae* is zoonotic and endemic in Israel, the awareness to *B. hensellae* associated clinical manifestations (i.e. CSD, peliosis hepatis, meningitis, encephalitis, neuroretinitis, endocarditis and osteomyelitis) should be increased among physicians and other health workers in Israel.

REFERENCES

1. Kennedy, M., Little, S.E. and Baral, R.M.: Bacterial infections. Bartonellosis. In: The Cat. Clinical Medicine and Management. Editor: Little, S.E. pp. 1070-1073, 2012.
2. Chomel, B.B., Kasten, R.W., Stuckey, M.J., Breitschwerdt, E.B., Maggi, R.G., Henn, J.B., Koehler, J.E. and Chang, C.C.: Experimental infection of cats with Afipia felis and various Bartonella species or subspecies. Vet. Microbiol. 27;172:505-10, 2014.
3. Guptill-Yoran, L.: Mycoplasma and Bacterial Diseases: Feline Bartonellosis. In: Infectious Diseases of the Dog and Cat. Editor: Greene, C.E. 4th Editon. pp. 543-562.
4. Guptill, L., Wu, C.C., HogenEsch, H., Slater, L.N., Glickman, N., Dunham, A., Syme, H. and Glickman, L.: Prevalence, risk factors, and genetic diversity of *Bartonella henselae* infections in pet cats in four regions of the United States. J. Clin. Microbiol. 42, 652-659, 2004.
5. Varanat, M., Broadhurst, J., Linder, K.E., Maggi, R.G. and Breitschwerdt, E.B.: Identification of *Bartonella henselae* in 2 cats with pyogranulomatous myocarditis and diaphragmatic myositis. Vet. Pathol. 49:608-611, 2012.
6. Pennisi, M.G., Marsilio, F., Hartmann, K., Lloret, A., Addie, D., Belák, S., Boucraut-Baralon, C., Egberink, H., Frymus, T., Gruffydd-Jones, T., Hosie, M.J., Lutz, H., Möstl, K., Radford, A.D., Thiry, E., Truyen, U. and Horzinek, M.C.: *Bartonella* species infection in cats: ABCD guidelines on prevention and management. J. Feline Med. Surg. 15:563-569, 2013.
7. Quimby, J.M., Elston, T., Hawley, J., Brewer, M., Miller, A. and Lappin, M.R.: Evaluation of the association of *Bartonella* species, feline herpesvirus 1, feline calicivirus, feline leukemia virus and feline immunodeficiency virus with chronic feline gingivostomatitis. J. Feline Med. Surg. 10:66-72, 2008.
8. Dowers, K.L., Hawley, J.R., Brewer, M.M., Morris, A.K., Radecki, S.V. and Lappin, M.R.: Association of *Bartonella* species, feline calicivirus, and feline herpesvirus 1 infection with gingivostomatitis in cats. J. Feline Med. Surg. 12:314-321, 2010.
9. Gutiérrez, R., Morick, D., Gross, I., Winkler, R., Abdeen, Z. and Harrus, S.: Bartonellae in domestic and stray cats from Israel: Comparison of bacterial culture and high-resolution melt real-time PCR as diagnostic methods. Vector Borne Zoonotic Dis. 13: 857-864, 2013.
10. Baneth, G., Kordick, D.L., Hegarty, B.C. and Breitschwerdt, E.B.: Comparative seroreactivity to *Bartonella henselae* and *Bartonella Quintana* among cats from Israel and North Carolina. Vet. Microbiol. 50: 95-103, 1996.
11. Gutiérrez, R., Nachum-Biala, Y. and Harrus, S.: Relationship between the Presence of *Bartonella* Species and Bacterial Loads in Cats and Cat Fleas (*Ctenocephalides felis*) under Natural Conditions. Appl. Environ. Microbiol. 81:5613-5621, 2015.
12. Gutiérrez, R., Cohen, C., Flatau, R., Marcos-Hadad, E., Garrido, M., Halle, S., Nachum-Biala, Y., Covo, S., Hawlena, H. and Harrus, S.: Untangling the knots: Co-infection and diversity of Bartonella from wild gerbils and their associated fleas. Mol. Ecol. 2018 27:4787-4807, 2018.
13. Pedersen, N.C., Griffey, S.M., Grahn, R. and Munn, R.: A transmissible myocarditis/diaphragmitis of cats manifested by transient fever and depression. Feline Prac. 21: 13-19, 1993.
14. Breitschwerdt, E.D. and Chomel, B.B.: Mycoplasma and Bacterial Diseases: Canine Bartonellosis. In: Infectious Diseases of the Dog and Cat. Editor: Greene, C.E. 4th Edition. pp. 552-563.
15. Ohad, D.G., Morick, D., Avidor, B. and Harrus, S.: Molecular detection of *Bartonella henselae* and *Bartonella koehlerae* from aortic valves of Boxer dogs with infective endocarditis. Vet. Microbiol. 141: 182-185, 2010.
16. Davis, A.Z., Jaffe, D.A., Honadel, T.E., Lapsley, W.D., Wilber-Raymond, J.L., Kasten, R.W. and Chomel, B.B.: Prevalence of *Bartonella* sp. in United States military working dogs with infectious endocarditis: a retrospective case-control study. J. Vet. Cardiol. 16;27:1-9. doi: 10.1016/j.jvc.2019.11.005.
17. Shtaya, A.A., Perek, S., Kibari, A. and Cohen, S.: *Bartonella henselae* endocarditis: An unusual presentation of an unusual disease. Eur. J. Case Rep. Intern. Med. doi: 10.12890/2019_001038, 2019.