Review article

Emergent opportunities in humans: playful kittens, an arthropod vector, and a zoonotic agent

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Bartonella henselae is implicated as the main etiologic agent of Cat scratch disease (CSD, Cat-scratch fever). A majority of domestic cats may harbor the intra-erythrocytic agent for extended periods without apparent disease. In humans, *B. henselae* most commonly results in a subacute, bacterial infection that presents with one or more reddish papules which may progress to pustules and regional lymph node enlargement. Usual features include fever, malaise, and a granulomatous lymphadenitis on biopsy. However, atypical clinical presentations occur, albeit with infrequency, and may result in a difficult and protracted diagnostic process. The infection in susceptible hosts such as immunocompromised or elderly patients may result in endocarditis, encephalitis, fever of unknown origin, and general malaise. It is not transmitted from person to person and quarantine is not necessary. The arthropod vector, *Ctenocephalides felis*, or the cat flea, plays a major role in transmission among cats and to humans. The transmission risk to humans can be substantially reduced through elimination of flea infestations in companion animals. There are numerous recent reviews and case reports in the veterinary and medical literature reflecting increased recognition of this zoonotic agent. All this notwithstanding, many physicians and other providers may not be familiar with this agent and the potential spectrum of human disease; this may lead to delays in diagnosis and unnecessary diagnostic procedures. This article emphasizes the aspects of *B. henselae* infection, including a typical case report and a table with selected human case reports of unusual clinical manifestations from the published literature.

Keywords: *Bartonella henselae*, cat scratch disease, zoonosis

The first description of a clinical syndrome involving localized lymphadenopathy occurred in the French literature by Henri Parinaud in 1889 [1]. In 1931, Dr. Robert Debré coined the term “Cat Scratch Disease” to describe the syndrome and associated epidemiologic characteristics [2]. Since then, the disease has been shown to occur globally and increasingly important as a zoonosis (diseases transmitted from animals to humans) [3-8]. Zoonoses have been estimated to cause over 60% of emerging infectious disease in the past 50 years (e.g. rabies, ebola, pulmonary hantavirus syndrome, New-variant

Creutzfeldt-Jakob disease, etc.) [9]. Professor Frederick Murphy of the School of Veterinary Medicine, University of California, commented on the unique nature of zoonoses, the challenges of funding, and research infrastructure, and the need for research for strategies of prevention and control [10]. Moreover, diagnosis and prevention of zoonotic diseases requires collaboration among diverse professionals in the medical, veterinary, research and public health arenas.

In this article, in addition to the case report below, we provide a brief overview of agent, occurrence, reservoir, vector, clinical presentation, transmission, diagnosis, prevention, and a table with selected case reports from the published literature underscoring the multiple potential clinical presentations of CSD in humans.

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Case report from Bangkok*

A 48-year-old healthy bachelor American engineer working in Myanmar (Burma) was referred to a Bangkok hospital for evaluation of low grade fever, malaise, anorexia, headaches of two weeks duration and for biopsy of a persistently enlarged lymph node in his axilla. He had been treated with an unknown "broad spectrum" antibiotic by a local physician who reported normal complete blood counts and an aspiration of the node that was negative for microorganisms by acid-fast bacilli and Gram stains.

Physical examination on admission revealed normal temperature and vital signs. The patient's right axillary lymph node was tender and slightly enlarged measuring approximately two centimeters in diameter. There were no other abnormal physical findings. The complete blood count, urinalysis, aspartate aminotransferase, adenylate kinase, blood glucose, and chest X-ray were normal. A tuberculin skin test was negative. His erythrocyte sedimentation rate was 58. A surgeon performed an incisional biopsy of the enlarged node, which yielded negative acid-fast bacillus (AFB) and Gram stains. A later culture grew no bacteria and an AFB culture was not done. An infectious disease consultant was asked to see the patient, who reported extensive sexual contacts with different partners. Lymphogranuloma venereum had been diagnosed in one of his contacts. A more detailed history then revealed that he had acquired a kitten shortly before his illness and that after playing with it, he had noted a papule on his right index finger that persisted for about one week before he first

noted fever, headaches and about one week later the enlarging lymph node. A presumptive diagnosis of Cat Scratch Disease was then made, he was started on doxycycline 100 mg twice daily (even though he had already improved considerably), and serum was sent to the London School of Tropical Medicine which later returned a negative serology report.

At the time of clinical illness in the mid 1990's, no PCR or other serologic tests were available in Bangkok or Singapore. The patient returned to Myanmar with a two weeks empirical course of doxycycline. Consultants from the veterinary faculty in Bangkok recommended that he treat his kitten with a flea insecticide and tetracycline for 10 days. The patient reported one month later that his enlarged lymph node had resolved and that he had fully recovered. He managed his cat, which had always appeared healthy, as recommended. No other person in his household had any similar illness.

Agent

Bartonella species are important emerging zoonotic agents [3, 5, 8, 11]. The genus *Bartonella* includes at least 24 species or sub-species, of which half have been described to be responsible for human disease [12]. *Bartonella* species are small, fastidious, intracellular gram-negative bacilli that are aerobic and oxidase-negative. The organisms are most easily visualized by using a Warthin-Starry silver impregnation stain (**Fig. 1**) or a Brown-Hopps tissue Gram-stain [13]. At least, five species are associated with cats, most often with a subclinical occurrence. In addition

Fig. 1 Demonstration of *Bartonella henselae* in cardiac valve of a patient with blood-culture-negative endocarditis. The bacilli appear as black granulations (Warthin-Starry stain). Source-CDC/EID February 2002;8(2).

*This case report was provided by Professor Wilde H, Chulalongkorn University.

to cats, numerous wild and domestic species can serve as chronically infected reservoir hosts for various species of *Bartonella* [11]. *Bartonella henselae* is implicated as the main etiologic agent of Cat scratch disease (CSD, Cat-scratch fever) [11]. Two main genogroups of *B. henselae* have been identified in humans and cats: Houston-1 and Marseille (also known as genotype II) [14]. These two genogroups are further subdivided into four variants: Marseille, CAL-1, Houston-1, and ZF-1 [15-17].

Occurrence

Bartonella species occur worldwide and may result in a variety of clinical presentations in humans. Recently, there may be increased recognition of clinical syndromes associated with these pathogens [7, 18].

Reservoir

Cats are the major reservoir for *B. henselae*. In populations of domestic cats throughout the world, seroprevalence surveys indicate that substantial proportions appear to have been exposed to *Bartonella* spp [19, 20]. Bacteremia is more likely in younger cats and seropositivity is more likely in older cats [11, 19]. *B. henselae* infection in cats is typically subclinical or non-specific and mild, and may not be obvious to the pet owner. Fever and lymphadenopathy may occur. Lymphadenopathy can be local or generalized and long-standing, lasting a month or more. When infection is coincident with other agents such as feline immunodeficiency, it is associated with the presence of more prominent clinical disease, such as uveitis, stomatitis, urinary tract disorders, and neurologic disease [21, 22]. The spectrum of clinical illness remains in need of elucidation, as evidenced by at least one case of vegetative aortic valve endocarditis due to *B. henselae* that was culture-negative but fatal [23].

Treatment of cats with antibiotics can reduce bacteremia, but recrudescence may occur and cats are still subject to re-infection [24]. Antibiotic treatment should be reserved for clinically ill cats where there is a definitive diagnosis or a high index of suspicion [25]. Diagnostic confirmation can be difficult. In sick cats, culture of blood or tissue biopsy is reliable but not always sensitive. Depending upon the molecular approach and laboratory expertise, PCR, nested PCR or real-time PCR may equal or exceed culture in diagnostic sensitivity. Serologic techniques are most

useful for population surveys, rather than for diagnosis of acute infection, as antibodies persist beyond active infection. Indirect fluorescent antibody, enzyme immunoassay, and Western blot tests may be useful, but depending upon the source of antigen and the genetic diversity of the *Bartonella* sp. in an individual or population, the tests may have limited sensitivity.

Comprehensive vector control (i.e., flea control for animals and environmental management of the home) and client education should always be implemented when antibiotic treatment is instituted, as the most reliable management tool for prevention of infection (or re-infection) of pets and humans is flea control.

Vector

The arthropod vector, *Ctenocephalides felis*, or the cat flea, plays a major role in transmission among cats and to humans [26]. Human infection can be prevented through elimination of flea infestations [8, 27, 28]

Clinical presentation

In humans, *B. henselae* most commonly results in a subacute, bacterial infection which presents with one or more reddish papules which may progress to pustules (**Fig. 2**) and regional lymph node enlargement [6]. Usual features include fever, malaise, and a granulomatous lymphadenitis on biopsy. However, atypical clinical presentations occur, albeit with infrequency, and may result in a difficult and protracted diagnostic process. These infrequent clinical presentations may include lesions suggestive of malignancy (e.g. lymphoma) or other infectious processes such as tuberculosis, brucellosis, tularemia, and plague [29]. Other clinical presentations include optic neuritis, osteomyelitis, encephalitis, and the Parinaud oculoglandular syndrome (Unilateral conjunctivitis with associated pre-auricular lymphadenopathy) [30-50]. In susceptible hosts such as immunocompromised or elderly patients, the infection may result in endocarditis, encephalitis, fever of unknown origin, and general malaise - the hallmark lymphadenitis characteristic in younger patients is often absent [51]. Submandibular swelling and a presumed dental abscess may lead to clinical recognition of the infection upon presentation to a dentist rather than to a physician [52]. Other reported manifestations include hepatitis and pneumonia [53-55].

Fig. 2 Cat Scratch lesion on thumb. Source: CDC's Public Health Image Library (<http://phil.cdc.gov/public/1269.htm>).

The response to infection with *B. henselae* depends on the immune status of the infected host. In immunocompetent humans, the response is granulomatous and suppurative, as compared with a vasoproliferative response in immunocompromised patients [14, 29]. In an immunocompetent patient, lymphoid hyperplasia, arteriolar proliferation, and widened arteriolar walls progress to granulomatous disease and stellate microabscesses.

Immunodeficient patients are at risk for bacillary angiomatosis (**Fig. 3**), which manifests as cutaneous angiogenic lesions [56]. These lesions consist of vascular proliferation composed of endothelial cells and a mixed inflammatory cell infiltrate. The mechanism by which *B. henselae* induces angiogenesis is not fully understood. One hypothesis is that

Bartonella modulates host or target cell cytokines and growth factors, which lead to angiogenesis.

Transmission

B. henselae is not transmitted from person to person and quarantine is not necessary. Although the exact mode of transmission from cats to humans is unclear, it is generally accepted that the infectious agent is inoculated when human skin is scarified by the claws or teeth of a cat contaminated with infected flea feces or through direct contact of conjunctival membranes, with infected feces [14, 26, 57]. This mode of transmission is similar to that of *B. quintana* to humans which also relies upon mechanical transmission through infected arthropod feces, with *B. Quintana* most commonly from the human body louse.

Fig. 3 Bacillary angiomatosis due to *Bartonella. henselae* in HIV-AIDS patient (Biopsy: Whartin-Starry stain. Insert: electron microscopy). *B. henselae* shows up black red-like or coccobacillary elements. Definitte diagnosis relies on amplification and sequencing of 16rDNA as well as serology. Image courtesy of Aids Images Library (www.aidsimages.ch).

Diagnosis

A definitive diagnosis may involve a combination of clinical, epidemiologic, serologic, histologic, and molecular criteria [6, 58]. A presumptive diagnosis is often based on history and clinical criteria: contact with a cat, patient-reported presumed site of inoculation resulting from a scratch or bite to the skin or primary lesion of eye or mucous membrane, and a subsequent regional lymphadenopathy. At this time, there is no single criterion that can be considered the diagnostic gold standard for *B. henselae*. Recent diagnostic investigation supports the usefulness of testing for *B. henselae* DNA by PCR analysis in patients with an isolated superficial lymphadenopathy [59]. With a positive PCR result, the diagnosis of CSD can be confirmed with excellent specificity. If there is a negative result, the diagnosis would rely upon at least two of the following: (i) positive serology, (ii) histology compatible with CSD (pyogenic granuloma), or (iii) contact with cats during the days or weeks preceding lymphadenopathy, together with elimination of other causes of lymph node enlargement.

Prevention

There is strong evidence that spread of infection between cats depends on the arthropod vector

Ctenocephalides felis, or the cat flea [14, 57]. Elimination of arthropod infestation in the pet, especially flea infestation, is often successful in disrupting the transmission cycle both cat-to-cat and cat-to-human.

Conclusion

There are numerous recent reviews and case reports in the veterinary and medical literature reflecting increased recognition of this zoonotic agent [3-8]. The 2009 online version of the American Academy of Pediatrics Red Book has several excellent clinical images of patients with CSD [60]. All this notwithstanding, many physicians and other providers may not be familiar with this disease; this may lead to delays in diagnosis and unnecessary diagnostic procedures. As part of a complete history for all patients, healthcare providers should actively elicit information about pets and other potential animal contact. Early serologic and molecular testing for CSD may be particularly useful for the pediatric patient to avoid unnecessary interventions and to expedite appropriate medical management [37, 57]. With reasonable precautions, even immunocompromised patients may still enjoy the benefits of the human-animal bond, including one with young cats [61].

Appendix. Unusual cases in humans

Patients	Unusual cases	Authors
6-year-old male	Cervical lymphadenopathy; contact with domestic dog	Da Silva and Chussid, 2009 [62]
9-year-old male	Osteomyelitis; dog scratch	Keret et al., 1998 [63]
11-year-old male	Inguinal lymphadenopathy, and osteomyelitis; exposure to kittens.	Rozmanic et al., 2007 [64]
9-year-old female	Multifocal osteomyelitis	De Kort et al., 2006 [65]
9-year-old female	Vertebral osteomyelitis; multiple cat scratches	Robson et al., 1999 [66]
9-year-old male	Meningo-encephalitis	Cherinet and Tomlinson, 2008 [67]
11-year-old male	Hemiplegia.	Rocha et al., 2004 [68]
17-year-old male	Anatomic diagnosis; hepatitis caused by <i>Bartonella henselae</i> contact with cats	Pelton et al., 2006 [69]
51-year-old female	Lymphadenopathy of hepatic hilum	Imperiale et al., 2008 [53]
Six school-aged patients	Status epilepticus.	Armengol and Hendley, 1999 [70]
Four acquired immunodeficiency syndrome (AIDS) patients	Angiomatous nodules; 2 with history of cat scratch	Koehler et al., 1988 [56]
3 HIV-positive patients	Ocular lesions (sub-retinal masses and abnormal vascular network)	Curi et al., 2006 [71]
40-year-old male with AIDS	Epithelioid angiomatosis, disseminated; cat scratch	Milam et al., 1990 [72]

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