From Cat Scratch Disease to *Bartonella henselae* Infection

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(See the article by Maman et al. on pages 1535–40)

Cat scratch disease (CSD) is a relatively common disease mainly caused by *Bartonella henselae*. In this issue of *Clinical Infectious Diseases*, Maman et al. [1] report on musculoskeletal manifestations of CSD, extending the spectrum of clinical manifestations of *B. henselae* infection by including chronic arthritis, as well as emphasizing the prevalence of arthralgias.

As a matter of fact, CSD is a paradigm for the evolution of knowledge following the discovery of an etiologic agent for an infectious disease. In many cases, such as the example outlined here, a very specific clinical form of a disease is described first. The first formal description of CSD was made in Paris and was named “maladie des griffes du chat” in 1950 to acknowledge the link between the disease and cats [2]. Typical CSD develops after contact with a cat and comprises subacute regional lymphadenopathies that can be associated with a primary skin lesion and systemic manifestations [3].

The etiologic agent of this clinical entity remained elusive for years; however, some serum samples (from patients with CSD) reacted with chlamydial antigens. Cross-reactivity occurred between *Chlamydia* species and *Bartonella* species, which was later determined to be the cause of CSD [4]. Significant progress was made with electronic microscopic methods [5] and when an argent histological staining method called Warthin Starry was used to detect bacteria-like black spots in lymph node specimens [3, 6]. In the AIDS era, a completely new clinical entity, bacillary angiomatosis, was described. It is antibiotic sensitive and involves cutaneous vascular tumors. Positive results by Warthin Starry staining of biopsy specimens suggested a possible link between bacillary angiomatosis and CSD [7, 8].

In November 1990, a single issue of the *New England Journal of Medicine* highlighted 3 different approaches to pathogen discovery. Relman et al. [9] used 16S rRNA–based universal amplification and sequencing to identify bacteria not yielded by culture in a patient with bacillary angiomatosis for the first time. Slater et al. [10] grew a fastidious gram-negative bacterium in specimens from febrile patients with AIDS, and finally, Perkocha et al. [11] identified Warthin Starry–positive bacteria in a biopsy specimen from a patient with hepatic peliosis and AIDS [12]. It was later recognized that the 3 teams were describing the same bacterium [12]. *B. henselae* was linked to CSD by chance. In fact, when Regnery et al. [13] from the Centers for Disease Control and Prevention were testing a new serologic assay to detect antibodies in HIV-infected patients, the control group (which happened to be patients with CSD) exhibited a higher ratio of HIV-positive serum samples then did the target patients [14]. Later, the same team was able to isolate *B. henselae* from the lymph node specimen of a patient with CSD [15]. Since the discovery of this new pathogen, diagnostic tools have been developed, including serologic testing and PCR. *B. henselae* was subsequently found to be an agent of blood culture–negative endocarditis [16]. Culture remains the main tool for the initial description of *B. henselae* infection, but is not very useful for diagnostic purposes in many cases.

The wide use of diagnostic tools for *B. henselae* allowed investigators to test samples from patients with diseases other than typical CSD. Finally, because of the discovery of the etiologic agent, the clinical spectrum of *B. henselae* extended rapidly, and it has been implicated as the etiologic agent of stellar retinitis, meningoencephalitis, and liver and splenic abscesses. However, bacillary angiomatosis, as well as endocarditis and a few cases of CSD, have also been associated with closely related *Bartonella quintana*. We then have to shift from CSD to *B. henselae* infection, which presents with a wide variety of clinical manifestations, including CSD.

Epidemiologically, *B. henselae* is mainly linked to cats among patients with CSD [17], bacillary angiomatosis [7], or endocarditis [16]. *Bartonella* species generally use erythrocytes as their reservoir [18]. *B. henselae* is commonly found in the blood of cats and other felids [19], but cases linked to ticks have also been reported [20]. Following the initial culture positive for *B. henselae*, both clinical spectrum and epidemiological source extend...
rapidly, as soon as the etiologic agent has been identified and grown on culture. As reported by Maman et al. [1], *B. henselae* is also a recognized cause of musculoskeletal lesions. Rare cases of osteomyelitis and arthritis have been clearly linked to *B. henselae*. In the article by Maman et al. [1], the high prevalence of myalgias and arthralgias, including chronic arthritis, is emphasized.

Treatment of diseases associated with *B. henselae* remains a challenge, because CSD is resistant to antibiotic therapy, treatment of endocarditis requires aminoglycosides, and treatment of bacillary angiomatosis requires macrolide antibiotics [21]. In this respect, treatment of *B. henselae* infection is instructive, because it emphasizes the fact that the clinical effect of antibiotics on a disease relies not only on antibiotic susceptibility, but also on the bacterial location in the body and the immune status of the patient. Because of this empirical therapy, results have contradicted in vitro tests.

Finally, the use of diagnostic tests to describe a disease is not without pitfalls. Serologic testing is hampered by high seroprevalence in the tested population. This is evidenced by reports of cancer in the lymph nodes and by tuberculosis associated with results of serologic tests that are positive for *B. henselae* [22]. Clinicians should be cautious of concluding a diagnosis on the basis of a single positive serologic test result. PCR may also have sensitivity and specificity problems [22], and the results rely heavily on the quality of the laboratory in which the assays are conducted. Moreover, *B. henselae* can be associated with lymph node cancer and tuberculosis, and a positive PCR result does not rule out these diagnoses [22].

In conclusion, knowledge regarding the common infectious agent *B. henselae* has rapidly evolved since 1990. However, the reason for such a wide variability in clinical manifestations remains an unresolved question. Most factors, such as sex and age, as reported by Maman et al [1], immunological status [7], and previous valve lesions [23], are important. After infection with *B. henselae*, a patient with AIDS eventually experienced bacillary angiomatosis or peliosis, and a patient with a valve lesion experienced endocarditis [23]. Strain specificity may play a role in the clinical expression of *B. henselae* infection, because there is significant variability among different strains [24]. Finally, inoculum size and source of infection may also play a role in the clinical course of *B. henselae* infection, because patients who are infected by a tick bite have bacteremia but not lymphadenopathy [20].

Acknowledgments

Potential conflicts of interest. D.R.: no conflicts.

References