EDITORIAL COMMENTARY

From Cat Scratch Disease to *Bartonella henselae* Infection

Didier Raoult

Unité des Rickettsies, CNRS UMR 6020, Faculté de Médecine, Marseille, France

(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 argentic 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 16 S 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 abscess. 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

Received 30 August 2007; accepted 14 September 2007; electronically published 6 November 2007.

Reprints or correspondence: Dr. Didier Raoult, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 6020, Faculté de Médecine, 27, bd Jean Moulin, 13005 Marseille, France (didier.raoult@gmail.com).

Clinical Infectious Diseases 2007; 45:1541–2

1058-4838/2007/4512-0002$15.00
DOI: 10.1086/523716

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

1. Maman E, Bickels J, Ephros M, et al. Musculoskeletal manifestations of cat scratch disease. Clin Infect Dis **2007**; 45:1535–40 (in this issue).
2. Debré R, Lamy M, Jammet ML, Costil L, Mozziconacci P. La maladie des griffes de chat [in French]. Bull Mem Soc Med Hop Paris **1950**; 66:76–9.
3. Spach DH, Kaplan SL. Microbiology, epidemiology, clinical manifestations, and diagnosis of cat scratch disease: UpToDate 2007. Available at: http://www.utdol.com. Accessed 23 October 2007.
4. Maurin M, Eb F, Etienne J, Raoult D. Serological cross-reactions between *Bartonella* and *Chlamydia* species: implications for diagnosis. J Clin Microbiol **1997**; 35:2283–7.
5. Kitchell CC, DeGirolami PC, Balogh K. Bacillary organisms in cat scratch disease. N Engl J Med **1985**; 313:1090–1.
6. Wear DJ, Margileth AM, Hadfield TL, Fischer GW, Schlagel CJ, King FM. Cat scratch disease: a bacterial infection. Science **1983**; 221: 1403–5.
7. Koehler JE, Quinn FD, Berger TG, Leboit PE, Tappero JW. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. N Engl J Med **1992**; 327: 1625–31.
8. Leboit PE, Berger TG, Egbert BM, et al. Epithelioid haemangioma–like vascular proliferation in AIDS: manifestation of cat scratch disease bacillus infection? Lancet **1988**; 1: 960–3.
9. Relman DA, Loutit JS, Schmidt TM, Falkow S, Tompkins LS. The agent of bacillary angiomatosis: an approach to the identification of uncultured pathogens. N Engl J Med **1990**; 323:1573–80.
10. Slater LN, Welch DF, Hensel D, Coody DW. A newly recognized fastidious gram-negative pathogen as a cause of fever and bacteremia. N Engl J Med **1990**; 323:1587–93.
11. Perkocha LA, Geaghan SM, Yen TS, et al. Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med **1990**; 323:1581–6.
12. Relman DA, Falkow S, Leboit PE, et al. The organism causing bacillary angiomatosis, peliosis hepatitis, and fever and bacteremia in immunocompromised patients. N Engl J Med **1991**; 324:1514.
13. Regnery RL, Childs JE, Koehler JE. Infections associated with *Bartonella* species in persons infected with human immunodeficiency virus. Clin Infect Dis **1995**; 21(Suppl 1):S94–8.
14. Regnery RL, Olson TG, Perkins BA, Bibb W. Serological response to *Rochalimaea henselae* antigen in suspected cat-scratch disease. Lancet **1992**; 339:1443–5.
15. Dolan MJ, Wong MT, Regnery RL, et al. Syndrome of *Rochalimaea henselae* adenitis suggesting cat scratch disease. Ann Intern Med **1993**; 118:331–6.
16. Raoult D, Fournier PE, Drancourt M, et al. Diagnosis of 22 new cases of *Bartonella* endocarditis. Ann Intern Med **1996**; 125:646–52.
17. Giladi M, Avidor B. Images in clinical medicine. Cat scratch disease. N Engl J Med **1999**; 340:108.
18. Jacomo V, Kelly PJ, Raoult D. Natural history of *Bartonella* infections (an exception to Koch's postulate). Clin Diagn Lab Immunol **2002**; 9:8–18.
19. Chomel BB, Boulouis HJ, Maruyama S, Breitschwerdt EB. *Bartonella* spp. in pets and effect on human health. Emerg Infect Dis **2006**; 12: 389–94.
20. Breitschwerdt EB, Maggi RG, Duncan AW, Nicholson WL, Hegarty BC, Woods CW. *Bartonella* species in blood of immunocompetent persons with animal and arthropod contact. Emerg Infect Dis **2007**; 13:938–41.
21. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by *Bartonella* species. Antimicrob Agents Chemother **2004**; 48:1921–33.
22. Rolain JM, Lepidi H, Zanaret M, et al. Lymph node biopsy specimens and diagnosis of cat-scratch disease. Emerg Infect Dis **2006**; 12: 1338–44.
23. Gouriet F, Lepidi H, Habib G, Collart F, Raoult D. From cat scratch disease to endocarditis, the possible natural history of *Bartonella henselae* infection. BMC Infect Dis **2007**; 7:30.
24. Fournier PE, Raoult D. Cat scratch disease and an overview of other *Bartonella henselae* related infections. In: Schmidt A, ed. *Bartonella* and *Afipia* species emphasizing *Bartonella henselae.* Basel, Switzerland: Karger, **1998**:32–62.