Rickettsia felis and Changing Paradigms about Pathogenic Rickettsiae

To the Editor: Mediannikov et al. recently reported several features common to the epidemiology of *Rickettsia felis* infection and malaria in Africa (*1*). Similar to the findings of several other recent studies in Africa (*2*,*3*), the authors diagnosed *R. felis* infection in febrile—and to a lesser extent in afebrile—persons by detecting *R. felis* DNA in human blood samples processed by highly sensitive real-time PCR. These results challenge some paradigms in rickettsiology that need to be more critically evaluated.

Because *R. felis* DNA was detected in circulating blood of asymptomatic persons (albeit more frequently in patients with mild febrile illness), Mediannikov et al. proposed that humans could be a natural reservoir of *R. felis*, as they are for malaria parasites. *R. felis* antibodies failed to develop in nearly all patients in whom *R. felis* DNA was detected, even after repeated detection of *R. felis* DNA. In 2 other studies, the same researchers proposed that patients might have several episodes of *R. felis* infection (relapse or reinfection) to explain why DNA of the agent was detected in the blood at multiple times (*2*,*3*). They also proposed that the absence of an antibody response would explain why the disease relapses in some persons (*3*).

These changing paradigms in rickettsiology require thorough evaluation. Once inside a vertebrate host, pathogenic rickettsiae have been believed to multiply primarily within endothelial cells in the patient's organs. As far as we know, rickettsiae do not multiply within circulating blood cells (*4*). In contrast, the agents of malaria (*Plasmodium* spp.) are typically parasites of erythrocytes. Therefore, a blood sample from a person with malaria is an excellent source for PCR diagnostic testing. The sensitivity of PCR for rickettsiae in human blood samples is very low because the sensitivity depends on the magnitude of the vasculitic lesions, i.e., the number of endothelial cells destroyed or detached by rickettsial growth, resulting in circulating rickettsiae. *R. conorii* (*5*) and *R. rickettsii* (*6*) were detected by highly sensitive PCR in 100% of fatal cases and in only very few nonfatal cases.

In addition to never having been isolated from humans, *R. felis* has many characteristics of a symbiotic organism. It possesses a mosaic structure genome (size 1.48 Mb) with a high coding capacity (83%) that is typical of symbiotic bacteria (*7*). Merhej et al. have proposed that within a given bacterial genus (including *Rickettsia*), pathogenic species have smaller genomes than nonpathogenic species (*8*). In the genus *Rickettsia,* the pathogens *R. rickettsii*, *R. prowazekii*, *R. sibirica*, *R. typhi*, *R. parkeri*, and *R. conorii* have genomes of ≈1.2–1.3 Mb, whereas the apparently nonpathogenic *R. bellii* has a 1.5-Mb genome, similar to that of *R. felis*. In contrast to the well-known pathogenic *Rickettsia* species, *R. felis* has been reported in a variety of invertebrate hosts, including hematophagous (fleas, ticks, flies, mosquitoes) and non-hematophagous (book lice) arthropods (*9*). Behar et al. have suggested that *R. felis* is responsible for inducing parthenogenesis in book lice, similar to the manner of *Wolbachia* organisms in various invertebrate hosts (*9*). Furthermore, *R. felis* forms mycetomes in book lice, a growth feature typical of bacterial endosymbionts (*10*).

The current view in rickettsiology has a strong anthropocentric bias because the studies have concentrated on parasitic arthropods that feed on humans rather than on free-living arthropods. In fact, the number of *Rickettsia* species associated with non-hematophagous hosts might be much greater than the ones of medical importance (*9*). Thus, considering *R. felis* as an important pathogen in Africa (and in the world) might be premature. Several questions need to be answered before such a conclusion. In asymptomatic persons in whom endothelial cells are likely to be intact, where does *R. felis* grow to be released at detectable levels in the circulating blood? Considering that all classical spotted fever agents induce an antibody response (*4*), why do *R. felis* antibodies fail to develop in humans after a clinical illness attributed to *R. felis*? In addition, repeated reports that the main vector of *R. felis* is the cat flea, *Ctenocephalides felis*, need to be proven by experimental demonstration of its vector capacity.

Given the numerous questions about *R. felis*, we would add another: could *R. felis* be a symbiont of a human parasite, such as a protozoon or a helminth? Obviously, the answer is unknown. However, had we not known that *Wolbachia* organisms are typically endosymbiotic bacteria of both human and animal filarial nematodes, what would we conclude if we detected *Wolbachia* DNA in blood of either asymptomatic or ill patients?

Marcelo B. Labruna and David H. Walker

Author affiliations: University of São Paulo, São Paulo, Brazil (M.B. Labruna); and University of Texas Medical Branch, Galveston, Texas, USA (D.H. Walker)

DOI: http://dx.doi.org/10.3201/eid2010.131797

References

1. Mediannikov O, Socolovschi C, Eduoard S, Fenollar F, Mouffok N, Bassene H, et al. Common epidemiology of *Rickettsia felis* infection and malaria, Africa. Emerg Infect Dis. 2013;19:1775–83. http://dx.doi.org/10.3201/eid1911.130361
2. Mediannikov O, Fenollar F, Bassene H, Tall A, Sokhna C, Trape JF, et al. Description of "yaaf", the vesicular fever caused by acute *Rickettsia felis* infection in Senegal. J Infect. 2013;66:536–40. http://dx.doi.org/10.1016/j.jinf.2012.10.005

3. Socolovschi C, Mediannikov O, Sokhna C, Tall A, Diatta G, Bassene H, et al. *Rickettsia felis*–associated uneruptive fever, Senegal. Emerg Infect Dis. 2010;16:1140–2. http://dx.doi.org/10.3201/eid1607.100070
4. Yu XJ, Walker DH. Genus *Rickettsia* da Rocha-Lima 1916. In: Brenner DJ, Krieg NR, Staley JR, editors. Bergey's manual of systematic bacteriology. Vol. 2, part C. 2nd ed. New York: Springer; 2005, p, 96–106.
5. Leitner M, Yitzhaki S, Rzotkiewicz S, Keysary A. Polymerase chain reaction–based diagnosis of Mediterranean spotted fever in serum and tissue samples. Am J Trop Med Hyg. 2002;67:166–9.
6. Santos FCP, Brasil RA, Nascimento EMM, Angerami RN, Colombo S, Pinter A, et al. Evaluacion de la PCR en tiempo real para el diagnostico de la Fiebre Manchada Brasilena. Acta Med Costarric. 2013;55(supp):77.
7. Merhej V, Raoult D. Rickettsial evolution in the light of comparative genomics. Biol Rev Camb Philos Soc. 2011;86:379–405. http://dx.doi.org/10.1111/j.1469-185X.2010.00151.x
8. Merhej V, Georgiades K, Raoult D. Postgenomic analysis of bacterial pathogens repertoire reveals genome reduction rather than virulence factors. Brief Funct Genomics. 2013;12:291–304. http://dx.doi.org/10.1093/bfgp/elt015
9. Behar A, McCormick LJ, Perlman SJ. *Rickettsia felis* infection in a common household insect pest, *Liposcelis bostrychophila* (Psocoptera: Liposcelidae). Appl Environ Microbiol. 2010;76:2280–5. http://dx.doi.org/10.1128/AEM.00026-10
10. Thepparit C, Sunyakumthorn P, Guillotte ML, Popov VL, Foil LD, Macaluso KR. Isolation of a rickettsial pathogen from a non-hematophagous arthropod. PLoS ONE. 2011;6:e16396. http://dx.doi.org/10.1371/journal.pone.0016396

Address for correspondence: David H. Walker, University of Texas Medical Branch—Galveston, 301 University Blvd, Galveston, TX 77555-0609, USA; email: dwalker@utmb.edu

Pulmonary Disease Caused by *Mycobacterium marseillense*, Italy

To the Editor: *Mycobacterium marseillense* was recently described as a new species belonging to the *Mycobacterium avium* complex (MAC) (*1*). We describe a case of pulmonary disease caused by *M. marseillense* in an immunocompetent patient. All strains isolated from the patient were preliminarily identified as *M. intracellulare*; however, a retrospective molecular analysis corrected the identification to *M. marseillense*.

In December 2005, a 65-year-old man was admitted to the University Hospital, Modena, Italy, with a 2-week history of fever, cough, and hemoptysis. Physical examination detected diffuse rales, and chest radiographs showed a diffuse nodular opacity and bronchial thickening, confirmed by high-resolution computed tomography (CT) of the chest (Figure, panel A). The patient had experienced several previous episodes of hemoptysis and persistent productive cough since 1998, and tubular bronchiectasis had been detected on previous high-resolution CT images. The patient had a history of thalassemia minor, was HIV negative, and was formerly a mild smoker (10 cigarettes/day for 4 years during his youth). He had no chronic disorders and no history of immunosuppressive-drug or alcohol use.

Bacterial and fungal cultures and a smear for acid-fast bacilli performed on a bronchoalveolar lavage (BAL) sample were all negative. A nontuberculous mycobacterium strain was isolated by culture and preliminarily identified as *M. intracellulare* by using the GenoType Mycobacterium CM/AS Kit (Hain Lifesciences, Nehren, Germany). At that time, a drug susceptibility test for isoniazid, rifampin, streptomycin, and ethambutol was improperly performed (i.e., was not applicable for MAC) by using the agar proportion method; sensitivity information for macrolides was unavailable. The strain was resistant to ethambutol and susceptible to the other drugs. The physician prescribed rifampin, isoniazid, and amikacin. After remission of fever and hemoptysis and improvement of chronic cough, the patient was discharged from the hospital.

In March 2006, he was readmitted to the hospital for worsening of his condition and onset of side effects associated with rifampin and isoniazid use. The treatment was discontinued and replaced by levofloxacin, terizidone, and azithromycin, which resulted in remission of symptoms. This therapy was continued after hospital discharge.

In 2007, the patient was twice admitted for follow-up and microbiological testing to determine bacteriologic status. All 3 separate sputum samples were negative for mycobacteria, other bacteria, and fungi. However, BAL sample culture results were positive for the same mycobacterium despite continued therapy with levofloxacin, terizidone, and azithromycin.

During 2008, as an investigation of the possibility of persistent excretion of organisms, additional samples were collected 5 times. The sputum cultures were intermittently positive, while the BAL sample cultures were persistently positive.

In May 2009, after the patient had been persistently stable and had negative culture results for 14 months, the antimicrobial drug therapy was stopped. In December 2010, the patient's only symptom was persistent productive cough; however, the sputum culture was again positive, and high-resolution CT revealed a worsening condition of his lungs (Figure, panel B). A new antimycobacterial drug regimen of ethambutol, rifampin, and azithromycin was started, in accordance with the international