Persistent Generalized Lymphadenopathy and Non-Hodgkin’s Lymphoma in AIDS: Association with *Rochalimaea henselae* Infection

JAMES B. PETER,1,4 MICHAEL BOYLE,2 MADHUMITA PATNAIK,1 TED L. HADFIELD,3 NOORI E. BARKA,1 WILLIAM A. SCHWARTZMAN,4 AND RONALD S. PENNY2

Specialty Laboratories, Inc., Santa Monica, California 90404; St. Vincent’s Hospital, Sydney, New South Wales 2010, Australia; Armed Forces Institute of Pathology, Washington, D.C. 20306; and Sepulveda VAMC, Sepulveda, California 91434

Received 13 August 1993/Accepted 28 September 1993

Cat scratch disease, which is caused by infection with *Rochalimaea henselae*, is often manifested as lymphadenopathy. *R. henselae* has also been isolated from human immunodeficiency virus (HIV)-positive patients with bacillary angiomatosis. In order to determine the frequency of *R. henselae*-reactive antibodies in HIV-positive patients with persistent generalized lymphadenopathy (PGL) or non-Hodgkin’s lymphoma (NHL), we tested a total of 124 HIV-positive patients for *R. henselae*-reactive immunoglobulin G (IgG), IgM, and IgA antibodies by an enzyme immunoassay procedure using whole *R. henselae* antigen. Of the patients, 7 had PGL, 17 had NHL, and 100 were HIV stage IV (Centers for Disease Control criteria). A total of 86% of PGL patients (6 of 7) were positive for *R. henselae* antibodies (three were positive for IgG, IgA, and IgM, one was positive for IgG and IgA only, and two were positive for IgG only). A total of 29% of NHL patients (5 of 17) were positive for *R. henselae* antibodies (two were positive for IgG, IgA, and IgM and three were positive for IgG only). Only 5% of HIV stage IV patients without adenopathy (5 of 100) were positive for *R. henselae*-reactive IgG, IgA, and IgM. The high prevalence of *R. henselae*-reactive antibodies in HIV-positive PGL and NHL patients suggests that *R. henselae* is a potential etiologic agent or cofactor in these patients.

Elsewhere, we have shown that *Rochalimaea henselae* infection is associated with AIDS encephalopathy (4). The studies leading to that publication were initiated because cat scratch disease (CSD), which is due to *R. henselae* infection (5), is occasionally complicated by encephalopathy (6). Because regional lymphadenopathy is typical of CSD and because generalized lymphadenopathy is known to occur with CSD in immunosuppressed individuals (6), we studied the frequency of immunoglobulin G (IgG), IgM, and IgA antibodies to *R. henselae* in patients with AIDS-related persistent generalized lymphadenopathy (PGL) as well as in AIDS-related non-Hodgkin’s lymphoma (NHL) and in consecutively-obtained human immunodeficiency virus (HIV)-positive serum samples. Enzyme immunoassay for *R. henselae*-reactive antibodies was performed as previously described (4). As disease controls, we assayed serum samples from 30 patients with multiple sclerosis, 82 patients with other bacterial and viral diseases, and 132 patients with various autoimmune diseases. IgG antibodies to *R. henselae* were found in 86% of patients with PGL (6 of 7; *P* < 10^-6); in 29% of patients with NHL (5 of 17; *P* < 0.001), in 5% of HIV-seropositive control patients (5 of 100), and in 0.4% of control patients with other diseases (1 of 244); *P* values (versus HIV-positive controls) were obtained by the *t* test for differences between means. *R. henselae*-reactive IgM and/or IgA antibodies were also detected in 43% of PGL patients (3 of 7), 12% of NHL patients (2 of 17), and in 1% of HIV-seropositive control patients (1 of 100).

The pathology records available for four of the five NHL patients whose sera contained *R. henselae* antibodies showed nodal presentation in three (patient 1, with undifferentiated high-grade NHL; patient 2, with small, non-cleaved-cell NHL; and patient 3, with large cell immunoblastic NHL and marrow involvement) and hepatic presentation in one (patient 4, high-grade, unclassified NHL). Patients 2 and 3 died of progressive central nervous system disease. The remaining 12 AIDS-related NHL patients had similar spectra of histopathology, and two died of progressive central nervous system disease. Records on patient 5, with NHL and positive *R. henselae* serology, are not available. The varieties of NHL found in our *R. henselae* antibody-positive patients are common in AIDS-related NHL (3) in general and do not differ significantly from the types of NHL found in our AIDS-related NHL patients who were seronegative for *R. henselae* antibodies.

Elsewhere, we showed that 95% of patients (38 of 40) with typical clinical, skin test, and histopathologic evidence of CSD have IgG antibodies to *R. henselae* (1). In that study, there was also a group of patients who were suspected of having CSD but were proved not to have it, and in four of those individuals the final diagnosis was lymphoma, including one individual with NHL. Of these four lymphoma patients with suspected CSD, three were positive for *R. henselae*-reactive IgG and IgM and one was negative for *R. henselae*-reactive IgG, IgM, and IgA (1).

To date, our studies of the six PGL patients with positive *R. henselae* serology have yielded no distinguishing features. Unfortunately, records of all patients studied are deficient in...
comments about exposure to animals; it remains to be determined whether cat ownership identifies a subset of HIV-positive patients more likely to be infected by *R. henselae* and/or develop AIDS-related PGL or NHL. However, none of the five *R. henselae*-seropositive AIDS-related NHL patients and none of the six *R. henselae*-seropositive PGL patients had a diagnosis of bacillary epithelioid angiomatosis, which is due to infection with *R. henselae* or *R. quintana* (2).

Our data demonstrate a high frequency of antibodies to *R. henselae* in patients with PGL and a lesser but still very elevated frequency in patients with AIDS-related NHL and in patients with NHL who are suspected of having CSD. Our data are relevant to the reported association (2) of PGL (25%) and opportunistic infections (11%) in patients who subsequently develop NHL. Clearly, the clinical spectrum of AIDS-related diseases associated with *R. henselae* infection, including central nervous system disorders, bacillary angiomatosis, and parenchymal bacillary peliosis must be extended to include PGL and NHL. Extensive studies of cause-effect relationships and of the influence of antimicrobial therapy are clearly indicated.

REFERENCES


