Prevalence of Cryoglobulinemia and Serological Markers of Autoimmunity in Human Immunodeficiency Virus Infected Individuals: A Cross-Sectional Study of 97 Patients

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ABSTRACT. ***Objective.*** Autommune diseases could constitute one emerging cause of morbidity in patients infected with human immunodeficiency virus (HIV) due to the chronicity of the infection and to the high level of B cell stimulation induced by HIV. We conducted a cross-sectional study investigating the clinical and biological signs of autoimmunity in HIV infected patients.

Methods. We studied the following plasma immunological variables: antinuclear antibodies (ANA) and antibodies to extractable nuclear antigens, antiphospholipids, anticardiolipins (aCL), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), cryoglobulinemia, total complement, and C4 factor. HIV-RNA, CD4+ cell count, and serological status for hepatitis B (HBV) and C virus (HCV) were also studied. Clinical signs of autoimmune diseases were noted.

Results. In total, 97 patients were investigated (men 74%). Median age was 38 years (range 20–64). Median CD4+ count and HIV-RNA were 333/mm^3 and 1662 copies/ml, respectively. Coinfection by HBV and HCV was present in 7% and 64% of the patients. In patients with HIV only, we detected cryoglobulinemia in 17% of patients, a positive RF in 19%, ANA > 1/100 in 21%, aCL in 51%, and ANCA > 1/20 in 17% (most of them type C by ELISA). There was a trend for a higher level of cryoglobulinemia and aCL in patients having CD4 lymphocyte counts > 350/mm^3 than in others (25% vs 11%, p = 0.26, and 63% vs 42%, p = 0.23, respectively). Patients coinfected with HCV had a higher prevalence of cryoglobulinemia than HCV-free patients (42% vs 17%; p = 0.01). Prevalence of other immunological abnormalities was not different between patients with HIV only and HCV coinfected patients. Thirty patients expressed at least one clinical sign compatible with autoimmune disease. Patients with cryoglobulinemia more often had coinfection with HCV (OR 6.64, 95% CI 1.87–23.57) and IgM > 1.9 g/l (OR 6.16, 95% CI 2.15–17.67).

Conclusion. Humoral immunological abnormalities are frequent in patients with HIV, but are rarely associated with severe clinical signs. (J Rheumatol 2003;30:2005–10)

Key Indexing Terms:
AUTOIMMUNITY CRYOGLOBULINEMIA HEPATITIS C VIRUS
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Human immunodeficiency virus (HIV) infection is associated with cellular and humoral immunity disturbances, resulting in a decrease of CD4+ T lymphocytes and a polyclonal hypergammaglobulinemia[1,2]. Highly active antiretroviral therapy (HAART) has dramatically decreased mortality and incidence of opportunistic infections since 1996-97 due to reduction of plasma HIV-RNA and increase of the CD4+ T lymphocyte level and change to a status of chronic viral infection with persistent lymphocyte stimulation[3]. This possibly constitutes a risk situation for the development of serological markers of autoimmunity and cryoglobulinemia, as reported in other chronic infections. Reports describe cases of polyarthritis, vasculitis, myositis, systemic lupus erythematosus, Sjögren's syndrome, or glomerulonephritis associated with HIV[4-12]. Nevertheless, few studies have evaluated the prevalence of serological markers of autoimmunity and cryoglobulinemia in HIV infected patients, and none was conducted during the era of HAART. Further, the relationship between markers of autoimmunity, immunovirological indicators, and hepatitis status and the impact of antiretroviral therapy has never been exhaustively studied.

In a cross-sectional study we investigated the prevalence

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of routine serological markers of autoimmunity and cryoglobulinemia to correlate the presence of these markers with hepatitis C virus (HCV) coinfection, immunovirological markers of HIV disease, and antiretroviral therapy.

MATERIALS AND METHODS

Patients. A cross-sectional study was performed to collect data on autoimmune clinical and biological manifestations among patients with HIV followed in our clinic in the Department of Internal Medicine and Infectious Diseases in Bordeaux. For inclusion, consenting patients were to be at least 18 years old and HIV positive (by Western blot). They were enrolled between January 1, 2000, and June 30, 2001.

A clinical questionnaire was completed, including (1) epidemiological information on age, sex, stage of HIV infection, first HIV positive serology, HIV transmission category, nadir of CD4+ T lymphocytes during HIV history, and antiretroviral drugs; and (2) clinical autoimmune manifestations: rheumatologic symptoms (arthralgia, arthritis, myalgias), cutaneous signs (Raynaud's phenomenon, red finger syndrome, purpura, urticaria, vasculitis), neurologic signs (neuropathy), and sicca syndrome. Criteria of the American College of Rheumatology were applied to identify potential cases of different types of connective tissue diseases.

Viral markers. HIV-RNA was measured by quantitative polymerase chain reaction (PCR) using the Quantiplex HIV 3.0 kit (Bayer Diagnostics, Puteaux, France) according to manfacturer's recommendations. Serologic status was determined using a 3rd-generation immunoassay Ortho HCV 3.0 ELISA Test System (Ortho Clinical Diagnostics, Raritan, NJ, USA) completed by a second 3rd-generation immunoassay test if positive with Monalisa anti-VHC Plus, Version 2 (Biorad, Marne la Coquette, France), as recommended by the manufacturer. A patient was defined positive when the 2 tests were positive. HCV genome was detected by PCR using a Cobas Amplicor VHC 2.0 kit (Roche Diagnostics, Meylan, France). Tests for hepatitis B virus used commercial immunoassays (Dade Behring, Paris La Défense, France).

Autoantibodies. Antinuclear antibody (ANA) detection was performed by indirect immunofluorescence on HEp-2 cells (Manarini, Anthony, France). Following the manufacturer's instructions, a titer > 1/40 was observed in 2.5% of 200 healthy individuals and in 97.5% of patients with lupus erythematosus. Their positivity was defined as 1/100 in our study. Anti-DNA antibodies were detected by ELISA (BMD, Marne la Coquette, France). Antiextractable nuclear antigen antibodies were tested by ELISA (Bioadvance, Emerainville, France) (soluble nuclear antigens tested: nRNP/Sm, Sm, SSA, SSB, Scl-70, JO-1). Anti-smooth muscle cell was detected by indirect immunofluorescence (Biorad) as well as by antimitochondrial test (Gill, Bois-d'Arcy, France). A titer of 1/20 was noted in 1% of healthy controls. Anticardiolipin (aCL) and antiphospholipid antibodies were detected by ELISA (Biorad). According to the manufacturer, among samples from 94 healthy blood donors, the cutoff values for autoantibodies of the IgG and IgM isotypes were defined at 23 and 11 units, respectively. This value was defined as the mean antibody level plus 2 standard deviations, for each isotype. Three to five percent of healthy controls have aCL > 23 units for IgG isotype or 11 units for IgM isotype. ANCA were screened by indirect immunofluorescence (Manarini) and identified by ELISA (Biorad). According to the manufacturer, 1% of healthy controls have positive ANCA > 1/20. RF were detected using an immunonephelometry test (Dade Behring); all samples > 11 IU/ml were also analyzed with the Waaler-rose reference (Polyartitre, Fumouze, Levallois-Perret, France). A positive RF was retained in case of Waaler-rose value > 12 IU/ml and as observed in 3% to 5% of healthy controls.

Complement. CH50 classical pathway: hemolytic assay, results expressed as percentage of a pool of normal human sera. Fractions: immunonephelometry (Dade Behring).

Cryoglobulinemia. Blood was collected into a warm syringe and stored at 37°C until clotted. Serum was separated by centrifugation at 37°C and stored at 4°C for one week and controlled every day. The reversibility of the cryoprecipitation was always tested by rewarming the aliquot of precipitated serum to 37°C. Cryoprecipitate was then washed, purified, and dissolved in saline buffer. Cryoglobulinemia was characterized by immunofixation on Hydrasys-Sebia (Protocole Sebia, Issy les Moulineaux, France) using antisera to whole human serum and antisera monospecific to the light and heavy chain isotypes of human immunoglobulins. According to the manufacturer, cryoglobulinemia was detected in 5% of healthy controls, with a level always < 10 mg/l.

Lymphocyte count. Lymphocyte B, T-CD4+, and T-CD8+ counts were determined by Multitest CD3/CD4/CD45/CD8 (Becton-Dickinson, San Diego, CA, USA) with absolute number of cells (Trucount tubes, Becton-Dickinson).

Statistical analysis. Quantitative data were expressed as the mean ± standard deviation or median. Analysis was performed using the chi-square or Fisher test for qualitative variables. Student t test was used for quantitative variables when distribution was normal and variances equal in the 2 groups. When these conditions were not fulfilled, a Mann-Whitney test was used. Significance was assessed at $p = 0.05$. All variables associated with the presence of cryoglobulinemia with p value < 0.25 in univariate analysis were retained as explanatory variables in the multivariate regression. A stepwise logistic regression model was used to estimate the odds ratios. All analyses were performed with STATA software.

RESULTS

Study population. Ninety-seven patients (74 men) of median age 38 years (range 20–64) were studied. They had a history of HIV infection of median 9.8 years (range 5–14.6): 30% were classified in stage A, 35% in stage B, and 35% in stage C of the US Centers for Disease Control classification[13]. HIV transmission categories were intravenous drug users 54%, men who have sex with men 25%, heterosexuals 7%, blood recipients 4%, and unknown 9%. Nine percent of patients had not been treated for HIV infection, 16% received dual-nucleoside analog combination, and 72% HAART. A positive serology for HCV was detected in 62 (64%) patients. HCV-RNA was detected by PCR in 31 of 36 (86%) patients tested and 9.8% of patients carried HBs antigen. Median T-CD4+ lymphocyte count was 333/mm^3 (range 1–684) and HIV-RNA 1662 copies/ml (range 50–1,193,670). The prevalence of cryoglobulinemia and serological markers of autoimmunity for all patients are summarized in Table 1.

Prevalence of cryoglobulinemia and serological markers of autoimmunity in patients with HIV only (n = 35). We detected 6/35 (17%) patients with cryoglobulinemia (type 1 n = 0, type 2 n = 2, type 3 n = 1, undetermined n = 3) (Table 1). RF was present in 19%, ANA > 1/100 in 21%, aCL in 51%, and ANCA > 1/20 in 17% (most of them type C by ELISA). The prevalence of cryoglobulinemia and autoantibodies according to immunovirological status and therapeutic conditions showed a trend for a higher level of cryoglobulinemia and aCL in patients having CD4 lymphocyte counts > 350/mm^3 than in others (25% vs 11%, p = 0.26, and 63% vs 42%, p = 0.23, respectively) (Table 2). We observed no association of HIV-RNA plasma concentration and prevalence of immunologic disturbances. Moreover, we

Table 1. Clinical and immunological characteristics of 97 HIV infected patients with and without HCV coinfection.

Characteristics	HIV Infected Patients, n = 97	HIV + HCV–, n = 35	HIV + HCV +, n = 62	p**
Age, yrs	40	42	39	NS
Male, %	74	89	69	0.03
Intravenous drug users, %	54	3	82	< 0.001
T-CD3– lymphocytes, /mm^3*	279	265	302	NS
T-CD3+ lymphocytes, /mm^3*	1230	1385	1136	NS
T-CD4+ lymphocytes, /mm^3*	333	335	333	NS
T-CD8+ lymphocytes, /mm^3*	763	951	664	0.2
HIV-RNA, copies/ml*	1662	1662	2501	NS
Platelets < 100,000/mm^3, %	13	14	13	NS
TC < 70%, %	25	6	28	0.02
C4 < 0.2 g/l, %	55	34	67	0.004
IgG > 12.8 g/l, %	79	78	80	NS
IgA > 3.4 g/l, %	31	44	24	0.06
IgM > 1.9 g/l, %	40	31	44	0.22
Cryoglobulinemia, %	33	17	42	0.01
Level, mg/l*	22.3	11.9	28.4	NS
Rheumatoid factor, %	23	19	25	NS
ANA ≥ 1/100, %	31	21	29	NS
Anticardiolipin, %	47	51	45	NS
ANCA ≥ 1/20, %	16	17	16	NS
Clinical signs, %	31	32	28	0.07

* Median values. ** Difference between HIV+ HCV– patients and HIV+ HCV+ patients. TC: total complement, ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, NS: not significant.

Table 2. Prevalence of cryoglobulinemia and serological markers of autoimmunity in 35 HIV infected patients according to immunovirological and therapeutical conditions.

	CD4+ count, /mm^3			HIV-RNA, copies/ml			HAART		
	< 350, n = 19	≥ 350, n = 16	p	< 500, n = 15	≥ 500, n = 19	p	Yes, n = 24	No, n = 11	p
ANA > 1/100, %	47	60	0.46	53	56	0.90	58	40	0.33
Anticardiolipin > 15 IU/ml, %	42	63	0.23	47	58	0.52	38	82	0.02
Positive RF, %	27	12	0.32	20	13	0.62	23	10	0.36
C4 < 0.2 g/l, %	39	28	0.54	36	35	0.98	71	55	0.34
ANCA > 1/20, %	16	19	0.82	7	26	0.20	13	27	0.28
Positive cryoglobulinemia, %	11	25	0.26	13	21	0.67	13	27	0.28

ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, CD4+: CD4+ T lymphocytes, HIV-RNA: plasma HIV-RNA, HAART: highly active antiretroviral therapy.

found a significantly higher prevalence of aCL and a trend to a higher prevalence of ANCA and cryoglobulinemia in patients not treated with HAART compared to those receiving HAART (82% vs 38%, p = 0.02; 27% vs 13%, p = 0.28, respectively). Finally, we found no difference in the prevalence of immune disturbances according to sex (data not shown).

Comparison between patients with HIV only and HCV coinfected patients. The analysis showed that coinfected patients were less frequently male (69% vs 89%; p = 0.03) and more often intravenous drug users (82% vs 3%; p < 0.001) (Table 1). CD4+ T lymphocyte count and HIV-RNA were not different between the 2 groups. Cryoglobulinemia was found in 17% of HIV+ HCV– patients and in 42% of HIV+ HCV+ patients (p = 0.01): this proportion increased to 52% when analysis was restricted to patients with positive detection of plasma HCV-RNA. Total complement and its C4 fraction were more frequently diminished in coinfected patients, although 34% of HCV-free patients had a decrease of C4 fraction. We found no other difference in serological markers of autoimmunity between coinfected and HCV-free patients.

Comparison between cryoglobulin positive and negative patients. In univariate analysis, cryoglobulin positive patients were more frequently coinfected with HCV (81% vs 55%; p = 0.01), and more frequently had high plasma

levels of IgM (67 vs 25; p = 0.001) and low plasma levels of complement and C4 fraction (72 vs 47%; p = 0.02) (Table 3). HIV-RNA was higher in cryoglobulin positive than in cryoglobulin negative patients, with a difference close to significance (4142 vs 560 copies/ml; p = 0.06). Finally, comparing cryoglobulin positive and negative patients we found no differences in the immunological status, platelet count, or percentage of patients treated with HAART. By multivariate analysis, 2 variables were significantly associated with positive cryoglobulinemia: a positive serology for HCV and a high titer of IgM.

Comparison between patients positive and negative for aCL. Patients with aCL antibodies more frequently had IgA level > 3.4 g/l than patients without aCL (18% vs 9%; p = 0.04) and they had a tendency to have higher HIV-RNA (2680 vs 456 copies/ml; p = 0.09). There was no difference comparing HCV status, T-CD4+ lymphocyte count, and complement level (data not shown).

Comparison between ANCA positive and negative patients and ANA positive and negative patients. We found no difference between these groups of patients according to the different variables (HCV status, T-CD4+ lymphocyte count, HIV-RNA, plasma level of immunoglobulin, C4 complement; data not shown).

Clinical signs. Thirty patients complained of at least one clinical sign possibly related to autoimmune disturbances: 18 with sensory or motor neuropathy, 9 arthralgias, 8 myalgias, 3 cutaneous vasculitis, 2 urticaria, one each of sicca syndrome or arthritis. When neuropathy and myalgia possibly linked to the antiretroviral therapy were excluded, only 16 patients expressed clinical signs possibly due to autoimmune disease. One patient with polyarthritis had a positive RF and was the only one who could be classified with a chronic connective tissue disease.

There was no difference of frequency of clinical signs between the groups of HCV coinfected and HCV-free patients or in cryoglobulin positive and negative patients.

Among the 32 cryoglobulin positive patients, only 3 (one HCV coinfected) had moderate clinical symptoms (cutaneous vasculitis, polyarthritis, polyneuropathy in a patient without antiretroviral therapy) that were certainly related to cryoglobulinemia. Nine other patients had clinical signs possibly related to cryoglobulinemia, but they had also had several courses of HAART, and we could not characterize iatrogenic side effects and the independent role of cryoglobulinemia when the clinical signs were poorly specific (i.e., neuropathy, myalgias). We found no differences in the frequency of clinical signs between HCV coinfected patients and HCV-free patients, or between cryoglobulin positive and negative patients (Tables 1 and 2), even when we excluded patients with nonspecific symptoms (data not shown).

Among cryoglobulin negative patients, 2 expressed cutaneous vasculitis, one urticaria, and one a clinical sicca syndrome, but they had no immune biological marker of systemic inflammatory disease. The others expressed polyneuropathy and most of them were treated for a long period with antiretrovirals.

DISCUSSION

This study showed a high prevalence of humoral immunologic abnormalities in a group of patients infected with HIV. One important finding is that cryoglobulinemia was present in 17% of patients with HIV who were also HCV-free, suggesting that HIV itself could have a direct influence on the cryoprecipitate as described for HCV[14]. Recently, Dimitrakopoulos, *et al* identified antibodies to HIV and HIV-1 RNA sequences in 22 of 23 cryoprecipitates tested, suggesting that HIV could result in a cryoprecipitate[15]. One other indirect argument for the independent role of HIV in the cryoprecipitate is that we found a higher median level of HIV-RNA in cryoglobulin positive patients than in those who were cryoglobulin negative. These results are important in the era of HAART and chronic HIV infection, as Kordossis, *et al* have recently shown that mixed cryoglobu-

Table 3. Comparison of 97 HIV infected patients according to the presence or absence of cryoglobulinemia.

Characteristics	Cryoglobulin+, n = 32	Cryoglobulin–, n = 65	Univariate Analysis p	Logistic Regression OR	95% CI
HCV infection, %	81	55	0.01	6.64	1.87–23.57
CD4+, mm^3, median	333	333	0.5	—	—
HIV-RNA, copies/ml, median	4142	560	0.06	—	—
Platelets < 100,000/mm^3, %	19	11	0.2	—	—
IgG > 12.8 g/l, %	87	75	0.3	—	—
IgA > 3.4 g/l, %	23	36	0.3	—	—
IgM > 1.9 g/l, %	67	25	0.001	6.16	2.15–17.67
TC < 70%, %	39	10	0.002	—	—
C4 < 0.2 g/l	72	47	0.02	—	—
HAART	69	77	0.3	—	—
Clinical signs	31	31	0.96	—	—

TC: total complement, CD4+: CD4+ T lymphocytes, HAART: highly active antiretroviral therapy.

linemia was associated with increased risk for death or neoplasia in HIV-1 infection, and because the relationship between cryoglobulinemia and non-Hodgkin's lymphoma is controversial[16,17].

The high prevalence of HCV coinfected patients is explained by the high prevalence of intravenous drug users followed in our unit. The overall prevalence of cryoglobulinemia type II and III was 33%, and it was significantly higher in coinfected patients than in HCV-free patients (42% vs 17%; p = 0.01). Cohen, *et al* found differences of cryoglobulinemia prevalence between coinfected and HCV-free patients (47% vs 27%), although this difference did not reach significant value[18]. The association between HCV and cryoglobulinemia is now well established, explaining the high prevalence in our coinfected patients. Our results are in agreement with those of Cohen, *et al*, but much lower than those of Cacoub, *et al*, who found a prevalence of cryoglobulinemia of 81% in a study of 74 HIV/HCV coinfected patients and 51% in HCV infected patients[19].

The clinical expression of cryoglobulinemia in our study was limited and could be attributed to the low cryoglobulin concentration found in our population. Morover, our study is cross-sectional and could not take into account previous manifestations that disappeared through the influence of HIV or HCV antiviral drugs. We noted that cryoglobulin positive patients more frequently had an increase of IgM and a decrease of total complement and its C4 fraction. This finding reflects the high stimulation of B cells and the constitution of immune complex in patients who are cryoglobulin positive. Dimitrakopoulos, *et al* have shown that cryoglobulin positive patients had plasma levels of total immunoglobulin higher than cryoglobulin negative patients[15]; however, the elevation of IgM in particular reported in this study has not been previously observed.

We found no significant relationship in multivariate analysis between immunological status, HAART use, and cryoglobulinemia in the whole group, as suggested by some observations that cryoglobulins were no longer detectable in a patient with HCV associated type II mixed cryoglobulinemia after HIV-1 infection[20]. Nevertheless, in the group of patients with HIV only, we found a trend to a higher percentage of cryoglobulinemia and aCL in patients with CD4+ lymphocytes > 350/mm^3 and not treated with HAART, and the frequency of cryoglobulinemia was lower in HAART treated than in HAART-free patients, although this was not significant in the whole group of patients. These results suggest that immunologic and therapeutic conditions could have some effect on humoral immunologic indicators. Thus comparison of the prevalence of humoral immune disturbances in HIV infected patients is needed in larger studies to assess the role of HAART on these indicators.

Systematic research for autoantibodies in our population of HIV infected patients showed a high prevalence of ANA, aCL, ANCA, anti-smooth muscle cell, and RF. These results are in agreement with some studies describing these humoral immune disturbances in HIV infected patients and HCV infected patients[15,21,22], but not all[23]. Moreover we found no difference in the prevalence of these findings between HCV coinfected patients and HCV-free patients, suggesting that HIV itself could lead to an overproduction of autoantibodies through a polyclonal activation of B lymphocytes in frequency similar to HCV. The pathogenic role of these immune abnormalities remains uncertain because none of our patients except one (with rheumatoid arthritis) was affected by a connective tissue disease according to American Rheumatism Association criteria. We identified, in particular, a high prevalence of anticardiolipin antibodies, without associated thrombocytopenia, venous or arterial thrombotic events, as described with other infections. Nevertheless, the chronic positivity of antibodies such as ANCA could lead to clinical patterns of necrotizing vasculitis, as described in HIV infected patients[24,25]. A longterm cohort study is needed to evaluate the clinical prognostic role of these humoral immune abnormalities in patients chronically infected with HIV.

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