Serum non-organ specific autoantibodies in human immunodeficiency virus 1 infection

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Abstract

Serum samples from 66 seropositive subjects (56 with a history of intravenous drug abuse), including asymptomatic carriers and patients with persistent generalised lymphadenopathy (PGL), AIDS related complex (ARC), and AIDS, were tested by indirect immunofluorescence on rat tissue sections and HEP-2 cells for the presence of antibodies to nuclei, smooth muscle, intermediate filaments (anti-IMF) and microfilaments (anti-MF). Counterimmunoelectrophoresis was also used to detect antibodies to extractable nuclear antigens. Smooth muscle antibodies with the V pattern or antinuclear antibodies, mainly of the speckled type, or anti-IMF, occurred in 35 cases, being widely distributed in all groups. Such an autoantibody response resembles the "viral" autoimmunity described in various infectious diseases and in particular that of non-A, non-B post-transfusion hepatitis.

Autoantibodies may be of some prognostic relevance, as the prevalence of smooth muscle antibodies V increased as the disease progressed (asymptomatic carriers 20%, those with PGL 29%, those with ARC 47%, and those with AIDS 63%). In the PGL group autoantibody positivity correlated with the presence of skin anergy. The fact that autoantibodies were more frequently detected in patients with circulating immune complexes suggests that these can contain autoantibodies and the corresponding autoantigens.

Contrasting immune features coexist in human immunodeficiency virus (HIV) type 1 infection. On the one hand, a progressive decrease in numbers of CD4 lymphocytes and an attendant loss of function occurs: this leads to a variety of opportunistic infections and, possibly, tumours.^{1,2} On the other hand, hypergammaglobulinemia due to B cell polyclonal activation³ and serological,⁴⁻¹⁰ as well as clinical,^{11,12} manifestations of autoimmunity develop. Little is known about non-organ specific serum autoantibodies in HIV infection: antinuclear antibodies have been reported as absent,¹³ but data on other autoantibodies such as those directed to smooth muscle and cytoskeleton components are scarce.

To test whether HIV associated hypergammaglobulinemia can be at least in part due to the development of autoimmune phenomena, we studied patients with the full clinical spectrum of HIV pathology for the presence of a panel of non-organ specific autoantibodies. We also wanted to determine the relevance of CD4 lymphocyte function in the genesis of autoantibodies.

Methods

Sixty six subjects positive for serum antibodies to HIV 1 by enzyme linked immunosorbent assay (ELISA) or Western blot assay, or both, were studied. The male:female ratio was 2.9 (49:17) and the median age was 24 years (range 3-48). They included 56 (85%) intravenous drug abusers, nine (14%) homosexual men, and one child infected in utero. They were categorised as follows: 15 asymptomatic carriers (group II, according to the Centers for Disease Control classification system),¹⁴ 28 patients with persistent generalised lymphadenopathy (PGL) and no constitutional symptoms (group III), 15 with AIDS related complex (ARC) (group IV-A), and eight with overt AIDS (group IV-B, C, and D). The control group included 20 intravenous drug abusers (male:female ratio 3, median age 25 years) negative for HIV antibodies by both ELISA and Western blot assay. In all seropositive subjects the following variables were evaluated: number of circulating CD4 lymphocytes and CD4:CD8 ratio, platelet count, serum concentration of total immunoglobulins and their IgG, IgA, and IgM fractions, presence of circulating immune complexes (detected by a Clq binding enzyme immunoassay) and skin anergy (no response to any of the following antigens: tetanus, diphtheria, tuberculin, *Candida*, *Proteus*, trichophyton and streptodornase). Sera were stored at -20°C until use.

Indirect immunofluorescence was performed according to standard procedures¹⁵ on cryostat sections of rat tissues (kidney and liver) and cultured HEP-2 cells (Kallestad, Austin, Texas, USA). The former was used to detect smooth muscle antibodies and antinuclear antibodies, the latter antinuclear antibodies, antibodies to intermediate filaments (anti-IMF), and microfilaments (anti-MF). Sera were screened at a 1 in 40 dilution. Smooth muscle antibodies and antinuclear antibodies patterns were defined on kidney sections and HEP-2 cells, respectively, according to accepted criteria.^{16,17}

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Figure 1 Immunofluorescence on rat kidney section. Serum from a patient with AIDS. Smooth muscle antibodies with the V pattern: isolated positivity of smooth muscle cells of vessel walls.

Figure 2 Immunofluorescence of HEp-2 cells. Serum from a patient with ARC. Antinuclear antibodies with speckled pattern.

Figure 3 Immunofluorescence on HEp-2 cells. Serum from a patient with AIDS. Anti-IMF.

Positive reactions detected in the subjects with HIV antibodies were titrated by serial dilutions to the end point using a fluorescein isothiocyanate, conjugated sheep anti-human F(ab)₂ (Wellcome Diagnostics, Dartford, England), and the immunoglobulin class of the autoantibodies was assessed by the use of monospecific fluorescein isothiocyanate conjugated rabbit anti-human IgG, IgA, and IgM (Boehringerwerke, Marburg, West Germany).

Antibodies to extractable antigens, nuclear (anti-ENA), and non-nuclear, were searched for as previously described.¹⁸ A saline extract of lyophilised rabbit thymus acetone powder (Pel-Freez Biologicals, Rogers, Arkansas, USA) was used as source of the antigens.

The following tests were applied according to their own indications: the χ^2 test with or without Yates' correction, the trend χ^2 test, Fisher's exact test and the Wilcoxon two-tailed test.

Results

As expected, patients with AIDS had a median number of CD4 lymphocytes ($170 \times 10^6/l$) and a median CD4:CD8 ratio (0.16) lower than that of asymptomatic carriers (569 and 1.19, respectively), PGL (747, 1.02), and ARC patients (643, 0.79) ($p < 0.05$ to < 0.001 , Wilcoxon). Similarly, patients with AIDS exhibited skin anergy at a higher prevalence (100%) than each of the remaining groups (asymptomatic carriers 0%, PGL 25%, ARC 40%) ($p < 0.02$ to < 0.0001 , Fisher's exact test). In particular, the occurrence of skin anergy increased as the disease progressed ($p < 0.004$, χ^2). No significant difference was recorded among asymptomatic carriers and patients with PGL, ARC, and AIDS with respect to sex, age, and any of the other laboratory variables considered.

The autoantibody state is reported in table 1. Smooth muscle antibodies with the V pattern (isolated positivity of smooth muscle cells of vessel walls), antinuclear antibodies mainly of the speckled type, and anti-IMF occurred with similar overall prevalences in the seropositive population (35%, 27%, and 29%, respectively) as well as in seronegative controls (25%, 15%, and 25%, respectively). Smooth muscle antibodies with the G or T pattern—positivity of vessel walls plus glomerular (G) or peritubular structures (T), homogeneous antinuclear antibodies, anti-MF, and antibodies to extractable antigens were consistently absent. In particular, the smooth muscle antibodies V prevalence showed a significant trend to increase with the progression of the disease (asymptomatic carriers 20%, PGL 29%, ARC 47%, AIDS 63%: $p < 0.05$). Smooth muscle antibodies and anti-IMF occurred independently from each other in both seropositive and control cases. Thirty five of the 66 (53%) seropositive subjects were positive for at least one autoantibody, and 19 of them exhibited the co-existence of two or more distinct specificities. Autoantibodies occurred with similar

Table 1 Serum smooth muscle antibodies, antinuclear antibodies, and antibodies against intermediate filaments, microfilaments, and extractable antigens in HIV positive study population and controls (HIV negative intravenous drug abuse)

	Asymptomatic carriers (n = 15)	Patients with PGL (n = 28)	Patients with ARC (n = 15)	Patients with AIDS (n = 8)	Total HIV (n = 66)	Controls (n = 20)
<i>Immunofluorescence on tissue sections:</i>						
Smooth muscle antibodies						
V pattern	3 (20%)	8 (29%)	7 (47%)	5 (63%)*	23 (35%)	5 (25%)
G-T pattern	0	0	0	0	0	0
antinuclear antibodies	0	0	1 (7%)	0	1 (2%)	2 (10%)
<i>Immunofluorescence on HEp-2 cells</i>						
Antinuclear antibodies						
speckled	4 (27%)	7 (25%)	3 (20%)	1 (12%)	15 (23%)	3 (15%)
nucleolar	1 (6%)	1 (4%)	1 (7%)	0	3 (4%)	0
homogeneous	0	0	0	0	0	0
all patterns	5 (33%)	8 (29%)	4 (27%)	1 (12%)	18 (27%)	3 (15%)
Anti-IMF	3 (20%)	7 (25%)	6 (40%)	3 (37%)	19 (29%)	5 (25%)
Anti-MF	0	0	0	0	0	0
CIE						
Antibodies to extractable antigens	0	0	0	0	0	0

*: AsC→PGL→ARC→AIDS $p < 0.05$ (χ^2 test).

Immunofluorescence: 1 in 40 serum dilution. Counterimmunoelectrophoresis: undiluted serum).

Table 2 Titre and class of serum smooth muscle antibodies, antinuclear antibodies, and antibodies to intermediate filaments (detected in HIV positive subjects by indirect immunofluorescence on rat kidney sections and HEp-2 cells)

	n	Titre				Ig class						
		1/40	1/80	1/160	$\geq 1/320$	G	A	M	G + A	G + M	A + M	G + A + M
Smooth muscle antibodies	23	15	5	1	2	9	2	—	7	1	—	4
Antinuclear antibodies	18	11	2	4	1	11	—	2	—	2	1	2
anti-IMF	19	8	6	4	1	4	—	7	—	6	1	1

prevalences in seropositive subjects with and without a history of intravenous drug abuse (31/56, 55%, and 4/10, 40%, respectively). The number of patients with autoantibodies was 53% (eight of 15) in the asymptomatic carriers, 46% (13 of 28) in those with PGL, 53% (eight of 15) in those with ARC, 75% (six of eight) in those with AIDS and 55% (11 of 20) in the control group. The number of antinuclear antibodies positive cases considerably increased when HEp-2 cells instead of tissue sections were used (21 compared with three).

Titre and class of autoantibodies detected in seropositive subjects are reported in table 2. Most positive reactions, (47 of 60, 78%) were at a low titre (1/40 or 1/80). No significant variation of the titre was observed among the various clinical groups. The commonest immunoglobulin class was IgG for both smooth muscle antibodies (21 of 23, 91%) and antinuclear antibodies (15 of 18, 83%), but

IgM for anti-IMF (14 of 19, 74%). In 25 of the 60 (42%) positive reactions the auto-antibody belonged to at least two distinct classes.

Table 3 shows the comparison of sex, age, and laboratory variables between seropositive patients with and without autoantibodies. Circulating immune complexes were more frequently detected in the autoantibody positive (20 of 35, 57%) than negative cases (eight of 31, 26%) ($p < 0.02$, χ^2 test). In the PGL group, besides the association with serum immune complexes ($p < 0.01$), the occurrence of autoantibodies correlated with the presence of skin anergy ($p < 0.005$).

Discussion

This study provides evidence that serum non-organ specific autoantibodies occur in about 50% of HIV 1 positive patients, most of them with a history of intravenous drug abuse, and

Table 3 Comparison between presence of serum autoantibodies (smooth muscle or antinuclear, or intermediate filaments antibodies) and sex, age, and laboratory variables in HIV positive subjects

	Asymptomatic carriers		Patients with PGL		Patients with ARC		Patients with AIDS	
	abs + (8)	abs - (7)	abs + (13)	abs - (15)	abs + (8)	abs - (7)	abs + (6)	abs - (2)
Males	5 (62%)	5 (71%)	9 (69%)	14 (93%)	5 (62%)	6 (86%)	3 (50%)	2 (100%)
Age (years) (median)	22	20	23	27	26	27	26	44
CD4 cells ($10^6/l$) (median)	451	603	759	590	584	702	246	76
CD4:CD8 ratio (median)	0.82	1.41	1.04	0.72	0.71	1.13	0.30	0.08
Platelets ($10^9/l$) ($\times 1000$) (median)	89	80	150	150	115	150	80	115
Gammaglobulin (g/dl) (median)	1.69	1.65	2.25	1.76	1.83	1.51	2.08	1.92
IgG (mg/dl) (median)	1985	2025	2505	1741	2063	1686	2331	1525
IgA (mg/dl) (median)	161	157	127	180	171	199	255	968
IgM (mg/dl) (median)	320	333	246	300	311	338	206	136
Patients with circulating immune complexes	4 (50%)	1 (14%)	11 (85%)*	5 (33%)	4 (50%)	0	1 (17%)	2 (100%)
Patients with skin allergy	0	0	7 (54%)*	0	3 (37%)	3 (43%)	6 (100%)	2 (100%)

*abs + vs abs - $p < 0.01$ (Fisher's exact test)

†abs + vs abs - $p < 0.005$ (Fisher's exact test).

that they are widely distributed across the clinical spectrum of HIV infection, from asymptomatic carriers to patients with overt AIDS. In a previous study smooth muscle antibodies and antinuclear antibodies were not detected by immunofluorescence on mouse liver sections in a large series of homosexual men with ARC and AIDS.¹³ Such a discrepancy may be due to technical reasons, because mouse liver is not the substrate of choice for the detection of smooth muscle antibodies¹⁶ and is less sensitive than HEp-2 cells for the demonstration of antinuclear antibodies.^{19,20} Selection of seropositive subjects belonging to different risk groups could also be relevant. In our small series no significant difference in autoantibody prevalence occurred between intravenous drug abusers and homosexual men. Further studies on larger series, however, are needed to elucidate this point.

The spectrum of autoimmune reactivities occurring in HIV infection is wide and includes smooth muscle antibodies with the V pattern, speckled antinuclear antibodies, and anti-IMF. The finding of a similar autoimmune state in seronegative drug abusers suggests that these autoantibodies, although compatible with HIV infection, are not specific for it. Drug abuse could itself account for their appearance, presumably because this facilitates the development of infectious diseases. In fact, the above antibody pattern resembles that described in several viral infections characterised by smooth muscle antibodies V²¹ and IgM anti-IMF detected on human fibroblasts.²²⁻²⁶ This "viral" autoimmunity seems to be mainly related to vimentin antibodies, which could account for both smooth muscle antibodies V²¹ and anti-IMF.²⁷ The fact that in our series the two antibodies did not occur together and belonged to different immunoglobulin classes would favour an effect of anti-IMF other than anti-vimentin. It must be borne in mind that the use of epithelial cell lines (HEp-2 cells) as immunofluorescence substrate does not differentiate between anti-IMF with anti-vimentin and anti-cytokeratin specificity. In fact, both cytoskeletal components are well expressed in epithelial cultures,²⁸ as proved by the use of specific monoclonal antibodies. The hypothesis has even been made that both structures share common epitopes.²⁹ Indirect evidence has already been produced on the occurrence of anti-cytokeratin anti-IMF in a viral disease such as hepatitis C virus (HCV) related post-transfusion hepatitis.³⁰ It is worth mentioning that both HIV and HCV virus infections are common in the same risk groups (drug addicts, homosexual men). The recent availability of a test for the detection of HCV antibodies³¹ should clarify this point.

"Viral" autoimmunity in seropositive subjects is clearly different from that found in connective tissue disease (absence of high titre antinuclear antibodies and anti-ENA -19) and autoimmune chronic liver disease (lack of homogeneous antinuclear antibodies -20 - and anti-actin antibodies, identified as smooth muscle antibodies with the T or G pattern

-16-, anti MF -25-, and antibodies against the XR extractable antigen -18).

The presence of autoantibodies even in patients with overt AIDS, where a profound impairment of T cell function occurs, suggests that their expression might be independent of T cells. In particular, autoantibodies might result from polyclonal B lymphocyte activation, a well known immune abnormality induced in seropositive subjects by HIV³² or Epstein-Barr virus superinfection.³³

In view of our findings, it is worth remembering that Epstein-Barr virus activated human B cells have been shown to secrete anti-IMF³⁴ with anti-cytokeratin specificity.³⁵ The fact that serum immunoglobulin concentrations were similarly raised in patients with and without autoantibodies suggests that their contribution to hypergammaglobulinemia is negligible and that B cell activation may well occur in HIV infection without autoantibody production. Other mechanisms may, theoretically, be involved, such as a molecular mimicry between viral and cellular constituents.³⁶

Serum autoantibodies may be of some prognostic relevance, on clinical grounds. In fact, the presence of smooth muscle antibodies points to an advanced rather than an early stage of the HIV induced disease and, in patients with PGL, autoantibody positivity is significantly associated with a profound impairment of the delayed type hypersensitivity reactions. Finally, serum autoantibodies occur more frequently when circulating immune complexes are found. Whether serum immune complexes in seropositive subjects contain not only HIV antibodies, as already reported,³⁷ but also the aforementioned autoantibodies and the corresponding autoantigens, remains to be clarified.

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