

Immunodeficiency and other clinical immunology

Immunologic aspects of hyperimmunoglobulinemia E-like syndrome in patients with AIDS

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In this study we describe a series of nine patients affected by acquired immunodeficiency syndrome (AIDS) or AIDS-related complex who had hypereosinophilia and hyperimmunoglobulinemia E (hyper-IgE) with chronic dermatitis and recurrent staphylococcal infections. These patients had features similar to those present in hyper-IgE syndrome, a primary immunodeficiency disease. In addition, immunologic characterization of these patients with human immunodeficiency virus (HIV) infection, compared with 51 HIV-positive patients without hyper-IgE, both atopic and nonatopic, and three patients affected by the primary hyper-IgE syndrome, also revealed an increase in IgA and a severe decrease in B and CD4+ lymphocytes. Spontaneous in vitro synthesis of IgE by peripheral blood mononuclear cells was confirmed in both hyper-IgE conditions, together with increased levels of circulating eosinophil cationic protein. Serum-soluble CD23, usually increased in atopic conditions and hyper-IgE, was similar to that of normal control subjects in the HIV-positive patients with hyper-IgE. On the basis of our findings, we conclude that a hyper-IgE-like syndrome represents a distinct aspect of the clinical manifestations associated with HIV infection and that the immunologic mechanisms in this condition seem to differ from those known in primary hyper-IgE syndrome, because CD4+ T_{H2} type cells, which are currently believed to have a role in IgE production, are severely depleted in HIV-positive patients. (J ALLERGY CLIN IMMUNOL 1995;95:995-1003.)

Key words: AIDS, hyper-IgE, eosinophils, CD4, eosinophil cationic protein, soluble CD23

Hypereosinophilia accompanied by very high levels of IgE are observed in the hyperimmunoglobulinemia E syndrome (HIES), a primary immune deficiency diagnosed in childhood and clinically man-

Abbreviations used

AIDS:	Acquired immunodeficiency syndrome
ARC:	AIDS-related complex
CDC:	Centers for Disease Control
ECP:	Eosinophil cationic protein
HIES:	Hyperimmunoglobulinemia E syndrome
HIV:	Human immunodeficiency virus
hyper-IgE:	Hyperimmunoglobulinemia E
IL:	Interleukin
sCD23:	Soluble CD23

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ifested by eczematous lesions, cutaneous and visceral abscesses caused by *Staphylococcus aureus*, mucocutaneous candidiasis, recurrent severe viral infections, and frequent spontaneous bone fractures.¹

TABLE I. Characteristics of HIV-positive patients with hyper-IgE

Patient No.	Sex	Age (yr)	Diagnosis	Opportunistic and other infections	WBC	Lymphocytes (L/ μ l)	CD4 (%)	CD4 (cell/ μ l)	Eosinophils (%)	Eosinophils (cell/ μ l)
1	M	30	AIDS	EC, PCP	3300	462	1	4.6	16	528
2	M	38	AIDS	EC, PCP	6100	1281	0.3	4	18	1098
3	M	54	AIDS	EC, PCP, CMV	3300	1155	3	34	40	1320
4	F	38	AIDS	EC, CMV	3800	684	1.4	9.5	30	1200
5	M	40	ARC	Oral thrush	2978	1221	15	183	20	740
6	M	30	ARC	Oral thrush	2941	500	4	20	12	353
7	M	60	AIDS	EC, PCP, MS	2000	580	10	58	14	280
8	M	34	AIDS	EC, PCP, TOX	2520	605	1.6	9.5	20	500
9	M	32	AIDS	EC, PCP	3000	930	2	18	18	540

WBC, White blood cell count; EC, esophageal candidiasis; PCP, *P. carinii* pneumonia; CMV, cytomegalovirus retinitis; TOX, toxoplasmosis; MS, mycobacterial sepsis.

Clinical manifestations of atopic allergy, drug reactions, and increased serum levels of IgE have already been described during the course of human immunodeficiency virus (HIV) infection.² The relationship of such findings to the immunologic derangements found in patients with HIV is not entirely clear; however, a correlation between the rise in IgE level and the decline in numbers of CD4+ lymphocytes has been described.^{3,4} The increase of IgE is threefold to fourfold compared with the levels measured in a normal nonatopic population and is also present in patients with HIV who do not have clinical manifestations of allergy. The occurrence of rising IgE levels and the simultaneous reduction of CD4+ cells is not easily reconciled with current knowledge on the regulation of IgE production in atopic allergy.⁵ Indeed, type 2 helper T cells (T_{H2}) producing interleukin (IL)-4 and IL-5, a subset of CD4+ lymphocytes, are increased in allergic patients,^{6,7} and IL-4 represents the essential factor for isotype switching to IgE.⁸ We have observed nine patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) who had hyper eosinophilia with hyperimmunoglobulinemia E (hyper-IgE) (levels were 100 times greater than those of nonatopic control subjects), and chronic dermatitis with recurrent infections resembling those found in patients with primary HIES. In 1988 hyper-IgE in HIV-positive patients was first described by Lin,⁹ who did not investigate the possible immunologic mechanisms of this disorder. However, no other reports have been published since then. Here we report the clinical and immunologic characteristics of these patients and compare these findings with those observed in patients with primary HIES.

METHODS

Patients

In the past 9 years, more than 1300 patients with HIV infection have been followed up in our department, and about 4 years ago, we started investigating the appearance of atopy in the course of the disease. Since then, nine patients who had unusually severe skin symptoms complicated by abscesses, unlike those manifested by HIV-infected patients with common atopy or allergic drug reactions, have been observed.

Seven of these patients were affected by AIDS (classified according to the criteria of the Centers for Disease Control [CDC]¹⁰ as stage IVC1, see Table I), and two were affected by ARC (CDC stage IVC2). They had diffuse severe pruritic dermatitis, lasting for more than 8 months, associated with elevated IgE serum levels and blood hypereosinophilia. Six of the nine patients had recurrent esophageal candidiasis, six had *Pneumocystis carinii* pneumonia, and three had cytomegalovirus retinitis. Oral thrush or cutaneous candidiasis was found in all patients, and four had subcutaneous abscesses caused by *S. aureus*.

Because various parasitic infections may induce eosinophilia, we excluded their presence by means of several tests: gastroduodenal fiberoptic endoscopy with mucosal biopsies; direct examination of stools for 3 consecutive days for parasites and helminths, repeated after laxative administration. Any other infections such as *P. carinii* or toxoplasmosis, reported in Table I, had been treated with complete resolution, at least 18 months before this study, although *Candida* infection was recurrent.

The symptoms were not correlated with drug abuse. To further exclude that the dermatitis was caused by an allergic drug reaction, all prescribed drugs were withdrawn in these patients for at least 2 weeks, without clinical benefit. In three patients a skin biopsy specimen was taken.

Three patients (two women and one man) with primary HIES, diagnosed according to established criteria¹ were also studied for comparison. Twenty-five healthy

nonatopic subjects and a total of 51 HIV-positive patients in CDC stages IV A, C1, and C2, both atopic (22 patients) and nonatopic (29 patients), were also studied for different parameters as controls.

Blood collection

Blood was collected by venipuncture and allowed to clot; after centrifugation, serum was stored in aliquots at -20°C until analysis. For eosinophil count and phenotyping of lymphocyte subpopulations, a blood sample was also anticoagulated with 1.5 mg of ethylenediamine-tetraacetic acid- K_2 per milliliter of blood.

IgE in vitro synthesis

Peripheral blood mononuclear cells were isolated from heparinized peripheral blood by Ficoll/Hypaque (Lymphoprep; Pharmacia, Uppsala, Sweden) density centrifugation, washed three times in phosphate-buffered saline (PBS), and suspended in 10% fetal calf serum-supplemented RPMI 1640 (Gibco, Grand Island, N.Y.). Peripheral blood mononuclear cells at $10^6/\text{ml}$ were cultured in complete medium for 8 days in humidified 5% CO_2 incubator at 37°C . Duplicate cultures of 1 ml each received either the protein synthesis inhibitor cycloheximide (100 $\mu\text{g}/\text{ml}$; Sigma Chemical Co., St. Louis, Mo.) or no addition. Supernatants collected on the eighth day were stored at -20°C until they were examined for IgE content. IgE in cycloheximide-treated cultures was subtracted from spontaneous production to obtain net de novo synthesis. This study was carried out in only four of nine patients with HIV infection and hyper-IgE, because the others had already died at the time this part of the study was performed. Normal subjects and HIV-positive patients without hyper-IgE do not demonstrate IgE synthesis in vitro.

Lymphocyte subpopulations

Aliquots (100 μl) of anticoagulated blood sample were lysed and stained with the appropriate amounts of monoclonal antibodies (20 μl of phycoerythrin or fluorescein isothiocyanate conjugated for 30 minutes in an ice bath). After two washings, the cells were resuspended in PBS and analyzed by flow cytometry after electronic gating on lymphocytes. The following monoclonal antibodies were used: anti-CD3 (Leu4), CD19 (Leu12), CD4 (Leu3a), CD8 (Leu2a), HLA-DR, and CD23 (Leu20); all were purchased from Becton Dickinson Immunocytometry Systems (Mountain View, Calif.). The absolute count of the subpopulations was obtained by extrapolation of their percentage on the number of circulating lymphocytes assessed by standard methods.

IgE levels in serum and culture

IgE levels were measured by the semiautomated fluorimetric method (CAP IgE FEIA; Pharmacia). Culture supernatants were also assessed by this method, because levels of IgE were well within the measuring range (2 to

2000 IU/ml; 1 IU = approximately 2.4 ng). For serum samples above this level, serial twofold dilutions of sera were made. Specific IgE to pollens (ryegrass, *Parietaria* species, mugwort), house dust mites, cat dander, and *Candida albicans* were determined by CAP RAST FEIA (Pharmacia).

Immunoglobulin and subclasses serum levels

Serum levels of IgG, IgA, and IgM were measured by nephelometry with a TDX analyzer (Abbott Diagnostics, Irving, Texas) and expressed as mean (milligrams per deciliter) $\pm$ SEM. IgG subclasses were measured by radial immunodiffusion with specific monoclonal antibodies (Combi RID kit; The Binding Site, Birmingham, U.K.).

Eosinophils and eosinophil cationic protein

The absolute count of peripheral eosinophils was obtained by conventional methods. Serum levels of eosinophil cationic protein (ECP) were assessed by radioimmunoassay (Pharmacia, Uppsala, Sweden) according to the method used by Venge et al.¹¹ with a sensitivity of 2 $\mu\text{g}/\text{L}$. Radioactivity detected was inversely proportional to the amount of ECP. Values were expressed as means $\pm$ SEM.

Soluble CD23 levels

Serum levels of soluble CD23 (sCD23) were quantified by ELISA (Human sCD23 EIA Kit; Birmingham Research Park, Birmingham, U.K.) with a sensitivity of 4.1 $\mu\text{g}/\text{L}$. Results were expressed as means $\pm$ SEM.

Statistical analysis

Student's *t* test and analysis of variance were used to determine significance of mean differences between groups, as appropriate.

RESULTS

The patients we studied had clinical features similar to those found in primary HIES, such as diffuse eczematous lesions, *Candida* infection, *S. aureus* abscesses, and severe viral infections (Table I). Clinical history of atopy preceding HIV infection was present in only one patient, who had had perennial rhinitis since adolescence.

All nine selected patients with AIDS and ARC had hypereosinophilia, with 12% to greater than 40% eosinophils and absolute counts up to 1320/ μl .

Serum levels of IgE were also elevated, ranging from 800 to greater than 10,000 IU/ml (Table II). These levels are slightly lower than those found in patients with primary HIES (usually over 10,000 IU/ml) but much higher than IgE levels reported in HIV-positive patients at the same clinical stage. Specific IgE antibodies to *C. albicans* were detected in eight of nine patients. Other IgE antibodies were directed to house dust mites (3 patients),

TABLE II. Immunoglobulin levels

Group	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgE (IU/ml)	IgG ₁ (mg/dl)	IgG ₂ (mg/dl)	IgG ₃ (mg/dl)	IgG ₄ (mg/dl)
Healthy control (25)	1035 ± 65	190 ± 21	133 ± 12	22 (5-240)	533 ± 12	219 ± 16	45.5 ± 7	24 ± 5
Nonatopic HIV+ (29)	1942 ± 125*	193 ± 27	197 ± 22	63† (6-297)	1217 ± 47‡	345 ± 36§	72 ± 6	36 ± 3.3
Atopic HIV+ (22)	1960 ± 101*	338 ± 43	178 ± 29	95 (19-920)	1324 ± 94‡	311 ± 37	91 ± 9.5‡	31 ± 3.2
HIES HIV+ (9)	2188 ± 266¶	567 ± 151#	136 ± 18	2190** (773-10000)	1323 ± 247‡	545 ± 50††	112 ± 15‡‡	165 ± 60§§
Primary HIES (3)	929 ± 233	243 ± 62	64 ± 14	33992** (24000-37000)	766 ± 116	139 ± 66	37 ± 15	56 ± 16

Mean serum immunoglobulin values (± SEM) are reported, except for IgE, where geometric (and range) are indicated.

* $p < 0.001$ versus healthy control group; $p < 0.02$ versus primary HIES group.

† $p < 0.05$ versus healthy control group.

‡ $p < 0.001$ versus healthy control group.

§ $p < 0.004$ versus healthy control group.

|| $p < 0.01$ versus healthy control group.

¶ $p < 0.001$ versus healthy control group; $p < 0.03$ versus primary HIES group.

$p = 0.001$ versus healthy control group; $p < 0.001$ versus nonatopic HIV+ group; $p = 0.058$ versus atopic HIV+ group.

** $p < 0.001$ versus all groups.

†† $p < 0.001$ versus healthy control group; $p = 0.001$ versus atopic HIV+ group; $p = 0.002$ versus primary HIES group; $p = 0.008$ versus nonatopic HIV+ group.

‡‡ $p < 0.001$ versus healthy control group; $p = 0.023$ versus primary HIES group; $p = 0.006$ versus nonatopic HIV+ group.

§§ $p < 0.001$ versus healthy control group; $p = 0.001$ versus atopic HIV+ group; $p < 0.001$ versus nonatopic HIV+ group.

||| $p < 0.05$ versus healthy control group; $p < 0.03$ versus atopic HIV+ group.

grass and *Parietaria* pollens (4 patients), and cat dander (1 patient). In three patients the only IgE specificity detected was to *Candida* species.

Hypergammaglobulinemia of IgG class was also present (Table II); however, levels were similar to those observed in other HIV-positive patients. Among IgG subclasses, IgG₂ levels were increased compared with both normal groups and other groups of patients, IgG₁ levels were increased compared with primary HIES and normal groups but not compared with other HIV-positive patients, and IgG₄ levels were increased in comparison with all other groups except patients with primary HIES. Serum IgA levels were significantly increased when compared with control subjects and atopic and nonatopic HIV-infected patients. Lymphopenia and CD4+ cell counts much lower than 100/μl were present in all but one patient (Tables I and III). This contrasted with the significantly increased CD4+ cell numbers in patients with primary HIES (Table III). A reduction in the total number of T lymphocytes was observed in HIV-positive patients, whereas

CD8+ cells were only increased as percentage. T lymphocytes coexpressing HLA-DR represented about one fourth of all CD3+ cells (Table III), indicating the presence of activated CD8+ cells, which are present in much lower numbers in normal subjects and patients with primary HIES.

B cells identified by the expression of CD19 were reduced in HIV-positive patients with hyper-IgE compared with normal subjects and patients with HIES. This latter group also had a significantly increased number of circulating B lymphocytes compared with normal subjects. Within B lymphocytes, CD23+ cells represented one third in both HIV-positive patients with hyper-IgE and normal control subjects. In HIES, this proportion rose to over two thirds of all B lymphocytes (Table III). Very few T cells stained for CD23 (i.e., less than 1%). When compared with the patients with primary HIES, HIV-positive patients had much lower numbers of CD3+, CD4+, and CD19+ lymphocytes. DR+ T lymphocytes were also present in patients with HIES, but at a lower percentage.

TABLE III. Lymphocyte subpopulations

Group	CD3+	CD19+	CD4+	CD8+	CD3+ DR+	CD23+
Healthy control (n = 14)	74 ± 7 1608 ± 333	8 ± 3 165 ± 80	38 ± 9 833 ± 179	27 ± 7 597 ± 177	2 ± 2 40 ± 28	3 ± 2 64 ± 49
HIV-positive with HIES (9)	66 ± 16 569 ± 328§	13 ± 12 93 ± 75	4 ± 5 40 ± 60§	58 ± 14* 491 ± 258	18 ± 13† 147 ± 133¶	5 ± 4‡ 35 ± 38#
Primary HIES (3)	64 ± 8 2856 ± 293	20 ± 9 892 ± 461	38 ± 6 1724 ± 352	20 ± 11 912 ± 443	2 ± 1 88 ± 31	14 ± 7 643 ± 340

Percentage (± SD) and absolute number per microliter (± SD) are indicated for each subpopulation.

**p* < 0.001 versus healthy control group; *p* = 0.002 versus primary HIES group.

†*p* < 0.001 versus healthy control group.

‡*p* = 0.018 versus primary HIES group.

§*p* < 0.001 versus healthy control and primary HIES groups.

||*p* = 0.043 versus healthy control group; *p* < 0.001 versus primary HIES group.

¶*p* = 0.008 versus healthy control group.

#*p* < 0.001 versus primary HIES group.

Notably, no eosinophils or B cells were observed in the skin biopsy specimens, which revealed a mild inflammatory infiltrate composed of mononuclear cells with a CD4 to CD8 ratio of 2:1.

Spontaneous IgE production in vitro was studied in four HIV-positive patients with hyper-IgE and in the three patients with primary HIES. Supernatants of 8-day cultures consistently contained high levels of IgE, so it was possible to measure them by routine methods for serum IgE. Values obtained in cycloheximide-treated cultures were subtracted from spontaneous levels to evaluate only de novo in vitro synthesis. This ranged from just below 4 IU/ml (equivalent to 9.6 ng/ml) to over 60 IU/ml (about 145 ng/ml). Net spontaneous IgE in vitro synthesis in the three patients with HIES was also in this range (Table IV). No spontaneous in vitro production of IgE was detected in 10 normal and HIV-positive control subjects studied (not reported in Table IV).

Eosinophilia is not usually found in HIV disease in the absence of parasitic infection. However, these HIV-positive patients were selected because they were first seen with eosinophilia (900 ± 150 eosinophils/μl) without other infections accompanied by increase of circulating eosinophils. ECP serum levels were found to be abnormally high in HIV-positive patients with hyper-IgE (Fig. 1). Patients with primary HIES also had elevated levels of serum ECP, although slightly lower than those of HIV-positive patients.

Serum levels of sCD23 were 5.09 ± 0.55 μg/L in normal nonatopic subjects and 8.25 ± 1.17 in HIV-positive patients without features of hyper-IgE (only 19 patients were evaluated because of

TABLE IV. Net spontaneous IgE production in vitro (ng/ml)

Patient No.	HIV-positive HIES	Primary HIES
1	163	12.5
2	8.7	11.1
3	12.4	4.2
4	63.8	—
Mean ± SEM	61.98 ± 35.96	9.27 ± 2.57

insufficient serum from the others). Patients with primary HIES showed increased amounts of sCD23 (Fig. 2), whereas patients with hyper-IgE and HIV infection had levels comparable to those of normal subjects.

DISCUSSION

In this investigation we describe a series of HIV-infected patients who had clinical features similar to those of patients with primary HIES. These symptoms include a chronic diffuse pruritic dermatitis with lichenification, mucocutaneous infections with *C. albicans*, subcutaneous abscesses caused by *S. aureus*, and several viral infections. In this respect, these subjects are very different from other HIV-positive patients, including those who have newly developed or reexacerbated atopic symptoms¹² or allergic reactions to drugs.²

The first description of hyper-IgE-like syndrome in HIV disease was made by Lin⁹ in three patients whose clinical characteristics were compatible with CDC stage III, despite the very low number of CD4+ cells. However, this clinical

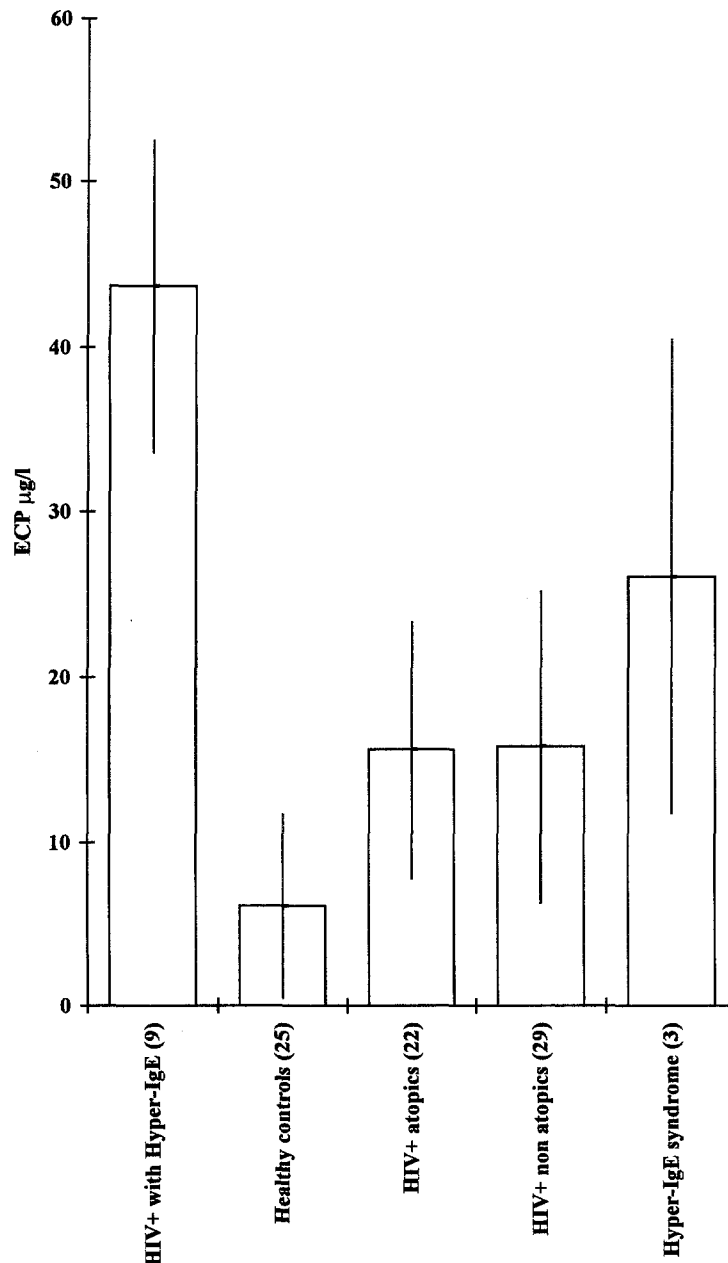


FIG. 1. Serum levels of ECP in patients with HIV infection and hyper-IgE, normal control subjects, HIV-positive atopic and nonatopic control subjects, and patients with primary HIES. Mean $\pm$ SEM (vertical bars) is shown. ECP levels in HIV-positive patients with hyper-IgE were significantly higher ($p < 0.001$) compared with those in healthy control subjects and HIV-positive patients, both atopic and nonatopic.

description was not accompanied by detailed immunologic studies. Our evaluation indicates that together with some similarities between HIV-positive patients and those with primary HIES, there are also important differences. Among the findings in common, high IgE serum levels and hypereosinophilia constitute the hallmark of these syndromes. The absolute CD4⁺ lymphopenia in HIV-

positive patients and the characteristics of other lymphocyte subsets represent the main distinctive features in comparison with primary HIES.

The increase of serum IgE in the patients we describe is well above the levels reported in HIV-positive patients with less than 200 CD4⁺ cells/ μ l,^{3,4} although the mean levels are lower than those observed in patients with primary HIES. An

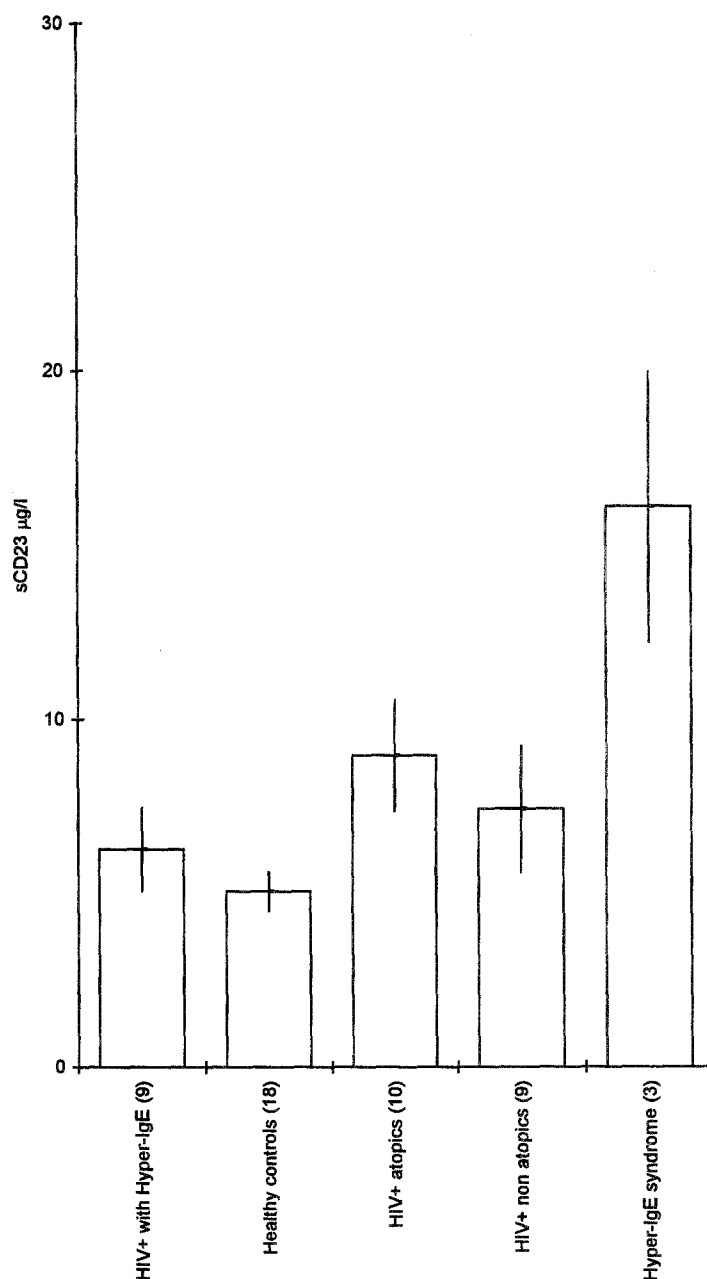


FIG. 2. Serum levels of sCD23 in HIV-infected patients with hyper-IgE, normal control subjects, HIV-positive control subjects (both atopic and nonatopic), and patients with primary HIES. Mean $\pm$ SEM (vertical bars) is shown. Numbers in parentheses refer to the number of subjects in each group. A total of 32 subjects in the control groups could not be evaluated because of insufficient serum available.

inverse relationship between absolute numbers of CD4⁺ lymphocytes and serum IgE has been described.⁴ In six of nine HIV-positive patients with hyper-IgE reported by us, CD4 depletion was nearly total, with fewer than 20 cells/ μ l surviving. In cases of primary HIES, increases of CD4⁺ lymphocytes are found,¹³ most of them belonging to the T_{H2} subset,¹⁴ which is unable to produce

interferon- γ but is the main source of IL-4 and IL-5. This is in agreement with the essential role of IL-4 in IgE synthesis and the suppressing effect of interferon- γ .⁶⁻⁸ Defective production of interferon- γ has been observed both in primary HIES^{12,13} and in HIV infection.¹⁵ Increased IL-4 production in HIV-positive patients without AIDS has been found.¹⁶ A shift from a T_{H1} to a T_{H2} type

of response has been postulated to contribute to HIV disease progression.¹⁷ However, the preferential T_{H2} type responses, which have been found in the progression of HIV infection, do not seem to be directly involved in the pathogenesis of this hyper-IgE-like syndrome because of the low frequency of HIV-positive patients with very high IgE levels (about 0.6% in our experience) and the almost complete absence of CD4+ helper cells in these cases.

It should be noted that none of the nine patients with hyper-IgE-like syndrome had measurable levels of IL-4 in their serum, although CD8+ T cell lines from two patients were able to produce IL-4 after *in vitro* stimulation (Scala et al. Unpublished data). It is unlikely that the severely reduced circulating CD4+ lymphocytes in our HIV-positive patients could be the source of IL-4. We may postulate that either skin-infiltrating CD4+ cells or other lymphoid cells (mainly CD8+) drive the hyperproduction of IgE through increased IL-4 synthesis.

Other critical factors needed for IgE switching are the engagement of CD40 on B cells by a ligand expressed on the surface of CD4+ cells^{18,19} and the release of cleaved CD23, an IgE-binding factor with regulatory activities.^{20,21} It is unlikely that these interactions can occur in the skin, because no B lymphocytes could be identified. More probably, dysregulation of IgE production takes place in the lymphoid organs, and it may be induced by HIV infection, as reported for polyclonal B-cell activation.^{22,23} The increase of IgG₄, also regulated by IL-4,²⁴ and hypergammaglobulinemia of IgG and IgA classes^{22,25} may also be due to abnormal cytokine production.

Soluble CD23, the cleaved portion of surface FcεR-II, participates in IgE regulation, and its interaction with surface CD21 seems to play a role in IgE switching.^{21,26} Increased levels of serum sCD23 have been reported in atopic patients with high IgE serum levels,²⁷ and we have also found increased amounts in patients with primary HIES. Surprisingly, sCD23 was not elevated above normal levels in sera of HIV-positive patients with hyper-IgE. This finding, which may be related to the significantly lower numbers of circulating B lymphocytes bearing this surface marker in HIV-positive patients compared with patients with primary HIES, represents an additional distinctive feature of these two syndromes.

Blood hypereosinophilia is prominent in patients with HIES,¹ as well as in our HIV-positive patients, despite the absence of eosinophils in the

skin infiltrate. Eosinophil production and activation are regulated by cytokines such as IL-5 and granulocyte-macrophage colony-stimulating factor.²⁸ The occurrence of eosinophil activation and release of cytotoxic mediators can be indirectly deduced by the extremely high levels of serum ECP measured in both primary and HIV-associated HIES. We previously reported increased levels of ECP both in atopic and nonatopic HIV-infected subjects,²⁹ although the amounts measured were significantly lower than those in HIES and eosinophilia was not observed.

Because eosinophils express surface CD4³⁰ and can be infected *in vitro* by HIV,³¹ it is possible that HIV infection can be the cause of both eosinophil increase and release of mediators through autocrine production of IL-5 and granulocyte-macrophage colony-stimulating factor.³² It would have been very useful to isolate eosinophils from these patients to assess the presence of proviral DNA, but unfortunately this could not be done because the patients all died.

The clinical findings in the patients we studied are very suggestive of primary HIES, but the immunologic data delineate both similarities to and differences from patients affected by HIES. This syndrome should be considered a distinct expression of the spectrum of HIV-related manifestations, characterized by extensive dermatitis, hypereosinophilia in the absence of known causative agents, and hyper-IgE, occurring mainly in late stages of the disease and having a very poor prognosis. It may represent a useful model for defining helper activity for IgE synthesis by cells other than CD4+.

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