

Cytokine profile of a long-term pediatric HIV survivor with hyper-IgE syndrome and a normal CD4⁺ T-cell count

Christine M. Seroogy, MD,^a Diane W. Wara, MD,^a Martin H. Bluth, MD, PhD,^b
Alejandro Dorenbaum, MD,^a Carmen White, BS,^a Helen G. Durkin, PhD,^b and
Melissa E. Elder, MD, PhD^a San Francisco, Calif

Background: An elevated IgE level and increased production of T_{H2} cytokines are factors associated with poor prognosis in HIV infection. We report a pediatric long-term survivor of vertically acquired HIV infection with a normal CD4 count and a low viral burden despite the lack of antiretroviral therapy and a phenotype resembling hyper-IgE syndrome. **Objective:** We sought to characterize the patient's T_{H1} versus T_{H2} cytokine profile and anti-HIV-specific immune responses. **Methods:** Supernatants collected from cultures of peripheral blood T cells stimulated with phorbol myristate acetate plus ionomycin were assayed for T_{H1} and T_{H2} cytokines by means of ELISA. Specific IgE antibodies were determined by immunoblot. HIV-specific cytotoxic T-lymphocyte responses were measured from cell lysis by fresh T cells of autologous B-lymphoblastoid cells expressing recombinant HIV proteins. **Results:** Patient CD4⁺ T cells secreted significantly more T_{H2} cytokines, IL-4 ($P < .003$) and IL-5 ($P < .03$), than HIV-infected and seronegative control cells. No difference was noted in T_{H1} cytokine production. IgE specific for HIV gp160, p24, p17, and p66 proteins and *Aspergillus fumigatus* was detected in patient sera. Despite predominance of T_{H2} cytokines, HIV-specific cytotoxic T-lymphocyte activity was vigorous. **Conclusions:** The patient demonstrated predominantly T_{H2} cytokine production in vitro. Unlike other patients with HIV who have hyper-IgE and increased T_{H2} cytokine production, our patient has maintained HIV-specific immune responses, a low viral load, and a normal CD4 count without antiretroviral therapy. These findings support a diagnosis of primary hyper-IgE syndrome. Presence of anti-HIV-specific IgE may represent a protective mechanism against HIV replication in our patient. (*J Allergy Clin Immunol* 1999;104:1045-51.)

Key words: HIV, hyper-IgE syndrome, anti-HIV IgE, T_{H1}, T_{H2}, cytokine

Abbreviations used

AIDS:	Acquired immunodeficiency syndrome
B-LCL:	B lymphoblastoid cell line
CTL:	Cytotoxic T lymphocyte
FACS:	Flow cytometry analysis
HIES:	Hyper-IgE syndrome
IVGG:	Intravenous gammaglobulin
PMA:	Phorbol myristate acetate
TBST:	Tris-buffered saline with Tween 20 detergent
vSC8:	Control vaccinia virus vector
vvDK1:	Recombinant vaccinia vector expressing HIV-1 gag

Patients with advanced HIV infection demonstrate increased plasma viral loads, declining CD4⁺ T-cell numbers, and decreased HIV-specific immune responses, such as cytotoxic T-cell (CTL) activity. In comparison with HIV-infected adults, the natural history of perinatally acquired HIV infection includes higher viral burdens, more rapid CD4⁺ T-cell attrition, and more rapid clinical progression to acquired immunodeficiency syndrome (AIDS).¹⁻³ An association between elevated serum IgE levels and progression to AIDS has been observed in both HIV-infected adults⁴⁻⁸ and children.⁹⁻¹³ A subset of HIV-infected adults has been identified with symptoms resembling the primary immunodeficiency, hyper-IgE syndrome (HIES), in which affected patients have recurrent staphylococcal infections, dermatitis, eosinophilia, and an IgE level 20- to greater than 100-fold above normal.^{14,15} These adults have AIDS and low to virtually no peripheral CD4⁺ T cells.¹⁴⁻¹⁶ This relationship between elevated serum IgE levels and declining numbers of CD4⁺ T cells has not been as clearly established in pediatric HIV studies.^{17,18} We have identified a pediatric long-term survivor of perinatally acquired HIV infection with HIES but without evidence of disease progression. Unlike other HIV-infected adults and children with hyper-IgE or a HIES-like phenotype, our patient has maintained a normal CD4 count with a low to undetectable viral burden in the peripheral blood despite the absence of antiretroviral therapy.

CD4⁺ T cells are the preferred targets of HIV infection, resulting in progressive loss of these cells over time. The majority of CD4⁺ T cells are T_H lymphocytes, the central role in the immune response of which is the production of cytokines required for effector functions, such

From ^athe Department of Pediatrics, Division of Immunology, Allergy, and Rheumatology, University of California, San Francisco; and ^bthe Department of Pathology, State University of New York Health Science Center at Brooklyn.

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Reprint requests: Christine M. Seroogy, MD, Department of Medicine, Division of Immunology and Rheumatology, Stanford University, 300 Pasteur Dr, Rm S021, Palo Alto, CA 94305.

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as cytotoxicity and antibody production. T_H cells can be differentiated into subsets (T_{H1} and T_{H2}) according to their patterns of cytokine production, but the events that establish subset polarization have not been clearly delineated.¹⁹⁻²² However, several mechanisms have been proposed, including antigen density, presence of particular costimulatory molecules, and the cytokine milieu.²³ T_{H1} cells, which produce IL-2, IFN- γ , and TNF- β , are critical for inflammatory responses and promotion of cell-mediated immunity against intracellular organisms. T_{H2} cells produce primarily IL-4, IL-5, IL-10, and IL-13 and induce humoral, parasitic, and allergic immune responses, including production of IgE.

Mechanisms responsible for eventual HIV disease progression and increased viral load over time are multifactorial but are thought to include a shift from a T_{H1} to a T_{H2} cytokine profile.^{24,25} To elucidate mechanisms responsible for our patient's markedly increased IgE level, we analyzed the cytokines produced by her stimulated CD4⁺ and CD8⁺ T cells.

METHODS

Subjects

The patient is a 12-year-old girl born to an HIV-infected woman. The patient was referred to the University of California, San Francisco (UCSF), primary immunodeficiency clinic because of recurrent episodes of staphylococcal pneumonia when she was 4 months old and was found to be HIV-culture positive at the age of 5 months. Since infancy she has had frequent hospitalizations for *Staphylococcus aureus* infections. The patient underwent a lobectomy of her left upper lung at age 1 year and a left nephrectomy at age 10 years. At the age of 6 years, multiple pneumatoceles caused by recurrent staphylococcal infections developed, and at the age of 11 years was found to have lower respiratory tract colonization with *Aspergillus fumigatus* without evidence of invasive disease. She underwent splenectomy for refractory thrombocytopenia at 11 years of age.

The patient was diagnosed with clinical AIDS (Center for Diseases Control and Prevention clinical category C1) at the age of 3 years because of recurrent bacterial infections but did not receive antiretroviral therapy because of age-corrected normal CD4 counts. Currently, she requires hospitalization every 3 to 6 months for intravenous antibiotic treatment of staphylococcal infections despite receiving prophylactic antibiotics and monthly intravenous gamma globulin (IVGG) since 5 years of age.

The patient is enrolled in AIDS Clinical Trial Group protocol 219, which is designed to monitor late outcomes in HIV-infected children. The HIV-infected control for cytokine studies is an asymptomatic child who was selected because of a viral load profile similar to that of our patient. Two healthy volunteers were used as HIV-uninfected control subjects. Approval was obtained from the UCSF Institutional Review Board to study these subjects.

Flow cytometry analysis

Flow cytometry analysis (FACS) was performed with conjugated mAbs (Becton Dickinson, San Jose, Calif) directed against CD3, CD4, and CD8 on peripheral blood lymphocytes, as described elsewhere.²⁶

Specific and total IgE levels

Serum IgE levels were measured by personnel at the UCSF Clinical Immunology Laboratory. Total IgE was measured by means of a sandwich ELISA; antigen-specific IgE levels were measured by means of a radioallergosorbent test.

T-cell subset isolation

PBMCs were isolated by Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) gradient centrifugation, as previously described.²⁶ After removal of non-T cells by adherence to polystyrene, CD4⁺ and CD8⁺ mAb-conjugated magnetic beads (Dynabeads M450; Dynal AS, Oslo, Norway) were used to isolate T-cell subpopulations from the remaining nonadherent lymphocytes. Purity of negatively selected CD4⁺ T cells ranged from 76% to 94%, as determined by FACS analysis. Purity of positively selected CD4⁺ T cells was indirectly measured by FACS analysis of both preselected and eluted cells and was routinely greater than 95%. Selected cells were resuspended in complete RPMI media (RPMI 1640; Gibco, Grand Island, NY) supplemented with 2 mmol/L L-glutamine, 50 U/mL penicillin, 50 μ g/mL streptomycin, and 10% heat-inactivated human serum (NABI, Miami, Fla).

Cytokine production

PBMCs or isolated T cells were cultured in 12 $\times$ 75-mm round-bottom polystyrene tubes at a concentration of 1×10^6 cells/mL with complete RPMI medium plus 0.5 ng/mL phorbol myristate acetate (PMA; Sigma, St Louis, Mo) plus 1 μ mol/L ionomycin (Calbiochem, La Jolla, Calif) for 72 hours at 37°C. After stimulation, supernatants were collected and stored at -20°C until ELISA analysis. Time-course studies found that 72 hours of culture provided peak supernatant levels for all cytokines tested.

Cytokine measurement

Cytokines were assayed by using commercial ELISA kits (R&D Systems, Minneapolis, Minn for IL-4 and IFN- γ detection; Biosource, Camarillo, Calif for IL-5 measurement). Concentrations of cytokines from duplicate or triplicate samples were determined by interpolation from standard curves prepared simultaneously. Lower limits of assay detection were 7.8 pg/mL for IL-4 and IL-5 and 15.6 pg/mL for IFN- γ .

Immunoblot assays

Presence of IgE against various HIV proteins was detected by means of Western blotting, as previously described,²⁷ with the following modifications. HIV protein-coated strips (Cambridge Biotech Corp, Worcester, Mass) were incubated with sera diluted 1:50 or 1:100 in blotting buffer (Tris-buffered saline with 3% normal goat serum and 5% powdered milk at pH 7.4) for 20 hours and washed in Tris-buffered saline plus Tween 20 (TBST). Strips were then incubated with goat anti-human IgG or IgE mAb (ICN, Aurora, Ohio) for 1 hour, after which the strips were washed and incubated with horseradish peroxidase-conjugated rabbit anti-goat mAb (ICN) for 1 hour and developed by using enhanced chemiluminescence. Positive control serum containing IgE anti-HIV-specific antibodies was obtained from a previously described HIV-infected child²⁷; negative control serum was obtained from an HIV-seronegative adult.

For dot-blot analysis of specific antibodies, nitrocellulose strips coated with serial dilutions from 0.8 ng to 25 ng of *S aureus* (Sigma), human albumin (Sigma), and tetanus toxoid (Pasteur-Merieux Connaught, Swiftwater, Pa) were incubated with sera diluted 1:50 for 90 minutes and washed in TBST, as previously described.²⁸ Alkaline phosphatase-conjugated anti-human IgE (Protos Immunoresearch, San Francisco, Calif) or alkaline phosphatase-conjugated anti-human IgG (Protos) was then added for 1 hour. After washing in TBST, strips were developed in chromogenic substrate solution.

Cytotoxic T-lymphocyte HIV-1 specific bulk assay

The CTL assay was performed as previously described.²⁹ Stimulator and target cells were prepared by infecting autologous EBV-

transformed B-lymphoblastoid cell lines (B-LCL) at a multiplicity of infection of 1:1 with either control vaccinia virus (vSC8; National Institutes of Health Repository, Bethesda, Md) or a recombinant vaccinia vector encoding an HIV gag-gene product (vvDK1; National Institutes of Health Repository). Stimulator B-LCLs were inactivated by incubation with 10 μ g/mL 4'-aminomethyl-4,5,8-trimethylpsoralen (HRI Associates, Concord, Calif), followed by exposure to ultraviolet light. To produce effector T cells, freshly isolated PBMCs were cultured in complete RPMI medium plus 20 U/mL recombinant human IL-2 (Boehringer-Mannheim, Indianapolis, Ind) for 14 days at 37°C with autologous vvDK1-infected B-LCL at an effector/stimulator cell ratio of 10:1. Hot chromium 51 (^{51}Cr)-labeled (New England Nuclear, Boston, Mass) and cold target cells were prepared on day 13.

The CTL assay is a standard ^{51}Cr release method that is performed by coculturing effector and target (either autologous vSC8- or vvDK1-infected B-LCL) cells at various effector/target cell ratios in complete RPMI medium in round-bottom 96-well plates for 6 hours at 37°C. Background lysis by vaccinia- or EBV-specific cytotoxic T cells was reduced with cold target inhibition, whereby excess unlabeled vSC8-infected B-LCLs were added to wells at a cold/hot target ratio of 50:1. Supernatants were collected, and counts per minute of ^{51}Cr release, as a measure of target cell lysis, were determined in a betaplate liquid scintillation counter (Wallac, Gaithersburg, Md).

Statistical analysis

Statistical analysis was performed by using the 2-tailed Student *t* test and assuming equal variance. Probability (*P*) values of .05 or less were considered statistically significant.

RESULTS

Clinical history

The patient is a 12-year-old girl with perinatal acquisition of HIV, chronic dermatitis, recurrent severe staphylococcal infections, progressive lung disease with development of pneumatoceles colonized by *A fumigatus*, and an elevated serum IgE level (>10,000 IU/mL). She clinically resembles patients with primary HIES and meets established criteria for this immunodeficiency diagnosis.³⁰ Physical findings include dermatitis predominantly involving the back of the neck, recurrent impetigo on the face and eyelids, progressive coarsening of her facial features, soft tissue scarring from multiple incisions in her axillae, and clubbing of her fingers.

Our patient was diagnosed with AIDS (category C1) at the age of 3 years because of recurrent staphylococcal infections. She has never had opportunistic infections and has not received antiretroviral therapy. Despite a lack of treatment, consecutive plasma viral load studies by the branched-DNA method (Chiron, Inc, Emeryville, Calif) revealed either no detectable virus or, on one occasion, a relatively low viral load of 30,000 copies/mL. Therefore on the basis of her clinical and laboratory findings, we conclude that our patient has primary HIES and does not meet criteria for an AIDS-defining illness. Instead, she should be reclassified as HIV clinical category B1 because of her history of IVGG-resistant thrombocytopenia requiring splenectomy.

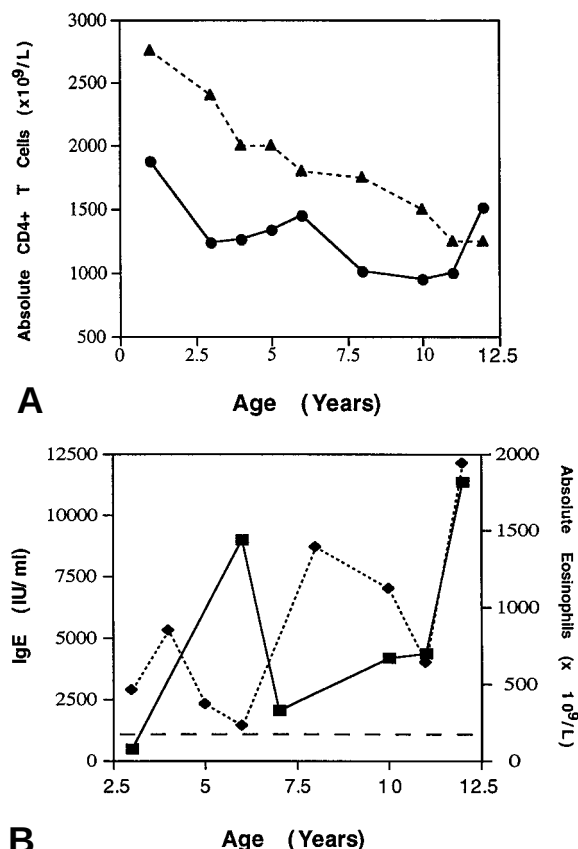


FIG 1. Laboratory findings. **A**, The patient's absolute peripheral CD4 counts over life span (circles) versus age-appropriate normal values (50th percentile;⁴⁹ triangles). **B**, Absolute peripheral eosinophil numbers (squares; dashed line represents normal values for children⁵⁰) and serum IgE (diamonds) over the life span of patient.

Laboratory findings

Serial values for absolute CD4⁺ T-cell number, serum IgE level, and absolute peripheral eosinophil count are shown in Fig 1. The time course demonstrates a stable CD4 count within normal limits for age, a long-standing elevation in serum IgE level, and peripheral eosinophilia. Of note, the patient does have an inverted CD4/CD8 ratio and greater than 50% memory (CD45RO⁺) CD4⁺ T cells. Other laboratory studies included normal complement levels (C3, C4, CH₅₀), repeatedly normal neutrophil oxidative burst, and a normal in vitro *S aureus* killing curve (data not shown). Her serum Ig levels reveal an elevated total IgG level (1870-3060 mg/dL) while receiving monthly IVGG infusions, a normal IgM level (167-224 mg/dL), and a normal IgA level (40-174 mg/dL).

Antibody responses

The presence of IgG and IgE antibodies against HIV proteins and specific antigens in the patient's serum was determined by immunoblot analysis. IgG-specific antibodies to HIV gp160 and p24, *S aureus*, and tetanus were detected in patient serum (data not shown). IgE-specific

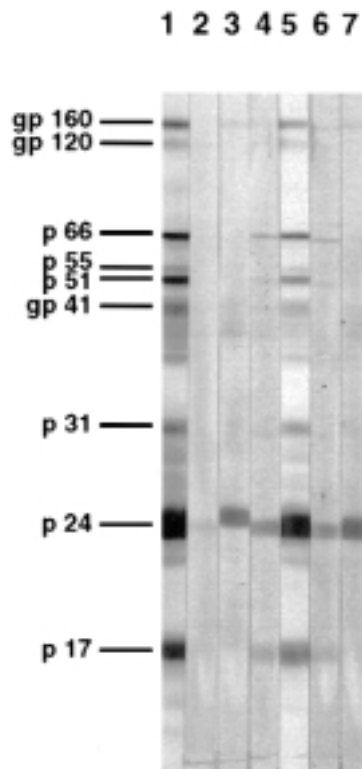


FIG 2. HIV Western blot. HIV protein-coated strips were incubated with the following: control HIV-seropositive serum diluted 1:50 (lane 1) or 1:100 (lane 5), control seronegative serum diluted 1:50 (lane 2), control HIV-specific IgE⁺ serum²⁷ diluted 1:50 (lane 3) or 1:100 (lane 7), or patient serum diluted 1:50 (lane 4) or 1:100 (lane 6). The secondary goat-anti-human mAb was either to IgG (lanes 1 and 5) or IgE (lanes 2-4, 6, and 7).

antibodies to HIV gp160, p24, p17, and p66 proteins were also detected (Fig 2). Of significance, IgE-specific antibodies directed against HIV proteins have been previously reported in a cohort of HIV-infected children with hyper-IgE and were suggested to be a protective mechanism against HIV progression.²⁷ Although anti-*S aureus* IgE is typically found in sera from patients with HIES and atopic disease, IgE-specific antibodies to *S aureus* and common aeroallergens (dust mite and cockroach) were not detected in the patient's serum (data not shown). However, *A fumigatus*-specific IgE and *A fumigatus* precipitins were detected and have been reported in some patients with primary HIES.³¹ Our patient also has lower respiratory tract colonization with *A fumigatus* without invasive disease.

CD4⁺ T-cell cytokine production in vitro

Purified CD4⁺ T cells from the patient and control subjects were stimulated with PMA plus ionomycin for analysis of cytokine production. Positively selected patient CD4⁺ T cells produced significantly more of the T_{H2} cytokines IL-4 and IL-5 than that produced by HIV-infected and seronegative control cells ($P < .003$ and $P < .03$, respectively; Fig 3). Furthermore, production of a

T_{H1} cytokine, IFN- γ , by patient CD4⁺ T cells was reduced, although not statistically significant. IL-2 production was similar to that found in the control subjects (data not shown). CD4⁺ T cells isolated by negative selection showed similar results to those obtained with positively selected CD4⁺ T cells (data not shown). Of interest is our finding that the patient's positively selected CD8⁺ T cells did not produce detectable levels of either IL-4 or IL-5 (data not shown). In contrast to a prior study in patients with AIDS who had HIES,³² T_{H2} cytokines appear to be produced primarily by CD4⁺ rather than CD8⁺ T cells in our patient.

HIV-specific CTL response

The patient's HIV-specific CTL response demonstrated greater than 70% killing of HIV gag targets at an effector/target ratio as low as 12.5:1. The magnitude of the patient's CTL response is the most vigorous demonstrated in the UCSF Pediatric AIDS Clinical Trial Group Laboratory, and, as a result, her cells are used as a laboratory positive control.

DISCUSSION

This is the first description of a pediatric HIV-infected long-term survivor with primary HIES. Our patient has a normal CD4 count, a low viral burden, and has no opportunistic infections despite distinct T_{H2} cytokine skewing of her CD4⁺ T cells and a serum IgE level of greater than 10,000 IU/mL. The cytokine profile of the patient's stimulated T lymphocytes and her clinical manifestations are consistent with a preponderance of T_{H2} cells.

HIV-specific CTL responses are thought to be important for control of HIV infection in that they correlate with long-term survival and low viral load.^{33,34} In perinatal transmission, HIV-specific CTL activity may eliminate HIV altogether.^{35,36} In a previous report examining T_{H2} cytokine effects on HIV-specific CTL activity,³⁷ CD8⁺ T cells from long-term survivors exposed to IL-4 produced less IL-2 and had reduced ability to suppress HIV replication in vitro. In contrast, our report is the first to demonstrate that, in spite of predominantly T_{H2} cytokine production and a markedly elevated serum IgE level, strong HIV-specific CTL responses could be elicited. Moreover, IL-2 production was similar to that of control subjects despite increased T_{H2} cytokines. The increased levels of IL-4 and IL-5 produced by our patient's CD4⁺ T cells are unlikely to be an in vitro artifact. The patient's clinical phenotype is consistent with primarily T_{H2} cytokine production in vivo, and T-cell incubation with PMA plus ionomycin in vitro should result in equal activation of all cells and not just CD4⁺ T_{H2} lymphocytes. In addition, effector memory T_{H1} or T_{H2} CD4⁺ cells produce the same cytokine profile on restimulation,³⁸ and the majority of our patient's peripheral blood CD4⁺ T lymphocytes are CD45RO⁺ cells.

Studies by others have shown that CD4⁺ T_{H2} cells are more permissive to HIV infection than T_{H1} cells in vitro,³⁹ and HIV-infected individuals with increased

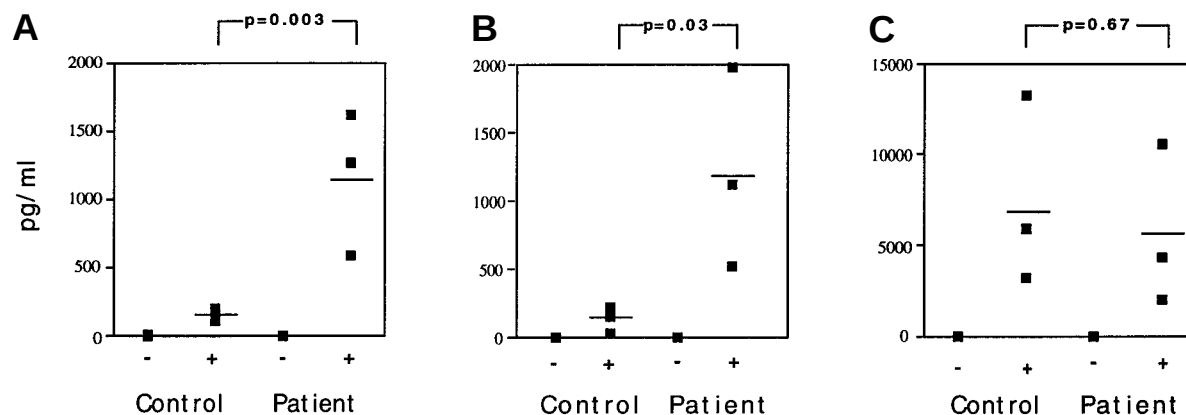


FIG 3. In vitro cytokine production. Comparison of cytokine levels produced by stimulated (+) and resting (-) positively selected CD4⁺ T cells from the patient versus HIV-infected and uninfected control subjects (**A**: IL-4, $P = .003$; **B**: IL-5, $P = .03$; **C**: IFN- γ , $P = .67$). These data represent 3 independent experiments with samples run in duplicate or triplicate.

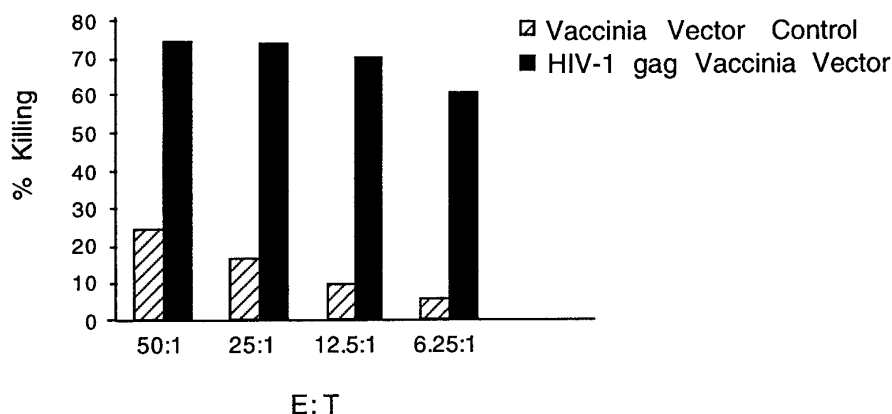


FIG 4. HIV-specific CTL activity. Patient HIV-1 gag-specific CTL responses at various ratios of effector (E) to target (T) cells against a control vaccinia vector (hatched bars) or a recombinant HIV-1 gag-expressing vaccinia vector (filled bars).

serum IgE levels have more rapid CD4⁺ T-cell depletion and progression to AIDS.⁴⁰ In contrast, our patient with HIES, who maintains a total serum IgE level of greater than 10,000 IU/mL, has a normal CD4 count that has remained stable since infancy and a low viral load without antiretroviral therapy. Although it is possible that monthly IVGG therapy may be providing some CD4⁺ T-cell sparing effect, the presence of repeatedly low to undetectable viral loads and the absence of opportunistic infections suggest that our patient may have additional mechanisms to explain her long-term survival.

Secord et al²⁷ previously reported detection of HIV-specific IgE in a cohort of healthy vertically infected pediatric patients. In contrast to our patient, those children had low peripheral CD4 counts and only modestly elevated IgE levels (100-1000 IU/mL), and they did not exhibit the physical or clinical findings of primary HIES. Like our patient, they had significantly fewer opportunistic infections in comparison with age-matched HIV-

infected control subjects with comparable CD4 counts but without increased serum IgE levels. These HIV-specific IgE antibodies have subsequently been shown to inhibit HIV replication in vitro, supporting the authors' hypothesis that anti-HIV-specific IgE delays AIDS progression.^{27,41} Similarly, our findings suggest that anti-HIV IgE antibodies may provide protection against HIV replication for certain seropositive individuals.

Our patient demonstrated specific IgE to HIV gp160, p24, and p17 proteins. In addition, anti-p66 IgE was detected, which has not been previously observed (Bluth and Durkin, unpublished data). This finding is intriguing because our patient does not demonstrate the clinical or laboratory features previously described in patients with detectable anti-HIV-specific IgE,²⁷ and this suggests that she may have additional protective factors preventing development of AIDS. In particular, it has been shown that certain mutations in the HIV coreceptors CCR5 and CCR2 provide protection from HIV infection

or delay progression to AIDS.⁴²⁻⁴⁴ However, neither the patient nor her mother was found to be a carrier for a CCR5 mutation (S. Stranford and J. Levy, personal communication, 1999). Although her mother has a CCR2 V64I polymorphism that may hinder HIV progression in African Americans, the patient did not inherit this allele. Because the susceptibility of T_{H2} cells to HIV infection may in part be caused by upregulation of functional surface CXCR4 expression and simultaneous downregulation of CCR5 expression on primary CD4⁺ T cells,⁴⁵ sequencing of CXCR4 is in progress. Certain exogenous chemokines that have been shown to inhibit HIV infection in vitro^{46,47} are currently being investigated as potential protective mechanisms in our patient as well.

The clinical similarity between our patient and individuals with primary HIES is striking. We propose that our patient has diagnoses of both primary HIES and HIV infection. Unlike most HIV patients with hyper-IgE who have AIDS with low peripheral CD4 counts and primarily CD8⁺ T cell-derived synthesis of T_{H2} cytokines,³² our patient has maintained a normal CD4 count, a low viral load, and primarily CD4⁺ T-cell production of T_{H2} cytokines. Moreover, her physical examination and clinical course are those of primary HIES rather than hyper-IgE secondary to HIV: coarse facies, atopic disease, early-onset severe staphylococcal infections, development of pneumatoceles colonized with *A fumigatus*, eosinophilia, and a strikingly elevated serum IgE level but normal IgA and IgM levels. Elevated serum IgE levels in patients with primary HIES appear to be independent of T_{H2} cytokines (predominantly IL-4),⁴⁸ suggesting that IgE production in these patients is regulated by another currently undefined pathway. The role of cytokine dysregulation in primary HIES remains controversial, and until the genetic basis for the disease is characterized, findings in our patient support diagnoses of both primary HIES and coexisting HIV infection.

In summary, this patient represents a unique phenotype for a pediatric long-term HIV survivor with hyper-IgE and specifically with primary HIES. The current approach to treatment of vertically acquired HIV infection is to treat early and aggressively to suppress viral replication and immune system destruction. However, this approach may not be advantageous for all HIV-infected children. It is currently impossible to identify prospectively those patients who would be candidates for no treatment, monotherapy, or combination antiretroviral therapy. Continued investigation to characterize possible protective mechanisms or resistance to high-titer viral production in our patient may improve our understanding of AIDS pathogenesis and improve antiretroviral regimens, as well as suggest strategies for immunotherapy, for HIV-infected patients.

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