IDIOPATHIC CD4+ T-LYMPHOCYTOPENIA — IMMUNODEFICIENCY WITHOUT EVIDENCE OF HIV INFECTION

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Abstract *Background.* The human immunodeficiency virus (HIV), the etiologic agent of the acquired immunodeficiency syndrome (AIDS), infects and depletes CD4+ T lymphocytes. Recently, patients have been described with profound CD4+ T-lymphocytopenia but without evident HIV infection, a condition now termed idiopathic CD4+ T-lymphocytopenia, and a national surveillance network has been set up to investigate such cases.

Methods. We studied 12 patients with CD4+ T-lymphocytopenia who were referred to us from three U.S. cities. Blood samples were tested for HIV with specific antibody assays, viral cultures, and polymerase-chain-reaction (PCR) techniques.

Results. The patients (10 men and 2 women) ranged in age from 30 to 69 years. Eight had risk factors for HIV infection. The clinical manifestations were heterogeneous: five patients had opportunistic infections, five had syndromes of unknown cause, and two had no symptoms. Two patients died from acute complications of their immunodeficiency. The patients' lowest CD4+ lymphocyte counts ranged from 3 to 308 per cubic millimeter (mean, 149). Three patients had complete or partial spontaneous reversal of the CD4+ T-lymphocytopenia. Concomitant CD8+ T-lymphocytopenia was noted in three patients, and abnormal immunoglobulin levels were found in five. Multiple virologic studies by serologic testing, culture, and PCR were completely negative for HIV in all patients.

Conclusions. Our 12 patients with idiopathic CD4+ T-lymphocytopenia appear to be epidemiologically, clinically, and immunologically heterogeneous. It is unclear whether this syndrome is new, transmissible, or acquired. Many of the clinical and immunologic features are distinct from those found in AIDS, and our extensive virologic studies found no evidence of HIV infection. The cause of this condition remains unknown. (N Engl J Med 1993; 328:380-5.)

IT is now clear that infection with human immunodeficiency virus type 1 (HIV-1)[1] or type 2 (HIV-2)[2] can result in the depletion of CD4+ T-helper lymphocytes and the development of the acquired immunodeficiency syndrome (AIDS).[3] However, Kaposi's sarcoma and *Pneumocystis carinii* pneumonia, two of the major manifestations of AIDS, have also been seen in persons with normal CD4+ lymphocyte counts without evidence of HIV-1 or HIV-2 infection.[4,5] More recently, several groups have described HIV-negative patients with CD4+ lymphocyte depletion in conjunction with opportunistic infections[6-9] or Kaposi's sarcoma.[10] These preliminary reports, coupled with extensive coverage in the lay press,[11,12] have prompted the Centers for Disease Control and Prevention (CDC) to institute a surveillance network to investigate cases of this condition, now termed idiopathic CD4+ T-lymphocytopenia.[13,14] Our group has been evaluating similar cases of immunodeficiency since 1988,[15] and we describe a series of 12 patients who presented with diverse clinical syndromes in association with profound depletion of CD4+ lymphocytes in the absence of detectable HIV-1 or HIV-2 infection.

CASE REPORTS

Twelve patients (10 men and 2 women) from three cities (Los Angeles, New York, and Denver) were referred for evaluation from 1988 through 1992 for CD4+ lymphocyte depletion or AIDS-like illnesses in the absence of HIV infection. They ranged in age from 30 to 69 years, and none had a family history of immunodeficiencies. Ten patients were symptomatic, whereas 2 were asymptomatic; 8 had risk factors for HIV infection, whereas 4 did not; and 2 have died, whereas 10 are alive. The individual case histories are presented below. The salient clinical features are summarized in Table 1, and the results of retroviral studies are shown in Table 2.

Patient 1, a 69-year-old Hispanic woman, had been well until July 1990, when oral ulcers developed that were consistent with herpes simplex infection. She felt sluggish for two months and had a 10-lb (4.5 kg) weight loss, leading up to a three-day illness with fever, dyspnea, and nonproductive cough. A subsequent workup, including bronchoscopy, revealed *P. carinii* pneumonia. The patient was anergic to multiple skin tests, and her CD4+ lymphocyte count was only 3 per cubic millimeter. CD8+ T-lymphocytopenia and hypogammaglobulinemia were also observed (Table 1). Because her HIV studies were negative (Table 2), bone marrow examination and abdominal computed tomography (CT) were performed. No evidence of cancer was found. Despite therapy with trimethoprim and sulfamethoxazole, the patient died of her pneumonia. Postmortem examination confirmed the presence of *P. carinii* pneumonia, as well as that of disseminated cytomegalovirus infection, but there was no neoplasm or other abnormalities.

Patient 2 (also described in the accompanying article by Smith et al.[16] as Patient 25) was a 55-year-old white man who was referred in August 1989 with a history of persistent CD4+ lymphocytopenia, chronic fatigue, arthralgia, myalgia, and night sweats. He stated that in 1982 he had been told that his CD4:CD8 ratio was 0.2. His subsequent HIV-antibody tests were repeatedly negative, however, a finding consistent with the absence of risk factors for HIV infection. He was found to have a low CD4+ lymphocyte count (90 per cubic millimeter), as well as low levels of IgG and IgA, but his HIV studies were entirely negative (Tables 1 and 2). The patient was also unreactive to multiple recall antigens on skin testing. His clinical status remains unchanged as of this writing, and a recent CD4+ lymphocyte count was still less than 100 per cubic millimeter. Repeated HIV studies were negative.

Patient 3 (Patient 22 in the article by Smith et al.[16]) was a 32-year-old homosexual white man who had had multiple sexual partners, including one who died of AIDS. This patient had been well until January 1989, when he noted visual floaters. On ophthalmologic evaluation, an isolated cotton-wool spot was found in his right retina. Although his HIV-1-antibody test was negative, his CD4+ lymphocyte count was only 274 per cubic millimeter. Repeat testing in February 1989 again showed no evidence of HIV infection and a CD4+ lymphocyte count of 252 per cubic millimeter. In the ensu-

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Table 1. Summary of Case Histories and Results of Immunologic Studies.*

Patient No.	Age/Sex	Risk Factors for HIV	Description	Lymphocytes†		Serum Immunoglobulins‡			Skin Tests
				CD4+	CD8+	IgG	IgA	IgM	
				per mm³			*mg/dl*		
1	69/F	None	PCP, disseminated CMV, death	3	112	416	71	77	Anergic
2	55/M	None	Chronic fatigue, myalgia, arthralgia	90	890	630	57	75	Anergic
3	32/M	Homosexual sex	Transient retinal cotton-wool spot	252	ND	1050	217	98	ND
4	32/M	Homosexual sex	Asymptomatic	184	368	1010	126	79	ND
5	34/M	Homosexual sex	Asymptomatic§	150	490	ND	ND	ND	Anergic
6	54/M	None	Cirrhosis, thrombocytopenia	154	59	1130	369	56	ND
7	36/M	Multiple sex partners	Cerebral toxoplasmosis	207	223	2185	253	180	Anergic
8	30/M	Homosexual sex	Fever, sweats, lymphadenopathy	308	361	1270	341	132	Reactive
9	61/M	None	Paraspinal TB; septic arthritis	205	340	3710	645	182	Reactive
10	45/M	Homosexual sex	Thrombocytopenia	57	709	1927	420	122	ND
11	41/F	Multiple sex partners	Refractory papillomavirus infection	127	423	1460	380	181	Anergic¶
12	40/M	IV drug use	Cryptococcal infection, death	45	135	1420	262	271	ND

*PCP denotes *P. carinii* pneumonia, CMV cytomegalovirus, ND not done, TB tuberculosis, and IV intravenous.

†The normal range for CD4+ lymphocytes is from 537 to 1571 per cubic millimeter, and for CD8+ lymphocytes from 235 to 753 per cubic millimeter. When multiple CD4+ measurements were available, the lowest value is shown.

‡Normal ranges for immunoglobulins are as follows: IgG, 723 to 1685 mg per deciliter; IgA, 69 to 382 mg per deciliter; and IgM, 63 to 277 mg per deciliter.

§This patient later acquired HIV-1 infection after a new sexual exposure.

¶This patient was anergic in September 1991 but reactive to mumps antigen in December 1991.

ing years, the retinal lesion partially resolved without treatment. His CD4+ lymphocyte counts in January 1990 and August 1992 increased markedly, to 600 and 516 per cubic millimeter, respectively (Fig. 1). Extensive studies at those times found no evidence of HIV infection (Table 2). The patient remains well at this writing.

Patient 4 was a 32-year-old white man who had unprotected sexual contact over a prolonged period with his male lover, who later died of AIDS. He has been asymptomatic, and routine HIV-antibody tests have been repeatedly negative since 1986. However, his CD4+ lymphocyte counts decreased from 623 and 612 per cubic millimeter in 1986 and 1987, respectively, to approximately 200 per cubic millimeter on two separate determinations in 1989; his most recent count was 288 per cubic millimeter (Fig. 1). Extensive HIV studies conducted in June 1989 and again in August 1992 were completely negative (Table 2).

Patient 5 was a 34-year-old homosexual white man who had been asymptomatic. On routine examination in 1988, he was found to be anergic and to have a CD4+ lymphocyte count of less than 200 per cubic millimeter despite a negative HIV-1–antibody test and culture. In November 1989, his CD4+ lymphocyte count was 150 per cubic millimeter, and all studies for HIV were negative (Tables 1 and 2). Subsequently, the patient continued to have both HIV seronegativity and CD4+ T-lymphocytopenia (<200 cells per cubic millimeter) until early 1992, when he seroconverted to HIV-1 shortly after a new sexual contact. Since then new AIDS-related symptoms have developed, and his CD4+ cell count has decreased further, to 40 per cubic millimeter at this writing.

Patient 6 was a 54-year-old white man who reported no risk factors for HIV infection. In 1988, he was found to have cryptogenic cirrhosis, and his CD4+ lymphocyte count was said to be low. Thrombocytopenia due to hypoplastic bone marrow was also noted, as well as dermatomal zoster in 1989. In February 1990, his CD4+ lymphocyte count was 320 per cubic millimeter, and there was no evidence of HIV infection (Table 2). The CD4+ cell count dropped

Table 2. Results of Retroviral Studies.*

Patient No.	Plasma Antibodies			Plasma Antigens		Viral Cultures		HIV-1 PCR			HIV-2 PCR	HTLV-I/II PCR
	HIV-1†	HIV-2‡	HTLV-I/II	HIV-1 (p24)	HIV-2 (p27)	HIV-1	HIV-2	LTR/*gag*	gp120	gp41	*pol*	*tax/rex*
1	–	–	–	–	–	–	–	–	–	–	–	–
2	–	–	–	–	–	–	–	–	–	–	–	–
3	–	–	–	–	–	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–	–	–	–	–	–
5§	–	–	–	–	–	–	–	–	–	–	–	–
6	–	–	–	–	–	–	–	–	–	–	–	–
7	–	–	–	–	–	–	–	–	–	–	–	–
8	–	–	–	–	–	–	–	–	–	–	–	–
9	–	–	–	–	–	–	–	–	–	–	–	–
10	–	–	–	–	–	–	–	–	–	–	–	–
11	–	–	–	–	ND	–	–	ND	ND	ND	ND	ND
12	–	–	ND	–	ND	–	–	ND	ND	ND	ND	ND

*ND denotes not done, and minus signs negative tests.

†Specific antibodies to HIV-1 were tested by enzyme immunoassay, radioimmunoprecipitation assay, and Western blot assay.

‡Specific antibodies to HIV-2 were tested by enzyme immunoassay and Western blot assay.

§This patient later acquired HIV-1 infection after a new sexual exposure.

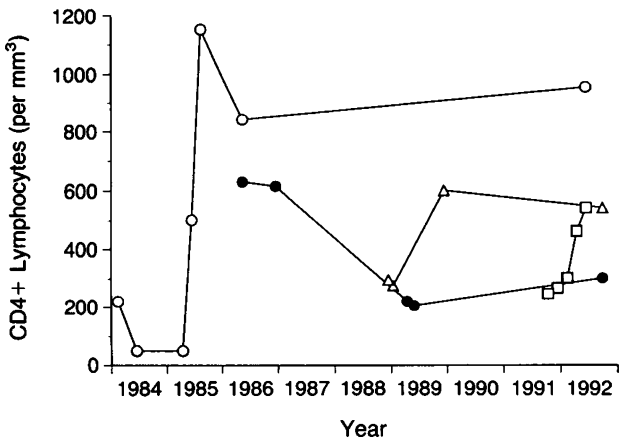

Figure 1. Sequential CD4+ Lymphocyte Counts in Four Patients. Triangles denote Patient 3, solid circles Patient 4, squares Patient 7, and open circles Patient 10.

to 175 per cubic millimeter in 1991. Repeated lymphocyte determinations near the time of this writing showed CD4+ and CD8+ cell counts of 154 and 59 per cubic millimeter, respectively. HIV studies were again completely negative.

Patient 7 (Patient 7 in the article by Smith et al.[16]) was a 36-year-old black male prisoner in whom lobar pneumonia developed in August 1991, at which time an HIV-1–antibody test was negative. He said that he had not engaged in homosexual sex or intravenous drug use but acknowledged having had sex with female prostitutes, as well as a history of both syphilis and gonorrhea. In November 1991, he presented to the hospital with lethargy, nystagmus, and facial weakness. Cranial CT revealed multiple ring-enhancing lesions. These findings, coupled with a positive test for toxoplasma antibodies, led to a presumptive diagnosis of cerebral toxoplasmosis. Skin tests showed anergy, and his CD4+ and CD8+ cell counts were 207 and 223 per cubic millimeter, respectively. An array of tests for HIV were negative (Table 2). Treatment with pyrimethamine and sulfadiazine led to a prompt clinical resolution, along with the gradual disappearance of the intracranial lesions. In addition, his CD4+ lymphocyte counts have increased substantially over the past few months (Fig. 1), and the HIV studies have remained entirely negative (Table 2).

Patient 8, a 30-year-old homosexual Venezuelan man, presented in October 1991 with fever, night sweats, malaise, and lymphadenopathy. HIV-1 infection was suspected, because he had an infected sexual partner and the patient's CD4+ lymphocyte count was only 308 per cubic millimeter. Antibody tests for HIV-1 were negative, however, and he recovered spontaneously after two months of illness. No adequate explanation for the acute syndrome was found despite a thorough evaluation. Another CD4+ cell count in August 1992 was again 308 per cubic millimeter, and no evidence of HIV infection was found after extensive laboratory studies (Tables 1 and 2).

Patient 9 was a 61-year-old Hispanic man who reported no risk factors for HIV infection. In May 1992, he presented to the hospital with a paraspinal abscess, an aspirate of which yielded *Mycobacterium tuberculosis*. A skin test with purified protein derivative was positive. The patient was then treated with a four-drug antituberculous regimen. At that time, his CD4+ and CD8+ lymphocyte counts were 205 and 340 per cubic millimeter, respectively. An HIV-antibody test was negative, and immunoglobulin levels were found to be high (Table 1). One month later, fever, macular rash, and painful swollen knee joints developed. Arthrocentesis showed that the effusion contained 561 white cells per cubic millimeter, 95 percent of which were neutrophils. Bacterial cultures of this fluid and of the patient's blood were negative. The patient was treated empirically with cefotaxime, with a prompt resolution of all signs and symptoms. A repeat CD4+ cell count showed 336 cells per cubic millimeter, and the results of a large group of HIV studies were all negative (Table 2).

Patient 10, a 45-year-old homosexual black man, was found in 1983 to have a platelet count of 50,000 per cubic millimeter and a CD4+ lymphocyte count of 218 per cubic millimeter. These findings, together with his symptoms of fatigue and night sweats, led to a presumptive diagnosis of AIDS. Nevertheless, he did not receive any treatment for the thrombocytopenia. His CD4+ cell counts declined to 60 per cubic millimeter in 1984 and to 57 per cubic millimeter in 1985. By June 1985, however, his symptoms had resolved and the CD4+ lymphocyte count was 588 per cubic millimeter. HIV-1–antibody tests since 1985 have been negative, and his CD4+ cell counts are normal at this writing (Fig. 1). Extensive HIV studies in August 1992 were negative (Table 2).

Patient 11, a 41-year-old white woman, had been in good health until 1989, when she acquired a genital herpes infection. This was followed by the development of extensive vaginal papillomata that were refractory to intralesional injections of interferon. Her medical history included a transfusion of seven units of blood and unprotected sex with several high-risk partners. Immunologic evaluations showed normal immunoglobulin levels, but three CD4+ lymphocyte counts obtained from September 1991 through March 1992 were low (127 to 149 per cubic millimeter). Studies for evidence of HIV infection were completely negative in April 1992 (Table 2).

Patient 12 was a 40-year-old white man who presented in July 1991 with hemoptysis and a left lingular mass. A bronchoscopic biopsy of the lesion revealed *Cryptococcus neoformans*. CT of the head showed multiple ring-enhancing lesions consistent with cryptococcoma. He was treated initially with amphotericin B and later with fluconazole. His CD4+ lymphocyte count was 37 per cubic millimeter. He had a history of intravenous drug use, but HIV-antibody tests were negative. The patient's subsequent course, however, was complicated by staphylococcal endocarditis, requiring mitral-valve replacement. He died in October 1991 of an intracranial hemorrhage. Four CD4+ cell counts during his hospitalization ranged from 27 to 288 per cubic millimeter. Evaluation for HIV was negative (Table 2).

Methods

The presence of antibodies to HIV-1 in serum or plasma was determined with a commercial enzyme immunoassay (Abbott Laboratories, Abbott Park, Ill.) and a Western blot test (Bio-Rad Laboratories, Hercules, Calif.). All the samples were also examined for specific antibodies by a radioimmunoprecipitation assay, as described elsewhere.[17] The presence of antibodies to HIV-2 was determined with a published Western blot technique[18] and with a synthetic-peptide assay (SynthEIA, United Biomedical, Lake Success, N.Y.) based on a gp41 sequence that permits the detection of both HIV-1 and HIV-2 antibodies. The presence of antibodies to human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II) was determined with a commercial enzyme immunoassay (Abbott) and a Western blot assay (Bio-Rad), respectively. The presence of HIV-1 p24 antigen and HIV-2 p27 antigen in serum or plasma was assessed with antigen-capture assays from Abbott Laboratories and Coulter (Hialeah, Fla.), respectively.

Peripheral-blood mononuclear cells (PBMCs) were cultured for HIV-1 or HIV-2 with a technique described elsewhere.[19] Viral expression was monitored by the detection of HIV-1 p24 or HIV-2 p27 antigen in the culture supernatants.

The polymerase chain reaction (PCR) was used to search for DNA sequences of HIV-1, HIV-2, HTLV-I, and HTLV-II in samples of PBMCs from the patients. DNA was extracted directly from PBMCs and then subjected to PCR with three sets of nested primers — p51, p52b, p53b, and p54; p5-2, p2b, p7b, and p4b; and p31, p18, p32b, and p16b — to detect sequences corresponding to HIV-1 LTR/*gag*, gp120, and gp41, respectively (Table 3). Each reaction mixture consisted of 0.5 to 1.0 μg of DNA, 10 mM TRIS–hydrochloric acid (pH 8.3), 50 mM potassium chloride, 0.2 mM each deoxynucleotide triphosphate, 2 mM magnesium chloride, 10 pmol of each primer, and 2.5 units of AmpliTaq polymerase (Perkin–

Elmer Cetus, Norwalk, Conn.) in a total volume of 100 μl. Thermocycling was then carried out for 1 minute at 94°C, 1 minute at 55°C, and 1.5 minutes at 72°C, for 30 cycles. Five microliters of the product was used as target DNA for the second round of amplification. Ten microliters of the final product was analyzed by electrophoresis and visualized by staining with ethidium bromide. Nested PCR to detect HIV-2 *pol* sequences in PBMCs from the patient was performed similarly, except that the primer set used was *pol*A, *pol*B, *pol*C, and *pol*D (Table 3), which permits the amplification of DNA from HIV-2 and simian immunodeficiency viruses of macaque and sooty mangabey monkeys. Single-round, 40-cycle PCR (carried out at 94°C for one minute and at 68°C for two minutes) was performed to detect sequences common to both HTLV-I and HTLV-II with primers in the *tax/rex* region[20] (Table 3).

Results

By definition, all the patients studied had abnormally low CD4+ lymphocyte counts (Table 1). The lowest values ranged from 3 to 308 per cubic millimeter (mean, 149). Given the known polymorphism at the OKT4 epitope of the CD4 molecule,[21] the CD4+ lymphocyte determinations for six patients were verified with monoclonal antibodies (OKT4A and Leu-3a) directed against nonpolymorphic epitopes. In some patients (Patients 3, 7, and 10), the CD4+ T-lymphocytopenia was completely or partially reversible (Fig. 1), whereas in others (such as Patients 2 and 4) the abnormality was persistent (Table 1 and Fig. 1). Concomitant CD8+ lymphocytopenia was observed in three patients (Patients 1, 6, and 12), and none of the patients had markedly elevated CD8+ cell counts. Serum IgG levels were depressed in Patients 1 and 2, whereas elevated levels were found in Patients 7, 9, and 10. No patient had grossly abnormal concentrations of IgA or IgM. Of the seven patients in whom skin tests were performed, five were anergic to multiple recall antigens.

The results of serologic studies conducted to look for evidence of infection by known human retroviruses are summarized in Table 2. No antibodies to HIV-1 were detected in the serum or plasma of patients by enzyme immunoassay, Western blot assay, or radioimmunoprecipitation assay. Antibodies to HIV-2 were also not detected by Western blot assay or synthetic-peptide assay in any patient, nor were antibodies to HTLV-I or HTLV-II found by enzyme immunoassay or Western blot assay, although one patient (Patient 12) was not tested.

HIV-1 or HIV-2 core antigens were not detected in the patients tested (Table 2). In addition, highly sensitive cultures for HIV-1 and HIV-2 were negative in every patient (Table 2). Electron-microscopical analysis of cultured cells from Patients 7 and 8 failed to demonstrate any lentiviral particles.

PCR studies were performed on samples from 10 of the 12 patients, the findings of which were entirely negative for HIV and HTLV (Table 2). Examples of the negative studies are shown in Figure 2. HIV-1 and HIV-2 studies were performed with a nested PCR assay capable of detecting five or more molecules of the target DNA. The negative results for HTLV were obtained with a single-round PCR protocol that had been shown to be highly sensitive in previous studies.[20,21]

Discussion

The CDC has broadly defined idiopathic CD4+ T-lymphocytopenia as a reproducible depletion of CD4+ lymphocytes below 300 per cubic millimeter in the absence of HIV infection or other known causes of immunodeficiency.[13,14] Our 12 patients were studied before the official definition was formulated; however, their clinical profiles are generally compatible with it. Overall, the clinical manifestations have been hetero-

Table 3. Oligonucleotide Primers Used in the PCR.*

Primers	Sequence (5′–3′)	Nested PCR	Gene	Location	Viral Clone
HIV-1					
p51	CACTGCTTAAGCCTCAATAAAGCTTGCCTT	Outer set	LTR	512–541	NL4-3
p52b	TTTGGTCCTTGTCTTATGTCCAGAATGC		*gag*	1658–1631	
p53b	GTGGAAAATCTCTAGCAGTGGCGCCC	Inner set	LTR	617–633	
p54	ATTTCTCCTACTGGGATAGGTGGATTA		*gag*	1571–1545	
p5-2	CCAATTCCCATACATTATTGT	Outer set	gp120	6847–6867	NL4-3
p2b	GACGCTGCGCCCATAGTGCTTCCTGCTGC		gp120	7815–7786	
p7b	GTTAAATGGCAGTCTAGCAGAAGAAGA	Inner set	gp120	6994–7020	
p4b	ACTTCTCCAATTGTCCCTCATATCT		gp120	7657–7633	
p31	TAGGAGTAGCACCCACCAAGGCAAAGAGAAGAG	Outer set	gp120	7695–7727	NL4-3
p18	TTCTGCCAATCAGGGAAGTAGCCTTGTGTGTG		gp41	9163–9132	
p32b	CTATAGTGAATAGAGTTAGGCAGGGAT	Inner set	gp41	8322–8350	
p16b	TAAGTCATTGGTCTTAAAGGTACCTGAGGT		gp41	9028–8999	
HIV-2/SIVmac					
*pol*A	AGGGGAGGCTATACATGGGCAAGTAAATGC	Outer set	*pol*	4642–4671	SIVmac/BK28
*pol*B	CTGCCTTCTCTGAAATAGACCCGAAAA			5196–5168	
*pol*C	CAGTACATGTTGCAAGTGGATTTATAGA	Inner set	*pol*	4731–4758	
*pol*D	CTTCTTTTAAAATTCATGCAATGAACTGCC			5067–5036	
HTLV-I/II					
p20	CGGATACCCAGTCTACGTGTT	NA	*tax/rex*	7336–7356	HTLV-I
p21	GAGCCGATAACGCGTCCATCG		*tax/rex*	7474–7454	

*Retroviral sequences were derived from the HIV Sequence Database, Los Alamos National Laboratory. SIVmac denotes simian immunodeficiency virus obtained from macaque monkeys, and NA not applicable.

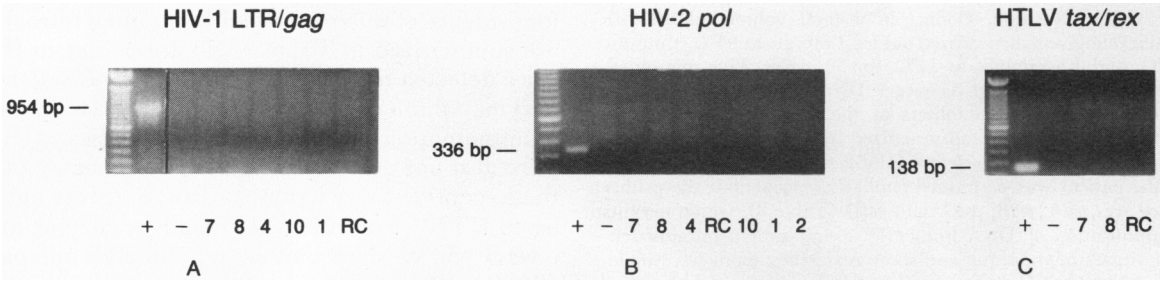

Figure 2. Examples of PCR Studies Conducted to Detect Retroviral DNA Sequences in the Blood Cells of Patients.
PCR was used to search for DNA sequences of HIV-1 (Panel A), HIV-2 (Panel B), and HTLV-I and HTLV-II (Panel C). Plus signs below the figure denote infected-cell DNA controls, minus signs negative controls with cells from normal donors, and RC reagent controls; the numbers identify the patients.

geneous: five patients with opportunistic infections, five with syndromes of unknown cause, and two with no symptoms (Table 1). It is certainly not possible to link the conditions of all these patients, as well as those described by others,[6-9,13,14] together into one syndrome on clinical grounds alone. The shared feature of CD4+ T-lymphocytopenia may simply reflect the inherent bias in case acquisition. On the other hand, although it is a distinct possibility that there may be multiple causes of idiopathic CD4+ T-lymphocytopenia, it is also conceivable that a subgroup of these patients may share a common cause. At this time, it is simply unclear whether this syndrome is a new clinical entity or even an acquired syndrome.

The clinical course of idiopathic CD4+ T-lymphocytopenia appears to differ from the unrelenting, progressive course of AIDS. Two of our patients died from acute complications, but 10 were stable without evidence of disease progression. Similarly, of the 30 patients studied to date by the CDC,[13,14] only 1 has died. Aside from low CD4+ lymphocyte counts, the immunologic findings in our patients are also distinct from the abnormalities found in HIV infection. In general, we did not observe a steady decline in CD4+ cells; indeed, several patients had a spontaneous reversal, partial or complete, of the lymphocytopenia (Fig. 1), suggesting a transient cause such as an acute infection. This immunologic picture would be highly unusual for HIV infection. In addition, only three of our patients had the hypergammaglobulinemia that is typically seen in HIV-infected persons. Low levels of immunoglobulins, as well as low CD8+ lymphocyte counts, were noted in some patients (Table 1), raising the possibility of a more generalized state of immunodeficiency (primary or acquired) in select cases of the condition.

From the available clinical and epidemiologic data, it is not known whether idiopathic CD4+ T-lymphocytopenia is due to a transmissible agent. Given the results of the extensive retroviral studies summarized in Table 2 and illustrated in Figure 2, we are confident in concluding that neither HIV-1 nor HIV-2 was etiologically involved in our patients with idiopathic CD4+ T-lymphocytopenia. The lack of specific antibodies, infectious virus, and HIV DNA was demonstrated by multiple sensitive methods. These findings, together with the obvious clinical and immunologic differences between idiopathic CD4+ T-lymphocytopenia and AIDS, suggest that the cause of this newly recognized syndrome is not likely to be a retrovirus closely related to HIV or simian immunodeficiency virus.

Although the clinical and immunologic profile of idiopathic CD4+ T-lymphocytopenia is not consistent with that of HTLV-I or HTLV-II disease, we tested for these two human retroviruses and determined that they were absent from our patients (Table 2 and Fig. 2). Is a new human retrovirus responsible for this newly recognized condition? Laurence et al.[8] have reported reverse transcriptase activity in cultures from two of their patients with idiopathic CD4+ T-lymphocytopenia, but their subsequent studies have yet to confirm the existence of a putative human retrovirus.[22] Gupta et al.[9] have also detected reverse transcriptase activity in the culture from one patient, and have reported the visualization by electron-microscopical analysis of envelope-defective intracisternal A-type particles. However, it is still unclear how a defective and presumably noninfectious viral particle could be etiologically linked to the syndrome.[22] Therefore, additional studies are warranted to clarify the potential link between idiopathic CD4+ T-lymphocytopenia and an as yet undefined human retrovirus distinct from HIV and HTLV. It is perhaps more important to work harder to track the epidemiologic features of idiopathic CD4+ T-lymphocytopenia closely, to define the associated immune deficits carefully, and to search broadly for the cause.

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