Elevated CD4+/CD8+ Ratio in HIV Elite Controller

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ABSTRACT

Elite controllers of HIV have the unique ability to maintain a healthy CD4+ count (>500 cells/uL) and suppressed viral load (HIV RNA <400 copies/mL) without the use of antiretroviral therapy (ART). This case report illustrates a case of HIV viral suppression in the absence of ART in a well-appearing 60-year-old Puerto Rican male with a history of multiple incarcerations. Although the presentation seen in this patient is rare, the importance of maintaining a healthy CD4+/CD8+ ratio appears to be a strong protective measure against non-AIDs associated morbidity and mortality in HIV-infected individuals, including ischemic heart disease, stroke, and non-AIDS malignancies. Recognition of the unique social, behavioral, and biological characteristics of "elite controllers" is critical to understanding the mechanisms through which the HIV virus may be controlled. Overall, the CD4+/CD8+ ratio can be used as a predictive measure of non-HIV associated morbidities and providers should work with patients to maintain a protective CD4+/CD8+ ratio.

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CASE PRESENTATION

A 60-year-old male presented to clinic with HIV and a history of intravenous drug use more than a decade ago. While incarcerated more than 10 years ago, he was diagnosed with HIV (via two ELISA tests, followed by a confirmatory western blot) but never followed up for care. Three years prior to presentation, he was incarcerated again, during which time routine testing reconfirmed his HIV, but he was told that he did not need treatment because his CD4+ count was above the threshold (>250 cells/uL) for consideration of ART. Upon discharge from the penitentiary, the patient planned to follow up in the community but had not done so until 2 years ago. At that visit two years prior to current presentation, he reported feeling "very good" and experienced no symptoms related to his HIV. Laboratory testing showed a CD4+ count of 6900/uL, HCV viral load <43 copies/mL, and HIV viral load <48 copies/mL (Table 1). The patient was then lost to follow up. At this presentation, the patient reported being in good health over the past two years. He stated he did not have any symptoms related to his HIV infection and did not return to clinic because he felt healthy.

The patient denied currently taking ART or any other medication. He had no known medication allergies. Besides HIV (western blot positive at current presentation), his past medical history

included Hepatitis C and spinal disc herniation. He did not have any surgical history or past hospitalizations. Family history is positive for maternal diabetes. Social history included origin from Puerto Rico and nine children with multiple women. He states that his most recent partner, from whom he is separated, tested negative for HIV when their last child was born. He denied recent sexual activity or illicit drug use. He reported rare alcohol consumption and smoking 2-3 cigarettes per day.

On physical exam, vital signs included a temperature of 98.2°F, heart rate of 111 beats/minute, and blood pressure of 150/98 mmHg. The physical exam was unremarkable with the exception of tachycardia and old track marks on bilateral forearms. The patient's laboratory values were all within normal to high ranges (Table 1). Western blot testing revealed a positive HIV result. Of note, the patient had negligible viral loads for HIV and HCV. Furthermore, he had normal CD4+ and CD8+ lymphocyte counts; therefore, the patient also had an elevated CD4+/CD8+ ratio. It was noted that lymphocyte values had remained relatively constant over the past two years.

DISCUSSION

Although the number of new HIV infections continues to decline, a total of 2.7 million people worldwide (~50,000 in US) acquired HIV infec-

Table 1. Laboratory Values

	Normal Reference Ranges	**Non-Elite HIV Reference Ranges**	**Initial Visit: 2 prior to current presentation**	**Current Presentation**
HIV viral load	N/A	$100 – 10^6$ copies/mL[A]	<48 copies/mL	<20 copies/mL
WBC count	4500 – 11,000 cells/uL	variable[B]	6900 cells/μL	8200 cells/μL
Lymphocyte Values (cells/uL)	CD4+ 0.500-1.200 (40%) CD8+ 0.300-0.800	CD4+ <0.400 (<25%)[C]	CD4+ 0.968 (46.1%) CD8+ 0.420 (20.0%)	CD4+ 1.297 (39.3%) CD8+ 0.564 (17.1%)
CD4+:CD8+ ratio	0.9-1.9	<0.9	2.305	2.299
HCV PCR	N/A	N/A[D]	< 43 copies/mL	TND[E]

Relevant laboratory data from patient visits. The patient has maintained below average HIV viral load and an above average lymphocyte count for an HIV infected individual. Normal reference ranges indicate the standard values for each laboratory measure. The laboratory values above vary significantly depending on the stage of infection.

[A]Non-elite HIV infected individuals have a HIV RNA level, also called the viral load, that can range from 100 to as high as 1,000,000 copies/mL.

[B]Non-elite HIV infected individuals and uninfected individuals both have a wide WBC range that changes with infection.

[C]Non-elite HIV infected individuals have an impaired cell-mediated immunity due to the decrease in CD4+ cells.

[D]HCV viral loads vary widely based on the acuity of the infection. HCV infected viral loads range from hundreds to millions.

[E]TND is "Target Not Detectable," which indicates that the virus is below detectable levels (<20 copies) in the blood but still present throughout the body. TND is the goal of HIV treatment.

tion in 2010, contributing to the global number of 34 million people (1.2 million in US) living with HIV in 2010.[1] HIV is described as acute viremia defined by >5x10^6 viral particles/mL. Without ART, CD4+ T lymphocyte levels decline and when levels fall below 200 cells/mL, AIDS is diagnosed.[2] Certain individuals, termed "elite controllers" or natural viral suppressors (NVS), maintain normal CD4+ counts (500-1200 cells/mL), rarely develop clinical disease, and are less likely to transmit HIV. One study examining 40 elite controllers found a very low rate of progression to AIDS, with only one subject progressing 15 years after the initial diagnosis.[3] Elite controllers represent a very small percentage of the HIV population with studies estimating an incidence of 1.1% and a prevalence ranging from 0.6% - 1.5%.[3,4] The International HIV Controllers Study evaluated 974 NVS and identified >300 genome wide single-nucleotide polymorphisms (SNP) within major histocompatibility complex (MHC) that dictate human leukocyte antigen (HLA) viral peptide interaction as the major genetic factor modulating durable control of HIV infection.[5] Once inside an antigen presenting cell (APC), HIV associated proteins are degraded into small peptides, typically nine amino acids in length, and expressed on the cell surface HLA class I molecule. This virus processing and protein presentation are genetically determined and the major determinant of host control of HIV. Specifically, the molecular structure of HLA is associated with disease progression, with one of the most significant polymorphisms resulting in position 97 in the floor of the peptide-binding groove of HLA-B.[5] However, when looking at large, clinically well-defined cohorts, researchers have also pinpointed other binding sites within HLA-B accounting for the varying progression of HIV to AIDS. For example, amino acid substitutions at positions 114 and 116 of the HLA-B heavy chain alter the ability of the protein complex to bind tyrosine at the carboxy-terminal anchor. This varying ability to bind tyrosine may be the critical distinction between HLA-B genotypes and ultimately influence the presentation of specific HIV epitopes to cytotoxic T lymphocytes. Because of the overlying genetic effect on disease progression, genetic testing of HIV infected patients, specifically aimed at the HLA-B alleles, could be developed in order provide more or less aggressive therapeutic regimens for patients. Furthermore, researchers believe further study aimed at characterizing cytotoxic-T-lymphocyte activity in HIV infected patients, especially in elite-controllers, may highlight mechanisms involved in HIV susceptibility.[6]

This patient has maintained normal laboratory values during a two-year period for HIV, despite having never received ART. He also managed to autonomously clear Hepatitis C. NVS patients clear HCV infection at an elevated rate (23.3%) compared to HCV-monoinfected (9.1%) and HIV/HCV-coinfected individuals (6.5%).[7] Therefore, the patient qualifies as an "elite controller" of the HIV infection. Of note, the patient maintained an elevated CD4+/CD8+ ratio without need for ART for the past two years. With a greater prognostic value than either the absolute or percentage CD4+ count, the CD4+/CD8+ ratio has been noted to be protective over various types of non-AIDS associated morbidity and mortality, including ischemic heart disease, stroke, and non-AIDS malignancies.[8-11] Furthermore, the CD4+/CD8+ ratio has been shown to be better than CD4+ or CD8+ alone to determine risk of non-AIDS events including hypertension, diabetes, cardiovascular disease, liver failure, kidney failure, peripheral neuropathy, and cognitive decline.[8,11] According to the US Department of Defense HIV Natural History study, researchers concluded that elite controllers not only had significantly fewer AIDS defining events but also had a longer time to death and AIDS diagnosis compared to HIV noncontrollers.[12] As seen with this patient, the elevated CD4+/CD8+ ratio has proven to be a protective

measure of overall health status. Moving forward, researchers hope to identify characteristics of patients, including lifestyle and cellular markers that predispose patients to a healthy CD4+/CD8+ ratio. Learning from the unique characteristics of elite controllers, especially their innate and adaptive immunity, opens the door to develop treatment modalities such as T cell vaccines aimed at reducing HIV replication, progression, and transmission. However, to achieve this understanding, immune protection in vivo as in elite-controllers must be thoroughly determined.[13] From this point researchers plan to identify the unique social, behavioral, and biochemical characteristics of "elite controllers" in order to understand the mechanisms by which HIV can be autonomously controlled and apply these factors to the HIV population at large.

LEARNING POINTS

- Elite controllers of HIV have the unique ability to maintain a healthy CD4+ count and suppressed viral load without the use of antiretroviral therapy (ART).
- Elite controllers of HIV may clear HCV infection at an elevated rate.
- The elevated CD4+/CD8+ ratio in this HIV patient may be a protective measure over various types of non-AIDS associated morbidity and mortality, including hypertension, diabetes mellitus, cardiovascular disease, pulmonary hypertension, cancer, osteopenia, osteoporosis, liver and kidney failure, peripheral neuropathy, frailty, and cognitive decline.

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