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CD8 T-Cell Lymphocytosis and Associated Clinical Syndromes in HIV-Infected Patients

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Abstract

An inverted CD4:CD8 T lymphocyte ratio is frequently observed in individuals infected with HIV. A subset of these individuals develops an exuberant and persistent CD8 T-cell lymphocytosis response to HIV infection that may occur despite virologic suppression on treatment and has been associated with adverse clinical effects and disorders. This review describes clinical syndromes that have been reported primarily in HIV-infected individuals with CD8 T-cell lymphocytosis including their presentation, management, and clinical outcomes where known. **(AIDS Rev. 2015;17:202-11)**

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Key words

HIV infection. HIV-1. Human. Lymphocytosis.

Introduction

Some individuals with HIV infection, including those with fully suppressed viral loads on antiretroviral therapy (ART), develop an exuberant CD8 T lymphocyte response to their infection. It is important to recognize CD8 T-cell lymphocytosis because its persistence has been linked with important clinical disorders, which often go unrecognized by clinical providers or are misdiagnosed as other HIV or non-HIV associated conditions[1].

These disorders include CD8 T-cell lymphocytosis without visceral infiltration, diffuse infiltrative lymphocytosis syndrome (DILS) characterized by multiorgan CD8 T lymphocyte infiltration[2,3], and the more recently described but less defined CD8 encephalitis[4]. Other reported but less common CD8 T lymphocyte infiltrative syndromes include primary cutaneous T-cell lymphoma[5], and panuveitis[6].

CD8 T-cell lymphocytosis has also been associated with accelerated progression of atherosclerosis[7], increased risk of acute myocardial infarction (AMI)[8], and other similar markers of age-associated disease[9]. On the other hand, CD8 T-cell lymphocytosis is associated with enhanced virologic control with lower viral "set points" and delayed progression to AIDS[10].

There is limited information on the spectrum of clinical conditions associated with this immunologic condition and their appropriate management. Treatment ranges from institution or resumption of ART in treatment-naive patients or those with interrupted therapy, respectively, to the use of immune-modulating therapies. In this article, we review the literature and discuss what is known about the prevalence, classification, etiopathogenesis, associated clinical manifestations, management, and prognosis of CD8 T-cell lymphocytosis syndromes in HIV-infected patients.

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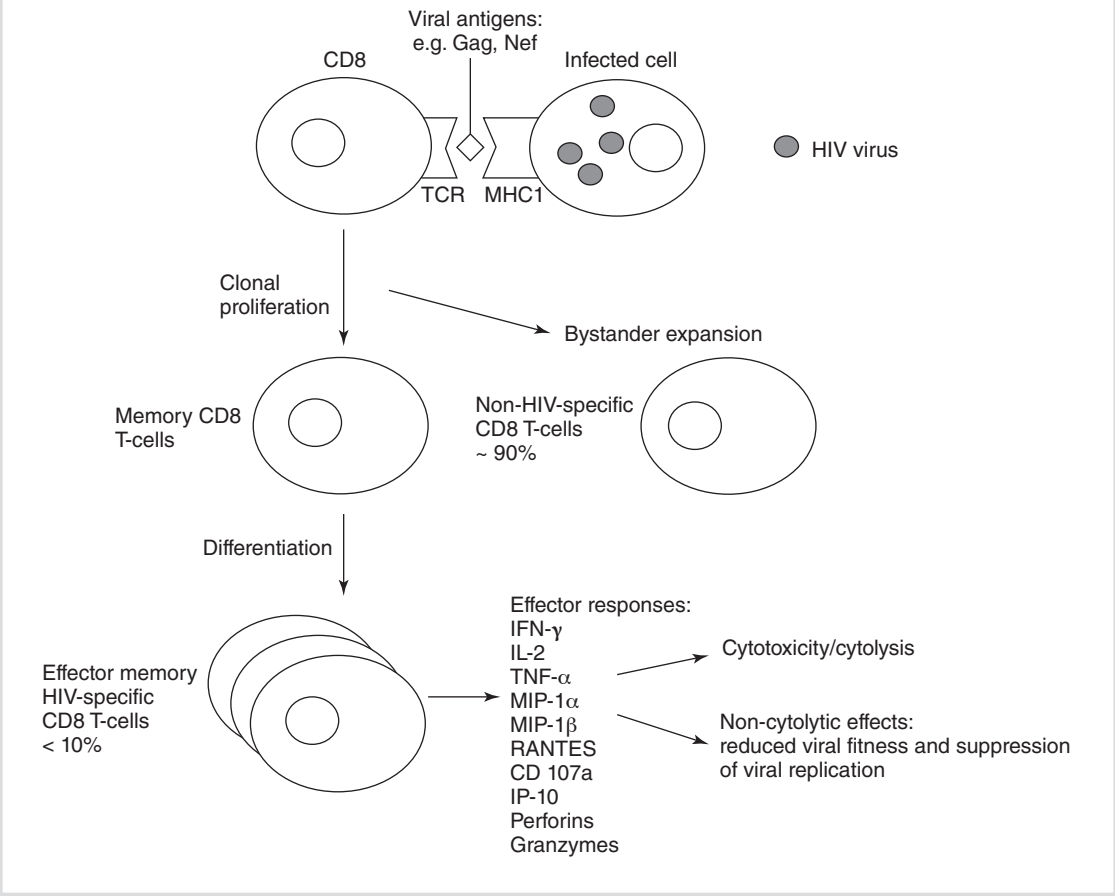

Figure 1. *CD8 T-cell response to HIV infection. The CD8 T-cell receptor binds to MHC1-HIV viral antigen complex on the surface of an infected cell. This triggers the CD8 T-cell to undergo clonal proliferation. There is also bystander expansion of non-HIV-specific CD8 T-cells. Only about 10% of the CD8 expansion is specific towards HIV epitopes, whereas 90% of the expanded CD8 T-cell population is not specific towards HIV and is an indirect result of other antigenic stimuli. The resulting memory CD8 T-cells then undergo differentiation to effector memory HIV-specific CD8 T-cells. The effector memory HIV-specific CD8 cells have both cytotoxic (cause cytolysis of infected cells) and non-cytotoxic effects, which result in reduced viral fitness and suppression of viral replication through effector responses including the cytokines and chemokines listed. TCR: T-cell receptor; MHC1: major histocompatibility complex 1; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; MIP: macrophage inflammatory protein; RANTES: regulated on activation normal T-cell expressed and secreted: CD: cluster of differentiation; IP: interferon gamma-inducible protein.*

CD8 T lymphocyte responses in HIV infection

During HIV infection, CD8 T lymphocytes play a role in virologic control by targeting infected cells through surface class I human leukocyte antigen (HLA) glycoproteins presenting viral antigens (Fig. 1). Antigen-specific CD8 T lymphocytes subsequently undergo clonal proliferation yielding virus-specific effector responses. Such HIV-specific CD8 T lymphocyte proliferation occurs through the aid of CD4 T helper cells[11,12]. This phenomenon has been documented in HIV-1 elite controllers[13,14].

Individuals with acute HIV infection experience a marked CD8 T lymphocyte activation and expansion that includes both HIV-specific as well as bystander CD8 T lymphocyte clones inactive against HIV that may persist throughout the course of infection[15-17]. There is a relationship between the development of these effector HIV-specific CD8 T lymphocytes and decrease in viral load[18,19]. Early *in vitro* studies have demonstrated that these HIV-specific cytotoxic CD8

T lymphocytes are capable of inhibiting virus replication[20-22].

The initial CD8 T lymphocyte response is directed towards a very limited range of HIV epitopes[23]. As the infection progresses, however, the breadth of the CD8 T lymphocyte response increases without any additional benefit to virologic control suggesting that the response during chronic infection is composed of impaired CD8 T lymphocytes[23]. The impaired immunologic response is believed to be secondary to CD8 T lymphocyte exhaustion in the setting of chronic infection in patients with high levels of antigenemia. In this setting, cells undergo a progressive change towards exhaustion, beginning with an inability to proliferate, followed by an inability to produce and secrete cytokines and chemokines, then a loss of cytolytic activity, and finally entering the stage of exhaustion[15,23]. In similar fashion, CD8 T lymphocytes also exhibit immunosenescence, marked by loss of CD28 and expression of CD57 surface markers as well as a diminution in responses to antigen stimulation[15].

It is worth highlighting that only about 10% of the total circulating CD8 T lymphocytes in chronically infected patients are specific for HIV[15]. Therefore, it is thought that the overall CD8 T lymphocyte proliferation is secondary to the generalized inflammation from chronic infection and that rather than being specific to HIV epitopes, it is a "bystander" reaction to the inflammation[15]. It is also possible that other concurrent viral infections, like cytomegalovirus (CMV), human T-cell lymphotropic virus (HTLV)-1 and Epstein-Barr virus (EBV) may play a role in promoting CD8 T lymphocyte activation and proliferation[24].

Pathogenesis

In the context of HIV infection, a principal function of CD8 T lymphocytes is to eliminate viral infection, but the breadth and complexity of antiviral responses can be deleterious to healthy tissue. Several theories have been proposed on the pathogenesis of CD8 T lymphocyte-associated clinical syndromes.

The CD8 T lymphocytes produce a variety of cytokines in response to viral infections including IFN-γ, IL-2, TNF-α, macrophage inflammatory protein-1α (MIP-1α), MIP-1β and regulated upon activation normal T-cell expressed and secreted (RANTES), all of which contribute to a generalized inflammatory response[25]. For instance, MIP-1α, MIP-1β and RANTES are rapidly released from CD8 T lymphocytes upon activation and they promote inflammation by recruiting leukocytes to sites of infection[25]. The specific recruitment of lymphocytes, particularly uninfected CD4 T lymphocytes, promotes immune activation and more inflammation by recruiting uninfected target cells to sites of active infection[25].

The CD8 T lymphocytes have direct cytotoxic effects against HIV-infected CD4 T lymphocytes, but have also been associated with cellular and tissue injury in organs they infiltrate as well as the promotion of an environment that favors carcinogenesis[25,26]. As an example of the former, it has been recognized that CD8 T lymphocytes may replicate and persist in the CNS with promotion of neuronal damage, but the mechanisms by which this occurs is not entirely known[27]. Further studies are needed to define the exact mechanisms of CD8 T lymphocyte-mediated pathogenesis.

Clinical CD8 T-cell lymphocytosis syndromes

Diffuse infiltrative lymphocytosis syndrome

Certain HIV-infected individuals with persistent CD8 T cell lymphocytosis will experience cellular infiltration of multiple organ systems manifesting as DILS. This is characterized by a persistent CD8 T cell lymphocytosis and infiltration of visceral organs and salivary glands by CD8 T lymphocytes[28]. The lungs, kidneys, liver, and gastrointestinal tract are some of the visceral organs that are typically involved in the syndrome[3,29-31]. DILS has been referred to as Sjogren's-like syndrome as it has a similar clinical presentation to the autoimmune disorder Sjogren's syndrome[32].

Itescu, et al. first described the term "DILS" when they reported on a case series of 12 patients, the majority of whom were black, who had CD8 T-cell lymphocytosis and bilateral parotid gland enlargement associated with increased prevalence of HLA-DR5[28]. In their report, there was evidence of inflammation in the parotid, lacrimal, and submandibular glands in all patients who had gallium scans performed[28]. Seven of the 12 patients had histologically proven involvement of the pulmonary interstitium, two had periportal lymphocytic infiltration of the liver, and four had involvement of the nervous system manifesting as nerve palsy, aseptic meningitis, and motor neuropathy. In all patients, the CD4:CD8 ratio was less than one. Ten of the 11 black patients were found to have HLA-DR5, suggesting that the MHC class II allele was associated with the development of the CD8 T-cell lymphocytosis[28].

The prevalence of DILS among HIV-infected individuals ranges from 0.85 to 48% on clinical and histopathological surveys[20,32-34], with a higher frequency of occurrence in blacks compared to other racial groups[29,34,35]. In one of the largest epidemiological studies, which included 4,100 outpatients with HIV infection, 35 patients were diagnosed with DILS, resulting in a prevalence of 0.85%[29]. Two separate studies found the prevalence of DILS to be 3-4% and 7.8% among HIV-infected individuals in outpatient settings[32,34]. A study in Cameroon suggested that the prevalence was much greater, with 48% of surveyed HIV-infected individuals found to have histological evidence of salivary gland CD8 T lymphocyte infiltration, but this study may be limited by selection bias[33].

Diffuse infiltrative lymphocytosis syndrome is distinguished from the other CD8 T-cell lymphocytosis syndromes by the presence of visceral infiltration with the requirement for involvement of the salivary glands and the distinct HLA allelic association and immunophenotypic profiles of the circulating CD8 T lymphocytes.

The host response to HIV infection that leads to the development of DILS may have a genetic basis. Certain MHC class II alleles have been associated with DILS, including DRB1*1102 of DR5 specificity and DRB1*1301 of DR6 specificity[36]. The alleles were associated with certain racial demographics. Nearly 80% of blacks with DILS were enriched with either the DR5 or DR6 specificities[36].

Examination of the structure of the T-cell receptor repertoire in five patients with DILS found that they shared similar structural features with a restricted usage of Vβ and Jβ gene segments as well as a preference for specific amino acids at position 97 in the third complementary-determining region thought to contact the peptide antigen, and these gene segments did not carry any germ line nucleotide sequences[37]. Overall, these findings are consistent with a process driven by MHC-restricted antigen presentation to the T lymphocytes that contributes to developing DILS.

Patients with CD8 T-cell lymphocytosis, compared to those without it, have a consensus phenotype of $CD8^+$ DR^{high} $CD11a^+$ $CD11c^+$ $CD16^-$ $CD28^{+/-}$ $CD56^-$ $CD57^+$, which is consistent with activated large granular T lymphocytes[38]. Among DILS patients, the circulating CD8 T lymphocyte phenotype has been shown to be consistent with a memory/effector phenotype with increased CD57 expression, CD11a/CD18, and CD29 markers[2].

The degree of CD8 T-cell lymphocytosis associated with development of DILS ranges widely among studies. Several studies collectively reported CD8 T-cell lymphocytosis to > 1,400 cells/mm^3 in range[3,28,39-41], while others have reported wider ranges including 562-4,994 cells/mm^3 in range[29] and 1,304 ± 521 cells/mm^3 in range[34]. The CD4:CD8 ratio was usually less than 0.50[29,32].

The proposed diagnostic criteria for DILS requires that the patient be HIV positive, have bilateral salivary gland enlargement or xerostomia for greater than six months, and have histologic confirmation of salivary gland lymphocytic infiltration without evidence of granulomatous or neoplastic processes[42].

The most common clinical finding in DILS is bilateral parotid gland enlargement. Therefore, the clinical presentation of DILS is similar to Sjogren's syndrome, but may be differentiated from it by CD8 T lymphocyte infiltration, lack of autoantibodies, and extraglandular visceral infiltration[28]. Patients with DILS typically present with sicca symptoms, including xerostomia and xerophthalmia as well as parotid gland enlargement[3,28,43]. In one study, only 6% of patients with DILS were without sicca symptoms[29].

Compared to Sjogren's syndrome, DILS is associated with a different immunologic and immunogenetic profile. There is no direct association between DILS and the presence of α-La/SSB antibodies, although a minority of individuals may have evidence of rheumatoid factor and antinuclear antibodies[28,35]. A case report on a patient presenting with symptoms similar to DILS reported the patient had α-Ro/SSA, rheumatoid factor, anticardiolipin antibody, and antinuclear antibody[40], but the majority of reported DILS cases have no evidence of autoantibodies.

Numerous studies have demonstrated that the most common extraglandular organ infiltrated by CD8 T lymphocytes in DILS patients is the lungs, typically presenting as a lymphocytic interstitial pneumonitis[3,29,35]. Clinically, patients can present with dyspnea on exertion and diffuse infiltrates on radiographic studies[29,35].

Other organ infiltration syndromes have been associated with DILS in HIV patients on ART. In a case series of patients identified with DILS among a US outpatient cohort, 23% of patients presented with hepatomegaly with abnormal liver function tests and a biopsy of one of these patients demonstrated lymphocytic infiltration[29]. In a separate study, eight out of 129 patients diagnosed with DILS were found to have lymphocytic hepatitis[35]. Other rare conditions reported in patients with DILS include distal renal tubular acidosis, persistent generalized lymphadenopathy, neuropathy, myositis, and polyarthritis[29,39]. There was a case of associated acute renal failure[44] and several reported cases of lymphocytic interstitial nephritis[35].

One study examined the peripheral nerves of HIV-infected patients to determine whether CD8 T lymphocyte infiltration was related to a neoplastic process or secondary to DILS[39]. In this study, nerve biopsies were examined from six patients with DILS and compared to that obtained from controls with HIV-associated peripheral neuropathies. The biopsies from the patients with DILS contained a significantly higher amount of HIV-1 proviral DNA compared with nerve biopsies from controls[39]. The presence of high proviral load in the setting of a CD8 T-cell lymphocytic infiltration of the nerves in these patients suggested that HIV was a causative factor related to the neural infiltration of the lymphocytes.

The management of DILS is focused on initiation or reinstating ART[2,3,29,30,34,40,42]. As DILS is a consequence of an immune response to HIV infection, it should resolve with or be prevented by the institution of ART[39]. Real world epidemiologic observations seem to support the impact of ART on DILS. With the advent of combination ART, the prevalence of DILS has significantly decreased since the 1990s, suggesting a protective effect[35].

A retrospective study examining the prevalence of DILS in a rheumatology clinic from 1994 to 2003 found that among the 129 DILS diagnoses, 111 were diagnosed before 1998 and only 18 were diagnosed after 1998[35]. They also noted that patients taking protease inhibitors were less likely to have histologic evidence of salivary gland lymphocytic infiltration[35]. The use of prednisone has been shown to reduce parotid gland enlargement and improve patient survival in some cases[29,34,41]. Intravenous immune globulin has been used in a patient with DILS-associated myositis with success[27].

The prognosis of patients with DILS is quite favorable. In fact, HIV-infected patients with DILS may experience a survival advantage. In two separate studies, DILS patients were followed for several years and only one patient each among groups of 12 and 17 patients, respectively, followed over time were found to develop an opportunistic infection during the study[28,36]. Another study found that, compared with other HIV-infected controls, patients with DILS were less advanced in their HIV clinical stage at the same duration of illness[34]. However, due to the rarity of DILS and small numbers of patients studied, definitive conclusions cannot be made regarding these observations.

CD8 Encephalitis

Recently there have been reports of HIV patients with well-controlled viremia on ART presenting with inflammatory encephalitis resulting from CD8 T-cell lymphocytic infiltration of the central nervous system (CNS)[1,4,45]. In a retrospective study of 9,500 HIV-infected patients, 14 individuals who were previously classified as having encephalitis of undetermined origin were found to have multiple linear gadolinium-enhanced perivascular lesions by brain magnetic resonance imaging (MRI) with features of brain injury, neurologic symptoms compatible with acute or sub-acute encephalitis, and brain biopsies with extensive perivascular CD8 T lymphocyte infiltration. These were reported as cases of CD8 encephalitis and, based on the survey, the prevalence among the study population was 0.015% although this most likely under-represents the true prevalence as it was a previously unrecognized entity[4].

Eight out of the 14 patients with CD8 encephalitis were virologically controlled on ART[4]. Of the 14 patients found to have encephalitis, nine were from Africa[4]. Cerebrospinal fluid (CSF) analysis revealed significant pleocytosis ranging from 9-220 WBC/μl with > 90% lymphocytes composed mostly of CD8 T lymphocytes, and a mean CSF HIV viral load of 5,949 copies/ml[4]. Immunophenotypic studies of the lymphocytes in the CSF revealed an activated phenotype expressing CD38 biomarkers[4].

Brain biopsies confirmed an inflammatory encephalitis with diffuse infiltration by CD8 T lymphocytes, with a high concentration of cells located perivascularly and these findings were distinct from other known entities including HIV-associated encephalopathies and acute disseminated encephalomyelitis (ADEM)[4]. Very few CD4 T lymphocytes were found in the brain biopsies and because of the imbalance between CD8 and CD4 T lymphocytes, the authors of the study argue that the encephalitis syndrome may represent an immune reconstitution effect[45]. In a separate publication by the same group, the patients that had unfavorable outcomes were found to have biopsies composed of mostly CD8 T lymphocytes, whereas the patients with good clinical outcomes had biopsies with a mixed inflammatory reaction including numerous CD8 T lymphocytes and activated macrophages with a number of CD4 T lymphocytes[45].

In one case report, a patient was described that presented with subacute headaches, confusion, and seizures. A brain MRI revealed multiple right intra-axial frontal gadolinium-enhanced lesions with perilesional edema and mass effect[1]. Brain biopsy of the lesion revealed a dense infiltration of CD8 T lymphocytes, rare CD4 T lymphocytes, and many CD68 macrophages and microglial cells[1]. A workup was negative

for malignancy and other viral, bacterial, or fungal infections of the CNS. The patient was treated successfully with five-day course of steroids, but her disease relapsed and she was found to have a peripheral blood CD8 T lymphocyte count of 1,333 cells/μl[1]. Positron emission tomography (PET) imaging revealed multiple enlarged lymph nodes, with biopsies of the axillary nodes revealing a non-malignant polyclonal CD8 T-cell lymphocytic infiltration[1]. Unfortunately, the patient died after discontinuing her treatment.

As with other CD8 T lymphocyte syndromes, the pathogenesis of CD8 encephalitis is not clear. Proposed theories center on an HIV-driven process, including minor infections in well-controlled patients, CNS immune reconstitution syndrome (IRIS), HIV escape in patients on ART and HIV treatment interruption[1,4]. During HIV replication, HIV antigens promote the entry of CD8 and CD4 T lymphocytes into the CNS[46]. The presence of cytotoxic lymphocytes may promote an inflammatory reaction that causes CNS destruction. In the above studies, no opportunistic infection was found to explain the CNS inflammation, one of the defining findings in IRIS. Therefore, CD8 encephalitis is similar to the clinical presentation of CNS IRIS, but differs in its pathogenesis by the absence of opportunistic infection.

In the case series by Lescure, et al. all patients with CD8 encephalitis were treated with steroids for a median period of six months, with excellent clinical and radiological response in the majority of patients; however there were three patients who had moderate cognitive dysfunction after treatment and one patient with severe cognitive dysfunction[4]. In a second study by the same group, six out of ten patients treated with steroids had a favorable clinical response, whereas four patients died within 9-13 months after biopsies were performed[45].

Prior to these above studies, among the very few cases of encephalitis secondary to CD8 T-cell lymphocytic infiltration that were recognized and reported, and in which no additional therapies were employed including steroids other than ART, 100% were fatal within three months of diagnosis[46]. This suggests an important role for steroids in the management of the disorder. However, even where treatment exists for this newly defined syndrome, it remains unclear why some individuals respond fully to steroids whereas others have neurologic sequelae or die. Because of its high mortality, clinicians would do well to consider evaluating for CD8 encephalitis in any HIV-infected patient, on or off ART, with clinical features of encephalitis that is of undetermined cause.

Inverted CD4:CD8 ratios and non-AIDS-related events

There have been other observed disease associations with CD8 T-cell lymphocytosis in HIV-infected patients. With the aging of the HIV-infected population, and in spite of suppressive ART, there are a growing number of published reports on a higher incidence of non-AIDS-related events among the patient population. These include non-AIDS-defining malignancies, premature or accelerated cardiovascular and cerebrovascular disease, as well as renal disease[47,48]. Patients with these events appear to show higher rates of T lymphocyte activation, including both CD4 and CD8 T lymphocytes[47].

Compared with HIV-uninfected controls, HIV-infected patients with lower CD4:CD8 ratios have also been found to have increased progression of intima-media thickness (IMT), a marker used for atherosclerosis and age-associated disease[7]. Another study observed that in individuals with well-controlled HIV infection, a lower CD4:CD8 ratio was associated with increased risk of subclinical atherosclerosis, arterial stiffness, and decreased estimated glomerular filtration rate (eGFR)[9]. Badejo, et al. noted not only an increased rate of AMI in patients with high CD8 T-cell counts, but also observed a stepwise increase in AMI with increasing CD8 T lymphocyte counts[8].

While these studies suggest that CD8 T-cell lymphocytosis is associated with higher rates of non-AIDS-related illness, the etiologic and/or pathogenetic mechanisms are unclear. Interestingly, some studies in animal models have shown that CD8 T lymphocyte activation may result in severe renal injury, suggesting that end-organ damage may directly result from immune activation irrespective of the triggering mechanism or insult, including HIV disease[49,50]. Another potential mechanism of renal and vascular injury is the products of activated T lymphocytes, which may adversely impact cellular metabolic and homeostatic processes. There are some suggestions that CD8 T lymphocytes may cause a rise in blood pressure and cause vascular injury through the release of vasoactive cytokines and reactive oxygen species or indirectly through effects on perivascular adipose tissue[51,52]. The latter hypothesis would provide a broader explanation for the range of non-AIDS-related events observed in HIV patients with disproportionate CD8 T-cell lymphocytosis. Evidently, more studies are needed to better understand the pathogenetic mechanisms of CD8 T lymphocyte end-organ injury in order to guide targeted

therapeutic strategies, especially as these events are occurring in both treated and untreated HIV-infected patients.

Inverted CD4:CD8 ratios and mortality

In a study which included HIV-infected patients who had been on ART with at least a year of virologic suppression, Serrano-Villar, et al. reported an intriguing finding of increasing non-AIDS mortality that was inversely and proportionally related to the CD4:CD8 ratio when compared to controls with preserved T-cell ratios[53]. They found that the CD4:CD8 ratio was a stronger predictor of non-AIDS morbidity than CD4 T lymphocyte counts. The most common cause of morbidity (50.5%) and mortality (29.6%) was cardiovascular events (ischemic heart disease and cerebrovascular accidents). Of the non-AIDS-defining cancers, lung cancer was the leading cause of death (29.6%), with gastrointestinal cancers causing 14.8% of deaths overall.

Interestingly, older studies from earlier periods in the HIV epidemic had already reported the finding that the presence of activated CD8 T lymphocytes was more strongly related to mortality from AIDS than viral load or virus chemokine receptor usage[54]. Taylor, et al., in an even earlier study, identified that along with CD4 T lymphocyte absolute counts and percentage, the CD4:CD8 ratio was a strong prognostic indicator for disease progression in patients with HIV infection. The index has the advantage of retaining its prognostic value even in patients on long-term ART who have experienced immune recovery[55]. Chisenga, et al., in a study performed in Zambia, showed that high senescent and low proliferating CD8 T lymphocyte subsets, in particular, were independent predictors of mortality in HIV-infected patients after the initiation of ART[56].

As with non-AIDS-related events, the link between mortality and immune activation remains yet to be definitely proved or clearly defined. However, it is becoming evident that HIV-infected individuals with inverted CD4:CD8 ratios, including those with fully suppressed viral loads on ART, are at increased risk of mortality. Further efforts to understand this phenomenon are justified and interventions to raise CD4:CD8 ratios would be welcome. For example, one group has shown that patients treated with regimens containing integrase-strand transfer inhibitors, compared to protease inhibitor, nucleoside(tide) reverse transcriptase inhibitor and non-nucleoside reverse transcriptase inhibitor-based treatment regimens, were the most likely to result in a normalized CD4:CD8 ratio at one year post ART initiation (odds ratio: 7.67; 95% CI: 2.54-23.2)[57]. Early initiation of ART is also another strategy that has been shown to preserve or increase CD4:CD8 ratios[58].

Other syndromes

In the published literature, there are reports of other end-organ injury syndromes or systemic disorders associated with CD8 T-cell lymphocytosis without parotid gland enlargement (summarized in Table 1). A case series described four African patients with HIV infection and CD8 T-cell lymphocytosis who presented with bilateral panuveitis without a recognized cause[6]. One of the four patients was previously diagnosed with DILS complicated by hepatic lymphocytic infiltrate, and none of the four patients were on ART at the time of presentation. Only one patient had positive antinuclear antibodies and rheumatoid factor, and none of the patients had autoantibodies suggesting Sjogren's syndrome. Treatment in these patients consisted of ART initiation and either a steroid taper or topical steroids, with clinical improvement and reduction in the CD8 T-cell lymphocytosis[6].

A recent case report described an HIV-infected patient who developed a primary cutaneous aggressive epidermotropic T-cell lymphoma, a rare cancer that is caused by an epidermotropic CD8 T lymphocyte neoplastic infiltrate. The lymphoma presents as an aggressive non-focal distribution of ulcerated skin plaques, nodules, and tumors[5]. Despite aggressive chemotherapy, the patient had a very poor outcome due to the aggressive nature of this lymphoma[5].

A case of acute transverse myelitis with subacute paraparesis was reported in an African female who was not on ART but had a robust CD4 T lymphocyte count. She had histologic evidence of CNS CD8 T lymphocyte infiltration and responded to high-dose steroids and re-initiation of ART[30].

Non-HIV-associated CD8 T-cell lymphocytosis?

Interestingly, there was a case report on histologically proven DILS in a patient who did not have HIV infection[59]. Ghrenassia, et al. also reported on 14 patients with CD8 T-cell lymphocytosis, including patients who were non-HIV infected but immunocompromised for other reasons, including having received chemotherapy for treatment of malignancies[24]. Two of the

Table 1. Non-diffuse infiltrative lymphocytosis syndrome CD8 T-cell lymphocytosis clinical syndromes

Clinical syndrome	Epidemiology	HIV status	On ART? (Y/N)	Common symptoms	Management	Outcome	Source
Transverse myelitis	African female	CD4: 409 cells/ul CD8: 1,807 cells/ul HIV VL: 7,500 copies/ml	N	Paraparesis/ bilateral leg weakness	IV methylprednisolone 1 g/day x 5 days, then tapering dose of Prednisone x 2 months ART (3 weeks later)	I	Moulignier, et al. 2014[27]
CD8 encephalitis	14 patients (8 male, 6 female)	CD4 range: 84-742 cells/ul HIV VL range: 0-65,800 copies/ml	12 Y 2 N	Confusion, dizziness, cognitive impairment, memory loss, headaches, nerve palsies, seizures, status epilepticus, coma.	Corticosteroids (all patients)	5 D 5 R 4 I	Lescure, et al. 2013[4]
T-cell lymphoma	1 male	CD4: 460 cells/ul, HIV VL: 0 copies/ml	Y	Diffuse maculopapular erythema with secondary extensive purpuric papulopustules and impetiginized ulcerated plaques	Two chemotherapy regimens: CHOEP and ACBVP then bendamustine	D	Karkouche, et al. 2014[5]
Bilateral panuveitis	4 patients (2 male, 2 female)	CD4 range: 136-500 cells/ul, CD8 range: 1,120-2,090 cells/ul, HIV VL range: 37,805-315,218 copies/ml	N	Blurred vision, floaters, photophobia, bilateral granulomatous uveitis, conjunctivitis, dry eyes	ART and oral prednisolone taper (80 mg starting dose), ART and topical dexamethasone, artificial tear supplements, orbital floor methylprednisolone injections	4 I	De Silva. et al. 2005[6]

VL: viral load; I: improved; R: resolved; D: dead; ART: antiretroviral therapy; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; ACBVP: doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone.

HIV-negative individuals had a unique clonal CD8 lymphocyte proliferation with peripheral blood cytopenias and STAT 3 mutation consistent with large granular lymphocyte leukemia[24].

The observation of CD8 T-cell lymphocytosis outside the context of HIV infection raises questions about other etiologies of the syndrome. It is plausible that other viral infections contribute to the development of CD8 T-cell lymphocytosis, including CMV, EBV, other herpes viruses, and HTLV-1. For example, one study out of Venezuela discovered EBV proteins by immunohistochemistry in biopsies of salivary glands of HIV-positive patients with DILS[60]. On the other hand, other studies have demonstrated that biopsies from affected individuals were negative for CMV and HSV[33]. Further studies are needed to characterize the involvement of other viral infections in the development of CD8 T-cell lymphocytosis.

Conclusion

Persistent CD8 T-cell lymphocytosis is associated with multiple clinical syndromes that contribute significantly to morbidity and mortality in HIV-infected patients. These syndromes may present even in virologically controlled individuals and are frequently unappreciated and/or unrecognized for long periods of time by clinicians. It is important for clinicians to be aware of these syndromes, some of which are potentially reversible with ART, may require adjunctive immune-modulating therapies or for non-AIDS events, may inform more aggressive screening or preventative measures.

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