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Note

CD4/CD8 ratio predicts the cellular immune response to acute hepatitis C in HIV-coinfected adults☆

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ABSTRACT

Hepatitis C virus (HCV) coinfection is a strong risk factor for death of HIV-infected patients. Immune dysfunction affects the clinical course of acute hepatitis C (AHC). CD4/CD8 ratio is a biomarker of both persistent inflammation and immunosenescence in HIV-infected adults on effective antiretroviral therapy. A low CD4/CD8 ratio predicts immunosenescence and is associated with increased morbidity and mortality in both HIV-infected adults and elderly HIV-uninfected adults. Additionally, immunosenescence is associated with unresponsiveness to vaccine and could affect the immune reaction to pathogens during their primary infection. We retrospectively evaluated 12 AHC patients to assess the association between CD4/CD8 ratio and liver damage in AHC. We used the Spearman rank correlation test to assess the correlation. We found that CD4/CD8 ratio and peak alanine aminotransferase level (peak ALT) were positively correlated ($r = 0.8322$, $p = 0.0013$). The CD4 counts did not correlate with peak ALT ($r = 0.5245$, $p = 0.0839$). $CD8^+$ T cells expansion for AHC did not affect these results, because the CD4/CD8 ratio before the onset of AHC and peak ALT positively correlate ($n = 11$; $r = 0.7909$, $p = 0.0055$) and there was no significant difference between CD4/CD8 ratios before and after the onset of AHC ($n = 11$; $p = 0.9766$). Immunosenescence may be negatively associated with the cellular immune response to acute HCV infection. We suggest that clinicians consider using CD4/CD8 ratio as a marker of immunosenescence in their management of patients with HIV infection and other complications.

Liver-related diseases are a major cause of death in HIV-infected patients in the antiretroviral therapy era [1]. Hepatis C virus (HCV) co-infection is a strong risk factor for death of HIV-infected patients [2]. Recently, the incidence of HCV infection has been increasing among HIV-infected men who have sex with men (MSM) but are non-injection drug users in Japan [3]. ART can suppress viral replication and ART-mediated CD4 count increase is associated with reduced morbidity and mortality. However, regaining an apparently normal CD4 count does not fully restore the human immune system. Compared with the general population without HIV infection, HIV-infected patients on effective ART were at higher risks of increased mortality and morbidity. Serrano-Villar S et al. reported that a low CD4/CD8 ratio predicts immunosenescence in HIV-infected adults and is associated with increased morbidity [4]. Among elderly HIV-uninfected adults, inverted CD4/CD8 ratio predicts mortality and is considered part of the immunosenescent phenotype [5]. Persistent inflammation and immunosenescence could contribute to the high incidence of age-associated diseases [6]. Additionally, immunosenescence is associated with unresponsiveness to vaccine and could affect the immune reaction to pathogens during their primary infection [7]. Acute hepatitis C (AHC) is probably immunopathological because it coincides temporally with expansion of virus-specific $CD8^+$ T cells [8]. On the basis of these findings, we hypothesized that persistent inflammation and immunosenescence can affect the immune response to AHC in patients with HIV infection.

The aim of this study is to elucidate the relationship between the cellular immune response to AHC and the immunosenescence in HIV-infected patients. We searched the medical records of HIV-

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infected patients who visited IMSUT hospital, The Institute of Medical Science, The University of Tokyo between January 2009 and May 2017. AHC was defined by the appearance of anti-HCV antibody after the increase in aminotransferase level by more than 10-fold the upper normal limit and exclusion of alternative causes of hepatic injury and biliary tract diseases. In all patients, negative HCV antibody test results were confirmed at least once before the onset of AHC. We assessed the clinical makers of cellular immunity, including CD4 count, CD8 count, and CD4/CD8 ratio. The peak ALT level corresponded to the highest alanine aminotransferase (ALT) level measured from the onset to the resolution of AHC. CD4 count and CD8 at the onset of AHC were obtained 2 [-3–113] days (median [range]) before ALT level peaked. CD4 count and CD8 before the onset of AHC 77 [28–150] days (median [range]) before ALT level peaked. We used the Spearman rank correlation test to analyze correlations between peak ALT level and CD4 count, CD8 count, or CD4/CD8 ration and the Wilcoxon signed-rank to assess the changes in CD4 count, CD8 count and CD4/CD8 ratio between matched-pair data. P values of <0.05 were considered statistically significant. This study was approved by the institutional review board of the Institution of Medical Science, The University of Tokyo (accession number. 29-24-B0707).

A total of 12 AHC patients were included in this study. All the patients were male and Japanese. The median age of this population was 44 (range, 32–48 years). Of 12 patients, 11 patients were on ART and their laboratory data right before the onset of AHC showed <400 copies/ml of HIV-RNA and 82% of them showed <50 copies/mL. The median CD4 count at the onset of AHC was 368 cells/μL. CD4/CD8 ratios between 1.5 and 2.5 are generally considered normal. Of the 12 patients, 10 patients showed CD4/CD8 ratios of less than 1.0. The HCV subtype was not examined in 1 patient, while 10 patients were infected with HCV serotype 1 and one patient with serotype 2. We found that CD4/CD8 ratio at the onset of AHC and peak ALT level positively correlated ($r = 0.8322$, $p = 0.0013$; Fig. 1A). CD4 count did not correlate with peak ALT level ($r = 0.5245$, $p = 0.0839$), but CD8 count and peak ALT level negatively correlated ($r = -0.8322$, $p = 0.0013$; Fig. 1B). Normal CD4/CD8 ratios can invert through the targeted cell death of circulating $CD4^+$ T cells, expansion of $CD8^+$ T cells, or a combination of both phenomena. Considering that $CD8^+$ T cells expansion related to AHC could occur, we compared the CD4/CD8 ratio and CD8 count before the onset of AHC. In 11 patients whose CD4/CD8 ratios were available before the onset of AHC, CD4/CD8 ratio and peak ALT level positively correlated ($r = 0.7909$, $p = 0.005$; Fig. 1A). There was no significant difference between CD4/CD8 ratios before and after the onset of AHC as determined by the Wilcoxon signed-rank test ($n = 11$; $p = 0.9766$) and the CD8 count in acute HCV infection did not increase (Fig. 1B). These findings revealed that $CD8^+$ T cells expansion did not occur and were not associated with CD4/CD8 ratios. Peak ALT level did not correlate with age, HCV-RNA, or HCV subtype. There was no significant correlation between CD4/CD8 ratio and age. In 11 patients, HCV-RNA was detected 24 weeks after the onset of AHC and spontaneous viral clearance was observed in 1 patient whose peak ALT level was 1312 IU/mL.

In the general population, strong $CD8^+$ T cell immunity in acute resolving hepatitis C is matched by vigorous, sustained CD4 cell proliferation [9]. Immune dysfunction affects the clinical course of AHC. However, clinical data regarding liver damage in AHC among HIV-infected patients are limited. Danta et al. reported that HIV coinfection is associated with HCV persistence after the resolution of AHC and HCV-HIV coinfection significantly reduced IFN-γ ELISpot responses relative to those in HCV-monoinfected individuals, especially against nonstructural proteins [10]. The severity of AHC may be related to impaired immunity caused by HIV infection. In this study, liver damage which was monitored on the basis of the levels of transaminases positively correlated with CD4/CD8 ratio. CD4/CD8 ratio is a maker of T cell defects associated with immunosenescence, and a persistently low CD4/CD8 ratio during effective ART is associated with increased innate and adaptive immune activation, and an immunosenescent phenotype [4]. Our findings indicate that immunosenescence may be an important factor in cellular immune response to acute HCV infection.

Our study has several limitations, including the small sample size and a single-center study. AHC patients who resolved without showing increases in the levels of serum transaminase are not included. We did not evaluate HCV-specific cellular immune responses. We used peak ALT level as a marker of the cytotoxic T lymphocyte (CTL) response to HCV and a small number of infected hepatocytes in these individuals might limit the extent of CTL-mediated liver damage. Gender, ethnicity, genetics, and other potential infections could impact the CD4/CD8 ratio, but we were not able to evaluate these factors.

This study showed that CD4/CD8 ratio could be a predictive marker of AHC activity associated with HIV infection. Some patients on ART will restore CD4 count and experience a decline in CD8 count. However, in other individuals, the high levels of circulating $CD8^+$ T cells are maintained and their ratios fail to improve despite the improvement of CD4 levels. CD4 count and CD4/CD8 ratio have been measured for decades to manage and monitor HIV infection. CD4/CD8 ratio is a marker used in the management of patients with HIV infection and other complications. A greater understanding of the CD4/CD8 ratio and the impact of its manipulation should be a

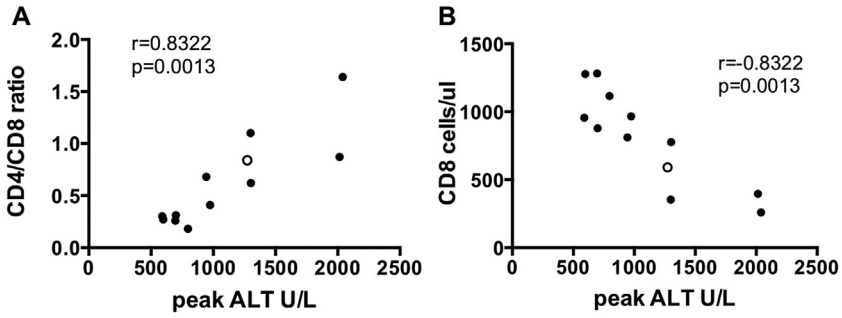

Fig. 1. Correlation between peak ALT level and CD4/CD8 ratio or CD8 count at the onset of acute hepatitis C. A. CD4/CD8 ratio, B. CD8 count. Open circles indicate the patients with untreated HIV infection. Closed circles indicate the patients on antiretroviral therapy. All of 11 patients whose CD4/CD8 ratios were available before the onset of acute hepatitis C were on antiretroviral therapy.

target for the study of immunosenescence and chronic inflammation in HIV infection.

Conflicts of interest

The authors declare that they have no competing interests.

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