Correspondence

Free Light Chains and the Risk of Nonmalignant AIDS Events in HIV-Infected Patients Treated With Combination Antiretroviral Therapy

To the Editor—We read with interest the recent article by Shiels et al in *Clinical Infectious Diseases* [1]. The study investigates the relationship between elevation of serum free light chain (FLC), a biomarker of B-cell dysfunction, and the risk of opportunistic infections associated with AIDS among persons infected with human immunodeficiency virus (HIV). This study was a nested case-control study with a relatively large number of prestored specimens. Compared to controls, nonmalignant AIDS events in HIV-infected individuals were strongly associated with polyclonal serum FLC elevation. However, to better address this issue, we believe that several points need additional discussion.

First, renal function, a very important potential confounder, has not been evaluated in this study. It is well accepted that the absolute serum concentrations of FLCs in a given patient are influenced by the rates of production and renal clearance [2]. Because serum FLC raises as renal clearance is reduced, it is mandatory to have knowledge of the renal function of the patients included in the study.

Second, hepatitis C virus is considered a confounder for the serum FLC elevation [3, 4], but no information is given about hepatitis C virus infection in case patients and controls, and it would be very interesting to have this additional information from the authors.

Third, increased circulating polyclonal FLCs may reflect primarily an immunologic defect that is shared among many inflammatory and malignant diseases, many more of which were considered as exclusion criteria in this study (here only Kaposi sarcoma and non-Hodgkin lymphoma were considered). Thus, for example, it is possible that developing or undiagnosed conditions that are characterized by chronic B-cell activation/dysfunction as autoimmune rheumatic disorders, diabetes mellitus, inflammatory bowel disease, cardiovascular diseases, and malignancies may have caused the elevation in the FLC years before AIDS diagnosis [4, 5].

Around the time of publication of Shiels et al's study [1], we also investigated the association between polyclonal FLCs and prognostic biomarkers routinely used in the setting of HIV infection [6]. In this study, cases were selected randomly in the cohort among patients without known confounding comorbidities for serum FLC elevation. Indeed, in our series, patients had data of HIV load and nearly all samples were collected in the era of highly active antiretrovial therapy, so we were able to evaluate the association of time with a suppressed viral load and with CD4 cell count achieved on combination antiretroviral therapy (cART). Notably, we found that polyclonal FLCs above the upper limit of normal are strongly correlated with shorter time of undetectable HIV viremia, higher viral load, and lower CD4 cell count at sample. In any case, the association with AIDS-defining opportunistic infections did not reach significance at multivariate logistic regression analysis, probably because of our small sample size.

Finally, large longitudinal clinical studies with precise selection criteria should be performed before the measurement of polyclonal FLCs can be considered as a useful tool to monitor ongoing immune activation and dysfunction in HIV-positive patients, especially those with comorbidities on cART.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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