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Polyclonal Serum Free Light Chains: A Biomarker of Disease Prognosis or of Immune Senescence?

TO THE EDITOR: The article by Pardanani et al¹ is part of a growing body of literature on the prognostic role of elevated polyclonal serum free light chains (sFLCs) in clinical settings. Of note, increased polyclonal sFLCs have been detected in conditions that are characterized by chronic B-cell activation: rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, severe atopic and nonatopic asthma and dermatitis, idiopathic pulmonary fibrosis, and chronic hypersensitivity pneumonitis. Furthermore, infections, diabetes mellitus, renal impairment, and inflammatory bowel disease are significant known causes of polyclonal increase in sFLCs.^{2,3}

Because the incidence of these diseases increases with age, and aging is another cause of elevated polyclonal sFLCs, I would have expected that the authors¹ would include the presence of comorbidities in their analysis. The sFLC half-life of only 2 to 6 hours would potentially indicate the immediate occurrence of B-cell dysfunction/activity; thus, inpatient variations are strictly correlated with the activity of the underlying disease and may be influenced by therapy.³ Even if the primary end point of this study was to assess the prognostic value of this biomarker on overall survival, no data were provided on the impact of therapy on the disease. So only a few potential confounders have been evaluated in this study, and it would be very interesting to have additional information from the authors.

Some points that are quite pertinent to this topic need additional discussion. The article introduces new scenarios: the finding that elevated polyclonal sFLCs might have a role in predicting inferior survival is extended for the first time to myeloid neoplasia. In fact, this biomarker has been linked with inferior event-free and overall survival only in lymphoproliferative disorders, namely diffuse large B-cell lymphoma, Hodgkin's lymphoma (HL), and chronic lymphocytic leukemia (CLL).⁴⁻⁶ Again, polyclonal elevation was shown to be a strong risk factor for development of CLL in the normal population and for non-Hodgkin's lymphoma (NHL) in patients infected with HIV.^{7,8} Furthermore, our group has data that support the independent predictive value of sFLCs for both HL and NHL in individuals with HIV.⁹ All of these findings lead to the hypothesis that chronic immune stimulation and polyclonal B-cell expansion/dysfunction could have an important pathogenetic role in the development and progression of autoimmune disorders and lymphoid malignancies. The overproduction of polyclonal sFLCs could, in this case, somehow be related to disease biology, therefore limiting the role of such a biomarker to a nonspecific measure of adaptive immunity only.

On the contrary, recent findings suggest that increased polyclonal sFLC levels could reflect diverse biologic activities; the most intriguing

is the ability to impair human dendritic cell maturation.^{10,11} Of note, dendritic cells are an essential link between the innate and adaptive immune responses. For this reason, elevated polyclonal sFLCs may also represent a biomarker of the innate immune system dysfunction and defective immune surveillance and, finally, of immune senescence. In fact, nonclonal sFLCs have been recently reported as a marker of overall survival in the general population, predicting mortality among individuals older than age 50 years.¹² Given that unresolved inflammation seems to be a common denominator in the genesis and progression of nearly all of the diseases discussed here,¹³ one can hypothesize that elevation of polyclonal sFLCs could quantify this immunologic chaos and could be useful in monitoring a patient's immune system function in several clinical settings.

In the era of targeted and personalized therapy, there is an essential need to personalize both diagnosis and prognosis. So, for example, because this biomarker is detected with a simple blood test, it could be used frequently in combination with normal follow-up procedures to predict important complications before they are clinically evident (ie, lymphomas in patients with HIV, and CLL in normal patient populations); provide a reliable tool in selecting the appropriate timing of a given treatment (ie, starting earlier antiretroviral therapy in patients with HIV); identify patients with malignancies who are likely to have inferior survival and may conversely be treated with new or immune-based therapies (ie, for NHL, CLL, and myeloid neoplasms); or assess disease progression or regression under a current treatment (ie, for inflammatory diseases, CLL, and lymphomas).

Finally, a better understanding of the mechanisms that underlie the elevation of this biomarker will answer some questions. Could this biomarker discriminate more precisely which elderly patients with no comorbidities are able to receive full-dose chemotherapy or autologous bone marrow transplantation? Could the determination of polyclonal sFLCs assist us in the definition of physiologic age and thus predict successful aging in a nonsubjective manner? Additional studies should be performed to uncover the potential role of this and other biomarkers in defining the host's immune system status with the fascinating approach of cancer immunotherapy.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Reply to M. Bibas

The overarching point in the letter by Bibas,¹ which we alluded to in our article,² is that increased circulating polyclonal free light chains (FLCs) may reflect primarily an immunologic defect that is shared among many inflammatory and malignant diseases, as well as aging, rather than a disease-specific prognostic biomarker. Although this point is self-evident, given the multiple published associations of increased FLC levels with inferior clinical outcome in various settings, it also raises important and hitherto unanswered questions with respect to cause-and-effect relationship(s), mechanism(s) of immune dysregulation, and potential interaction of comorbid conditions with immunologic dysfunction.

In our proof-of-principle study,² increased FLC levels were associated with inferior survival in primary myelofibrosis and myelodysplastic syndromes even after adjusting for age and renal impairment in the multivariate Cox model. However, it is not clinically meaningful or practical to account for every comorbid condition in this analysis, given the potential significant interaction of comorbidities with increased FLC levels. For instance, excess deaths in the subgroup of patients with increased FLC levels were not accounted for by leukemic transformation or otherwise progressive disease, which suggests that this association ensued from worsening comorbid conditions (eg, increased cardiovascular deaths); unfortunately, a verifiable cause of death was frequently not available in our retrospective study to confirm this point.

We agree that it would be of interest to study treatment effect on FLC levels; it would be even more useful to extend this analysis and correlate treatment-related FLC changes with specific immunologic end points (for example, improvements in dendritic cell function or maturation, as suggested by Bibas¹) that may serve to clarify potential mechanisms for treatment response or lack thereof.

Finally, there are no data to clarify whether the presumptive immunologic defect (reflected and quantified by elevated FLC levels) develops primarily as a host response to the presence of a malignancy or is a de novo defect that provides the fertile soil for the development of disease.

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