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Serum free light chains in the differential diagnosis and prognosis of primary and secondary hypogammaglobulinemia

To the Editor:

In adult patients the diagnosis of common variable immunodeficiency (CVID) is often an exclusion process, and lymphoproliferative disorders (LPDs) or plasma cell dyscrasias (PCDs)

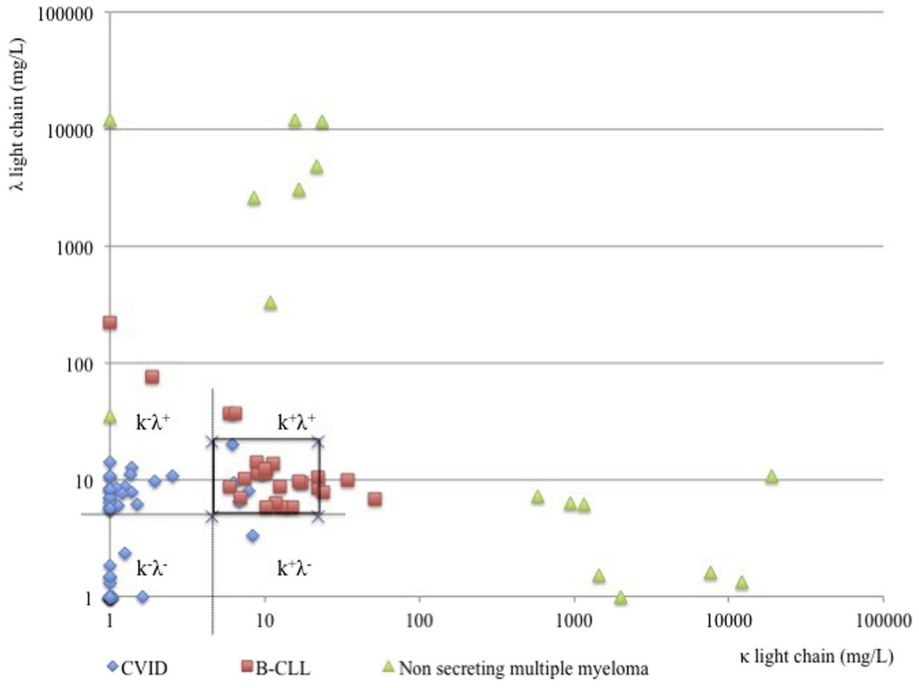

FIG 1. sFLC levels in the differential diagnosis of hypogammaglobulinemia. The scatter plot shows sFLC levels for 45 patients with CVID and 44 patients with secondary antibody deficiency. Patients with CVID have an sFLC pattern different from that of patients with secondary hypogammaglobulinemia. sFLC patterns in patients with CVID are divided by *dashed lines*, as indicated. The *square* represents reference sFLC values. *B-CLL*, B-cell chronic lymphocytic leukemia.

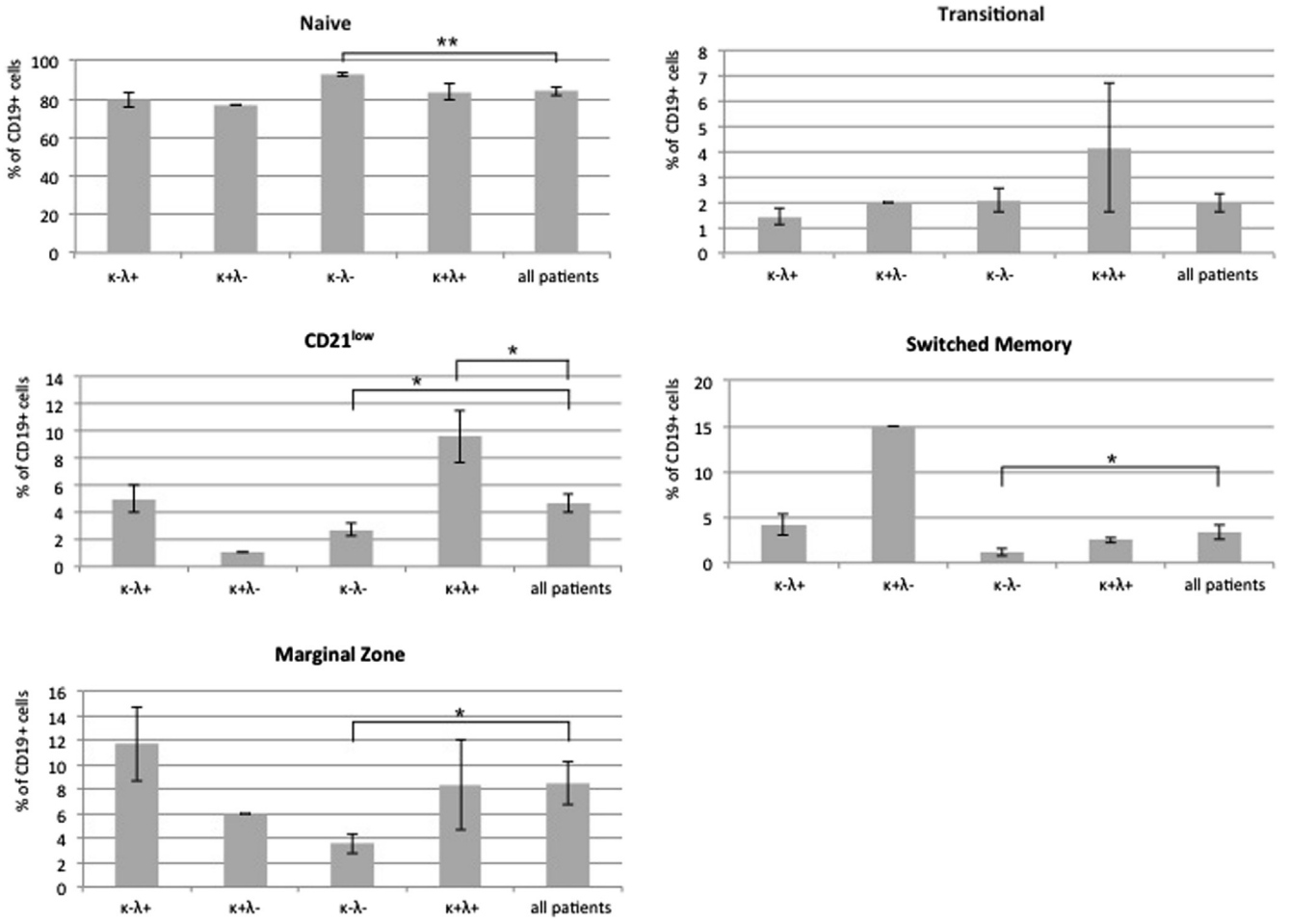

FIG 2. B-cell subpopulations in the 4 sFLC subgroups and the whole CVID cohort (means and SEs). sFLC patterns seem to be able to differentiate between biological subgroups of the disease. Because only 1 patient presented with a $\kappa^{+}\lambda^{-}$ pattern, we did not look for significant differences in B-cell subtypes for this group. *$P < .05$ and **$P < .01$.

have to be carefully ruled out. Differential diagnosis might represent a real challenge because of similar clinical aspects. In adults with antibody deficiency, a bone marrow examination might be required to rule out hematologic malignancies. The serum free light chain (sFLC) assay is widely used in patients with LPDs and PCDs to obtain prognostic information on the disease's clinical course.[1,2] Because primary antibody deficiency (PAD) has been associated with a low production of light chains,[3] in this retrospective study we evaluated the role of sFLCs in the differential diagnosis between patients with primary and secondary antibody defects.

Clinical data and sFLC levels were collected from clinical records of 45 patients with CVID, 10 patients with other PADs, and 44 patients initially referred because of hypogammaglobulinemia, in which a secondary antibody deficiency resulted as final diagnosis (patients' demographic and clinical details are summarized in the Methods section and Table E1 in this article's Online Repository at www.jacionline.org). All patients with CVID fulfilled the European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency diagnostic criteria.[4] On the basis of sFLC levels, patients with CVID were classified into 4 groups (Fig 1): in 3 groups κ ($\kappa^{-}\lambda^{+}$ pattern, 24/45 patients), λ ($\kappa^{+}\lambda^{-}$ pattern, 1/45 patients), or both ($\kappa^{-}\lambda^{-}$ pattern, 15/45 patients) light chains were reduced or undetectable. We defined these 3 patterns as CVID-like because only 5 of 45 patients presented with normal sFLC levels ($\kappa^{+}\lambda^{+}$). In our cohort the sensitivity of the CVID-like pattern of sFLCs was 89% (95% CI, 76% to 96%), and the specificity was 100% (95% CI, 92% to 100%). By using this pattern as a diagnostic marker for CVID, the positive predictive value was 100% (95% CI, 92% to 100%), and the negative predictive value was 90% (95% CI, 78% to 97%). Measurement of sFLC levels over the years revealed superimposable levels of both chains in each patient not influenced by replacement therapy with immunoglobulins; this suggests a diagnostic value of the test, even in patients in whom replacement therapy has been started to prevent infections. It is intriguing that in all patients with CVID, κ and λ chains, as determined by using flow cytometric analysis, were normally expressed on B-cell surface immunoglobulins (mean surface κ/λ ratio, 1.23 ± 0.23). Concerning other kinds of PADs, in 2 of 2 patients with X-linked agammaglobulinemia, sFLC levels resulted undetectable. In 1 of 7 patients with IgG