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LETTER TO THE EDITOR

Serum free light chains as predictors of lymphomagenesis in patients with autosomal dominant hyper-immunoglobulin E syndrome (Job's syndrome)

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Autosomal dominant hyper-immunoglobulin E (IgE) syndrome, or Job's syndrome, is a primary immunodeficiency caused by dominant negative mutations in *STAT3* [1,2]. Clinically, it manifests as eczema, recurrent staphylococcal infections of the lungs and skin, and connective tissue and skeletal abnormalities [1,2]. Similar to other primary immunodeficiencies, Job's syndrome is associated with an increased risk of lymphoproliferative malignancies, especially B-cell non-Hodgkin lymphoma, which is considered to be due to chronic immune activation [3]. Emerging data support a role for serum free light chains (FLCs) as predictors of lymphomagenesis in patients with primary or acquired immunodeficiency [4–6]. This motivated us to assess FLC levels in peripheral blood from patients with Job's syndrome who subsequently developed lymphoma compared to patients with Job's syndrome without lymphoma.

We identified two patients with Job's syndrome: a 29-year-old female (patient 1) and a 22-year-old male (patient 2), who subsequently developed diffuse large B-cell lymphoma (DLBCL) (Table I). Both patients had clinical stage IV disease (patient 1 had DLBCL in the liver and duodenum; patient 2 had DLBCL in bone marrow and the spleen). Both patients were treated successfully with six cycles of EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) and achieved complete remission. For both patients, we identified stored serum collected prior to (2.7 and 5.4 years) and after (3.3 and 8.1 years) DLBCL, respectively. As a

comparison group, we identified five lymphoma-free patients with Job's syndrome (ages 7–38 years) with comparable levels of disease activity and available stored serum (Table I).

Using a quantitative FLC assay (Freelite™; The Binding Site, Birmingham, UK), we measured FLC levels in serum [7]. Among patients with Job's syndrome who subsequently developed DLBCL, we estimated the median κ and λ FLC concentrations to be 1.58 (0.77–2.38) and 2.78 (2.22–3.34) mg/dL in serum obtained prior to lymphoma, respectively. In serum obtained after successful treatment for lymphoma, the median κ and λ FLC concentrations were 2.16 (1.79–2.54) and 2.61 (2.55–2.66) mg/dL, respectively. Among patients with Job's syndrome who were lymphoma-free a median of 4.0 (2.4–6.0) years after sample collection, we estimated the median κ and λ FLC concentrations to be 0.76 (0.06–1.00) and 0.77 (0.14–1.52) mg/dL, respectively.

As previously described [6], we used κ and λ serum FLC concentrations to define polyclonal (elevated $\kappa + \lambda$ mg/dL) and monoclonal (skewed κ/λ -ratio) FLC patterns. Similar to prior observations, in patients with primary or acquired immunodeficiencies who subsequently developed lymphoma [4–6], patients 1 and 2 had evidence of polyclonal FLC patterns, compared to the five patients with lymphoma-free Job's syndrome (Figure 1). In patients 1 and 2 the polyclonal FLC levels at baseline were 4.61 mg/dL and 4.12 mg/dL, respectively; in the five patients with lymphoma-free Job's syndrome the mean baseline level was substantially lower

Table I. Patients' characteristics at study baseline.

Patient no.	Sex	Age	κ FLC (mg/dL)	λ FLC (mg/dL)	$\kappa + \lambda$ FLC (mg/dL)	κ/λ FLC-ratio	Creatinine (mg/dL)	β_2 -Microglobulin (mg/L)
1	Female	29	2.38	2.22	4.61	1.07	1.0	4.1
2	Male	22	0.77	3.34	4.12	0.23	0.9	NA
3	Male	7	0.90	0.76	1.66	1.18	0.42	1.3
4	Female	29	0.95	1.52	2.48	0.63	1.0	3.2
5	Female	38	0.63	0.78	1.41	0.8	0.66	1.5
6	Female	25	0.06	0.14	0.21	0.44	0.59	1.4
7	Female	37	1.00	1.48	2.48	0.68	0.83	2.2

FLC, free light chain; NA, not available.

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There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.

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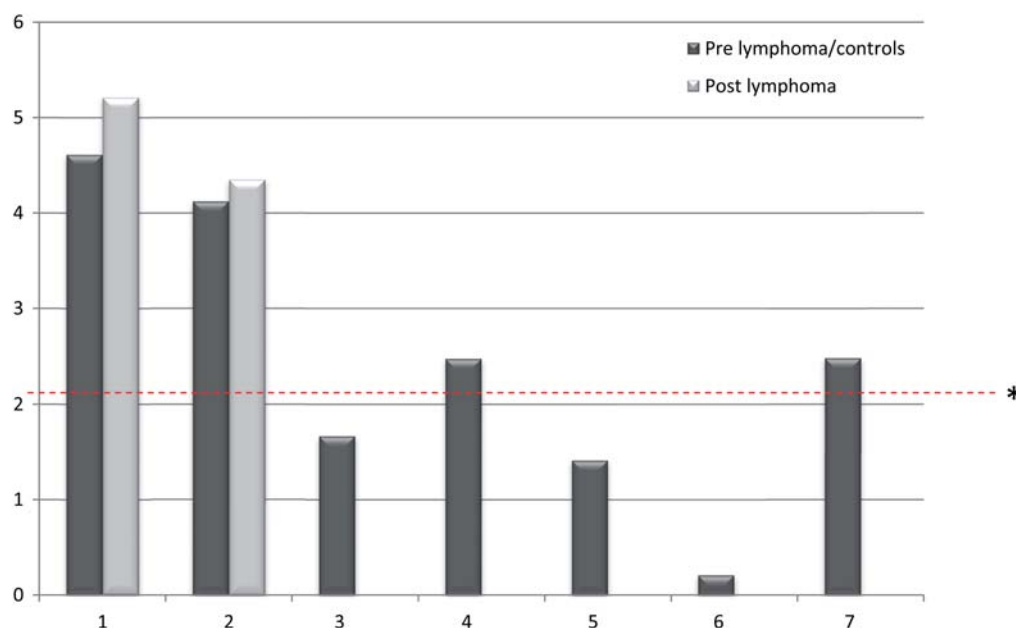


Figure 1. Serum free kappa and lambda light chain patterns ($\kappa + \lambda$ mg/dL) in patients with Job's syndrome who developed diffuse large B-cell lymphoma (patients 1 and 2) and those who did not (patients 3-7). *Proposed normal reference value for $\kappa + \lambda$ serum FLC is 2.05 mg/dL [6]. Patients 1 and 2 have evidence of polyclonal (elevated $\kappa + \lambda$ mg/dL) FLC patterns both prior to (2.7 and 5.4 years) and after (3.3 and 8.1 years) lymphoma diagnosis.

(1.65 mg/dL) (Figure 1). Interestingly, both patients 1 and 2 maintained elevated polyclonal FLC patterns (5.21 mg/dL and 4.35 mg/dL) after they had achieved a complete remission for their lymphomas, at 6.3 and 8.1 years after complete remission (Figure 1), suggesting that there may be some underlying immune activation associated with the development of DLBCL. We have speculated that such immune activation could either be due to host-related factors (e.g. susceptibility genes), acquired immune triggers (e.g. infections and inflammation), disease related factors (e.g. subset of patients with Job's syndrome) or a combination of these factors. None of the seven patients had monoclonal FLC patterns (i.e. κ/λ -ratios < 0.26 or > 1.65).

Furthermore, to expand on the role of polyclonal (elevated $\kappa + \lambda$ mg/dL) FLC patterns, Dispenzieri *et al.* recently reported that elevated $\kappa + \lambda$ FLCs is a significant predictor for worse overall survival in the general population [8]. The underlying mechanisms of this observation remain to be defined.

In summary, we found polyclonal serum FLC patterns to be associated with lymphomagenesis in patients with Job's syndrome. Even after curative treatment of DLBCL, patients maintained patterns of polyclonal FLCs, supporting an underlying (constitutional or acquired) immune activation causing lymphoma in these individuals.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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