

## To the editor:

### Non-Hodgkin lymphoma in familial amyloid polyneuropathy patients in Sweden

Amyloidosis is characterized by deposition of fibrillar protein amyloids in a single organ or systematically in many organs.<sup>1,2</sup> At least 27 precursor proteins to amyloids are known.<sup>1,2</sup> Some forms of amyloidosis are associated with neoplasms, most notably immunoglobulin light-chain amyloidosis with multiple myeloma, monoclonal gammopathy of unknown significance, and, rarely, with non-Hodgkin lymphoma (NHL).<sup>2,3</sup> The most common and widespread hereditary amyloidosis, familial amyloid polyneuropathy (FAP), is caused by transthyretin mutations.<sup>4</sup> It is endemic in northern Sweden, showing variable presentation even for the same mutations; the mean age of onset is 56 years and the range of survival time is 5 to 15 years.<sup>5</sup> The ultimate treatment is liver transplantation. Because there are no data linking FAP to cancer, we carried out a follow-up study of Swedish FAP patients identified from the nationwide Hospital Discharge Register (1997-2010) and the Outpatients Register (2001-2010); the data sources and calculation of standardized incidence ratio (SIR) were described elsewhere;<sup>6</sup> the reference cancer patients without FAP, diagnosed in the same period, were from the endemic northern provinces. The start of follow-up in 1997 was the first year when FAP could be identified from the records. Cancers were identified from the Swedish Cancer Registry (1997-2010).

The population included 224 men and 145 women with FAP in whom a total of 30 cancers were diagnosed (Table 1, data shown for cancers with at least 2 cases). Only NHL was significantly increased to an SIR of 5.02. The increase was significant both for diffuse large B-cell NHL and the “other” types, which were nonspecified forms of B-cell NHL (2 patients), NHL (2 patients), and T-cell NHL (1 patient). When stratified by gender, the SIR in women was 7.81 compared with 4.13 in men. All NHL cases were diagnosed in FAP patients older than 60 years at hospitalization. The first hospitalization for FAP was concurrent to or before the diagnosis of NHL in 6 patients; in 2 patients, NHL diagnosis appeared to be 3 to 4 years earlier, but because FAP is chronic disease, the disease was in progress probably years before. According to the Hospital Discharge Register, none of the 8 patients had undergone liver transplantation; none were first-degree relatives to each other. No cases of myeloma were recorded. The overall cancer risk was decreased to 0.68, which may be a result of underdiagnosis or underreporting of cancer in seriously ill patients with a progressive disease.

One can only speculate about the mechanisms. NHL is often related to immune suppression or excessive immune stimulation. It is possible that amyloid particles elicit an immune stimulation either directly or through inflammation in tissue deposits. Even though FAP is a rare disease, wild-type transthyretin is the amyloid precursor in senile amyloidosis, which at least in Sweden and Finland is the most common systemic amyloidosis, affecting up to 25% of individuals older than 70 or 85 years.<sup>7,8</sup> Thus, an urgent question is whether NHL would also associate with this common wild-type transthyretin-related senile amyloidosis.

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**Table 1. SIR for cancer of patients diagnosed with FAP from 1997 to 2010**

Cancer site	Men				Women				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Colon	1	0.47	0.00	2.68	2	2.20	0.21	8.09	3	0.98	0.19	2.91
Rectum	2	1.47	0.14	5.40	0				2	1.13	0.11	4.15
Breast	0				2	0.54	0.05	1.99	2	0.54	0.05	1.97
Endometrium	0				2	2.27	0.21	8.33	2	2.27	0.21	8.33
Prostate	7	0.54	0.21	1.12	0				7	0.54	0.21	1.12
<b>Non-Hodgkin lymphoma</b>	5	<b>4.13</b>	<b>1.30</b>	<b>9.72</b>	3	<b>7.81</b>	<b>1.47</b>	<b>23.11</b>	8	<b>5.02</b>	<b>2.14</b>	<b>9.94</b>
Diffuse large B cell	1	3.06	0.00	17.57	2	<b>12.10</b>	<b>1.14</b>	<b>44.50</b>	3	<b>6.10</b>	<b>1.15</b>	<b>18.06</b>
Others	4	<b>5.78</b>	<b>1.50</b>	<b>14.94</b>	1	7.18	0.00	41.18	5	<b>7.70</b>	<b>2.43</b>	<b>18.10</b>
Leukemia	0				2	7.97	0.75	29.32	2	1.66	0.16	6.11
All	19	<b>0.59</b>	<b>0.36</b>	<b>0.93</b>	11	0.92	0.46	1.65	30	<b>0.68</b>	<b>0.46</b>	<b>0.98</b>

The reference population was from the 2 endemic northernmost provinces (Norrbotten and Vasterbotten, Sweden). SIR was standardized for age and gender. Bold type indicates 95% confidence interval, but does not include 1.00. O, observed number of cases; CI, confidence interval.

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**Contribution:** K.H. conceived the study and wrote the paper; A.F. commented on the results; X.L. carried out statistical analysis; and J.S. and K.S. provided the database. All authors read and approved the final manuscript.

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## References

1. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. *Amyloid*. 2010;17(3-4):101-104.

- Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. *J Clin Oncol*. 2011;29(14):1924-1933.
- Telio D, Bailey D, Chen C, Crump M, Reece D, Kukreti V. Two distinct syndromes of lymphoma-associated AL amyloidosis: a case series and review of the literature. *Am J Hematol*. 2010;85(10):805-808.
- Benson MD. The hereditary amyloidoses. *Best Pract Res Clin Rheumatol*. 2003;17(6):909-927.
- Suhr OB, Svendsen IH, Andersson R, Danielsson A, Holmgren G, Ranløv PJ. Hereditary transthyretin amyloidosis from a Scandinavian perspective. *J Intern Med*. 2003;254(3):225-235.
- Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health*. 2012;12:974.
- Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40(3):232-239.
- Westermarck P. Systemic amyloidoses—new treatment methods make early and exact diagnosis more and more important. *Lakartidningen*. 2007;104(19):1517-1521.

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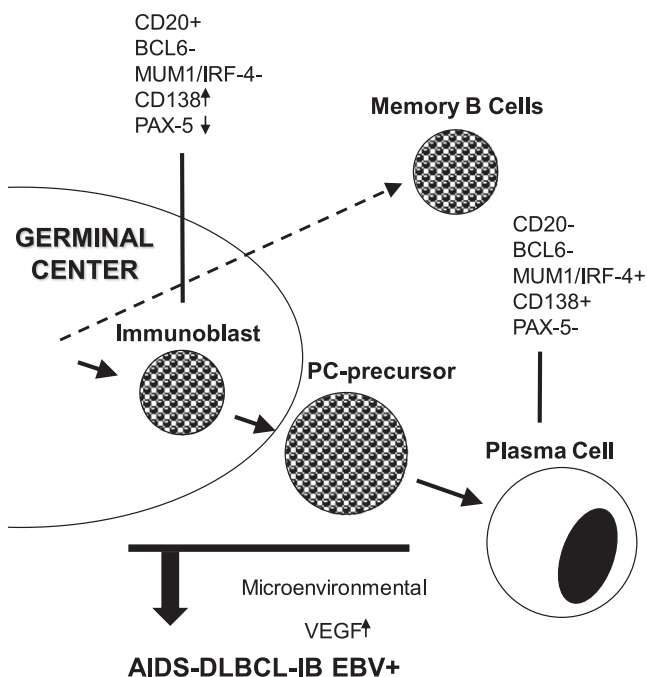
## To the editor:

### The microenvironment of AIDS-related diffuse large B-cell lymphoma provides insight into the pathophysiology and indicates possible therapeutic strategies

We read with great interest the article by Liapis and Colleagues<sup>1</sup> that was published in *Blood* on May 7, 2013 (online ahead of print). The authors investigated the tumor, microenvironment, and viral components in AIDS-related diffuse large B-cell lymphoma (DLBCL). The results of the study showed that AIDS-related DLBCL is highly angiogenic, with markedly higher blood-vessel density than sporadic DLBCL cases. Importantly, the investigation also highlighted the role

of Epstein-Barr virus (EBV) in angiogenesis.<sup>1</sup> In a previous work,<sup>2</sup> we used gene expression profile (GEP) analysis (~12 000 genes) to further define the phenotype of AIDS-related non-Hodgkin lymphoma (AIDS-NHL).<sup>2</sup> The AIDS-NHL cases selected for the study included several subtypes displaying distinct histologic appearance. Indeed, the spectrum of AIDS-NHL ranged from DLBCL of the centroblastic or immunoblastic type to primary effusion lymphoma and Burkitt lymphoma. In agreement with their distinct morphologic appearance, the results indicated that EBV-positive AIDS-DLBCL of the immunoblastic type (AIDS-DLBCL-IB) represented a separate entity relative to AIDS-NHL. Among the various subtypes of AIDS-NHL, EBV-positive AIDS-DLBCL-IB seemed to be more similar to primary effusion lymphoma.<sup>2</sup>

Since an additional aim of the original work<sup>2</sup> was to investigate the relationship of AIDS-NHL to normal B cells and to AIDS-unrelated NHL, we would like to raise 2 more questions about EBV-positive AIDS-DLBCL-IB: (1) what is the relationship with the supposed lymphoma counterpart in immunocompetent hosts?, and (2) where do tumor cells derive from? To determine the relationship with the lymphoma counterpart in the immunocompetent hosts, we compared GEPs by unsupervised and supervised analyses. The results of the comparative analysis revealed that AIDS/Burkitt lymphoma and AIDS-DLBCL of the centroblastic type, but not EBV-positive AIDS-DLBCL-IB, were indistinguishable from their counterparts in immunocompetent hosts. To define the cellular origin, we compared the GEPs of the individual AIDS-NHL cases with the specific gene expression signatures of normal B-cell subsets. We included in the comparative analysis EBV-immortalized B-cell lines as representative of immunoblasts and multiple myeloma cell lines as representative of the terminally differentiated plasma cell stage. We found relatedness of the GEP of the EBV-positive AIDS-DLBCL-IB cases to the multiple myeloma cell lines. In summary, EBV-positive AIDS-DLBCL-IB represented a distinct entity when compared with the other AIDS-NHL subtypes and its supposed counterpart in immunocompetent hosts. Moreover, by GEP analysis, EBV-positive AIDS-DLBCL-IB displayed a phenotype related to plasma cells (Figure 1).<sup>3</sup> This finding was not surprising, since it is known that



**Figure 1. EBV-positive AIDS-related DLBCLs of the immunoblastic type display a phenotype related to plasma cells.** The tumor cells display immunoblast-associated antigens together with plasma-cell-associated markers. The figure also shows the putative role of EBV in the microenvironmental angiogenesis by inducing vascular endothelial growth factor (VEGF) upregulation.