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Commentary

Anatomical site as a parameter in the predictive model of diffuse large B cell lymphoma

Classification is essentially about prediction. Being a member of a class connotes specific qualities that are characteristic of class membership. We rely on classification to inform our thoughts and expectations.

Diagnostic categories rely on this same paradigm. A patient with high random blood sugar, high fasting blood glucose, a high oral glucose tolerance result, and elevated A1C is diagnosed with diabetes. This classification provides us with a prediction of the patient's clinical course without therapy and a prediction of the patient's progress with appropriate insulin treatment and a prediction of the occurrence of characteristic sequelae. The power of diagnosis is prediction.

Diffuse large B cell lymphoma (DLBCL) is classified by cellular morphology and tissue histology [1]. Large lymphocytes arranged in a diffuse pattern that effaces the typical tissue architecture are characteristic and confer class membership. Nevertheless, in this case, class membership has not provided reliable predictions of clinical course.

There is significant heterogeneity in patients diagnosed with DLBCL. The morphology of the large B cells of DLBCL demonstrate variability with a blend of centroblastic, immunoblastic, and anaplastic features. The immunophenotype of the tumor cells is also variable. DLBCL cells from some patients express CD30 or PD-L1 but others do not. Not unexpectedly, this heterogeneity in pathological evaluation is reflected in variable clinical presentation and course. Unfortunately, the cellular morphology and tissue histology that define the category are not reliably prognostic.

Gene expression profiling has revealed clustering of DLBCL samples into 2 distinct subgroups [2,3]: germinal center B cell type (GCB) and activated B cell type (ABC). GBC DLBCL characteristically expresses BCL6, a transcription factor associated with germinal center B lymphocytes, and AID, an enzyme involved in the somatic hypermutation that occurs in germinal center B cells. ABC DLBCL cells demonstrate constitutive activation of the nuclear factor-κB (NFκB) pathway, which is implicated in disease progression for many different types of cancer [4]. The value of this dichotomy defined by gene expression profiling relates to prognostic significance. Patients with GCB DLBCL have significantly better overall survival than patients with ABC DLBCL [2,3]. It seems likely that gene expression profiling has been able to provide reliable prognostic information because it is based on factors, such as the NFκB pathway, that influence disease course.

Gene expression profiling has provided a valuable analysis of DLBCL cells but this technique is not an accepted diagnostic platform. It requires high levels of technical capability because of its significant degree of complexity, and it is expensive. Consequently, several immunohistochemical algorithms have been proposed as substitutes for gene expression profiling. For instance, the International DLBCL Rituximab-CHOP Consortium Program Study has developed the Visco-Young algorithm which relies on the expression of CD10, FOXP1, and BCL6 to distinguish GCB from ABC DLBCL samples [5]. Most likely, this algorithm is concordant with gene expression profiling since they both rely on the activity of the NFκB pathway. NFκB pathway activity suppresses CD10 expression [6], BCL6 downregulates NFκB components [7], and FOXP1 acts in concordance with the NFκB pathway to promote cell survival [8].

This coherent picture of DLBCL is reassuring, but a closer examination reveals an important unresolved issue. Patients with DLBCL present with either primary nodal disease or primary extra-nodal disease. The disease processes are included in the same classification because of morphological and histological identity although we know that these criteria are not powerful enough to confer prognostic significance. The gene expression profiles [2,3] and the immunohistochemical algorithms [5] were established without definitive stratification based on the anatomical site of the primary lesion. Because 30–40% of DLBCL are primary extra-nodal, resolution of this concern is essential.

In this issue of ***Leukemia Research***, Hallas et al. have presented data demonstrating that the Visco-Young algorithm is consistent with NFκB-activating mutations segregating between ABC and GCB subtypes for nodal DLBCL but not for primary extra-nodal DLBCL. They also found interesting variations in the NFκB-activating mutations relating to the specific anatomical site of the primary tumor. For instance, primary testicular DLBCL cells demonstrated a high prevalence of combined MYD88 and CD79 mutations that activate the NFκB pathway but no CARD11 activating mutations. Conversely, primary extra-nodal DLBCL cells from other anatomical sites had no combined MYD88 and CD79 activating mutations whereas CARD11 activating mutations were observed. The implication is inescapable that a new algorithm incorporating the anatomical site in the predictive model is needed.

The idea that the primary anatomical site is an important facet of lymphoma pathogenesis and consequently molecular subtype is not novel. Marginal zone lymphomas of mucosa-associated lymphoid tissue occur in various extra-nodal sites. Gastric tumors are associated with *Helicobacter pylori* induced gastritis whereas ocular adnexal tumors are related to *Chlamydophila psittaci* infection [9]. Marginal zone lymphomas from these 2 anatomical sites show striking differences in the prevalence of specific chromosomal translocations [10,11]. Gastric tumors exhibit t(11;18)(q21;q21) while ocular adnexal lymphomas are more likely to demonstrate t(14;18)(q32;21). Additionally, differences in mutations were found among marginal zone lymphomas from nodal, extra-nodal, and splenic sites by whole exome sequencing [12]. Lymphoid tissue from distinct anatomical sites have divergent pathogenetic influences resulting in lymphomas with distinct molecular characteristics.

Lymphocytes are exposed to different signals at different anatomical sites. Besides being exposed to distinct microbial influences that may affect lymphomagenesis, each tissue has unique purposes and

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consequent organizational structures that affect cellular signaling. Lymphocytes in the skin are exposed to a constant barrage of environmental factors. Lymphocytes in the testes exist in a cooler milieu with potential for exposure to high concentrations of active hormones. Influences in the central nervous system are filtered by the blood-brain barrier. A specific tissue may support lymphomagenesis without an activating mutation because of constitutive signals delivered through the local milieu. Another tissue without those specific constitutive signals may require activating mutations for the development of a lymphoid malignancy.

Hallas et al. have presented compelling results that are concordant with the idea that DLBCL is manifest with distinct characteristics at diverse anatomical sites. Their results emphasize the concept that the anatomical location should be included in predictive models of lymphoma pathogenesis.

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