consistent with the existence of nonviral mechanisms capable of promoting DDR1 expression in the absence of EBV. Therefore, the DDR1 pathway described by Cader et al[1] is likely to be an alternative or additional pathway to already known signaling pathways in the pathogenesis of Hodgkin lymphoma. The supposed existence of EBV-unrelated mechanisms upregulating DDR1 expression envisages that DDR1 activation by its ligand collagen(s) plays a significant pathogenetic role in EBV-related and unrelated Hodgkin lymphoma (see figure).

Besides the relationship of EBV-driven oncogenesis with the tumor microenvironment, the article by Cader et al[1] focuses the reader's attention on interesting, but still poorly known, microenvironmental factors in Hodgkin lymphoma such as ECM and fibroblasts. The Hodgkin lymphoma microenvironment, in fact, also contains a collagen-rich ECM, mesenchymal stem cells, and a large number of fibroblasts defined as Hodgkin lymphoma-associated fibroblasts. There is a wide range of interactions between RS cells and Hodgkin lymphoma-associated fibroblasts,[7,10] which produce collagen-rich reticular fibers composed of collagen I, III, and IV covered by the ECM. Interestingly, collagen IV is recognized by DDR1.[4] The study of the interactions among DDR1, fibroblasts, and ECM might be an interesting field of research because of their potential impact on DDR1 upregulation and activation.

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● ● ● LYMPHOID NEOPLASIA

Comment on Hartmann et al, page 4246

A novel prognostic scoring system for NLPHL

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In this issue of *Blood*, Hartmann and colleagues from the German Hodgkin Study Group (GHSG) conducted a review of pathologic features and clinical data from 423 patients with nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) treated across 9 of their prospective clinical trials.[1] First, they determined that patients with histologic variants have a higher chance of having advanced-stage disease and a greater risk for disease progression or relapse at 5 years. Second, they were able to establish a prognostic scoring model that defines 3 discrete risk groups based on the factors of variant histopathologic growth pattern, low serum albumin, and male gender.

NLPHL comprises only approximately 5% of the diagnoses of Hodgkin lymphoma. A longstanding view, given its often indolent clinical behavior and CD20 positivity, was that there was significant pathologic similarity with follicular lymphoma. Brune and colleagues demonstrated through gene expression profiling analysis that NLPHL most closely overlaps with T-cell–rich B-cell lymphoma (TCR-BCL), a subset of diffuse large B-cell lymphoma (DLBCL), and classical Hodgkin lymphoma (cHL)[2]

The rarity of this diagnosis makes it challenging to conduct large randomized clinical trials, and thus most data come from single-arm phase 2 and retrospective clinical studies. Overall outcomes are generally excellent, with a 50-month freedom from treatment failure (FFTF) of 88% and early-stage patients having the best outcomes.[3] Although later relapses occur more commonly than in cHL, overall survival (OS) is typically not negatively significantly impacted.

Therapeutic strategies for early-stage NLPHL patients are centered on radiation

Prognostic scoring model for NLPHL patients

a. Features and assigned score

Feature		Scoring points
Histopathologic subtype	Typical pattern (A and/or B)	0
	Morphologic variant (C, D, E, and/or F)	1
Albumin	≥4 g/dL	0
	<4 g/dL	1
Gender	Female	0
	Male	2

Adapted from Table 3 in Hartmann et al that begins on page 4246.

b. Risk groups and corresponding outcomes

Risk group	Overall score	5-y PFS, %	5-y OS, %
Low risk	0-1	95.2	98.7
Intermediate risk	2	87.5	96.2
High risk	3-4	68.7	88.3

Adapted from Table 3 in Hartmann et al that begins on page 4246.

therapy based on the excellent outcomes seen across multiple studies. Chen et al described 10-year progression-free survival (PFS) rates of 85% for stage I and 61% for stage II for radiation therapy.[4] Advanced-stage disease represents only approximately 20% to 25% of the total cases. Thus therapeutic options are broad and range from cHL-directed regimens such as doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) to B-cell lymphoma–directed regimens such as rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). We have previously reported favorable outcomes with R-CHOP with a durable complete remission rate of 90% at 3.5 years.[5] The use of rituximab is based on two phase 2 trials conducted by Stanford and the GHSG.[6,7] Stanford treated patients with limited (4 weeks) versus extended dosing (2 years) and demonstrated a CR of 56% with limited rituximab, which increased to 88% with extended rituximab. The median freedom from progression (FFP) was 24 months with limited dosing, and has not been reached with extended dosing.

A higher risk of transformation exists for NLPHL compared with cHL. In a British Columbia Cancer Agency (BCCA) study reported by Al-Mansour and colleagues, there was a 14% transformation rate at a median of 8.1 years, with an increased rate of transformation seen with advanced stage and splenic involvement.[8] Although advanced-stage disease has been known to be a risk factor for transformation and relapse, the pathologic risk factors historically have not been well defined.

The current work of Hartmann and colleagues builds on variant patterns of NLPHL described by Fan and colleagues a decade earlier through a retrospective study that identified 6 distinct immunoarchitectural patterns (A: classic B-cell–rich nodular; B: serpiginous/interconnected nodular; C: nodular with prominent extranodular lymphocytic and histiocytic (L&H) cells; D: T-cell–rich nodular; E: diffuse with a T-cell–rich background (TCR-BCL–like); and F: a diffuse B-cell–rich pattern), with the T-cell–rich background being an independent predictor of relapse.[9] In addition, sequential biopsies taken at time of relapses demonstrated a steady progression to a more diffuse pattern with time. Hartmann et al used these defined patterns and expert review by 10 pathologists to categorize patients into 3 groups: those with typical NLPHL (A and/or B only), histopathologic variant NLPHL (C, D, E, or F), and tumor cell–rich cases presenting with a high number of tumor cells in focal sheets.

Overall, 74.6% of patients had a typical NLPHL histology. The other patients either had a major variant component of C, D, E, and F, seen in 15.2% of the cases, or there was a minor component of one of these 4 patterns in the remaining 10.2% of the cases. Patients with the histopathologic variants more frequently had advanced-stage disease ($P = .0012$) or progression/relapse of disease ($P = .0009$), and as anticipated, the inferior PFS for those with variant histology did not significantly affect OS. At the next step, they used the factors for risk of progression/relapse of univariate significance in a multivariate regression analysis to develop a prognostic score model and identified male gender ($P = .0119$), low serum albumin ($P = .0055$), and a variant histopathologic growth pattern ($P = .0038$) as independent risk factors for progression/relapse within 5 years. A scoring system for these 3 risk factors was then developed (see the table) that can be used to stratify 5-year PFS and OS rates.

This GHSG prognostic scoring model is a distinct, clinically relevant advance for NLPHL patients, particularly because the role of interim positron emission tomography (PET) in predicting outcomes is not established. Another scoring model that focuses solely on histopathologic features was presented recently by Panjwani and colleagues.[10] Although it is not routine to describe each of the 4 histopathologic variants in full detail, in this model only the simplified description of a typical vs a morphologic variant is considered. Given concern for inferior outcomes, patients with NLPHL variants have been considered for treatment within our institution along a DLBCL-focused platform. Yet this scoring system suggests that patients with a variant histopathologic pattern, but otherwise absent risk factors, will have a 5-year PFS of 95.2%. However, because some of these patients received BEACOPP, related to the trials in which they were treated, it would be important for other groups to validate this model in non-BEACOPP–managed patients as well. A key advantage of this prognostic model can be used in future prospective trials to best define high-risk disease patients and can be readily integrated in multiinstitutional trials. Furthermore, our increasing knowledge of the driving biological factors in this disease, including the microenvironment surrounding the L&H cells, can be used to further define novel therapeutic strategies, as well as further refine prognostic models.

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