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Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Special Type of (Follicular) B-Cell Lymphoma?

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Abstract: The clinicopathologic spectrum of nodular lymphocyte-predominant Hodgkin lymphoma, now termed "nodular lymphocyte-predominant B-cell lymphoma" (NLPBCL), may include incipient, typical and transformed forms. On the basis of its clinicopathologic spectrum, NLPBCL is very similar to follicular lymphoma not associated with *BCL2* translocation. In addition, NLPBCL, based on biopathologic features (gene profiling signature, and phenotypic and morphotypic characteristics), is a germinal center-derived B-cell neoplasm; therefore, it could be included in the follicular lymphoma group of non-Hodgkin lymphoma.

Keywords: Hodgkin lymphoma; B-cell lymphoma; follicular lymphoma; in situ neoplasia; transformed lymphoma

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There are currently two parallel lymphoma classification systems: the WHO-HAEM5 [1] and the International Consensus Classification (ICC) of Mature Lymphoid Neoplasms [2]. Regarding Hodgkin lymphoma (HL), the WHO-HAEM5 maintains the subtype termed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) in addition to classical HL (CHL). The ICC [2] renamed the so-called NLPHL [3] to "nodular lymphocyte-predominant B-cell lymphoma", because this entity is closely related to T/histiocyte-rich large B-cell lymphoma (THRLBCL). The ICC classified NLPHL and THRLBCL into the group of large B-cell lymphomas. In most instances, both lymphomas represent a true biological continuum [2] (Tables 1 and 2). NLPHL should no longer be considered a Hodgkin subtype of lymphoma [2], since there is robust evidence that NLPHL differs morphologically, immunophenotypically and clinically from CHL [4] (Table 1). It also differs from CHL in its tumor cell microenvironment [5], biology and genomic features [4].

The Fan system for NLPHL [6], which identifies six histopathogical grades (A, B, C, D, E and F), could distinguish typical NLPHL (which encompasses grades A, B and C), from the more clinically aggressive tumors (which encompass D, E and F) [6,7]. Hartmann et al. [7] evaluated the prognostic implication of 'histopathologic NLPHL variants', encompassing grades D, E and F of Fan et al. [6], characterized by the large amount of LP tumor cells outside the B-cell nodules or the B-cell depletion of the microenvironment, versus typical NLPHL. According to the results of the study, 'histopathologic variants' were associated with more advanced disease and a higher relapse rate than typical NLPHL [7]. Histological patterns of NLPHL encompassing the D, E and F grades of the Fan system [6] are morphologically and clinically related to THRLBCL, a specific variant of DLBCL. Figure 1 demonstrates that NLPHL may exhibit, in incipient forms, an intranodular pattern (Panel A), whereas in advanced forms, it may exhibit a THRLBCL-like pattern (Panel B), clearly different from a DLBCL not otherwise specified (Panel C). For these reasons, it seems appropriate to include NLPHL within the group of non-Hodgkin lymphomas (NHLs) and to term it "nodular lymphocyte-predominant B-cell lymphoma" (NLPBCL), as recently reported by the ICC [2].

Table 1. Tumor cell phenotype, cell of origin, and virologic and genetic features of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)/nodular lymphocyte-predominant B-cell lymphoma (NLPBCL) compared with classic Hodgkin lymphoma (CHL), T/histiocyte cell-rich B-cell lymphoma (THRLBCL) and diffuse large cell B-cell lymphoma (DLBCL), NOS.

		NLPHL/		DLBCL
	CHL	**NLPBCL**	**THRLBCL**	**NOS**
CD15	+/−	−	−	−
CD30	+	Usually−/+	−/+	+/−
EMA	−	Usually+	Usually+	−
CD20	−/+	+	+	+
CD79a	−	+	+	+
CD45	−	+	+	+
BCL6	−	+	+	+
MUM1	+	−/+	−/+	−/+
PU.1	−	+	−/+	−/+
OCT2	−/+	+	+	+
BOB1	−/+	+	+	+
PAX5	+/−	+	+	+
EBV	+/−	-(rare cases+)	−	−/+
IGVH gene rearrangements	Clonal rearrangement with high load of SHM and crippling mutations	Clonal rearrangement with high load of SHM and on-going mutations	Clonal rearrangement with high load of SHM and on-going mutations	

Table 2. Tumor cell microenvironment in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)/nodular lymphocyte-predominant B-cell lymphoma (NLPBCL) compared with classic Hodgkin lymphoma (CHL) and T/histiocyte cell-rich B-cell lymphoma (THRLBCL).

Cellular Microenvironment	CHL	NLPHL/NLPBCL	THRLBCL
Small B cells	−/+	+	+
T cells	+	−/+	+
B cell/B and T cells	+	+	−
Cytotoxic TIA-1	−/+	−/+	+
Granzyme B	−/+	−/+	+
CD4+ rosetting T cells	+	+	−
CD8+ rosetting T cells	−	−	−
CD57+ rosetting T cells	−	−/+	−
CD40L+ rosetting T cells	+	−	−
MUM1+ rosetting T cells	−	+	−
Histiocytes	−	−/+	+
DRC meshworks	−	+	−

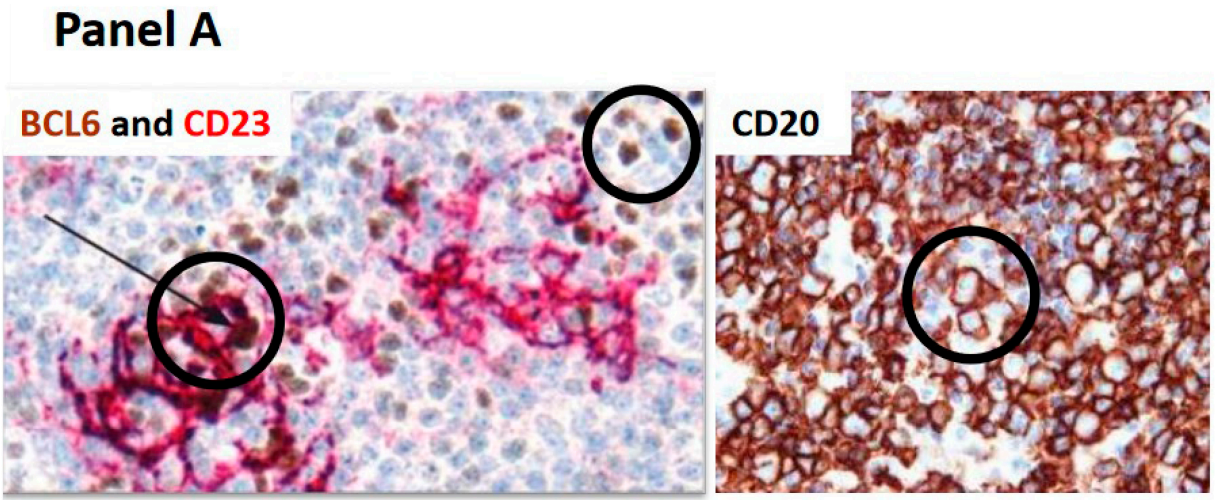

Figure 1. *Cont.*

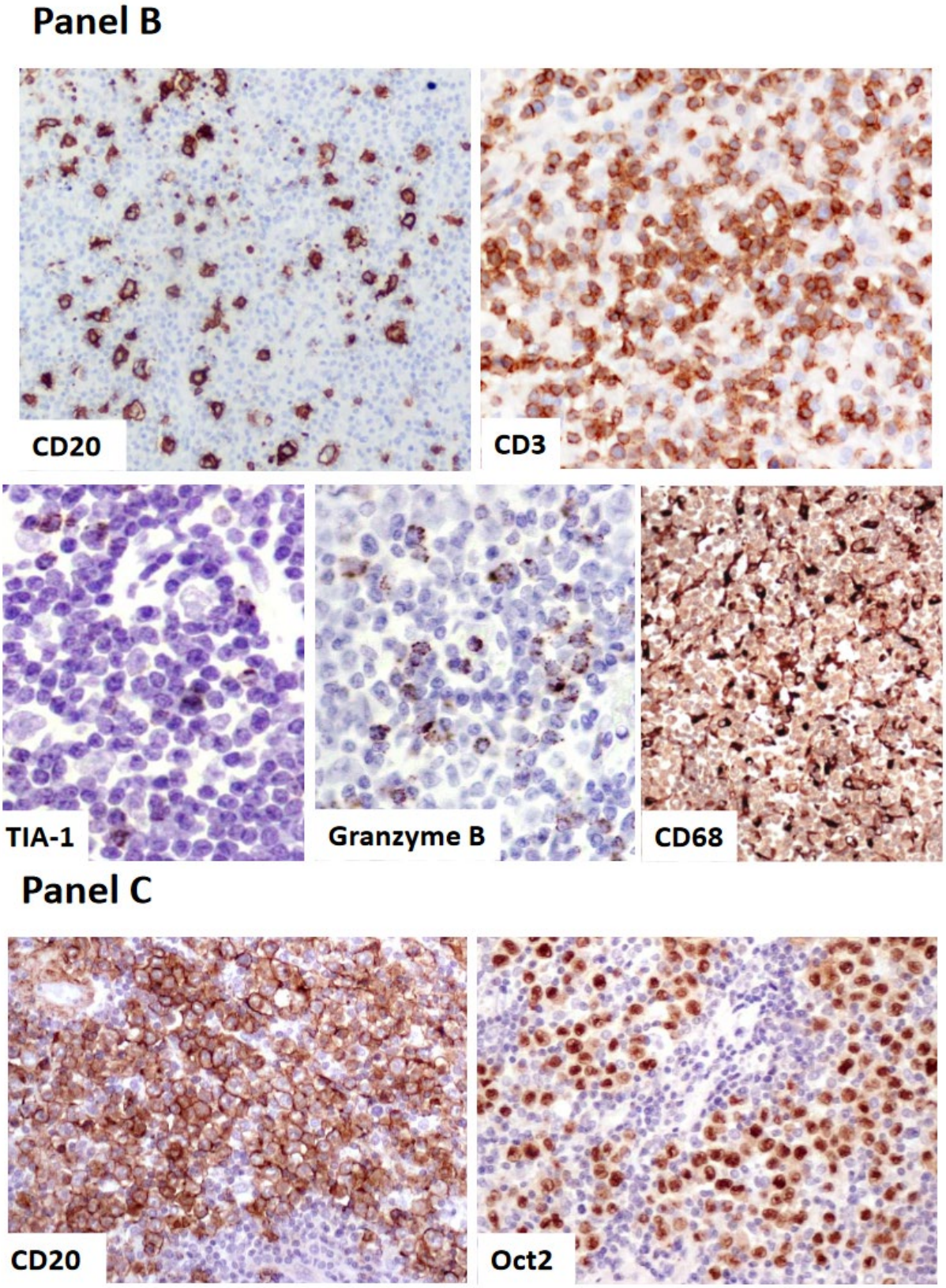

Figure 1. (**A**) shows incipient, intranodular, nodular lymphocyte-predominant Hodgkin lymphoma/nodular lymphocyte-predominant B-cell lymphoma in which BCL6-positive tumor cells (encircled) are admixed with the meshwork of CD23-positive follicular dendritic cells (indicated by an arrow). Furthermore, intranodular CD20-positive tumor cells are surrounded by CD20-negative cells (T-cells) (encircled). (**B**) shows a T/histiocyte-cell rich large B-cell lymphoma (THRLBCL) in which

CD20-positive tumor cells are admixed with many CD3-positive T-cells. A large number of T cells express TIA-1 and Granzyme B. The background is rich in CD68-positive histiocytes. (**C**) shows a T/diffuse large B-cell lymphoma with numerous CD20-positive and OCT2-positive tumor cells. Original magnification: 20 (**B**,**C**); 40× (**A**). Immunohistochemical staining; Hematoxylin counterstaining. The first image of Panel A is derived from double immunostaining using BCL6 (brown) and CD23 (red).

An additional pattern of NLPHL, the "intranodular pattern", in which the so-called LP tumor cells reside in nodules reminiscent of lymphoid follicles and do not invade the extranodular space, has been recognized [8–10]. This histological feature may be regarded as an early NLPHL pattern limited to the lymphoid follicle. Like "in situ follicular neoplasia [11]", belonging to the spectrum of follicular lymphoma (FL), this early pattern of NLPHL is likely to be an in situ step that potentially, though rarely, leads to overt lymphoma.

Over the past few years, the clinicopathologic spectrum of FL has become better understood [11]. Interestingly, it has been demonstrated that it may include incipient forms, typical FL (associated with *BCL2* translocation or not) and forms of histologic transformation including diffuse large B-cell lymphomas (DLBCL) [11,12]. A similar model is recognizable in NLPHL whose spectrum includes incipient, typical and transformed forms.

NLPBCL, based on biopathologic features (gene profiling signature, and phenotypic and morphotypic characteristics), is a germinal center-derived B-cell neoplasm; therefore, it could be included in the FL group of NHL. In addition, also on the basis of its spectrum, it is very similar to FL not associated with *BCL2* translocation, as its spectrum includes an incipient intranodular form, a typical form with nodules, and transformed forms including DLBCL that often display THRLBCL-like features (Figure 2).

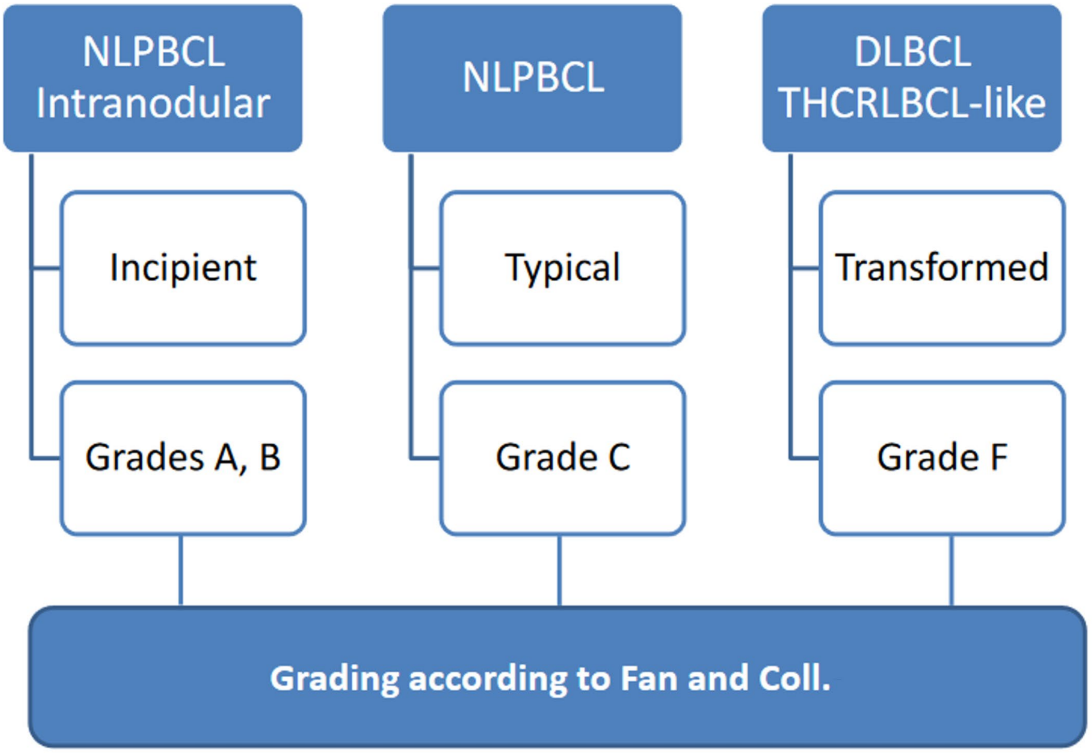

Figure 2. Like follicular lymphoma, the pathologic spectrum of nodular lymphocyte-predominant Hodgkin lymphoma, now termed "nodular lymphocyte-predominant B-cell lymphoma" [2], may include incipient, typical and transformed forms. The Figure also shows the correspondence of these forms with the grades proposed by Fan and colleagues [6].

DLBCL—diffuse large B-cell lymphoma; NLPBCL—nodular lymphocyte-predominant B-cell lymphoma; THRLBCL—T/histiocyte-rich large B-cell lymphoma.

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References

1. Alaggio, R.; Amador, C.; Anagnostopoulos, I.; Attygalle, A.D.; Araujo, I.B.O.; Berti, E.; Bhagat, G.; Borges, A.M.; Boyer, D.; Calaminici, M.; et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* **2022**, *36*, 1720–1748. [CrossRef] [PubMed]
2. Campo, E.; Jaffe, E.S.; Cook, J.R.; Quintanilla-Martinez, L.; Swerdlow, S.H.; Anderson, K.C.; Brousset, P.; Cerroni, L.; de Leval, L.; Dirnhofer, S.; et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. *Blood* **2022**, *140*, 1229–1253. [CrossRef] [PubMed]
3. Mason, D.Y.; Banks, P.M.; Chan, J.; Cleary, M.L.; Delsol, G.; de Wolf Peeters, C.; Falini, B.; Gatter, K.; Grogan, T.M.; Harris, N.L.; et al. Nodular lymphocyte predominance Hodgkin's disease. A distinct clinicopathological entity. *Am. J. Surg. Pathol.* **1994**, *18*, 526–530. [CrossRef] [PubMed]
4. Ansell, S.M. Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. *Am. J. Hematol.* **2022**, *97*, 1478–1488. [CrossRef] [PubMed]
5. Hartmann, S.; Soltani, A.S.; Bankov, K.; Bein, J.; Hansmann, M.L.; Rosenwald, A.; Bernd, H.W.; Feller, A.; Ott, G.; Möller, P.; et al. Tumour cell characteristics and microenvironment composition correspond to clinical presentation in newly diagnosed nodular lymphocyte-predominant Hodgkin lymphoma. *Br. J. Haematol.* **2022**, *199*, 382–391. [CrossRef] [PubMed]
6. Fan, Z.; Natkunam, Y.; Bair, E.; Tibshirani, R.; Warnke, R.A. Characterization of variant patterns of nodular lymphocyte predominant hodgkin lymphoma with immunohistologic and clinical correlation. *Am. J. Surg. Pathol.* **2003**, *27*, 1346–1356. [CrossRef] [PubMed]
7. Hartmann, S.; Eichenauer, D.A.; Plütschow, A.; Mottok, A.; Bob, R.; Koch, K.; Bernd, H.W.; Cogliatti, S.; Hummel, M.; Feller, A.C.; et al. The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: A report from the German Hodgkin Study Group (GHSG). *Blood* **2013**, *122*, 4246–4252, quiz 4292. [CrossRef] [PubMed]
8. Carbone, A. Does "in situ lymphoma" occur as a distinct step in the development of nodular lymphocyte-predominant Hodgkin lymphoma? *Cancer* **2012**, *118*, 15–16. [CrossRef] [PubMed]
9. Carbone, A.; Gloghini, A. "Intrafollicular neoplasia" of nodular lymphocyte predominant Hodgkin lymphoma: Description of a hypothetic early step of the disease. *Hum. Pathol.* **2012**, *43*, 619–628. [CrossRef] [PubMed]
10. Medeiros, L.; O'Malley, D.; Caraway, N.; Vega, F.; Elenitoba-Johnson, K.; Lim, M. *Tumors of the Lymph Nodes and Spleen*; American Registry of Pathology: Washington, DC, USA, 2017; Volume 25.
11. Jaffe, E.S.; Carbone, A. Evolution in the Definition of Follicular Lymphoma and Diffuse Large B-Cell Lymphoma: A Model for the Future of Personalized Medicine. *Hemato* **2022**, *3*, 466–474. [CrossRef]
12. Jaffe, E.S.; Carbone, A. B- and T-/NK-Cell Lymphomas in the 2022 International Consensus Classification of Mature Lymphoid Neoplasms and Comparison with the WHO Fifth Edition. *Hemato* **2024**, *5*, 157–170. [CrossRef]