

## Leukaemia Section

### Short Communication

# Classification of Hodgkin lymphoma over years

Antonino Carbone, Annunziata Gloghini

Department of Pathology Centro di Riferimento Oncologico Aviano (CRO), Istituto Nazionale Tumori, IRCCS, Aviano, Italy; acarbone@cro.it (AC); Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; annunziata.gloghini@istitutotumori.mi.it (AG)

Published in Atlas Database: December 2016

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/ClassifHodgkinID1767.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/68739/12-2016-ClassifHodgkinID1767.pdf>

DOI: 10.4267/2042/68739

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2017 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Abstract

Histologic classification of Hodgkin lymphoma (HL) evolved through different systems, starting from the modern histologic classifications by Jackson and Parker in 1944 and Lukes and Butler in 1966, to the 2008 World Health Organization (WHO) classification. HL has been classified into classical HL, which accounts for 95% of all HL cases, and the less common nodular lymphocyte predominant HL (NLPHL). Classical HL is a distinct neoplastic entity with typical clinical and epidemiological characteristics and unique pathological, genetic, and virological features.

### Keywords

Hodgkin lymphoma; Histologic classification; Rye classification; REAL classification; WHO classification.

## Clinics and pathology

### Disease

The modern classification scheme of Hodgkin lymphoma (HL) (Lukes, Craver, et al., 1966) is based on the concept that the histologic subtypes represent morphologic patterns of a neoplasm in which rare Hodgkin and Reed-Sternberg (HRS) cells, the HL tumor cells, are embedded in a dominant reactive background. Based on the morphologic characteristics of the HRS cells (lacunar cells, multinucleated giant cells, pseudosarcomatous cells) and the composition of the reactive infiltrate, four histologic subtypes have been distinguished: lymphocyte-rich cHL

(LRCHL), nodular sclerosis (NS) cHL, mixed cellularity (MC) cHL, and lymphocyte depletion (LD) cHL. (Stein, 2001; Stein et al., 2008; Swerdlow et al., 2016). The background shows a cellular composition which is characteristic for each histotype. In MC cHL, microenvironmental cell types include T- and B-reactive lymphocytes, eosinophils, granulocytes, histiocytes/macrophages, plasma cells, mast cells. In addition, a great number of fibroblast-like cells and fibrosis are frequently found in NS cHL.

Lymphocyte predominant (LP) HL, is characterized by a lymphocyte-rich background with admixed histiocytes. In 1944 Jackson and Parker called it in as "paragranuloma" to separate it from Hodgkin "granuloma". In 1966 Lukes and Butler (Lukes and Butler JJ, 1966) renamed paragranuloma "lymphocytic and/or histiocytic predominance HD", recognizing a nodular and a diffuse pattern and used the term of lymphocytic and histiocytic (L&H) RS-cell variant for the diagnostic cell (Lukes, Butler et al., 1966), now called LP cell. At the Rye symposium, it was decided to combine the nodular and diffuse types of the Lukes and Butler classification into LPHL (Lukes, Craver et al., 1966) (Table 1).

In the last decades, a considerable body of evidence has indicated that LPHL exhibits features of a B-cell lymphoma, with a characteristic antigen profile and clinical behavior (reviewed in Younes et al., 2014). This led the authors of the REAL classification proposal to separate LPHL as a distinct clinicopathologic entity from the other subtypes of HL, which were grouped under the

term "classical HL (CHL) ID: 1569> " (Harris et al.,1994; Mason et al., 1994; Stein, 2001; Stein et al., 2008) (Table 1). According to its cell of origin, phenotype and type of progression to large B-cell lymphoma, NLPHL should probably be considered as a B-cell lymphoma tout court.

**Phenotype/cell stem origin**

HL with a nodular growth pattern and a lymphocyte-rich background encompasses two entities, i.e. NLPHL and LRCHL with distinct phenotypical features. NLPHL which may contain a broad morphologic spectrum of neoplastic cells, exhibit a characteristic immunophenotype with expression of B-cell-specific antigens and absent expression of CD30 and CD15.

LRCHL cases also exhibit, in the majority of cases, a nodular growth pattern as well as a broad morphologic spectrum of the neoplastic cells. The tumor cell phenotype, however, is always characteristic of CHL with expression of CD30 and CD15, infrequent expression of B-cell antigens (Figure 1). Furthermore, it could be shown by means of immunostains that the vast majority of LPHL cases contain areas with nodular growth pattern, whereas purely diffuse cases are extremely rare. Probably these cases, could be classified as grey zone lymphomas because they exhibit intermediate features between NLPHL and THCRLBCL (Figure 1) (Younes et al., 2014).

**Clinics**

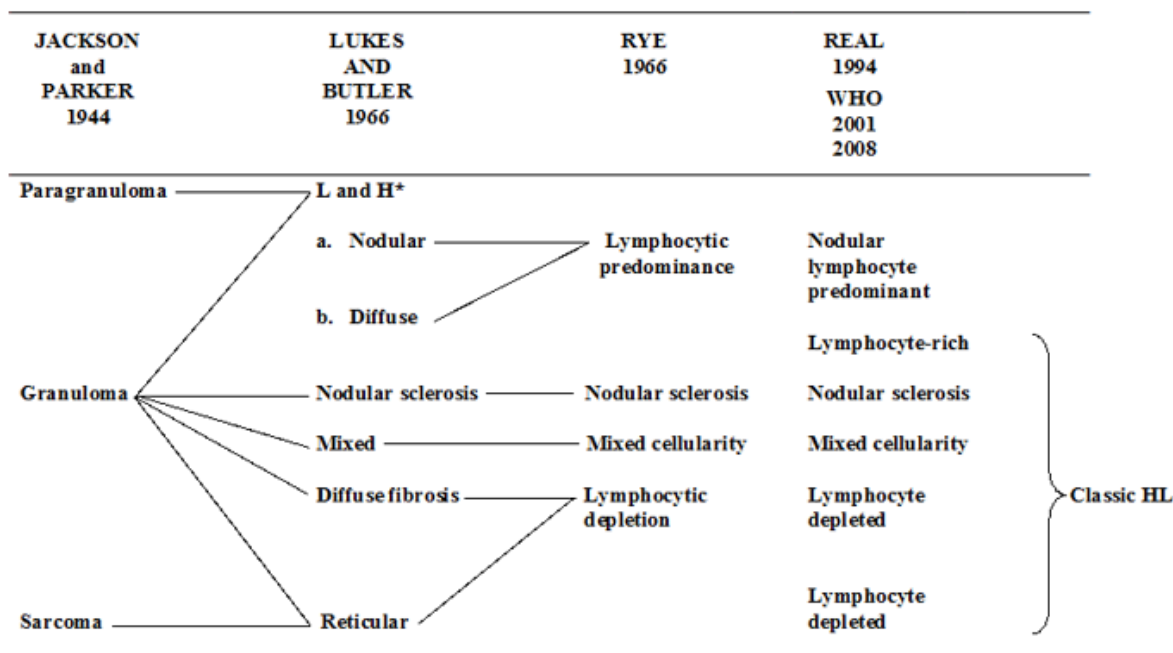
Patients with LPHL and LRCHL usually differ

from patients with NS cHL or MC cHL, as they presented with an earlier disease stage and infrequent mediastinal involvement. As most LPHL cases show a complete or partial nodular growth pattern, their differentiation from THCRLBCL is a rare problem (Table2).

**Pathology**

The question of the existence of diffuse LPHL became more complex when other authors described a diffuse large B-cell lymphoma variant, the so-called T-cell or histiocyte-rich large B-cell lymphoma (THCRLBCL), which frequently simulate the morphology of diffuse LPHL but exhibited an aggressive disease course (De Wolf-Peeters et al., 2008; Carbone and Glohini, 2016a). The cases identified as diffuse LPHL exhibit loosely distributed neoplastic cells embedded in a reactive background without evidence of nodularity .In these cases, which closely resemble THCRLBCL by conventional histology, a majority of the neoplastic cells have the morphologic features of LP cells. Immunophenotypic analysis can disclose an LP cell-characteristic phenotype with expression of CD20, CD79a, and EMA, whereas in-situ hybridization for EBER-transcripts does not provide evidence of a latent EBV infection. Due to the overlapping features between THRLBCL and LPHL, it is sometimes impossible to distinguish these two entities; thus, "grey zone" lymphoma is used to define some of those cases (De Wolf-Peeters et al., 2008; Younes et al., 2014) (Figure 1).

**Table 1. Classifications of Hodgkin lymphoma over years.**



L and H, lymphocytic and/or histiocytic; REAL, Revised European-American Lymphoma; WHO, World Health Organization; HL, Hodgkin lymphoma

Also, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) are closely related: both diseases contain neoplastic cells with similar morphologic and immunophenotypic features but differ with respect to their architecture and the nature of the reactive background (table 2). An additional type of HL with an abundance of lymphocytes was subsequently recognized. It was termed "lymphocyte-rich (LR) form of classical HL" and included in the REAL classification. This variant of classical HL (cHL), resembles, in terms of nodular growth and lymphocyte-richness, nodular LPHL and, in terms of the immunophenotype of the tumor cells, CHL (Figure 1). Clinically, patients with LPHL and LRCHL show similar disease characteristics at presentation but differ in the frequency of multiple relapses and prognosis after relapse (Gloghini and Carbone, 2016a; Gloghini and Carbone, 2016b).

### Other features

In addition to immunophenotyping, in-situ hybridization for EBV detection can assist in the differential diagnosis between the two HL entities as the neoplastic cells in LPHL appear not to be permissive for an EBV infection (Table 3). EBV is found in HRS cells preferentially in cases of MC and LD cHL, and less frequently in NS and

LRCHL. Notably, EBV is found in HRS cells in nearly all cases of cHL occurring in patients infected with HIV (Younes et al., 2014; Dolcetti et al., 2016; Carbone et al., 2016).

The virologic characteristics of cHL vary according to the immunocompetence status of the host and cHL subtype (Carbone et al., 2016).

### Evolution

NLPHL may evolve to a completely diffuse T-cell-rich proliferation lacking any follicular dendritic cells which would be consistent with a THRLBCL or can be associated with such a proliferation at a separate site.

NLPHL may evolve to a completely diffuse T-cell-rich proliferation lacking any follicular dendritic cells which would be consistent with a THRLBCL or can be associated with such a proliferation at a separate site.

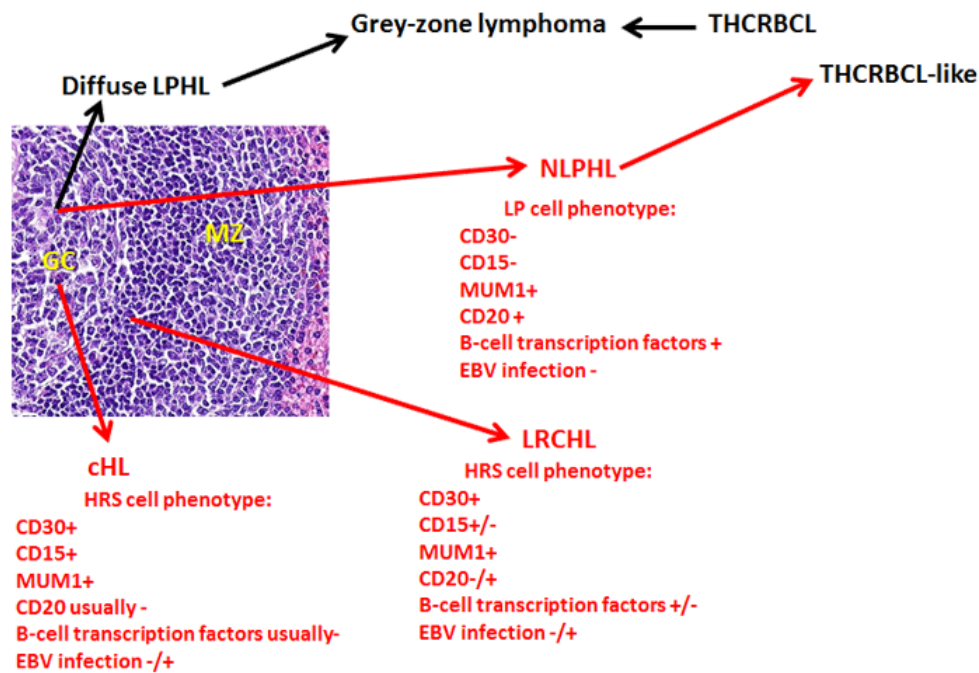
### Genetics

#### Note

See the pertinent sections within the CARDS of the Atlas of Genetics and Cytogenetics in Oncology and Haematology describing the general features of NLPHL and cHL (Küppers, 2011; Carbone and Gloghini, 2016b; Gloghini and Carbone, 2016a).

		<b>cHL</b>	<b>NLPHL</b>	<b>THRLBCL</b>
<b>Phenotype</b>				
	CD15	+	-	-
	CD20	Usually -	+	+
	CD30	+	-	- or +
	IRF4/MUM1	+	+	- or +
	BCL6	+(30%)	+	-
	EMA	-	+	Usually -
<b>EBV infection</b>				
		-/+*	-	-
<b>Background</b>				
	T cells	+	-	+
	B cells / B and T cells	+	+	-
	CD57+ rosetting cells	-	+	-
	CD40L+ rosetting cells	+	+	-
	Histiocytes	+/-	+/-	+
	Eosinophils	+	-	-
	Plasma cells	+	-	-
	DRCs meshworks	- /+	+	-
	Fibrosis	+(Common)	+(Rare)	-

**Table 2.** Phenotypic and virologic features of neoplastic cells of classic Hodgkin lymphoma (cHL), nodular lymphocyte predominance Hodgkin lymphoma (NLPHL) and T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) \*Association with EBV is less frequent in NS than in MC cHL and LRCHL.



Host	Hodgkin lymphoma subtype	EBV infection
HL of the general population		
	Nodular lymphocyte predominance	-
	cHL, nodular sclerosis	Usually -*
	cHL, mixed cellularity	Usually +*
	Rare types	
	cHL, lymphocyte rich	Variably +
	cHL, lymphocyte depleted	Variably +
Immunodeficiency-associated HL		
HIV-associated HL		
	cHL, lymphocyte depleted	+
	cHL, mixed cellularity	+
	Less frequent	
	cHL, lymphohistiocytoid	+
	cHL, nodular sclerosis	+

**Table 3. Morphologic and virologic characteristics of Hodgkin lymphoma.** Abbreviations. cHL, classical Hodgkin lymphoma; -, negative; +, positive. \*Association with EBV is less frequent in ns (10-40%) than in mc cHL (approximately 75% of cases)

## References

Anagnostopoulos I, Hansmann ML, Franssila K, et al. European Task Force on Lymphoma project on lymphocyte predominance Hodgkin disease: histologic and immunohistologic analysis of submitted cases reveals 2 types of Hodgkin disease with a nodular growth pattern and abundant lymphocytes. *Blood*. 2000 Sep 1;96(5):1889-99

Brune V, Tiacci E, Pfeil I, Döring C, Eckerle S, van Noesel CJ, Klapper W, Falini B, von Heydebreck A, Metzler D, Bräuninger A, Hansmann ML, Küppers R. Origin and

pathogenesis of nodular lymphocyte-predominant Hodgkin lymphoma as revealed by global gene expression analysis. *J Exp Med*. 2008 Sep 29;205(10):2251-68

Carbone A, Glohini A, Caruso A, De Paoli P, Dolcetti R. The impact of EBV and HIV infection on the microenvironmental niche underlying Hodgkin lymphoma pathogenesis. *Int J Cancer*. 2017 Mar 15;140(6):1233-1245

De Wolf-Peeters C, Delabie J, Campo E, Jaffe ES, Delsol G.. T cell/histiocyte-rich large B-cell lymphoma. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele H, Vardiman JW (eds.) World Health Organization Classification of Tumours, Pathology and Genetics of

Tumours of Haematopoietic and Lymphoid Tissues, Lyon: IARC Press, 2008: 238-239.

Dolcetti R, Gloghini A, Caruso A, Carbone A. A lymphomagenic role for HIV beyond immune suppression? Blood 2016 Mar 17;127(11):1403-9 doi: 10

Gloghini A, Carbone A. Lymphocyte-rich classical Hodgkin lymphoma (LRCHL) Atlas Genet Cytogenet Oncol Haematol 2016 (b) <http://atlasgeneticsoncology.org/Anomalies/LymphRichClassicalHodgkinID1567.html>

Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group Blood 1994 Sep 1;84(5):1361-92

Jackson H, Parker F.. Hodgkins disease. I. General considerations. N Engl J Med 1944; 230(1): 1-8

Jackson H.. Classification and prognosis of Hodgkins disease and allied disorders. Surg Gynecol Obstet 1937; 64: 465-467

Küppers R. Hodgkin lymphoma Atlas Genet Cytogenet Oncol Haematol. 2011; 15(6): 527-528. <http://atlasgeneticsoncology.org/Anomalies/HodgkinID2068.html>

Lukes RJ, Butler JJ, Hicks EB.. Natural history of Hodgkins disease as related to its pathologic picture. Cancer 1966; 19(3): 317-344

Lukes RJ, Craver LF, Hall TC, Rappaport H, Ruben P.. Report of the nomenclature committee. Cancer Res. 1966;

26: 1311.

Mason DY, Banks PM, Chan J, Cleary ML, Delsol G, de Wolf Peeters C, Falini B, Gatter K, Grogan TM, Harris NL, et al. Nodular lymphocyte predominance Hodgkin's disease A distinct clinicopathological entity Am J Surg Pathol

Stein H, Delsol G, Pileri SA, Weiss LM, Poppema S, Jaffe ES.. Classical Hodgkin lymphoma, introduction. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele H, Vardiman JW (eds.) World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Lyon: IARC Press, 2008: 326-329

Stein H.. Classical Hodgkin lymphoma, introduction. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds.) World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, Lyon: IARC Press, 2001: 239

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms Blood 2016 May 19;127(20):2375-90

Younes A, Carbone A, Johnson P, Dabaja B, Ansell S, Kuruvilla L.. Hodgkin's lymphoma. De Vita VTJ, Lawrence TS, Rosenberg SA (eds). De Vita, Hellman, and Rosenberg's Cancer: Principles Practice of Oncology: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.

---

*This article should be referenced as such:*

Carbone A, Gloghini A. Classification of Hodgkin lymphoma over years. Atlas Genet Cytogenet Oncol Haematol. 2017; 21(10):365-369.

---