Int J Clin Exp Pathol 2010;3(1):39-46
www.ijcep.com/IJCEP906002

Review Article

Pitfalls in diagnostic hematopathology – Part II

Xianfeng F. Zhao

Department of Pathology, University of Maryland School of Medicine, Baltimore, MD

Received June 18, 2009; accepted August 20, 2009; Available online September 10, 2009

Abstract: The overlapping features of malignant lymphomas create a diagnostic "grey zone", and lead to the invention of "grey zone lymphomas". There are several major grey zone lymphomas: 1) Lymphomas with overlapping features of Hodgkin lymphoma and large B-cell lymphoma; 2) Lymphomas with overlapping features of Burkitt lymphoma and diffuse large B-cell lymphoma; 3) Lymphomas with overlapping features of nodular lymphocyte predominant Hodgkin lymphoma and T-cell/histiocyte rich large B-cell lymphoma; 4) Lymphomas with overlapping features of Hodgkin lymphoma, anaplastic large cell lymphoma (ALCL) and peripheral T-cell lymphoma (PTCL); 5) T-cell classical Hodgkin lymphoma and ALCL-HL. The second review of this series will be dedicated to discussion of the "grey zone" features of the lymphomas and how to narrow down the "grey zone" between those lymphomas.

Key words: DLBCL, Hodgkin lymphoma, Burkitt lymphoma, grey zone lymphoma, diagnostic pitfalls

Introduction

Another common pitfall in diagnostic hematopathology is the "grey zone" between different lymphomas. On the one hand, "grey zone" reflects our limitations in understanding the biology of malignant lymphomas. On the other hand, it indicates the complexity and overlapping features of malignant lymphomas, and the occasional arbitrary nature of our classification. Generally, related lymphomas create the "grey zone". Despite advances in immunohistochemistry, flow cytometry, cytogenetics and molecular studies, distinctions between classical Hodgkin lymphoma (cHL) and related diseases such as primary mediastinal large B-cell lymphoma (PMLBL), nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), T-cell/histiocyte rich large B-cell lymphoma (T/HRLBL) and anaplastic large cell lymphoma (ALCL) are still difficult in many cases (**Table 1**). Previous lack of clear-cut diagnostic criteria imposed a problem for both pathologists and clinicians. Recognizing this fact, a term "grey zone lymphoma" was first introduced at a workshop held in 1998 by a group of 12 expert hematopathologists from the U.S., Canada and Europe [1]. Although more strict criteria were utilized to define the well-established entities, 11 years later, cases that have overlapping features remain pitfalls in the hematopathological diagnosis. These overlapping features are increasingly acknowledged by the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues (hereafter referred to as "WHO Classification") [2].

In my experience, it may not be difficult to diagnose a "grey zone lymphoma", but it is sometimes hard to determine where to draw the line for the "grey zone". In the second part of this review series, I will discuss the pitfalls in diagnosing "grey zone lymphoma" and review the criteria that help differentiate lymphomas with "grey zone" features.

Classical Hodgkin lymphoma versus primary mediastinal large B-cell lymphoma – classical "grey zone lymphoma"

Hodgkin lymphomas were classified by the WHO Classification into cHL and NLPHL. While NLPHL will be discussed in the next section, cHL is characterized by proliferation of large atypical neoplastic cells with abundant cytoplasm, large vesicular nuclei (one or multiple) and prominent eosinophilic nucleoli. The binucleated forms were often referred to as "Reed-Sternberg cells". Currently, all the large neoplastic cells in cHL, including Reed-Sternberg (RS) cells and its

Table 1. Common lymphomas with overlapping or "grey zone" features

Classical Hodgkin lymphoma Primary mediastinal large B-cell lymphoma
Burkitt lymphoma Diffuse large B-cell lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma T-cell/histiocyte rich large B-cell lymphoma
Classical Hodgkin lymphoma ALK-negative anaplastic cell lymphoma (ALCL) Peripheral T-cell lymphoma
Classical Hodgkin lymphoma T-cell classical Hodgkin lymphoma ALCL-like Hodgkin lymphoma

variants (**Figure 1A**), are collectively called Hodgkin-Reed-Sternberg (HRS) cells in memory of the three pioneers in the description and diagnosis of cHL [3-5]. Recent investigation suggests that HRS cells are *bona fide* B-cells that are crippled in the production of immunoglobulin [6, 7], as a result of aberrant expression of transcription regulators [8]. Because of this, HRS cells are weakly PAX5+, occasionally express CD20, and have *IGH* rearrangement [9]. However, cHL is usually CD30+ and CD15+, but is negative for CD45, CD3, and CD79a. Since the HRS cells secret many cytokines such as PDGF, TGF-β and IL-6 etc. [10, 11], cHL is often associated with a background of reactive lymphocytes, plasma cells, eosinophils and fibrosis (**Figure 1A**). The reactive background is so characteristic that some hematopathologists believe that a diagnosis of cHL cannot be made without the associated reactive background. However, similar features can also be seen in the PMLBL, which is characterized by proliferation of large atypical lymphoid cells in a background of compartmentalizing fibrosis, or delicate mesh-like sclerosis. Sometimes individual neoplastic cells are scattered in a background of fibrosis, resembling shells in the sand (**Figure 1B**). These fibrotic backgrounds can also be seen in DLBCL, particularly in DLBCL of retroperitoneal lymph nodes. In contrast, the cHL fibrosis is usually band-like, with neoplastic cells forming clusters surrounded by fibrotic bands. These patterns are particularly useful in evaluating needle core

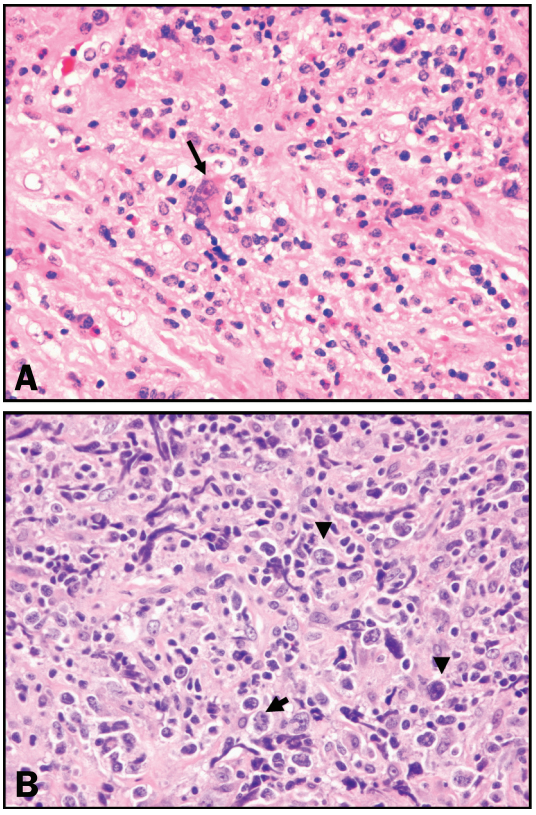

Figure 1. Comparison of nodular sclerosis cHL (A) and PMLBL (B). (A) One large RS cell (indicated by an arrow) is surrounded by bands of fibrosis in a background of small lymphocytes, eosinophils and plasma cells. (B) Scattered large RS-like cells (arrow heads) are in a background of delicate fibrosis, reactive small lymphocytes and histiocytes. Eosinophils are rare to absent.

biopsy specimens that have limited amount of tissue and usually lack a histological architecture. Since both cHL and PMLBL are lymphomas of the mediastinum, the overlapping features of cHL and PMLBL cause a major challenge in lymphoma diagnosis.

To distinguish these two entities, several features (**Table 2**) are useful: 1) cHL usually have classical RS cells; while neoplastic cells in PMLBL resemble RS cells; 2) cHL fibrosis is usually band-like and surrounding the aggregates of neoplastic cells; while fibrosis in PMLBL is compartmentalizing and mesh-like; 3) CD45 and CD79a are positive in PMLBL and negative in cHL; 4) PAX5 is weakly positive in cHL, but strongly positive in PMLBL; 5) CD15 is usually negative in PMLBL; only rarely, large B-cell lymphoma could express CD15 [13]. MAL is usually expressed in PMLBL [14], but not in cHL. When MAL is indeed expressed,

Table 2. Features to differentiate classical Hodgkin lymphoma (cHL) and Primary mediastinal large B-cell lymphoma (PMLBL)

Features	cHL	PMLBL
Morphologic		
Neoplastic cells	Hodgkin-Reed-Sternberg (HRS) cells	HRS-like cells
Background	Reactive small lymphocytes, eosinophils and plasma cells	Reactive small T-cells and B-cells; rare eosinophils
Fibrosis	Band-like; nodular	Mesh-like; compartmentalizing
Immunophenotypic		
CD15	+/-	-
CD20	-/+	+
CD30	+	weak +
CD45	-	+
CD79a	-	+
BCL6	-	+
MAL	-/+	+
PAX5	weak +	+

the cHL is usually associated with an adverse prognosis [15], and may be transforming into large B-cell lymphoma. Although recent work showed that these two lymphomas had similarities in molecular signature [16], the clinical management differs [17, 18].

Simply, when the large neoplastic cells are CD45-negative, diagnosis favors cHL. When the large neoplastic cells are CD45+/CD79+, but are negative for CD15, diagnosis favors large B-cell lymphoma. When lymphoma cells express CD15, CD20, CD30, CD45, CD79a, PAX5 and/or MAL, they represent a "grey zone lymphoma". The "grey zone lymphoma" is currently defined by the 2008 WHO Classification as "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL" [2]. It is reasonable to believe that "grey zone lymphoma" and lymphocyte-depleted cHL may be the intermediate between these two lymphomas. The cHL to DLBCL transformation may represent an example of lymphoma evolution (**Figure 2**). Currently, "grey zone lymphoma" is managed as DLBCL by using REPOCH regimen [19].

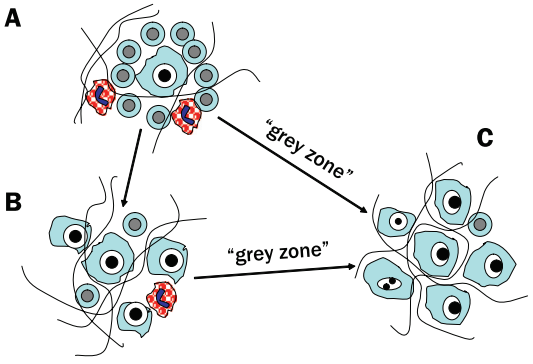

Figure 2. Lymphoma evolution from cHL to DLBCL. "Grey zone lymphoma" may be an intermediate stage between cHL (A) and DLBCL (C). Lymphocyte-depleted cHL may represent another intermediate stage during lymphoma evolution (B).

Burkitt lymphoma versus diffuse large B-cell lymphoma

Burkitt lymphoma (BL) is a well established pathologic and clinical entity, which is featured by the characteristic "starry-sky" histology, monotonous medium-sized cytology with vacuolated basophilic cytoplasm and multiple small nucleoli, extremely high proliferation index and presence of c-*MYC* rearrangement [20]. Due to its germinal center origin, the cells are CD10+ and BCL6+, and negative for BCL2. Morphologic variants that have prominent nucleoli and c-*MYC* rearrangement exist. Historically, they were called "Burkitt-like" or "Atypical Burkitt" lymphoma because of their atypical morphologic features and similar aggressive clinical behavior as classical Burkitt lymphoma [21]. Most of the DLBCL originate from germinal center B-cells, and thus

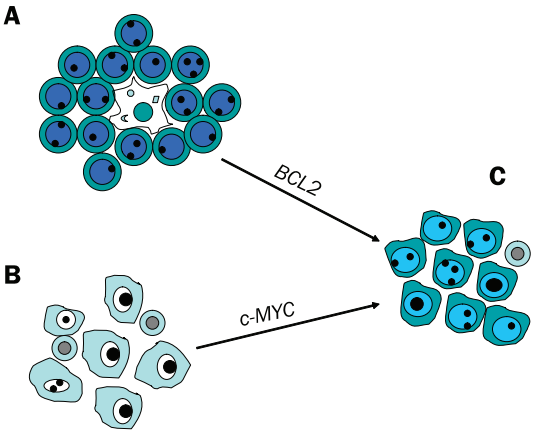

Figure 3. A model to explain the occurrence of aggressive B-cell lymphoma with atypical morphology. Aggressive B-cell lymphoma with atypical morphology occurs when either BL (A) acquires aberrant activation of *BCL2* or DLBCL (B) acquires c-*MYC* activation.

they have a similar immunophenotype as BL. In contrast, approximately 30% of DLBCL have a t(14;18)(q32;q21) chromosomal abnormality and typically no c-*MYC* rearrangement. Morphologically, DLBCL cells are large and pleomorphic, and they frequently also have a high proliferation index. It is generally not difficult to differentiate classical BL from DLBCL. However, due to their similar origin, overlaps between atypical BL and DLBCL do exist and impose a challenge for the hematopathologists.

Lymphomas with overlapping features of DLBCL and BL have long been recognized [22]. Lymphomas with DLBCL morphology and c-*MYC* rearrangement were identified and diagnosed as DLBCL with c-*MYC* rearrangement [23]. DLBCL with both t(14;18)(q32;q21) and c-*MYC* rearrangement were found to have a more aggressive clinical course than DLBCL without c-*MYC* rearrangement [24]. A group of aggressive B-cell lymphomas with atypical morphology (atypical for either BL or DLBCL) have been identified [25], which could have BCL2 expression, lower (than classical BL) proliferation rate and presence of c-*MYC* rearrangement. These lymphomas could also have "starry-sky" histology, extremely high proliferation rate, and absence of c-*MYC* rearrangement. Clinically, these lymphomas behaved aggressively and responded favorably to high-intensive chemotherapy for BL. The atypical morphology of these lymphomas is determined by their genetic abnormalities, such as the coexistence of t(14;18)(q32;q21) and c-*MYC* rearrangement, trisomy 8, or other yet unidentified abnormalities that have a similar effect as c-*MYC* (**Figure 3**). In 2005, an American group and a European group independently identified the BL molecular signature in both classical BL and some DLBCL [26, 27]. Based on accumulating information of these lymphomas, the 2008 WHO Classification listed them as a separate entity [28]. It is generally agreed that these lymphomas should be managed aggressively as BL.

Since c-*MYC* rearrangement is a hallmark of BL, detection of c-*MYC* rearrangement is required for the diagnosis of BL. Although t(2;8)(p12;q24), t(8;14)(q24;q32) and t(8;22)(q24;q11) could cover up to 90% of the c-*MYC* rearrangements, other c-*MYC* rearrangement was also detected [29]. Whether c-*MYC* rearrangement is specific for BL remains controversial. Besides BL, c-*MYC* rearrangement has been identified in chronic lymphocytic leukemia [30], follicular lymphoma [31], and DLBCL [32]. Presence of c-*MYC* rearrangement is often associated with an aggressive clinical course and poor prognosis in all those lymphomas.

Nodular lymphocyte predominant Hodgkin lymphoma versus T-cell/histiocyte rich large B-cell lymphoma

It is currently believed that progressively transformed germinal center (PTGC), NLPHL and T/HRLBL are related and represent different stages of a progressive disease [33, 34]. PTGC is a benign disease, whereas NLPHL is a mature B-cell lymphoma with indolent clinical course. T/HRLBL has an aggressive clinical course and should be treated as DLBCL. Because of this clinical implication, distinguishing NLPHL from T/HRLBL is critically important.

NLPHL is limited to lymph nodes of a young patient, while T/HRLBL often involves the extranodal sites, such as bone and soft tissue, in addition to lymph node. Several arbitrary features were proposed to differentiate NLPHL and T/HRLBL (**Table 3**). It is generally believed that NLPHL is almost always associated with a background of reactive small B-cells. Previous studies used <10% of the background small B-cells to favor T/HRLBL. In my experience, classical T/HRLBL has hardly any small B-cells in the

Table 3. Features to distinguish nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte rich large B-cell lymphoma (T/HRLBL)

Features	NLPHL	T/HRLBL
Morphologic		
Architecture	Nodular	Diffuse
Neoplastic cells	"Popcorn"-like L&H cells	Centroblastic, immunoblastic or RS-like
Background	Mixed populations of small T- cells and B-cells; rosette small T-cells; aggregate small B-cells; nodular follicular dendritic cell meshwork	Scattered small T-cells and numerous reactive histiocytes; rare small B-cells
Immunophenotypic		
Neoplastic cells	CD20+/CD45+/CD79a-/BCL2-	CD20+/CD45+/CD79a+/BCL2+
Background cells	CD3+/CD57+ (rosette T-cells); CD21+ (follicular dendritic cells)	CD3+ (small T-cells); CD68+

background. Background small lymphocytes are almost entirely CD3+ T-cells. Reactive histiocytes can be prominent (**Figure 4**). Some believe that vague nodularity favors NLPHL; however nodular large cell transformation has been reported [35]. In these cases, "NLPHL with focal large cell transformation" is preferred for the diagnosis.

It is rare that NLPHL involves bone marrow [36]. When marrow or other organs are involved, it is usually diagnosed as T/HRLBL [37]. NLPHL may be regarded as an "in situ" T/HRLBL – when it goes to an extranodal site, it becomes T/HRLBL. Even if there are rare cases of true NLPHL involving bone marrow, it should be managed as DLBCL or T/HRLBL [38].

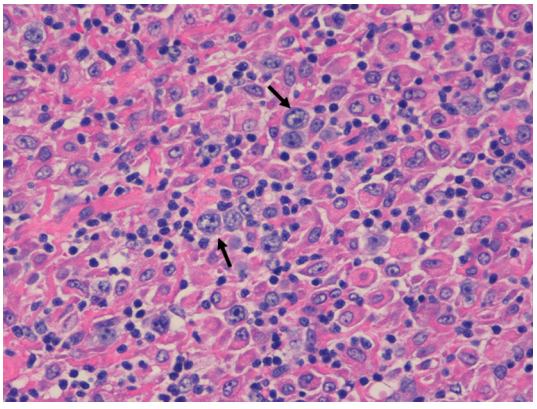

Figure 4. Classical T/HRLBL. Scattered large neoplastic B-cells (indicated by arrows) are in a background of numerous reactive histiocytes and small numbers of reactive small T-cells. Reactive small B-cells are extremely rare.

Classical Hodgkin lymphoma versus anaplastic large cell lymphoma versus peripheral T-cell lymphoma

ALCL is another CD30+ lymphoma that should be differentiated from cHL [39]. Morphologically, ALCL cells can resemble HRS cells and often show "hall-mark" cells. ALK-positivity distinguishes ALK+ ALCL from cHL [40, 41]. However, differentiating ALK-negative ALCL from cHL can be a challenge. Since cHL is of a B-cell origin [6, 7], it is often weakly positive for PAX5. Conversely, ALK-negative ALCL is a T-cell lymphoma, and is almost never positive for PAX5. When peripheral T-cell lymphoma (PTCL) expresses CD30, it becomes another differential entity in this complicated "trio". As in ALK-negative ALCL, PTCL is also negative for PAX5. A consensus is still lacking among experts on the definition of ALK-negative ALCL [42]. Some believe that ALK-negative ALCL should be included in PTCL, unspecified. Others argue that ALK-negative ALCL has distinctive morphological features. A recent large study from the Internaltional Peripheral T-cell Lymphoma Project suggested that ALK-negative ALCL was clinically and immunophenotypically different from PTCL [43]. This study also showed that patients with ALK-negative ALCL had a superior failure free survival (FFS) and overall survival (OS) rate than those with PTCL (36% vs 20%; and 49% vs 32%, respectively).

Classical Hodgkin lymphoma, B-cell or T-cell origin?

T-cell cHL has been reported [44, 45]. The neoplastic cells in those reported cases were even weakly positive for PAX5 [45], a B-cell specific activator protein (BSAP). There was an

ongoing debate over the existence of a "T-cell cHL". A recent study analyzed 259 cases of cHL and identified that 5% of the HRS cells expressed at least one T-cell markers [46], indicating that T-cell antigens could be aberrantly expressed in HRS cells. The REAL classification also proposed an ALCL-like HL (ALCL-HL) as a provisional entity [47] based on its RS-like morphology and CD30+/CD15+ immunophenotype. However, some PTCL can also be CD30+/CD15+ [48]. Although a randomized clinical trial concluded that ALCL-HL had an equal response to regimens for high-grade lymphomas and regimens for cHL [49], microarray studies showed that this lymphoma clustered with T-cell lymphomas rather than cHL [50], suggesting that it is a *bona fide* T-cell lymphoma. Although some pathologists believe T-cell cHL does exist [51], almost all the microdissected single cell analyses of cHL pointed to a B-cell origin [52, 53]. Currently, "T-cell cHL" is not recognized by the WHO Classification [2].

Summary

In summary, overlapping features are common between malignant lymphomas, reflecting a continuum of lymphocyte development and lymphoma evolution. Awareness of these features will help us to deal with atypical lymphomas with a prepared mind. Recognizing the challenges in diagnosis of lymphomas with "grey zone" features will increase our confidence in committing to an accurate diagnosis.

Please address all correspondences to: X. Frank Zhao, MD, PhD, Department of Pathology, University of Maryland School of Medicine, 10 S. Pine Street, MSTF 611B, Baltimore, MD 21201; Tel: 410-328-2146, Fax: 410-328-5508; E-mail: xzhao@umm.edu

References

[1] Rudiger T, Jaffe ES, Delsol G, deWolf-Peeters C, Gascoyne RD, Georgii A, Harris NL, Kadin ME, MacLennan KA, Poppema S, Stein H, Weiss LE, Muller-Hermelink HK. Workshop report on Hodgkin's disease and related diseases ('grey zone' lymphoma). *Ann Oncol.* 1998; 9 Suppl 5: S31-38.

[2] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues.* IARC: Lyon 2008.

[3] Watkins SM. The legacy of Thomas Hodgkin (1798-1866). *J R Coll Physicians Lond.* 2000; 34: 100-104.

[4] Reed D. On the pathological changes in Hodgkin's disease, with special reference to its relation to tuberculosis. *Johns Hopkins Hosp Rep*. 1902; 10: 133-196.

[5] Sternberg C. Uber eine eigenartige unter dem Bilde der Pseudoleukamie verlaufende Tuberculose des lymphatischen Apparates. *Ztschr Heilk.* 1898; 19: 21-90.

[6] Küppers R, Hansmann ML, Rajewsky K. Clonality and germinal centre B-cell derivation of Hodgkin/Reed-Sternberg cells in Hodgkin's disease. *Ann Oncol.* 1998; 9 Suppl 5: S17-20.

[7] Marafioti T, Hummel M, Foss HD, Laumen H, Korbjuhn P, Anagnostopoulos I, Lammert H, Demel G, Theil J, Wirth T, Stein H. Hodgkin and reed-sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood.* 2000; 95: 1443-1450.

[8] Mathas S, Janz M, Hummel F, Hummel M, Wollert-Wulf B, Lusatis S, Anagnostopoulos I, Lietz A, Sigvardsson M, Jundt F, Jöhrens K, Bommert K, Stein H, Dörken B. Intrinsic inhibition of transcription factor E2A by HLH proteins ABF-1 and Id2 mediates reprogramming of neoplastic B cells in Hodgkin lymphoma. *Nat Immunol.* 2006; 7: 207-215.

[9] Hummel M, Ziemann K, Lammert H, Pileri S, Sabattini E, Stein H. Hodgkin's disease with monoclonal and polyclonal populations of Reed-Sternberg cells. *N Engl J Med.* 1995; 333: 901-906.

[10] Hsu SM, Waldron JW Jr, Hsu PL, Hough AJ Jr. Cytokines in malignant lymphomas: review and prospective evaluation. *Hum Pathol.* 1993; 24: 1040-1057.

[11] Skinnider BF, Elia AJ, Gascoyne RD, Trümper LH, von Bonin F, Kapp U, Patterson B, Snow BE, Mak TW. Interleukin 13 and interleukin 13 receptor are frequently expressed by Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood.* 2001; 97: 250-255.

[12] Traverse-Glehen A, Pittaluga S, Gaulard P, Sorbara L, Alonso MA, Raffeld M, Jaffe ES. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. *Am J Surg Pathol.* 2005; 29: 1411-1421.

[13] García JF, Mollejo M, Fraga M, Forteza J, Muniesa JA, Pérez-Guillermo M, Pérez-Seoane C, Rivera T, Ortega P, Piris MA. Large B-cell lymphoma with Hodgkin's features. *Histopathology.* 2005; 47: 101-110.

[14] Copie-Bergman C, Plonquet A, Alonso MA, Boulland ML, Marquet J, Divine M, Möller P,

Leroy K, Gaulard P. MAL expression in lymphoid cells: further evidence for MAL as a distinct molecular marker of primary mediastinal large B-cell lymphomas. *Mod Pathol.* 2002; 15: 1172-1180.

[15] Hsi ED, Sup SJ, Alemany C, Tso E, Skacel M, Elson P, Alonso MA, Pohlman B. MAL is expressed in a subset of Hodgkin lymphoma and identifies a population of patients with poor prognosis. *Am J Clin Pathol.* 2006; 125: 776-782.

[16] Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, Chan WC, Zhao T, Haioun C, Greiner TC, Weisenburger DD, Lynch JC, Vose J, Armitage JO, Smeland EB, Kvaloy S, Holte H, Delabie J, Campo E, Montserrat E, Lopez-Guillermo A, Ott G, Muller-Hermelink HK, Connors JM, Braziel R, Grogan TM, Fisher RI, Miller TP, LeBlanc M, Chiorazzi M, Zhao H, Yang L, Powell J, Wilson WH, Jaffe ES, Simon R, Klausner RD, Staudt LM. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med.* 2003; 198: 851-862.

[17] Federico M, Luminari S, Iannitto E, Polimeno G, Marcheselli L, Montanini A, La Sala A, Merli F, Stelitano C, Pozzi S, Scalone R, Di Renzo N, Musto P, Baldini L, Cervetti G, Angrilli F, Mazza P, Brugiatelli M, Gobbi PG; HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol.* 2009; 27: 805-811.

[18] Johnson PW, Davies AJ. Primary mediastinal B-cell lymphoma. *Hematology Am Soc Hematol Educ Program.* 2008; 2008: 349-358.

[19] Dunleavy K, Pittaluga S, Grant N, Steinberg S, Shovlin M, Tay K, Janik JE, Jaffe ES, Wilson WH. Gray Zone Lymphomas: Clinical and Histological Characteristics and Treatment with Dose-Adjusted-EPOCH-R. American Society of Hematology 2008, San Francisco (Moscone Center) 12/8/2008, Abstract 3590.

[20] Leoncini L, Raphael M, Stein H, Harris NL, Jaffe ES, Kluin PM. Burkitt lymphoma. In Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues.* IARC: Lyon 2008, pp262-264.

[21] Ziegler JL, Cohen MH, Vogel CL, Sheagren JN, Carbone PP. Immunologic studies in American patients with Burkitt-like lymphoma. *Cancer Res.* 1967; 27: 2527-2531.

[22] Ladanyi M, Offit K, Jhanwar SC, Filippa DA, Chaganti RS. MYC rearrangement and translocations involving band 8q24 in diffuse large cell lymphomas. *Blood.* 1991; 77: 1057-1063.

[23] Steven Le Gouill, Pascaline Talmant, Cyrille Touzeau, Anne Moreau, Richard Garand, Nadine Juge-Morineau, Fanny Gaillard, Thomas Gastinne, Noël Milpied, Philippe Moreau, Jean Luc Harousseau, Hervé Avet-Loiseau. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. *Haematologica*. 2007; 92: 1335-1342.

[24] Kanungo A, Medeiros LJ, Abruzzo LV, Lin P. Lymphoid neoplasms associated with concurrent t(14;18) and 8q24/c-MYC translocation generally have a poor prognosis. *Mod Pathol.* 2006; 19: 25-33.

[25] Zhao XF, Hassan A, Perry A, Ning Y, Stass SA, Dehner LP. C-MYC Rearrangements are Frequent in Aggressive Mature B-Cell Lymphoma with Atypical Morphology. *Int J Clin Exp Pathol.* 2008; 1: 65-74.

[26] Hummel M, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. *N Engl J Med.* 2006; 354: 2419-2430.

[27] Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. *N Engl J Med*. 2006; 354: 2431-2442.

[28] Kluin PM, Raphael M, Harris NL, Campo E, Stein H, Jaffe ES, Leoncini L. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues.* IARC: Lyon 2008: pp265-266.

[29] Sandlund JT, Kastan MB, Kennedy W, Behm F, Entrekin E, Pui CH, Kalwinsky DT, Raimondi SC. A subtle t(3;8) results in plausible juxtaposition of MYC and BCL6 in a child with Burkitt lymphoma/leukemia and ataxia-telangiectasia. *Cancer Genet Cytogenet.* 2006; 168: 69-72.

[30] Huh YO, Lin KI, Vega F, Schlette E, Yin CC, Keating MJ, Luthra R, Medeiros LJ, Abruzzo LV. MYC translocation in chronic lymphocytic leukaemia is associated with increased prolymphocytes and a poor prognosis. *Br J Haematol.* 2008; 142: 36-44.

[31] Lee JT, Innes DJ Jr, Williams ME. Sequential bcl-2 and c-myc oncogene rearrangements associated with the clinical transformation of non-Hodgkin's lymphoma. *J Clin Invest*. 1989; 84: 1454-1459.

[32] Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of de novo diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations. *Leukemia.* 2009; 23: 777-783.

[33] Chan WC. Cellular origin of nodular lymphocyte-predominant Hodgkin's lymphoma:

immunophenotypic and molecular studies. *Semin Hematol.* 1999; 36: 242-252.

[34] Zhao FX. Nodular Lymphocyte-Predominant Hodgkin Lymphoma or T-cell/Histiocyte Rich Large B-cell Lymphoma: The Problem in "Grey Zone" Lymphomas. *Int J Clin Exp Pathol.* 2008; 1: 300-305.

[35] Boudová L, Torlakovic E, Delabie J, Reimer P, Pfistner B, Wiedenmann S, Diehl V, Müller-Hermelink HK, Rüdiger T. Nodular lymphocyte-predominant Hodgkin lymphoma with nodules resembling T-cell/histiocyte-rich B-cell lymphoma: differential diagnosis between nodular lymphocyte-predominant Hodgkin lymphoma and T-cell/histiocyte-rich B-cell lymphoma. *Blood.* 2003; 102: 3753-3758.

[36] Pappa VI, Norton AJ, Gupta RK, Wilson AM, Rohatiner AZ, Lister TA. Nodular type of lymphocyte predominant Hodgkin's disease. A clinical study of 50 cases. *Ann Oncol.* 1995; 6: 559-565.

[37] Couronné L, Schneider P, Picquenot JM, Laberge S, Bastard C, Vannier JP. Refractory nodular lymphocyte predominant Hodgkin lymphoma transformed to T-cell/histiocyte-rich B-cell lymphoma in an adolescent: salvage therapy with allogeneic bone marrow transplantation. *J Pediatr Hematol Oncol.* 2008; 30: 959-962.

[38] Khoury JD, Jones D, Yared MA, Manning JT Jr, Abruzzo LV, Hagemeister FB, Medeiros LJ. Bone marrow involvement in patients with nodular lymphocyte predominant Hodgkin lymphoma. *Am J Surg Pathol.* 2004; 28: 489-495.

[39] Perkins PL, Ross CW, Schnitzer B. CD30-positive, anaplastic large-cell lymphomas that express CD15 but lack CD45. A possible diagnostic pitfall. *Arch Pathol Lab Med.* 1992; 116: 1192-1196.

[40] Herling M, Rassidakis GZ, Viviani S, Bonfante V, Giardini R, Gianni M, Morris SW, Cabanillas F, Medeiros LJ, Sarris AH. Anaplastic lymphoma kinase (ALK) is not expressed in Hodgkin's disease: results with ALK-11 antibody in 327 untreated patients. *Leuk Lymphoma.* 2001; 42: 969-979.

[41] Vassallo J, Lamant L, Brugieres L, Gaillard F, Campo E, Brousset P, Delsol G. ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin's lymphoma: report of 10 cases. *Am J Surg Pathol.* 2006; 30: 223-9.

[42] Medeiros LJ, Elenitoba-Johnson KS. Anaplastic Large Cell Lymphoma. *Am J Clin Pathol.* 2007; 127: 707-722.

[43] Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, Rimsza L, Pileri SA, Chhanabhai M, Gascoyne RD, Armitage JO, Weisenburger DD; International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood.* 2008; 111: 5496-5504.

[44] Müschen M, Rajewsky K, Bräuninger A, Baur AS, Oudejans JJ, Roers A, Hansmann ML, Küppers R. Rare occurrence of classical Hodgkin's disease as a T cell lymphoma. *J Exp Med.* 2000; 191: 387-394.

[45] Willenbrock K, Ichinohasama R, Kadin ME, Miura I, Terui T, Meguro K, Fukuhara O, DeCoteau JF, Hansmann ML. T-cell variant of classical Hodgkin's lymphoma with nodal and cutaneous manifestations demonstrated by single-cell polymerase chain reaction. *Lab Invest.* 2002; 82: 1103-1109.

[46] Tzankov A, Bourgau C, Kaiser A, Zimpfer A, Maurer R, Pileri SA, Went P, Dirnhofer S. Rare expression of T-cell markers in classical Hodgkin's lymphoma. *Mod Pathol.* 2005; 18: 1542-1549.

[47] Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink HK, Pileri SA, Piris MA, Ralfkiaer E, Warnke RA. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 1994; 84: 1361-1392.

[48] Barry TS, Jaffe ES, Sorbara L, Raffeld M, Pittaluga S. Peripheral T-cell lymphomas expressing CD30 and CD15. *Am J Surg Pathol.* 2003; 27: 1513-1522.

[49] Zinzani PL, Martelli M, Magagnoli M, Zaccaria A, Ronconi F, Cantonetti M, Bocchia M, Marra R, Gobbi M, Falini B, Gherlinzoni F, Moretti L, De Renzo A, Mazza P, Pavone E, Sabattini E, Amendola A, Bendandi M, Pileri SA, Mandelli F, Tura S. Anaplastic large cell lymphoma Hodgkin's-like: a randomized trial of ABVD versus MACOP-B with and without radiation therapy. *Blood.* 1998; 92: 790-794.

[50] Vanhentenrijk V, Vanden Bempt I, Dierickx D, Verhoef G, Wlodarska I, De Wolf-Peeters C. Relationship between classic Hodgkin lymphoma and overlapping large cell lymphoma investigated by comparative expressed sequence hybridization expression profiling. *J Pathol.* 2006; 210: 155-162.

[51] Küppers R. The biology of Hodgkin's lymphoma. *Nat Rev Cancer.* 2009; 9: 15-27.

[52] Tamaru J, Hummel M, Zemlin M, Kalvelage B, Stein H.Hodgkin's disease with a B-cell phenotype often shows a VDJ rearrangement and somatic mutations in the VH genes. *Blood.* 1994; 84: 708-715.

[53] Küppers R, Rajewsky K, Zhao M, Simons G, Laumann R, Fischer R, Hansmann ML. Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. *Proc Natl Acad Sci USA.* 1994; 91: 10962-10966.