

Case Study

Lymphocyte-Rich Classical Hodgkin Lymphoma: A Case with Difficulty in Distinguishing from Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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A 35-year-old man was referred to our hospital because of left supraclavicular and cervical lymphadenopathies. Histopathological examination of the lymph nodes revealed reactive lymphadenopathy. He visited our hospital three years after the initial diagnosis because of enlarged left cervical lymph nodes. Histopathologically, both Hodgkin/Reed-Sternberg (H/RS) and lymphocyte-predominant (LP) cells were found in the lymph node. We first suspected nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), because these cells were CD15⁻ and CD30⁻. However, the diagnosis of lymphocyte-rich classical Hodgkin lymphoma (LRCHL) was finally confirmed, because these cells were found to be CD20⁻, Bob.1⁺, Oct.2⁻, and BCL6⁻ by additional immunostaining. The patient was treated with six cycles of ABVD chemotherapy, and a complete response was achieved. However, he underwent autologous stem-cell transplantation after high-dose chemotherapy owing to a relapse 10 months after primary treatment. Distinguishing LRCHL from NLPHL was difficult in this patient, because histopathological examination showed both H/RS and LP cells, and immunostaining revealed these cells to be triple negative (CD15⁻, CD30⁻ and CD20⁻). Accumulation of such cases are necessary to establish better criteria for the differential diagnosis and assessment of clinical behavior. [*J Clin Exp Hematop* 55(1) : 23-28, 2015]

Keywords: lymphocyte-rich classical Hodgkin lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, ABVD

INTRODUCTION

Classical Hodgkin lymphoma (CHL), including lymphocyte-rich CHL (LRCHL), which comprises 95% of Hodgkin lymphoma cases, is characterized by CD15^{+/-}, CD30⁺, and CD20^{-/+} Hodgkin/Reed-Sternberg (H/RS) cells.¹ On the other hand, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), which accounts for approximately 5% of HL cases, is characterized by CD15⁻, CD30^{-/+} and CD20⁺

lymphocyte-predominant (LP) cells.¹ However, distinction of the two categories is not always straight forward. Here we report such a patient in whom histopathological examination revealed both classical H/RS cells and LP cells, and immunostaining showed them to be triple negative (CD15⁻, CD30⁻ and CD20⁻).

CASE REPORT

A 35-year-old man was referred to our hospital because of four-month history of left supraclavicular and cervical tumors. Physical examination revealed one left supraclavicular and three ipsilateral cervical lymphadenopathies measuring 30 mm in the maximal diameter. Computed tomography (CT) scan revealed left supraclavicular (45 × 32 × 31 mm), left cervical, and anterior mediastinal lymphadenopathies. Histopathological examination of the left supraclavicular and cervical lymph nodes showed reactive change was composed of mature lymphocytes and granulocytes without atypical cells (Fig. 1A, 1B). Therefore, we diagnosed the process to be one of reactive lymphadenopathy. The patient was followed up as an out-patient basis at another hospital, but he visited our hospital again due to the obvious increment of the

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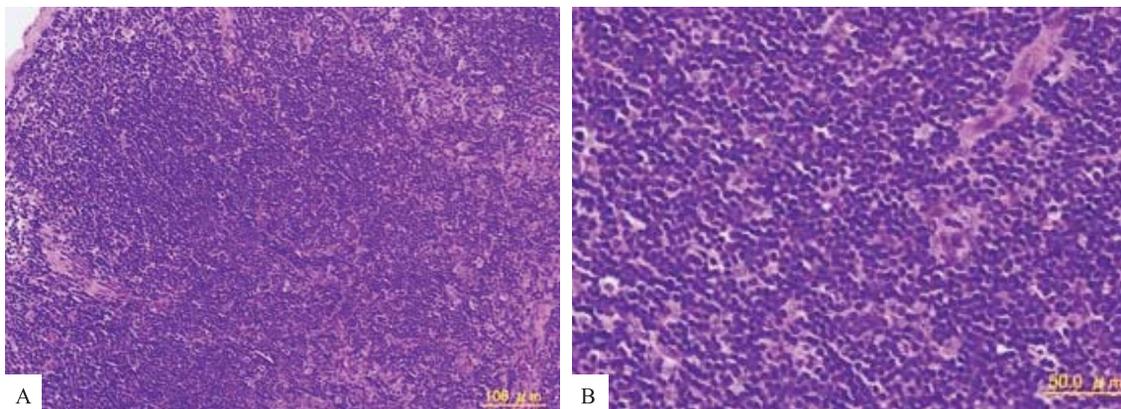


Fig. 1. Histopathology of the left supraclavicular and cervical lymph nodes. In lymph nodes, mature lymphocytes and granulocytes were interspersed without atypical cells (1A; H&E, $\times 200$, 1B; H&E, $\times 400$).

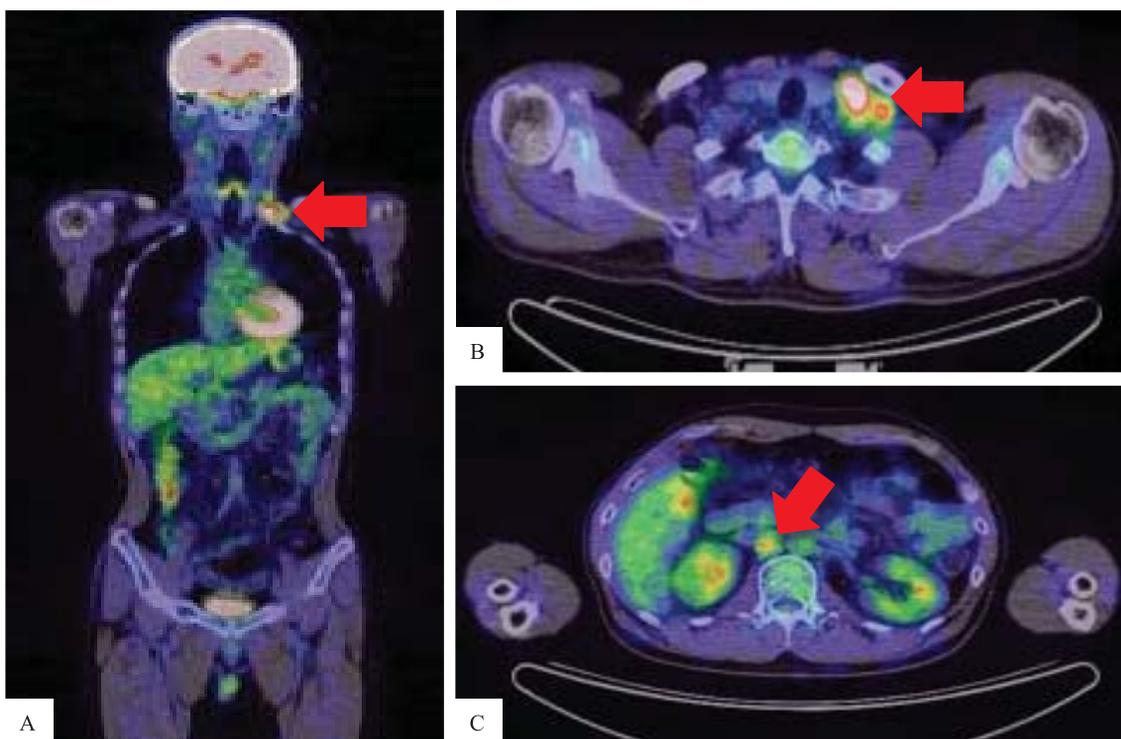


Fig. 2. ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography revealed high FDG accumulation in the left cervical ($\text{SUV}_{\text{max}} = 10.1$) (2A), anterior mediastinal ($\text{SUV}_{\text{max}} = 14.8$) (2B), and para-aortic lymph nodes ($\text{SUV}_{\text{max}} = 4.19$) (2C).

left cervical lymphadenopathies three years after the diagnosis. His body temperature was 36.7°C and physical examination revealed two palpable left cervical lymphadenopathies, each measuring 20 mm in diameter. No other superficial lymphadenopathy or hepatosplenomegaly were noted. Laboratory examination showed 84 IU/L of alanine aminotransferase, 179 IU/L of lactate dehydrogenase, and 376 U/

mL of soluble interleukin-2 receptor. ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET)/CT scan revealed high accumulation of the radioactive material in the regions corresponding to the left cervical, anterior mediastinal, and para-aortic lymph nodes (Fig. 2). Histopathological examination of the left cervical lymph node showed that it was composed of vague follicular proliferation without neu-

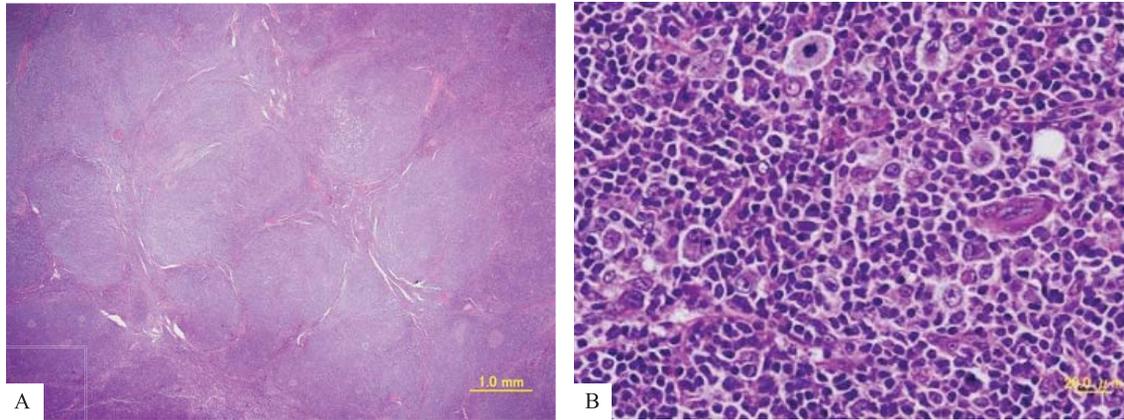


Fig. 3. Histopathology of the left cervical lymph node. The node is occupied by vague follicular structures of different size (3A; H&E, $\times 200$). In follicular structures, H/RS cell-like large atypical cells and LP cell-like atypical cells are interspersed in the expanded mantle zone around the atrophic germinal center (3B; H&E, $\times 400$).

trophilic or eosinophilic infiltration (Fig. 3A), and both H/RS cell-like large atypical cells and LP cell-like atypical cells were interspersed in the expanded mantle zone around the atrophic germinal center (Fig. 3B). Immunostaining revealed that they were CD15⁻ (Fig. 4A), CD30⁻ (Fig. 4B), CD20⁻ (Fig. 4C), Bob.1⁺ (Fig. 4D), Oct.2⁻ (Fig. 4E), PAX-5⁺ (Fig. 4F), BCL6⁻, and EBER⁻. Chromosomal examination showed 39, XY, inv(2)(p13q11.2), -3, -5, -6, -8, -10, -11, -12, ?inv(14)(q11.2q32), -19, +mar[1]/46, XY[19].

Based on these morphologic and immunophenotypic features of the atypical cells, we finally diagnosed the lesion to be one of LRCHL. Clinically, the patient was evaluated to have stage IIIA disease according to the Ann Arbor staging system, and the International Prognostic Score was 1 (low-risk group). Complete response (CR) was achieved following six cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) combination chemotherapy. However, 10 months after treatment, signs of relapse were found in lumbar and pelvic bones. The patient, then, underwent autologous stem-cell transplantation after high-dose chemotherapy.

DISCUSSION

CHL, including LRCHL, is characterized by proliferation of H/RS cells in nodular or diffuse background which is composed of small lymphocytes with/without plasma cells, histiocytes, or eosinophils, and these H/RS cells are generally CD15⁺, CD30⁺, and CD20⁻.¹ On the other hand, NLPHL is characterized by proliferation of CD15⁻, CD30⁻, and CD20⁺ LP cells in large nodules which are composed of small lymphocytes, histocytes, and dendritic cells.¹ However, CHL, particularly LRCHL, and NLPHL are morphologically difficult to distinguish, because, in addition to similar infiltrating reactive cells in the background,^{1,2} 98% of LRCHL cases have LP cell-like atypical cells, whereas 55% of NLPHL cases

have H/RS cell-like large atypical cells.^{1,3} Because of these similar and overlapping features, many of these cases that are initially diagnosed as NLPHL are actually reclassified as LRCHL after detailed immunostaining.^{1,3} According to these reports, our case that presented H/RS cell- as well as LP cell-like atypical cells required immunostaining. In addition to CD15 and CD30, immunostaining for CD20 and B-cell transcription factors, such as Bob.1, Oct.2, PAX-5, BCL6, and MUM-1 is useful to differentiate these two lymphoma types.^{1,4} It is generally accepted that the vast majority of NLPHL cases are positive for CD20 and the B-cell transcription factors except for MUM-1. In contrast, CHL cases, including LRCHL, are less often positive for these factors (Table 1). In addition, the rate of programmed death-1 (PD-1)⁺ T cells in the background is different; 90% in NLPHL cases vs. 30-40% in LRCHL cases.⁸ The presence of CD57⁺ T-cell rosettes seems to be another useful feature in the diagnosis of NLPHL, although it is less effective than PD-1 positivity.⁸⁻¹⁰ Atypical cells in the present case were CD15⁻, CD20⁻, CD30⁻, Bob.1⁺, Oct.2⁻, and BCL6⁻, whereas the surrounding T cells were PD-1⁻ and CD57⁻. Based on these findings, the patient was finally diagnosed to have LRCHL. To distinguish CHL from NLPHL, chromosomal examination is also reported to be useful. In CHL, chromosomal gains frequently involve chromosome 2p, 17q, 9p, 16p, and 17p, whereas its losses primarily affect chromosome 13q and 6q.¹¹⁻¹⁴ In NLPHL, chromosomal gains frequently involve chromosome Xq, Xp, 1p, 3p, and 5q, whereas its losses primarily affect chromosome 17q/17 and 16p.¹⁵ However, no specific chromosomal abnormality associated with CHL or NLPHL was found in our case.

The treatment modalities provided for CHL and NLPHL are different. Primary treatment modalities for advanced NLPHL include not only chemotherapy but also use of rituximab and radiation therapy.¹⁶ Treatment outcomes of both

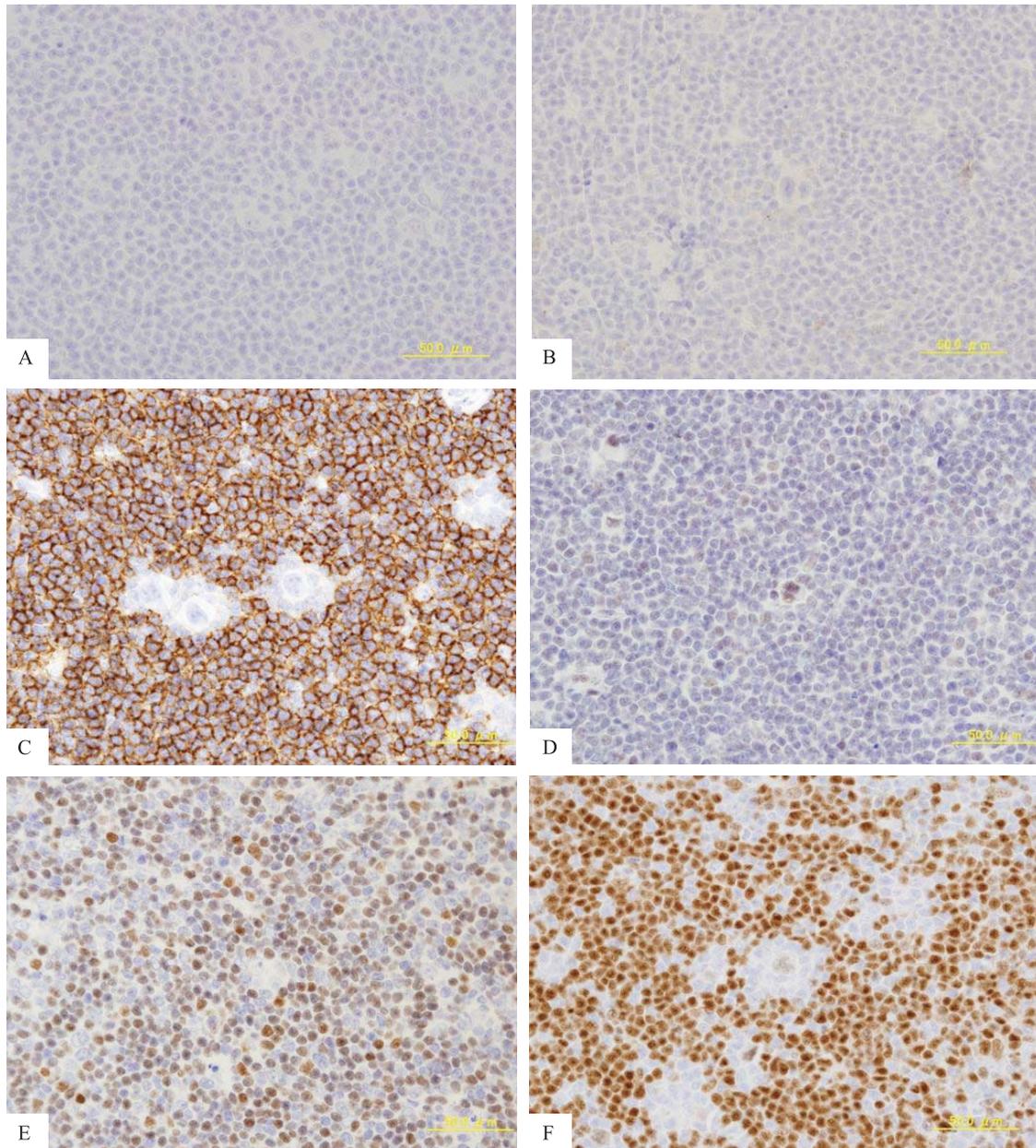


Fig. 4. Immunohistochemical staining of the left cervical lymph node biopsy specimen revealed these atypical large cells to be CD15⁻ (4A), CD30⁻ (4B), CD20⁻ (4C), Bob.1⁺ (4D), Oct.2⁻ (4E), and PAX-5^{-/+} (4F). (4A-4F, × 400).

advanced CHL and NLPHL are reported to have a high CR rate (77% vs. 76%) and low rate of early relapse during the first year after primary therapy (4.1% vs. 1.2%).¹⁷ A case, in which the diagnosis of either CHL or NLPHL is unclear, has been reported as an intermediate type.¹⁸ This case had CR after ABVD chemotherapy and radiation therapy, but showed rapid relapse nine months after primary treatment.¹⁸ Because this case appears to be similar to ours in terms of both lymphoma classification and clinical outcome, accumulation of

further such cases is necessary to establish better criteria for the differential diagnosis and assessment of clinical behavior.

Gene expression profiling is a useful tool in distinguishing CHL from NLPHL for the case in which the distinction is difficult by morphological, immunohistological, and chromosomal examinations. Gene expression profile of NLPHL shows homology to that of CHL rather than other B cell lymphoma.^{19,20} However, that of CHL reveals higher expression of some genes, such as *REL*, *JAK2*, and *JUNB*.^{13,14,21} In

Table 1. Summary of the immunological findings of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL)⁴⁻⁷

Antibody	NLPHL	LRCHL	CHL	This case
CD15	4%	40-56%	52-70%	-
CD20	98%	27-31%	7-30%	-
CD30	0%	60-100%	90-100%	-
Bob.1	97-100%	50-62%	19-37%	+
Oct.2	100%	56-72%	34-74%	-
PAX-5	94-100%	94-100%	65-100%	+/-
BCL6	82-100%	31%	0%	-
MUM-1	20%	100%	98-100%	-

LRCHL, lymphocyte-rich classical Hodgkin lymphoma

contrast, genes expression of *BCL6*, *NFKBA*, and *TNFAIP3* are up-regulated in NLPHL.²⁰⁻²² Therefore, genes that show consistent differences in expression between NLPHL and CHL, such as abnormal *REL* expression by chromosome 2p,¹¹ may be helpful for the distinction.

H/RS cells of LRCHL and mixed cellularity CHL are similar to LP cells of NLPHL, whereas the nodular sclerosis and lymphocyte-depleted CHLs are similar to other B-cell lymphomas.²² Based on immunohistochemical findings, the rate of B-cell transcription antigen-positive LRCHL cases seems to be at an intermediate position between CHL and NLPHL. Because LRCHL is immunohistochemically and genetically very similar to NLPHL, these two Hodgkin lymphoma types may be more or less similar when gene mutations cause up- or down-regulation of expression of B-cell transcription antigens. Thus, the atypical phenotypic features, *i.e.*, CD15⁻, CD30⁻, CD20⁻ and negative for a majority of B-cell transcription antigens, of our patient might be due to mutations of the corresponding genes. Accumulation of such cases are necessary to establish better criteria for the differential diagnosis and assessment of clinical behavior.

REFERENCES

- Stein H, Poppema S, Weiss LM, Anagnostopoulos I, Benharroch D, *et al.*: Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al.* (eds): WHO Classification of Tumors, Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.321-334, 2008
- Bräuninger A, Wacker HH, Rajewsky K, Küppers R, Hansmann ML: Typing the histogenetic origin of the tumor cells of lymphocyte-rich classical Hodgkin's lymphoma in relation to tumor cells of classical and lymphocyte-predominance Hodgkin's lymphoma. *Cancer Res.* 63:1644-1651, 2003
- Anagnostopoulos I, Hansmann ML, Franssila K, Harris M, Harris NL, *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.* 96:1889-1899, 2000
- Herbeck R, Teodorescu Brinzeu D, Giubelan M, Lazăr E, Dema A, *et al.*: B-cell transcription factors Pax-5, Oct-2, BOB.1, Bcl-6, and MUM1 are useful markers for the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma. *Rom J Morphol Embryol.* 52:69-74, 2011
- Nam-Cha SH, Montes-Moreno S, Salcedo MT, Sanjuan J, Garcia JF, *et al.*: Lymphocyte-rich classical Hodgkin's lymphoma: distinctive tumor and microenvironment markers. *Mod Pathol.* 22: 1006-1015, 2009
- García-Cosío M, Santón A, Martín P, Camarasa N, Montalbán C, *et al.*: Analysis of transcription factor OCT.1, OCT.2 and BOB.1 expression using tissue arrays in classical Hodgkin's lymphoma. *Mod Pathol* 17:1531-1538, 2004
- McCune RC, Syrbu SI, Vasef MA: Expression profiling of transcription factors Pax-5, Oct-1, Oct-2, BOB.1, and PU.1 in Hodgkin's and non-Hodgkin's lymphomas: a comparative study using high throughput tissue microarrays. *Mod Pathol.* 19:1010-1018, 2006
- Churchill HR, Roncador G, Warnke RA, Natkunam Y: Programmed death 1 expression in variant immunohistochemical patterns of nodular lymphocyte predominant Hodgkin lymphoma: comparison with CD57 and lymphomas in the differential diagnosis. *Hum Pathol.* 41:1726-1734, 2010
- Uherova P, Valdez R, Ross CW, Schnitzer B, Finn WG: Nodular lymphocyte predominant Hodgkin lymphoma. An immunophenotypic reappraisal based on a single-institution experience. *Am J Clin Pathol.* 119:192-198, 2003
- Kraus MD, Haley J: Lymphocyte predominance Hodgkin's disease: the use of bcl-6 and CD57 in diagnosis and differential diagnosis. *Am J Surg Pathol.* 24:1068-1078, 2000
- Joos S, Menz CK, Wrobel G, Siebert R, Gesk S, *et al.*: Classical Hodgkin lymphoma is characterized by recurrent copy number gains of the short arm of chromosome 2. *Blood.* 99:1381-1387, 2002
- Chui DT, Hammond D, Baird M, Shield L, Jackson R, *et al.*: Classical Hodgkin lymphoma is associated with frequent gains of 17q. *Genes Chromosomes Cancer.* 38:126-136, 2003
- Hartmann S, Martin-Subero JI, Gesk S, Hüsken J, Giefing M, *et al.*: Detection of genomic imbalances in microdissected Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma by array-based comparative genomic hybridization. *Haematologica.* 93:1318-1326, 2008
- Steidl C, Telenius A, Shah SP, Farinha P, Barclay L, *et al.*: Genome-wide copy number analysis of Hodgkin Reed-Sternberg cells identifies recurrent imbalances with correlations to treatment outcome. *Blood.* 116:418-427, 2010
- Franke S, Wlodarska I, Maes B, Vandenberghe P, Delabie J, *et al.*: Lymphocyte predominance Hodgkin disease is characterized by recurrent genomic imbalances. *Blood.* 97:1845-1853, 2001
- Advani RH, Hoppe RT: How I treat nodular lymphocyte predominant Hodgkin lymphoma. *Blood.* 122:4182-4188, 2013

- 17 Xing KH, Connors JM, Lai A, Al-Mansour M, Sehn LH, *et al.*: Advanced-stage nodular lymphocyte predominant Hodgkin lymphoma compared with classical Hodgkin lymphoma: A matched pair outcome analysis. *Blood*. 123:3567-3573, 2014
- 18 Fujii S, Miyata A, Ichimura K, Yoshino T: A case report considered intermediate type of nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma. *J Clin Exp Hematop*. 103:47, 2007 (*Abstract in Japanese*)
- 19 Brune V, Tiacci E, Pfeil I, Döring C, Eckerle S, *et al.*: Origin and pathogenesis of nodular lymphocyte-predominant Hodgkin lymphoma as revealed by global gene expression analysis. *J Exp Med*. 205:2251-2268, 2008
- 20 Weiss LM, Hansmann ML, Chan JKC, Müller-Hermelink HK, Harris NL, *et al.*: Pathology of Hodgkin Lymphoma. In: Hoppe RT MM, Armitage JO, Diehl V, Weiss LM (eds): *Hodgkin Lymphoma*. 2nd ed, Philadelphia, Lippincott Williams & Wilkins, 2007
- 21 Schmitz R, Stanelle J, Hansmann ML, Küppers R: Pathogenesis of classical and lymphocyte-predominant Hodgkin lymphoma. *Annu Rev Pathol*. 4:151-174, 2009
- 22 Schumacher MA, Schmitz R, Brune V, Tiacci E, Döring C, *et al.*: Mutations in the genes coding for the NF- κ B regulating factors I κ B α and A20 are uncommon in nodular lymphocyte-predominant Hodgkin's lymphoma. *Haematologica*. 95:153-157, 2010