

## 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

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### Abstract

In some instances, the overlap in morphologic features and antigen expression between nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL) can cause confusion in the diagnosis. In these cases, the transcription factors (TFs) B-cell specific activator protein (BSAP)/Pax-5, octamer binding protein-2 (Oct-2), B-lymphocyte-specific co-activator BOB.1/OBF.1, Bcl-6 protein and multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF-4) may aid in clarifying the diagnosis. Twenty-two cases of NLPHL were studied for the immunohistochemical expression of Pax-5, Oct-2, BOB.1, Bcl-6 protein and MUM1/IRF-4. Our results sustain the usefulness of the selected set of TFs to diagnose and distinguish NLPHL from cHL since Pax-5, Oct-2, BOB.1 and Bcl-6 are consistently expressed by lymphocyte predominant (LP) cells and reported by others to be often unexpressed in Hodgkin and Reed–Sternberg cells. By contrast, MUM1/IRF-4 protein scored negative in the majority of LP cells, but is reported to be expressed in almost all cases of cHL. Thus, although the expression of transcription factors is very heterogeneous, their simultaneous implementation for positive and differential diagnosis may be useful.

**Keywords:** Hodgkin lymphoma, transcription factors, diagnosis, immunohistochemistry.

### Introduction

Since its introduction in the early 1940s, immunohistochemistry (IHC) has developed over the last couple of decades into an integral part of diagnostic hematopathology. The application of IHC has not only led to greater complexity but also enabled more precise and reproducible diagnosis. In particular, it generated more rational classifications of the large group of lymphoid neoplasms. Moreover, REAL classification explicitly includes the IHC profile in the pathologic diagnosis. The current lymphoma diagnostic criteria are established by the *World Health Organization (WHO) Classification* [1], which divides lymphoma into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). This classification also accord significantly importance to IHC along with morphological examination in setting diagnosis.

Based on differences in both, the morphology and the immunophenotype of the tumor cells, HL is nowadays distinguished into nodular lymphocyte predominant HL (NLPHL) and four subsets of classical HL (cHL) – nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted. It is now

widely recognized that cHL (more than 95% of cases) and NLPHL are derived from germinal center (GC) B-cells, probably at different stages of differentiation [2–6]. NLPHL is a monoclonal B-cell neoplasm characterized by a total or partial replacement of the lymph node architecture, usually dominated by large nodules composed of reactive B-lymphocytes and a few tumor cells that resemble classical Hodgkin and Reed–Sternberg (H/RS) cells, but shows special morphological and immunohistochemical features. The neoplastic cells, known as popcorn or lymphocyte predominant cells (LP cells), formerly called L&H cells for lymphocytic and/or histiocytic Reed–Sternberg cell variants [1], account for only ~1% of the cellularity in tissues involved with HL and this is why in some instances the recognition of these cells may be difficult. Immunophenotypically, LP cells express multiple B-cell markers, as for instance CD20, CD79a, CD75 and CD45, but are negative for CD30 and CD15 in contrast to cHL, in which H/RS-cells are usually positive for CD30 and often positive for CD15 and lose the expression of some B-cell markers.

In some instances, the overlap in morphologic features and antigen expression between NLPHL and

cHL can cause confusion in the diagnosis. Some cHL may have expression of CD20, with variable intensity in a subset of H/RS-cells [7, 8] and, on the other hand, weak membrane staining for CD30 was detected in a small subset of LP cells in rare cases of NLPHL [9].

The aim of this study is to investigate the expression of different B-cell line specific transcription factors (TFs) in order to define a set of antibodies useful to diagnose and to discriminate between NLPHL and cHL. Therefore, we evaluated the immunohistochemical expression of B-cell specific activator protein (BSAP)/Pax-5, octamer binding protein 2 (Oct-2), B-lymphocyte-specific co-activator BOB.1/OBF.1, Bcl-6 protein and multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF-4) which are transcription factors with different expression at consecutive stages of B-cell development.

## Materials and Methods

### Tissue sample selection

Paraffin-embedded tissue samples from 22 cases of NLPHL were retrieved from the files of the Pathology

**Table 1 – Antibodies used in the present study**

Antibody specificity	Clone	Antibody supplier	Catalog no.	Dilution
Pax-5	polyclonal	DCS-Innovative Diagnostik Systeme	PI74C002	1:100
Oct-2	C-20	Santa Cruz Biotechnology	sc-233	1:500
BOB.1	C-20	Santa Cruz Biotechnology	sc-955	1:1500
Bcl-6	PG-B6P	Dako	M7211	1:25
MUM1	MUM1P	Dako	M7259	1:200

### Interpretation of results

Expression of the Pax-5, BOB.1, Oct-2, Bcl-6 and MUM1 was scored by counting the number of positive cells and evaluating the signal intensity. Positivity was defined as staining of at least 30% of the cells of interest. The intensity of staining was graded as weak (+), moderate (++) and strong (+++).

## Results

### Morphological findings

All examined cases showed a partially or totally replacement of the lymph-node architecture by a nodular or nodular and diffuse proliferation. The infiltrate consisted predominantly of small lymphocytes, histiocytes, epithelioid cells and intermingled LP cells. The number of tumor cells varied from case to case, and the cells displayed the typical immunophenotype of LP cells, with most or all cells being positive for CD20 and negative for CD30 and CD15. Tumor cells are often ringed by CD3-positive T-lymphocytes in a rosette-like manner.

#### Pax-5

All cases showed Pax-5 expression in tumor cells. The neoplastic cells of NLPHL showed positive nuclear staining with moderate to strong intensity in more than 70% of the malignant cells in all examined cases. In addition, a weak cytoplasmic staining was observed in some tumor cells of a few cases. The nuclei of the

Department of the University of Frankfurt/Main, Germany. Diagnosis was established according to standard procedures after morphological and immunohistological analyses according to WHO criteria.

### Immunohistochemistry

Immunostaining techniques were performed on paraffin-embedded tissue. Four µm sections of the tissue blocks were mounted onto positively charged slides, deparaffinized in xylene, rehydrated in graded alcohols, and rinsed. For heat-induced epitope retrieval, the tissue sections were subjected to an antigen retrieval protocol consisting of one minute high-temperature heating in EDTA (pH 8) using a high pressure cooker. After cooling at room temperature, the sections were incubated for 30 minutes with the primary antibodies Pax-5, BOB.1, Oct-2, Bcl-6 and MUM1.

Antibody suppliers and used dilutions are summarized in Table 1. Further, all biopsy specimens were routinely processed using the Dako REAL Detection System, Alkaline Phosphatase/RED, Rabbit/mouse.

non-neoplastic bystander B-cells showed strong nuclear positivity (Figure 1). In the isolated residual GCs, an intense to moderate nuclear staining of small lymphocytes in the follicular mantle and an intense positivity of GC-cells was seen.

#### Oct-2 and BOB.1

The prevailing staining pattern of the LP cells was nuclear, with a strong or moderate intensity for Oct-2 and BOB.1, with occasional cells showing a moderate cytoplasmic expression of Oct-2. Oct-2 was highly expressed in all cases, while BOB.1 was expressed in the majority of tumor cells in 21 of the 22 examined cases. One case showed no tumor cell staining for BOB.1. The non-neoplastic bystander B-cells and plasma cells in tumoral areas showed a moderate labeling of their nuclei and in part of their cytoplasm (Figures 2 and 3).

In areas of remnant non-tumoral lymphoid tissue, Oct-2 staining showed strong nuclear positivity of GC-cells, a less intense nuclear staining of the small lymphocytes in the follicular mantle zone and an intense nuclear staining of few lymphoid cells in the marginal zone and in the interfollicular areas. BOB.1 staining exhibited a strong nuclear positivity in GC-cells and in a few dispersed mantle zone cells and interfollicular lymphocytes. The lymphocytes of the mantle zone showed a weak nuclear staining.

#### Bcl-6

Bcl-6 expression was detected in all examined cases. The expression pattern was nuclear with strong intensity



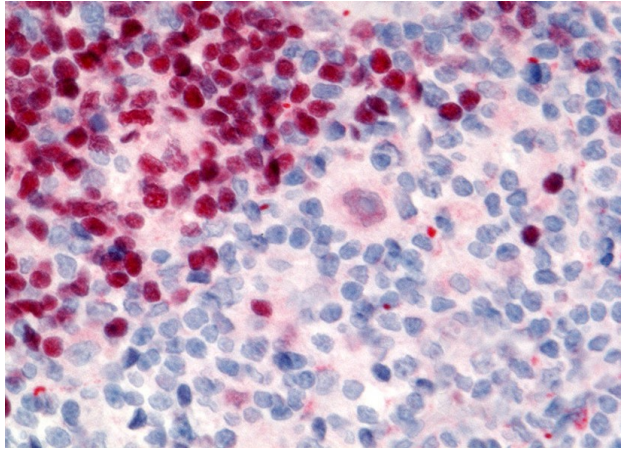
in the majority of neoplastic cells. The residual GC B-cells in neoplastic as well as non-neoplastic areas displayed a strong and specific nuclear reactivity for Bcl-6, while the B-lymphocytes of mantle and paracortical zones stained negative for Bcl-6 (Figure 4).

### MUM1

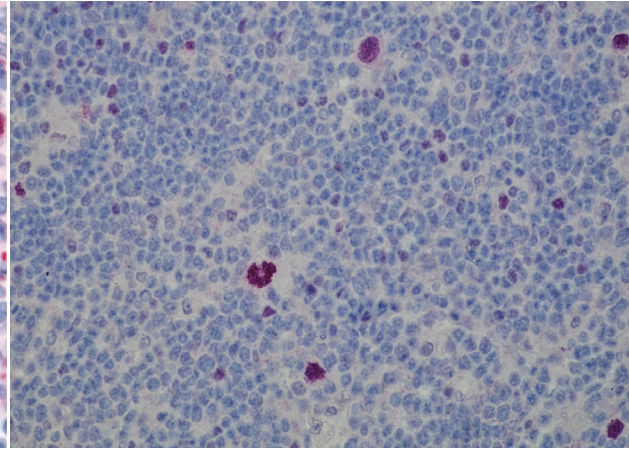
In 16 of 22 cases, LP cells scored negative for

MUM1 expression. In the six remaining NLPHD cases, a moderate or weak nuclear staining in addition to a weaker cytoplasmic expression of MUM1 was detected on less than 30% of the malignant cells (Figure 5).

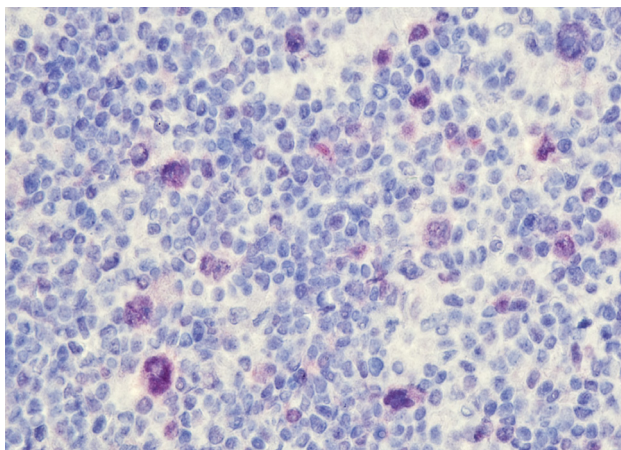
A particular pattern was observed in two cases, with MUM1 expressing lymphocytes mainly located in close proximity to the LP cells as rosettes (Figure 6).



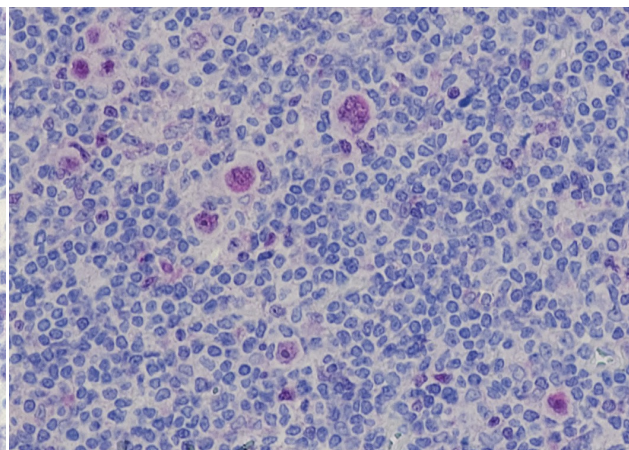
**Figure 1** – Positive expression for Pax-5 in the nucleus of a LP cell; the positive cell display a weaker labeling as compared to normal B-cells,  $\times 400$ .



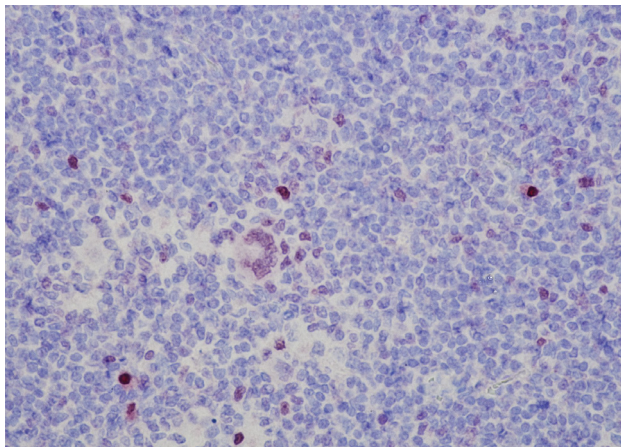
**Figure 2** – Increased nuclear positivity for Oct-2 in LP cells as compared to scattered positive non-neoplastic bystander B-cells,  $\times 200$ .



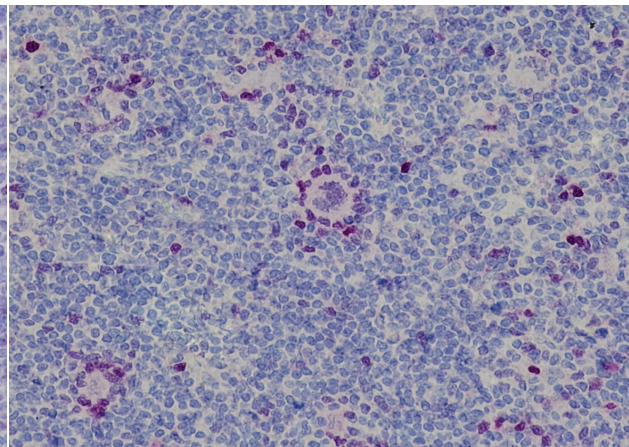
**Figure 3** – Nuclear BOB.1-expression with weak cytoplasmic staining in LP cells,  $\times 200$ .



**Figure 4** – Strong nuclear positivity for Bcl-6 in LP cells,  $\times 200$ .



**Figure 5** – One MUM1-positive LP cell in a background of some positive lymphocytes and plasma cells,  $\times 200$ .



**Figure 6** – One MUM1-positive LP cell; the expression intensity is lower than that of the rosette-forming surrounding lymphocytes,  $\times 200$ .

In addition to the malignant cells, plasma cells often presented with an intense nuclear and cytoplasmic immunostaining. Lymphocytes of the mantle zone were usually negative for MUM1. Furthermore, a positive reaction of some lymphocytes in the T-cell area was detected (Table 2).

**Table 2 – Immunohistochemical expression of B-cell transcription factors in tissues involved by NLPHL**

Case no.	Pax-5	Oct-2	BOB.1	Bcl-6	MUM1
1.	++	+++	+++	+++	-
2.	+++	+++	+++	+++	-
3.	+++	+++	+++	+++	-
4.	+++	+++	++	+++	++
5.	++	+++	+++	+++	-
6.	++	+++	+++	+++	+
7.	+++	+++	+++	+++	-
8.	+++	++	++	+++	-
9.	++	+++	+++	+++	-
10.	+++	++	+++	+++	++
11.	+++	++	+++	+++	-
12.	+++	++	-	+++	-
13.	++	+++	+++	+++	-
14.	+++	+++	+++	+++	-
15.	++	+++	+++	+++	++
16.	+++	+++	++	+++	+
17.	+++	++	++	+++	-
18.	+++	+++	+++	+++	-
19.	+++	+++	+++	+++	-
20.	++	+++	+++	+++	+
21.	++	+++	+++	+++	-
22.	++	+++	+++	+++	-

## Discussion

The transcription factors B-cell specific activator protein (BSAP)/Pax-5, B-cell Oct binding factor-1 (OBF-1/BOB.1), octamer binding protein-2 (Oct-2), Bcl-6 protein and multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF-4) were selected for immunohistochemistry, because of their sequential expression at different stages of B-cell development and their importance for the regulation of gene expression during B-cell development. They were also selected because it is now recognized that tumor cells of NLPHL display a phenotype consistent with derivation from GC B-cells, while H/RS-cells of cHL derive from the final differentiation steps of intra-GC B-cells.

The Pax-5 gene encoding the transcription factor BSAP (also known as B-cell-specific activator protein) is required for progression of B-lymphopoiesis beyond the pro-B-cell stage [10]. Pax-5 is expressed in the early stages of B-cell development (pro-B and pre-B-cells), in naive and other mature B-cells but not in plasma cells [11, 12]. Previous studies have shown that Pax-5 is not constantly expressed in cHL cases and the intensity in positive cases varies from weak to moderate and is rarely strong [12, 13]. We noted the expression of Pax-5 in more than 70% of LP cells in all examined cases, often weaker than that seen in normal bystander B-lymphocytes.

In combination, the transcription factor Oct-2 and

his co-activator BOB.1 regulate immunoglobulin gene transcription [14–16]. Oct-2 is largely B-lineage specific and has been implicated in the control of B-lymphocyte-specific gene expression [17–21] and activate immunoglobulin gene transcription, whereas BOB.1 as a specific cofactor is recruited into the transcription complex [22–23]. We have found that the octamer transcription factor Oct-2 is highly overexpressed in LP cells. BOB.1, the co-activator of Oct-2, proved to be co-expressed in all LP cells, excepting only one case, at a level equivalent to that seen in reactive GC B-cells. Expression of both B-cell-specific transcription regulators was reported in only a small fraction of H/RS-cells in cHL cases [24–27]. This correlates with the fact that neoplastic cells of cHL originate from germinal or post-germinal center B-cells, which lose their capacity to transcribe and to express surface immunoglobulins (Ig) [28].

The Bcl-6 protein (B-cell CLL/lymphoma-6), a POZ/Zinc finger transcription repressor, is expressed by GC B-cells and is required for GC-formation and function [20, 21, 29]. Conversely, expression of Bcl-6 is negative in all other stages of B-cell differentiation, including virgin and memory B-cells as well as plasma cells [21]. In our study, Bcl-6 was expressed in all cases of NLPHL in a significantly number of LP cells.

Even though H/RS-cells in cHL have been shown in many cases to be derived from GC B-cells, they show low or no expression of typical GC B-cell differentiation proteins (such as Bcl-6) and almost constant expression of the late GC/post-GC B-cell differentiation proteins, like MUM1/IRF-4 [30–32].

Multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF-4) is a lymphocyte-specific member of the interferon regulatory factor (IRF) family of transcription factors, which is expressed in the final step of intra-GC B-cell differentiation, in subsequent steps of B-cell maturation towards plasma cells, and in lymphoid neoplasms thought to be derived from these cells [33]. The fact that in our observation MUM1 was expressed inconsistently in NLPHL is in agreement with previous observations that tumor cells of NLPHL display a phenotype consistent with derivation from GC B-cells [33]. By contrast, MUM1 protein is reported to be expressed in almost all cases of cHL [32, 34, 35].

The small lymphocytes surrounding LP cells, in two of the examined cases of NLPHL, were similar to the non-rosetting lymphocytes of cHD, which may also express MUM1 [33]. The almost exclusive presence of MUM1-expressing lymphocytes rosetting around LP cells may provide a further support for the definition of the microenvironment in NLPHL.

## Conclusions

The transcription factors (TFs) that control the intricate machinery of multistep differentiation and activation programs of the lymphoid system represent a complex array of proteins, whose identification and function have only partially been completed. TFs are usually expressed during specific differentiation or activation of cellular programs, making them interesting tools in diagnostic immunohistochemistry.



Currently, the expanding knowledge of the TFs involved in the differentiation programs and in the activation processes of T-lymphocyte and B-lymphocyte in normal and neoplastic conditions and the availability of antibodies able to efficiently recognize these TFs in histological material represent a powerful tool in diagnostic hematopathology.

Our results sustain the usefulness of the selected set of TFs to diagnose and distinguish NLPHL from cHL since Pax-5, Oct-2, BOB.1 and Bcl-6 are consistently expressed by LP cells and reported by others to be often unexpressed in H/RS-cells of cHL. By contrast, MUM1 protein scored negative in LP cells, but is reported to be expressed in almost all cases of cHL.

Although, the expression of transcription factors is very heterogeneous, their simultaneous implementation for positive and differential diagnosis may be useful.

### Acknowledgements

We are grateful to Prof. Dr. Martin-Leo Hansmann from the Institute for Pathology, Frankfurt/Main, Germany, for offering the possibility to perform this study in his department.

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*Received: May 25<sup>th</sup>, 2009*

*Accepted: January 12<sup>th</sup>, 2011*

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