Chapter 6
Pathobiology of Nodular Lymphocyte Predominant Hodgkin Lymphoma

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Abbreviations

CGH	Comparative genomic hybridization
cHL	Classical Hodgkin lymphoma
DLBCL	Diffuse large B-cell lymphoma
HLA	Human leukocyte antigen
NF-kappaB	Nuclear factor kappa B
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
PTGC	Progressive transformation of germinal centers
THRLBCL	T cell/histiocyte rich large B-cell lymphoma

History

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) was first recognized as a special subtype of Hodgkin lymphoma (HL) in the classification by Jackson and Parker in 1947 (Jackson and Parker 1947) and termed lymphocytic and histiocytic variant by Lukes and Butler in 1966 (Lukes and Butler 1966). Lennert distinguished already in 1974 (Lennert and Mohri 1974) between a nodular and a diffuse type of NLPHL. The tumor cells of NLPHL were previously called L and H cells, according to the lymphocytic and histiocytic appearance of the infiltrate. In the WHO classification of 2008 (Swerdlow et al. 2008) their name was revised to "lymphocyte predominant" or LP cells.

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S.D. Hudnall, R. Küppers (eds.), *Precision Molecular Pathology of Hodgkin Lymphoma*, Molecular Pathology Library,
https://doi.org/10.1007/978-3-319-68094-1_6

Clinical Characteristics

NLPHL has a predilection for the male gender, which is affected in about 75% of cases (Anagnostopoulos et al. 2000; Jackson et al. 2010). Male gender does not only represent an increased risk for the development of NLPHL but bears furthermore an even sixfold higher risk for relapse in diseased patients (Hartmann et al. 2013a). Usually, NLPHL affects middle-aged patients around 40 years. However, the age range is broad, including pediatric patients from approximately the age of 8 years up to elderly persons. In most cases, NLPHL is diagnosed in early stage, usually stage I or II (Jackson et al. 2010). Axillary and cervical lymph nodes are most frequently affected. Only a small subgroup of patients presents with advanced disease. These patients have often liver and spleen involvement. Although NLPHL is generally an indolently behaving lymphoma, relapses are much more frequently observed than in classical HL (cHL) (Anagnostopoulos et al. 2000). These can occur after a long latency of about 10 years. Some patients even present with multiple relapses, and in long standing disease, there is an important risk of transformation into an aggressive diffuse large B-cell lymphoma (DLBCL) (Biasoli et al. 2010; Al-Mansour et al. 2010), which can be fatal. The histological criteria when to diagnose transformation are not well defined, and small sheets of blasts do not seem to impact the clinical outcome (Hartmann et al. 2013a). Due to this reason, the outcome of patients with NLPHL and transformation into DLBCL is heterogeneous (Biasoli et al. 2010; Al-Mansour et al. 2010; Huang et al. 2004; Sundeen et al. 1988; Hansmann et al. 1989; Hartmann et al. 2014a).

Pathology

Growth Patterns

NLPHL can generally be divided into cases with nodular and diffuse growth patterns (Fig. 6.1a and b), (Hansmann et al. 1991; Boudova et al. 2003). Apart from their growth pattern, these also differ in the composition of the microenvironment. Cases with a

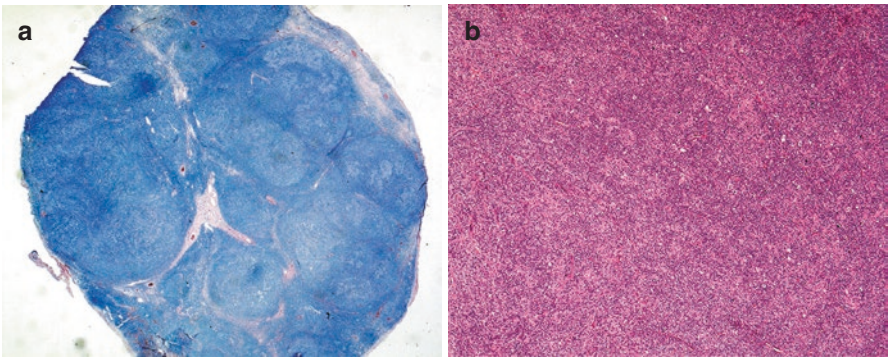

Fig. 6.1 (**a**) NLPHL with a typical nodular growth pattern. Giemsa stain, 5×. (**b**) NLPHL with a predominant diffuse growth pattern. HE, 10×

predominant nodular pattern usually have a high content of reactive B cells, whereas in cases with a predominant diffuse growth pattern, ill-defined follicular dendritic cell meshworks in a T-cell-rich background can be observed (Hansmann et al. 1991). In 2003 a minute analysis of the different growth patterns and their combination was performed by Fan et al. (2003). Six different growth patterns were described (Fig. 6.2) including nodular patterns with a T-cell-rich background as well as a rare purely diffuse

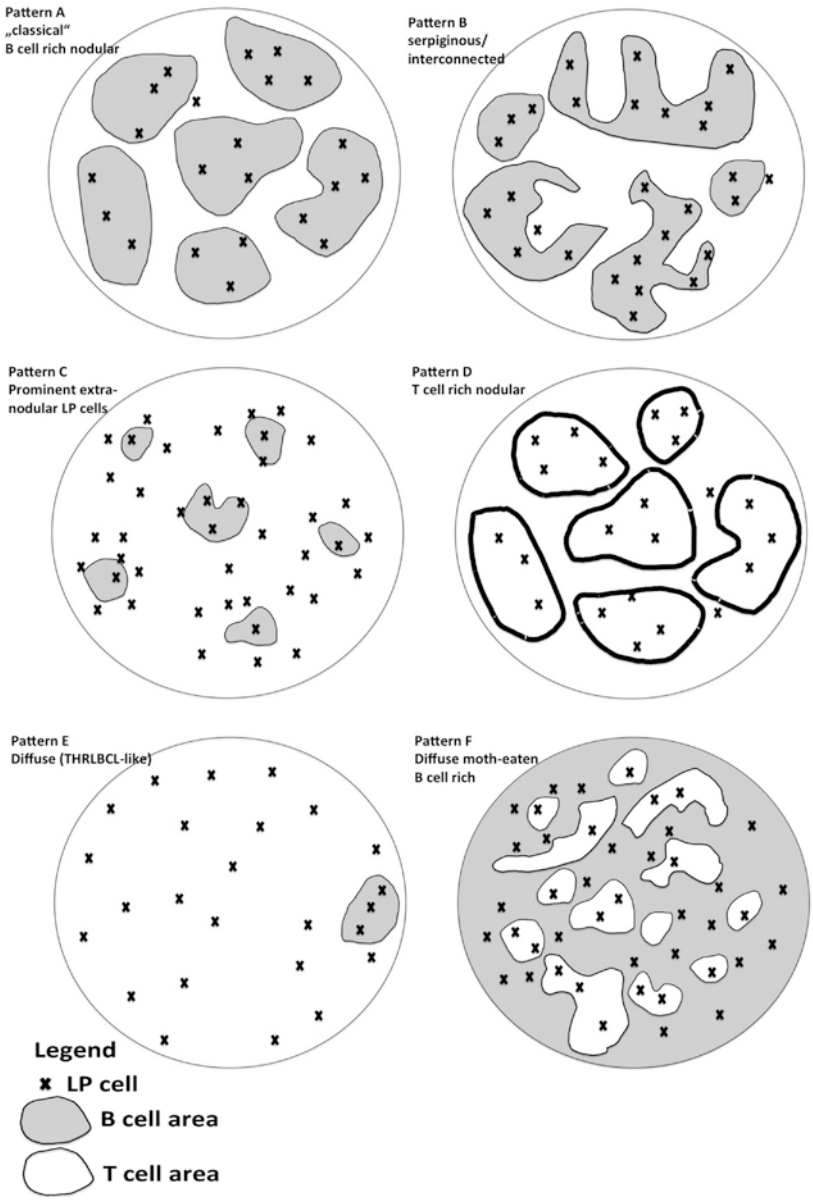

Fig. 6.2 Schematic representation of NLPHL growth patterns (**a**–**f**), modified after Fan et al. (2003)

growth pattern with a B-cell-rich background. It was furthermore noted that the cases with a purely diffuse growth pattern and morphologic features resembling T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), i.e., diffusely distributed scattered large blasts in a background poor of B cells, had a higher risk of recurrence. This observation was confirmed in a large study involving 413 NLPHL patients from the German Hodgkin Study Group (Hartmann et al. 2013a), in which the cases with an atypical growth pattern presented significantly more frequently with an advanced clinical stage and a higher relapse rate. In some cases, the growth pattern can very closely resemble THRLBCL, and the revised WHO classification from 2016 (Swerdlow et al. 2016) suggests to label these cases NLPHL with THRLBCL-like transformation.

Tumor Cells: The LP Cells

Although the growth pattern in NLPHL can vary, the LP cells, the tumor cells in NLPHL, almost always consist of mononucleated large blasts with folded, popcorn-like nuclei and usually one nucleolus (Fig. 6.3). The cytoplasm is usually a small rim. Tumor cells resembling classical Hodgkin-Reed-Sternberg (HRS) cells can only rarely be found in NLPHL. LP cells generally show a scattered distribution in the tissue with hot spot areas in the nodules of the typical nodular variants. LP cells derive from germinal center B cells and usually show a preserved B-cell phenotype, which can be slightly downregulated. They are positive for CD20, CD79a, OCT2,

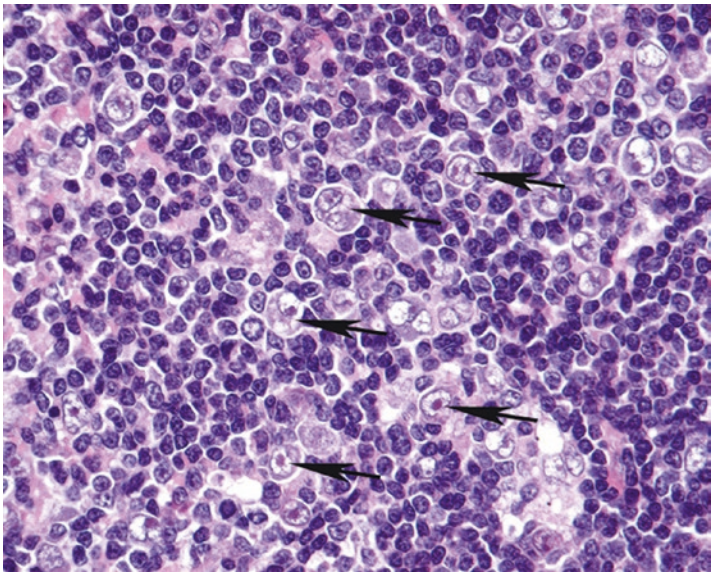

Fig. 6.3 LP cells represent mononucleated large blasts with folded, popcorn-like nuclei and usually one nucleolus (*arrows*). HE, 40×

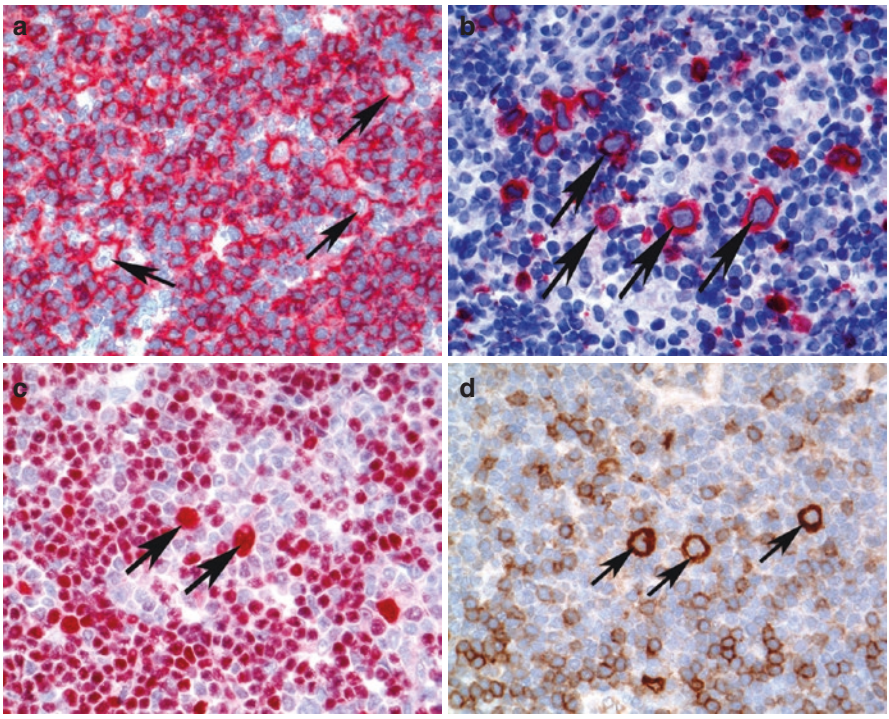

Fig. 6.4 LP cells (*arrows*) are positive for B-cell antigens, including (**a**) CD20, (**b**) CD79a, and (**c**) OCT2 as well as (**d**) IgD. Magnification 40× each

PAX5, BOB.1 (Fig. 6.4), and the germinal center markers BCL6, HGAL, and CD75 (Anagnostopoulos et al. 2000; Natkunam et al. 2005; Carbone and Gloghini 2014; Kraus and Haley 2000). LP cells are furthermore positive for J chain (Stein et al. 1986) and EMA (Delsol et al. 1984) in a fraction of cases (Table 6.1). CD19 expression, which is found by almost all reactive B cells, is lost in the LP cells in more than half of the cases (Nathwani et al. 2013). A subset of NLPHL cases expresses IgD in the LP cells (Fig. 6.4) (Prakash et al. 2006). These are often pediatric male patients (Prakash et al. 2006; Huppmann et al. 2014). Furthermore, LP cells express the immunoglobulin kappa light chains more frequently than lambda light chains (Schmid et al. 1991). Infection by the Epstein-Barr virus (EBV) is only very rarely observed in LP cells (Anagnostopoulos et al. 2000; Huppmann et al. 2014).

Differential Diagnoses

Differential diagnoses to NLPHL include all kinds of lymphomas which present with scattered single B-cell blasts. This includes on the one hand cHL with CD20 expression, which occurs in rare cases. However, in these cases usually CD30 is

Table 6.1 Immunophenotype of LP cells

Antigen	Immunophenotype of LP cells
CD20	++/+
CD79a	++/+
CD19	+/−
OCT2	+++
PAX5	++/+
BOB.1	++/+
CD30	− (+)
CD15	− (+)
IgD	+/−
CD75	++/+
BCL6	+++
EMA	+/−
J chain	+/−
CD10	− (+)
BCL2	−/+
HGAL	++/+
MUM1	+/−

much stronger expressed than CD20, and additionally CD15 is positive. Despite the fact that CD20 can be expressed by HRS cells, the expression intensity is mostly weak, and other B-cell antigens are negative in HRS cells of cHL. Both CD15 and CD30 can be expressed in rare cases of NLPHL, but usually they are not coexpressed (Hartmann et al. 2014a). Moreover, EBV is present in the HRS cells of cHL in around 30–40% of the cases in the Western world. This, however, depends very much on the country of origin, and EBV infection of HRS cells is more frequently encountered in developing nations. Other lymphomas that can be a differential diagnosis to NLPHL are all kinds of nodal peripheral T-cell lymphomas with Hodgkin-like cells (Quintanilla-Martinez et al. 1999; Moroch et al. 2012). Hodgkin-like cells in peripheral T-cell lymphomas usually do not belong to the T-cell lymphoma clone and are frequently EBV-infected B cells with a preserved B-cell phenotype and CD30 expression. Frequently the background infiltrate of nodal peripheral T-cell lymphomas can contain nodular areas of reactive B cells, resembling atypical variants of NLPHL. However, the most striking difference to NLPHL is the aberrant immunophenotype of the T cells, usually of T-helper cell origin and the clonality of the T cells, which helps to confirm an underlying T-cell neoplasia.

Another differential diagnosis to NLPHL is the progressive transformation of germinal centers (PTGC) (Poppema et al. 1979; Hansmann et al. 1990). Like in NLPHL, large nodular areas composed of naive B cells can occur in lymph nodes with PTGC. However, the important difference to NLPHL is that within these nodules still germinal center residues of variable size exist, which are completely

destroyed in NLPHL. Moreover, although in PTGC scattered centroblasts can be found within germinal center residues, LP cells surrounded by rosetting T cells do not occur. PTGC follows exact morphological patterns (Hartmann et al. 2015a). Knowledge of these patterns can help to distinguish PTGC from NLPHL. However, in every lymph node with PTGC, a close workup is necessary, since sometimes NLPHL can coexist with PTGC in the same lymph node.

Cellular Origin

Applying single-cell PCR from micromanipulated LP cells, it was shown that LP cells are clonal and that they have ongoing somatic hypermutation of their immunoglobulin genes (Braeuninger et al. 1997). LP cells furthermore present an aberrant somatic hypermutation of the genes *PIM1*, *PAX5*, *RhoH/TTF*, and *MYC* (Liso et al. 2006) which are also mutated in germinal center B cells. Some of these mutations show intraclonal diversity in the LP cells, consistent with ongoing aberrant somatic hypermutation. All these data suggest that LP cells derive from germinal center B cells. This is furthermore consistent with the observed expression of germinal center B-cell markers in the LP cells. Interestingly, also in THRLBCL the tumor cells have clonal immunoglobulin gene rearrangements and show ongoing somatic hypermutation (Bräuninger et al. 1999), further supporting the close relationship between NLPHL and THRLBCL. When microdissected LP cells were investigated by gene expression profiling (Brune et al. 2008), they showed a similar degree of relationship to germinal center B cells and memory B cells, suggesting that they resemble an intermediate developmental stage in the transition between germinal center and memory B cells.

NLPHL Cell Line DEV

The NLPHL cell line DEV was established in 1985 by Poppema et al. (1985). Originally, it was assumed to be derived from cHL and only later reclassified as NLPHL (Poppema et al. 1989). The DEV cell line expresses B-cell antigens like CD20 and CD19 but is additionally positive for CD30. Moreover, it has an alternative *BCL6* break and complex translocations involving chromosome 3 (Atayar et al. 2006). It furthermore displays a mutation in the start codon of the *B2M* gene, resulting in very low levels of B2M expression (Liu et al. 2014). DEV is negative for both human leukocyte antigens (HLA) classes I and II due to complex genomic rearrangements, including the gene locus of the HLA class II transactivator gene *CIITA* (Liu et al. 2014; Mottok et al. 2015).

Deregulated Transcription Factor Networks and Signaling Pathways

Primary LP cells have an active JAK-STAT signaling related to frequent mutations in *SOCS1* (Mottok et al. 2007), which is a negative regulator of *JAKs*. Mutations in *SOCS1* were usually found in motifs of somatic hypermutation, and they presented intraclonal diversity, in line with ongoing somatic hypermutation and the germinal center B-cell derivation of LP cells. JAK2 is phosphorylated in approximately 39% of NLPHL cases, whereas phosphorylation of STAT6 occurrs in 49% of NLPHL (Mottok et al. 2009). In contrast, phosphorylation of STAT3 and STAT5 was not seen in LP cells. It was furthermore observed by gene expression profiling that LP cells have a constitutive active NF-kappaB signaling, and a subset of cases shows activation of ERK (Brune et al. 2008). NF-kappaB activity in NLPHL is usually not related to mutations in *NFKBIA* or *TNFAIP3*, which are frequent in cHL (Schumacher et al. 2010).

Genetic Lesions

A variety of genetic lesions has been observed in NLPHL (Table 6.2). LP cells are always strongly positive for BCL6, and translocations involving both the *BCL6* locus and the immunoglobulin loci have been identified in up to 30% of NLPHL (Wlodarska et al. 2003; Renné et al. 2005). Additional NLPHL carries *BCL6* translocations with diverse non-Ig locus partners (Wlodarska et al. 2003). By classic comparative genomic hybridization (CGH), a high number of genomic imbalances were detected both in NLPHL and THRLBCL (Franke et al. 2001, 2002).

Table 6.2 Genetic lesions observed in LP cells

Gene	Type of lesion	References
SOCS1	Point mutations/deletions	Mottok et al. (2007) and Hartmann et al. (2016)
BCL6	Translocations	Wlodarska et al. (2003) and Renné et al. (2005)
MYC	Point mutations	Liso et al. (2006) and Hartmann et al. (2016)
PIM1	Point mutations	Liso et al. (2006)
PAX5	Point mutations	Liso et al. (2006)
RhoH/TTF	Point mutations	Liso et al. (2006)
B2M	Point mutations	Liu et al. (2014) (DEV cell line)
CIITA	Translocations	Mottok et al. (2015) and Hartmann et al. (2016)
REL	Copy number gains	Hartmann et al. (2015b)
SGK1	Point mutations/deletions	Hartmann et al. (2016)
DUSP2	Point mutations	Hartmann et al. (2016)
JUNB	Point mutations	Hartmann et al. (2016)
NPAT	Germline deletions	Saarinen et al. (2011)
FAS	Germline mutations	van den Berg et al. (2002)

Surprisingly, in these studies, the number of aberrations was higher in NLPHL when compared with THRLBCL. However, the NLPHL cases investigated were not subtyped according to their growth patterns. Using array CGH, the number of aberrations was higher in THRLBCL and atypical NLPHL variants compared with typical NLPHL (Hartmann et al. 2015b). Despite the differences in the number of aberrations, common genomic events, e.g., gains of the *REL* locus, were recurrently detected in both NLPHL and THRLBCL.

Whole genome sequencing of two DLBCL derived from and clonally related to NLPHL and a subsequent targeted analysis of primary NLPHL revealed frequent mutations in *SOCS1*, *DUSP2*, *JUNB*, and *SGK1* (Hartmann et al. 2016). Whereas JUNB works as an oncogene in classical HL, it was frequently affected by heterozygous stop mutations in NLPHL, leading to a very weak expression of the wild-type allele in the LP cells and suggesting a tumor suppressor function in NLPHL. SGK1 was strongly expressed both in the LP cells of primary NLPHL and the NLPHL cell line DEV. Application of a specific SGK1 inhibitor resulted in a high rate of apoptotic DEV cells, suggesting that SGK1 may act as an oncogene in NLPHL.

Familial NLPHL

There are several reports on families with accumulation of NLPHL (Merli et al. 2013; Saarinen et al. 2011, 2013). In one Finnish study, this was associated with a small germline deletion of serine 724 of the *NPAT* gene (Saarinen et al. 2011). However, there were also family members which were not affected by NLPHL. This small germline *NPAT* deletion was furthermore also observed in non-familial NLPHL patients, suggesting an increased risk for the development of NLPHL. Furthermore, genetic syndromes leading to a defect in the innate and adaptive immune system as well as the autoimmune lymphoproliferative syndrome, which can occur in children, have been associated with the development of NLPHL (Lorenzi et al. 2013; van den Berg et al. 2002).

Microenvironment

The microenvironment is considerably different in NLPHL with a typical nodular growth pattern compared to cases with a predominantly diffuse growth pattern. In typical NLPHL, where LP cells are mainly located within the B-cell nodules, the microenvironment has a strong similarity to that observed in normal germinal centers. Rosetting T cells around the LP cells are frequently observed, and these represent follicular T-helper cells, which are usually PD1 positive (Fig. 6.5) (Nam-Cha et al. 2008; Churchill et al. 2010). Furthermore a high number of CD57-positive cells are observed within the nodules of typical NLPHL (von Wasielewski et al. 1997). These

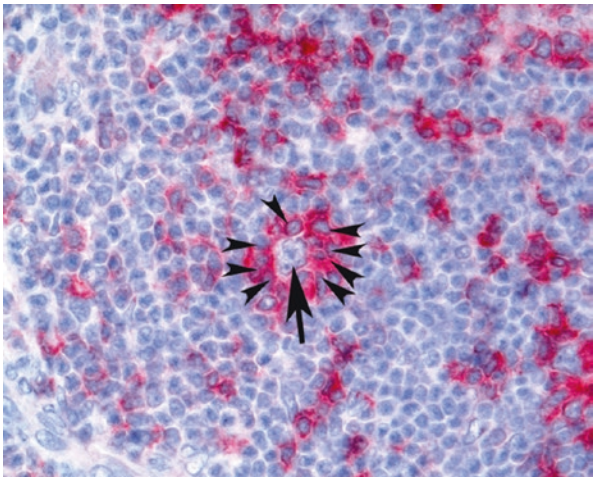

Fig. 6.5 Rosetting PD1-positive T cells (*arrow heads*) around an LP cell (*arrow*). PD1 immunostaining, 40×

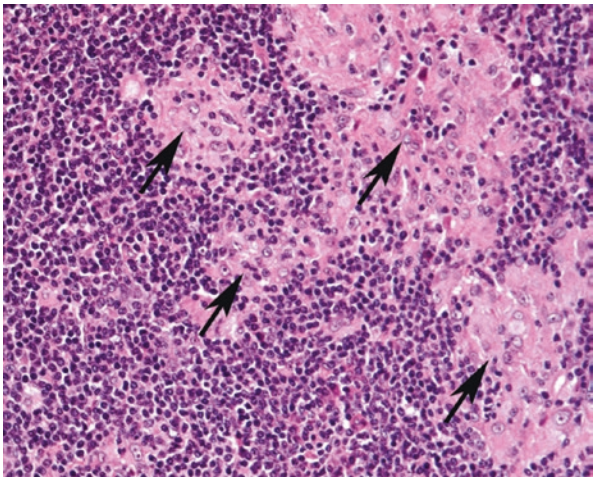

Fig. 6.6 Abundant epithelioid cells (arrows) forming granulomas in NLPHL. HE, 20×

CD57-positive cells are in the majority also CD4 and PD1 positive (Sattarzadeh et al. 2015). Other components in the microenvironment represent epithelioid cells which can be so abundant that they form granulomas (Fig. 6.6). A prominent epithelioid cell reaction was associated with a tendency to show less frequent relapses (Hartmann et al. 2014b).

In NLPHL with mainly diffuse areas, PD1- and CD57- as well as MUM1-positive rosetting T cells were less frequently observed (Churchill et al. 2010; Hartmann et al. 2013b). However, even rare cases of THRLBCL showed PD1-

positive rosetting T cells. The NLPHL cases with predominant diffuse areas resembling THRLBCL present a high content of macrophages, like observed in THRLBCL (Hartmann et al. 2013b). Furthermore, a low lymphocyte-monocyte ratio in the peripheral blood was observed to be an independent risk factor for progression-free and overall survival in NLPHL (Porrata et al. 2012), likely reflecting the composition in the nodal compartment.

A specific double-positive T-cell population was observed in the microenvironment of NLPHL. This population consists of $CD4^+CD8^+$ double-positive T cells and occurs both in NLPHL and in PTGC (Rahemtullah et al. 2006, 2008). It can be detected by flow cytometry and can be helpful in the diagnosis of NLPHL. This double-positive T-cell population usually constitutes a minority of the T cells in the microenvironment (10–38% of the T cells) and probably represents an activated T-cell population.

Relationship to THRLBCL

Already a long time ago, it was noticed that both NLPHL and THRLBCL occur predominantly in middle-aged men, the tumor cells have the same immunophenotype, and NLPHL patients exist, who present with relapses under the morphologic picture of THRLBCL (Rüdiger et al. 2002). Vice versa, it has also been observed that THRLBCL patients developed NLPHL in the relapse situation (Rüdiger et al. 2002). The tumor cells in NLPHL and THRLBCL are both of germinal center origin (Braeuninger et al. 1997) and they have a high similarity in their gene expression patterns (Brune et al. 2008; Hartmann et al. 2013b). Furthermore they share common genetic events (Hartmann et al. 2015b). However, the clinical behavior of THRLBCL is usually aggressive (Achten et al. 2002) and distinct from that of typical NLPHL. Therefore, THRLBCL seems to be a lymphoma entity which is closely related to NLPHL but which may represent a tumor-cell poor transformation like a DLBCL with an abundant microenvironment. To date, the relationship between NLPHL and THRLBCL is not fully understood, and further workup is necessary.

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