Chapter 5
Definition of Burkitt Lymphoma

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Definition

Burkitt lymphoma (BL) is defined by the World Health Organization (WHO) as a highly aggressive lymphoma often presenting at extranodal sites [1], or as an acute leukemia [2], composed of monomorphic medium-sized B-cells with basophilic cytoplasm and numerous mitotic figures [3, 4]. Chromosomal translocation involving *MYC* is the most frequent genetic feature [4–6]. Epstein–Barr Virus (EBV) is found in a variable proportion of cases. Three clinical variants of Burkitt lymphoma are recognized; these differ in geographic distribution, clinical presentation, as well as association with infectious agents and cell biology (Table 5.1).

Epidemiology and Clinical Features

Endemic BL (eBL) occurs in the malaria belt of equatorial Africa and in Papua New Guinea. In endemic regions there is a correlation between the geographical occurrence and some climatic factors (rainfall, altitude, etc.), which corresponds to the geographical distribution of endemic malaria, vectors of certain arboviruses such as Chikungunya Virus (CHIKV), and EBV-activating plants such as *Euphorbia tirucalli* [1, 7–9]. BL represents the most common childhood malignancy in these areas,

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Table 5.1 Characteristic features of BL subtypes

	Endemic Burkitt's lymphoma	Sporadic Burkitt's lymphoma	AIDS-related BL
Geographical distribution	Equatorial Africa	Worldwide	Worldwide
Incidence	Children	Children and adults	Adults
Sites	Jaws, facial bones, kidneys, liver, gonads, breast	Ileocecal region, Waldeyer's ring, gonads, breast	Nodal, central nervous system (CNS)
EBV infection	100%	5–30%	25–40%
Enviromental factor	Malaria, arbovirus, euphorbia	–	–
Myc breakpoint in t(8;14)(q24;32)	Far 5′ (centromeric) of MYC (class III)	Exon and intron 1 (class I) and 5′ (centromeric) of MYC (class II)	Exon and intron 1 (class I)
Predominant IGH breakpoint in t(8;14)(q24;32)	VDJ region	Switch region	Switch region
Somatic IGH mutation	Yes	Yes	Yes

with a peak in incidence between 4 and 7 years and a male-to-female ratio of 2 to 1. Endemic BL is associated with EBV infection in almost 100% of cases. In endemic BL, the jaws and other facial bones (orbit) are the sites of presentation in about 50% of cases [1, 4]. The distal ileum, cecum and/or omentum, gonads, kidneys, long bones, thyroid, salivary glands, and breast may also be involved. Breast involvement, often bilateral and massive, has been associated with onset during puberty, pregnancy or lactation. Retro-peritoneal masses may result in spinal cord compression with paraplegia. Involvement of the lungs, mediastinum, and spleen is relatively rare. Although localization may sometimes occur in the bone marrow, no manifestation of leukemia in the peripheral blood has been reported [1, 4].

Sporadic BL (sBL) is seen throughout the world, and shows age-specific incidence peak occurring near 10 and 70 years [6, 10, 11]. The incidence is low, representing 1–2% of all lymphomas in Western Europe and the USA. However, sporadic BL accounts for approximately 30–50% of all childhood lymphomas. The male-to-female ratio is about 2 or 3 to 1, and is even higher in children [12]. EBV is seen in less than 30% of cases, and in most Western countries it is found in 10–20%. In some parts of the world, e.g. in South America and North Africa, the incidence is intermediate between true sporadic and endemic variants [9]. Low socioeconomic status and early EBV infection are associated with a higher prevalence of EBV-positive BL. Sporadic BL can also occur in people leaving in endemic regions and may account for some cases of atypical presentation and a lack of association with infectious agents [13]. In sporadic BL, jaw tumors are very rare, while the majority of cases present with abdominal masses ([6, 10]) and the ileocecal region represents the most frequent site of involvement [14]. Similar to endemic BL, the ovaries, kidneys, and breasts are also frequently involved. Lymph node presentation is seen

more commonly in adults than in children. Waldeyer's ring and mediastinal involvement are rare. A leukemic phase can be observed in patients with bulky disease, but only rare cases present purely as acute leukemia [1], with bone marrow involvement and circulating B-blasts resembling Burkitt cells [10, 15].

Immunodeficiency-associated BL (ID-BL) is primarily seen in association with human immunodeficiency virus (HIV) infection, often occurring as the initial manifestation of acquired immunodeficiency syndrome (AIDS) [16]. EBV is identified in 25–40% of cases [16]. In some cases, tumors may arise in immunocompetent patients, when the CD4 count is still high, thus suggesting that HIV itself may have an oncogenic role [17].

BL is seen less often in other immunodeficiency states. In immunodeficiency-associated BL, nodal localization is frequent, as is bone marrow involvement [16, 18].

Morphology

The prototype of BL is observed in endemic BL and in a high percentage of sporadic BL cases, particularly in children [19]. The tumor cells of BL are medium-sized and show a diffuse monomorphous and cohesive pattern of growth. Rare cases with a follicular pattern may be seen, but is not possible to distinguish a true follicular growth pattern from colonization of residual benign lymphoid follicles in the majority of cases [20]. The nuclei are round with clumped chromatin and relatively clear parachromatin, and contain multiple basophilic, medium sized, centrally situated nucleoli. The cytoplasm is deeply basophilic and usually contains lipid vacuoles. Such cellular details are better seen in imprint preparations or fine needle aspiration cytology (FNAC) (Fig. 5.1). The tumor has an extremely high proliferation rate (Ki-67-index >95%) as well as a high rate of spontaneous cell death (apoptosis). A "starry sky" pattern is usually present, due to numerous benign macrophages that have ingested apoptotic tumor cells (Fig. 5.2). The nuclei of the tumor cells approximate

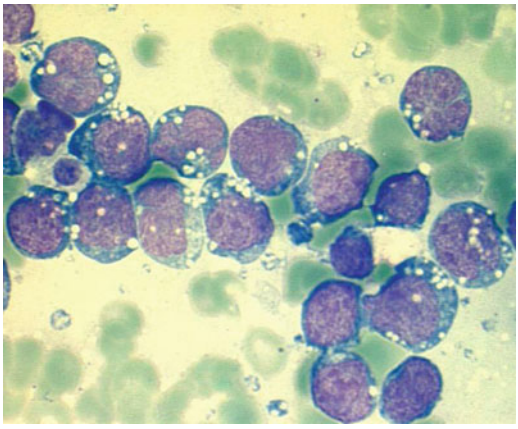

Fig. 5.1 The neoplastic cells show basophilic cytoplasm and contain lipid vacuoles on FNAC

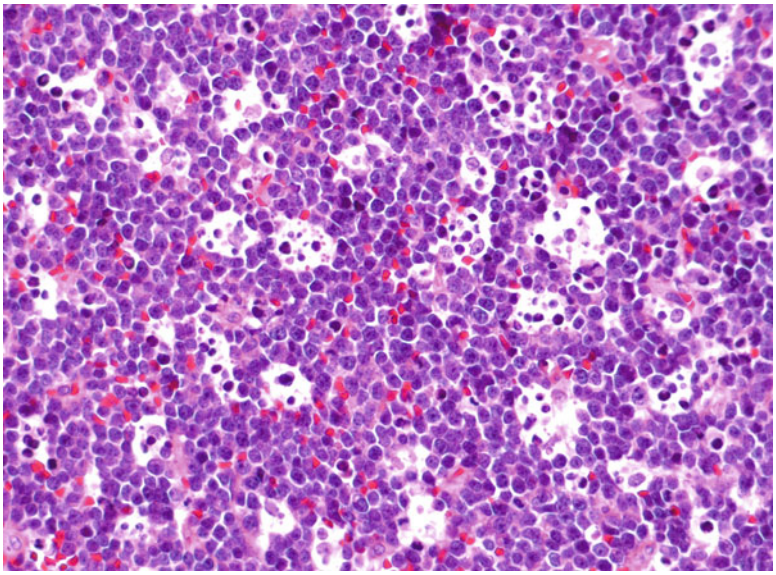

Fig. 5.2 A starry-sky pattern is present, due to numerous benign macrophages [Hematoxylin and Eosin, Original Magnification (O.M.): 20×]

in size those of the admixed starry-sky histiocytes. However, some cases of BL may show greater nuclear pleomorphism, despite clinical, immunophenotypical, and molecular characteristics all pointing to typical BL. In these cases the nucleoli may be more prominent and fewer in number. In other cases, the tumor cells exhibit plasmocytoid differentiation with eccentric basophilic cytoplasm and often a single central nucleolus. Such cases can be observed in children but are more common in immunodeficiency states [16]. These morphological features are in line with gene expression profile studies suggesting that the morphological spectrum of BL is broader than previously expected [21]. Undoubtedly, borderline cases between BL, diffuse large B-cell lymphoma (DLBCL), and "double-hit" lymphoma do exist. These might be better designated as "high-grade B cell lymphoma, unclassifiable" and additional data, such as growth fraction and molecular abnormalities, should be reported for prognostic information and to facilitate the choice of treatment.

Immunophenotype

Tumor cells express membrane IgM with light chain restriction and B-cell-associated antigens CD19, CD20, CD22, and CD79a [19]. The neoplastic cells are negative for CD23, CD44, CD138, cyclinD1, and TdT [22, 23]. BCL2 is characteristically negative, although it may be expressed in some cases and its expression does not

exclude the diagnosis of BL [19]. It should be considered, however, that phenotypic heterogeneity is more common in sporadic BL, while endemic BL shows a more homogenous immunoprofile.

The expression of CD10, BCL6, and CD38 point towards a germinal center origin for the tumor cells. CD21, the receptor for C3d, can be expressed in the endemic form, but sporadic cases are usually negative [15]. A very high growth fraction is observed: nearly 100% of the cells are positive for Ki-67 [19]. Tumor-infiltrating T cells are few in number. Blasts of BL presenting with leukemia have a mature B-cell phenotype, in contrast to the blasts of precursor B-cell acute lymphoblastic leukemia (B-ALL). The blasts of BL are CD34 negative and TdT negative. They express membrane light chain restricted Ig and usually are positive for CD19, CD20, CD22, and CD79a.

Genetics

BL was the first lymphoma for which a recurrent chromosomal aberration was detected. The molecular hallmark of BL is, in fact, a translocation of *MYC* at band q24, from chromosome 8 to the Immunoglobulin (Ig) heavy chain region on chromosome 14 [t(8;14)] at band q32 or, less commonly, to light chain loci on 2p12 [t(2;8)] or 22q11[t(8;22)]. The molecular breakpoint within the *MYC* locus at 8q24 depends on the translocation partners and shows considerable inter-individual variation. In the case of classic t(8;14), the breakpoints in 8q24 typically lie within the centromeric (5′) part of the *MYC* locus. These have been classified according to the position of the chromosomal breakpoints in relation to the *MYC* gene translocations, with breakpoints in the first (5′) exon or intron of *MYC* being designated as class I, those with breakpoints immediately upstream of the gene designated as class II, and those with distant breakpoints as class III. In sporadic and immunodeficiency-associated BL, class I (and II) translocations are predominant, whereas in endemic African cases, class III translocations with breakpoints dispersed over several hundred kilo bases upstream of the gene are most frequent. The t(8;14) leads to activation of *MYC* on the der(14) chromosome, containing the intact coding region of the gene. The deregulation of *MYC* plays a decisive role in lymphomagenesis, by driving the cells through the cell cycle [24, 25]. The breakpoints in the *IGH* locus at 14q32 usually occur 5′ of the intron enhancer in a joining (J) or diversity (D) segment in endemic BL and 3′ of the intron enhancer in the switch mu region in sporadic and HIV-associated BL, suggesting that these translocations occur during an aberrant VDJ or class switch recombination process, respectively. There is also evidence that Burkitt translocation might be the result of a misdirected somatic mutation. Somatic and, in part, ongoing VH mutations have been observed in several cases of BL [26]. Similarly, mutations of the *MYC* gene are very frequent, presumably owing to somatic hypermutation driven by the immunoglobulin sequences juxtaposed to the *MYC* locus on the derivative chromosome 14. Mutations in *MYC* may further enhance its tumorigenicity and some of these mutations lead to decreased

expression of *BIM*, which binds and inactivates BCL-2 [27]. Enigmatically, in normal cells *MYC* activation leads to two counteracting effects, i.e. induction of proliferation and apoptosis, but genetic and epigenetic alterations other than *MYC* have been reported in BL. These include *P53* point mutation and *P16INK4a* gene silencing by promoter methylation [28]. Other genetic alterations occurring in a subset of BL, including *P73*, *BAX*, *RBL2*, *BCL6,* and *A20* may promote cell growth and/or antagonize apoptosis [13, 29, 30]. In recent years, global genetic analyses, including conventional karyotyping, comparative genomic hybridization, and array-based comparative genomic hybridization, have described secondary genomic alterations in BL. One of the larger studies using CGH described gains of 12q, 22q, Xq, and losses of 13q as the most frequent alterations in BL. Moreover, abnormalities in 1q and 7q were associated with an inferior outcome [31].

Gene Expression Profile

Gene expression profiling (GEP) analysis by microarray has become an important part of biomedical and clinical research. The resulting data may provide important information regarding pathogenesis and may be extrapolated for the diagnosis and prognosis of non-Hodgkin lymphomas (NHLs) [32]. In particular, this technology has revealed that the existing diagnostic categories of NHLs are comprised of multiple molecularly and clinically distinct diseases. In addition, GEP studies may lead to the identification of novel targets for the development of new therapeutic agents for NHL.

Great progress in understanding the molecular features of BL was made by two gene expression profile studies, which differ in many important ways, but both reach the same conclusion: the gene-expression profiling of cases classified as Burkitt lymphoma identifies a characteristic genetic signature that clearly distinguishes this tumor from cases of DLBCL [21, 33]. In particular, the signature NF-κB target genes and MHC class I genes were expressed at very low levels in BL, whereas, due to the very nature of BL pathogenesis, the MYC and target gene signatures were increased. Germinal center B cell-associated genes showed a heterogeneous picture. In addition, these studies identified a new provisional category with morphologic features that are intermediate between those of Burkitt lymphoma and those of diffuse large B-cell lymphoma, which has been termed B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (DLBCL/BL) [34]. Despite the existence of some cases with an ambiguous gene expression signature, the studies by Dave et al. [33] and Hummel et al. [21] clearly show that categories which are homogeneous according to gene expression patterns overlap only partially with categories which are homogeneous according to the traditional criteria of morphology and immunophenotype, and two additional criteria should be applied: correlation with cytogenetic abnormalities and with clinical features. Both these studies were mainly performed on sporadic BL cases. We have more recently performed GEP including endemic and HIV-related BL cases [35].

This study demonstrated that, although BL is relatively homogeneous, differences among BL subtypes exist. In particular, a differential expression profile was observed between eBL and sBL, clustering HIV-BL with eBL and mainly involving genes controlling the cell cycle, proliferation, transcription, and nucleic acid metabolism. In particular, gene set enrichment revealed an enhancement of the B-cell receptor (BCR) signaling pathway in eBL, thus suggesting an active role for chronic antigenic stimulation and infectious agents in these cases and pointing to a possible different pathogenetic mechanism. Because the terms sporadic and endemic are mainly based on epidemiology, a better classification should take into account the causative pathogenetic mechanisms.

Another important finding that emerged from these molecular studies was the identification of BL cases that cluster as molecular Burkitt lymphomas, but do not carry *MYC* translocation. Interestingly, these cases express *MYC* at comparable levels to translocated ones. This prompts the question whether *MYC* translocation should still be considered the gold standard for defining BL [36]. We can conclude that *MYC* rearrangement alone is not sufficient for a diagnosis of BL and that *MYC*-negative cases may have a different pathogenetic mechanism. This issue will be discussed at length in the next paragraph.

More recently, dysregulation of small noncoding RNAs, known as microRNAs (miRNAs), has been proposed as a cofactor for Burkitt lymphomagenesis. MicroRNAs are a class of small (~22nt) noncoding RNAs that are able to regulate gene expression by miRNA cleavage or translational inhibition [37]. They are usually expressed in a tissue-specific manner and play important roles in apoptosis, differentiation, and cell proliferation [38]. Several experimental studies have reported miRNA involvement in cancer and their association with fragile sites in the genome [39–41], suggesting that these molecules could act as tumor suppressors or oncogenes [42]. Even though an increasing amount of evidence highlights their possible role in malignant transformation, little is known about their expression and deregulation in malignant lymphomas. A recent study compared BL with DLBCL to determine whether miRNA profiles reflect the molecular differences between BL and DLBCL revealed by mRNA profiling. The miRNA profiling confirmed that BL and DLBCL represent distinct lymphoma categories, thus endorsing the GEP data [43]. Interestingly, a few BL cases were included in the miRNA DLBCL category, thus identifying a subgroup reminiscent of the cases intermediate between BL and DLBCL, as detected by mRNA expression profiling. In addition, a comparison of sBL and eBL revealed only a few differentially expressed miRNAs and demonstrated that the three BL variants are representative of the same biological entity, with only marginal differences in miRNA expression between eBL and sBL.

MYC-Translocation Negative BL Cases

Two pivotal studies, aimed at unraveling the differences between various lymphoma entities, have revealed the existence of BL cases with comparable GEP to the classical profiles, but lacking the typical translocation [21, 33]. These cases were

negative for *MYC* translocation by FISH analysis using both split and fusion probes for t(8;14), as well as using IgH and IgL split probes. There is increasing evidence that about 10% of classical BL cases lack an identifiable *MYC* rearrangement. The current WHO classification states that the diagnosis of this subset of BL must be confirmed by typical morphology, immunophenotyping and clinical features. In other words, these cases must be typical in all other aspects for a diagnosis of BL to be made. Although none of the techniques currently used to diagnose genetic changes can unambiguously rule out all *MYC* translocations [44], it can be postulated that alternative molecular mechanisms, possibly resulting in *MYC* deregulation, also exist.

Quantitative Reverse Transcriptase-Polymerase Chain Reaction (qRT-PCR) has been used to identify two miRNAs, hsa-miR-34b and hsa-miR-9*, which are differentially expressed between *MYC* translocation-positive and negative BL cases [45, 46]. In particular, a strong down-regulation of both miRNAs was only reported in *MYC*-translocation-negative BLs, due to epigenetic events. This finding suggests that a dysregulated expression of miRNAs may represent one of the mechanisms leading to *MYC* over-expression in BL cases lacking a *MYC* translocation, through either a direct or indirect mechanism. In addition, it may be argued that *MYC* itself also induces a specific miRNA pattern that, in turn, might be responsible for differential gene expression, and for functional alterations in tumor cells. A miRNA microarray strategy has recently been developed in order to gain an overview of the differences between the miRNA expression profile of *MYC* translocation-positive and negative BL cases [46]. Using this approach, a clear-cut microRNA signature has been identified, which distinguishes between *MYC* translocation-positive and negative BLs. Of note, these miRNAs control relevant biological processes, such as angiogenesis, apoptosis, and cell proliferation, according to Gene Ontology categories. Furthermore, the impact of miRNA deregulation on the gene expression pattern identified genes, which are more likely to be regulated by the selected miRNA.

The identification of miRNAs, which are specifically altered in BL cases lacking *MYC* translocation, may represent a model for understanding the *MYC* regulatory network not only in BL but also in other human cancers. In fact, their deregulation may represent a valid alternative molecular mechanism leading to MYC over-expression in the absence of genetic alteration.

A Practical Approach to the Diagnosis of Burkitt Lymphoma

For therapeutic and prognostic purposes, BL needs to be distinguished from the subset of lymphomas that compose the newly identified borderline category DLBCL/BL. Moreover, it should be remembered that a proportion of cases of DLBCL may also have some of the individual characteristics of BL. In children, Burkitt and non-Burkitt types seem not to differ clinically, whereas in adults, most cases classified as non-Burkitt lymphoma are similar to diffuse large B-cell lymphoma [19].

RNA extraction and microarray analysis are laborious and expensive and therefore not ready for real-time diagnosis, but other tools currently available to pathologists

can be used to identify some of the distinguishing features of cases with the molecular signature of BL [36]. IGH, IGL, MYC, BCL2, and BCL6 rearrangement can be detected by FISH in paraffin sections, while down-regulation of class I HLA and CD44 and up-regulation of germinal center markers can be detected by immunohistochemistry [36]. In conclusion, no single parameter, such as morphology, genetic analysis, or immunophenotyping, can be used as a gold standard for the diagnosis of BL, but a combination of diagnostic techniques is necessary. The combined application of genomics and immunophenotyping, in conjunction with consensus reviewed histology and clinical features, appear to constitute a reliable approach that enables a reproducible and clinically meaning full characterization of BL [19].

Most endemic BL and a large portion of other BL occur in locations in which the necessary infrastructures and technical expertise are not currently available, and may not be available in the near future. This aspect makes it pertinent to construct a diagnostic algorithm that would facilitate reliable diagnosis of BL using less resources. Such a systematic approach is also relevant in the setting of developed countries, as none of the parameters currently used in diagnostic evaluation can clearly distinguish between BL, DLBCL/BL, and DLBCL on an individual basis.

A feasible scoring system has recently been proposed for the differential diagnosis between BL and non-BL. This scoring system [20] was applied to 252 cases and was based on morphology, immunohistochemistry, and fluorescent in situ hybridization (FISH), employed in three phases: phase 1 (morphology with CD10 and BCL2 immunostainings), phase 2 (CD38, CD44, and Ki-67 immunostainings) and phase 3 (FISH on paraffin sections for *MYC*, *BCL2*, *BCL6,* and immunoglobulin family genes). Using this algorithm, a specific diagnosis of BL or non-BL was determined in 82, 92, and 95% cases in phase 1, 2, and 3, respectively (Fig. 5.3).

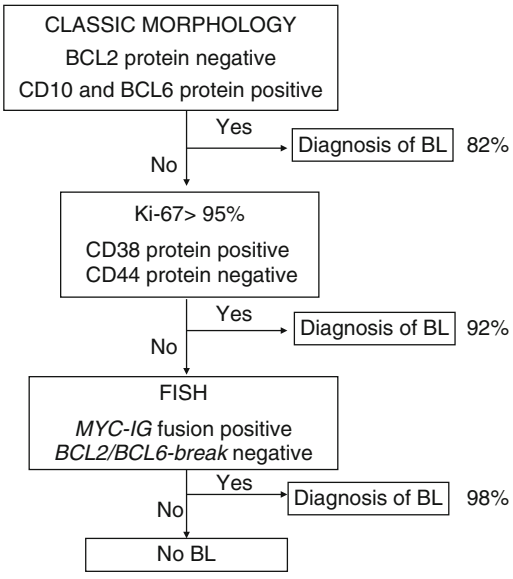

Fig. 5.3 Using the algorithm proposed by Naresh et al. [20] a specific diagnosis of BL or non-BL was determined in 82, 92, and 95% cases in phase 1, 2, and 3

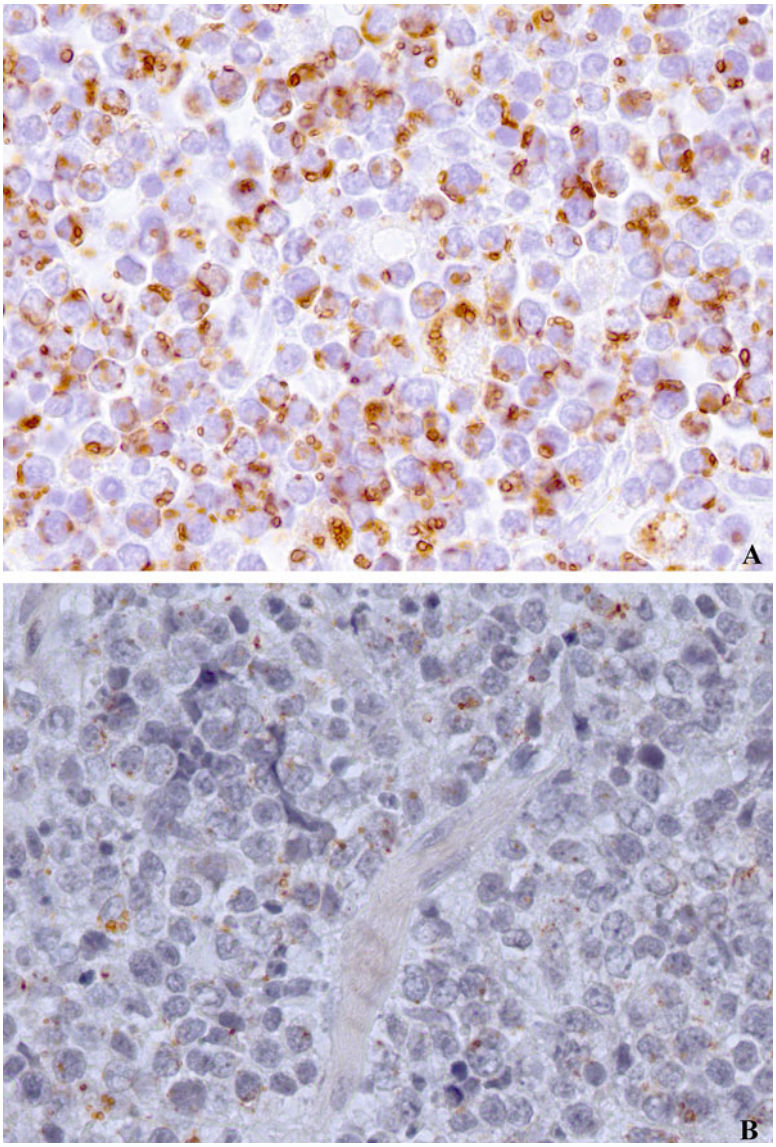

Fig. 5.4 A monoclonal antibody against the adipophilin is able to specifically recognize cytoplasmic vacuoles in typical BL (**a**); on the other hand, in non-BL adipophilin shows a weak positivity in few cells (**b**) (**a**–**b**: Adipophilin stain, OM: 10×)

With FNAC, diagnosis of BL is facilitated by the identification of the characteristic cytoplasmic vacuoles in the lymphoid cells [48]. However, these lipid-containing vacuoles cannot be seen on histological preparations. A recently performed GEP of BL cases found a marked up-regulation of some genes (*ADPF, SCD5, FASN, USF1*)

involved in lipid metabolism in BL. One of these genes (*ADPF*) encodes for a protein, known as adipophilin (adipocyte differentiation-related protein), which is a member of the PAT (perilipin, adipophilin, and TIP47) family of proteins and is mainly involved in fatty acid transport and in preserving the cellular content of triacylglycerols. A monoclonal antibody against the adipophilin is able to specifically recognize the cytoplasmic vacuoles of BL by immunohistochemistry and was tested on a large series of aggressive B-cell lymphomas (Fig. 5.4). The preliminary results suggest adipophilin as a novel marker that maybe useful for the diagnosis of BL in histological sections, especially in challenging cases, such as DLBCL/BL [49].

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