"Double hit" lymphoma or secondary MYC translocation lymphoma?

Abstract

Chromosomal translocations that juxtapose different genes required for proliferation and differentiation are frequently associated with hematologic neoplasms. A term "double hit" lymphoma refers to a group of mature B-cell malignancies that harbor MYC rearrangement accompanied with another translocation commonly found in lymphomas (i.e. IGH/BCL2). A complex karyotype with multiple abnormalities and very aggressive course of disease are additional characteristics of this group. The response to currently available treatment regimens is unsatisfying, thus reported overall survival of these patients is usually very short. Today, the precise mechanisms of "double hit" lymphoma development are still unclear, although several possible pathways have been proposed in the literature. Similar oncogenic chain of events was also observed in another common hematological malignant neoplasm – multiple myeloma. MYC translocation as a secondary pathogenic phenomenon has been demonstrated in multiple myeloma, as well as complex cytogenetics and very aggressive course of the disease. Therefore, secondary translocation involving MYC gene might be a potential marker of aggressive neoplasms emerging from different cells of origin, and united under the umbrella of "MYC-plus" malignancies. That concept might, in the future, result in a novel therapy, targeting this distinct, but not unique cytogenetic aberration.

WHO CLASSIFICATION OF LYMPHOMAS

A commonly used term 'lymphoma' portrays not a single disease, but more than 40 biologically, morphologically and clinically different entities within the category of malignant neoplasms of lymphoid lineage. Classifications are an essential part of modern medicine, offering a consensus on terminology and disease definitions to be used interdisciplinary both in research and clinical practice. Evolution of lymphoma classifications includes numerous attempts from descriptive schemes, relying on morphology (in the Rappaport classification) to strictly clinically oriented stratifications proposed by hematologists (as in the Working Formulation), usually without significant international acceptance (1). The 3rd edition of The World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues that was published in 2001 was regarded as a milestone, because it was the first classification consistently to be used worldwide (2).

The WHO classification divides lymphomas primarily into Hodgkin lymphomas and non-Hodgkin lymphomas. Non-Hodgkin lymphomas are further stratified according to the stage of differentiation, as
well as B or T cell (NK cell) lineage (precursor lymphoid neoplasms and mature B-cell and T/NK-cell neoplasms). The principles of classification of lymphoid neoplasms include a multiparameter approach to disease definition: they are based on morphology, immunophenotype and genetics, as well as clinical features of disease entities. Furthermore, lymphomas are usually classified according to their presumed normal counterpart, although some of them, especially the aggressive forms, lack obvious normal counterparts. The currently used 4th edition of the WHO classification brought important changes based mainly on new genetic information; redefined consensus guidelines for some diseases, introduced new entities, subtypes and variants of lymphomas, provisional categories, and importantly borderline (grey zone) categories. In this review we will focus on a particular subgroup of mature lymphoid neoplasms with B-cell immunophenotype and aggressive clinical behavior, "double hit" lymphomas.

### Aggressive B-cell lymphomas

In previous classifications most aggressive B-cell neoplasms were conveniently designated as diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) or Burkitt-like lymphoma (atypical Burkitt lymphoma). In the current WHO classification the complexity of this subgroup is reflected in a long list of entities and disease variants (Table 1), and the diagnosis of Burkitt-like lymphoma is abolished. Interestingly, some of them are defined by specific genetic abnormalities (e.g. ALK-positive large B-cell lymphoma), and others by viral agents contributing to B-cell transformation (e.g. primary effusion lymphoma, large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease) or even age (EBV-positive DLBCL of the elderly). It also introduced two new, controversial categories of grey zone lymphomas, both defined by overlapping morphological, immunophenotypic and clinical features, with majority of "double hit" lymphomas currently classified as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma. Some of these aggressive malignancies of B-cell origin share striking morphologic similarities (Figure 1), as well as genetic aberrations involving MYC gene, and will be further discussed in more details.

### Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a B-cell lymphoma composed of monomorphous small to medium-sized lymphoid cells with irregular nuclei and a translocation involving the cyclin D1 gene (3). Postulated normal counterpart of the tumor cell is a mature B-cell of inner mantle zone (usually of naïve pre-GC type). It usually affects middle-aged to older patients with a median age of approximately 60 (4). Microscopically, several architectural patterns of MCL are observed, such as diffuse, nodular, mantle zone, and rarely marginal zone pattern. Morphologic variants include the small cell variant with a more indolent course and blastoid/pleomorphic variants, usually with high proliferation fraction, dispersed chromatin pattern and associated with an aggressive clinical behavior (5). Immunohistochemically tumor cells

### TABLE 1

Aggressive B-cell lymphomas in the WHO Classification (2008).

<table>
<thead>
<tr>
<th>Variants of mantle cell lymphoma</th>
<th>Diffuse large B-cell lymphoma, not otherwise specified</th>
<th>Diffuse large B-cell lymphoma subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Varies by histology/rich large B-cell lymphoma</td>
<td>- Primary Large B-cell lymphoma</td>
<td>- Primary cutaneous Large B-cell lymphoma</td>
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<td></td>
<td></td>
<td>- EBV-positive Large B-cell lymphoma</td>
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<tr>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
<td>Intravascular large B-cell lymphoma</td>
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<tr>
<td>DLBCL associated with chronic inflammation</td>
<td>ALK-positive Large B-cell lymphoma</td>
<td></td>
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<tr>
<td>Large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease</td>
<td>Lymphomatoid granulomatosis</td>
<td></td>
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<tr>
<td>Burkitt lymphoma</td>
<td>Plasmablastic lymphoma</td>
<td></td>
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<tr>
<td>*B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma</td>
<td>Primary effusion lymphoma</td>
<td></td>
</tr>
<tr>
<td>*B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma</td>
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</table>

* Variants of mantle cell lymphoma

diffuse large B-cell lymphoma, not otherwise specified

Diffuse large B-cell lymphoma subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL of the elderly

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

DLBCL associated with chronic inflammation

ALK-positive large B-cell lymphoma

Lymphomatoid granulomatosis

Plasmablastic lymphoma

Primary effusion lymphoma

Large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease

Burkitt lymphoma

*B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma

*B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

* Aggressive variants include blastoid and pleomorphic mantle cell lymphoma

§ In most patients the disease is aggressive (grade 3), although patients with grade 1 and 2 lesions follow a more indolent clinical course

* Borderline (grey zone categories)
typically express CD20, BCL2 and CD5, as well as cyclin D1, although rare cases can be CD5- and cyclin D1-negative. The t(11;14)(q13;q32) is present in almost all cases and is considered the primary genetic event, although some MCL with no evidence of such translocation have been reported (6). Some of them harbor a t(2;12)(p12;p13) translocation involving cyclin D2 and kappa light chain gene (lgK) (7).

**Diffuse large B-cell lymphoma**

For a long time DLBCL was a "wastebasket" diagnosis comprising myriad of morphologically similar, but pathogenetically and clinically different disease entities. Today it is divided in many variants, subgroups and subtypes, largest of which is DLBCL – not otherwise specified (NOS). It is a tumor defined by diffuse proliferation of large B-cells. Even DLBCL-NOS is morphologically and immunophenotypically a heterogeneous category of lymphomas, divided in several variants (Table 2) (3).

Postulated normal counterparts are mature B-cells of either germinal center or post-germinal center stage of differentiation.

Most patients present with a rapidly enlarging mass and the disease affects nodal and extranodal sites. It usually occurs in adults and the frequency increases with age. The tumor cells are positive for B-cell markers (CD20, CD19, CD79A), and some cases demonstrate aberrant differentiation.

**Burkitt lymphoma**

This is an aggressive lymphoma that often presents in extranodal sites or as an acute leukemia, characterized by the translocation involving MYC gene. There are three main clinical variants of the disease: endemic BL (typically affecting children in equatorial Africa and commonly associated with EBV), sporadic BL (mainly in children and adolescents throughout the world), and immunodeficiency-associated BL (primarily in the setting of HIV infection), showing differences in clinical features, biology, and even morphology (3). The tumor is composed of cohesive proliferation of monotonous, medium-sized cells with finely clumped and dispersed chromatin and deeply basophilic cytoplasm. Postulated cell of origin is a GC or post GC mature B-cell. This lymphoma has an extremely high proliferation index, as well as high fraction of apoptotic cells, with a typical "starry sky" pattern. Tumor cells typically express pan-B markers (CD19, CD20, CD22), almost invariably show diffuse positivity for CD10, BCL6 and are uniformly negative for TdT (marker of immature lymphoid cells expressed in precursor lymphoid neoplasms). BCL2 is usually negative or rarely weakly positive in a minority of tumor cells. MYC translocation is present in virtually all BL, although it is not specific, and usually involves the IGH gene (3). MYC translocation is considered a primary event in BL, and typically no other (or very few) cytogenetic abnormalities are present, depicted by the term "simple karyotype" (18). This is a very aggressive, but potentially curable disease in cases of endemic and sporadic BL.

**B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma – grey zone lymphoma**

This controversial category comprises rare B-cell lymphomas that demonstrate overlapping morphological and genetic features of both DLBCL and BL and particularly aggressive clinical course. They usually affect adults and older individuals. Before the 2008 classification many of them were diagnosed as Burkitt-like lymphoma or atypical Burkitt lymphoma. It is a heterogeneous category, incorporating several biologically and pathogenetically different entities, but today the methods to precisely diagnose and define those are still lacking. Nevertheless, the importance of this grey zone lies in the fact that these lymphomas are resistant to currently available treatment regimens, hence these patients should not be included into the well-defined categories of DLBCL or BL. Morphologically these tumors consist of diffuse proliferation of medium and large-sized atypical lymphoid cells, with variable number of cells with typical centroblastic morphology. The variability of cell size and shape is usually greater than in BL, and some cases are morphologically indistinguishable from DLBCL. Tumor cells express B-cell markers, and often share most immunophenotypical features with BL (CD20+, CD10+, BCL6+, BCL2-), although many of them show strong and diffuse expression of BCL2, which is incompatible with the diagnosis of BL. The proliferation index is usually very high (19).

### Table 2

**DLBCL, NOS – variants and subgroups.**

<table>
<thead>
<tr>
<th>Common morphologic variants</th>
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<tbody>
<tr>
<td>• Centroblastic</td>
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<tr>
<td>• Immunoblastic</td>
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<tr>
<td>• Anaplastic</td>
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<table>
<thead>
<tr>
<th>Molecular subgroups</th>
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<tbody>
<tr>
<td>• GCB (germinal center B-like)</td>
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<tr>
<td>• ABC (activated B-cell-like)</td>
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</table>

<table>
<thead>
<tr>
<th>Immunohistochemical subgroups</th>
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</thead>
<tbody>
<tr>
<td>• CD5-positive DLBCL</td>
</tr>
<tr>
<td>• GCB</td>
</tr>
<tr>
<td>• Non-GCB</td>
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</tbody>
</table>

These tumors often harbor MYC translocations as a secondary oncogenic event, but unlike in BL, the translocation partner is frequently a light-chain or a non-IG gene (20). A complex karyotype with multiple abnormalities is another feature differentiating these lymphomas from BL (21). A subgroup of grey zone lymphomas that has recently received an overwhelming attention in the field of hematopathology are so called "double-hit" lymphomas. They are characterized by dual translocations, involving MYC and BCL2, or other genes such as BCL6, CCND1, BCL3. They can occur de novo, or as a result of follicular or mantle cell lymphoma transformation (22, 23). The diagnosis of "double-hit" lymphoma is challenging because no specific morphological or immunophenotypic criteria have been defined. These patients often have significant extranodal involvement including the bone marrow and CNS, and a very poor prognosis with a median survival of only 0.2-1.5 years (20, 21).

**Plasmablastic lymphoma**

This is a lymphoma composed of large cells that morphologically resemble immunoblasts, but demonstrate a plasma cell immunophenotype. The postulated cell of origin is a plasmablast (immature lymphoid cell of B-lineage switched to the plasma cell gene expression program). It usually occurs in the setting of HIV infection, mainly in adults. The typical sites of involvement are oral cavity, and other extranodal mucosal sites ( sinonasal cavity, orbit, gastrointestinal tract) (24). Tumor cells express plasma cell markers CD138, CD38, MUM1/IRF4, EMA, and are usually negative for pan-B markers (CD20, PAX5). In situ hybridization for detection of EBV is positive in the majority of plasmablastic lymphomas. This is an aggressive disease with a median survival of 6 to 7 months (25, 26).

**Plasma cell myeloma (multiple myeloma)**

This is a plasma cell neoplasm with a wide spectrum of clinical presentations including indolent and highly aggressive forms. It is characterized by a clonal proliferation of mature plasma cells associated with an M-protein in serum and urine, and generalized bone marrow involvement. Postulated normal counterpart is a post-GC plasma cell demonstrating IG class switch and somatic hypermutation. Tumor cells typically express CD138, CD79A, and CD38, but unlike normal plasma cells they are usually CD19 negative and often show aberrant expression of CD56. Cyclin D1 can also be positive in a subset of myelomas (27). Numerous genetic abnormalities include trisomies, hyperdiploidy, deletions and translocations. Complex cytogenetic aberrations are common (28). The most frequent translocations affect IGH and partner genes such as CCND1, C-MAF, FGFR3/MMSET.
CCND3, and MAFB (29). One of the most common structural abnormalities that occurs early in the pathogenesis is monosomy or partial deletion of chromosome 13 (13q14), and it is associated with disease progression (30). MYC rearrangement occurs as a secondary event during the pathogenesis (3). Plasma cell myeloma is incurable, with a wide range of survival (from 6 months to 10 years and more) (31).

**Genes involved in the "double hit" concept**

**MYC**

MYC or c-MYC (myelocytomatosis viral oncogene homolog) gene located at 8q24.21 was recognized in 1982 as a significant part of the translocation present in Burkitt lymphoma (32, 33). In the following years it was confirmed that c-MYC is translocated not only in mouse plasmacytomas, but also in human Burkitt lymphoma cells, with different translocation (most frequently with IG partners) constituting a possible reason for observed high level of its transcripts. It was also proposed that aberrant transcription control is one of the characteristics of B-cell neoplastic transformation (34-39). Moreover, it was vaguely suggested that c-MYCL translocation is, at least in plasmacytoma, "not the only step in induction", but possibly a secondary translocation (40). The first studies of human protein encoded by c-MYC suggested that this protein has affinity for both single and double stranded DNA and that it is localized in the nucleus (41, 42). Furthermore, it was shown that c-MYC protein has a role in DNA synthesis and that it forms a dimer with MAX protein, resulting in a complex that binds to DNA in a sequence-specific manner, thus regulating activation of various genes and influencing proliferation and differentiation (43-47). Numerous studies were performed and revealed that c-MYC gene regulation control works in dual manner: it induces genes involved in activation of translational initiation, cell cycle regulators, DNA repair genes, genes involved in metabolism and stress response, but also represses genes involved in cell growth arrest and cell adhesion (48, 49). Beside direct control of gene expression, c-MYC can regulate expression indirectly, through repression of various miRNA (50, 51).

In neoplastic cells genomic alterations of c-MYC most frequently involve translocations and amplifications, MYC rearrangement being the main aberration associated with the development of Burkitt lymphoma, diffuse large B-cell lymphoma and double-hit lymphoma. In all those entities, c-MYC rearrangements mark aggressive tumor behavior (3). In B-cell lymphomas, activation-induced cytidine deaminase (AID) is necessary for chromosomal breaks leading to IGH/MYC translocation (t(8;14)(q24;q32)), suggesting that this translocation occurs during the stages of B-cell development in which antibody class switch recombination or somatic hypermutation take place (52-54). t(8;14)(q24;q32) is also found in plasmacytoma/multiple myeloma where it is regarded as a secondary translocation. IGH switch recombination and somatic hypermutation mechanism in normal plasma cells and neoplastic plasma cells are turned off, therefore the mechanism of this translocation in plasma cells differs from the one in B-cell lymphomas. Interestingly, the same translocation is again associated with the unfavorable outcome of the disease (55-57). Moreover, IGH/MYC translocations are observed as a frequent event in plasmablastic lymphoma, an aggressive lymphoma in which MYC activation is believed to hold very important role in disease development (58).

**BCL2**

BCL2 (B-cell CLL/lymphoma 2), located at 18q21, is a gene that encodes the protein located in the inner membrane of mitochondria and serves as an antiapoptotic guardian (59-62). There are two isoforms of BCL2 protein that differ slightly in hydrophobic binding groove, and therefore have different binding properties responsible for interaction with Bad and Bak proteins, suggesting a role in at least two different antiapoptotic pathways (63). BCL2 gene was first described in 1984 in follicular lymphoma cells where it forms translocation with the immunoglobulin heavy chain locus on chromosome 14 (64). The same translocation was later found in diffuse large B-cell lymphoma, primary cutaneous marginal zone B-cell lymphoma, histiocytic/dendritic cell sarcomas arising from follicular lymphoma, chronic lymphocytic leukemia, monoclonal B-cell lymphocytosis, small lymphocytic lymphoma and splenic marginal zone lymphoma. In all these entities IGH/BCL2 is responsible for constitutive expression of BCL2 protein (65-70). Apart from being an important factor contributing to lymphomagenesis, IGH/BCL2 was observed in healthy individuals. A clone of normal lymphocytes harboring this translocation can be persistent and more frequently present in elderly individuals (71, 72). The presence of the translocation in healthy individuals, as well as its relatively early occurrence in the B-cell development (during V(D)J recombination) suggest it is indeed important, but also an insufficient step in lymphoma development (73). World Health Organization Classification takes into account its importance not only in follicular lymphomagenesis, but also as a variable needed for assessment of "double-hit" lymphomas (3).

**BCL6**

BCL6 (B-cell CLL/lymphoma 6) is located at 3q27. Baron B W et al. proposed its name in 1993 and considered it as a gene that "plays a role in the pathogenesis of certain B-cell lymphomas" (74). It codes a transcription factor that can, due to its N-terminal POZ domain, self-interact or interact with many different proteins and act as a sequence-specific repressor of transcription (75-78). Its expression is especially important for formation and function of germinative centers where it protects B-cells from apoptosis induced by double strand DNA breaks (DNA breaks required for immunoglobulin class switch recombination and somatic hypermutation) (79-82). BCL6 is involved in cell cycle regulation, DNA repair mechanisms, apoptosis, proliferation and differentiation
"Double hit" lymphomas

BCL3

BCL3 (B-cell leukemia/lymphoma 3) gene is located at 19q13.32. Translocation (14;19)(q32;q13.1), which brings together BCL3 and switch region of the IGH gene, was first found in chronic lymphocytic leukemia and acute biphenotypic leukemia (103, 104). Breakpoints responsible for this translocation are believed to be the result of aberrant class switch recombination (105). On a mouse model, it was shown that BCL3 expression varies through different stages of B-cell development and that its transcripts are present in a higher amount during mature B-cell stages (106). BCL3 codes a protein that belongs to a 1 kappa B group. It specifically binds to a NF-kappa B p50 subunit, thus interfering with inhibitory role that those homodimers have on a transcription of various genes (107, 108). BCL3 activity is mediated by phosphorylation that allows its association with different partners and subsequently controls expression of different targets genes. (109) Furthermore, BCL3 inhibits p53-induced apoptosis (110).

Possible mechanisms of "double hit" lymphoma development

"Double hit" lymphomas are defined as aggressive B-cell lymphoma variants that are marked by MYC rearrangement and at least one other recurrent translocation (5). (Figure 2) In mature B-cell lymphomas the other "hit" usually involves BCL2, BCL6 and/or CCND1 genes. Along with a second hit, so far, all reported cases show complex cytogenetics with additional genetic alterations (23). In all cases of mature B-cell "double hit" lymphomas MYC translocation is considered to be a secondary event based on a timing of breakpoints responsible for certain translocations during normal B-cell development (23).

In BCL2+/MYC+ lymphomas, there are two possible scenarios. The first possibility is that BCL2 translocation is already present in a B-cell clone of a healthy individual. MYC translocation happens as a part of complex pathogenic karyotype and forms additional change on the ground of the already present aberration. In the other possible scenario, BCL2 translocation is indeed one part of the oncogenic pathway (as in follicular lymphoma), followed by further aberrations involving the MYC gene (23). In both cases, the result is a "double hit" that might cause ant apoptotic behavior of cells, with changes in gene expression control through suppression of growth arrest, and induction of constitutive proliferation and differentiation signals. The promotion of such aberrant differentiation could be the key point that affects the severity of the disease. An idea that such pathways exist has been implied incoherently during last decade. In 2005 Martin-Subero et al. described two cases, showing that IGH/BCL2 accompanied by MYC aberration causes aggressive behavior of germinal center B-cell lymphomas (111). In the same year, another group reported a case of follicular lymphoma with IGH/BCL2 and its subsequent transformation to atypical Burkitt lymphoma (according to the 2008 WHO classification, grey zone lymphoma), due to additional IGH/MYC translocation (112).
"Double hit" lymphomas could share similar oncogenic pathways: IGH/CCND1 is either a non-oncogenic aberration present in a small population of B-cells of healthy individuals, or the first step in the pathogenesis, similar as in the pathogenesis of mantle cell lymphoma. MYC rearrangement brings an additional change that adds aggressive potential to the neoplastic cell (23). IGH/CCND1 results in constitutively induced CCND1 that forces B-cell to enter mitosis possibly without enough time required for damage checkpoints, thus allowing multiple aberrations to persist and cause more changes in the transcription control. MYC rearrangement, again, could additionally promote proliferation and/or activate transcription of other oncogenes causing aggressive behavior of the neoplasm.

Third group are BCL6+/MYC+ lymphomas that are mostly "triple hit" BCL2+/BCL6+/MYC+ lymphomas (23). This entity displays synergistic action of BCL2 and MYC with an additional event, which might result in protection of B-cells from apoptosis, induced by double strand DNA breaks. Rare BCL6+/MYC+ lymphomas could manifest a constant antiapoptotic signal from constitutively active BCL6 accompanied by induced proliferation due to constant activation of various oncogenes by MYC.

BCL3+/MYC+ lymphomas are extremely rare "double hit" entities. The underlying oncogenic pathway is most probably based on a constant antiapoptotic BCL3 activity, followed by transcriptional activation of genes required for proliferation and differentiation induced by MYC rearrangement.

**Clinical presentation, current treatments and future need for therapy**

In 2011, Aukema SM et al. analyzed the Mitelman database and cases reported in published studies, in order to review clinical data and treatment protocols concerning "double hit" lymphomas. They reported that "double hit" lymphoma patients were mostly in their 5th and 6th decades, have elevated LDH levels, extranodal involvement, high International Prognostic Index (IPI) stage and that the diagnosis was established usually in the advanced stage of the disease. In different studies, they documented various treatment protocols: high-dose chemotherapy, stem cell transplantation, specific antibody treatment (rituximab), bone marrow transplantation, radiotherapy, combination of those, and even in some cases steroids as a form of palliative therapy. Overall survival was never longer than a year and a half (23).

Hence, it seems that the category "double hit" lymphoma is just a temporary title for B-cell lymphomas with highly aggressive biologic potential, evident not only in gene rearrangements behind its development, but also in different clinical aspects that accompany such disease progression. Subsequently, patients that belong to this group require a new treatment regimen, possibly a therapy based on repression of oncogenic mechanisms arising from a "double hit" concept, or a protocol that would eliminate the effect of complex cytogenetic aberrations in the neoplastic cells.

**DISCUSSION**

"Double hit" lymphomas are, by definition, a highly aggressive B-cell lymphomas with MYC rearrangement plus additional recurrent translocation and a very complex karyotype (3). In the recent literature, it was clearly stated that this is a temporary category that should be used until enough data for better classification were collected (23).

All disease classifications were written out of a need for better understanding of disease development in order to stratify and treat patients with adequate therapies. In case of hematological neoplasms, detailed attempts of lymphoma classification go back to Rappaport classification (1). Classification was at first based on tumor cell morphology and its similarity to normal cell counterparts. Later, gradually, different classifications take into account clinical behavior, cell surface markers, different antigen expression and genetic aberrations (2, 3, 113, 114). With time, due to gathered knowledge, it was possible to divide hematological diseases in many different groups, describe them very precisely, recognize pathways responsible for their development, and therefore to treat them almost specifically aiming at certain tumor characteristics (115-118). Today, the abundant available data about tumorigenesis allow us to stratify patients precisely, although it is still impossible to decipher crucial and therapeutically applicable pathogenic events. "Double hit" lymphomas represent a group that encounters this problem. In the latest WHO classification, "MYC- plus B-cell lymphomas" belong to the grey zone category called "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma" (3). As explained so far, the clinical presentation of those lymphomas most probably stems from the secondary MYC rearrangement and/or complex cytogenetics observed in almost all cases. Interestingly, the addition of MYC aberration to an already active pathogenetic pathway and its clinical manifestation in a form of aggressiveness is not a new concept, neither is it restricted to mature B-cell lymphomas. Adams MJ et al. in 1983 suggested that "plasmacytoma oncogenesis appears to involve both translocation of c-MYC and activation of another oncogene". Although their research was based on plasmacytoma cells lines, the postulated oncogenic mechanism involved MYC rearrangement plus additional aberration (40). MYC rearrangement as a secondary event was also observed in multiple myeloma and plasma cell leukemia. Mechanism responsible for MYC rearrangement in those neoplasms is still unclear, but it is most certainly different from those in mature B-cell lymphomas (55-58). Shared characteristics between plasma cell neoplasms and B-cell "double hit" lymphoma involve secondary MYC aberration (the result of different breakpoint mechanisms), complex karyotype, aggressive biological behavior and a decrease, or even loss of CD20 expression (3, 119). Moreover, in 2010 Ouansafi I et al. described a case of follicular lymphoma with transformation to plasmablastic lymphoma, possibly due to MYC rearrangement (120).
In conclusion, all secondary MYC hematological neoplasms display fascinating similarities. Their morphology, phenotype, basic genetic aberrations and postulated cells of origin differ, but the clinical aspect of those aggressive neoplasms and the main underlying pathogenic mechanisms might put them in the same category. The key event—a secondary MYC translocation, could integrate neoplasms emerging from different cells of origin into one group, with potential novel therapy targeting a distinct, but not unique aberration (121).

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"Double hit" lymphomas

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