Follicular Lymphoma grade 3B. A separate entity?
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CHAPTER 1

GENERAL INTRODUCTION

1.1 Classification of Non-Hodgkin Lymphomas

Non-Hodgkin Lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies that can be divided in distinct subgroups. The World Health Organization (WHO) classification of lymphoid neoplasms lists the major distinct lymphoma types based on the currently available morphologic, immunologic and genetic techniques\(^{(1,2,3,4)}\). This classification stratifies all hematologic neoplasms primarily according to lineage: myeloid, lymphoid, histiocytic neoplasms and mast cell disorders. The subtypes in each category are further defined according to a combination of genetic features, immunophenotype, morphology and clinical symptoms. Within some of the entities different histological grades have been identified. Treatment of each lymphoma is guided by this diagnosis, in combination with clinical stage and prognostic factors that categorize it as more or less favorable.

Follicular lymphoma grade 3B (FL3B) is recognized as a separate subgroup of follicular lymphomas, with characteristics that differ from the more common subgroups referred to as grade 1, 2 and 3A, (FL1,2,3A) in the WHO classification\(^{(5,6,7)}\).

1.2 Morphology and immunophenotype

1.2.1 Morphology

There is a general consensus that follicular lymphoma should be graded, based on the Berard cell counting method\(^{(8)}\), in at least two separate groups, low grade (FL1,2) and high grade cases (FL3). Application of the Berard cell-counting method has been repeatedly tested in the literature and is the standard for grading (grade 1: 0-5 centroblasts/hpf; grade 2: 6-15 centroblasts/hpf; grade 3: >15
centroblasts/hpf). FL grade 3 can be divided in grade 3A and 3B. FL3B is composed of solid sheets of centroblasts with no residual centrocytes, such in contrast to FL1,2 and 3A and frequently have diffuse areas (Fig.1A/B). The diffuse areas in all grades of follicular lymphoma seem to have impact on the prognosis and can be reported and quantified according to the recommendations of the REAL classification: predominantly follicular (>75% follicular), follicular and diffuse (25-75% follicular) and predominantly diffuse (>25% follicular)\(^9\). In FL3B diffuse areas may represent areas of diffuse large B-cell lymphoma (DLBCL) and therefore need more aggressive therapy\(^6\).

The cells of follicular lymphoma are reminiscent of those in the normal germinal center. Centrocytes have a spectrum of nuclear size ranging from less than twice the nuclear size of a small lymphocyte to as large as centroblasts. The nuclei appear irregular in tissue sections and are designated as cleaved. The chromatin is less dense than that of small lymphocytes and single or multiple small nucleoli may be present. Centroblasts usually have a nucleus three to four times the size of a nucleus of small lymphocytes; the nuclei are oval or round but also may be irregular, indented or even cleaved. The nucleus is vesicular, with a clear center and some condensation of chromatin; with one to three basophilic nucleoli, usually apposed to the nuclear membrane. The cytoplasm is basophilic and usually only a small rim. Occasional immunoblasts with one or two big central nucleoli and a wider rim of very basophilic cytoplasm may be found as well. In about 10\% of the cases, FL may show discrete foci of marginal zone- or monocytoid-like B cells, typically at the periphery of the neoplastic follicles\(^10\). Plasmacytoid differentiation rarely occurs\(^11\).
DLBCLs are composed of large neoplastic B lymphoid cells with nuclear size of more than twice the size of a normal lymphocyte. Most cases will conform to one of the following morphologic variants: centroblastic (Fig. 2), being the most common variant, immunoblastic, anaplastic and T-cell/histiocyte rich DLBCLs\(^{(2,3,12)}\).

Figure 2: DLBCL: The common centroblastic variant is composed of medium-sized to large lymphoid cells with oval to round nuclei with fine chromatin and 2 to 4 membrane bound nucleoli. The cytoplasm is generally sparse and amphophilic or basophilic.

1.2.2 Immunophenotype
BCL2 protein is expressed in the majority of follicular lymphomas ranging from nearly 100% in grade 1 up to 50~75% in grade 3B\(^{(13)}\). BCL2 protein can be useful in distinguishing neoplastic from reactive follicles, but is not useful in distinguishing follicular from other types of low-grade B-cell lymphoma, most of which also express BCL2 protein. BCL6 protein expression is commonly found in germinal center B cells of normal tissue and occurs in all follicular lymphomas as well as in approximately 70-80% of DLBCL with and without $BCL6$ gene rearrangement\(^{(14,15,16,17)}\).

CD10 (CALLA), a cell surface endopeptidase is expressed on the majority of immature B cells, but also on germinal center B cells and is often regarded as a marker for FL\(^{(18,19)}\). Other mature B cells, plasma cells and B-cell lymphomas fail to express CD10\(^{(20)}\). Approximately 40% of DLBCL express the protein and therefore are considered to belong to the germinal center B cell type of DLBCL. FL3B cases manifesting with a t(14;18) often express CD10, suggesting a relation to the other FL\(^{(21)}\). FL3B cases without a t(14;18) generally do not express CD10 and in this respect resemble 60% of all DLBCL that lack CD10\(^{(21,22)}\).

Another marker, MUM1/IRF4, is a transcription factor involved in various developmental stages of B cell differentiation and generally is expressed in a minority of normal germinal center (GC) B cells with plasmacytoid differentiation.

\(^{11}\)
as well as in a minority of the tumor cells of most GC lymphomas. In DLBCL MUM1/IRF4 expression is considered to be an indicator of the activated B-cell (ABC) like gene expression profile.

Within the clinically and morphologically heterogeneous group of DLBCL a distinction can be made into two prognostically important subgroups known as germinal center B-cell-like (GCB) and ABC-like or non-GCB DLBCL’s. As reported in several studies, patients with GCB phenotype have a significantly better survival than those with ABC-like phenotype. The expression patterns of BCL6, CD10 and MUM1 have been suggested as important tools to identify the GCB and non-GCB groups. CD10 and BCL6 are common markers of germinal center B cells and cases can be classified as GCB if both BCL6 and CD10 were positive or if CD10 alone is positive. MUM1 is expressed in later stages of B-cell development and in plasma cells, and is associated with ABC (non-GCB) DLBCL’s. Thusfar such a distinction has not been demonstrated in FL grade 3B.

1.3 Clinical behaviour

A clinically relevant prognostic model for NHL is the International Prognostic Index (IPI). The IPI is based on different parameters like patient age, stage, serum lactose dehydrogenase (LDH) level, performance status, hemoglobin level and number of extranodal sites.

The prognostic significance of cytogenetic abnormalities, aberrant gene expression and different biological markers in both patients with indolent NHL and aggressive NHL has been evaluated by several International Working Groups.

FL is the most common adult NHL comprising 30 to 40 % of all NHL and up to 75 % of low grade B-cell lymphomas. It affects predominantly older adults, with a nearly equal male : female incidence. At diagnosis, most patients have widespread disease, affecting predominantly lymph nodes, but also spleen, bone marrow and occasionally extranodal sites or peripheral blood. The clinical course is generally indolent. Both the number of centroblasts as well as the proportion of tumor that has a diffuse pattern correlate with prognosis. These feature may herald histologic transformation to DLBCL which confers a worse prognosis.

At diagnosis, involved-field radiotherapy (XRT) is generally accepted as the treatment of choice. Currently available treatment of patients with disseminated indolent NHL is chemotherapy, CVP (cyclophosphamide, vincristine,
prednisone), fludarabine and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), with in addition rituximab for advanced stages (R-CHOP).

DLBCL is the second most common lymphoma occurring in the middle-aged and older adult with a median age of incidence of 57 years and has an equal incidence in male and female\(^{(30)}\). Unlike FL, DLBCL is a potentially curable disease. Accurate and complete staging at the time of diagnosis is important for treatment planning. The staging system used for these lymphomas is the Ann Arbor staging system. Currently available treatment for patients with DLBCL is R-CHOP + XRT for stage I and R-CHOP for advanced stages.

Clinically, FL3B have more in common with the majority of the more aggressive DLBCL of germinal center cell origin than with their indolent FL1,2,3A counterparts. Reported differences in clinical outcome between FL1,2,3A and 3B might be dependent on the presence of diffuse areas in the lymphoma\(^{(5)}\).

Patients with FL3B who have been treated according to guidelines used for DLBCL with aggressive chemotherapy regimens have survival outcomes comparable to DLBCL\(^{(39,40,9)}\).

1.4 Cytogenetics

Several cytogenetic and molecular genetic studies of human lymphoma, leukemia and solid tumors have led to the conclusion that acquired alterations of the genetic material in somatic cells cause initiation and progression of a neoplasm\(^{(41)}\). Many of these acquired alterations are detectable by microscope as changes in number or structure of the chromosomes. Most of these chromosomal alterations are involved in the pathogenesis of the disease through mechanisms including activation of a proto-oncogene, disruption of a tumor suppressor gene or generation of a fusion gene\(^{(42)}\). Extensive cytogenetic analyses of human tumors have revealed the nonrandom nature of many chromosomal aberrations and their specificity in certain types of malignant and benign neoplasms\(^{(43,44,45,46)}\). The first consistent chromosomal aberration in cancer was the finding of the Philadelphia chromosome in chronic myeloid leukemia (CML)\(^{(47,48)}\). The first structural aberration in human lymphoma was the 14q+ marker in Burkitt’s lymphoma (BL)\(^{(49)}\). Despite morphologic, immunologic and genetic differences within entities, the currently defined NHL categories generally have well defined cytogenetic abnormalities. In most mature B-cell neoplasms chromosomal translocations result in the transcriptional deregulation of an oncogene by juxtaposing it to regulatory sequences of genes that are constitutively expressed in mature B-cells, most often the immunoglobuline (Ig) genes\(^{(50)}\).
In most NHL cases cytogenetic analysis can be performed with differences in success rate between low-grade and high-grade lymphomas. Large studies have shown that almost all successfully karyotyped lymphomas display clonal chromosome aberrations with a low frequency of apparently normal karyotypes\(^{(51,52,53,54)}\). The finding of a normal karyotype in lymphoma preparations generally can be explained by the presence of nonneoplastic, reactive cells that have the capacity to divide in vitro\(^{(52,55)}\). In few other cases, the degree of resolution, even in excellent banded preparations, may be too low to visualize subtle rearrangements. In tumors with a normal karyotype, an alteration may have occurred at the molecular level and therefore cannot be visualized by cytogenetic techniques.

The karyotype of cytogenetically abnormal NHLs is generally complex and infrequently displays a single clonal aberration. The chromosomal translocations t(14;18)(q32.3;q21.3) and aberrations involving the chromosome 3q27 region are the most common in B-cell NHL of germinal center cell origin\(^{(56,57)}\).

The single most frequently observed reciprocal translocation t(14;18)(q32.3;q21.3) (Fig.3) has an incidence in FL1,2 of 80-90% and in DLBCL of 20-30%\(^{(53-56)}\). The occurrence of a t(14;18) in part of the DLBCL, is possibly related to the finding that at least one-third of follicular lymphomas transform to a higher histologic grade. This has led to the suggestion that DLBCL carrying a t(14;18) has evolved from FL.

Figure 3
Translocation t(14;18)(q32;21); the breakpoints of the cytogenetic t(14;18) are located at chromosome 14q32.3 and chromosome 18q21.3 using a 550 G-banding pattern.
Translocations involving the 3q27 region are also common in B-cell lymphomas of germinal center origin and are most frequently found in DLBCL (~40%) and in FL3B, but occur less frequent in FL1,2 (~10%)\(^{(58,59)}\). Cytogenetic studies of NHL have demonstrated that chromosome alterations affecting band 3q27 are predominantly represented by reciprocal translocations between the 3q27 region and several alternative partner chromosomes, including the sites of the Ig genes at 14q32 (IGH), 2p11 (IGK), and 22q11 (IGL), but also many other chromosomal regions. The variability of the partner chromosomes juxtaposed to 3q27 in DLBCL translocations suggests that these abnormalities belong to a group with a fixed chromosome breakpoint on one side and on the other side different chromosome partners. The most frequently found translocation is t(3;14)(q27;q32) and involves the immunoglobulin heavy chain locus and 3q27 (Fig.4).

Figure 4
Rearrangement of the 3q27 breakpoint region as a result of the t(3;14)(q27;q32)
As mentioned before, approximately 85% of FL cases have a t(14;18) and about 40% of DLBCL cases have an aberration involving the 3q27 region; in both groups cases have been reported that harbour both a t(14;18) and a 3q27 aberration\[^{60,61,62}\].

Besides these translocations, additional clonal structural and numerical aberrations are seen in almost all NHL cases. In FL, these additional cytogenetic changes are commonly associated with progression to a higher grade or to DLBCL\[^{63,64}\]. Commonly observed secondary numerical aberrations are gain of chromosome X, 7, 12 and 21 whereas structural aberrations frequently include breakpoints at 1p36, 6q13 and del(6q), dup(7q) and der(18)\[^{55,65}\].

A frequent secondary chromosomal aberration in NHL is a deletion of the long arm of chromosome 6. In some cases the pathogenetic role of 6q deletions is suggested by the observation that the deletion occurs as the sole abnormality\[^{54,64}\]. Although loss of 6q has been reported in systemic DLBCLs, the frequency is clearly higher in lymphomas located at immunoprivileged sites. Primary central nervous system (CNS) lymphomas and testicular lymphomas show 6q deletions in up to 75% of the cases, whereas the frequency in systemic DLBCLs is less than 35% \[^{66,67,68,69}\]. This suggests an important role for one or more genes on chromosome 6q in the pathogenesis of these lymphomas. Three minimal molecular deletion regions (RMD) were identified in NHL. RMD1, mapping to chromosome bands 6q25-q27 is associated with intermediate grade NHL, RMD2 located at 6q21-q23 is associated with high grade NHL, and RMD3 located within the region 6q23-q25 seems to be associated with low grade NHL\[^{70,71,72}\]. All RMD’s have been reported independent of a t(14;18) or 3q27 aberration\[^{72}\]. The prognosis of NHL with testicular or CNS localisation is clearly worse than other primary extra-nodal DLBCLs of e.g. skin and stomach; most patients die of disseminated NHL within a few years\[^{73}\].

Translocations involving chromosome 8q24, are the cytogenetic hallmark of Burkitt lymphoma (BL)\[^{49,74}\]. Although commonly described in BL, a t(8;14) has also been observed upon transformation or progression from a low grade to a high grade lymphoma\[^{75,76}\]. This translocation results in deregulation of the MYC gene by juxtaposition to immunoglobulin regulatory sequences and loss or disruption of its 5’ regulatory sequences\[^{77,78}\]. In about 85% of the BL cases the translocation partner of MYC is the IGH locus on chromosome 14 and in the remaining 15% the IGK or IGL loci on chromosome 2 and 22 respectively\[^{79,80}\].
1.5 Molecular Genetics

**BCL2**

BCL2 protein is one of the major anti-apoptotic (programmed cell death) proteins in the mitochondrial membranes of lymphoid cells. During the normal follicle center B-cell proliferation, BCL2 protein is downregulated and B cells that fail to execute successful Ig gene rearrangement during VDJ recombination or lack subsequent affinity maturation enter the apoptotic pathway. However, t(14;18) carrying B cells have a strong survival advantage since they maintain BCL2 expression by juxtaposition of the BCL2 gene to the immunoglobulin heavy chain (IgH) locus \(^{(81,82,83)}\). Most breakpoints (60%-70%) are located within a 2.8 kb major breakpoint region (MBR) in the 3' untranslated exon of the BCL2 gene. Another breakpoint cluster can be identified (10%-15%) in the minor cluster region (mcr) approximately 20 kb further downstream and a third breakpoint cluster (5%-10%) in between the MBR and mcr \(^{(84,82)}\). As a result, BCL2 is deregulated by juxtaposition to the centromeric part of the IgH complex containing the IgH enhancers, leading to a disturbance of the BCL2 expression regulation \(^{(85,86)}\). The breakpoints on chromosome 14 generally occur at the 5’ side of one of the J segments. The causal effect of the t(14;18) seems to be the formation of a configuration on the der(14) in which the J segments and in particular the intronic IgH enhancers (Eu) from the IgH chain are juxtaposed to exon 3 of the BCL2 gene \(^{(87)}\) (Fig.5). This molecular configuration indicated that the translocation has its origin from abnormal VDJ recombination. More recently, juxtaposition of the BCL2 gene with the more centromeric switch sequences from the IGH locus instead of the J segment was reported indicating an origin of the translocation from class switching events in germinat center B cells \(^{(88)}\). A large proportion of the cases with a der(14)t(14;18) carry a deletion in the constant (µ) region with unknown significance thusfar \(^{(89)}\). In most FL, both IgH genes are rearranged. One IgH allele is involved in the t(14;18) which is present in 70-90% of the cases. The other allele contains a functional gene rearrangement and is responsible for surface Ig expression observed in most FL \(^{(90,91)}\).
Figure 5: Translocation t(14;18)(q32;q21) recombines the BCL2 oncogene in 18q21 with the locus in 14q32. Through the resulting deregulation of BCL2, the normal rate of preprogrammed cell death (apoptosis) is disturbed.

**BCL6**

The high frequency of 3q27 region breakpoints in DLBCL suggested that a gene mapping to 3q27 is associated with DLBCL pathogenesis\(^{(92)}\). Cloning of the 3q27 breakpoint of several cases led to the identification of a gene named BCL6\(^{(93,94,59)}\). Most translocations lead to promoter substitution of BCL6\(^{(15)}\). The BCL6 gene codes for a protein that contain six zinc-finger motifs that are also present in a number of related transcription factors and are able to mediate protein binding to specific DNA sites\(^{(95)}\). BCL6 is a 95kd nuclear phosphoprotein belonging to the POZ/Zincfinger (ZF) family and is composed of 706 amino-acid residues\(^{(96)}\). The amino-terminal region of the BCL6 protein contains a domain, termed POZ, which is homologous to domains found also in other zinc-finger transcription factors\(^{(97,98,99)}\). The structural features of the BCL6 protein are consistent with functional studies indicating that BCL6 can indeed function as a transcription factor that binds a specific DNA sequence and represses transcription from linked promoters\(^{(100)}\).
The majority of breakpoints in the BCL6 gene cluster in a 4 kb major breakpoint region (MBR) in the first non-coding exon and 5' region of the first intron, and are commonly seen in DLBCL (96). Recently another breakpoint region on the BCL6 gene has been detected, located within the genomic region between 245 kb and 285 kb telomeric from the MBR, called the alternative breakpoint cluster region (ABR) (101) (Fig.6). This breakpoint occurs mostly in FLs grade 1,2 and only in a very low frequency in DLBCLs (102).

Figure 6
Schematic representation of genetic lesions affecting the BCL6 gene in DLBCL. In its germline configuration, the BCL6 gene is composed of 10 exons. The coding region of BCL6 is indicated by black boxes, and the non-coding exons, or parts of exons, are indicated by white boxes. The breakpoint sites, indicated by arrows, span the first exon and its adjacent sequences on both sides. The majority of breakpoints map to 3' sequences close to the BCL6 first exon, indicated by a thick arrow. The ABR breakpoint region is located within the genomic region between 245kb and 285kb telomeric of the MBR.
TP53
Translocations or deletions involving chromosome 17p13 result in deregulation of the tumor suppressor gene TP53. The TP53 gene encodes the P53 protein that is involved in controlling the cell cycle, particularly in repressing the transition of the cell from the G1 to S phase in case of genotoxic stress\(^{103}\). The P53 protein can also induce apoptosis\(^{104}\). Given the role of P53 it is likely that disruption of normal P53 functions may contribute to tumor progression directly by providing FL cells with a high proliferation rate, or indirectly, by allowing the accumulation of additional genetic lesions\(^{105,106}\). Mutations of the TP53 gene are common and found in a variety of lymphoid neoplasms. P53 expression and mutation is virtually absent in DLBCL cases arising de novo, whereas they are frequently found in cases resulting from histologic transformation or progression from a low-grade lymphoma to a higher grade lymphoma\(^{106,107}\).

1.6 Progression markers
Several genes are associated with transformation from FL to DLBCL, generally designated as a transformation pathway\(^{106}\). Whereas some of these genes are already present in the FL phase e.g. \(BCL2\),\(^{107}\) others seem to appear during the histologic transformation e.g. loss of \(TP53\) or \(MYC\) rearrangement\(^{108,109}\). Non-random secondary chromosomal changes include partly or full gains or losses of chromosomes 1,6,7,9,12,18 and 21, and are commonly associated with progression\(^{110,111}\).

A deletion in chromosome 6q can be associated with a transformation pathway or a de novo pathway, because it has been found as a secondary chromosomal aberration in FLs with progression, but is also in DLBCLs without a pre-existing FL\(^{112,113,114,68,69}\). Testicular and CNS DLBCL both show this aberration, without a history of FL or other low-grade lymphoma.

A model of a molecular transformation pathway should consider the transformation of a pre-existing FL to a DLBCL or a de novo pathway in which a DLBCL develops without a pre-existing FL (Fig.7). There are two mechanisms to be considered in the de novo pathway: rearrangement of the \(BCL6\) gene, deletion in chromosome 6q and presently unknown additional genetic lesions. In the transformation pathway, various additional genetic lesions in combination with an already present \(BCL2\) rearrangement might cause transition of FL to DLBCL. \(MYC\) and \(TP53\) seem to appear only in cases presenting with transformation from a low grade to a high grade lymphoma. The presence of these alterations in a FL may thus suggest transition to DLBCL. It may also enable subdivision of FL3B
into subsets with different pathogenetic pathways.

**Transformation pathway**

![Transformation pathway diagram](image)

Figure 7
Transformation pathway model of a preexisting FL to a DLBCL or a de novo pathway in which a DLBCL develops without a preexisting FL.

1.7 **Summary of features specific for FL and DLBCL**

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<th>BCL2</th>
<th>BCL6</th>
<th>MYC</th>
<th>P53</th>
<th>CD10</th>
<th>+7</th>
<th>Del (6q)</th>
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<tr>
<td>FL1.2.3A</td>
<td>80-90%</td>
<td>5-15%</td>
<td>&lt;5%*</td>
<td>&lt;5%</td>
<td>~100%</td>
<td>50%*</td>
<td>10-20%</td>
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<tr>
<td>DLBCL</td>
<td>20-30%</td>
<td>30-40%</td>
<td>5-15%</td>
<td>20-30%</td>
<td>&lt;40%</td>
<td>15%</td>
<td>30-40%**</td>
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* more common in FL cases with progression to DLBCL, ** more common in Testicular DLBCL, CNS DLBCL and AIDS related lymphomas; up to 70%

The most striking differences are in bold marked entities specific for FL and DLBCL.
1.8 *Aim of the thesis*

The aim of these thesis is to better define the nature of follicular lymphoma grade 3B (FL3B) and its relationship to follicular lymphoma grade 1,2 (FL1,2) and diffuse large B-cell lymphoma (DLBCL). The architecture of FL3B is follicular by definition but in most cases there are also diffuse areas, whereas the cellular composition is similar to that of DLBCL. Clinically, FL3B appears to respond to treatment according to protocols used for DLBCL in terms of remission and freedom of tumor progression rates.

The aim of the study in chapter 2 was to determine if FL3B is a homogeneous group or whether different subgroups can be identified. In chapter 3 one of the identified subgroups of chapter 2 is investigated in further detail. In chapter 4 additional cytogenetic and molecular genetic analyses are described to investigate whether a better subdivision can be reached of the different subgroups established in chapter 2. The aim of the study in chapter 5 is to characterize a group testicular lymphomas with cytogenetics and array CGH.
Chapter 1

List of References


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Chapter 1


