# High-grade B-cell lymphoma/leukemia associated with t(14;18) and 8q24/*MYC* rearrangement: a neoplasm of germinal center immunophenotype with poor prognosis

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Chromosomal translocations involving the immunoglobulin genes (*IG*) are common in malignant lymphomas.[1,2] The t(14;18)(q32;q21), which juxtaposes the *BCL-2* gene, normally located at 18q21, with the *IG* heavy-chain locus on 14q32, is the genetic hallmark of follicular lymphoma (FL). Similarly, the t(8;14)(q24;q32), which juxtaposes the *MYC* (previously known as *c-MYC*) gene normally located at 8q24 with the *IG* heavy-chain locus, as well as the so-called variant translocations, t(2;8)(p12;q24) and t(8;22)(q24;q11), involving the *IG* light chain genes, are considered genetic hallmarks of Burkitt's lymphoma (BL). However, these translocations are not specific. The t(14;18)(q32;q21) also occurs in about 25-30% of cases of *de novo* diffuse large B-cell lymphoma (DLBCL) and has been rarely described in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Likewise, the 8q24/*MYC* rearrangement can be observed in a small subset of DLBCL and up to 40-50% of high grade B-cell lymphomas other than BL.[3] Furthermore, the 8q24/*MYC* rearrangement has been reported in a variety of other lymphoma or leukemia types including CLL/SLL, B-cell prolymphocytic leukemia, mantle cell lymphoma and FL, and usually these tumors are in transformation to higher-grade lymphoma.[4-6] It is believed, therefore, that the 8q24/*MYC* rearrangement may exist either as a primary initiating event in classical BL or as a secondary event (that is, acquired during clonal evolution) in other lymphoma types. Rarely, *MYC* deregulation can also result from 8q24/*MYC* rearrangement with non-IG partners, such as the t(8;9)(q24;p13), as described by Le Gouill and colleagues[7] as well as others.

In adults, the 8q24/*MYC* rearrangement is most commonly encountered in B-cell lymphomas other than BL. This is because DLBCL, which can carry the 8q24/*MYC* rearrangement in 10-15% of cases, is a very common type of lymphoma, representing 30-40% of all lymphomas, whereas BL represents only 1-2% of lymphomas in adults. The frequency of the 8q24/*MYC* rearrangement is even higher when lymphoid neoplasms with morphologic and immunophenotypic features intermediate between BL and DLBCL, or cases of DLBCL with a high proliferation rate (>80%) are selectively analyzed. In this subgroup up to 60% of the neoplasms carry 8q24/*MYC* rearrangements.[3] In a subset of these lymphomas, both 8q24/*MYC* rearrangement and the t(14;18)/*BCL2-IgH* can be detected and this is the subgroup that is the focus of the paper by Le Gouill and colleagues in this issue of the journal.[7] There are approximately 100 such cases reported in the literature; most as single case reports or as small series. From this point forward, we will refer to these neoplasms as MYC/BCL2 (M/B) high-grade B-cell lymphoma/leukemia for convenience. Alternative terms used by others for these neoplasms include *dual fusion* or *double hit* lymphomas although we believe these terms are less specific. Table 1 summarizes the results of selected reports presenting four cases or more. The series studied by LeGouill and colleagues is the largest reported to date.[7] Subsequent to our previous publication of patients with M/B high-grade B-cell lymphoma/leukemia,[8] we have identified 11 additional cases at our institution for a total of 23 cases. The key clinicopathologic features of these cases of M/B high-grade B-cell lymphoma/leukemia are summarized in Table 2. We also have identified this combination of molecular abnormalities in rare cases of plasmablastic myeloma and low-grade B-cell lymphoma, but these cases are not included in this total. Clinically, these neoplasias fall into two general categories: *de novo* or following a history of FL. In our experience, most tumors (18 of 23; 78%) arise *de novo*, likewise, most cases reported in the literature also belong to the *de novo* category.[3,6,8-37] Affected patients are usually adults. The age range in our experience was 29-77 years with a median age of 58 years. The patients with a history of lymphoma tend to be older. The disease may present primarily as lymphoma or leukemia, usually at an advanced stage, with a propensity for extranodal involvement, especially of the gastrointestinal tract and central nervous system.[7,8,24,26] Regardless of presentation, patients at our institution and those reported by others generally have a rapidly progressive clinical course characterized by refractory disease and short survival, usually <1 year, despite aggressive therapy.[7,8,26] The overall poor outcome of these patients appears to be independent of other clinical prognostic indicators and is thought to be related to clonal evolution and the synergys of growth promotion by *MYC* and the anti-apoptotic effect of *BCL-2* gene dysregulation.

Classification of these neoplasms is problematic as their features fall within a morphologic and immunophenotypic spectrum that pathologists have attempted to capture using terms such as small non-cleaved cell lymphoma, Burkitt-like lymphoma, atypical BL, DLBCL with high-grade features, and high-grade B-cell lymphoma not otherwise specified.[3,6-8,16,21,24-26,31-36] Sometimes, these high-grade tumors can co-exist with a low-grade FL at the same or a different site. Use of the term high

grade B-cell lymphoma not otherwise specified perhaps most accurately reflects the dilemma of classifying these neoplasms, in particular, drawing a clear line between atypical BL and DLBCL. It is well known that atypical BL and DLBCL share overlapping features and that diagnostic reproducibility, even among expert hematopathologists, is as low as 53%.[38] Cases presenting primarily as a leukemic process have been classified as pre-B (surface light chain negative, TdT positive) or mature B-cell acute lymphoblastic leukemia (ALL), with the blasts showing cytologic features along the L1-L3 spectrum defined by the French-American-British classification.[9,10,13,15,17-19,22,23,29]

Much of our knowledge about the immunophenotype of M/B high-grade B-cell lymphoma leukemia is derived from studies of small series of cases or indirectly from studies focusing on the differential diagnosis of BL and DLBCL with the 8q24/*MYC* rearrangement.[39-41] Unlike classical BL, which are usually CD10$^+$, CD19$^+$, CD20$^+$, BCL2$^-$, and BCL6$^+$, with virtually all cells proliferating as shown by their being strongly positive for Ki-67, most M/B high-grade B-cell lymphomas are CD10$^+$, BCL2$^+$ and BCL6$^+$; However, a subset of these cases can be negative for CD10, BCL2, or BCL6. The proliferation (Ki-67) rate in most studies is variable and ranges from 60-100%, with the Ki-67 staining intensity also being variable.

The karyotype of M/B high-grade B-cell lymphoma leukemia is often complex and the 8q24/*MYC* and t(14;18)(q32;q21) abnormalities are part of multiple aberrations.[30] The *IGH* joining region is usually involved in cases with the t(8;14), as is the case in sporadic BL. Variant translocations involving the *IG* $\lambda$ light chain, t(8;22)(q24;q11), are also common whereas the *IG* $\kappa$ light chain is involved rarely, as are non-IG partners such as the t(8;9)(q24;p13).[7] Although 8q24/*MYC* rearrangement in many of these cases is thought to be secondary, rare direct analysis has been performed to confirm this presumption. Indirect evidence in favor of this hypothesis comes from fluorescence *in situ* hybridization (FISH) analyses, which have found the 8q24/*MYC* rearrangement in only a subset of tumor cells.[8] Sequential acquisition of t(14;18) and *MYC* rearrangement has been documented to coincide with transformation from indolent to aggressive lymphoma in occasional case reports and in transgenic mice experiments.[42] However, the fact that M/B high-grade B-cell lymphoma/leukemia can present in some patients as acute onset, primarily bone marrow disease and leukemia suggests that both the t(14;18)(q32;q21) and 8q24/*MYC* rearrangement can occur simultaneously in a subset of these neoplasms.

Two recent studies using gene expression profiling methods have shown that BL has a characteristic molecular signature, and that cases considered to be BL at the gene expression level are not consistently recognized using the current diagnostic criteria of the WHO classification scheme.[43,44] As many as 17% and 34% of cases with the molecular signature of BL were designated as DLBCL or unclassifiable high-grade B-cell lymphoma using traditional histologic and immunophenotypic criteria,[43,44] respectively, in these publications. Approximately 3% and 8% of cases diagnosed as DLBCL or unclassifiable highgrade B-cell lymphoma using traditional criteria had a molecular BL signature,[43,44] respectively. Specifically, cases expressing BCL2 or having a Ki-67 (MIB-1) index <90%, which are usually not classified as BL according to the recommendations of the WHO classification, can carry a molecular signature characteristic of BL. Of particular interest here, five cases of M/B high-grade B-cell lymphoma/leukemia in the study by Dave and colleagues had a molecular signature of BL, yet only two of them had been classified as BL according to the WHO criteria.[43] In the study by Hummel and colleagues, gene expression profiling showed that the molecular signatures covered a spectrum between cases of classical BL and typical DLBCL. One case of M/B high-grade B-cell lymphoma/leukemia had a molecular signature of BL, and 16 other cases with dual (*MYC* and *BCL2* or *BCL6*) or all three translocations had a molecular signature of either DLBCL or intermediate between BL and DLBCL.[44] Thus, these results confirm the spectrum of morphologic findings that pathologists have long appreciated. Despite the presence of the t(14;18), some cases can have a molecular signature of BL. Conversely, despite the presence of the *MYC* rearrangement, some cases have a molecular signature of DLBCL or of high-grade lymphoma intermediate between BL and DLBCL.

**Table 1. Summary of previously published series of M/B high-grade B-cell lymphoma/leukemia.**

| Authors | Number of cases | Prior or concurrent FL | Morphology | Survival (months) |
|---|---|---|---|---|
| Stamatoullas A *et al.*[27] | 5 | 0 | 5 ALL-L3 | <7 |
| Thangavelu M *et al.*[17] | 6 | 2 | 3ALL-L2, 2 ALL-L3, 1 DLBCL | 5/6 ≤12 |
| D'Achille P *et al.*[37] | 7 | 0 | 5 ALL-L3, 2 ALL-L2 | 5/7 ≤6 |
| Cogliatti SB *et al.*[3] | 4 | Not specified | 1 BL, 2 BLL, 1 DLBCL | Not specified |
| Haralambieva E *et al.*[32] | 5 | Not specified | 1 BLL, 4 DLBCL | Not specified |
| McClure RF *et al.*[34] | 5 | Not specified | 3 BLL, 2 DLBCL | 4/5 <12 |
| Macpherson N *et al.*[26] | 13 | 6 | 13 BLL | <7 |
| LeGouill S *et al.*[7] | 16 | 4* | 16 DLBCL | 15/16 ≤10 |
| Kanungo A *et al.*[8†] | 23 | 6 | 4 BL, 12 BLL, 7 DLBCL | 8/10 ≤12 |

*BL: Burkitt's lymphoma; ALL: acute lymphoblastic leukemia; BLL: Burkitt's like lymphoma; DLBCL: diffuse large B-cell lymphoma; *Two of the four patients had a presumptive diagnosis of FL based on bone marrow histology. †Eleven additional cases were identified after the original report of 14 cases, one case of myeloma and one case of low-grade B-cell lymphomas exclided. see Table 2 for details.*

**Table 2.** Key features of the patients with M/B high-grade B-cell lymphoma/leukemia identified at M.D. Anderson Cancer Center.

| *Case* | *A/G* | *BM* | *Extramedullary sites* | *Therapy* | *Follow-up (mo.)* | *Histology* | *CD10* | *BCL-2* | *Ki-67* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 54/F | - | Small intestine | R-CHOP<br>RICE<br>R-HCVAD | A (7) | DLBCL | + | + | 95 |
| 2 | 54/M | - | Lung, chest wall, testis | R-CHOP<br>R-ESHAP | D (10) | DLBCL | + | + | 95 |
| 3 | 64/M | + | – | HCVAD | D (81) | DLBCL | ND | + | 90 |
| 4 | 29/M | + | – | R-CHOP<br>RICE<br>R-HCVAD | D (5) | BL | + | + | 99-100 |
| 5 | 72/M | + | – | R-HCVAD | A (11) | BL | + | + | 99-100 |
| 6 | 50/F | + | – | R-HCVAD | D (3) | BL | + | + | 95 |
| 7 | 32/M | + | Mesenteric LN | HCVAD | D (8) | BL | + | + | 95 |
| 8 | 67/M | + | Pelvic LN, small intestine | R-HCVAD<br>Velcade | D (9) | BLL | + | + | 70 |
| 9 | 61/M | + | Retroperitoneal LN, colon, prostate | HCVAD<br>MOAP | D (9) | BLL | ND | + | 80 |
| 10 | 42/F | + | Small intestine, omentum, breast | ProMACECytaBOM<br>CHOP, ESHAP<br>H-CVAD, BMT, RT | D (12) | BLL | + | + | 90 |
| 11 | 63/M | + | Testis, lip | Magrath regimen<br>CHOP, DT-PACE<br>HCVAD | D (18) | BLL | + | + | 95 |
| 12 | 55/M | | Ileocecal valve | H-CVAD | A (5) | BLL | ND | + | 99-100 |
| 13 | 65/M | u | Inguinal and cervical LN | R-CHOP<br>HCVAD + SCT | D (7) | BLL | + | – | 100 |
| 14 | 77/M | – | Cervical LN | R-CHOP | Lost | BLL | + | + | 100 |
| 15 | 43/M | – | Cervical LN | R-HCVAD | A (6) | BLL | + | – | 100 |
| 16 | 42/M | + | – | R-HCVAD | Lost | BLL | + | ND | ND |
| 17 | 45/M | + | Abdominal LN | R-HCVAD | A (1) | BLL | – | + | 100 |
| 18 | 64/M | + | – | R-HCVAD | A (2) | BLL | + | + | 90 |
| 19 | 58/M | + | Testicle<br>Kidney,<br>Inguinal LN | R-CODOX-M<br>+ IVAC | A (21) | BLL | + | + | 99-100 |
| 20 | 58/M | – | Cervical LN | R-CHOP | A (21) | DLBCL + FL | + | ND | ND |
| 21 | 58/M | u | Abdominal LN | U | Lost | DLBCL + FL | + | + | 90 |
| 22 | 53/M | + | Inguinal LN | RFND<br>R-Cytoxan+Paxil | A (2) | DLBCL + FL | + | + | 90 |
| 23 | 72/M | u | Abdominal L | U | Lost | DLBCL | + | + | 60 |

*R: Rituximab; RICE: rituximab, ifosfamide, carboplatin, and etoposide; HCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with cytarabine and methotrexate; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone Magrath regimen: cyclophosphamide, doxorubicin, vincristine, prednisone, high-dose methotrexate alternating with ifosfamide, VP-16, high dose cytarabine and intrathecal methotrexate; MOAP, PEG-asparaginase, vincristine, methotrexate, prednisone; CODOX-M+ IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate + ifosfamide, mesna, etoposide, cytarabine; ProMACE-CytaBOM: prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, leomyecin, vincristine, methotrexate, leucovorin ESHAP: methylprednisone, etoposide, cisplatin, cytarabine; DT-PACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; RFND: rituxan, fludarabine, nitoxantrone, dexamethasone, SCT: stem cell transplantation Highlighted cases had concurrent or prior FL. LN: lymph node, U: unknown. ND: not done, A: alive; D: dead. Cases 1-12 have been reported previously.*[8]

These gene expression profiling results challenge the current diagnostic scheme of BL presented in the WHO classification and have implications for daily clinical practice. First, pathologists have been reluctant to designate a M/B high-grade Bcell lymphoma/leukemia as BL because of the presence of the t(14;18) and expression of BCL2. Since BL is treated differently from other tumors and requires more aggressive treatment, not using the term BL could potentially result in undertreatment in patients who require more aggressive therapy.

Secondly, M/B high-grade B-cell lymphoma/leukemia tumors histologically often most closely resemble DLBCL. As currently defined, DLBCL is a heterogeneous disease that encompasses several morphologic variants

as well as clinical subtypes. In an attempt to define prognostically meaningful groups, gene expression profiling has identified two major subgroups: germinal center B-cell (GCB) and non-GCB, the latter including an activated B-cell (ABC) group and a more poorly defined subset.[45] The 5-year survival of patients with GCB tumors is 73% compared with 15% for non-GCB tumors. As gene expression profiling is not available for routine diagnosis, a panel of monoclonal antibodies, including those specific for CD10, BCL6 and MUM1/IRF4, has been suggested as a surrogate to aid in sub-classification.[46] The t(14;18) is primarily found in DLBCL of the GCB type, but not in the ABC type.[45] Although, there is no consensus as to the value of the t(14;18) in predicting prognosis, t(14;18)-positive DLBCL is somewhat unique[47,48] Compared with its t(14;18)-negative counterpart within the GCB subgroup, the t(14;18)-positive group is significantly more likely to express markers such as BCL2 (88% versus 24%), and CD10 (72% versus 32%) and overexpression of *BCL2*-related genes is the dominant feature. M/B high-grade B-cell lymphoma/leukemia typically has a GCB immunophenotypic profile and, therefore, a favorable outcome might be predicted. However, the prognosis of patients with these neoplasms is poor, presumably because the presence of 8q24/*MYC* rearrangement obliterates the prognostic value of the GCB immunophenotype.

Thirdly, although gene expression profiling has improved diagnostic precision, some high-grade B-cell lymphomas are borderline cases that still cannot be definitively categorized as BL or non-BL. Furthermore, molecular profiling is not routinely available currently. Thus, it appears that proper classification of M/B high-grade B-cell lymphoma leukemia will remain challenging. In our previous publication, we tried to emphasize that these tumors have morphologic features that range from typical BL to atypical BL to DLBCL, but that they all have a poor prognosis. Although the study by Le Gouill and colleagues,[7] published in this issue of the journal, suggests that most of their tumors resemble DLBCL, some of their cases had features of atypical BL and the prognosis of their group was similarly poor. Thus, the same message is being conveyed: proper identification of cases of M/B high-grade B-cell lymphoma/leukemia is important and the use of ancillary studies to establish this diagnosis is currently mandatory. It seems reasonable to consider that all high grade B-cell lymphomas with a high proliferation index are candidates for cytogenetic, FISH, or molecular analysis for the presence of the 8q24/*MYC* rearrangement and t(14;18)/*BCL2-IGH*.

In summary, most tumors with the t(14;18) and 8q24/*MYC* rearrangement fall into a morphologic spectrum with features more akin to either BL or DLBCL or something in between. A subset of cases may present with prior or concurrent FL; in these cases, the 8q24/*C-MYC* gene arrangement is thought to arise as a result of clonal evolution and disease progression. Cytogenetic analysis invariably reveals a complex karyotype. Regardless of their histologic classification, and despite their GCB immunophenotype, these tumors are clinically aggressive and affected patients have a poor prognosis.

Therapy for patients with M/B high-grade B-cell lymphoma/leukemia is currently problematic. Although the use of short intensive chemotherapy for adults with BL has resulted in complete remission and overall survival rates of 75-90% and 50-70%, respectively,[49,50] the use of these regimens in patients with M/B high-grade B-cell lymphoma/leukemia has not reproduced the success seen in patients with BL. Innovative therapeutic approaches are clearly needed.

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