Aggressive B-Cell Lymphomas With Translocations Involving BCL6 and MYC Have Distinct Clinical-Pathologic Characteristics

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Key Words: Double hit; Lymphoma; MYC; BCL6; Burkitt; Large B cell; Immunohistochemistry; FISH

ABSTRACT

Objectives: Recently described, aggressive B-cell lymphomas with genetic abnormalities involving MYC and BCL2 have been shown to have a poor prognosis when treated with regimens for diffuse large B-cell lymphomas. Similar data on cases with concurrent MYC and BCL6 translocation are still scant. Moreover, little is known regarding the morphologic and immunophenotypic characteristics of these cases, which further complicates their identification. This study describes six cases of aggressive B-cell lymphoma with translocations involving MYC and BCL6.

Methods: Six cases of large B-cell lymphoma with translocation involving MYC and BCL6 confirmed by fluorescence in situ were identified. The morphologic, immunophenotypic, and clinical features of the cases were examined.

Results: All the patients were older women, and in 50% of cases, the presentation was extranodal. In two cases, the liver was involved at presentation. A starry-sky pattern was a constant feature of the cases in which the morphology could be reliably assessed. Five of six cases had an immunophenotype corresponding to the germinal center B cells, and only one was positive for BCL2, an immunophenotype reminiscent of that of Burkitt lymphoma.

Conclusions: B-cell lymphomas with translocations involving MYC and BCL6 have morphologic and immunophenotypic features suggestive of Burkitt lymphoma or gray zone lymphoma, and they tend to be diagnosed mainly in women, often in extranodal locations.
between BL and DLBCL.\textsuperscript{6,7} Interestingly, most of these cases had morphologic and immunophenotypic features similar to those of the cases that historically have been difficult to classify. Moreover, a significant subset of these cases harbored translocations involving MYC, sometimes associated with BCL2 or BCL6 translocations.\textsuperscript{6,7} This finding led to the proposal that the classification of lymphomas includes a new category, that of a B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (gray zone lymphoma).\textsuperscript{1} Cases in this category have intermediate morphologic and immunophenotypic features and in many cases harbor genetic abnormalities, including translocations involving MYC.

In BL, the MYC translocations are part of a relatively simple karyotype,\textsuperscript{8} but in gray zone lymphomas and in DLBCLs, these cases are often accompanied by multiple other abnormalities, most often involving BCL2 and/or BCL6.\textsuperscript{1,6,7,9-11} When not accompanied by abnormalities involving MYC, translocations involving BCL6 have been detected in approximately 10% to 30% of DLBCL cases.\textsuperscript{9,12,13} In cases with translocations involving MYC, the BCL6 translocations have been reported in approximately 10% of cases, in contrast to the more frequent translocations involving BCL2, detected in up to 57% of cases.\textsuperscript{5} According to the World Health Organization (WHO) 2008 classification, most of these “double-hit lymphomas” are included in the gray zone lymphoma category.\textsuperscript{1}

The morphologic and prognostic characteristics of lymphomas with translocations involving MYC and BCL2 have been relatively well studied.\textsuperscript{10,13} In contrast, similar data on double-hit cases with abnormalities involving MYC and BCL6 cases have started to emerge only recently and include a very small number of cases.\textsuperscript{1,4} Other recent articles identify such cases in larger series of large B-cell lymphomas, but they do not exhaustively characterize them from a morphologic and immunophenotypic point of view.\textsuperscript{5} We are reporting six additional cases in an attempt to independently validate and expand the findings reported.

Materials and Methods

Case Selection

After approval from the Cleveland Clinic Internal Review Board was obtained, the archives of the fluorescence in situ hybridization (FISH) laboratory were searched for cases on which studies for translocations involving MYC and BCL6 have been performed. Positive cases were selected and their histologic, immunophenotypic, and molecular features were reviewed. When available, the medical history of the cases was retrieved from the electronic medical records.

Immunohistochemistry

Immunohistochemical stains for CD3, CD10, CD20, CD21, CD79a, BCL2, BCL6, Ki-67, MUM1, and MYC were performed, and 4-μm-thick sections of formalin-fixed, paraffin-embedded tissue were stained on automated immunostainers (BenchMark XT or BenchMark Ultra; Ventana Medical Systems [VMS], Tucson, AZ). A biotin/ streptavidin–horseradish peroxidase/diaminobenzidine tetrahydrochloride (DAB) detection kit (iView DAB Detection; catalog No. 760-091; VMS) was used to identify the protein-antibody complexes.

The antibody name, type, manufacturer, and antigen retrieval conditions are listed: CD3, rabbit polyclonal (catalog No. CMC365; CellMarque, Rocklin, CA), CC1 buffer (catalog No. 950-124; VMS) at 95°C for 60 minutes, 1:600, 28 minutes at 37°C; CD10, mouse monoclonal (catalog No. NCL-CD10-270; Novoceastra, Leica Microsystems, Buffalo Grove, IL), incubation in high-pH Tris-EDTA buffer at 95°C for 60 minutes, 1:5, 32 minutes at 37°C; CD20, mouse monoclonal (catalog No. M0755; DAKO, Carpinteria, CA), CC1 buffer at 95°C for 30 minutes, 1:25, 60 minutes at 42°C; CD21, mouse monoclonal (catalog No. M0784; DAKO); Protease 2 (catalog No. 760-2019; VMS) for 12 minutes, 1:10, 32 minutes at 37°C, followed by amplification with the Ventana Amplification Kit (catalog No. 760-080; VMS); CD79a, mouse monoclonal (catalog No. M7050; DAKO), CC1 buffer at 95°C for 30 minutes, 1:20, 26 minutes at 37°C; MUM1, mouse monoclonal (catalog No. M7259; DAKO), CC1 buffer at 95°C for 60 minutes, followed by treatment with the Ventana Endogenous Biotin Blocking Kit (catalog No. 760-050; VMS), 1:20, 1 hour at room temperature; BCL2, mouse monoclonal (catalog No. 760-4240; CellMarque), CC1 buffer at 95°C for 60 minutes, manufacturer prediluted mixture, 32 minutes at 37°C; BCL6, mouse monoclonal (catalog No. M7211; DAKO), CC1 buffer at 95°C for 90 minutes, 1:5, 80 minutes at room temperature, followed by amplification with the Ventana Amplification Kit (catalog No. 760-080; VMS); Ki-67, rabbit monoclonal, clone 30-9 (catalog No. 790-4286; VMS), CC1 buffer at 95°C for 30 minutes, manufacturer prediluted mixture, 8 minutes at 37°C; and c-MYC, rabbit monoclonal Y69 (catalog No. ab 32072; Abcam, Cambridge, MA), CC1 buffer at 95°C for 30 minutes, 1:50 for 32 minutes at room temperature.

Cases were reported as positive for BCL2 or BCL6 if more than 25% of neoplastic cells were positive at an intensity significant above the background. In our laboratory, the cases for c-MYC are reported either as a percentage of positive cells or as negative when less than 10% of cells are positive. Cases with more than 30% positive cells are further investigated by FISH.
Chromogenic In Situ Hybridization for Epstein-Barr Virus–Encoded Small RNA

Formalin-fixed, paraffin-embedded tissues were sectioned and stained by use of the Epstein-Barr virus–encoded small RNA DNP probe (VMS).

FISH

FISH for MYC (8q24): slides were baked at 65°C overnight, followed by three immersions in xylene (5 minutes each) and rehydration (final step: immersion in molecular-grade Milli Q water [Millipore, Billerica, MA]). Slides were incubated with a target retrieval solution (catalog No. S1700; DAKO) for 40 minutes at 95°C and then rinsed, followed by incubation with a 1:5,000 dilution of proteinase K solution (in 50 mmol/L Tris-HCl, pH 7.6) at room temperature for 8 minutes. After that the slides were washed and dehydrated in alcohol. Then, 1 μL of the LSI MYC dual-color, break-apart rearrangement probe (catalog No. 05J91-001; Abbott Molecular, Des Plaines, IL) was added to 2 μL of high-performance liquid chromatography water and 7 μL of hybridization buffer (Vysis, Downers Grove, IL). Probe solution was added to each slide, and the slides were sealed and heated to 73°C for 5 minutes and then held at 37°C overnight for hybridization. The coverslips were removed, and slides were incubated in 0.4× SSC/0.3% NP-40 for 2 minutes and then rinsed in 2× SSC/0.1% NP-40 for 3 to 5 seconds. The slides were then counterstained with Vectashield with 4′,6-diamidino-2-phenylindole mounting medium (catalog No. H-1200; Vector Laboratories, Burlingame, CA) and coverslipped. Examination was performed on an Olympus BX40 microscope (Olympus, Tokyo, Japan). Count signals were examined from 200 nonoverlapping nuclei. Cases with more than 10% nuclei positive were called positive.

FISH for BCL2 (18q21): slides were processed identically to those for MYC. Then, 1 μL of the LSI BCL2 dual-color, break-apart rearrangement probe (catalog No. 07175-001; Abbott Molecular) was added to 2 μL of high-performance liquid chromatography water and 7 μL of hybridization buffer (Vysis), followed by processing similar to that for MYC. Signals from 200 nonoverlapping nuclei were examined. Cases with more than 10% nuclei positive were called positive.

FISH for BCL6 (3q27): 1 μL of the LSI BCL6 dual-color, break-apart rearrangement probe (catalog No. 01N23-020; Abbott Molecular) was used. Signals from 200 nonoverlapping nuclei were examined. Cases with more than 10% nuclei positive were called positive.

Results

Patient data and location of lesion at presentation are provided in Table 1. All our specimens originated from female patients aged 56 to 77 years. The neoplasm involved lymph nodes in three cases, the lesion was extranodal but associated with the lymphoid tissue in the nasopharynx in one case, and the neoplasm was diagnosed in the liver in two cases. In all cases, the histologic features were those of an aggressive lymphoma, with a “starry sky” pattern present in four of the six Image 1A (Table 1). In two cases, the pattern of the infiltrate was not reliably assessable due to extensive crush artifact or to the limited size of the biopsy specimen. In two cases, the cells were intermediate sized, with an appearance reminiscent of that of the lymphoma cells in BL Image 1B. In four cases, the cells were large and centroblastic. The mitotic and apoptotic rates were high in all cases (Images 1A
Table I
Clinical, Morphologic, and Immunophenotypic Characteristics

<table>
<thead>
<tr>
<th>Age, y/Sex</th>
<th>Presentation</th>
<th>Bone Marrow Involvement</th>
<th>Starry-Sky Pattern</th>
<th>CD10</th>
<th>BCL2</th>
<th>BCL6</th>
<th>MUM1</th>
<th>e-MYC, %</th>
<th>Germinall Center B-Cell Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>56/F</td>
<td>Nasopharynx</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>60</td>
<td>Yes</td>
</tr>
<tr>
<td>61/F</td>
<td>Cervical lymph node</td>
<td>No</td>
<td>Yes</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>50</td>
<td>Yes</td>
</tr>
<tr>
<td>76/F</td>
<td>Cervical lymph node</td>
<td>NA</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>77/F</td>
<td>Liver</td>
<td>No</td>
<td>Yes</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>60</td>
<td>Yes</td>
</tr>
<tr>
<td>62/F</td>
<td>Liver</td>
<td>No</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>50</td>
<td>No</td>
</tr>
<tr>
<td>64/F</td>
<td>Retroperitoneal lymph node</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>60</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BLU, B-cell lymphoma, unclassifiable with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; –, negative; NA, not available; +, positive; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, doxorubicin, vincristine, etoposide, cyclophosphamide, and prednisone.

and 1B). All cases were positive for BCL6 (Table 1) by immunohistochemistry, and the neoplastic cells were positive for CD10 in three cases (Table 1).

Five of the six cases were negative for MUM1 and according to the algorithm by Hans et al, these five cases had an immunophenotype corresponding to germinal center B cells (Table 1). One case was positive for MUM1 and did not have the germinal center immunophenotype. Ki-67 was detected in more than 90% of the cells in all cases and most cases (five of six) were negative for BCL2 (Table 1). The only case that stained for BCL2 did so with an intensity significantly lower than that usually seen in cases with translocations involving BCL2, since the 60% positive cells showed an average intensity similar to that of intratumoral T cells. By immunohistochemistry, more than 50% of the cells in each case were positive for MYC. In none of the cases were networks of CD21-positive dendritic cells detected (Table 1). FISH with break-apart probes for MYC, BCL2, and BCL6 showed that in all cases, MYC and BCL6 and BCL6 were involved in translocations, while BCL2 was intact. Bone marrow biopsy specimens were available in four cases, and in none did the lymphoma involve the bone marrow.

The original diagnosis was B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL in four cases and that of DLBCL in two cases. Of note, in cases diagnosed as DLBCL, the results of FISH analysis were known only after the cases were signed out. Upon review, there were no consistent morphologic differences between these two cases and the cases diagnosed as gray zone lymphomas.

Data regarding the treatment received were available in four cases (Table 1). Two patients received treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), while two others received treatment with R-EPOCH (rituximab, doxorubicin, vincristine, etoposide, cyclophosphamide, and prednisone). One of the patients with liver presentation died during the initial cycle of chemotherapy as a consequence of renal failure and pancreatitis. One of the patients responded to chemotherapy, and four months later she is alive but has been repeatedly admitted to the hospital due to neutropenic fever and infections. A third patient initially received three cycles of R-EPOCH with methotrexate, followed after a few months by four cycles of R-CHOP and allogeneic bone marrow transplant. Twenty months after the initial diagnosis, she continues to show no evidence of disease. A fourth patient is still receiving chemotherapy (2 months after diagnosis). The outcome of two patients is unknown.

Discussion

To investigate the morphologic, immunophenotypic, and clinical characteristics of double-hit lymphomas with abnormalities involving MYC and BCL6, we identified six cases that by FISH with break-apart probes showed MYC and BCL6 translocations. The partners of translocation were not identified. An interesting finding was the marked female predominance of the patients. While further conclusions cannot be drawn, since the series is relatively small, this is a novel finding. Another unusual finding was the relatively high frequency of liver involvement. There is no clear explanation for this; since hepatic function is routinely interrogated by laboratory tests, this may lead to a higher probability of identification of neoplastic processes involving this organ. The high proportion of cases with extranodal presentation (50%) is in agreement with the impression that these neoplasms are aggressive, with a tendency to spread rapidly. As anticipated, a morphologic aspect consistently associated with an aggressive lymphoma was present in most cases: a starry-sky pattern was encountered in four cases, and two cases had a cellular morphology reminiscent of that of the cells in BL. An interesting finding was the immunophenotype corresponding to the germinal center B cell. While this immunophenotype is usually associated with a favorable prognosis, in our series, this association could not be investigated reliably. However, as highlighted by the morphology and by the extranodal involvement, in double-hit cases, the germinal center B-cell phenotype may not indicate...
Table 1

<table>
<thead>
<tr>
<th>Original Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>BLU</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BLU</td>
<td>R-CHOP</td>
<td>Alive, 2 y</td>
</tr>
<tr>
<td>BLU</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BLU</td>
<td>R-CHOP</td>
<td>Dead, 2 mo</td>
</tr>
<tr>
<td>DLBCL</td>
<td>R-EPOCH</td>
<td>Alive, 6 mo</td>
</tr>
<tr>
<td>DLBCL</td>
<td>R-EPOCH</td>
<td>Alive, 2 mo</td>
</tr>
</tbody>
</table>

There are many common features between our patients and those reported by Pillai et al. Most of our patients and five of six patients reported by Pillai et al had an immunophenotype corresponding to the germinal center B cells. However, in our series, most cases were negative for MUM1, while three of four cases in the previous series were positive. Overall, positivity for CD10 or BCL6 and negativity for BCL2 or MUM1 are the most common combination of markers that characterizes this lesion in our experience. Noticeable differences between our patients and those previously reported are a markedly skewed female to male ratio (6:0) and the even nodal/extranodal presentation in our series.

The classification of the neoplasms with abnormalities including MYC and BCL2, most of our cases were negative for BCL2, which may result in erroneous diagnosis of BL in double-hit cases with intermediate-sized cells.

a favorable prognosis. In contrast with many DLBCLs, BLs, and double-hit lymphomas with translocations involving MYC and BCL2, most of our cases were negative for BCL2, which may result in erroneous diagnosis of BL in double-hit cases with intermediate-sized cells.

The particularities of the double-hit cases with translocations involving BCL6 and MYC are probably at least partially the result of overexpression of the two proteins. Immunohistochemical stains provide evidence that the translocations lead to increased amounts of BCL6 and MYC. In all cases in our series, the two proteins were seen by immunohistochemistry. The roles of MYC have been extensively studied, since it was one of the first proto-oncogenes identified and cloned. It belongs to a family that includes MYCL and MYCN and is located at 8q24. A transcription factor, MYC is expressed starting with early development and is constantly located downstream of many signal transduction pathways such as WNT. Its expression is controlled by CBP, FBP, and TCF, among others. After forming heterodimers with MAX, it binds transcriptional regulator elements, usually located in promoters, or E-boxes (CANNTG) leading to transcriptional regulation. MYC recruits additional proteins involved in transcriptional regulation and in the control of the structure of chromatin, such as TBP, TRRAP, GCN5, TBP, histone acetyltransferases, ChREBP, SREBP, HIF, and NRF1, leading to modification of the structure of chromatin and recruiting of polymerase II complexes. In consequence, MYC is involved in the expression control of up to 10% of all human genes. Experimental data indicate that in addition to gene activation, MYC may play a role in the transcriptional repression of at least a few genes such as CDKN2B and E2F1, probably through the recruitment of histone deacetylases. Many of the genes controlled by MYC are involved in cell growth, proliferation, and regulation of metabolism. MYC controls the transition from the G0 to S phase, through activation of CCND2 and CDK. It can induce apoptosis, probably through downregulation of BCL2 and BCL-XL and through upregulation of BIM. Recently, MYC has been shown to have similar effects on microRNAs (miRNAs) such as miR-15a, miR-26a, and miR-29. A group of 50 MYC-controlled genes have been studied and consistently identified in malignant processes and in embryonic stem cells. The ability of MYC to transform normal cells and its role in tumorigenesis have been widely studied. In addition, recent experiments have shown that MYC is one of the few transcription factors necessary in the reprogramming of mature cells to pluripotent stem cells.

BCL6 encodes a transcriptional repressor and is located at 3q27. It is a member of the BTB/POZ family of transcription factors and is normally expressed in the germinal center B cells and in subsets of follicular helper T cells and natural killer cells. Expression of BCL6 is mediated and induced morphology, with the hope that these cases are targeted for a different therapeutic approach than that which has been proven ineffective. Similar data for double-hit lymphomas positive for MYC and BCL6 are scarce, but these cases appear to have a similarly poor prognosis.

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by IRF8, while proliferating B cells in the germinal centers require the IL-21 receptor to maintain BCL6. BCL6 enables the proliferation of B cells in the germinal center through repression of ATR, TP53, CDKN1A, and EP300. It prevents premature terminal differentiation of these cells by repressing terminal differentiation factors IRF4 and PRDM1. As B cells exit germinal centers, expression of IRF4 and PRDM1 results in the downregulation of BCL6.\textsuperscript{20}

These insights into their functions suggest that MYC and BCL6 may affect the neoplastic cells in different ways. MYC may induce these cells to proliferate, while BCL6 allows them to survive despite DNA damage by repressing apoptosis-inducing mechanisms. Whether this is a mechanism normally present in germinal center B cells or whether this happens exclusively in malignant cells is unclear. Also, there is no extensive information regarding the coexpression of these proteins in neoplasms other than B-cell lymphomas. It would be interesting to see if other hematolymphoid neoplasms with cells of origin associated with the germinal centers, such as angioimmunoblastic T-cell lymphoma, also express an increased amount of MYC and BCL6.

In conclusion, we confirm that the double-hit B-cell lymphomas with translocations involving \textit{BCL6} and \textit{MYC} are an aggressive category of neoplasms, with an immunophenotype corresponding to the germinal center. Since the morphology and the immunophenotype are reminiscent but not always identical to those of BL, classifying these neoplasms as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL appears to be justified. This distinction between the double-hit lymphomas and
Image 2I (cont) E, No networks of follicular dendritic cells are detected (CD21, ×20). F, Less than 10% of neoplastic cells are positive for MUM1 (×20).

Image 3I A, MYC break-apart probes, ×100. Yellow signals correspond to the intact, nontranslocated MYC locus, while separate red and green signals indicate a translocation. B, BCL6 break-apart probes, ×100. Interpretation similar to that for the MYC probes. C, BCL2 break-apart probe, ×100. All cells show only yellow signals.
DLBCL may also be necessary from a therapeutic point of view, since patients with these neoplasms may benefit from treatment regimens different from those for BL or DLBCL.

References


