Primary High-Grade B-Cell Lymphoma of the Breast with Concurrent IGH-BCL2 and MYC-IGL Translocations in an Adolescent Patient

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ABSTRACT

BCL2 and MYC are oncogenes often deregulated in lymphomas. Concurrent IGH-BCL2 and MYC translocations result in a highly aggressive behavior of these tumors. Both primary breast lymphoma and lymphoma with concurrent BCL2-IGH and MYC translocations are rare and are primarily seen in adult patients. As a result of limited clinician experience and the condition’s rarity, it poses a great challenge to pediatric pathologists and oncologists in terms of making an accurate diagnosis and choosing better treatment regimens. In this article, we report a case of an adolescent patient who presented with high-grade breast lymphoma with concurrent BCL2-IGH and MYC-IGL translocations, and we review the clinical, pathological, and genetic features; management strategies; and outcomes associated with this unusual neoplasm.

Key words: B-cell lymphoma, BCL2, breast lymphoma, lymphoma, MYC

INTRODUCTION

The t(14;18)(q32;q21) is the genetic hallmark of follicular lymphoma (FL) in adults [1]. It is also present in adolescent patients but is generally not seen in pediatric patients younger than the age of 13 years [2]. This translocation results in the juxtaposition of BCL2/18q21 gene with the immunoglobulin (IG) heavy-chain (IGH) locus. Similarly, translocations involving the MYC/8q24 gene and IG partners, including IGH, IGK, and IGL, are considered genetic hallmarks of Burkitt lymphoma/leukemia (BL) [3,4]. Both BCL2 and MYC translocations are also found in a subset of cases of diffuse large B-cell lymphoma (DLBCL) [1,5]. B-cell lymphomas with concurrent IGH-BCL2 and MYC translocations are uncommon. These neoplasms are characterized by highly aggressive clinical behavior, complex karyotypes, and a broad morphologic and immunophenotypic spectrum that overlaps with BL and DLBCL and occasionally precursor B-lymphoblastic lymphoma/leukemia (PBL) [4].

Primary breast lymphoma is rare and constitutes less than 1% of all patient diagnoses with non-Hodgkin lymphoma [6]. The incidence of primary breast lymphoma combined with dual IGH-BCL2 and MYC translocations is exceedingly low [7]. As a consequence of their rarity and patients’ poor response to therapy, the diagnosis and classification as well as the selection of appropriate treatment are challenging. Here we report a case of primary breast lymphoma with concurrent IGH-BCL2 and MYC-IGL translocations in an adolescent patient, and we review the literature to help better recognize and characterize this uncommon tumor.

CASE REPORT

A 19-year-old female presented with a left breast mass that had grown rapidly over a 2-week period. She did not have night sweats or weight loss. Physical examination and mammogram confirmed the left breast mass. Magnetic resonance imaging demonstrated a lesion of her right breast. A biopsy of the left breast mass revealed a lymphomatous infiltrate. The patient was transferred to The Children’s Hospital. Computed tomography showed multiple masses of the bilateral breast (Fig. 1A) and axillary and left supraclavicular lymphadenopathy. Review of the breast biopsy at The Children’s Hospital showed that the
Table 1. Clinicopathologic features of high-grade B-cell lymphoma/leukemia with BCL2-IGH and MYC translocations in adolescent patients

<table>
<thead>
<tr>
<th>Case no./A/S Tumor sites</th>
<th>Histology</th>
<th>Immunophenotype</th>
<th>Mib-1 (%)</th>
<th>Karyotype</th>
<th>FISH</th>
<th>Treatment and outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/19/F</td>
<td>Dx: breasts, lymph nodes, bone</td>
<td>Precursor B-lymphoblastic lymphoma</td>
<td>&gt;90</td>
<td>Dx: 49,X,X,+1i(1)(q10),del(5)(p1),del(6)(p13q21),+7,+der(8)(p21)</td>
<td>MYC+, MYC−, IGL+, IGH-BCL2+</td>
<td>Dx: AALL0232 (COG) protocol, CR</td>
<td>Current patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dx: CD34−,TdT+, CD10−CD19+, CD20+CD79a+, PAX5+BCL2+BCL6−, CD30−CD3−κ−λ−</td>
<td></td>
<td>del(9)(p13), add(13)(p11), t(14;18)(q23q21), der(14)(14;18), +mar[10]</td>
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<tr>
<td></td>
<td></td>
<td>1st relapse: TdT+, CD10−CD20+BCL2+κ−λ−</td>
<td></td>
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<tr>
<td></td>
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<td>2nd relapse: breast, lymph nodes, bone</td>
<td></td>
<td></td>
<td></td>
<td>2nd relapse: 46−50,XX, +1i(1)(q10), add(2)(p13), del(6)(p13q21), +8,del(8)add(8)(p21)</td>
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<tr>
<td></td>
<td></td>
<td>2nd relapse: breast, lymph nodes, bone</td>
<td></td>
<td></td>
<td></td>
<td>2nd relapse: 46−50,XX, +1i(1)(q10), add(2)(p13), del(6)(p13q21), +8,del(8)add(8)(p21)</td>
<td></td>
</tr>
<tr>
<td>2/15/M</td>
<td>Peripheral blood, bone marrow</td>
<td>Precursor B-lymphoblastic leukemia</td>
<td>ND</td>
<td>46,XY,(8;14)(q24q32), t(14;18)(q21q32)</td>
<td>ND</td>
<td>Daunomycin, vincristine, cyclophosphamide, steroid, CR, relapsed 5 mo later</td>
<td>11</td>
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<tr>
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<td></td>
<td>HLA-DR+,TdT+,CD10+,CD3−CD4−CD8−clgM−</td>
<td></td>
<td></td>
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<td>DOD in a few days</td>
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<tr>
<td>3/15/M</td>
<td>Lymph nodes</td>
<td>B-cell lymphoma, CD10−CD20+BCL2+, BCL6−MUM1−</td>
<td>80</td>
<td>Not available</td>
<td>MYC+, BCL2−/IGH+</td>
<td>HCVAD, alive at 18 mo</td>
<td>12</td>
</tr>
</tbody>
</table>

A indicates age (in years); BL, Burkitt lymphoma/leukemia; COG, children oncology group; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DOD, died of disease; Dx, at diagnosis; F, female; FISH, fluorescence in situ hybridization; HCVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HSCT, hematopoietic stem cell transplant; ICE, ifosfamide, carboplatin, and etoposide; M, male; mo, month(s); ND, not done; PW, partially well; S, sex; TdT, terminal deoxynucleotidyl transferase; +, positive; −, negative.
Figure 1. A. Computed tomography showed bilateral breast masses. B. The tumor cells were homogeneous and exhibited high nuclear cytoplasmic ratio, scanty cytoplasm, finely dispersed chromatin, and distinct nucleoli (hematoxylin and eosin [H&E], ×400). C-D. The tumor cells immunohistochemically expressed terminal deoxynucleotidyl transferase (×400) (C) and BCL2 (×400) (D), respectively. E. Cytogenetic karyotype showed the tumor cells carrying both t(14;18)(q32;q21) (blue arrows) and t(8;22)(q24;q11) (red arrows). The uncolored arrows point to i(1)(q10), add(2)(p13), del(6)(q21q23), add(8)(p21).
tumor cells had lymphoblastic features (Fig. 1B). Immunohistochemical stains of the tumor cells were positive for terminal deoxynucleotidyl transferase (TdT) (Fig. 1C), CD10, CD45, CD79a, and BCL2 (Fig. 1D) and negative for CD3, CD20, CD34, and cytokeratin. Mib-1 was positive in more than 90% of tumor cells. kappa and lambda light chains were not detected by either in situ hybridization (at diagnosis) or flow cytometric analysis (at relapse).

The cytogenetic analysis of the breast biopsy revealed a complex karyotype with t(8;22)(q24;q11) and t(14;18) (q32;q21) (Fig. 1E). Fluorescence in situ hybridization confirmed IGH-BCL2 (Fig. 1F, left), MYC (Fig. 1F, right), and MYC-IGL rearrangements. The bone marrow (BM) and cerebrospinal fluid were unremarkable. A diagnosis of PBLL with concurrent IGH-BCL2 and MYC-IG rearrangements was made. The patient was treated according to the AALL0232 COG (Children Oncology Group) protocol for high-risk PBLL and initially showed a nice response.

At the completion of interim maintenance, 6 months following the initiation of therapy, a new mass of the left breast was found on her physical examination. A positron emission tomography performed shortly thereafter showed tumor spread with right breast mass and increased activity in an axillary lymph node and mid-umbilical marrow. Repeat biopsy of the left breast mass revealed a recurrent tumor with expression of CD20. The patient received Rituximab with ifosfamide, carboplatin, and etoposide therapy and attained a 2nd complete remission. Consolidation of remission was performed with myeloablative preparative chemotherapy followed by allogeneic cord blood hematopoietic stem cell transplant (HSCT). One month post-HSCT, the patient relapsed with bilateral disease for the 2nd time. She was treated with breast radiation for local control and with cyclophosphamide, intrathecal cytarabine, and vincristine, alternating with vincristine, followed by deacron for systemic control. One month later, the tumor cells were found in her blood and BM. Other therapies were considered too toxic but she continued on dexamethasone and died of the disease 1 month later, 13 months from diagnosis.

DISCUSSION

High-grade B-cell lymphoma with concurrent IGH-BCL2 and MYC translocations are heterogeneous in clinical presentation, morphology, immunophenotype, and outcome [8]. Clinically, these neoplasms fall into 2 general categories: de novo or following a history of FL [4]. In the adult literature [4,9], most reported cases belong to the de novo category (about 78%). The disease usually presents at an advanced stage, with a propensity for extranodal involvement (BM, central nervous system [CNS], blood, and pleural effusion) [4,10]. In addition to the patient described here, only 2 cases of adolescent patients with B-cell lymphoma carrying dual IGH-BCL2 and MYC translocations are noted in the literature [11,12] (Table 1). In accordance with adult data, all 3 cases of adolescent patients presented de novo. Two patients (cases 1 and 2) with extranodal diseases had BM and blood involvement. None of them had CNS disease or pleural effusion. These 2 patients underwent aggressive clinical courses with early and/or multiple relapse(s) and short time survival. The 3rd patient (case 3) only had nodal disease and achieved a complete remission for 18 months.

Pathologically, cases with concurrent IGH-BCL2 and MYC lymphoma/leukemia show a spectrum of morphology and immunophenotype, rendering recognition and classification of these tumors challenging. The cellular morphology varies from a monomorphous cell population closely resembling BL to one with a more pleomorphic appearance resembling DLBCL, features overlapping between BL and DLBCL, or lymphoblastic morphology. Cases presenting primarily as extramedullary lesions have been classified as BL, atypical BL, Burkitt-like lymphoma, or DLBCL with high-grade features [4,9,13]. Cases presenting primarily as a leukemic process have been classified as pre-B (surface light chain [sLgL]−, TdT−) or mature B-cell (sLgL+, TdT+) acute lymphoblastic leukemia (ALL), with the blasts showing cytologic features along the L1–L3 spectrum defined by the French-American-British (FAB) classification [4]. Immunophenotypically, unlike classical BL (CD10+, CD20−, CD38−, BCL2−, BCL6+, Mib-1 > 95%), most cases with double IGH-BCL2 and MYC translocations are CD10+, CD20+, CD38+, BCL2+, and BCL6+ [13,14]. The Mib-1 proliferation index ranges from 60% to 100% [4,10]. Given that (1) these tumors are positive for BCL2, (2) the Mib-1 index is high, and (3) morphologic appearances and genetic profiles are not typical for BL, but frequently overlap between DLBCL and BL, the 2008 World Health Organization classification recommended classifying these cases into a new proposed category, “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL” [13]. The classification of tumors with positive TdT, negative sLgL, and BCL2-MYC rearrangement is controversial, and the diagnosis of lymphoblastic lymphoma/leukemia generally is preferred [13].

There have been rare pediatric cases of precursor B-lymphoblastic leukemia by immunophenotype (CD34+, TdT+, sLgL−), FAB L3 morphology, and IGH-MYC t(8;14)(q24;q32) in the literature [15]. Because of discrepancies between immunophenotype, morphology, and genetic findings, the treatment strategies are controversial. These patients generally responded poorly to ALL therapy and better with BL therapy [15]. In our case, although the tumor cells at relapses revealed an appearance similar to L3 morphology, the Wright Giemsa–stained cytology was unavailable in the untreated tumor. Unlike our case, none of those reported cases carried IGH-BCL2 translocation.

and del(9)(p13q22), respectively. F. Left: Fluorescence in situ hybridization (FISH) revealed IGH-BCL2 rearrangement with split signals (G, green; R, red) in the arrow-pointed cells. Right: FISH revealed MYC rearrangement with split signals in the arrow-pointed cells.
Cases of concurrent IG-H-BCL2 and MYC lymphoma/leukemia often carry a complex karyotype, and BCL2 and MYC abnormalities comprise part of the multiple aberrations [4]. In some cases with history of FL and in a transgenic mouse experiment, IG-H-BCL2 translocation occurring before MYC-IG translocation has been documented by fluorescence in situ hybridization study [16, 17]. These observations indicate that the acquisition of secondary MYC rearrangement coincides with progression from indolent lymphoma to aggressive lymphoma and, therefore, cooperation of BCL2 and MYC contribute to multisite lymphomagenesis. On the other hand, the fact that a number of cases in the de novo category presented as acute onset and leukemia indicates that both IG-H-BCL2 and MYC rearrangement can occur simultaneously in at least a subset of these neoplasms [4].

Blast lymphoma, occurring either as a manifestation of primary extranodal disease or as secondary involvement by systemic disease, is a rare malignancy. It predominantly occurs in adults. In reviewing the literature, we have observed the following features: (1) primary blast lymphoma is outnumbered by secondary blast involvement by leukemia or systemic lymphoma [7, 18, 19] and (2) DLBC is the most common subtype in adult patients [7, 18], while PLL is most common in pediatric/adolescent group [19]. Although blast lymphoma tends to occur in younger patients, to be large in size and fast growing, and to have no calcifications in imaging studies, there is no consensus with regard to distinguishing features between blast lymphoma and other blast malignancies [6]. The main histological differential diagnosis in pediatric and adolescent patients includes rhabdomyosarcoma and neuroblastoma in addition to breast carcinoma. The uniqueness of our case lies in the combined presence of 2 uncommon lymphoma conditions, primary blast location and concurrent IG-H-BCL2 and MYC translocations at an adolescent age. It seems reasonable to consider that high-grade B-cell lymphoma in pediatric/adolescent patients with an unusual presentation is a candidate for genetic investigation for the presence of IG-H-BCL2 and MYC translocations.

The prognosis of lymphoid neoplasm with dual IG-H-BCL2 and MYC translocations is extremely poor. Most patients died within 1 year of the diagnosis in spite of aggressive chemotherapy. Extramedul involvement, a transient response to chemotherapy, repeated relapses, and frequent CNS progression were characteristic of this disease [16]. Currently, there is no consensus on the optimum treatment. High-dose chemotherapy based on the type of lymphoma with the addition of Rituximab for CD20-expressing lymphoma followed by HSCT should be considered for these patients [4, 16]. In our case, the patient was treated in accordance with the COG protocol for ALL based on blast morphology and TdT expression of the tumor cells.

Development of CD20 expression during her 1st relapse made the patient eligible for Rituximab treatment in addition to HSCT and chemotherapy. The response was temporary, and the tumor relapsed again. Breast radiation therapy was given for local tumor control, but the tumor spread widely, and the patient died of disease within 15 months of the initial diagnosis. To develop an optimal and effective therapeutic approach for this disease requires collection of more data through multi-institutional cooperation.

REFERENCES