Transformation of Follicular Lymphoma to a High-Grade B-Cell Lymphoma With MYC and BCL2 Translocations and Overlapping Features of Burkitt Lymphoma and Acute Lymphoblastic Leukemia: A Case Report and Literature Review

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ABSTRACT: Most commonly, histologic transformation (HT) from follicular lymphoma (FL) manifests as a diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Less frequently, HT may result in a high-grade B-cell lymphoma (HGBL) with MYC and B-cell lymphoma protein 2 (BCL2) and/or BCL6 gene rearrangements, also known as “double-hit” or “triple-hit” lymphomas. In the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms, the category B-cell lymphoma, unclassifiable was eliminated due to its vague criteria and limiting diagnostic benefit. Instead, the WHO introduced the HGBL category, characterized by MYC and BCL2 and/or BCL6 rearrangements. Cases that present as an intermediate phenotype of DLBCL and Burkitt lymphoma (BL) will fall within this HGBL category. Very rarely, HT results in both the intermediate DLBCL and BL phenotypes and exhibits lymphoblastic features, in which case the WHO recommends that this morphologic appearance should be noted. In comparison with de novo patients with DLBCL, NOS, those with MYC and BCL2 and/or BCL6 gene rearrangements have a worse prognosis. A 63-year-old woman presented with left neck adenopathy. Laboratory assessments, including complete blood count, complete metabolic panel, serum lactate dehydrogenase, and β2-microglobulin, were all normal. A whole-body computerized tomography (CT) scan revealed diffuse adenopathy above and below the diaphragm. An excisional node biopsy showed grade 3A nodular FL. The Ki67 labeling index was 40% to 50%. A bone marrow biopsy showed a small focus of paratrabecular CD20+ lymphoid aggregates. She received 6 cycles of bendamustine (90 mg/m² on days +1 and +2) and rituximab (375 mg/m² on day +2), with each cycle delivered every 4 weeks. A follow-up CT scan at completion of therapy showed a partial response with resolution of axillary adenopathy and a dramatic shrinkage of the large retroperitoneal nodes. After 18 months, she had crampy abdominal pain in the absence of B symptoms. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT (18F-FDG PET/CT) scan showed widespread adenopathy, diffuse splenic involvement, and substantial marrow involvement. Biopsy of a 2.4-cm right axillary node (SUVmax of 16.1) showed involvement by grade 3A FL with a predominant nodular pattern of growth. A bone marrow biopsy once again showed only a small focus of FL. She received idelalisib (150 mg twice daily) and rituximab (375 mg/m², monthly) beginning May 2015. After 4 cycles, a repeat CT scan showed a complete radiographic response. Idelalisib was subsequently held while she received corticosteroids for immune-mediated colitis. A month later, she restarted idelalisib with a 50% dose reduction. After 2 weeks, she returned to clinic complaining of bilateral hip and low lumbar discomfort but no B symptoms. A restaging 18F-FDG PET/CT in January 2016 showed dramatic marrow uptake. A bone marrow aspirate showed sheets of tumor cells representing a spectrum from intermediate-sized cells with lymphoblastic features to very large atypical cells with multiple nucleoli. Two distinct histologies were present; one remained consistent with the patient’s known FL with a predominant nodular pattern and the other consistent with HT (the large atypical cells expressed PAX5, CD10, BCL2, and c-MYC and were negative for CD20, MPO, CD34, CD30, and BCL6). Focal areas showed faint, heterogeneous expression of terminal deoxynucleotidyl transferase best seen on the clot section. Ki67 proliferation index was high (4+/4). Fluorescence in situ hybridization analysis showed 2 populations with MYC amplification and/or rearrangement and no evidence of BCL6 rearrangement; a karyotype analysis showed a complex abnormal female karyotype with t(14;18) and multiple structural and numerical abnormalities. She started dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with concomitant prophylactic intrathecal methotrexate and cytarabine. She had but a short-lived response before dying in hospice from progressive lymphoma. Whether idelalisib could provide a microenvironment for selection of more aggressive clones needs to be addressed. Our patient’s clinical course is confounded by the incorporation of idelalisib while being further complicated by the complexity of HT and the mechanisms in which first-line chemotherapy regimens affect double-hit lymphoma.

KEYWORDS: Follicular lymphoma, histologic transformation, double-hit lymphoma, MYC gene translocation, BCL2, idelalisib

Follicular lymphoma (FL), the most common type of indolent non-Hodgkin lymphomas (NHL), often presents with generalized adenopathy and is characterized by a variable clinical course. Follicular lymphoma arises from germinal center lymphocytes and typically overexpresses B-cell lymphoma protein 2 (BCL2), a regulatory protein associated...
with cell death (apoptosis) by either inducing (proapoptotic) or inhibiting (antiapoptotic) programmed cell death. The t(14;18)(q32;q21) chromosome translocation represents the defining cytogenetic hallmark of FL and is seen in 80% to 90% of cases. It effectively juxtaposes the BCL2 proto-oncogene with enhancer sequences of the immunoglobulin heavy chain gene (IgH) promoter region. The deregulation of this promoter region results in overexpression of Bcl-2 in neoplastic follicles. About 5% to 15% of FLs have abnormalities at 3q27 and/or BCL6 gene rearrangements, most commonly in grade 3B cases.

The histologic transformation (HT) of indolent lymphoma through somatic hypermutations to a more high-grade NHL is commonly defined by an increase in the proportion of large cells diffusely infiltrating lymph nodes and bone marrow, leading to effacement of the follicular architecture and crowding of normal marrow reserves. The HT of FL to an aggressive form of NHL occurs at a constant rate of 2% to 3% per year from diagnosis of FL and is typically associated with a poor clinical outcome. Despite the availability of combination chemotherapy and immunotherapy, the median survival following HT is 1.7 years.

Most commonly, HT from FL manifests as a diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Less frequently, HT may result in a high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 gene rearrangements, also known as “double-hit” or “triple-hit” lymphomas. In the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms, the category B-cell lymphoma, unclassifiable was eliminated due to its vague criteria and limiting diagnostic benefit. Instead, the WHO introduced the high-grade B-cell lymphoma (HGBL) category, characterized by MYC and BCL2 and/or BCL6 rearrangements. Cases that present as an intermediate phenotype of DLBCL and Burkitt lymphoma (BL) will fall within this HGBL category.

In extremely rare cases, HT results in both the intermediate DLBCL and BL phenotypes and exhibits lymphoblastic features, in which case the WHO recommends that this morphological appearance should be noted. In comparison with de novo patients with DLBCL, NOS, those with MYC and BCL2 and/or BCL6 gene rearrangements have a worse prognosis despite the benefits of R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, and prednisone) chemotherapy.

We present the case of a patient who experienced HT resulting in FL-derived HGBL with immunohistochemistry features overlapping with BL and acute lymphoblastic leukemia (ALL). Histologic transformation occurred while the patient was receiving idelalisib and rituximab for relapsed FL. We also review the literature regarding the risks and implications of HT of FL to high-grade NHL with a specific focus on Burkitt phenotype and the even more rare ALL variant.

Case Presentation
A 63 year-old Caucasian woman presented to medical attention in March 2012 after she noted a left supraclavicular mass. She had been in good health, save for mild hyperlipidemia, osteopenia, and prolapsed uterus for which she had undergone successful surgical repair. She had no fevers, night sweats, or weight loss. The patient’s family history was notable for a sibling with systemic lupus erythematosus, a paternal aunt previously diagnosed with lymphoma, and a maternal grandmother with Hodgkin disease.

At initial intake, she appeared healthy and somewhat younger than her stated age. Her general examination was remarkable for a left supraclavicular node that measured approximately 2 cm × 2 cm and 2 smaller adjacent neck nodes. She had no additional palpable adenopathy, and her abdomen was soft and without obvious hepatosplenomegaly.

Laboratory assessment included a normal complete blood count (CBC), complete metabolic panel (CMP), and serum lactate dehydrogenase (LDH). β2-Microglobulin level was 1.36 μg/L (normal <2.70 μg/L). Serum protein electrophoresis did not show a monoclonal band, and free serum kappa and lambda light chains were also in the normal range. She was seronegative for hepatitis viruses B and C and for human immunodeficiency virus. A computerized tomographic (CT) scan of the neck, chest, abdomen, and pelvis revealed diffuse adenopathy involving the left neck and supraclavicular fossa, left axilla, as well as the mediastinum and retroperitoneum. The largest of nodal areas measured 6.2 cm × 2.5 cm, and an excisional biopsy of a lymph node from the neck demonstrated grade 3A FL (Figure 1). Immunohistochemistry studies showed that the lymphoma cells stained positive for CD10, CD19, CD20, and Bcl-2 and with moderate monotypic immunoglobulin light chain lambda expression. The Ki67 labeling index was 40% to 50%. A bone marrow biopsy showed a small focus of paratrabecular CD20+ lymphoid aggregates, indicating stage IV disease.

We treated the patient with 6 cycles of bendamustine (90 mg/m² on days +1 and +2) and rituximab (375 mg/m² on day +2), with each cycle delivered every 4 weeks. Chemotherapy side effects were mild and included intermittent nausea, malaise, and rare emesis. A follow-up CT scan at completion of therapy showed a partial response (PR) with resolution of axillary adenopathy and a dramatic shrinkage of the large retroperitoneal nodes. She did not receive maintenance rituximab.

For 18 months she remained well before seeking evaluation of persistent crampy abdominal pain in the absence of fever, night sweats, or weight loss. Laboratory studies, including CBC, CMP, and LDH, were all within normal values. A CT scan showed advancing adenopathy above and below the diaphragm and mild splenomegaly. A subsequent positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT (18F-FDG PET/CT) showed widespread adenopathy with increased uptake in the neck, chest, abdomen,
and pelvis with diffuse splenic involvement and marrow involvement of C2, T10, and L3 vertebral bodies (Figure 2A). A 2.4-cm right axillary lymph node was associated with an SUVmax of 16.1 and on biopsy showed involvement by grade 3A FL and DLBCL with a predominant nodular pattern of growth. A bone marrow biopsy, required for consideration of clinical trial participation, showed, once again, a small focus of FL and no evidence of HT.

The patient was next treated with idelalisib (150 mg twice daily) and rituximab (375 mg/m², monthly) beginning May 2015. After 4 cycles of treatment, a repeat CT scan of the neck, chest, abdomen, and pelvis showed a complete radiographic response. Toward the end of her sixth cycle of chemotherapy, she experienced crampy abdominal pain and secretory diarrhea. She was given antimotility and bulk agents, but her diarrhea persisted. After 3 weeks and after stool studies were collected and proved unremarkable for infectious pathogens, idelalisib was placed on hold and she took prednisone for presumed immune-mediated colitis. Her laboratory studies then were notable only for mild hypokalemia and mild prerenal azotemia. Her diarrhea rapidly resolved and corticosteroids were discontinued after a 3-week course. She was instructed to restart idelalisib with a 50% dose reduction.

After 2 weeks, she returned to clinic complaining of bilateral hip and low lumbar discomfort. Her weight was stable and she had not had fevers or night sweats. Her general examination was without adenopathy or hepatosplenomegaly, yet she appeared unwell. Her blood studies included the following: white blood cells (WBCs), 4.0 × 10⁹/L; hematocrit, 32%; and platelet count, 15 × 10⁹/L. A serum LDH returned at >1995 IU/L (normal < 243 IU/L). The peripheral smear was disconcerting for scattered atypical large lymphocytes with irregular nuclei, coarse chromatin, and prominent single to multiple nucleoli. Flow cytometry of peripheral blood showed an abnormal B-cell population (90% of WBCs) with expression of CD10+/CD13+(low)/CD38+ (variably decreased)/CD45+ (decreased)/CD117+ (low)/HLA-DR+ (low)/TdT+ (low)/lambda surface light chain (small subset)/CD2+/CD3−/CD5−/CD7−/CD8+.

**Figure 1.** Histologic features of the patient’s excisional biopsy performed in 2012. (A) and (B) Hematoxylin-eosin sections at ×100 and ×400 magnification, respectively, showing effacement of lymph node architecture by neoplastic follicles containing centroblasts and centrocytes. Immunohistochemical studies confirm the diagnosis of follicular lymphoma, showing that the lymphocytes are B cells (CD20+) that express CD10 and BCL2. Ki67, the proliferation antigen, is expressed in 40% to 50% of B cells.
CD4−/CD5−/CD7−/CD8−/CD14−/CD15−/CD16−/CD20−/CD33−/CD34−/CD56−/CD64−/CD123−.

A restaging 18F-FDG PET/CT in January 2016 showed increased diffuse marrow uptake most notably involving vertebral bodies T7, T8, and T11 with the area of SUVmax in the right aspect of T8 of 11.4 (Figure 2B and 2C). In the absence of lymphadenopathy or splenomegaly, we performed a bone marrow aspirate and biopsy.

The aspirate consisted of sheets of tumor cells representing a spectrum from intermediate-sized cells with lymphoblastic features to very large atypical cells with multiple nucleoli. The core biopsy was hypercellular; the bone marrow showed diffuse and paratrabeular involvement by sheets of large lymphoid cells with finely clumped chromatin, pinpoint nucleoli, and scant cytoplasm. The aspirate smears showed cells with marked variation in cell size from intermediate lymphoblast-like cells to large atypical lymphoid cells. All abnormal lymphoid cells had deeply basophilic cytoplasm, with multiple cytoplasmic vacuoles. The bone marrow aspirate and biopsy clearly showed 2 distinct histologies; one remained consistent with the patient’s known FL with a predominant nodular pattern and the other consistent with HT. The large atypical cells expressed PAX5, CD10, BCL2, and c-MYC and were negative for CD20, MPO, CD34, CD30, and BCL6 (Figure 3). Focal areas showed faint, heterogeneous expression of terminal deoxynucleotidyl transferase (TdT) best seen on the clot section. Ki67 proliferation index was high (>90%). Fluorescence in situ hybridization (FISH) analysis showed 2 populations with MYC amplification and/or rearrangement and no evidence of BCL6 rearrangement; a karyotype analysis showed a complex abnormal female karyotype with t(14;18) and multiple structural and numerical abnormalities.

In summary, the cytologic features were not deemed typical of overt transformation to lymphoblastic lymphoma and were interpreted as “Burkitt-like” in morphology with deeply staining cytoplasm and cytoplasmic vacuolation. Complicating this interpretation was the faint TdT expression which raised the possibility of a lymphoblastic phenotype. It was impossible to determine whether the absence of CD20 was indicative of immaturity or, perhaps more likely, due to prior rituximab therapy. No normal B cells were identified. The cytogenetic studies indicated multiple subclonal populations, with the cytogenetic results revealing the presence of both MYC amplification and rearrangement. This genetic profile can be seen with lymphoblastic and high-grade Burkitt-like morphology and fulfills criteria for a secondary double-hit lymphoma (DHL). Per WHO (2016) criteria, this lymphoma would be best classified as a HGBL with both MYC and BCL2 translocations otherwise characterized as “DHL” with phenotypic features complicated by faint TdT expression and incongruent lymphoblastic morphology.12

The patient went on to receive her first of 5 cycles of dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) with concomitant prophylactic intrathecal methotrexate and cytarabine chemotherapy. Her LDH rapidly returned to normal and bone pain also improved following her first course of chemotherapy. Her clinical course was, however, complicated by neutropenic fever, pancytopenia, and need for periodic blood and platelet transfusions. A bone marrow collected after 3 cycles of chemotherapy showed a decrease in tumor burden, with 20% of marrow cellularity comprising an interstitial and nodular infiltrate of large atypical tumor

Figure 2. (A) Positron emission tomography with computerized tomographic (PET/CT) coronal image: fused arrows point to enlarged left cervical, bilateral axillary, retroperitoneal nodes, and spleen with severely increased 2-deoxy-2-[fluorine-18] fluoro-o-glucose uptake. (B) and (C) CT-PET sagittal spine and coronal images: intensely increased and diffuse marrow uptake, with resolution of multifocal sites of bulky adenopathy above and below the diaphragm, as well as complete resolution of splenic involvement.
lymphocytes with irregular multilobulated nuclei, condensed chromatin, distinct nucleoli, and small amounts of cytoplasm. There was a decrease in CD45 expression, positive for CD19, CD10, dim CD22, and CD28 and negative for both kappa and lambda surface light chains, CD5, CD103, CD23, and FMC7. Flow cytometry showed a miniscule neoplastic population, whereas immunohistochemical studies identified abnormal B cells positive for PAX5 and c-Myc and negative for TdT and CD20. IgH/MYC/CEP8 FISH testing showed atypical abnormal populations, one which showed 3 fusion signals and amplification of the probe centromeric to the MYC gene and a deletion of the region telomeric to the MYC gene. Collectively, there appeared to be a gain of intact MYC region as well as partial 8q24 amplification.

The patient received an additional 2 cycles of chemotherapy, but in the presence of persistent pancytopenia, increased bone pain, and markedly elevated LDH, it was apparent that her disease was progressing and she was referred to hospice. Several

Figure 3. Histologic features of the patient’s bone marrow biopsy in 2016. Replacement of the bone marrow by lymphoma (hematoxylin-eosin, original magnification ×100 and ×400). Wright-Giemsa–stained slide showing atypical lymphoid cells with some small- to intermediate-sized cells with round nuclei, fine chromatin, and small amounts of basophilic cytoplasm with vacuoles (×1000). Immunohistochemical studies showed that the tumor cells express PAX5 and partial terminal deoxynucleotidy transferase (TdT) and c-MYC and are negative for CD20 and CD34.
weeks later, she died from complications of advancing lymphoma. An autopsy was not requested.

**Discussion**

The HT of FL to an unclassifiable aggressive B-cell lymphoma has been described as a nonlinear genetic event characterized by recurrent mutations at the same locus and genomic driver mutations. It is the acquisition of these mutations that prompt the transformation to aggressive NHL, resulting in a higher mortality rate when compared with patients diagnosed with de novo DLBCL.

Advancements in immunohistochemistry techniques have sparked efforts to define incidence rates of DHL. In an analysis of 303 de novo and untreated patients with DLBCL, 26 (8.5%) had concurrent BCL2 and MYC rearrangements, whereas 10 (3.3%) had concurrent BCL6 and MYC rearrangements. In a second study of patients with de novo DLBCL, 189 patients were assessed for the BCL2 and MYC breakpoints, of which 11 (6%) were identified with the DHL phenotype. The presence of both BCL2 and MYC mutations encompasses a broad morphologic and immunophenotypic spectrum, including lymphoma subtypes such as Burkitt or Burkitt-like lymphoma, DLBCL, low-grade FL, plasmablastic lymphoma, and most uncommonly, TdT+ B-cell lymphoblastic lymphoma.

Double-hit lymphoma derived from FL is classified as germinal center B-cell (GCB) lymphoma. The GCB subtype, in this instance, is frequently associated with BCL2 translocations (84%, \( P < .0001 \)), whereas MYC aberrations are independent events varying from point mutations to gene amplification, translocation, and epigenetic reprogramming and enhanced translation, all of which can contribute to increased protein stability.

The rate of HT from low-grade FL to a more aggressive B-cell lymphoma is estimated to be 2% to 3% per year through 10 to 15 years and most commonly occurs 40 to 60 months from initial diagnosis. High scores on the Follicular Lymphoma International Prognostic Index (FLIPI) and the International Prognostic Index (IPI) are reliable tools when investigating associated risks of HT. Clinical adverse factors associated with a higher risk of HT include older age and above-normal serum LDH. The HT typically occurs several years following the initial diagnosis of FL as was demonstrated by a cohort of 276 patients with FL, in which 11% of patients presented with HT after a median time to transformation of 3.5 years. In this data set, the most significant variables associated with higher risk of HT were grade 3 FL (\( P = .003 \)) and high-risk FLIPI score (\( P = .001 \)). In addition to a sudden rise in serum LDH well above the upper limit of normal, HT also clinically presents with rapid and discordant localized tumor growth, new involvement of extranodal sites, new B symptoms, hypercalcemia, and a median increased SUV uptake of 14 by FDG-PET/CT scan.

Although clinical data for patients diagnosed with de novo DHL are accumulating rapidly, current studies have yet to adequately assess the rate at which DHL is derived from FL and whether the clinical outcomes of these patients are worse than those with de novo DHL. One study found that of the 157 patients diagnosed with DLBCL, 11% were confirmed DHL cases by FISH analysis. Of the 43 patients noted to have transformed DLBCL, 21% were identified as DHL patients suggesting that DHL is more common when HT occurs. De novo DHL is also characterized by an aggressive clinical course as well as frequent bone marrow involvement. Compared with other DLBCLs, DHL is more often associated with central nervous system (CNS) involvement; the incidence of CNS involvement at diagnosis is approximately 4% and increases to 13% at 3 years. The median overall survival (OS) for patients with CNS involvement is inferior to those free of CNS disease at diagnosis (6 months versus 36 months, respectively). Prophylactic intrathecal therapy reduced the risk of eventual CNS involvement from 13% to 5% at 3 years suggesting that such treatment should routinely be incorporated into the management of patients with DHL.

The HT to DHL has a more aggressive clinical course when MYC is translocated with an immunoglobulin (IG) partner gene. In a study of 574 patients with CD20+ DLBCL with interpretable FISH signals, 50 (6.6%) were identified to have MYC rearrangements and 24 (3.2%) of these patients had an IG partner gene coupled with MYC. In patients with DHL or isolated MYC translocations, the IG partner gene was associated with a significantly shorter OS and progression-free survival (PFS) (\( P = .0002 \) and \( P = .0023 \), respectively). Notably higher MYC protein expression was associated with the IG/MYC partner when compared with non-IG/MYC partner or MYC alone, demonstrating that this regulatory translocation plays a prominent role in tumor behavior. The emergence of the IG/MYC partner gene highlights a potentially significant variable which could be incorporated into prognostic models of tumor chemoresponsiveness.

Treatment options for patients with DHL are evolving and are no longer restricted to R-CHOP; however, the broad morphologic and immunophenotypic presentation of the disease makes standardization of treatment a challenge. In a nationwide retrospective analysis of 311 patients with de novo DHL, induction treatments consisting of DA-R-EPOCH, R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) were associated with higher OS and PFS rates when compared with R-CHOP. The difference in median PFS among those patients who were treated with non–R-CHOP regimens versus those who received R-CHOP was 21.6 and 7.8 months (\( P = .001 \)), respectively. Of the patients undergoing treatment with infusional DA-R-EPOCH, 65% had a complete response (CR) compared with 55% of patients treated with R-hyper-CVAD, 40% of patients treated with R-CODOX-M/IVAC, 30% of patients treated with other regimens, and 50% of patients treated with other regimens.
treated with R-CHOP. Patients who achieved a CR with a first-line therapy had a median OS of 103 months compared with those with relapsed or refractory disease undergoing salvage therapy who had a median OS of 17 months.13

Although current data support the use of more intensive chemotherapy regimens for DHL, the paradox of these therapies lies in the makeup of first-line treatments that typically include rituximab and an anthracycline. This combination therapy has been implicated in running the risk of resistance in patients with relapsed or refractory (R/R) disease. In a study of 396 DLBCL patients with first R/R disease, response rates decreased in patients treated with prior rituximab therapy compared with rituximab-naïve patients (83% versus 51%, $P < .001$), calling into question how best to use anti-CD20+ monoclonal antibodies as a component of first-line treatment.46

Consolidative hematopoietic stem cell transplantation (HSCT) has also been explored for patients with de novo DHL. Among 53 such patients treated with HSCT, 39 were treated at first CR (28 autologous HSCT, 11 allogenic HSCT), and 14 were treated with HSCT after achieving a PR. There was no difference in outcomes between those treated with HSCT at PR versus those who achieved CR with first-line therapy. Overall survival was 103 months ($P = .14$) for both of these groups. An obvious limitation of this study was the small number of patients evaluated.13,37 The benefits of HSCT for patients with DHL, particularly as a consolidative strategy after first CR, remain uncertain as is supporting evidence for HSCT as a salvage treatment.48 Although more data are needed to better define the optimal timing and benefit of HSCT, some investigators advocate for HSCT as a risk reduction strategy, perhaps in conjunction with other novel approaches such as radio-immunotherapy, using single-agent iodine–131 and tositumomab.38,39

As the management of patients with DHL remains unsatisfactory, there is an immediate need for developing new strategies for treatment. One such strategy involves targeting BCL2 and MYC rearrangements. Inhibiting BCL2 using a selective inhibitor, venetoclax, administered as a single agent yielded a 28% overall response rate among 18 patients with DLBCL.40 Current studies focus on combining venetoclax with conventional chemotherapy agents such as doxorubicin, methotrexate, cytarabine, or the protease inhibitor, bortezomib.41 Inhibiting MYC has been a greater challenge given the complex signaling cascades regulated by the MYC gene; progress is slowly being made by targeting the regulation of MYC through the inhibition of Bromo- and extra-terminal domains (BET) bromodomains. The BET bromodomain inhibitors are currently in phase I trials for patients with R/R lymphomas.41

Treatments aiming to modify the immune system as a way of treating R/R DLBCL have also been extended to treat patients with DHL. These approaches include use of antibodies, including anti-CD20, anti-CD40, and anti-PD1 monoclonal antibodies. Anti-CD19 chimeric antigen receptor T cells are also promising in the treatment of R/R DLBCL and could serve as a potential approach for patients with DHL.42

A unique aspect of our patient’s treatment evolution was the use of idelalisib at first relapse of FL. On July 23, 2014, the Food and Drug Administration (FDA) approved idelalisib based on a multicenter, single-arm trial of idelalisib monotherapy for patients with small lymphocytic lymphoma, chronic lymphocytic leukemia (CLL), and relapsed FL. Of the 72 patients with relapsed FL previously treated with rituximab-based therapy, 33 had a PR, 6 had a CR, 12 had progressive disease, and the remaining 21 patients discontinued treatment due to adverse events, including pneumonia, pyrexia, sepsis, febrile neutropenia, diarheaa, pneumonitis, pain, nausea, fatigue, cough, dyspnea, and rash.43 Several phase III trials used idelalisib in combination with standard therapies for patients with CLL and indolent NHL; however, these trials prompted safety concerns after being associated with alarming toxicity signals including drug-related adverse events and deaths in comparison with control groups. As a result, 7 clinical trials were halted by the FDA and remain under review. At present, there are no compelling data to suggest that idelalisib is correlated with higher rates of HT among patients diagnosed with FL nor is there any current correlation between idelalisib and higher rates of HT to DHL. Whether idelalisib could provide a microenvironment for selection of more aggressive clones needs to be addressed. Our patient’s clinical course is confounded by the incorporation of idelalisib while being further complicated by the complexity of HT and the mechanisms in which first-line chemotherapy regimens affect DHL.

Double-hit lymphoma is a challenging disease demanding fast, effective, and affordable methods for diagnostic purposes. Given the lack of truly effective criterion standard treatment, the creation of novel treatment strategies with the goal of improving OS remains a priority. Consequently, a better understanding of the pathogenesis of FL-derived DHL is needed with a focus on what makes patients vulnerable to HT. Further analysis of the role of the IG/MYC partner gene and how this and other pathways may affect disease progression are areas of active research.44–46 For the time being, regimens using standard agents such as DA-EPOCH and other agents will continue to be the primary approach to tackling FL-derived DHL.

**Author Contributions**

AMB and DMA contributed equally to the design and execution of the paper. DMA was the patient’s physician. RD provided expert review of pathology and provided photomicrographs and proof read the manuscript.

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