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Case Report

A Case of Double Expresser Diffuse Large B Cell Lymphoma Treated with R-CODOX-M/R-IVAC

Thomas Bemis[a] Jonathan Ioanitescu[a] Lynn Mackovick[b]
Azzam Hammad[b] Jascha Rubin[a]

[a]Drexel University College of Medicine, Department of Internal Medicine, Philadelphia, PA, USA; [b]Drexel University College of Medicine, Department of Pathology, Philadelphia, PA, USA

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Abstract
Diffuse Large B Cell Lymphoma (DLBCL) is a heterogeneous disease with a variety of chromosomal abnormalities contributing to differences in management. While it is known that Double Hit Lymphomas (DHL) warrant more aggressive chemotherapy regimens, debate remains on how to treat Double Expresser Lymphomas (DEL). We present a case of a DEL treated with an aggressive regimen of 2 alternating cycles of R-CODOX-M (rituximab, cyclophosphamide, doxorubicin, vincristine and methotrexate) and R-IVAC (rituximab, ifosfamide, etoposide and high dose cytarabine). The regimen resulted in a significant response to treatment with marked reduction in tumor size and avidity, and an acceptable side effect profile. There was, however, residual metabolic activity on repeat PET CT scan. After consolidation with 36 Grey radiotherapy, a PET CT demonstrated a complete metabolic response. Debate remains regarding treatment approaches in DEL. Our case supports the categorization of DEL alongside DHL as resistant lymphomas requiring a more aggressive regimen than standard therapy.

KARGER

Thomas Bemis
Department of Internal Medicine, Rittenhouse Hematology and Oncology
207 N Broad St., #6
Philadelphia, PA 19107 (USA)
E-Mail tsb39@cornell.edu

Introduction

The 2016 revision of the World Health Organization classification of lymphomas included new categories for Diffuse Large B Cell Lymphoma (DLBCL) by their gene expression profile [1]. One such classification of DLBCL was termed high grade B cell-lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangements, commonly referred to as double hit lymphoma (DHL) containing a MYC and one additional rearrangement, or triple hit lymphoma (THL) containing all three rearrangements. Another broader classification includes HGBL not otherwise specified (NOS), which include lymphomas with high expression of MYC and BCL2/BCL6 on immunohistochemistry (IHC) but without gene rearrangements; these lymphomas are referred to as double expresser lymphomas (DEL). In these cases IHC demonstrate ≥40% MYC and >50% BCL2, as described in the 2016 WHO classification of lymphomas. DELs are rather common, comprising approximately 20–30% of all DLBCL [2].

Standard treatment for DLBCL remains a regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [3, 4]. It has been observed that DHLs are less responsive to standard chemotherapy and have poor outcomes [5, 6]. The clinical significance of DHL status has prompted the investigation of using more aggressive chemotherapy regimens, however there remains debate as to whether DELs warrant similar consideration. In the following case report we present a case of a DEL treated as an aggressive lymphoma with R-CODOX-M (rituximab, cyclophosphamide, doxorubicin, vincristine) and methotrexate) R-IVAC (rituximab, ifosfamide, etoposide and high dose cytarabine).

Case Presentation

A 57 year old male with a past medical history of hypertension presented with 3 months of worsening right sided nasal congestion and facial swelling. A few days prior to presentation he developed right eye lacrimation and blurry vision. A maxillofacial CT scan revealed a 4.5 × 2.8 cm lobulated, rim enhancing hyperdense mass centered in the right nasal cavity with extension into the right choana and maxillary sinus with mass effect causing leftward bowing of the nasal septum. He was promptly evaluated by otolaryngology for biopsy.

Biopsy Morphology

Microscopic examination revealed respiratory mucosa with underlying proliferation of large lymphoid cells with centroblastic morphology. The cells exhibited high nuclear:cytoplasmic ratio, vesicular nuclei, one to three peripherally placed nucleoli, and frequent mitoses (Fig. 1).

Immunohistochemistry (IHC)

IHC stains showed large lymphoid cells to be positive for CD20, PAX-5, CD5 (weak), CD10, BCL2 (strong and diffuse), BCL6, MUM-1 and C-MYC, while negative for CD30, ALK-1, HHV8, EBV (ISH-EBER), and BCL1. CD3 and CD5 stains were positive in the scattered reactive T-cells. Ki-67 proliferation index >95%.

FISH

FISH analysis did not reveal a MYC or BCL-2 translocation; it did reveal an abnormal MYC-IGH and BCL2-IGH hybridization pattern in 96% and 97% of nuclei, respectively. FISH was also negative for rearrangements of MYC, BCL2, and BCL6. There were 3–4 copies of MYC in

71% of nuclei. BCL2 showed amplification in 86% of nuclei, and 3–8 copies of BCL6 were seen in 81% of nuclei. These findings were consistent with DLBCL-NOS. Given the high expression of MYC and BCL2, the tumor was further classified as a DEL.

Diagnosis

The overall morphologic, immunophenotypic and molecular characteristics of the tumor cells were consistent with DLBCL, not otherwise specified (NOS), and favored a germinal center B-cell subtype. The high proliferation index of Ki-67 (Fig. 2A) with coexpression of C-MYC (Fig. 2B) and BCL2 (Fig. 2C) on the tumor cells (DEL) suggested a resistant lymphoma.

Patient Course and Follow Up

Initial positron emission tomography-computed tomography (PET-CT) scan revealed marked diffuse FDG activity involving the right nasal cavity extending into the adjacent right frontal sinuses with SUV of 28.7 (Fig. 3A). PET-CT also revealed focal FDG activity in the right submandibular gland with SUV of 5.4. CT scan of the head, chest, abdomen, and pelvis was negative for any metastasis. A bone marrow biopsy did not reveal evidence of lymphoma on IHC or flow cytometry. Cerebrospinal Fluid (CSF) analysis did not reveal the presence of abnormal cells. The findings of additional lymph node involvement were consistent with DEL, stage IIB.

The patient underwent 4 alternating cycles of R-CODOX-M/R-IVAC, as follows:

R-CODOX-M (cycle 1 and 3):

Rituximab 375 mg/m^2 on day 1

Cyclophosphamide 800 mg/m^2 day 1–4

Doxorubicin 40 mg/m^2 day 1

Vincristine 1 mg/m^2 IV day 1–2

Methotrexate 300 mg/m^2 IV mg on day 8 with leucovorin rescue

Granulocyte colony-stimulating factor beginning 24 h after completion of IV chemotherapy and continuing until absolute neutrophil count >1,000/microL

R-IVAC (cycle 2 and 4):

Rituximab 375 mg/m^2 IV on day 1

Ifosfamide 1,500 mg/m^2 IV day 1–5 with mesna

Etoposide 60 mg/m^2 IV day 1–5

Cytarabine 2 g/m^2 IV on days 1 and 2 (total of four doses)

Intrathecal Methotrexate 12 mg on day 5

Granulocyte colony-stimulating factor beginning 24 h after completion of IV chemotherapy and continuing until absolute neutrophil count >1,000/microL

After the first cycle of R-IVAC, the patient experienced febrile neutropenia, grade 3, requiring readmission to the hospital and IV antibiotics. During the same admission the patient was found to have anemia, grade 3, and thrombocytopenia, grade 3, requiring transfusion of packed red blood cells and platelets. During cycle 2 of R-CODOX-M the patient developed acute kidney injury that improved with IV fluids; his renal function returned to baseline by cycle 2 of IVAC and he did not experience additional acute kidney injury. After cycle 2 of R-CODOX-M the patient also developed proctocolitis, grade 2, requiring treatment with antibiotics, as well as transaminitis with AST peaking at 200, ALT at 451, and ALP at 450, with all enzymes gradually returning to normal values. From the time of diagnosis through completion of chemotherapy, the patient experienced a 40 lb weight loss.

After completion of chemotherapy course, the patient had repeat PET-CT imaging which revealed SUV activity in the original right nasal cavity mass of 6.1 (Fig. 3B), with resolution of

SUV activity in the right submandibular gland. Given the persistent metabolic activity of the nasal cavity mass he was treated with radiotherapy consolidation with 36 Grey. PET/CT after radiation showed no residual uptake in the right nasal cavity (Fig. 3C), indicating a complete response.

Discussion

The pathogenesis of DLBCL is heterogeneous, with a variety of chromosomal abnormalities contributing to disease. The MYC gene, located at chromosome 8q24, encodes for the protein c-MYC which acts as a transcription factor with oncogenic potential that can transform cells through chromosomal translocation and gene amplification [7]. BCL2, located at chromosome 18q21, encodes a protein that inhibits apoptosis and is involved in physiological DNA repair; overexpression of BCL2 has been shown to promote resistance to chemotherapy [8]. BCL6, located at chromosome 3q27, encodes a protein that acts as a transcriptional repressor for a variety of processes in B cells, namely apoptosis; gene translocation or BCL6 overexpression can contribute to lymphoma development via prevention of normal BCL6 down regulation [9]. As reviewed in the introduction, the presence of both MYC and BCL6/BCL2 rearrangements confer a worse prognosis and may require more aggressive management. This highlights the importance of routinely assessing cytogenetics in DLBCL.

Debate remains regarding the appropriate treatment in DHLs and DELs. Despite the Cancer and Leukemia Group B 50303 trial not finding significant difference between R-CHOP and R-EPOCH in DLBCL [10], the study was not designed to specifically investigate outcomes in DHL and DEL. Furthermore, other studies have demonstrated worse outcomes in DEL with R-CHOP [11], as well as lack of improvement in outcomes using R-EPOCH in DEL [12]. These conflicting findings warrant investigation into alternative strategies in treating DELs.

Magrath and colleagues established favorable outcomes with CODOX-M/IVAC in a small cohort of patients with Burkitt's Lymphoma (BL) and Burkitt's like Lymphoma [13]. Low risk patients received CODOX-M alone while higher risk cases received the addition of alternating cycles of IVAC for a total of 4 cycles; the addition of IVAC improved 2 year event free survival (EFS) at 92% compared with 56% in the group receiving CODOX-M alone. The LY10 trial expanded the inclusion criteria for CODOX-M/IVAC to patients with high risk DLBCL (70 patients), all with proliferation index >95%; 2 year progression free survival reached 85% in low risk patients, but only 49% in high risk patients [14].

Given the poor outcomes observed in patients with DHL and DEL, research has focused on implementing more aggressive chemotherapy regimens such as CODOX-M/IVAC with the addition of rituximab. A phase II UK trial evaluated R-CODOX-M/R-IVAC in 116 patients with high risk DLBCL based on IPI score >3, with 44% of patients achieving complete remission [15]. Seven of these patients were DHL/THL and 5 patients were DLBCL-NOS without MYC translocation. Follow up survival data on the group of DLBCL/HGBL patients presented at the 2018 European Hematology Association meeting revealed 3 year PFS of 68.4% and 3 year overall survival of 76.2%.

Despite the absence of typical rearrangements of MYC or BCL2 in our patient's lymphoma, we considered it high risk for recurrence given the high expression of MYC and BCL2 on IHC, as well as the high Ki-67 proliferative index (>95%) and CNS proximity. He was treated aggressively with R-CODOX-M/R-IVAC followed by radiation as consolidation and achieved a complete metabolic response on PET/CT

In our presented case, the patient experienced manageable chemotherapy toxicities that included grade 2 proctocolitis, grade 3 febrile neutropenia, anemia, thrombocytopenia; all toxicities resolved without permanent sequelae. After completing 2 full courses of R-CODOX-M/R-IVAC, the patient had good response to high dose definitive chemotherapy, however he had significant residual SUV activity of 6.1 (decreased from 28.7) within the original right nasal cavity mass requiring consolidative radiation. After radiation, repeat PET/CT showed complete metabolic response with no residual activity in the original nasal mass and stable metabolic activity in lymph nodes in the chest. The lack of complete response on PET-CT with R-CODOX-M/R-IVAC suggests that DEL should be considered as aggressive and resistant as DHL, and warrants further evaluation for more effective therapies. Radiation is not typical for consolidation and was chosen in part given his single site of residual disease. Given that our patient achieved a complete response after receiving radiation as consolidation, it is a strategy that should be further investigated for DEL with residual single site disease after definitive chemotherapy. Long-term follow up on our patient will be required to further assess the outcome in our case. It should be noted that our patient did not have advanced age or significant comorbidities, and that the use of such an aggressive chemotherapy regimen may not be appropriate in all patients.

Evaluating chemotherapy regimens in different subtypes of DLBCL has been challenging given the evolution in how B cell lymphomas are defined. Much existing data evaluating responses to chemotherapy in DHL and DEL are retrospective and small in sample size due to lack of stratification for cytogenetics. Further prospective clinical trials comparing more aggressive and novel regimens to standard treatment in patients with DEL and DHL are warranted.

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Statement of Ethics

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from the patient for publication of the case and accompanying images.

Disclosure Statement

The authors have no competing financial interests to disclose.

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Author Contributions

Thomas Bemis, Jonathan Ioanitescu, and Jascha Rubin designed the case report and wrote the manuscript. Lynn Mackovich and Azzam Hammad performed the pathology analysis and contributed to the pathology sections in the patient case presentation. All authors have read and approved the final manuscript.

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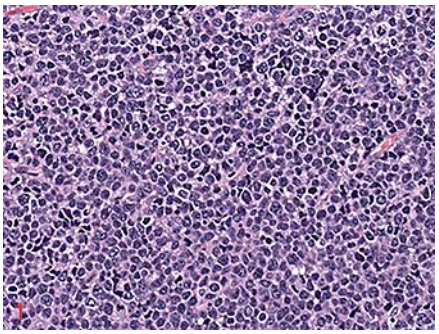

Fig. 1. Pathology slide of nasopharyngeal mass: large lymphoid cells with centroblastic morphology. These cells exhibit high nuclear:cytoplasmic ratio, vesicular nuclei, one to three peripherally placed nucleoli, and frequent mitoses.

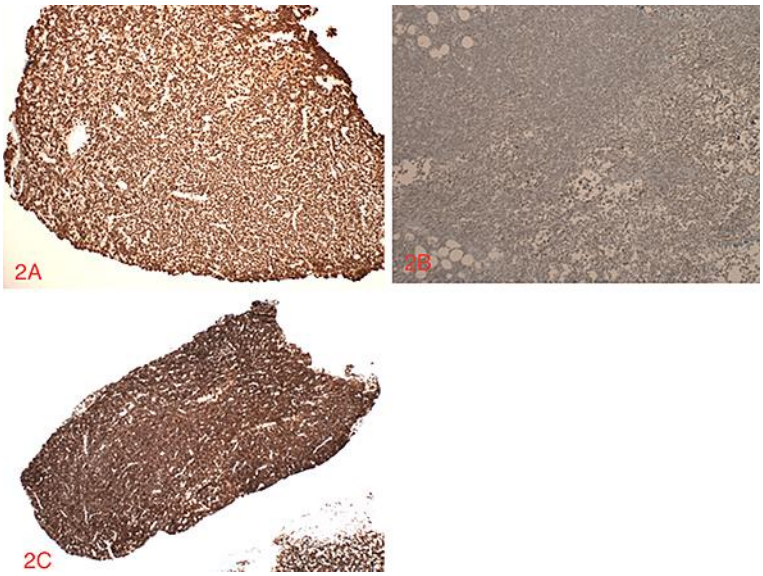

Fig. 2. Immunohistochemistry. **A**: Ki-67 proliferation >95%. **B**: C-MYC expression 71%. **C**: BCL-2 expression 83%.

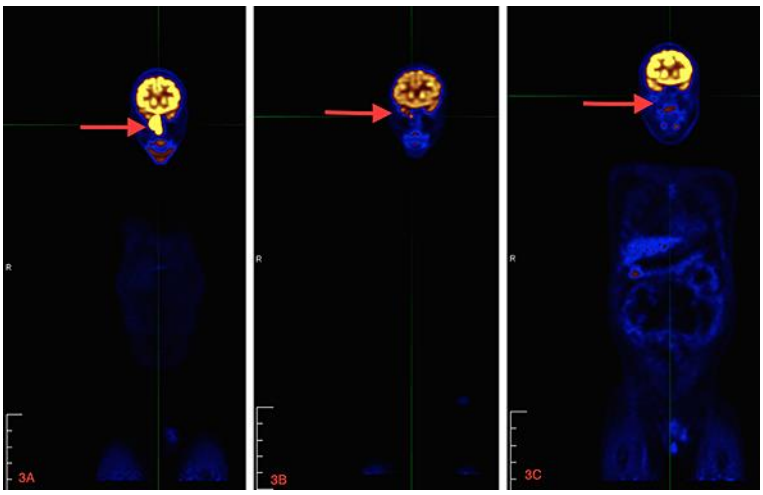

Fig. 3. PET/CT Images. **A**: Initial PET/CT scan showing right sided nasal mass with SUV 28.7. **B**: PET/CT After 2 cycles R-CODOX-M/R-IVAC, with primary tumor SUV 6.1. **C**: PET/CT After Radiation as Consolidation with 36 Grey, with no residual uptake in site of primary tumor.