



**Case Report**

**TdT Positive Lymphoma with MYC, BCL2 and BCL6 Rearrangements: A Review of Diagnosis and Treatment**

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**Abstract.** In the modern era, classification of neoplasms not only depends on immunomorphological features but also on specific disease-defining genetic events. Translocations/rearrangements of MYC/8q24 locus combined with BCL-2 or BCL6 translocations (double/triple hit) are considered hallmarks of high-grade B-cell lymphoma (HGBL), a type of aggressive mature B-cell lymphoma. When cases with immature immunophenotypes present these rearrangements, diagnosis becomes very difficult. We herein report an unusual case of an aggressive B-cell lymphoma/leukemia that presented with immature morphology and immunophenotype with triple hit gene rearrangements. This case highlights the difficulty in classifying and appropriately treating these patients. The novel aspect is the treatment and outcome with chimeric antigen receptor or CAR T-cell therapy.

**Keywords:** Lymphoma, Leukemia, Diffuse Large B-cell Lymphoma, Double/triple hit lymphoma, CAR T-cell therapy, Terminal deoxynucleotidyl transferase.

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**Introduction.** Classification of hematological malignancies is an important and evolving process. These malignancies are classified according to lineage and further subclassified into mature and immature neoplasms based on morphology, immunohistochemistry, and cytogenetics.<sup>1</sup> The distinction is of utmost importance in determining correct treatment modalities that differ significantly for mature and immature lymphoid neoplasms.

When classifying lymphoid neoplasms, terminal deoxynucleotidyl transferase (TdT) expression, CD34 expression, lack of surface immunoglobulin light chains, and morphology can help differentiate immature neoplasms from mature B cell neoplasms.<sup>2</sup> Similarly, specific genetic alterations can be considered pathognomonic for certain lymphomas aiding in their

classification. Triple hit/double-hit lymphomas are characterized by translocations/rearrangements of MYC/8q24 locus in combination with BCL-2 and/or BCL6 translocations. They are considered hallmarks of high-grade B-cell lymphoma (HGBL).<sup>3</sup> HGBL is usually TdT negative. TdT positive neoplasms with MYC and BCL2 and/or BCL6 rearrangements are classified as acute lymphoblastic lymphoma (ALL) under the current 2016 World Health Organization (WHO) classification.<sup>1</sup> Significant controversy exists about this classification. We report a rare case of a TdT positive triple hit neoplasm with concomitant follicular lymphoma, treated with CAR T-cell therapy.

**Case.** A 48-year-old Caucasian male with a past medical history of gastroesophageal reflux and mitral

valve prolapse presented with fatigue, malaise, intermittent abdominal pain, and loose stools which started about one week prior to presentation. Vital signs were stable and physical examination was unremarkable. Laboratory evaluation revealed hemoglobin of 14.7gm/dL; white blood cell counts 32920 cells/ $\mu$ L and platelet count 44000 cells/ $\mu$ L. Differential count showed absolute neutrophil count (ANC) 13830 cells/ $\mu$ L, absolute lymphocyte count (ALC) 6910 cells/ $\mu$ L, absolute monocyte counts 2300 cell/ $\mu$ L, and 30% blasts (**Figure 2 a**). Lactate dehydrogenase (LDH) >1800IU/L and uric acid 8.8mg/dL. CT scan of the chest, abdomen, pelvis showed few non-enlarged axillary lymph nodes,

enlarged paratracheal and subcarinal lymph nodes measuring 1.3 cm and 4.9 cm respectively, gastrohepatic ligament lymph node measuring 3 cm, the portal caval lymph node measuring 2.3 cm, peripancreatic lymph node measuring 2.8 cm, retroperitoneal lymph node measuring 2.9 x 4.5 cm, left renal hilar lymph node measuring 3.7 cm, enlarged common iliac lymph node measuring 2 cm, and mildly enlarged external iliac lymph nodes measuring 1.1 cm short axis and bilaterally. Enlarged bilateral inguinal lymph nodes were also noted (**Figure 1.a** and **1.b**). HIV (human immunodeficiency virus) and EBV (Epstein-Barr virus) tests were negative. A right iliac bone marrow biopsy was performed (**Figure 2.b** and **2.c**).

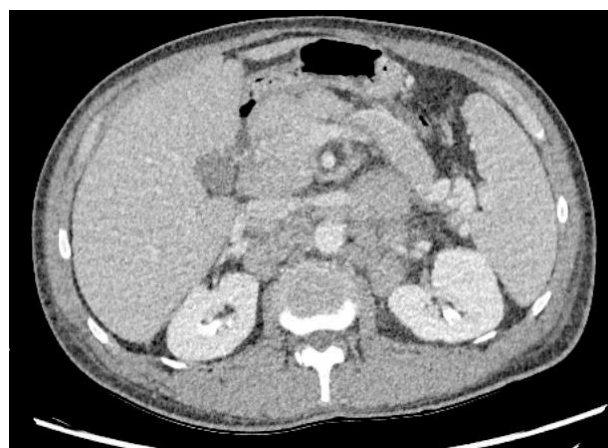


Figure 1.a and Figure 1.b.

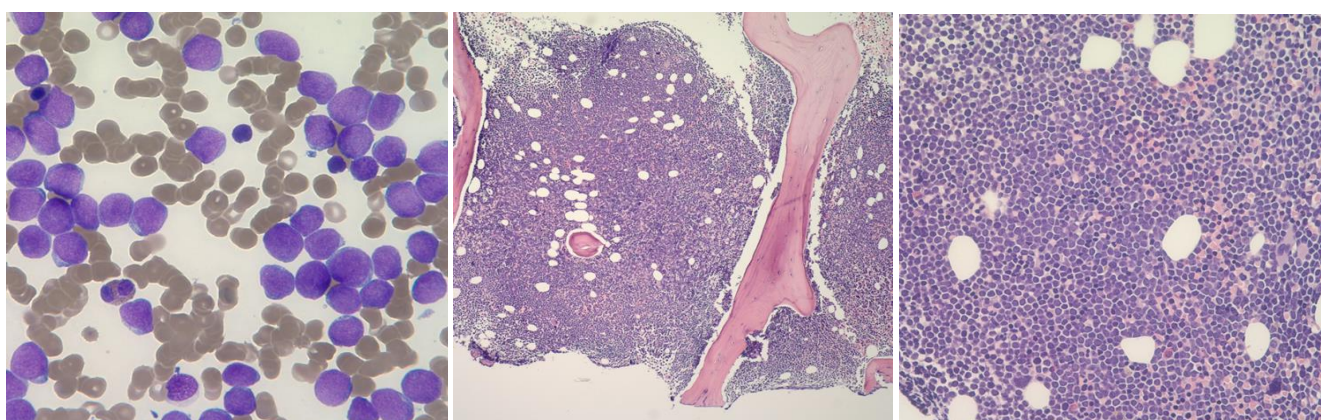
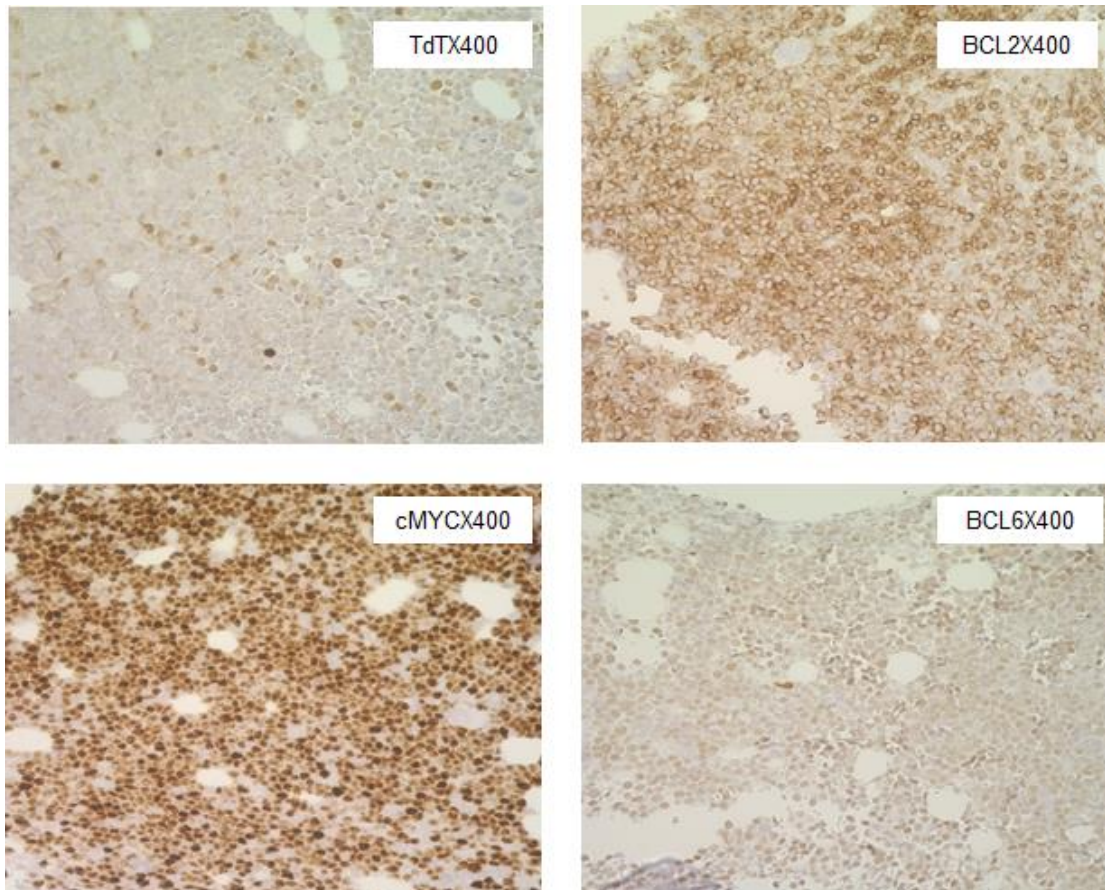


Figure 2.a, Figure 2.b and Figure 2.c.

The bone marrow core biopsy was hypercellular for age (>85% cellularity), with 90% blast-like cells infiltrating the marrow (**Figures 2.b, 2.c**). The neoplastic cells were large with fine nuclear chromatin, prominent nucleoli, and light basophilic cytoplasm. No Auer rods were identified. Flow cytometry showed monoclonal B-cells positive for CD10, CD19, CD38, and HLA-DR. Immunohistochemical staining showed blasts to be

positive for TdT, c-MYC, BCL2, and BCL6(dim); negative for CD20 (**Figure 3**). A diagnosis of acute B-cell lymphoblastic leukemia (B-ALL) was made. BCR-ABL by polymerase chain reaction (PCR) and molecular testing was negative. B-ALL specific FISH (fluorescence in situ hybridization) analysis was performed which included TCF3/PBX1 (E2A/PBX1) t(1;19), trisomy or tetrasomy 4, 6, 10, 17 (Cen 4, Cen 6,



**Figure 3.**

Cen 10, Cen 17), MYC (8q24), BCR/ABL1/ASS1 t(9;22), MLL (11q23), IgH (14q32). Only IgH rearrangement was positive.

Given the initial diagnosis of Philadelphia-negative B-ALL, he was started on induction chemotherapy with hyper-CVAD, without rituximab, as CD20 was negative.

Subsequent cytogenetic analysis showed abnormal male karyotype, dup (1)(q11q44), t(3,6)(q25; q13), t(8;22)(24.1; q11.2), and t(14;18)(q32; q21) in fourteen of twenty examined cells. This was a very atypical karyotype for B-ALL. The t(3;6)(q25; q13) was near, but not at the locus for BCL6 or MECOM rearrangements, and t(8;22)(24.1; q11.2) rearrangement is a variant of MYC-IGL. However, t(14;18)(q32; q21) was consistent with IGH-BCL2 rearrangement. FISH for cMYC, BCL2, and BCL6 were positive. These findings were suspicious for a double/triple hit HGBL rather than pre-B ALL.

Due to the dilemma in diagnosis, a right inguinal lymph node excisional biopsy was performed. At this time patient was still admitted inpatient, and therefore, a PET scan could not be obtained to assist in the diagnosis. The right inguinal lymph node biopsy was performed as it was thought to be the least invasive to perform. The pathology showed disruption of normal architecture by the proliferation of follicles with small lymphocytes having irregular nuclear contours. These cells were positive for CD10, CD20, CD79a, PAX-5, BCL6, and

BCL2 by immunohistochemistry. They were negative for cMYC, cyclin D1, MuM-1, and TdT. The Ki-67 was 10%. Flow cytometry identified a monoclonal B-cell population positive for CD10, CD19, and CD20, with monoclonal kappa light chain restriction. No cells in metaphase were present for cytogenetic analysis.

This was consistent with follicular lymphoma (FL).

Hyper-CVAD was continued due to overlapping efficacy for ALL and HGBL. However, after completing one course of each hyper-CVAD and HD-MTX-Ara-C, he had persistent blasts in his marrow. The immunophenotype was positive for CD22 during this time. A second induction with rituximab, methotrexate, vincristine, pegylated L-asparaginase, and dexamethasone (R-MOAD) was given. Bone marrow biopsy after this second induction showed persistent disease. He then received one cycle of inotuzumab ozogamicin but still had no disease response. The patient was so far treated with ALL regimens without any response. Although the CD19-directed chimeric antigen receptor (CAR) T-cell therapy was not approved for ALL patients above 25 years, he was evaluated for CAR T-cell therapy and was qualified to receive it due to overlapping features with HGBL for which CAR T-cell therapy was approved.

He underwent lymphocyte-depleting chemotherapy followed by tisagenlecleucel, a CD19-directed chimeric antigen receptor (CAR) T-cell therapy. The post CAR T-

cell infusion course was complicated by grade 3 cytokine release syndrome (CRS), grade 2 immune effector cell-associated neurotoxicity syndrome (ICANS), and macrophage activation syndrome requiring intensive care admission. He was treated with corticosteroids, tocilizumab, and anakinra. He made a full recovery and was discharged home. A follow-up bone marrow aspiration and biopsy performed one month later demonstrated a complete response. Unfortunately, another month later, a repeat marrow biopsy demonstrated recurrent high-grade B-cell lymphoma/leukemia with 90% blasts. His immunophenotype after the CAR-T was noted to be CD45(dim), CD10(heterozygous), CD38(heterozygous). It was negative for CD19, CD20, CD22, CD5, CD34, smKappa, smLambda, CD56, CD66b. Given the lack of effective treatment options, he was transitioned to supportive care and succumbed to the disease. His overall survival was eight months.

**Discussion.** Overlapping morphologies and phenotypes are commonly seen in lymphomas. Morphology alone is insufficient to differentiate between lymphoblastic leukemia or high-grade B-cell lymphoma. Blastoid morphology has been well described in high-grade B-cell lymphomas. Uchida and colleagues identified 47 patients with the initial manifestation of bone marrow infiltration by blastoid B cells with MYC and BCL2 and/or BCL6 rearrangements (MBR) and classified them as acute lymphoblastic leukemia (ALL)-like disease of HGBL-MBR (AL-HGBL-MBR). However, it should be noted that these patients had negative TdT expression.<sup>4</sup> Although TdT may be useful in identifying immature cells, a single marker alone may not be appropriate for characterizing a cell type. The degree of differentiation usually determines the immunophenotype of lymphoid malignancies. TdT and CD34 antigens are the hallmarks of immature lymphoid neoplasms in the earliest stage blasts (pro-B ALL cells). CD34 and TdT expressions are usually noted parallel to one another. However, TdT negative B-ALL, CD34 negative B-ALL, and dual negative B-ALL are well-described in literature.<sup>5,6</sup>

Similarly, TdT expression has also been seen in mature lymphoid neoplasms, including high-grade B-cell neoplasms.<sup>7,8</sup> Neoplastic cells, in our case, were positive for TdT but negative for CD34 expression. The absence of surface light chains is considered a feature of immature leukemias/lymphomas but can be seen in up to 20% of cases of high-grade B-cell lymphoma.<sup>8</sup> Of note, our patient did not have CD-20 expression on the neoplastic cells extracted from the bone marrow. CD20-negative de-novo mature diffuse large B cell lymphomas are rarely reported. Most cases include primary effusion lymphoma, plasmablastic lymphoma, ALK-positive large B-cell lymphoma, and large B-cell lymphoma

arising in HHV8 (human herpesvirus-8).<sup>25</sup> Gaur et al. described two unclassifiable CD20-negative high-grade lymphomas refractory to chemotherapy.<sup>26</sup> Molecular analysis using cytogenetics or FISH (fluorescent in-situ hybridization) to detect rearrangements or translocations of Bcl-2, Bcl-6, and MYC have been proposed to aid in diagnosing such cases.<sup>27</sup> CD20 expression is variable in B-ALL/LBL and can be found in neoplastic cells beyond the pro-B cell maturation stage.

40-50% of ALL cases have been noted to be CD20 positive which portends a poor prognosis.<sup>28</sup> Therefore, even immunophenotype in conjunction with morphology may not be enough to classify a neoplastic cell immature.<sup>5,6</sup> Khalnari et al. have recently proposed a scoring system to help classify challenging blastoid lymphoid malignancies. The scoring system is conceptually sound but needs external validation. They found that only the CD34 marker is sensitive and specific to make such a distinction. A score greater than or equal to 3 supports the diagnosis of blastoid HGBL. Our case scores 2 points if the scoring system is strictly applied and favors B-ALL.<sup>29</sup>

In the era of molecular genomics, the classification of lymphoid malignancies no longer relies predominantly on morphology or immunophenotype. The development of sophisticated techniques like fluorescence in situ hybridization (FISH), next-generation sequencing of cancer genomes, genome-wide analysis of copy number variations, and gene expression profiling has enriched our knowledge of distinct cytogenetic abnormalities associated with specific types of hematological malignancies. The importance of these new findings in the molecular landscape of lymphoid malignancies was highlighted in the 2016 revision of the World Health Organization classification of lymphoid neoplasms.<sup>1</sup> MYC dysregulation along with that of BCL2 and less frequently BCL6 are characteristic oncogenic events of lymphomagenesis in diffuse large B cell lymphomas.<sup>3,9,10</sup> These rearrangements can be seen in up to 20% of HGBL cases but are exceedingly rare in de novo ALL. In 2016, WHO updated all B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements, which were included in a single category of HGBL, except for cases that express TdT, which are classified as B-ALL. Given that this updated classification relies on genetic findings over immunomorphological findings, the use of TdT positivity to classify these cases as B-ALL needs further discussion.<sup>11-13</sup> In a recently published series of TdT positive lymphomas, Ok et al. propose that TdT positive cases with MYC and BCL2 and/or BCL6 rearrangements should be classified as HGBL with TdT positivity.<sup>8</sup>

Clinical characteristics, including the prognosis of these cases, seem to align more closely with HGBL than with B-ALL. Our patient had an extremely elevated LDH

and international prognostic index (IPI) score, as well as bone marrow involvement—all poor prognostic factors in HGBL. HGBL typically presents as an advanced disease with frequent extranodal and bone marrow involvement, as seen in our case.<sup>11</sup>

Treatment of these patients, either double/triple hit lymphoma or B-ALL, presents a bigger challenge. Treatment of double/triple hit HGBL with standard chemotherapy R-CHOP is associated with a dismal outcome with a median overall survival of 12 months from diagnosis.<sup>11</sup> Evidence to support the use of "Burkitt-like" intensified regimens like R-EPOCH, hyper-CVAD, and CODOX-M/IVAC comes from small retrospective studies.<sup>14,15</sup> Unfortunately, no molecularly targeted approach has yet shown any success but is an area of active investigation. Autologous stem cell transplantation (ASCT) has shown no benefit in either overall survival or disease-free survival in a small number of patients who achieve complete response.<sup>14</sup> The disease course is marked by progression or early relapse for most patients. Standard salvage treatment success rates for patients with relapsed/refractory disease with non-cross-resistant chemotherapy R-DHAP or R-ICE and ASCT are low.<sup>16–18</sup> Similarly, cases treated with ALL-type regimens, like hyper-CVAD, had similar poor outcomes.<sup>4,8</sup> Our patient was treated with several lines of ALL regimens with no response. He et al. reported a similar case about a 39-year-old male with retroperitoneal mass and lymphadenopathy. Biopsy of mass revealed malignant cells positive for TdT, CD99, CD10, PAX-5, BCL2 (70%), MYC (70%) with Ki-67 of 80%. FISH studies demonstrated 8q24/MYC rearrangement and IGH/BCL2 gene fusion. The patient had an excellent response to hyper-CVAD.<sup>30</sup>

For our patient, tisagenlecleucel appeared to be the only effective line of treatment. Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy approved for the treatment of relapsed/refractory DLBCL and patients with B-cell precursor ALL that is refractory or in second or later relapse. In the Juliet trial, which included 19 patients with double/triple hit gene rearrangement, median overall survival of 12 months was observed.<sup>19</sup> For patients with relapsed/refractory B-ALL, treatment with CAR T-cell therapy has shown a median time to progression of about 5.5 months and median survival of 7.4 months.<sup>20</sup> Unfortunately, CAR T-cell therapy was not approved for patients above the age of 25 years at the time of treatment for our patient. However, due to a dilemma in his exact diagnosis and suspicion of an alternate diagnosis of HGBL, he was qualified to receive

CAR T-cell therapy.

Our patient achieved complete response after CAR T-cell therapy but suffered a relapse in 30 days. This is the first reported case of TdT+ triple hit lymphoma/leukemia treated with CAR T-cell therapy. In addition, Brexucabtagene autoleucel is now approved for the treatment of adult patients (18 years and older) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) after the ZUMA3 trial showed a high and durable response in a heavily pretreated population of B-ALL.<sup>31</sup>

Of interest, our case also had synchronously diagnosed follicular lymphoma. Although we were unable to perform clonal studies, it is possible that this high-grade lymphoma/leukemia transformed from follicular lymphoma. Well-defined cases of HGBL transformed from a preexisting or concomitant follicular lymphoma by the acquisition of c-MYC exist in the literature.<sup>21</sup> As seen in our case, this antecedent FL are usually BCL2 positive. Several cases of follicular lymphoma transformation to TdT- HGBL and subsequently to TdT+ high-grade B-cell lymphoma/leukemia have also been proposed.<sup>8,22</sup>

Similarly, cases with composite morphology with co-existing TdT+ immature neoplasm and TdT- mature neoplasm has been reported, raising a possibility of an intermediate stage of TdT- HGBL in the development of TdT+ HGBL. It has been shown that mature neoplasms are capable of de-differentiating into immature cells.<sup>23</sup> Alternatively, a common progenitor cell (CPC) theory has also been proposed. It has been hypothesized that a CPC resides in the bone marrow niche and can evolve into FL, DLBCL, HGBL, and B-ALL.<sup>24</sup>

The current WHO classification of lymphoid neoplasms precludes patients such as ours from being involved in already scarce trials for the treatment of double/triple hit lymphoma. These TdT+ double/triple hit lymphoma/leukemia cases require further research for better understanding of the disease biology and therapeutic exploration of these aggressive neoplasms.

**Conclusions.** The clinical course of patients with ALL-like morphology with MYC and BCL2 and/or BCL6 rearrangements is aggressive. Unfortunately, the disease is refractory to the current standard treatments for both HGBL and B-ALL. As these cases are extremely rare and heterogeneous, large clinical trials exploring their treatment options are unlikely. Therefore, we believe that such cases should be reported.

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