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Case Report

Primary Diffuse Large B-Cell Lymphoma of the Breast with MYC and BCL2 Rearrangements with Terminal Deoxynucleotidyl Transferase Expression: A Case Report

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Keywords

Primary diffuse large B-cell lymphoma of the breast · MYC and BCL2 rearrangements · Terminal deoxynucleotidyl transferase expression · R-hyperCVAD/MA · Case report

Abstract

Introduction: Primary breast lymphoma represents only 1% of non-Hodgkin lymphomas. The most common histology is diffuse large B-cell lymphoma. When dual translocations of MYC and BCL2 or BCL6 occur, it is referred to as "high-grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6" according to the 4th edition of the WHO classification of hematolymphoid tumors. The expression of tdt in this type of malignancy is exceptional. ***Case Report:*** This is a case of a 54-year-old woman presenting with a rapidly growing painless mass. Ultrasound-guided core biopsy of the breast mass showed infiltrate of medium-sized neoplastic lymphocytes which stained as CD79a-positive B cells co-expressing CD10, BCL2, tdt, and MYC. Ki-67 is positive in 80%. There was rearrangement of MYC and BCL2 at FISH. Positron emission tomography (PET) scan was negative elsewhere. Final diagnosis was a DLBCL of the breast with tdt expression. She was treated with 6 cycles of R-hyperCVAD/MA (R = rituximab, C = cyclophosphamide, V = vincristine, A = cytarabine, D = dexamethasone, M = methotrexate) and intrathecal chemotherapy (IT CT). Restaging PET shows resolution of all avid uptake. We did a review of literature showing the importance of giving an intensive chemotherapy regimen, high-dose methotrexate, cytarabine, and IT CT for central nervous system (CNS) prophylaxis. ***Conclusion:*** Primary DLBCL of the breast with rearrangement of MYC and BCL2

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and tdt expression is an aggressive disease not very well studied that needs to be treated with an intensive CT and CNS prophylaxis. Stem cell transplant could be given after first remission.

Introduction

Primary breast lymphoma represents 1% of non-Hodgkin lymphomas and 2% of all extra nodal lymphomas [1]. The most common histologic type is diffuse large B-cell lymphoma (DLBCL) representing 60–85% of cases, followed by marginal zone lymphoma in 16% of cases and follicular lymphoma in 5.4% of cases with rare cases of Burkitt's lymphoma and Hodgkin lymphoma described in the literature [1–3].

The most common presentation of primary breast lymphoma is a unilateral painless breast mass in a middle age woman, but in up to 11% of cases, it can present bilaterally [2]. Large B-cell lymphomas with translocation of MYC and BCL2 and/or BCL6 as detected by FISH are known as "double hit" lymphomas (DHL) with the vast majority being germinal center B-like lymphomas classified as high-grade lymphoma in the World Health Organization WHO 2016.

DHL represent 1% of all non-Hodgkin lymphoma [4] and 10% of DLBCL [5, 6]. Half of these patients have an extranodal involvement including bone marrow 30–80%, pleural effusion 30%, central nervous system (CNS) 20–30%, and gastrointestinal 20% [4, 6–8] with very rare cases of primary breast lymphoma.

Terminal deoxynucleotidyl transferase (tdt) is not expressed normally in DLBCL even with rearrangement, albeit there are some exceptions. We report this case of DLBCL of the breast with tdt expression.

Case Report

A 54-year-old woman presented with a 2-week history of rapidly growing left breast mass with 3D left diagnostic mammogram showing multiple masses (Fig. 1). Ultrasound confirmed a 6.1 cm heterogeneous mass at 12:00 approximately, 3.0 cm from the nipple, with additional smaller masses including a 4.5 cm lesion at 9:00 and a 2.6 cm lesion at 9:00 with a solitary 1.4 cm axillary node with borderline cortical thickening (Fig. 2).

A review of systems was negative for any fevers, night sweats, or unintentional weight loss. A complete blood count showed a white blood count of 6.1 (normal range, 3.7–10.4 $\times 10^3/\mu L$) with a hemoglobin of 12.0 g/dL (normal range, 13.2–16.8 g/dL) and a normal platelet count. The lactate dehydrogenase was normal at 134 U/L (normal range, 120–246 U/L), and albumin was 4.3 g/dL (normal range, 3.3–5.2 g/dL), with otherwise normal liver function.

Ultrasound-guided core biopsy of the breast mass showed infiltrate of medium-sized neoplastic lymphocytes with round nuclear borders, inconspicuous nucleoli, and scant cytoplasm (Fig. 3) which stained as CD79a-positive B cells co-expressing CD10, BCL2, tdt, and MYC. Ki-67 is positive in 80% of neoplastic cells overall.

Figure 4a represents tdt staining, Figure 4b represents CD10 positivity, and Figure 4c represents MYC expressivity. CD20 is weakly expressed on a subset of cells which is presented in Figure 5. Reactive CD3-positive T cells were interspersed (Fig. 6) and FISH

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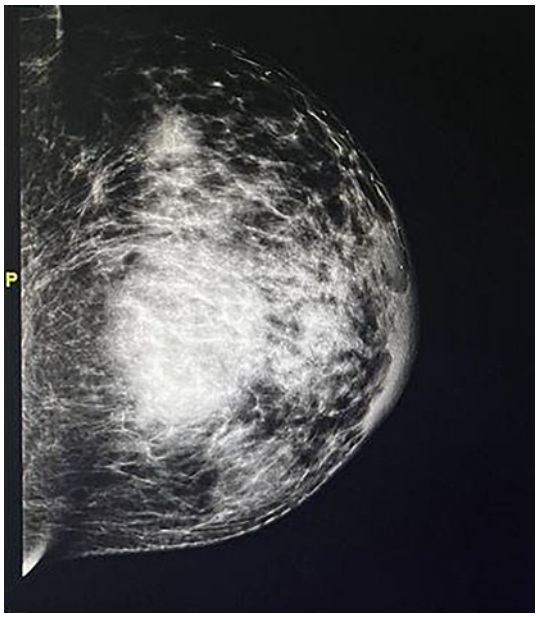

Fig. 1. 3D-diagnostic mammogram showing multiple masses in the L breast.

analysis for BLYM performed at Mayo Clinic in Rochester, MN, revealed that 75% of nuclei have IGH:MYC fusion and a BCL2 rearrangement with no rearrangement of BCL6. This finding is consistent with "high-grade B-cell lymphoma with MYC and BCL2 rearrangements" and tdt expression.

She underwent staging positron emission tomography scan (PET scan) that showed enlarged left breast with mild overlying skin thickening as well as underlying soft tissue nodularity with increased [18F]fluorodeoxyglucose uptake with focus in the upper inner quadrant demonstrating maximal SUV of 6.5 and focus in the subareolar region demonstrating maximal SUV of 2.9. There were no other sites of pathologic uptake demonstrated in the chest, abdomen, or pelvis. Bone marrow aspiration and biopsy as well as cytology and flow cytometry in cerebrospinal fluid were negative for lymphoma involvement, consistent with stage IEA. She was treated with six cycles of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine plus rituximab in addition to intrathecal methotrexate. No complications or adverse events were seen.

Restaging PET scan after the third cycle showed resolution of all avid uptake. She has remained in complete remission since. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536551).

Discussion

Tdt is a DNA polymerase that has a major role in augmenting antigen receptor diversity during recombination of immunoglobulin and T-cell receptor genes. Normally, it is expressed at the pro B stage in thymus and disappear gradually with maturation of B cell when IGH rearrangement is complete.

Tdt can be found in many tumors including lymphoblastic lymphoma/leukemia [9]. It can also appear at progression or relapse of a DLBCL or in de novo DLBCL.

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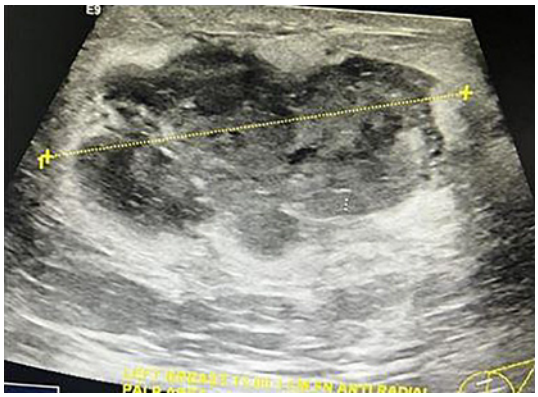

Fig. 2. US of the L breast showing a 6.1 cm heterogeneous mass at 12:00, approximately 3.0 cm from the nipple, with additional smaller masses including a 4.5 cm lesion at 9:00 and a 2.6 cm lesion at 9:00 with a solitary 1.4 cm axillary node with borderline cortical thickening.

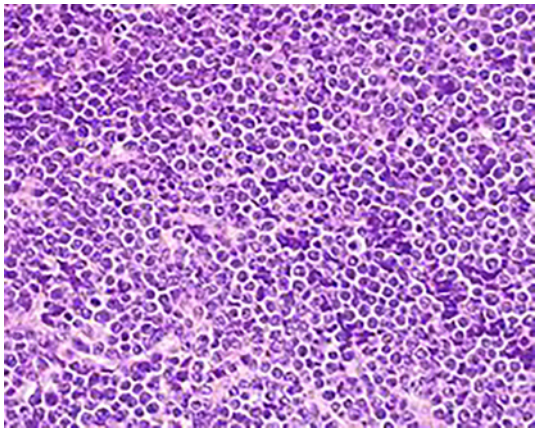

Fig. 3. Hematoxylin and eosin ×400 showing infiltrate of medium-sized neoplastic lymphocytes with round nuclear borders, inconspicuous nucleoli, and scant cytoplasm.

It is important to differentiate lymphoblastic lymphoma/leukemia from DLBCL with MYC and BCL2 rearrangements and tdt expression. For this, we need to have a morphologic review and a detailed immunophenotypic workup.

In our case, we did not have any other features supporting immaturity such as expression of CD34, CD99, or lack of expression of surface immunoglobulin. Also, MYC and BCL2 rearrangement is very rare in LBL (less than 0.2% of cases of LBL) [9].

There is no established treatment for de novo primary DLBCL of the breast with MYC and BCL2 rearrangements outside of a clinical trial. Also, CNS recurrence is more frequent than other extranodal lymphomas [10, 11] with a rate of 4.7% [12].

In addition to this, tdt expression seen in B lymphoblastic lymphoma and more recently described in DLBCL with MYC and BCL2 rearrangement brings additional risk for CNS involvement. Thus, intensive CNS prophylaxis must be included [12, 13].

Oki et al. [14] at MD Anderson did a retrospective study on 129 patients with DHL treated with RCHOP (C = cyclophosphamide, H = doxorubicine, O = vincristine, P = prednisone), dose adjusted (DA) EPOCH-R (E = etoposide P = prednisone, O = vincristine C = cyclophosphamide H = doxorubicin) or R-hyperCVAD/MA showing complete response in 20% after RCHOP, 68% after DA-EPOCH-R, and up to 70% after hyperCVAD.

OS after first progression was poor even after salvage stem cell transplant (SCT) (3yOS 15% vs. 7%). Albeit, SCT is an option for the treatment of DLBCL with MYC and BCL2 rearrangement, with same prognosis if done after first complete remission or after a second line of treatment with complete response [2] and less CNS progression ($p < 0.001$). So SCT is generally recommended to reduce CNS relapse rate.

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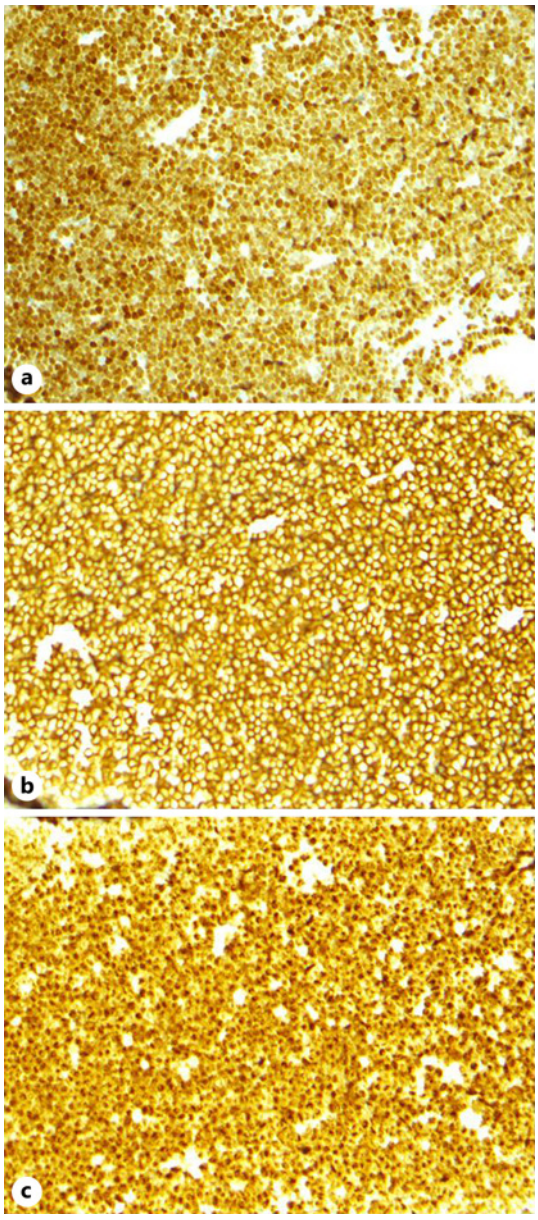

Fig. 4. a Immunohistochemistry (IHC) terminal deoxynucleotidyl transferase (tdt) positivity ×20 (**a**), CD10 positivity at IHC ×20 (**b**), and MYC expressivity at IHC ×20 (**c**).

A large multicenter retrospective study of 311 patients with double hit lymphoma showed that event-free survival increases in DA-EPOCH-R, RCODOXM/IVAC (=cyclophosphamide, O = vincristine, dox = doxorubicine I = ifosfamide, V = etoposide, ac = aracytine), R-hyperCVAD compared to RCHOP [15]. In absence of prospective studies, dose adjusted EPOCH-R and R-hyperCAVD are the most commonly used.

In our case, we opted for hyperCVAD and as per additions CNS penetrance with high-dose methotrexate plus cytarabine. We note that intrathecal chemotherapy is not sufficient for preventing CNS recurrence because recurrence is intraparenchymal more often than leptomeningeal. Thus, the importance of MA regimen, which decrease the risk of CNS recurrence from 22% to 10%.

A study done on 48 patients with PBL showed that SCT protects against early CNS progression ($p = 0.036$) [2]. Also, it increases OS and PFS with a p value <0.001 (5yOS 72.2 vs. 23.3%, 5yPFS 72.2 vs. 16.7%).

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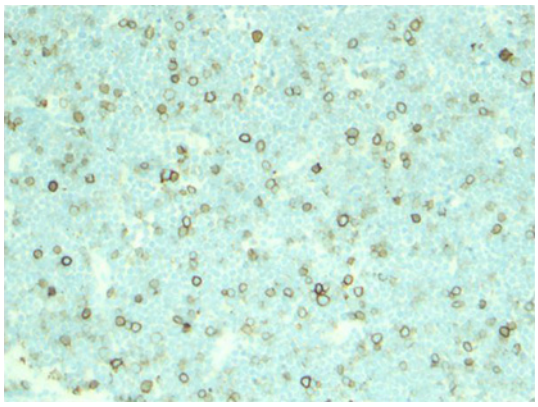

Fig. 5. CD20 weakly expressed at IHC.

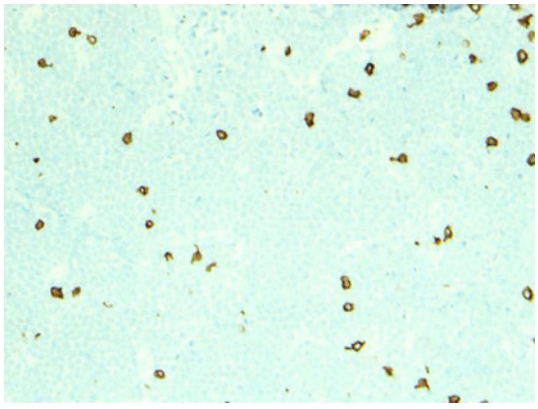

Fig. 6. Interspersed reactive CD3-positive T cells at IHC.

Conclusion

Primary DLBCL of the breast with MYC and BCL2 rearrangements is a rare and extremely aggressive malignancy with adverse prognosis and not completely defined optimal treatment. Herein we present a case with primary breast DLBCL with MYC and BCL2 rearrangement with tdt expression, treated with 6 cycles of R-hyperCVAD alternating with high-dose methotrexates cytarabine with complete resolution on PET. Review of literature supports our treatment choice.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Lebanese University on February 2022. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Our work follows internationally recognized guidelines as detailed on the Equator Network website.

Conflict of Interest Statement

There is no conflict of interest.

Funding Sources

No funding was needed for the case report.

Author Contributions

Dr. Bassam Matar – GROUP 1: conception of the work, design of the work, acquisition of data, analysis of data, and interpretation of data. GROUP 2: drafting the work and revising the work critically for important intellectual content. GROUP 3: final approval of the version to be published. GROUP 4: agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Maureen Chbat – GROUP 1: conception of the work, design of the work, acquisition of data, and analysis of data, and interpretation of data. GROUP 2: drafting the work and revising the work critically for important intellectual content. GROUP 3: final approval of the version to be published. GROUP 4: agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Houssam Bitar – GROUP 1: Conception of the work AND Design of the work AND Analysis of data. GROUP 2: Revising the work critically for important intellectual content. GROUP 3: Final approval of the version to be published. GROUP 4: Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Francisco Rosado – GROUP 1: conception of the work, design of the work, acquisition of data, analysis of data, and interpretation of data. GROUP 2: drafting the work and revising the work critically for important intellectual content. GROUP 3: final approval of the version to be published. GROUP 4: agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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