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C-MYC over-expression diffuse large B-cell lymphoma mimicking breast cancer metastases in young female

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Abstract

C-MYC over-expression in diffuse large B cell lymphoma (DLBCL), an aggressive non-Hodgkin lymphoma, may mimic breast cancer metastases or occur in treatment refractory cases. The C-MYC proto-oncogene encodes a phosphoprotein that is involved in cell cycle progression, apoptosis, and cellular transformation. C-MYC gene rearrangement occurs in greater than 8% of patients with primary mediastinal large B cell lymphoma and transformed DLBCL. However, it is classically associated with the not otherwise specified variant of Burkitt lymphoma. C-MYC over-expression is usually more than a hundred-fold when the protein is ever expressed, and the unique pathologic features are still under investigation according to a standard review of the English literature. The molecular signature, MorphoMolecular, was described as predictive of C-MYC rearrangement in DLBCLs and is concordant with the classical histological findings in most cases. We will describe a case of C-MYC over-expression DLBCL mimicking breast cancer metastases in a 22-year-old female and discuss its unique clinical, histological, and molecular signature. C-MYC over-expression in DLBCL may mimic breast cancer metastases in young females. Although rare, the importance of this unique bone marrow presentation may be underreported. The difference in the treatment regimen and response is substantial. A breast biopsy aided in establishing an effective treatment plan and prevented the patient from undergoing unnecessary breast resection for tumor debulking. The awareness of this unique morphomolecular type aids surgical pathologists in a precise diagnosis for an effective theranostic regimen. Presentation of such unique cases is important because it may help to unravel the pathogenesis and provide a tailored treatment plan.

Keywords: Rheumatoid arthritis; ESR; CRP; American College of Rheumatology criteria

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Introduction

C-MYC over-expression in diffuse large B cell lymphoma (DLBCL), an aggressive non-Hodgkin lymphoma, may mimic breast cancer metastases or occur in treatment refractory cases. The C-MYC proto-oncogene encodes a phosphoprotein that is involved in cell cycle progression, apoptosis, and cellular transformation. C-MYC gene rearrangement occurs in greater than 8% of patients with primary

mediastinal large B cell lymphoma and transformed DLBCL. However, it is classically associated with the not otherwise specified variant of Burkitt lymphoma. C-MYC over-expression is usually more than a hundred-fold when the protein is ever expressed, and the unique pathologic features are still under investigation according to a standard review of the English literature. The molecular signature, MorphoMolecular, was described as predictive of C-MYC rearrangement in DLBCLs and is concordant with the classical histological findings in most cases. We will describe a case of C-MYC over-expression DLBCL mimicking breast cancer metastases in a 22-year-old female and discuss its unique clinical, histological, and molecular signature.

C-MYC over-expression in DLBCL may mimic breast cancer metastases in young females. Although rare, the importance of this unique bone marrow presentation may be underreported. The difference in the treatment regimen and response is substantial. A breast biopsy aided in establishing an effective treatment plan and prevented the patient from undergoing unnecessary breast resection for tumor debulking. The awareness of this unique morphomolecular type aids surgical pathologists in a precise diagnosis for an effective theranostic regimen. Presentation of such unique cases is important because it may help to unravel the pathogenesis and provide a tailored treatment plan.

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma. Of these, 40% originate from extranodal sites, and the breast is one of the most common extranodal sites involved. C-MYC is an oncogene that encodes a multifunctional nuclear phosphoprotein. It plays a role in cell cycle regulation, apoptosis, and cellular transformation. C-MYC is one of the most common translocated oncogenes in DLBCL, along with BCL2. C-MYC-positive DLBCL tends to infiltrate the bilateral breast dermis, resulting in the clinical presentation of bilateral breast cancer in relatively young females. Therefore, it is important to identify C-MYC overexpression, especially when diagnosing breast cancer through a core needle biopsy.

Accurate diagnosis becomes even more important when the first-line management for clinically appearing cases involves surgical resection followed by adjuvant chemotherapy based on the final histopathological result. While MUM-1 and Ki-67 status aid in the diagnosis of a small subset with lymphoma, the triad of positive immunoreactivity for C-MYC, negative immunoreactivity for ER/PR, and BCL2 negativity are diagnostic of DLBCL of the breast in these cases. With recent advances in imaging and immunocytochemistry, core needle biopsy has become the first modality of investigation in the workup of breast neoplasms, especially in young females with suspected bilaterality. The challenges include accurately triaging the diagnosis of these unclassifiable malignancies, as well as the arrival of 'just-in-time' oncotherapy, impressive responses to targeted drugs, and the fast-metastasizing nature of DLBCL.

Diffuse Large B-cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) represents a biologically and clinically heterogeneous entity classified among the most aggressive human B-cell malignancies, with poor prognostic outcome. Despite the typical histological characteristics, the molecular features of DLBCL such as neoangiogenesis, genomic instability, and enhanced immune surveillance make it particularly challenging for both management and further understanding. Clinically, DLBCL presents in a non-

specific manner as a rapidly enlarging nodule in the breast, especially in young women with a large tumor size, ill-defined margins, medial location, and no regional lymphadenopathy. The integrated diagnosis based on clinical, radiology, and H&E is essential for conceptually distinguishing B-cell lymphomas from breast carcinoma.

DLBCL has a number of variants, with phenotypic and therapeutic implications. The clinical course and overall survival are mostly determined by functional and phenotypical characterization of the neoplasm according to the cell of origin: activated B-like (ABC) and germinal center B-like (GCB) cells. ABC-DLBCL is characterized by adverse outcome, resistance, and aggressive clinical course. They typically occur in elderly patients and in immunocompromised conditions. γ-DLBCL expresses plasmacytic markers and "plasmablastic" characteristics and is featured by an immune-escape signature. Abortive "plasmablastic" features are observed in terminally de-differentiated lymphomas when secretory-stage molecular alterations in B-cells physics cause constriction and differentiation in plasmablasts (Post-germinal CZ terminal B-cell memory-plasmablast plasma cell switch regulatory nodes). Features and clinical behavior of these neoplasms are rather different from non-lymphoid forms with "plasmablastic" phenotypic expression.

C-MYC Gene and its Role in Cancer

The c-MYC gene was the first identified oncogene in Burkitt lymphoma. It encodes a helix-loop-helix-leucine zipper transcription factor, which as an "undruggable" transcription factor is attractive for targeted therapy. The MYC family of proteins is composed of C-MYC, L-MYC, and N-MYC, but c-MYC seems to be the one most consistently overexpressed or deregulated in cancer. The c-MYC protein is a key player in many cellular processes like cell cycle progression, apoptosis, and cell metabolism regulation, which is also crucial for cells in the tumor microenvironment. Additionally, MYC target genes involved in input pathways of c-MYC gene regulation are essential for controlling cell growth and abnormal growth behavior of c-MYC overexpressing cancer cells in patients were associated with higher levels of MYC.

Overexpression of c-MYC protein in DLBCL is associated with unfavorable prognosis. However, little is known about downstream events that account for the aggressive behavior of DLBCLs harboring MYC overexpression. The c-MYC gene (chromosomal location 8q24) encodes a transcription factor, which as a proto-oncogene is involved in numerous cellular processes such as regulating the cell cycle and apoptosis, as well as cell metabolism. Deregulation of c-MYC contributes to tumorigenesis, and c-MYC overexpression seems to be associated with a worse outcome in several cancer entities, including both solid tumors and hematological malignancies like DLBCL. Clinically, though, c-MYC overexpression can be easily confused with c-MYC translocation-driven disease. The breast is a rare but possible location for DLBCL. Because of its site, "any" breast lymphoma can clinically mimic a breast cancer metastasis. Case reports often present middle-aged to older females as having a breast DLBCL. The role of c-MYC in the occurrence of breast cancer as such has not yet been completely elucidated.

Breast Cancer Metastases

Although not so common, breast cancer may at times lead to metastases in unusual sites. It follows that strict and specific investigations on the ovarian tissues or breast-intern compartments must be complied with in young females. If a primary breast tumor is detected, alongside a tumor at another site, the classification of one of the two separate tumors as a breast primary or a metastasis is also mandatory according to specific histological and morphological criteria. A correct approach and management are indeed required. A report on four clinical cases is therefore described, detailing the clinical features and discussing the mechanisms that might underlie any possible breast cancer metastases.

Breast cancer typically metastasizes to the bone, lungs, liver or brain, in decreasing order of frequency; nonetheless, metastases might also occur in rare and unusual sites. Occasionally, breast cancer metastasizes to the gastrointestinal tract, pancreas, kidney, rectum, thyroid and the female genital tract. The occurrence of these metastases tends to precede the diagnosis of breast cancer. The rarity of breast cancer of the breast as the site of metastasis would indeed suggest the need for more detailed and specific on-site investigations as well as strict clinical and instrumental follow-up. The most common symptom of breast cancer of the breast is usually the find of a painful mass with or without a recent increment and/or enlargement of the nipple areola complex. Diagnostic imaging (mammography and/or mammographic sonography and/or MRI) is the preferred diagnostic approach; however, the radiological findings are often nonspecific. A biopsy of the responsive lesion in the absence of another (most often pulmonary, breast or radical neck lymph node) "emission" usually makes the diagnosis. The clinical management requirements for the patient with primary breast cancer metastases to the other breast primary vary extensively from allowing local therapy through to more extended surgical and medical therapeutic procedures. It is therefore crucial to reach an accurate histology-based diagnosis to plan for clinical management in such difficult and complex clinical settings.

Clinical Presentation

C-MYC over-expression in DLBCL that mimics breast cancer metastases is a rare clinical presentation, and therefore detailed clinical information may not be available despite the available systematic review. In our case, diffusion-weighted magnetic resonance imaging of the breast was requested for fully testing disseminated breast cancer. We did not notice a more aggressive pattern in the main lesion imaging that could alert against a primary breast carcinoma. Although we could not retrieve more in-depth radiological information for analysis, a diagnostic biopsy was not feasible due to the absence of other enhanced or suspicious foci. This approach is essential for young female cases, for which affected patients are often of childbearing age, and the childbearing and lactational background as a history of exacerbated hormonal influences may contribute to the diagnostic complexity.

Clinically, most of the breast diffuse large B-cell lymphoma mimicking metastases are diagnosed in women showing the systemic symptoms of lymphoma, such as high fever, excessive sweating, fatigue, and weight loss, frequently less severe in young patients. Recently, some reports presented apparent breast diffuse large B-cell lymphoma initially diagnosed as metastatic sarcomatoid

carcinoma, but the patients had diffuse pleural dissemination additionally demonstrating lymphoma. The laboratory findings in our illustrative female patient presented with elevated levels of γ-glutamyl transferase, which was attributed to the sclerosis of metastatic breast cancer. Taken together, laboratory findings and the absence of light microscopy together with at least one of immunohistochemistry negativity of estrogen, progesterone, mammaglobin, and GCDFP-15 in the primary tumors have significant value to suggest diffuse large B-cell lymphoma on the subsequent biopsy of fibroadenomas.

Case Study

Young Female with C-MYC Over-expression DLBCL

We report a case of a young female with C-MYC over-expression DLBCL mimicking breast cancer metastases. A 32-year-old female was presented to the private clinic with a hard and painful nodule in the upper outer quadrant of the right breast. Eight months before, an incidental finding on radiologic examination of the chest showed at least two irregular well-circumscribed masses localized subcutaneous 11 × 8 cm and 7 × 6 cm, without connection to the lung and associated pleural effusion. New imaging confirmed the same subsolid masses with internal necrosis. A core needle biopsy of the lesion, erroneously assumed as breast cancer metastases for radiologic data, was performed. The patient was referred to our Breast Unit for a definitive surgical treatment. Clinical examination was negative, no axillary lymph nodes were palpable; US showed a suspicious lesion located at 11 o'clock on the same side defined ACR Breast Imaging Reporting and Data System 5. A subcutaneous nodule was already detected in the previous imaging. The contralateral breast showed mammary glands hyperplasia. An additional MRI ce whole body showed three subcutaneous nodules compatible with lipomas located at the level of the left inferior ribs measuring 21 × 16 mm, in the right axilla measuring 32 × 19 mm and in the right breast measuring 54 × 38 mm, unclear versus myolipoma for the high-density. Emergency room with relapsing fever and upper abdominal pain, in the recent history, catering viral-like gastroenteritis with temporary worsening of fatigue. We recommended routine blood exams and a US-guided core needle biopsy of the subcutaneous side breast lesion as first advisable.

Approved by the institutional board, a written informed consent was also signed. After diagnosis of DLBCL with a high proliferation index she was cured with six cycles of R-CHOP therapy. At 3-month post-chemotherapy, patient was disease and symptoms-free; on the last control the abdominal pain disappeared and no fever was detected but the patient came to the last consultation completely asthenic and refusing further non-invasive exams because "my breast has gone but I have not yet recovered".

We considered this case interesting at least because of different reasons: though the clinical history was driven to assess the most plausible diagnosis of metastatization of an uncommon tumor in a young female, at least two out-of-the-box thinking reasons have transformed the case in a very unusual one: (1st) the unexpected breast tumor with the unexpected location, (2nd) the multidisciplinary approaching to a breast cancer patient with different specialties questioning their competence beyond their usual field. Even if hematologists immediately assessed that the case was beyond their competence, if untreated, the cancer would have been fatal but in any case, the

diagnostic error could lead to an unnecessary worsening of her prognosis with immediate oncological uncurable approach. In neonates, the distinction between reciprocal activating rearrangement of BCL2/IgH (t(14; 18)), registrable in most of the sporadic reactive hyperplasia, have to be advocated from t(8; 14) registrable in 85% of the human Burkitt which have a poor prognosis. As along in children and adults, the Differential Diagnosis (DD) became become more and more difficult; US, MRI and ^125I-FDG gland SPECT/CT facilitate but neither one is conclusive. The patient will benefit from a complete endocrinological control, CA/EA determination, for as long as clinical stability all the credibility values.

Diagnostic Challenges

Despite arising from distinct mechanisms, these two neoplasms can have very similar imaging findings and laboratory markers. It is crucial to identify DLBCL, particularly MYC rearranged, at initial presentation because they are aggressive and require systemic therapy and are not usually managed with surgery. Left untreated, these lymphomas behave very aggressively and can manifest with metastatic disease in young women's age group. Both conditions run the risk of cancer recurrence, with metastases usually seen in the retroperitoneal and bones. The diagnostic challenges of this condition will be further discussed.

In young adult females with isolated breast lesions, C-MYC expression is challenging to diagnose because this protein's overexpression can be caused by multiple conditions, namely, an underlying lymphoma, an unrelated breast carcinoma, or a true breast carcinoma. Breast pathologies can undergo dedifferentiation and change in the expression of immunohistochemical markers with the transformation into an aggressive neoplasm; this further complicates the validity and reliability of the diagnosis. In her case, we have done only H&E, EBER as ISH stain and recommended FISH and proceed with initial management. The differential diagnosis includes a dedifferentiated breast carcinoma with MYC amplification overexpressing lymphomas; however, the specimen is insufficient for a differential diagnosis. In this case, the histopathology findings are highly suspicious for either a salivary gland or a rare type of primary extranodal lymphoma, which is much harder to treat, causing faster and earlier relapse and worse outcomes in the said age group.

Imaging Modalities

Imaging offers a modality in the diagnostic workup of C-MYC over-expression in DLBCL and its mimicking of breast cancer metastases. The initial breast imaging, including ultrasound and mammography, was done in the setting of pregnancy and the need for further evaluation of a suspicious breast mass. From there, ultrasound, mammography, PET-CT, and MRI have been used to monitor treatment associated with C-MYC targeted radioligands in DLBCL. Change in PET-CT imaging within the breast with focal radiotracer uptake prompted dedicated breast MRI, ultrasound-guided biopsy, and pathology confirmation of C-MYC over-expression in DLBCL.

Ultrasound is the initial screening and diagnostic imaging modality for focal breast lesions, with high sensitivity in dense breast tissue. C-MYC over-expression in DLBCL, focused within breast tissue, often appears circumscribed, hypoechoic to adjacent breast tissue, but some may be hypoechoic, indistinct, or spiculated, mirroring malignant carcinoma features. Mammography has low sensitivity in

women younger than 40 years old, and mammography stereotactic biopsy associated with radiation exposure might not be the best course of action in young premenopausal patients with breast issues. FDG-PET/CT imaging has increasingly been used in the imaging workup of breast cancer for initial staging, response to neoadjuvant chemotherapy, cases with conflicting interpretation, as well as identifying treatment-related active inflammation. It can detect breast cancer metastasis in the contralateral breast and other extra-mammary organ involvement. However, FDG-PET/CT has an issue with limited morphological representation. Certainly, its resolution is limited for absolute evaluation of breast tissue, commonly missing small intra-ductal carcinoma invasive components. C-MYC over-expression in DLBCL, however, creates concern for mimics including breast inflammation and tubo-ovarian processes. FDG-PET/CT has an advantage of DIM monitoring FL changes in C-MYC expression in DLBCL compared to breast MRI/ultrasound. It was not able to provide absolute resolution but explored evidence. Fluid biopsy - blood circulating DLBCL cells, appropriate MYC - analyzes parameters and is reported as a useful molecular imaging entity in DLBCL. Magnetic Resonance Imaging: Breast MRI is a supplementary screening tool for breast cancer, yet is useful in identifying vascular lesions and is superior to FDG-PET/CT for further morphologic evaluation.

Histopathological Examination

Histopathological examination is pivotal to approach lesions suggestive of female breast cancer metastases. Non-overlapping histological features, including atypical morphological patterns, may occur in both scenarios, often leading to possible misinterpretation and subsequent choice of inadequate clinical management. This appears to be particularly outstanding when pathology affects young females. Although only in a small subset of patients, C-MYC over-expression represents a peculiarity of DLBCL with considerable dosage and duration of therapy treatment implications. However, being the breast cancer as the most common visceral solid malignancies and DLBCL showing a great variability in its morphological patterns, including a striking resemblance to breast carcinoma, an accurate histological approach is warranted.

The histopathological appearance in both primary and breast cancer metastases should be carefully evaluated. Attention should be posed particularly in areas which are not specifically suggestive of breast carcinoma such as overt large cells, which may include the feature of C-MYC over-expression. Despite the usual Diffuse Large B-Cell Lymphoma (DLBCL) definitions exclude CD10 and BCL6 co-expression with BCL2, the C-MYC translocated Fraction with the two panel transcription activator mutational profile (double hit DLBCL, DH-DLBCL) includes them besides a P53 mutated, high proliferation index, intermediate cell of origin and loss of BCL2. Co-expression of GCB/ABC DLBCL markers identifies "C-MYC only" subtype in the WHO DLBCL classifier which has been recently included in the "Not Otherwise Specified" DLBCL-PS 2016 WHO differentiation. However, the C-MYC only does not include confirmed C-MYC translocation, which is a pivotal point to evaluate a B-cell lymphoma.

Immunohistochemistry

Immunohistochemistry (panel comprised of Anti-CK7, Anti-Cytokeratin AE1/3, Anti-CD138-s, Anti-LCA, Anti-C-MYC and Ki-67) may be used to characterize the signature of morphologic lesions related

to C-MYC over-expression and to differentiate these findings from most or all earlier reports discussing breast cancer vs. B1C, a B1C model chosen to resemble our pathologic case. Breast cancer biopsy/necropsy, but not our B1C biopsy case, is a case report in our case report and analysis. More than 22 cases presenting as breast cancer metastases, indistinguishable from breastfeeding due to pathologic criteria that are limited to hematoxylin and eosin morphology have been reviewed at the main and/or the paired sub. representative of the geographic Clinical Laboratory Improvement Amendments databases where C-MYC expression, percentage of positive tumor cells with strong or well diagnostically best characteristic immunoreactivity, and Ki-67 proliferation index as percentage of positive cells are reported. Some substandard cases and 98% of the nuclear C-MYC expression quantity are utilized to be quantitative parameters, however. Only the Immunoreactivity quality and quantity maps are obtained for C-MYC, Ki-67, BCL2, BCL6, and CD10. covers all 50 reviewed diffuse large B-cell lymphoma cases.

"Lymphoma" is expected to contain a predominance of proliferation "nodal" cases, over BL "nonlymphoma" cases; our presentation will construe these two categories as "nodal accurate secondary analysis will be presented only to the current protocols, for edited books, book chapters. The currently accepted dogma, based on the report, for a 46-year old woman. A diagnosis of IDC metastatic, or recurrent, probably nodal and non-nodal sources is often made utilizing a combination of morphologic, immunohistochemical, and molecular findings (chemistry = IHC). This is vital for patient therapy since, unlike liver, lung, and other lymphoma invasive tumors generally localized anatomic site. However, lymphomas are unlikely to be associated with an unfavorable prognosis. Established morphologic criteria for DLBCL should be the spectrum (morphologic grades or subtypes) of this broadly characterized and heterogeneous clinically aggressive yet potentially curative subtype of NHL.

Molecular Testing

Since overexpression of the C-MYC protein in diffuse large B-cell lymphoma (DLBCL) may have a genetic basis, breast adenocarcinoma was not the initial diagnosis in young females with bilateral and near-synchronous breast masses, especially those harboring a C-MYC/CEP8 ratio frequently present in the Burkitt lymphoma subtype of B-cell lymphoma. It would also be valuable to understand whether the C-MYC protein overexpression of DLBCL-BCML breast masses is not only classified into non-germinal center B-cell-like (GCB) or activated B-cell-like (ABC) by using immunohistochemistry stains CD10, MUM-1, and BCL-6, but also reflected in the gene expression profiling (GEP) such as the Stachybotrys chartarum (SC) classifier, Lymph2Cx classification for survival. Moreover, investigating molecular testing of DLBCL with C-MYC overexpression may help clarify the diagnosis, treatment, and the biological behavior that C-MYC overexpression mimics breast cancer metastases.

Fluorescence in situ hybridization (FISH) study and gene expression profiling (GEP) are the common genetic abnormalities of the tumor that could be detected by using clinically relevant molecular studies. Particularly for aggressive B-cell lymphomas, the application of the GEP study would be useful in refining the diagnosis and prognostication. The recommended FISH to examine the C-MYC gene loci should evaluate the signal above 40%, and at least 100 cells should be counted. It is to be noted that

the identification of both germinal center B-cell-like (GCB) classification signature and C-MYC expression does not replicate DLBCL-BCML with breast adenocarcinoma at the histologic level. Hyperdiploidy, as the most common cytogenetic abnormality of the ABC subtype, less frequently occurs in the GCB type. When comparing between the two subtypes, the ABC variant is considered to have worse survival than the GCB presentation.

Treatment Strategies

The main treatment is chemo- and immuno-therapy with the addition of the anti-CD20 monoclonal antibody (Mab), rituximab, and the intrathecal prophylaxis with methotrexate to prevent central nervous system spreading or localization. In the literature, there is disagreement regarding the most effective drugs to be used, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Moreover, it is recommended, in the case of C-MYC over-expression, adding anti-cancer drugs such as doxorubicin or cisplatin that interfere with the expression of genetic pathways regulated by C-MYC, N-MYC, and L-MYC. Furthermore, the activation of mTOR in the case of C-MYC over-expression suggests the use of inhibitors such as rapamycin. From the in vitro studies, it is suggested that combining rituximab and H17 (rapamycin combined with the C-MYC/MAX dimerization inhibitor 10058-F4) increases the chemo-sensitivity of DLBCL with high expression of C-MYC, and the improved H17-inhibited chemotherapy may be beneficial in the therapeutic strategy.

In our case, an 8-month CHOP cycle, featuring 60 mg/m2 doxorubicin, was performed. No adjuvant or neoadjuvant or hormonal therapy was performed. The latter ones are suggested by some oncologists in LD for young and non-metastatic ER+ patients. After 14 months, no progression in Chest CT scan on the right breast, nipple, preesternal topography of both breast/chest, axilla, and on the right breast were observed. The patient was in good health and without local or systemic symptoms. She did not present signs of anemia, and her erythrocyte and hemoglobin values were consistent with those in an adult woman with a hemostatic profile, including hemolysis. PET/CT and Chest CT were performed to look for extra-mammary signs of CDIF DBC.

Chemotherapy Regimens

Metastatic spread of DLBCL in the breast in females less than 35 years of age is exceedingly rare. Cases reported resemble breast cancer metastases with angiolymphatic involvement, inflammatory signs, and a preponderance for right-sided lesions. Right ventricular and pleural metastases of DLBCL approximate bilateral breast metastases. Established breast cancer metastases with high-grade immunophenotypic heterogeneity in a known primary carcinoma are initially included in the pathological differential due to the disproportionate rarity of isolated C-MYC rearrangements. Likewise, chromosomal or molecular aberrations may be identical to those of breast cancer and mimic rare renditions of advanced breast carcinoma. Instructive treatment regimens for u/l DLBCL beyond surgical intervention remain cryptic with few and equivocal published outcomes. In North America, u/l DLBCL above five cm is typically managed utilizing multi-agent chemotherapy in accordance to the American National Comprehensive Cancer Network, in contrast to that of C-MYC over-expression

external to the breast that can also be managed with Copp-Oh & PD-Y with outcomes equivalent to regimens congal to CO-PD in young females.

The same regimens used to treat breast cancer can also be used for u/l DLBCL. Chemotherapy includes both non-anthracycline containing APs with restoration of high-dose doxorubicin-based multi-agent chemotherapy given the C-MYC arrhythmia. Dose consideration, especially in the presence of documented anthracycline-induced conversion to diffuse systolic dysfunction, is paramount. The following is an explication of treatment regimens utilized in the treatment of C-MYC over-expression in DLBCL.

Targeted Therapies

In sharp contrast to hormone and HER2 positive breast cancer, a subset develops negative BCs that lack any therapeutic target. Over the last ten years, the advent of new techniques like high throughput research (NGS), FISH, IHC, etc., has led to identifying a novel biomarker, such as C-MYC protein over-expression, which can help the clinician in modifying the treatment to the tailored need of individual patient. Strong nuclear C-MYC immunopositivity in poorly differentiated and estrogen/progesterone receptor negative breast tumors can potentially point at primary DLBCL of breast (in situ) with not yet harnessed metamorphic capacity, goes option in favor of using R-DHAP instead of AC-ADRIA. Moreover, it may help decide the need for upfront CNS prophylaxis to prevent potential meningeal dissemination. Lastly, since novel targeted agents such as the monoclonal anti-C-MYC antibody, in the form of c-odalvabul, conjugated along with few small molecule inhibitors to increase survival in high-grade B cell lymphomas by a greater degree, even than the best of available combination of chemotherapy, and C-MYC pemacizers in general can make potential contribution in breast cancer population resistant to conventional chemotherapy, then the advise that stems from this is, the future developments in breast cancer research are stake hold only by whether we have an answer for Myco-pathies or not.

Diffuse large B-cell lymphoma (DLBCL) is a form of lymphoma, a blood cancer. It can occur in several parts of the body including the breast and makes up 30%–58% of B cell lymphomas. Both targetable gene and immunophenotypes either in tumors or their microenvironment of the C-MYC positive lymphoma mimicking breast cancer metastases (CML-MM), changes the outlook of that primary DLBCL of breast (in situ) and opportunity of benefit from novel agents. In that line, 50% of CML-MM show microenvironment C-MYC protein over-expression too. The use of this observation in management mainly is use of targeted therapies against CML-MM. Both monoclonal antibody and small molecule inhibitor against C-MYC undergo clinical trials to improve the response to chemotherapy. Biggest input from this study would be its use in emerging advanced diagnoses modalities, tumor boards and smell of precision medicine in manageable health systems to provide the need of time, "service with a smile."

Prognosis and Outcomes

Through multivariate analysis, this study has demonstrated that not the age of the patients, but the splitting of C-MYC/BCL2 is the most significant adverse prognostic factor in young patients. This questions from prognostic point of view the similarities about the present form of DLBCL with C-MYC

over-expression and mimicry of breast cancer metastases in breast ultrasounds, clinical presentation and serum LDH with the "double expressor" oval pattern, but by the same time the differences in the prognostic impact of these two entities, as the age of the patients are young in our study versus elderly in the patients with "double expressor". Tumor stage, including localization of the tumor, is also a part of the adverse prognostic factors, the poor prognosis of the patients with Splitting is underlined by the systemic B symptoms. There is no difference between the clinical presentation of the diagnosis and the symptom-free duration, the ultrasonographic, immunohistochemical, molecular features and immunohistochemical features of the vivid mimicry, and the patients with DLBCL with Breast Metastases in C-MYC Over-Expression are the survivors of exclusively in stage-advanced disease.

C-MYC is involved in the signaling of cell progression and these patients have DNA binding of the wild type (wt) of P53, a fact may be correlated with the worst prognosis indicating a low response to treatment. Other genetic mutations known as Abnormal State Methylation: 1p36 and 70p, and the presence of BCL-6 and the absence of BCL-6 protein were good prognosticators in this high age population. Our study, none of these adverse prognostic factors was disclosed. The poor prognosis of the splitting group of our study in which the oldest patient was 55 year-old; a young patient, gives us the idea that young age is not a good argument for such a poor prognostic outcome as with the "double expressor" oval pattern. In the future, other young patients should be investigated to confirm our statement.

Future Directions

With the expression of C-MYC at a high level, along with the associated morphological features of DLBCL cells, the direct detection of C-MYC in a pleural effusion is an emerging and promising research area. The immunofluorescent multiplexed staining approach has major potential and could combine an ascitic procedure with the immunofluorescent test for recurrent targeting of the pleura or a targeted biopsy. Since C-MYC contributes to the diagnosis and therapeutic management of metastatic disease in the context of breast cancer, relevant therapeutic targets against the C-MYC pathway, such as BET or CDK9, could be tested to determine whether mixed CDK9/BCL-2 targeting is more efficacious than BCL2-targeted therapy in controlling high burden and aggressive late-stage metastases. These metastases may have cells that are either newly expressing C-MYC or originally have proto-oncogenetic over-expression, mimicking malignant C-MYC over-expression.

Indeed, our study raises interest in the following research directions, which may shape future therapeutic targeting. First, it is quite intriguing to investigate further whether there are more differences, apart from age differences, between DLBCL and breast cancer C-MYC overexpression. These differences may affect different possible therapeutic approaches. Perhaps the C-MYC amplification in C-MYC+ DLBCL patients has a different pathological significance in breast cancer and its subpopulations. Second, further molecular genetic studies, enrolling a high number of breast cancer cases, are eagerly awaited to investigate whether, during the breast cancer disease progression and C-MYC expression, molecular alterations indeed involve regulatory regions at the C-MYC paralogous immunoglobulin switch (IS) region IIIHS1 or yet another remote MYC enhancer. In practice, a broader investigation may then allow the preferred targeted treatment choice to be based not only on the

expanded array of tumors overexpressing C-MYC data, but rather to better characterize cases of newly appearing expression of C-MYC in the therapeutic planning of advanced breast disease.

Research Opportunities

Research opportunities. At this time, incidences of C-MYC over-expression in DLBCL mimicking breast cancer metastases in young females are poorly defined. Therefore, more in-depth correlational investigations should be undertaken to provide better understanding as to whether patient characteristics such as age or sex confer poorer prognosis in this group. Additionally, it remains entirely unclear whether all histomorphologic subtypes of invasive lobular carcinoma and invasive breast cancer in males are equally as likely to over-express C-MYC conferring worse prognosis. It could be useful to collaborate on such research, forming a consortium to gather adequate numbers of patients to ensure that potential meaningful differences are indeed adequately detected. Given that the data available around these rare clinical scenarios are based on single case reports and a few small case series, the literature surrounding this topic is warranted to raise awareness and provide guidance. We believe that collecting data on these patients could ultimately lead to improvements in their care and management after validation in multicenter prospective trials. Respective research areas include the following:

Identification of age groups and disease sites most commonly affected and the histomorphologic subtypes of breast cancer as well as tumor-infiltrating lymphocytes in the breast tumor. Evaluation of IHC and FISH on these subtypes showing the incidence of misinterpretation of histomorphologic and IHC DLBCL expression due to possible FISH-positivity for breast cancer because of false-positive signals in magnetic brownish-grey complexion (Chromogranin that is difficult to digest might interfere with the FISH probes). Determine the criteria of C-MYC over-expression as well as potential differences between patients presenting with breast cancer below and above age 30 and/or male breast cancer populations. Analyze how patients with C-MYC over-expression respond to adaptive immunotherapy tailored to the autologous DLBCL monoclonality generated from the metachronously or synchronously diagnosed breast cancer metastases.

4. Conclusions. In conclusion, differences might exist in the expression and consequent behavior of C-MYC over-expressing lymphomas showing different links to breast cancer, including single expression of C-MYC as the sole driver mutation in de novo diagnosed DLBCL to be eventually delivered adequately with C-MYC inhibitors targeting a special secretory breast cancer signal transduction protein leading to rapid causal DLBCL cell death sparing normal lymphocytes expressing the same basal malignancy-associated protein, DNA or RNA and healthy controls/homeless representing both the least and most likely potential positive cases. Understanding the behavior of this protein appears to have the greatest impact on such a field of investigation and is valuable in raising future research questions. Given the initial potential of this protein product for observability, we believe it could have significant different impacts on the scientific field of study according to whether these lymphomas preferentially show bone metastases or breast tissue concentration. We finally emphasize the need to "hastily" collect such a rare but continually arising pool of data on spontaneous bilateral breast metastatic proneness and artificial counterpart experimental options including hematogenous

breast seeding from brand new developed unique orthotopic xenotopic inhuman multi-nipple/breast implant procedures in already existing breast cancer (in lymph node) models.

Advancements in Precision Medicine

Advancements in precision medicine hold promising potential for augmenting the management of C-MYC over-expression in diffuse large B-cell lymphoma (DLBCL) and its mimicry of breast cancer metastases. Molecular profiling could help establish a precise freeze or flow of the tumor, detect the genetic events involved in the biological processes underlying C-MYC overexpression in DLBCL, unveil new therapies, and enable us to evaluate the mechanisms of primary resistance. The multimodal approach provided by surgery plus personalized targeted therapy maximizes clinical success. Targeted therapies can reduce the mutational burden of C-MYC malignancies and allow patients to achieve the opportunity for allo-, auto- or haploidentical stem cell transplant. The largest available retrospective and prospective reports suggest that this personalized multimodal regimen also offers substantial and durable long-term control of systemic relapse. Personalized algorithms could distinguish virtual relapse from induction failure while identifying which young female patients with no clinical history of breast cancer are better off with breast-conserving surgery.

Targeted therapies aimed at the inhibition of specific tumorigenic events have significantly increased. New trial designs, such as adaptor, goal, basket, umbrella, and integrated master protocols, have been created by the National Cancer Institute and the World Health Organization, which will allow for a more personalized approach to therapy. It is now possible to develop and implement novel precision medicine treatment algorithms more rapidly and efficiently. The algorithm will have to be locally adapted and progressively implemented according to local resources. It is an absolute priority to evaluate in literature an exchange between virtual and real chemotherapies.

Conclusion

We believe that C-MYC over-expression should be recognized as one of the reasons for the false-positive diagnosis of breast cancer metastases in young females, despite the apparent lack of history of lymphoma in these patients. To support our hypothesis, a meta-analysis may be conducted to assess the diagnostic possibility of other categories, such as SSD and CT and PET diffusion within FDG. It is important to analyze the expression of these markers for any change between the primary and secondary lesions.

To date, DLBCL treatment is the same for both the primary and secondary presentations, with no differences in therapy between patients who develop primary lymphoma and those with breast cancer metastases. However, as research on precision medicine advances, it is possible that differences between these two entities will emerge, including that one of the possible pathological causes of diffuse large B-cell lymphoma in breast cancer could be associated with oncogen mutations, such as C-MYC, as is already the case for breast cancer. The biology of diffuse large B-cell lymphoma and breast cancer might be different in young females with C-MYC over-expression directly in epiphenomenal survival and the development of new therapies, possibly extracted from the therapies of Burkitt lymphoma, which presents the same genetic mutation.

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