Intravascular Large B Cell Lymphoma of the Breast: A Rare Entity

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ABSTRACT: Intravascular large B-cell lymphoma (IVLBC) is a rare and high-grade disease of neoplastic lymphoid cells within the vascular lumina of small- to medium-sized vessels. The disease carries a grim prognosis despite robust treatment protocols. We discuss the case of a 58-year-old female who presented with mammographic screening abnormality which led to more investigations and ultimately to this diagnosis. The patient had no prior history of a lymphoma or in situ and invasive carcinoma of the breast. To our knowledge, IVLBC of the breast is a very rare and an unusual location for this type of a lymphoma and so far, only five reported cases. Through our case report, we not only discuss the case but also review literature on this rare entity.

KEYWORDS: Intravascular, non-Hodgkin, B-cell lymphoma, breast

Introduction

IVLBC was first reported in 1959 by Pfeger and Tappeiner as “angioendotheliomatosis proliferans systemisata.”¹⁻⁴ IVLBC or angiotropic lymphoma is a rare entity characterized by exclusive or predominant growth of neoplastic cells within the lumina of blood vessels.¹⁻³,⁵⁻¹⁵ The understanding of intravascular lymphoma (IVL) is very limited considering that the literature available on this malignancy is almost exclusively based on case reports, cumulative reviews and occasional studies.⁵,⁶,⁹,¹³ The clinical and biological behavior of the neoplasm is largely unknown with approximately half the cases being diagnosed on autopsy, and many ante mortem diagnoses are rendered in biopsies performed for other reasons.⁵,⁸,⁹,¹¹ It usually affects middle-aged or elderly patients and follows a wide pattern of dissemination in extranodal sites while involvement of nodal sites is rare.²,⁴,⁶,¹³⁻¹⁷

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma worldwide.¹⁵ Most cases of DLBCL, about 80% are classified as DLBCL, NOS. These neoplasms show a wide spectrum of histopathological findings. About 20% of cases of DLBCL are classified as specific variants.¹⁶ IVLBC is one such distinct aggressive variant of DLBCL.

Non-Hodgkin lymphomas rarely affect the breast, the majority of which are primary. Primary breast lymphoma (PBL) affect women, with only about 10 cases being reported in men.¹⁷ The overall incidence of PBL is less than 1% of all breast neoplasms. All histological types of lymphomas have been described. PBL are most commonly B-cell lymphomas; approximately one-half are DLBCL.¹⁸

While in our case, the patient presented with a radiological abnormality that warranted additional imaging studies and a subsequent biopsy of the concerned abnormality, there was no history of carcinoma in the ipsilateral or contralateral breast. However, some of the other cases in the literature do have a history of intraductal carcinoma and or invasive ductal carcinoma concomitant with the history of IVLBC.

Material and Methods

A 58-year-old female underwent routine screening mammogram study. The patient has no personal or family history of breast cancer and underwent last clinical breast exam within the past 1 year of her mammogram. The patient had complaints of vague fullness of the right breast. Clinical examination did not detect any palpable lumps. In addition, the skin overlying the breast appeared unremarkable without puckering and dimpling at the time of clinical examination. However, further investigations including mammogram, magnetic resonance imaging (MRI) and ultrasound guided biopsy of the right breast was performed.

The right breast demonstrated large area of focal asymmetry that involved the lateral half and predominantly the upper quadrant of the right breast. The left breast was unremarkable. The mammogram study was concluded as inconclusive and an MRI study with and without contrast was performed on both breasts for better characterization of the lesion. This study showed asymmetric skin and trabecular thickening of the right breast in comparison to the left breast. Two additional nodules were identified in the right breast.

This was followed by a unilateral right diagnostic call back mammogram and tomosynthesis and breast ultrasound which showed an indeterminate complex lesion at 8 o’clock position. In addition, two circumscribed nodular densities in...
the lower quadrant of the right breast, corresponding to the masses that were identified on MRI. Ultrasonography of the right axilla demonstrated no suspicious findings or any axillary lymphadenopathy (Figure 1).

A core biopsy was performed at 8 o’clock position, from the upper outer quadrant of the right breast. The core biopsies was formalin fixed, paraffin embedded, and stained with hematoxylin and eosin (H&E) stain. The morphology of the biopsy showed breast parenchyma and adipose tissue. The breast parenchyma consisted of benign ducts and lobules. However, the vascular lumina within the breast and in the adipose tissue were filled with neoplastic lymphoid cells with high nuclear cytoplasmic ratio, vesicular chromatin and prominent nucleoli. Brisk mitotic activity was also present.

Immunohistochemical stains were performed on Ultra-Bench Mark Stainer as per the manufacturer’s instruction using the following primary antibody clones: CD3 (2GV6), CD5(SP19), CD20 (L-26), PAX5 (SP34), BCL-6 (G1191E/A8), BCL-2 (124), CYCLIN D1 (SP4), Ki67 (30-9), CD79a (JCB117), MUM-1 (MUM1p), D240 (D2-40), CD34 (QBEEnd/10), AE1.3 (AE1/AE3PCK26), C-MYC (Y69), CD10 (SP67), ALK1 (LK01), CD30 (Ber-H2), CD23 (SP23), CD71 (MRQ-48), CD31 (JC70A), EBER-DNP Probe, EBER was performed using Blue ISH Detection KIT.

Fluorescent in situ hybridization (FISH) testing was performed on formalin fixed paraffin embedded block by Genpath using break apart and dual fusion probes for Burkitt’s lymphoma, DLBCL and follicular lymphoma.

**Results**

The microscopic examination of core biopsy showed benign breast tissue, ducts and lobules and adipose tissue. The small- and medium-sized vessels of breast and adipose tissue showed atypical large lymphoid cells within the lumens (Figure 2). The large cells were positive for B cell markers (CD20, PAX 5, CD79a, and dim BCL6), (Figure 4) partial CD30, partial dim BCL2, MUM1 (Figure 5A) and C-MYC expression of greater than 60%. The CD34, CD31 and D240 (Figure 3) immunotoxins highlighted the endothelial cells lining the blood vessels. The CD33 stained the myeloid cells, CD71 stained the erythroid cells within the lumen of vessels. The p53 stain showed dim to moderate staining in the neoplastic cells. The CD3 and CD5 stains highlighted background T cells (Figure 4D and 5C) and were immunonegative in the neoplastic lymphoid cells. The FISH test was negative and did not demonstrate MYC rearrangement, BCL2-IGH translocation, BCL6 breakpoint translocation and translocation t (8; 14).

**Discussion**

Organ biopsies are mandatory for the accurate diagnosis of IVLBC.

The brain and skin are considered the most frequently involved sites. Among the laboratory findings, increased
serum levels of lactate dehydrogenase and β2-microglobulin were present in almost 90% of the cases, while anemia was present in two thirds of the cases. It remains mechanistically unknown why the tumor is confined to intravascular spaces. IVLBCl has been known as the "oncologists' great imitator" for its myriad presentations. There are three major presentations of

Figure 2. (A and B) 10x and 20x H&E photomicrographs showing the intravascular distribution of neoplastic lymphoid cells. (C) 40x H&E photomicrograph highlighting the distribution of dyscohesive neoplastic cells within a vascular lumen. (D) 60x H &E photomicrograph that shows pleomorphic lymphoid cells within the vascular spaces. A mitotic figure is also identified which is highlighted.

Figure 3. (A and B) AE1.3 immunohistochemical stain highlights epithelial tissue. The normal breast parenchyma stains positive while the neoplastic tissue in the background is negative. (C and D) D240 immunohistochemical stain showing positivity in the vasculature and negativity within the vascular lumina that contains the neoplastic lymphoid cells.
IVLBCL: classic variant, hemophagocytic variant previously known as the Western and Asian variants, respectively, and cutaneous variant. Patients with the hemophagocytic variant display hemophagocytic syndrome (HPS) with bone marrow involvement, hepatosplenomegaly, and thrombocytopenia, findings not observed in classical or cutaneous variants.

Figure 4. (A) CD20, 20x immunohistochemical stain. (B) PAX5, 20x immunohistochemical stain. (C) BCL6 40x immunohistochemical stain. (D) CD5 40x immunohistochemical stain. (A to C) CD20, PAX5 and BCL6 stains highlight positivity in the neoplastic B cells. (D) CD5 stain highlights only the background T cells and is negative in the neoplastic B cells.

Figure 5. (A) MUM1 20x, immunohistochemical stain is positive in the neoplastic lymphoid cells. (B) CD3, 20x, immunohistochemical stain highlights background T cells, but is negative within the vasculature. (C) Ki67 20x, immunohistochemical stain which shows a high labeling index of approximately 90%.
The histological appearance is characterized by blood vessels, dermal and hypodermal dilates in which there is proliferation of large B cells, which can be responsible for thrombosis of arterioles, venules, and capillaries. Immunophenotyping of tumor cells reveal an almost constant expression of B lymphocyte marker CD20. BCL6 is co-expressed with CD5 in 20% of the cases.3,4

The mechanism via which the lymphocytes home to blood vessels largely remains unknown though some theories are suggested. IVLBCL cells lack some molecules, such as CD29 (β1 integrin subunit), which are critical for extravasation of lymphocytes and CD54 (ICAM-1) adhesion beta molecules. A few homeostatic chemokine receptors such as CXCR5, CCR6 and CCR7 are known to act on lymphocyte migration across vascular structures are absent in the neoplastic lymphoid cells of IVLBCL. IVLBCL does not seem to express matrix metalloproteinase-2 and -9, both molecules are important for parenchymal invasion.7,9,14,19

Molecular analysis reveals mutations in the MYD88 and CD79B genes, which is critical for extravasation of lymphocytes and CD54 (ICAM-1) adhesion beta molecules. A few homeostatic chemokine receptors such as CXCR5, CCR6 and CCR7 are known to act on lymphocyte migration across vascular structures are absent in the neoplastic lymphoid cells of IVLBCL. IVLBCL does not seem to express matrix metalloproteinase-2 and -9, both molecules are important for parenchymal invasion.7,9,14,19

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Table 1. Documented cases of IVBCL with demographic, radiologic and clinical outcome details.

| CASE NO | NAME OF AUTHOR | AGE AT DIAGNOSIS | HISTORY OF INVASIVE OR IN SITU CARCINOMA | SITE | TREATMENT | CLINICAL OUTCOME |
|---------|----------------|------------------|----------------------------------------|------|-----------|-----------------|
| 1       | Ho et al       | 75 years         | Invasive ductal carcinoma               | Right breast | R-CHOP   | Tumor lysis after chemotherapy, death 2 weeks following chemotherapy. |
| 2       | Monteiro et al | 80 years         | Negative                               | Uniform bilateral breast engorgement with peau d’orange appearance | CNOP  | Patient expired after eighth chemotherapy cycle due to increasing fatigue. |
| 3       | Alakeel et al  | 65 years         | Ductal carcinoma in situ               | Left breast   | Unknown  | Patient lost to follow-up. |
| 4       | Moling et al   | 48 years         | Ductal carcinoma in situ               | Right breast  | R-CHOP Intrathecal Methotrexate, steroids, and cyclosporine for MAS | Patient known to be alive, 2 years after diagnosis. |
| 5       | Herrscher et al| 75 years         | Invasive ductal carcinoma               | Left breast   | COP      | Patient expired within 2 weeks of diagnosis of skin lesion. |

COP, cyclophosphamide, (Oncovin) vincristine, mitoxantrone and prednisolone; COP, cyclophosphamide, (Oncovin) vincristine and methylprednisolone; MAS, macrophage activation syndrome; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine) and prednisolone.

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Ho et al describe a 75-year-old female who presented with a spiculated mass in the right breast on imaging. Patient’s history was significant for endometrial carcinoma. The pathology from the spiculated right breast mass showed an invasive ductal carcinoma with minimal intraductal carcinoma. The background vessels in the tumor’s vicinity harbored an IVLBCL. Patient was administered chemotherapy consisting of rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine) and prednisolone (R-CHOP). However, patient developed tumor lysis syndrome and expired 2 weeks after chemotherapy.15

Monteiro et al report an 80-year-old female who presented with uniform breast engorgement with peau d’orange appearance. Radiology demonstrated moderately dense breast tissue with poorly defined reticular patterns. Histological diagnosis of IVLBCL was rendered. The patient was started on cyclophosphamide, vincristine, mitoxantrone and prednisolone (CNOP) regimen. She expired after the eighth chemotherapy session due to increasing fatigue. No autopsy was performed. This again reemphasizes the importance of postmortem diagnosis which may enable a better and more detailed understanding of this nebulous entity.8
Alakeel et al describe a 65-year-old female who presented with clustered calcifications in the upper outer quadrant of the left breast. Histology demonstrated solid and cribriform patterns of ductal carcinoma in situ (DCIS). The background vessels demonstrated atypical lymphoid population within the lumina of the blood vessels. However, their report doesn’t provide details about the clinical outcome or treatment protocols as the patient was lost to follow-up.²

In a study done by Herrscher et al, a 75-year-old female presents with an already established diagnosis of invasive ductal carcinoma of the left breast who was being evaluated for neurological functions due to repeated falls. At the same time, the patient also developed peau d’orange appearance of the left breast. A skin biopsy was performed which led to the diagnosis of IVLBCL. The patient’s clinical condition continued to rapidly deteriorate. She was started on a regimen of cyclophosphamide, vincristine, and methylprednisolone (COP protocol). Rituximab was not initiated due to the possibility of worsening tumor lysis syndrome. Despite the appropriate clinical interventions, the patient expired within 2 weeks of the appearance of first skin lesion.⁴

Two of the case reports, however, show a more promising outcome. Moling et al²⁰ report a 48-year-old female who presented with a mammographic abnormality which on histology was diagnosed as intraductal carcinoma following which she underwent skin sparing mastectomy and had a silicone prosthesis in place. Four years after this procedure patient presented with fever, pancytopenia and lab studies revealed hypertriglyceridemia and hyperferritinemia. A possibility of MAS/HLH (macrophage activation syndrome/hemophagocytic lymphohistiocytosis) was considered and patient was put on dexamethasone with immunoglobulin and cyclosporine. The patient’s capsule was a possible contributor to the patient’s condition. A histological examination of the capsule revealed a surprising diagnosis of IVLBCL. Patient was administered the R-CHOP regimen and intrathecal methotrexate. Follow-up on the patient revealed that she was alive and was continuing to regularly undergo 3 months follow-up visits. The relationship between silicone implants, MAS/HLH and IVLBCL is yet to be understood and this association needs to be explored.²⁰ Though this report is seen in the setting of a breast implant, we included this in our report to highlight the quotient of surprise and rarity of this lesion in this location be it breast or the capsule. Rahmani et al² describe a pregnant female patient who showed involvement of placental disk vessels and small bowel vessels with large lymphoid cells of IVLBCL. Subsequent bone marrow biopsy also showed involvement of marrow by IVLBCL. This patient received a matched related allogenic bone marrow transplant and was known to be alive at the time of the report which was 18 years post transplant.⁷ This report raises the important question of utility of bone marrow examination for staging and transplant in the setting of IVLBCL. Retrospective review of breast biopsy showed atypical small cells with immunophenotype similar to the large cells.

Our patient has a relatively new diagnosis of IVLBCL. She has no other significant risk factors at present. This patient is out of our hospital network and follow-up on her clinical history has been obscure. However, close attention needs to be paid to the patient’s clinical course as chemotherapy regimens can initiate tumor lysis syndrome which can be fatal if not treated promptly.

**Conclusion**

Since IVLBCL is a rare disease and can present itself as a great masquerader, immense attention needs to be paid lest this is an easily missed diagnosis. Careful review of fatty and parenchymal compartments of the breast must be performed as these entities can present exclusively or also in association with synchronous carcinomas. Although, the biological properties of neoplastic cells remain unclear, a better understanding of the immunophenotype, and understanding of the variants is of paramount importance. However, the relationship of this disease associated with solid tumors or other lymphomas and implants such as silicone need further investigation. As medicine continues to evolve every day and new treatment frontiers like immunotherapy become more accessible and easily available for patients improved treatment outcomes can be expected as newer drugs emerge.

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**Author Contributions**

All authors contributed to the study conception and design. The first draft of the manuscript was written by NP, HS, XZ and SS critically edited the manuscript.

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