

Case Report

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Asynchronous Bilateral Primary Breast Lymphoma: Case Report and Literature Review Case Report

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Abstract

Primary Breast Lymphoma (PBL) is a rare form of extra nodal lymphoma defined by the presence of a primary lesion within the breast with or without regional nodal involvement, but no other extra-mammary sites of involvement. Bilateral PBL is even rarer with very few cases reported in the literature. Herein, we report a case of PBL, who after 27 years, developed PBL of the contralateral breast. In this review we will describe incidence, clinical presentation, histological subtypes, treatment, outcomes, and etiologies for PBL.

1. Introduction

In 1995, at the age of 48, the patient presented with a rapidly growing, painless left breast mass. Staging with CT of the chest/abdomen/pelvis showed no other abnormalities. She underwent lumpectomy. Pathology showed a diffuse, high-grade, large cell, Non-Hodgkin's Lymphoma (NHL), LCA positive. Margins were positive. She underwent CHOP chemotherapy x 6 cycles and radiation therapy (5040 cGy in 28 fractions to left breast, supraclavicular, and axillary nodes and 1000cGy boost in 5 fractions to the lumpectomy site). There was No Evidence of Disease (NED) in follow up.

In 2022, at the age of 75, the patient presented with a rapidly growing, painless right breast mass. Right needle core biopsy showed atypical lymphoid infiltrate, favoring lymphoproliferative disorder. PET/CT showed a right breast mass measuring 6.7 x 3.2 cm with SUV maximum of 8.5 and a right axillary node measuring 14 x 5 mm with maximum SUV max of 1.5. Right breast excisional biopsy showed involvement by a Diffuse Large B-cell Lymphoma (DLBCL), germinal center phenotype. By IHC, the tumor was positive for CD10 (weak, subset), CD20, BCL6, PAX5 and negative for CD5, MUM1, BCL2, CD30, and cyclin D1. BCL2,

BCL6, and MYC rearrangements were not detected. EBV by in situ hybridization was negative. Ki-67 proliferation index was 50-60%. Patient elected for bilateral mastectomy. Right mastectomy showed diffuse large B-cell Non-Hodgkin's Lymphoma (NHL) as noted above with a positive margin. One axillary lymph node was negative. Left mastectomy showed benign breast tissue, negative for lymphoma.

Echocardiogram was normal. LDH was normal. ECOG status was 0. She underwent R-CHOP chemotherapy x 3 cycles (total Adriamycin dose 360 mg/m²) and radiation therapy (3600 cGy in 18 fractions to the right chest wall). The CNS International Prognostic Index showed her to be low risk with a score of 1 (due to age >60), but she did have Stage IE DLBCL of the breast which is a possible NCCN guideline for CNS prophylaxis. After discussion, mutual decision was made not to undertake CNS prophylaxis. Repeat PET/CT obtained six months following completion of therapy revealed NED. Patient has no family history of any cancers. Invitae Multi-Cancer Panel, Hereditary Lymphoma Panel, and Preliminary Evidence Genes for Lymphoma identified no pathogenic inherited variants (129 genes total assessed- see Figure).

Genes Analyzed:

ACAN, ACD, ADA, AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CARD11, CARMIL2, CASP10, CASP8, CASR, CD27, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A (p14ARF), CDKN2A (p16INK4a), CEBPA, CHEK2, CTLA4, CTNNA1, CTPS1, DICER1, DIS3L2, DOCK8, EGFR, EPCAM, FADD, FAS, FASLG, FCHO1, FH, FLCN, GATA2, GPC3GREM1, HOXB113, HRAS, IKZF1, IL10RA, IL2RA, IL2RB, ITK, JAK1, KIT, KLHDC8B, MAGT1, MAX, MCM4, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NPAT, NTHL1, PALB, PDGFRA, PHOX2B, PIK3CD, PICK3R1, PMS2, POLD1, POLE, POT1, PRF1, PRKAR1A, PRKCD, PTCH1, PTEN, RAC2, RAD50, RAD51C, RAD51D, RASGRP1, RB1, RECQL4, RELA, RET, RHOH, RMPRP, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SH2D1A, SMAD4, SMARCA4, SMARCB1, SMARCE1, STAT3, STK11, STK4, STXPB2, SUFU, TERC, TERF2IP, TERT, TET2, TMEM127, TNFRSF13B, TNFRSF9, TP53, TPP2, TSC1, TSC2, VHL, WAS, WRN, WT1, XIAP

Figure: Genes Analyzed within Invitae Multi-Cancer Panel, Hereditary Lymphoma Panel, and Preliminary Evidence Genes for Lymphoma Panel

2. Discussion

PBL, first defined by Wiseman and Liao, requires the primary lesion to be within the breast with or without regional nodal involvement but no other extra mammary sites of involvement and no antecedent diagnosis of lymphoma [1]. PBL tumors are classified as either Stage I (breast-limited) or stage II (limited to breast and ipsilateral axillary ganglia) [2]. Based on the SEER database, the overall incidence of PBL is 1.35/1,000,000 with a significant upward trend from 1975 to 2017 [3]. PBS accounts for <0.5 % of breast neoplasms and 2.2% of extra nodal lymphomas [4,5]. Asynchronous bilateral PBL has only rarely been reported. In this case report, there was a hiatus of 27 years between diagnoses of PBL. To our knowledge, the longest interval between asynchronous PBL was previously 11.5 years [5].

The average age at presentation for PBL is in the fifth and sixth decade of life [6]. Most are women, but male PBS has been reported [7]. Most PBL presents with a painless, enlarging breast mass and is found more commonly in the right breast compared to the left [8]. Most patients do not present with B symptomatology [9,10]. Bilateral involvement at presentation occurs in approximately 11% of PBL cases and more commonly affects younger women during pregnancy or in the postpartum period [11]. Mammogram and ultrasound are non-specific, usually showing a single ovoid, hyper dense mass with or without adenopathy [12].

B-cell PBLs are more common than T-cell subtype. Pathologically, 50% are DLBCL, followed by follicular lymphoma, and extra nodal marginal zone lymphoma [2]. Excisional biopsy and core biopsy are the preferred techniques for adequate tissue acquisition. Fine needle aspiration (FNA) is not recommended because although it may differentiate lymphoma from breast carcinoma, the FNA sample lacks architectural detail to accurately classify lymphoma subtypes [13].

The management of PBL has not been standardized; however, most authors recommend diagnostic biopsy followed by

chemotherapy and radiotherapy [14]. Since DLBCL is the most common histopathological subtype, R-CHOP remains the first-line treatment regimen [15]. For patients who undergo initial surgery management, adjuvant chemotherapy and radiation should be recommended to prevent recurrence. Radical mastectomy is not thought to have improved outcomes compared to simple resection [16].

Central nervous system (CNS) relapse is increased in PBL, occurring in 5-16% of cases, and usually occurs within two years following completion of therapy [16-20]. Currently, the NCCN guideline V 5.2023 gives a category 2A recommendation for CNS prophylaxis in DLBCL for high-risk patients based on the CNS International Prognostic Index (CNS-IPI) or should be considered for patients with Stage 1E DLBCL of the breast, which is what our patient had. Still, the role of CNS prophylaxis remains controversial [13,21]. According to Schmitz et al, the CNS-IPI has low positive predictive value between 10-12% [22]. There is no consensus on route of CNS administration. Intravenous methotrexate versus intrathecal methotrexate does not seem to yield significant differences in outcome [23]. CNS prophylaxis also has potential for toxicities such as renal impairment, delayed methotrexate clearance, post-lumbar puncture headaches, mucositis, and rarely hematologic toxicities, all of which could lead to delays in therapy [24]. In our case, mutual decision was made not to undertake CNS prophylaxis.

There is limited evidence on prognostic factors in PBL. High stage disease (including nodal and/or bilateral breast involvement at presentation), larger tumor size, elevated LDH, poorer performance status, and CNS relapse is associated with worse outcomes [25]. The 5-year overall survival rate for PBL with diffuse large B-cell subtype is between 50-60% [20].

Due to the rarity of PBL, a predictive genetic signature is difficult to determine. According to Zhang et al, the presence and frequency

of certain high-mutant somatic genes including PIM1, MYD88, DTX1, CD79B, KMT2D, TNFAIP3, and ITKB, do however seem to correlate with age at presentation, pathologic subtype, and have tendency to shorten overall survival and progression free survival in PBL [26]. In our case, these somatic genes were not assessed. This appeared to be a germinal center diffuse large B-cell subtype without any unfavorable features noted on IHC or FISH.

3. Conclusion

Not only is our patient's case of asynchronous primary breast lymphoma rare but having a 27-year gap between diagnoses has never previously been documented in the literature to our knowledge. There was no evidence for currently known inheritable genes for lymphoma found in this patient. Despite NCCN guidelines, mutual decision between patient and provider was made to not utilize CNS prophylaxis.

Written informed consent was obtained from participant. Ethical approval was none sought from an Institutional Review Board prior to writing manuscript.

References

1. Wiseman, C., & Liao, K. T. (1972). Primary lymphoma of the breast. *Cancer*, 29(6), 1705-1712.
2. Jennings, W. C., Baker, R. S., Murray, S. S., Howard, C. A., Parker, D. E., Peabody, L. F., ... & Broughan, T. A. (2007). Primary breast lymphoma: the role of mastectomy and the importance of lymph node status. *Annals of surgery*, 245(5), 784.
3. Peng, F., Li, J., Mu, S., Cai, L., Fan, F., Qin, Y., ... & Hu, Y. (2021). Epidemiological features of primary breast lymphoma patients and development of a nomogram to predict survival. *The Breast*, 57, 49-61.
4. Kim, S. H., Ezekiel, M. P., & Kim, R. Y. (1999). Primary lymphoma of the breast: breast mass as an initial symptom. *American journal of clinical oncology*, 22(4), 381-383.
5. Shapiro, C. M., & Mansur, D. (2001). Bilateral primary breast lymphoma. *American journal of clinical oncology*, 24(1), 85-86.
6. Wong, W. W., Schild, S. E., Halyard, M. Y., & Schomberg, P. J. (2002). Primary non-Hodgkin lymphoma of the breast: the mayo clinic experience. *Journal of surgical oncology*, 80(1), 19-25.
7. Jeon, H. J., Akagi, T., Hoshida, Y., Hayashi, K., Yoshino, T., Tanaka, T., ... & Kawabata, K. (1992). Primary non-hodgkin malignant lymphoma of the breast: An immunohistochemical study of seven patients and literature review of 152 patients with breast lymphoma in Japan. *Cancer*, 70(10), 2451-2459.
8. Sabate, J. M., Gomez, A., Torrubia, S., Camins, A., Roson, N., De Las Heras, P., & Villalba-Nuño, V. (2002). Lymphoma of the breast: clinical and radiologic features with pathologic correlation in 28 patients. *The breast journal*, 8(5), 294-304.
9. Domchek, S. M., Hecht, J. L., Fleming, M. D., Pinkus, G. S., & Canellos, G. P. (2002). Lymphomas of the breast: primary and secondary involvement. *Cancer*, 94(1), 6-13.
10. Schouten, J. T., Weese, J. L., & Carbone, P. P. (1981). Lymphoma of the breast. *Annals of Surgery*, 194(6), 749.
11. Ganjoo, K., Advani, R., Mariappan, M. R., McMillan, A., & Horning, S. (2007). Non-Hodgkin lymphoma of the breast. *Cancer*, 110(1), 25-30.
12. Lyou, C. Y., Yang, S. K., Choe, D. H., Lee, B. H., & Kim, K. H. (2007). Mammographic and sonographic findings of primary breast lymphoma. *Clinical imaging*, 31(4), 234-238.
13. Cheah, C. Y., Campbell, B. A., & Seymour, J. F. (2014). Primary breast lymphoma. *Cancer treatment reviews*, 40(8), 900-908.
14. Jain, M. F., Khandekar, S. L., Mahadani, J. W., & Raut, W. K. (2015). Report of a case of primary breast lymphoma highlighting the importance of fine needle aspiration cytology as an initial diagnostic tool. *Journal of Cytology/Indian Academy of Cytologists*, 32(2), 127.
15. Chen, M., Zhou, J., & Qu, X. (2021). Primary breast diffuse large B-cell lymphoma in a 42-year-old female: a case report and review of literature. *Journal of Medical Cases*, 12(5), 181.
16. Ryan, G., Martinelli, G., Kuper-Hommel, M., Tsang, R., Pruneri, G., Yuen, K., ... & Seymour, J. F. (2008). Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. *Annals of Oncology*, 19(2), 233-241.
17. Yhim, H. Y., Kim, J. S., Kang, H. J., Kim, S. J., Kim, W. S., Choi, C. W., ... & Kwak, J. Y. (2012). Matched-pair analysis comparing the outcomes of primary breast and nodal diffuse large B-cell lymphoma in patients treated with rituximab plus chemotherapy. *International journal of cancer*, 131(1), 235-243.
18. Hosein, P. J., Maragulia, J. C., Salzborg, M. P., Press, O. W., Habermann, T. M., Vose, J. M., ... & Lossos, I. S. (2014). A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. *British journal of haematology*, 165(3), 358-363.
19. Jeanneret-Sozzi, W., Taghian, A., Epelbaum, R., Poortmans, P., Zwahlen, D., Amsler, B., ... & Mirimanoff, R. O. (2008). Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. *BMC cancer*, 8(1), 1-7.
20. Aviles, A., Neri, N., & Nambo, M. J. (2012). The role of genotype in 104 cases of diffuse large B-cell lymphoma primary of breast. *American journal of clinical oncology*, 35(2), 126-129.
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22. Schmitz, N., Zeynalova, S., Nickelsen, M., Kansara, R., Villa, D., Sehn, L. H., ... & Savage, K. J. (2016). CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Journal of Clinical Oncology*, 34(26), 3150-3156.
23. Schmitz, N., & Frontzek, F. (2022). CNS prophylaxis in DLBCL: time to say goodbye?. *Blood, The Journal of the American Society of Hematology*, 139(3), 315-317.
24. Orellana-Noia, V. M., Reed, D. R., McCook, A. A., Sen, J. M., Barlow, C. M., Malecek, M. K., ... & Portell, C. A. (2022). Single-route CNS prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions. *Blood, The Journal of the American Society of Hematology*, 139(3), 413-423.
25. Aviv, A., Tadmor, T., & Polliack, A. (2013). Primary diffuse large B-cell lymphoma of the breast: looking at pathogenesis, clinical issues and therapeutic options. *Annals of oncology*, 24(9), 2236-2244.
26. Zhang, W., Huang, C., Liu, J., Wu, L., Zhang, H., Wu, X., ... & Liu, L. (2022). Genomic Mutation Landscape of Primary Breast Lymphoma: Next-Generation Sequencing Analysis. *Disease Markers*, 2022.

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