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Primary Bilateral Burkitt Lymphoma of the Lactating Breast

A Case Report and Review of the Literature

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Abstract

Burkitt lymphoma (BL) is a highly aggressive neoplasm, which frequently affects the ileocecal region in the sporadic form and the jaw in the endemic form; however, the breast is a rare primary site of this tumor. Here we describe a case of primary bilateral breast BL presenting during lactation in a 23-year-old woman. Excisional biopsy of breast masses demonstrated a B-cell lymphoma with a characteristic 'starry sky' pattern highly suggestive of BL. The neoplastic cells strongly expressed CD20 and CD10, and showed proliferative activity as measured by Ki-67. An *IGH-MYC* gene fusion indicating the presence of a typical Burkitt translocation t(8;14)(q24;q32) in the tumor tissue was detected by fluorescent *in situ* hybridization. The present case, along with a comprehensive review of the literature, demonstrates that BL of the breast should be considered in the differential diagnosis of lesions of the breast during lactation. Whether hormonal or antigenic factors trigger Burkitt lymphomagenesis in the lactating breast warrants further investigation.

1. Introduction

Primary breast lymphoma is a rare form of localized, extranodal, malignant lymphoma,[1-3] constituting 2% of extranodal malignant lymphomas, with an overall incidence of 0.04–0.53% of all malignant tumors of the breast.[4-6] Most primary breast lymphomas are of B-cell origin, and the diffuse large B-cell lymphomas seem to be the most common type.[2,5,7-10] Burkitt lymphoma (BL) is a malignancy arising from mature B-cell lymphocytes and is one of the most rapidly proliferating neoplasms, with a doubling time of only about 25 hours. It often presents in extranodal sites or as acute leukemia.[11,12]

Primary presentation of BL in the breasts is rare as compared with the typical presentation sites, which are the ileocecal region in sporadic and endemic BL and, additionally, the jaws in endemic BL.[2,13] If the onset of BL is in the breast, then it is often bilateral and massive and is usually associated with pregnancy or lactation, which might suggest hormonal influences on its pathogenesis.[11] In the present study, we report a new case of bilateral breast BL and provide an analytic review of all eligible, previously reported studies to ascertain the patients' clinical findings, characteristics, and treatment outcome.

2. Case Report

A 23-year-old woman presented with palpable, painful, and rapidly diffusible bilateral breast swelling, 3 months after delivery. She was able to breastfeed her healthy child. She had no past medical problems, and her vital signs were normal. She had

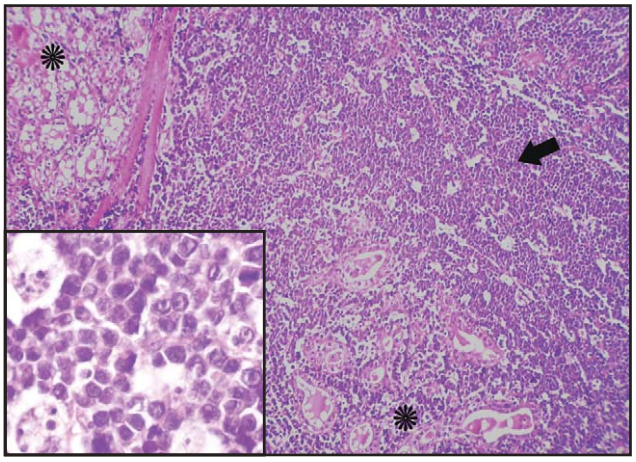

Fig. 1. Photomicrograph of excisional biopsy specimen of the breast, showing that normal lactational breast tissue (asterisks) has been replaced by diffuse infiltration of lymphoid cells with a characteristic 'starry sky' pattern (arrow) suggestive of Burkitt lymphoma. In the inset, macrophages with nuclear debris among small to medium-sized lymphoid cells, with slightly irregular round nuclei with prominent medium-sized nucleoli, impart a starry sky appearance (hematoxylin-eosin stain; magnification ×100, inset magnification ×200).

no family history of lymphoma or other cancer. There was no erythema or bloody discharge. The patient's biochemical and hematologic examinations (including a complete blood count, liver function tests, blood urea nitrogen, creatinine, potassium, and sodium) were within normal limits. The erythrocyte sedimentation rate was about 104 mm/h. On physical examination, there were multiple mobile, discrete, smooth, non-tender, and firm nodules in both breasts. The axillary and cervical lymph nodes were not palpable.

Bilateral breast ultrasonography showed numerous, variable sized (2–4 cm), well defined, discrete, echo-poor lesions, some of which demonstrated a heterogenous internal echogenic echotexture, more suggestive of abscess formation or galactocele. There was no lymphadenopathy, solid mass, free fluid, or skin edema in the ultrasonography findings.

The patient underwent excisional biopsy of bilateral breast masses under general anesthesia. Grossly, the tumors consisted of irregular fragments of creamy-gray to yellow soft tissues, measuring 5 × 3 × 2.1 cm in the right breast and 2.5 × 2 × 1.5 cm in the left breast. Multiple cut sections showed a partially homogenous, creamy-gray appearance.

Histologic examination revealed lactational breast tissue replaced by a high-grade lymphoma, with a characteristic 'starry sky' pattern highly suggestive of BL (figure 1). The lymphoid cells were small to medium sized, with slightly irregular round nuclei. The nuclei contained finely clumped and dispersed chromatin, with multiple prominent basophilic medium-sized nucleoli (figure 1 inset). The cytoplasm was markedly basophilic. Numerous mitoses were observed.

Immunohistochemistry was performed, using a polymer detection system and with primary monoclonal antibodies. Appropriate positive and negative controls were included. The neoplastic cells strongly expressed CD20 (clone L26; Novocastra, Newcastle, UK), CD10 (clone 56C6; Novocastra), and B-cell lymphoma (BCL)-6 (clone LN22; Novocastra). Almost 100% of the tumor cells showed proliferative activity and expressed Ki-67 (clone MM1; Novocastra) [figure 2]. They were negative for terminal deoxynucleotidyl transferase [clone SEN28; Novocastra], CD23 (clone 1B12; Novocastra), CD5 (clone 4C7; Novocastra), BCL2 (clone bcl-2/100/D5; Novocastra), estrogen receptor -α (clone 6F11; Novocastra), and progesterone receptor -α (clone 16; Novocastra).

By *in situ* hybridization with an Epstein-Barr virus (EBV)-encoded RNA (EBER) probe, there was no evidence of EBV. Interphase cytogenetic analysis by fluorescence *in situ* hybridization was performed on paraffin sections of the tumor cells, using LSI® *MYC* Break Apart and LSI *IGH*/*MYC* double color double fusion probes (Abbott Molecular, Abbott Park, IL, USA). Approximately 90% of the cells in the tumor tissue displayed signal patterns indicating a chromosomal breakpoint in the *MYC* locus (figure 2 inset) and an *IGH*/*MYC* fusion as characteristic of the typical Burkitt translocation t(8;14)(q24;q32). Based on routine histopathologic, immunohistochemical, and cytogenetic examinations, a final diagnosis of Burkitt lymphoma of the breast was made. Staging investigations (including

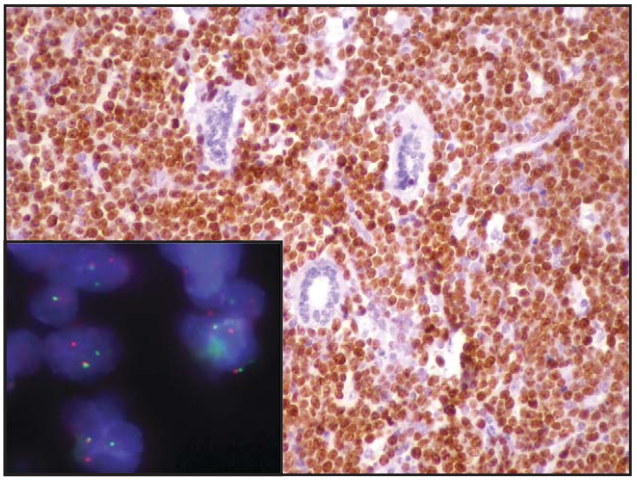

Fig. 2. Almost 100% of the tumor cells showed proliferative activity and expression of Ki-67 (immunoperoxidase stain; magnification ×200). In the inset, interphase fluorescent *in situ* hybridization with the LSI® *MYC* Break Apart probes revealed one co-localized red/green signal in most cells, indicating an intact locus and, in addition, separate red and green signals indicating the chromosomal breakpoint in the *MYC* locus due to t(8;14).

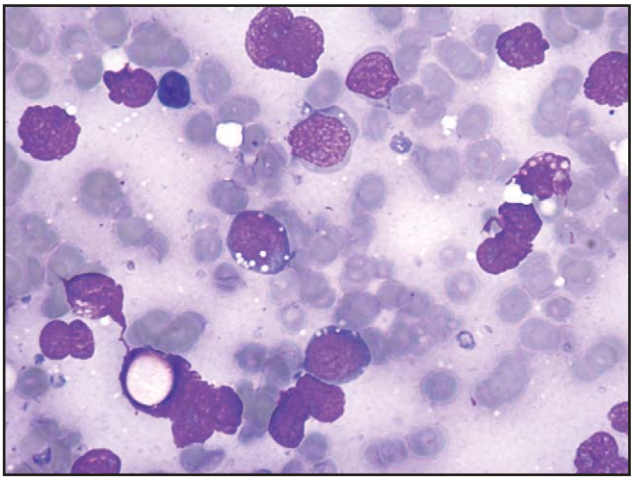

Fig. 3. Fine-needle aspiration biopsy specimen, showing monomorphic, medium-sized, atypical, non-cleaved-type lymphoid cells with fine vacuolated cytoplasm (Wright stain; magnification ×200).

bone marrow examination) and imaging studies (including chest radiography, CT scanning, and abdominal and pelvic ultrasonography) revealed no involvement of the other organs, and confirmed the breast as the primary site of disease.

Combination chemotherapy using a regimen of bleomycin 10 U/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisolone 100 mg (BACOP) was considered for the patient. Four weeks after the second cycle of chemotherapy, the disease recurred in the left breast and was diagnosed with fine-needle aspiration biopsy. The Wright-stained smears showed monomorphic, medium-sized, atypical, non-cleaved-type lymphoid cells with multiple nucleoli. The cytoplasm was moderate in amount, with fine vacuoles containing lipid (figure 3). Mitoses were present, with numerous tingible body macrophages. Because these findings suggested progression of the BL under therapy, the treatment regimen was changed to rituximab plus intensive chemotherapy combined with aggressive central nervous system therapy, using a dose-modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, mesna, etoposide, and cytarabine (IVAC) regimen.[14] The patient died 6 months after her first admission, despite chemotherapy.

3. Discussion

BL is an aggressive form of non-Hodgkin lymphoma resulting from B-lymphoid proliferation. BL is rare, accounting for fewer than 1% of all non-Hodgkin lymphomas in adults.[12,15] Primary non-Hodgkin breast lymphoma itself accounts for fewer than 1% of all breast tumors and approximately 2% of extranodal non-Hodgkin lymphomas.[6,16-18] Primary lymphoma of the breast and its extranodal spread to the breast as a result of systemic lymphoma are recognized, albeit uncommon, conditions.[3] BL of the breast is a specific and rare clinical manifestation of the disease, with a rapid spread and a poor prognosis, and it usually affects the breast of pregnant or breastfeeding patients bilaterally.[19]

Wiseman and Liao[18] reported that a diagnosis of primary malignant lymphoma of the breast must satisfy the following criteria: (i) adequate pathologic evaluation; (ii) close association of both mammary tissue and lymphomatous infiltration; and (iii) exclusion of either systemic lymphoma or previous extramammary lymphoma (the presence of ipsilateral axillary node involvement is considered acceptable). According to these standards, the tumor in our patient was considered to be primary BL of the breast.

We identified 28 reports (including 47 cases of BL with breast involvement) by a search of the English-language literature, using the term 'Burkitt lymphoma of breast' or 'primary breast lymphoma'. Twenty-four papers reported single cases[2,3,13,15,20-39] and four studies reported 2,[40] 4,[41] 5,[42] and 12[43] patients, respectively, with BL of the breast. Of these 47 cases, 14 occurred during the lactational period[39,42,43] and 13 occurred during pregnancy.[15,20-22,27,30-33,35,42] The times of occurrence of the other 20 cases were not defined.[2,3,13,23-26,28,29,34,36-38,40-42] Of these 47 cases, 32 cases occurred bilaterally, as in the present case.[13,15,22,23,27-31,34,36,38-43] There were 27 cases of primary BL[3,24-27,33-37,40-43] and 20 cases of secondary BL of the breast.[2,13,15,20-23,28-32,38-42] EBER *in situ* hybridization was done in four cases[15,33,40] and was positive in two of these.[15,33] In two patients, the presence of EBV was confirmed by positive blood serology.[3,15] Conventional karyotyping was reported in only three cases and identified the typical t(8;14).[15,20,36] Information on Burkitt lymphoma of the breast in the literature, together with this report, is summarized in table I.

According to the literature, BL in the breast seems to mostly affect young adult patients (89.3%) and rarely children in puberty (6.4%), although BL *per se* is much more frequent in children.[12] Our literature review also revealed that more than 50% of reported BL cases in the breast are associated with pregnancy or lactation. It is intriguing to speculate that this might indicate a role of hormones in the pathogenesis or could point to an antigenic stimulus in the lactating breast. The median age of incidence reported in patients with BL of the breast was 30.6 years (range 17–36), which is similar to the median age of the subset of patients with BL of the breast during lactation or pregnancy (28.5 years; range 15–42). Bilateral breast

Table I. Literature review of Burkitt lymphoma (BL) with breast involvement

Study (year)	Age (y)[a]	Time	Side	Primary or secondary[a]	Other sites	EBV/t(8,14) test and result	Treatment[a]	Outcome[a]	Mode of diagnosis
Shepherd and Wright (1967)[42]	20	Pregnancy	Bilateral	3 primary, 2 secondary	None	NP/NP	None	Died 48 h after diagnosis	Histology and FNAC of breast
	23	ND			Thyroid, abdomen, ovary		Chemo	Died <24 h after admission to hospital	
	15	Pregnancy			Intestine, ovary, kidneys		Chemo	Died 8 h after treatment initiation	
	36	Lactation			None		None	Complete remission	
	35	Pregnancy			None		None	Died 12 d after diagnosis	
Hübner and Littlefield (1975)[29]	15	ND	Bilateral	Secondary	Left inguinal lymph node, bone marrow	NP/NP	Chemo	Died	Histology of lymph nodes and bone marrow
Armitage et al. (1977)[22]	42	Pregnancy	Bilateral	Secondary	Bone marrow, peripheral blood	NP/NP	Chemo and radio	Died 22 wk after diagnosis	Histology of breast and bone marrow
Andrieu et al. (1980)[20]	29	Pregnancy[b]	Right	Secondary	Right supraclavicular extension, pleural effusion	NP/chromosome analysis positive	NA	NA	Histology of lymph node
Jones et al. (1980)[31]	17	Pregnancy	Bilateral	Secondary	Multiorgan involvement	NP/NP	None	Died	Histology of breast at autopsy
Kachel et al. (1980)[32]	34	Pregnancy	NA	Secondary	All abdominal organs	EBV Ab^+/NP	Chemo	Died 5 wk after diagnosis	FNAC of breast
Nomizu et al. (1986)[39]	34	Lactation	Bilateral	Secondary	Brain, ileocecal region, supraclavicular lymph node	NP/NP	Mastectomy, chemo and radio	Complete remission	Histology of breast

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Table I. Contd

Study (year)	Age (y)[a]	Time	Side	Primary or secondary[a]	Other sites	EBV/t(8,14) test and result	Treatment[a]	Outcome[a]	Mode of diagnosis
Poulsen et al. (1991)[40]	21	ND	Bilateral	Primary	None	$EBER^{-}$/NP	Chemo and radio	Died 2 mo after treatment initiation	Histology and FNAC of breast
	18	ND	Left	Secondary	Bone marrow	$EBER^{-}$/NP	Chemo and radio	NA	
Aghadiuno et al. (1994)[43]	17–36 (12 pts)	Lactation	All bilateral	All primary	NA	NP/NP	1 mastectomy and chemo, 11 chemo	12 died	Histology of breast
Fahmy et al. (1995)[28]	16	ND	Bilateral	Secondary	Multiorgan involvement	NP/NP	Chemo	Partial remission	Histology of lymph node, CT scan of breast, gallium scintigraphy
Illés et al. (1996)[30]	24	Pregnancy	Bilateral	Secondary	Multiorgan involvement	NP/NP	Chemo	Died	Histology of breast
Koulibaly et al. (1998)[33]	NA	Aborted pregnancy	NA	Primary	None	$EBER^{+}$/NP	Chemo	Complete remission	Histology and FNAC of breast
Antić et al. (2000)[21]	32	Pregnancy	Left	Secondary	Uterus, ovary, bone marrow, pleura	NP/NP	Chemo	Died 6 mo after diagnosis	Histology and IHC (LCA, L26, CD43) of uterus, ovary, and left breast; FNAC of lymph node
Asai et al. (2001)[23]	48	ND	Bilateral	Secondary	Bone marrow	NP/NP	Chemo	Alive	Breast ultrasonography and histology of bone marrow
Ribrag et al. (2001)[37]	37	ND	NA	Primary	None	NP/NP	Chemo	Complete remission	Histology and IHC (L26, CD20, CD10, CD3, CD5, BCL2)
Das et al. (2002)[24]	20	ND	Left	Primary	None	NP/NP	Mastectomy and chemo	Alive	Histology, FNAC, and IHC (LCA and CD20) of breast
Yamazaki et al. (2003)[38]	46	ND	Bilateral	Secondary	Intestine, peritoneum, meninges	NP/NP	Chemo	Died 6 mo after diagnosis	Histology and cytology of meninges
Gholam et al. (2003)[3]	NA	NA	NA	Primary	NA	NP/NP	Chemo	NA	Histology of breast

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Table I. Contd

Study (year)	Age (y)[a]	Time	Side	Primary or secondary[a]	Other sites	EBV/t(8,14) test and result	Treatment[a]	Outcome[a]	Mode of diagnosis
Kuper-Hommel et al. (2003)[41]	20–47 (4 pts)	NA	1 bilateral, 3 NA	1 primary, 3 secondary	NA	NP/NP	Surgery, chemo and radio	3 died, 1 alive	Histology and IHC (CD3, CD5, CD10, CD20, CD45, TdT)
Fadiora et al. (2005)[27]	27	Pregnancy	Bilateral	Primary	Multiorgan involvement	NP/NP	Chemo	Complete remission	Histology of breast
Ogawa et al. (2005)[36]	44	NA	Bilateral	Primary	None	NP/chromosome analysis positive	Chemo	Died 10 mo after admission to hospital	Histology, FNAC, and IHC (LCA, L26, Ki-67, CD10, CD20) of breast
Kyoung Jung et al. (2006)[13]	37	ND	Bilateral	Secondary	Bone marrow	NP/NP	Chemo	Died	FDG-PET and histology of breast and bone marrow
Esserman et al. (2006)[26]	56	ND	Right	Primary	None	NP/NP[c]	NA	NA	Histology, FNAC, and IHC (Ki-67) of breast
Miyoshi et al. (2006)[35]	27	Pregnancy	Right	Primary	None	NP/NP	Mastectomy and chemo	Alive	Histology and IHC of breast
Khalbuss et al. (2006)[2]	44	ND	NA	Secondary	Pelvic lymphoma	NP/NP[c]	Chemo	NA	FNAC and flow cytometry of breast
Duncan et al. (2006)[25]	81	ND	Left	Primary	None	NP/NP	NA	NA	Histology and IHC
Lingohr et al. (2009)[34]	12	ND	Bilateral	Primary	None	NP/NP	Mastectomy	Died 27 d after surgery	Histology and IHC (CD20, Ki-67, CD5, CD3) of breast
Cordeiro et al. (2009)[15]	40	Pregnancy	Bilateral	Secondary	Left supraclavicular lymph node, bone marrow, left latero-aortic lymph node	EBV Ab$^+$, EBER$^+$, DNA$^+$(PCR)/ chromosome analysis positive	Chemo	Alive	Histology and FNAC of breast
Present case (2009)	23	Lactation	Bilateral	Primary	None	EBER$^-$/FISH positive	Chemo	Died	Histology, IHC, and FNAC

a The numbers of cases are given in reports involving more than one case.

b BL occurred 6 y after chemotherapy/radiotherapy treatment for Hodgkin lymphoma and was assumed to be a consequence of this treatment.

c The pt was also HIV seropositive.

Ab = antibody; **BCL** = B-cell lymphoma; **chemo** = chemotherapy; **EBER** = EBV-encoded RNA; **EBV** = Epstein-Barr virus; **FDG** = fluorodeoxyglucose; **FISH** = fluorescent *in situ* hybridization; **FNAC** = fine-needle aspiration cytology; **IHC** = immunohistochemistry; **LCA** = leukocyte common antigen; **NA** = not available; **ND** = not defined; **NP** = not performed; **PET** = positron emission tomography; **pts** = patients; **radio** = radiotherapy; **TdT** = terminal deoxynucleotidyl transferase; **–** indicates negative; **+** indicates positive.

involvement was seen in all 14 patients with BL in the lactational period but in only 8 of 13 patients (61.5%) with BL in pregnancy ($p = 0.016$). As for the outcome, the survival rates for primary BL of the breast in the lactation period and in pregnancy were 14.3% and 30.8%, respectively (p = NS). Most of the lactation-associated BLs were stage I (92.8%), whereas those occurring in pregnancy were mainly stage IV (61.5%).

Based on the literature review by Hugh et al.,[44] there are two clinicopathologic types of primary breast lymphoma. One type affects younger patients, occurs in pregnant or lactating woman, and corresponds to BL with a rapidly fatal clinical course. The second and more common type is unilateral at presentation and affects a broad age range, but primarily older woman.

Most lymphomas of the breast are large B-cell lymphomas and, to a lesser extent, Burkitt or Burkitt-like lymphomas.[10] The breast has been considered as a potential site of so-called mucosa-associated lymphoid tissue as a low-grade B-cell lymphoma or extranodal manifestations of any systemic lymphoma (e.g. follicular lymphoma, small lymphocytic leukemia/lymphoma) or acute leukemia.[45,46] Leukemic involvement of the breast is very rare and occurs primarily in patients with acute myeloid leukemia or, even more rarely, in patients with acute lymphoblastic leukemia.[47] T-cell non-Hodgkin lymphomas (specifically anaplastic large cell lymphoma [ALCL]; including ALK positive and ALK negative), have also been reported in the breast, mainly as the consequence of breast implants. All patients who have ALCL with breast involvement are CD30 positive.[1]

In conclusion, although Burkitt lymphoma is rare, it should always be considered in the differential diagnosis of lesions of the breast, particularly during pregnancy and lactation.

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