Primary Breast Diffuse Large B Cell Lymphoma – Report of 6 Cases from South India with Review of Literature

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Received: 19 March 2013 / Accepted: 2 September 2013 / Published online: 5 October 2013
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Abstract The breast is an uncommon site of involvement in non-Hodgkin lymphoma, and primary breast lymphoma (PBL) is a disease localized to one or both breasts with or without regional lymph nodes involvement. The objectives of the study were to review the clinical profile, epidemiological parameters and assess the outcomes exclusively in women with primary diffuse large B cell lymphoma (DLBCL) of breast. This was a retrospective observational study done at Kidwai Memorial Institute of Oncology, Bangalore, India. We studied 6 consecutive female patients, diagnosed with primary DLBCL of breast between January 2007 and December 2011. Median age at diagnosis was 45 years (range 33–56 years). B symptoms were present in 3 patients. One patient had central nervous system involvement with high risk International Prognostic Index (IPI). 3 patients underwent lumpectomy and 3 core biopsy. All received anthracycline based chemotherapy, with rituximab in one patient and 3 received involved field radiotherapy. Three patients achieved complete response; one is disease free at 15 months. Two relapsed at 8 and 53 months and both were alive with disease. One achieved partial response, one had progressive disease and response was not assessed in one (but died due to toxicity). Primary breast DLBCL is a rare entity and multi modality combination therapy involving chemotherapy and radiation can give a longer overall survival and thus avoiding the morbidity of mastectomy.

Keywords Primary breast lymphoma · Extra nodal lymphoma · Diffuse large B cell

Introduction

The breast is a rare extra nodal site of non-Hodgkin lymphoma which constitutes approximately 1–2 % of extra nodal malignant lymphomas and 0.4–0.5 % of breast neoplasms [1]. Breast lymphoma has been classified into primary breast lymphoma (PBL) and secondary breast lymphoma (SBL). PBL as initially suggested by Wiseman [2] and later modified by Hugh and Coll [3, 4] has been arbitrarily defined as:

- Both mammary tissue and lymphomatous infiltrate present in close association in an adequate specimen;
- No evidence of widespread lymphoma by standard staging techniques or preceding extra mammary lymphoma, although ipsilateral axillary node involvement is allowed if both lesions are present simultaneously.

Although all histologic types of lymphoma have been described, PBL are most commonly B cell lymphomas; approximately one-half are diffuse large B cell lymphoma (DLBCL) [5]. There is a paucity of data regarding PBL, and especially DLBCL of breast from South India and hence we are reporting our experience of this entity.

Methodology

This was a retrospective observational study of 6 cases of primary DLBCL of breast in females diagnosed between January 2007 and December 2011, at Kidwai Memorial Institute of Oncology, a tertiary care oncology center in South India.

The histologic diagnosis of DLBCL was made on core or excision breast biopsy. PBL was defined as disease localized to one or both breasts with or without regional lymph nodes involvement. The patients were staged according to the

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Cotswold's modification [6] of Ann-Arbor [7] staging system, and the International Prognostic Index (IPI) [8] was determined for prognosis. The patient characteristics including clinical, pathological, treatment details and follow up were collected.

Results

Demographic and clinical profiles of all the 6 patients are summarized in Table 1. Median age at diagnosis was 45 years (33–56 years). B symptoms were present in 3 patients, both the breasts were equally involved with a median tumour size of 4.5 cms (2–9cms). One patient had central nervous system involvement with intraparenchymal lesion and was in high risk of IPI. Regional lymph nodes were involved in 1 patient and CD 20 was positive in all the cases. All patients were histologically DLBCL breast. Three patients underwent lumpectomy (Table 1- Case 1, 3, 5) and 3 core biopsy. All received anthracycline based combination chemotherapy, with rituximab in one patient (Case 2), 3 patients received radiotherapy (40 Gy/20#) to the breast (Case 1, 2, 6). Three patients achieved complete response (Case 1, 2, 6); one is disease free at 15 months. 2 relapsed at 8 and 53 months, who were salvaged with second line ICE (Ifosfamide, carboplatin, etoposide) and chlorambucil/prednisolone, they lost to follow up and alive with disease respectively. One patient (Case 4) received 2 cycles of R-CHOP chemotherapy. She developed febrile neutropenia following first cycle but recovered. Following second cycle of chemotherapy, she was administered growth factors (filgrastim) but succumbed to febrile neutropenia. One had progressive disease (Case 3- died after 13 months) and response was not assessed in one (Case 5) (died due to sepsis following febrile neutropenia).

Discussion

PBL is a rare entity and masquerades as breast malignancy and hence the importance for a clinician to be aware of this condition, its clinical presentation, management and prognosis [9].

There is a bimodal age distribution of PBL of DLBCL histology with a peak at 30–35 years and at 55–60 years [10]. The median age of presentation in our series was 45.5 years with a range of 33 and 56 years which is on par with other series.

Assessment of the contra lateral breast is essential since approximately 10 % of cases are bilateral, which is seen during pregnancy or post partum period probably due to increase proliferation [9]. There is a propensity for involvement of the right breast more than the left, the reason for this is

unknown, however in our study both the breasts were equally involved.

Breast lymphomas have been reported almost exclusively in women; however anecdotal cases in men have also been reported. Hence we decided to study the clinical profile and outcome in women exclusively [3].

The commonest presentation of PBL is a painless breast lump, most often in the upper outer quadrant. Other symptoms like nipple discharge, skin retraction, peau d' orange appearance, erythema and edema are quite unusual, but have been reported in anecdotal case reports where it can mimic inflammatory breast cancer [11].

Mammography or ultrasonography features have not been studied in detail previously to differentiate breast lymphoma from breast carcinoma [5]. Although a core biopsy is adequate to make a diagnosis of a breast lymphoma, an excisional biopsy is preferable. In our case series half of the patients underwent trucut biopsy and excision biopsy of the breast. Amongst the PBL, DLBCL is the most frequent lymphoma, but other histologies- follicular lymphoma, extra nodal marginal zone lymphoma, burkitt's lymphoma and small lymphocytic lymphoma, and anaplastic large cell lymphoma have also been reported [7]. Most recent studies on PBL with DLBCL are summarised in Table 2. Recently, the International Extra nodal Lymphoma Study Group (IELSG) reported the results of the largest international survey to date of 204 patients with primary localized DLBCL of the breast [12]. All the patients with PBL or SBL should undergo CSF analysis [13]. Cerebrospinal fluid analysis was not done in our patients.

Case reports of PBL have been reported from many parts of India. To mention a few, Anuradha et al [14]. reported a case of 23 year old woman with left sided breast lump with axillary lymphadenopathy. It was histologically a case of DLBCL. Singh et al [15]. reported the importance of fine needle aspiration cytology (FNAC) in diagnosing breast lymphoma. He studied 13 cases over 20 years of which all except one were females. Five were diagnosed on FNAC as high grade lymphoma, 2 as low grade lymphoma, 2 as poorly differentiated malignant tumour, and 1 each as Hodgkin's lymphoma, acute myeloid leukaemia (AML) and immature lymphoid cells. Chopra et al [16] reported an unusual case of synchronous mucosa-associated lymphoid tissue (MALT) lymphomas involving bilateral orbits and breasts.

Although Multimodality approach using a combination of surgery, chemotherapy and radiation have been used in most studies earlier [17], mastectomy does not appear to improve survival or risk of recurrence in the treatment of primary breast lymphoma [18].

In MabThera International Trial (MInT) trial, the addition of rituximab to chemotherapy has improved response rate, disease free survival and overall survival in patients with

Table 1 Showing patient characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age in years	48	52	33	43	35	56
B symptoms	No	Yes	No	Yes	Yes	No
ECOG PS	1	1	1	1	2	1
Tumour side/size (cms)	Right/2	Left/4	Right/5	Left/5	Right/8	Left/4
Ann-Arbor stage	IE	IE	IE	IE	IV(CNS involvement)	IIIe
Lymph nodes	No	No	No	No	No	Yes
Elevated LDH	No	No	No	Yes	Yes	No
IHC	CD20+, CD30–	LCA+, CD20+, CD3	LCA+, CD20+, CD3–	LCA+, CD20+, CD3–	CD20 +, CD 3–, CD 5+, Ki 67– 60 %	LCA+, CD20+, CD3–
Bulky disease	No	–	No	No	No	No
IPI	0	0	0	1	4	0
Surgery	Lumpectomy	–	Lumpectomy	–	Lumpectomy	–
Chemotherapy	CHOP	CHOP	CHOP	RCHOP	CHOP	CHOP
	6 cycles	6 cycles	8 cycles	2 cycles	1 cycles	6 cycles
IFRT	Yes	Yes	No	No	No	Yes
Response	CR	CR	PR,D	PR	–	CR
Outcome	Disease free at 15 m	Relapsed after 8 m	Died of Disease after 13 m	Died of Febrile neutropenia & sepsis	Died of Febrile neutropenia & sepsis	Regional nodal relapsed after 53 m
II Line	–	ICE x 6 cycles	–	–	–	Chl+pred x 6 cycles
Response	–	PR	–	–	–	CR
Follow up	Alive with no disease	Lost with disease	Dead	Dead	Dead	Alive with no disease
OS	15 m	14 m	13 m	2 m	1 m	75 m

CHOP±R- cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and prednisone 100 mg/day for 5 days±Rituximab 375 mg/m², every 21 days; CNS- central nervous system; CR- complete response; DFS- Disease free survival; ECOG PS: Eastern cooperative oncology group performance status; IHC- immunohistochemistry; IFRT- involved field radiation therapy; IPI – International Prognostic Index; ICE- ifosfomide, carboplatin, etoposide; Chl+pred- Chlorambucil and prednisolone; LDH- Lactate dehydrogenase; m- months; OS – Overall survival; PR- partial response; PR.D-progressive disease

Table 2 Summarizing the review of literature on PBL- DLBCL with treatment details and outcome

Study	No.	Duration	Histology	Treatment	Follow up	Survival
Mouna et al [1]. 2012	7	2002–10	DLBCL	Mastectomy -1 Excision- 3 Axillary dissection-3 Chemotherapy+radiotherapy-2 Chemotherapy- R-CHOP in 2;CHOP in 2	3 y	4/7 alive and free of disease
Sandeep Kumar et al [17]. 2011	10	2001–09	5 – DLBCL (FNAC diagnosis)	N.A.	N.A.	N.A.
Yhim et al [10]. 2010	68	1994 –2009	DLBCL	Chemotherapy +/- radiotherapy/surgery (Chemotherapy- CHOP/R-CHOP) Mastectomy -14 Quadrantectomy-9 Chemotherapy- 20	3.5 y	5y DFS 3.7 %, OS 60.3 %
Nicola Avenia et al [9]. 2010	23	1993 –2003	16- DLBCL 7- Maltoma	Radiotherapy- 2 Surgery/chemotherapy/radiotherapy/combined modality	10 y	DLBCL- DFS at 10 y 56.2 % OS at 10 y 62.5 %
Ryan et al [8]. 2008	204	1980 –2003	DLBCL	Chemotherapy- CHOP+intrathecal MTX R-CEOP q 2 weekly×6 cycles	5.5 y	Median DFS: 5.5y OS: 8 y
Aviles et al [18]. 2007	32	1999 – 2002	DLBCL	Mastectomy±chemotherapy±RT Concluded that mastectomy offers no protection from recurrence or benefit	5.3 y	CR: 87 %, EFS: 63 % DFS 44.5 %
Jennings et al [13]. 2007	465	1972 –2005	53 % DLBCL, 15.5 % FL, 12.2 % Maltoma	Lumpectomy -3 Chemotherapy- R-CHOP in 1;CHOP in 5 IFRT- 3	4 y	Median OS 13.5 months
Present study, 2013	6	2007–11	DLBCL			

CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, CEOP cyclophosphamide, epirubicin, vincristine, prednisone, CR complete remission, DLBCL diffuse large B cell lymphoma, R rituximab, DFS disease-free survival, EFS event-free survival, FL follicular lymphoma, FNAC fine needle aspiration cytology, IFRT involved field radiotherapy, MTX methotrexate, NA not available, No number, Y year

aggressive early stage nodal DLBCL [19] However, the impact of rituximab on survival has never been studied in patients with PBL. SWOG 0014 trial has shown that Patients with “limited” early stage disease have excellent outcomes with three cycles of CHOP with rituximab followed by involved field radiation therapy [20].

For DLBCL stage IE, options are abbreviated chemotherapy (CHOP-R x 3 cycles. [cyclophosphamide, doxorubicin, vincristine, prednisone combined with rituximab] plus involved field radiotherapy) or extended chemotherapy (CHOP-R x 6 to 8 cycles) with or without radiotherapy [20].

Preferably radiation therapy should be avoided in young females due to the increased risk of breast cancer 10 to 20 years later. Stage IIE (node-positive) and advanced DLBCL of the breast is treated with systemic chemotherapy (CHOP-R x 6 to 8 cycles).

Among our patients, all patients were treated with chemotherapy, three underwent lumpectomy (Table 1- Case 1,3, 5) and 3 patients received radiotherapy to the breast with dose of 40 Gy/20 fractions (Case 1,2,6). Among individual patients, one received combined modality treatment with chemotherapy, radiation and surgery (lumpectomy) (Case 1) with disease free survival of 15 months (alive with no disease) and two underwent surgery in the form of lumpectomy and chemotherapy (Case 3 and 5). Two received chemotherapy and radiation only (Case 2 and 6) and had a disease free survival of 8 months and 53 months. Only one of our patients could afford rituximab therapy (Case 4) but she developed febrile neutropenia with sepsis after second cycle and expired. The median overall survival was 13.5 months (1–75 months).

There have been no prospective trials of CNS prophylaxis in patients with PBL and it is controversial.

In one study, central nervous system relapse occurred in 10.2 % of patients in the PBL group and 5 % occurred in the IELSG survey [10, 13] There is no consensus till date on the use of intrathecal chemotherapy to prevent CNS progression, but IELSG survey no CNS progression occurred in a subgroup of patients who received prophylactic intrathecal chemotherapy. Cerebrospinal fluid analysis was not done in our patients and none received prophylaxis.

Primary breast lymphoma is reported to exhibit a poor prognosis among extra nodal B-cell lymphomas. The overall survival rate of primary breast lymphoma with a B-cell phenotype is 43 % at 5 years and even worse for DLBCL breast which has got a median survival of 36 months [1]. The hypothesis of such a poor overall survival is not clear but one study has shown that most of the PBL have a high proliferative rate and are of non germinal center B-cell subtype of DLBCL on gene expression profiling using cDNA microarray [21]. In some studies on PBL early stage, low International Prognostic Index (IPI) score, the use of anthracycline-containing chemotherapy and radiotherapy are significantly associated with longer overall survival [13, 17].

To conclude, the primary breast lymphoma is rare and presentation is quite similar to a breast malignancy. High index of clinical suspicion especially if B symptoms present and early diagnosis with biopsy including immunohistochemistry and appropriate rituximab and anthracycline based combination chemotherapy with involved field radiotherapy will cure most of the patients and may improve the survival without the morbidity associated with mastectomy.

Acknowledgments I thank all the staff and students of department of medical oncology, pathology, surgical oncology and radiation oncology for their help and support in preparing this article.

Conflict of Interest Nil

Source of Support Nil

References

1. Mouna B, Saber B, el Tijani H, Hind M, Amina T, Hassan E (2012) Primary malignant non-Hodgkin's lymphoma of the breast: a study of seven cases and literature review. *World J Surg Oncol* 10:151
2. Wiseman C, Liao KT (1972) Primary lymphoma of the breast. *Cancer* 29(6):1705–1712
3. Caon J, Wai ES, Hart J, Alexander C, Truong PT, Sehn LH et al (2012) Treatment and outcomes of primary breast lymphoma. *Clin Breast Cancer* 12(6):412–419
4. Hugh JC, Jackson FI, Hanson J, Poppema S (1990) Primary breast lymphoma. An immunohistologic study of 20 new cases. *Cancer* 66: 2602–2611
5. Jinming X, Qi Z, Xiaoming Z, Jianming T (2012) Primary non-Hodgkin's lymphoma of the breast: mammography, ultrasound, MRI and pathologic findings. *Future Oncol* 8(1):105–109
6. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC et al (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswold's meeting. *J Clin Oncol* 7:1630–1636
7. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 31:1860–1861
8. (1993) A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 329(14):987–994
9. Regina SO, Veronica A, Jessica C, Jarvis R, Derrick JB (2011) Primary Breast Lymphoma: A Rare Clinical Entity. *World J Oncol* 2(3):147–150
10. Yhim HY, Kang HJ, Choi YH, Kim SJ, Kim WS (2010) Clinical outcomes and prognostic factors in patients with breast diffuse large B cell lymphoma; Consortium for Improving Survival of Lymphoma (CISL) study. *BMC Cancer* 10:321
11. Anne N, Pallapothu R (2011) Lymphoma of the breast: a mimic of inflammatory breast cancer. *World J Surg Oncol* 9:125
12. Joks M, Mysliwiec K, Lewandowski K (2011) Primary breast lymphoma – a review of the literature and report of three cases. *Arch Med Sci* 7(1):27–33
13. Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruner G, Yuen K et al (2008) Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. *Ann Oncol* 19(2):233–241

14. Anuradha Sinha A, Ramrakhiani D (2005) Primary non-Hodgkin's lymphoma of the breast: a case report. *Acta Cytol* 49(6):661–665
15. Singh NG, Kapila K, Dawar R, Verma K (2003) Fine needle aspiration cytology diagnosis of lymphoproliferative disease of the breast. *Acta Cytol* 47(5):739–743
16. Chopra S, Bahl G, Ramadwar M, Ramani S, Nair R, Muckaden MA et al (2005) Synchronous mucosa-associated lymphoid tissue (MALT) lymphomas involving bilateral orbits and breasts: a rare clinical entity. *Leuk Lymphoma* 46(8):1247–1250
17. Jeanneret-Sozzi W, Taghian A, Epelbaum R, Poortmans P, Zwahlen D (2008) Amsler Bet al. Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. *BMC Cancer* 8:86
18. Jennings WC, Baker RS, Murray SS, Howard CA, Parker DE, Peabody LF et al (2007) Primary breast lymphoma: the role of mastectomy and the importance of lymph node status. *Ann Surg* 245:784
19. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Tmemy M, Imrie K et al (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 7(5):379–391
20. Miller TP, Unger JM, Spier C et al (2004) Effect of adding rituximab to three cycles of CHOP plus involved field radiotherapy for limited-stage aggressive diffuse B-cell lymphoma (SWOG-0014) (abstract). *Blood* 104:48a
21. Li D, Deng J, He H, Bu Y, Peng F, Tang X et al (2012) Primary breast diffuse large B-cell lymphoma shows an activated B-cell-like phenotype. *Ann Diagn Pathol* 16(5):335–343