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REVIEW ARTICLE

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Primary breast lymphoma (PBL) in men — a systematic review

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ABSTRACT

Introduction. Primary breast lymphoma (PBL) is a rare type of lymphoma, especially in men. Details of the clinical course are not well recognized, and a consensus on the treatment of PBL in male is not available. The objective of presenting this study was to find the most common presentation and the best treatment options for male PBL by collecting and analysing data of all reported cases published between 1985 and 2019.

Material and methods. A comprehensive search in Google Scholar, Ovid Medline, PubMed, and Scopus databases for any case of PBL presenting in men between 1985 and 2019 was performed. Patient information such as age, diagnosis, type of treatment(s), time to follow-up and patient status were recorded.

Results. A total of 28 studies containing data of 34 male patients with PBL were included in this review. The mean age of patients was about 61 (range: 26–85) years. The mean tumour size was 46.05 ± 20.37 mm. The majority of cases were presented with a palpable breast mass (unilateral or bilateral). Nine patients (26.5%) had previous comorbidities. Diffuse large B cell lymphoma was the most common histologic diagnosis (85.3%). Treatment consisting of systematic therapy combined with radiotherapy showed benefit outcome.

Conclusions. The results of the analysis showed that the response to different therapies was better in younger patients with PBL. It seems that systemic therapy combined with at least a 30 Gy dose of radiation has the best outcome in male patients with PBL. Considering limited data in each group of treatment modality, further follow-up studies in these patients are necessary.

Key words: breast, lymphoma, male, systematic review

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Introduction

Primary breast lymphoma (PBL) is a rare type of lymphoma involving only the breast, with or without axillary lymph nodes; and no extra-mammary disease [1, 2]. Overall, PBL accounts for approximately 1% of non-Hodgkin lymphomas (NHL) [3], less than 3% of extranodal lymphomas, and 0.5 % of breast malignancies [4]. More than 95% of PBL cases are female and the most frequent histological subtype is diffuse large B-cell lymphoma (DLBCL) [5, 6].

Owing to the limited number of male patients, details of treatment or clinical course are not sufficiently reliable, and no standard therapy has been established. Local control seems poor with surgical resection alone, so the combination of chemotherapy and radiation has been recommended [6, 7].

This review aimed to find all published cases of male PBL to understand the course of disease more precisely and also to reach a consensus about the optimal therapy.

Methods

Search strategy

A comprehensive search was performed in Google Scholar, Ovid Medline, PubMed, and Scopus databases for any case or detail of PBL presenting in men between

1985 and 2019. This date range was chosen because the earliest study was found in 1985. The keywords "breast" OR "mammary" AND "lymphoma" combined with "male" OR "man" OR "men" were used for the search. The initial screening was based on titles and abstracts of the returned results. Studies were included if they contained information about male patients with PBL and excluded if they reported secondary involvement of the breast in lymphoma, or did not report the male patient data in detail. To avoid bias with linguistic restriction, at first, the studies were selected regardless of the language of publication. Papers with available English abstracts were included in the first screening. In the next stage, full texts of all selected abstracts were studied. As in the first screening, articles that contained PBL as defined previously were included. Non-English papers were included if the abstract gave all the necessary information. References and tables of the included articles were also checked out for any omitted study, and detected papers were screened and included with the same criteria thereafter.

Types of studies selected

All observational studies (case report, case series) that reported PBL presenting in men were selected. Because of the scarcity of PBL in male, all studies were included even by incomplete data**.**

Data extraction

A data extraction form was designed a priori and three academic experts (two breast surgeon and one investigator) confirmed its face validation and ease of use for data extraction. Data items consisted of the name of the first author, publication year, patient's age, laterality of breast mass, tumour size, first presentation, diagnosis, stage of the disease, treatment, drug and comorbidity history, follow-up time and status. Patients' outcomes were categorized as no evidence of disease (NED); alive with the disease (AWD); dead of disease (DOD). Two reviewers extracted the data out of the included studies independently, and all data was checked by a third party. Continuous and proper monitoring of newly published papers went on until final data extraction.

Statistics

The statistical analyses were performed using IBM SPSS 26 (IBM Corp. Released in 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

Results

Totally 28 studies containing data of 34 male patients with PBL were included in this review (Tab. 1). Two studies had no English full text, so data was limited to the abstracts [8, 9]. The data of 5 cases were extracted from one study which was a case report and review article [10] and the review part of this study included data of 4 cases whose original articles (case reports) were not found.

Data of the 34 PBL male cases are summarized in Table 2. The mean age of patients was about 61 (range: 26–85) years. The majority of cases presented with a palpable breast mass (unilateral or bilateral). Nine patients (26.5%) had previous comorbidities including other cancers, HIV, hepatitis, cirrhosis, and previous history of a kidney transplant. Ten cases in this review had gynecomastia (4 bilateral & 6 unilateral) and one of the patients was transgender. Three patients had a previous history of hormone therapy with oestrogen (3 m, 5 y, and 9 y), two patients received hormone therapy (hormone pills and sex hormone), one patient had received 10 years of immunosuppressive therapy, and the other had undergone antiviral treatment for 4 years. Two patients had a brain and adrenal metastasis.

The most frequent histopathology was DLBCL, reported in 29 (85.3%). As far as information was available, the majority of patients in stage I (14 patients) reported no evidence of disease at the time of follow-up. Chemotherapy was the most frequently administered therapy and 27 patients had received chemotherapy, alone (8 patients) or in combination with surgery or radiotherapy (15 patients). Multi-agent chemotherapy consisted of CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) or CHOP-like regimen in 15 patients. Four out of five patients (80%) with available status received immunochemotherapy (R-CHOP: rituximab + CHOP) showed complete remission and one patient was alive with disease. However, in 9 patients who treated with CHOP without rituximab, two deaths occurred and one patient was alive with disease. Five patients were treated only by surgery. Treatment data of three patients were not available.

The treatment and outcome were not available in seven patients and one patient died due to other condition (cerebrovascular accident) while the final information about the outcome of their lymphoma was not reported. Therefore, after the mean follow up time of 19 months (range: 0–123) in 27 patients, the number of patients with NED, AWD, and DOD outcomes were 19, 3, and 5, respectively. In Table 3 are demonstrated the effects of some variables on disease outcomes (Alive or Dead) in 27 patients. Eight patients who received radiotherapy combined with other modality were alive.

Discussion

The breast is a rare extranodal site of involvement by lymphoma, especially in men. However, breast lymphoma should be included in the differential diagnosis of breast masses in male patients, particularly in immunocompromised ones [11].

Table 1. Characteristics of 34 male pr imary breast lymphoma patients

No	Ref	Author, Year	Age	Laterality	Diagnosis	Stage	Chemotherapy	RT, Gy	Surgery	Follow-up (month)	Status
1	24	López-Rodríguez, 2019	81	Lt	DLBCL	IE	4 × CP	Y, NA	No	0	NED
2	29	Bozkaya, 2019	82	Bilateral	DLBCL	IIIA	2 × R-CHOP	No	No	0	NED
3	30	Jonckheere, 2019	80	Lt	DLBCL	NA	NA	NA	NA	NA	NA
4	8	Tokuyama, 2017	74	Rt	DLBCL	IIA	6 × R-CHOP + 4 × intrathecal	No	No	0	NED
5	9	Goto, 2017	85	Rt	DLBCL	NA	NA	NA	NA	NA	NA
6	25	Corobea, 2017	56	Rt	DLBCL	IE	3 × R-CHOP	Y, 50Gy	MRM	17	NED
7	10	Ishibashi, 2016	75	Bilateral	DLBCL	IE	8 × rituximab monotherapy	Y, 40Gy, 50Gy	No	8	NED
8	10	Ishibashi, 2016	69	Unknown	DLBCL	IIE	Poly	No	MRM	18	DOD
9	10	Ishibashi, 2016	45	Unknown	DLBCL	IIE	No	No	Tumour excision	5	NED
10	10	Ishibashi, 2016	65	Unknown	DLBCL	IE	Poly	No	MRM	20	NED
11	10	Ishibashi, 2016	81	Unknown	LL	NA	No	No	MRM	4	AWD
12	11	Yim, 2015	63	Lt	DLBCL	IE	R-CHOP	No	No	11	AWD
13	31	Jung, 2014	46	Rt	FL	IEA	No	No	Surgery	40	NED
14	32	Lokesh, 2013	60	Lt	SLL	IIEA	9 × (COP)	No	No	Lost to follow-up	NA
15	32	Lokesh, 2013	46	Rt	DLBCL	IIEA	3 × CHOP	No	No	0	Dead
16	33	Mukhtar, 2013	50	Lt	DLBCL	IIB	CHOP	Y, 50Gy	No	0	NED
17	34	Mouna, 2012	76	Lt	DLBCL	IBE	No	No	Tumour Excision	3	DOD
18	35	Ko, 2012	51	Lt	DLBCL	IA	5 × CHOP	No	No	12	NED
19	36	Rastogi, 2012	48	Rt	DLBCL	IE	CHOP	No	No	0.63	DOD
20	37	Li, 2012	33	Rt	DLBCL	IA	CHOP	No	MRM	29	NED
21	37	Li, 2012	63	Rt	DLBCL	IA	No	No	Tumour Excision	NA	NA
22	26	Alhabashi, 2011	26	Rt	DLBCL	II	6 × CHOP	Y, 40±50Gy	No	24	NED
23	38	Rathod, 2011	48	Lt	DLBCL	II	14 × CHOP	No	No	7	AWD
24	39	Duman, 2011	62	Lt	MZBL	IIE	R-CHOP	Y, NA	Tumour Excision	NA	NA
25	40	Mahmood, 2011	50	Lt	DLBCL	IIE	NA	NA	NA	NA	NA
26	27	Miura, 2009	64	Lt	DLBCL	IEA	6 × R-CHOP	Y, 50Gy	No	12	NED
27	41	Gualco, 2009	65	Rt	ALCL	IE	Yes	Y, NA	No	18	Alive
28	42	Mpallas, 2004	67	Rt	DLBCL	II	Yes	No	MRM	12	DOD
29	28	Cabras, 2004	44	Lt	DLBCL	IIAE	ACOP-B	Y, 36Gy	Tumour Excision	123	NED
30	43	Evans, 2002	27	Lt	DLBCL	IA	Poly	No	No	NA	NED
31	20	Sashiyama, 1999	69	Lt	DLBCL	IE	3 × CHOP	No	MRM	12	NED
32	44	Hinoshita, 1998	65	Lt	DLBCL	IIAE	CPA, VDS, 6-mercaptopurine, Daunorubicin, PSL	No	LMRM	24	NED
33	45	Murata,1996	76	Rt	DLBCL	IE	5 × post-op CHOP	No	RMRM	39	NED
34	1	Hugh, 1990	81	Bilateral	DLBCL	IE	Yes	No	No	5	DOD

Rt — right; Lt — left; ALN — axillary lymph node; DLBCL — diffuse large B cell lymphoma; LL — Lymphoblastic lymphosarcoma; FL — follicular lymphoma; SLL — small lymphocytic lymphoma; MZBL — marginal zone breast lymphoma; Poly — multiagent chemotherapy; RT — radiotherapy; MRM — modified radical mastectomy; LMRM — left MRM; RMRM — right MRM; CP — cyclophosphamide and prednizone; CHOP — cyclophosphamide; adriamycin; vincristine; prednisolone; R-CHOP — rituximab + CHOP; ACOP-B — doxorubicin; cyclophosphamide; vincristine; prednisone; bleomycin; NA — not available; NED — no evidence of disease; AWD — alive with the disease; DOD — dead of disease

Table 2. Patient and disease characteristics of all patients

Variables		
Continuous variables	**Min–Max**	**Mean ± SD**
Age [yrs]	26–85	60.97 ± 16.04
Tumour clinical size [mm]	20–85	46.05 ± 20.37
Follow-up [m]	0–123	16.43 ± 24.16
Categorical variables	**Frequency**	**Percentage**
Breast side		
Right	12	35.3
Left	15	44.1
Bilateral	3	8.8
Unknown	4	11.8
Symptoms		
Palpable	16	47.1
Pain	9	26.5
Unknown	9	26.5
Diagnosis		
Diffuse large B-cell lymphoma	29	85.3
Anaplastic large cell lymphoma	1	2.9
Follicular lymphoma	1	2.9
Lymphoblastic lymphosarcoma	1	2.9
Marginal zone breast lymphoma	1	2.9
Small Lymphocyte lymphoma	1	2.9
Stage		
I	17	50
II	13	38.2
III	1	2.9
Unknown	3	8.8
Treatment		
Surgery	15	44.1
Chemotherapy	26	76.5
Radiotherapy	8	23.5
Unknown	3	8.8
Comorbidity	9	26.5
Cancer (colon & prostate)	2	5.9
HIV positive	2	5.9
Cirrhosis (alcoholic, non-alcoholic)	2	5.9
Hepatitis (B & C)	2	5.9
Kidney Transplant	1	2.9
Drug History		
Oestrogen	5	14.7
Antiviral	1	2.9
Immunosuppressive	1	2.9

PBL includes a lesion in the breast with or without the involvement of axillary lymph nodes, without any other extra-mammary lesion and a technically adequate pathologic exam confirms the presence of breast tissue near lymphoma [12, 13]. Diagnosis of primary breast non-Hodgkin lymphoma needs adequate histologic evaluation, presence of breast tissue close to the lymphoma in the specimen, no previous diagnosis of lymphoma, and no extramammary disease except ipsilateral axillary lymph nodes [1, 4]. The most common subtype is diffuse large B-cell lymphoma (DLBCL), but other subtypes including follicular lymphomas (FL), mucosa-associated lymphoid tissue (MALT) lymphomas and Burkitt's lymphomas (BL) are also seen [6, 14].

Because of the rarity, only a few scattered reports of these cases are published and many published series of breast lymphoma are a mixture of patients with PBL, extra-mammary lymphoma, secondary breast lymphoma, and recurrence of lymphoma in the breast. Additionally, many of the articles reported both male and female cases, so accurate and detailed data on the clinical course of the disease in men; its treatment and follow up is limited. The increasing number of reports in the recent past few years may represent increasing awareness toward the disease and the need for a comprehensive agreement about the management.

Age & laterality

The mean age of patients in this study (60.97 ± 16.04) was compatible with other studies [1, 4, 15]. In contrast to the Hugh et al study in women diagnosed with PBL (2 out of 20 cases were male) and Uesato study in Japanese cases (9 out of 380 cases were male) [1, 16], that showed younger cases had poorer prognosis and lower survival, the result of the current study in males showed that younger male cases had a better response to different therapies. Furthermore, left breast involvement in the authors' review of male patients was more common, however, the involvement of the right breast was more frequently observed in women [1, 4, 6, 15]. Bilateral involvement was seen in 3 patients (8.8%), nearly similar to female studies which reported bilaterality in 4–13% at the time of diagnosis [1, 4, 6, 15]. Based on previous studies, bilateral breast disease was thought to be associated with aggressive disease [17]. In the presented study, 1 out of 3 (33.3%) patients with bilateral PBL died of the disease, whereas the frequency of death due to PBL was 11.1% in unilateral cases (2 out of 18). These numbers are too small for any deduction; it can only be said that bilateral male patients with PBL had poorer outcome regarding disease-related death.

Comorbidity & drug consumption

In this review, nine cases had a previous history of comorbidities. Three common comorbidities were cancer, HIV positivity, and Cirrhosis. Overall, it is known that non-Hodgkin lymphoma is the second most common AIDS-associated malignancy [18]. In this review two patients were HIV-positive and one of them died after 19 days of treatment, which consisted of a CHOP regimen only. Ten reviewed cases had gynecomastia, and five patients had a history of hormone therapy.

Table 3. Disease outcome based on tumour features, patient comorbidity and type of treatment.

	NED & AWD (n = 22)	DOD (n = 5)	Total
Age	58.45 ± 17.13	68.20 ± 12.60	60.97 ± 16.04
Laterality			
Unilateral	17 (85)	3 (15)	20
Bilateral	2 (66.7)	1 (33.3)	3
Stage			
I	13 (81.3)	3 (18.8)	16
II	7 (77.8)	2 (22.2)	9
III	1 (100)	0 (0)	1
Unknown	3 (100)	0 (0)	3
Comorbidity			
No	16 (80)	4 (20)	20
Yes	6 (85.7)	1 (14.3)	7
Diagnosis			
— DLBCL	19 (79.2)	5 (20.8)	24
— ALCL	1 (100)	0 (0)	1
— FL	1 (100)	0 (0)	1
— LL	1 (100)	0 (0)	1
Treatment			
— Only Surgery	3 (75)	1 (25)	4
— Only Chemotherapy	6 (75)	2 (25)	8
— Surgery + Chemotherapy	5 (71.4)	2 (28.6)	7
— Chemotherapy + RT	6 (100)	0 (0)	6
— Surgery + Chemotherapy + RT	2 (100)	0 (0)	2

Data are presented as mean ± standard deviation and number with percentages in parenthesis; DLBCL — diffuse large B-cell lymphoma; ALCL — anaplastic large cell lymphoma; FL — follicular lymphoma; LL — lymphoblastic lymphosarcoma; RT — radiotherapy; NED — no evidence of disease; AWD — alive with the disease; DOD — dead of disease

Sex hormone dependency was reported in two female cases of a study with 20 PBL cases (all but two cases were female patients) and their tumour cells were positive for estrogen and progesterone receptors [1]. Also, a large cohort study in women has shown that the risk of non- Hodgkin lymphoma in females who received oestrogen therapy was 29% higher than those who never used hormone therapy, for follicular lymphoma and DLBCL [19]. This evidence suggests that non-Hodgkin lymphoma in the male breast may involve patients with elevated oestrogen levels [20]. Although the role of oestrogen in the aetiology of this disease is not clear, several biologic mechanisms like immunomodulatory effects have been proposed [19]. Meanwhile, the rare occurrence of PBL in males may suggest a role for oestrogen in its pathogenesis.

Treatment

Due to the heterogeneity of the information, comparison of cases and conclusion on the best treatment method in PBL male patients is not possible but it seems that in recent studies with a majority of women cases, a non-surgical approach is preferred and chemotherapy has become the first choice of therapy either in combination with other treatment strategies (radiation and surgery) or alone.

The result of a large retrospective study in 204 cases (including five male patients) of DLBCL of the breast with various types of treatment regimen reported that anthracycline-containing chemotherapy and radiation therapy was associated with longer survival, and mastectomy had no benefit as opposed to biopsy or lumpectomy alone; the authors proposed that extensive surgeries may have detrimental effects by delaying the commencement of systemic therapy [6]. This study reported the outcome for males did not differ from female cohort cases, with 5-year overall survival of 60% and a wide confidence interval due to the small sample size of male patients [6]. In a Japanese article of 380 cases (including 9 men) of PBL [16], they concluded that five-year survival for stage I and II was lower by surgical treatment alone compared with surgery and systemic therapy (40.5% and 25% *vs.* 57.2% and 47%). They also showed that minimal surgery for confirming diagnosis and planning treatment was necessary, but mastectomy, wide local excision, and axillary dissection seemed unnecessary. They did not report the results of treatment in females and males separately.

ESMO Guideline in 2016 confirmed surgical resection is inadequate in local control and mastectomy is associated with poor outcomes and they suggested that initial surgery should be offered only if chemotherapy delays can be avoided [21].

In the present review of PBL presenting in men, 1 out of 4 patients who were treated by surgery alone died due to lymphoma. One patient was alive with the disease after 4 months and two patients were alive with no evidence of disease after 5 and 40 months of follow-up. Although the majority of the previously reported studies were conducted in female patients, the presented study can confirm that surgery is not an appropriate treatment for male PBL patients.

The role of radiotherapy in local control of PBL was shown in many studies [1]. Radiotherapy is considered for the prevention of subclinical disease in the breast, however, the optimal dose and radiation fields are various among different reports. A randomized prospective study by Avilés on 96 patients with PBL in the early stage is consistent with the presented study finding and showed a better survival for patients who received combined chemotherapy and radiation therapy compared to either therapy alone [22]. The median dose in most studies was 40 Gy (range 30.6 to 60 Gy) [1, 15] and involved site radiotherapy include ipsilateral breast plus any additional site of pre-chemotherapy disease in the regional node or contralateral breast has replaced involved-field radiotherapy [12]. Radiotherapy to the whole breast with a dose of 30 Gy after receiving R-CHOP for complete response is recommended [23].

Interestingly in the present review, all eight male patients who received radiotherapy combined with other treatment modality were alive without evidence of disease after a median of 17 months [10, 24–28]. Four patients received higher than 30 Gy (they mostly received 50 Gy), and information about radiation dosage was not available in one patient [24].

The presented data may confirm that chemotherapy (with or without rituximab) is the optimal choice in combination with other modalities, especially with radiotherapy (Tab. 3) in male patients. However, chemotherapy alone didn't provide a good prognosis, as 2 out of 9 (22.2%) deaths occurred in those who received chemotherapy alone and 2 cases were alive with disease. In patients who received immunochemotherapy (R-CHOP), 80% had complete remission, and only one patient who didn't receive another modality is alive with disease.

ESMO clinical guideline in 2016, confirmed rituximab improves the progression-free survival and overall survival in PBL patients [21]. Although ESMO recommended six cycles of R-CHOP plus RT in patients who tolerate therapy well [21], the review of male cases shows five patients who received R-CHOP less than 6 cycles (2–5 cycles) were alive without evidence of disease during follow-up time (Tab. 1). It may be related to a hormone dependency of this disease and the difference in hormonal profiles of males and females. Further studies in male patients are recommended to find less aggressive treatment.

Study Limitation

Considering limited data and a scant number of patients in each group of treatment modality, any conclusions about the best treatment strategy in male PBL seems impossible.

Conclusions

For the time being, with rely on female's studies, which have shown that surgery has no therapeutic role beyond obtaining a histologic diagnosis to guide definitive treatment of PBL, the presented results in males also show surgery is not a good choice for treatment of PBL.

The presented study concludes some differences between previous female studies and males in the presentation of PBL disease, prognosis, and treatment. In contrast with females, left breast involvement in male patients was more common and younger age is associated with better outcomes and prognosis. In similar to females patients' treatment, immunotherapy accompanied with radiotherapy with a dose of at least 30 Gy, is the optimal treatment in male patients too, however, it seems fewer immunotherapy cycles may be enough to complete recovery. Further reports and series of the long-term follow-up of male patients with PBL after treatment are necessary to compare outcomes and achieve a consensus about a standard treatment strategy.

Conflict of interest

The authors have no conflict of interest to declare.

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