

## CASE REPORT



## Male breast involvement in chronic lymphocytic leukemia. A case report and review of the literature

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### Abstract

Male breast lymphoma is a rare extranodal lymphoma occupying the mammary gland, and it could be either primary or secondary. A 78-year-old man presented an enlargement of the right breast. He had no medical history of interest. On physical examination, a unilateral, painless breast lump was found, with no skin changes or nipple discharge. There was no palpable lymphadenopathy. Routine laboratory tests revealed leukocytosis and lymphocytosis. Excisional biopsy of the breast lesion revealed mammary tissue infiltration by chronic lymphocytic leukemia (CLL) with plasmacytoid features and immunoglobulin G/kappa monotypic expression. To our knowledge, this is the first report of male breast involvement by CLL. Considering important the collection of clinicopathological data of all reported male breast lymphoma cases, a literature review is presented.

**Keywords:** breast lymphoma, male breast, CLL, NHL, plasmacytoid differentiation of CLL.

### Introduction

Lymphomas rarely involve the breast gland and the majority of them are non-Hodgkin's lymphomas (NHL), whereas Hodgkin's lymphomas are presented in the literature only as exceptional cases [1]. NHL of the breast is an uncommon disease with primary breast lymphoma (PBL) having a reported incidence from 0.04% to 0.5% and with secondary breast lymphoma an incidence of 0.07% [2]. The majority of breast lymphomas are of B-cell origin [2]. In the literature, most of the cases presented with breast lymphoma correspond to female individuals, whereas male patients were only few. Diagnosis of breast lymphoma by imaging modalities may be difficult as there are no specific features [3] and fine-needle aspiration (FNA) or excisional biopsy is recommended to reach the correct diagnosis.

### Aim

A case of a male patient complaining of a breast lump, which proved to be a secondary involvement of a systematic lymphoma, is herein presented while reviewing the primary and secondary male breast lymphomas, which are reported or referred to in English literature.

### Case presentation

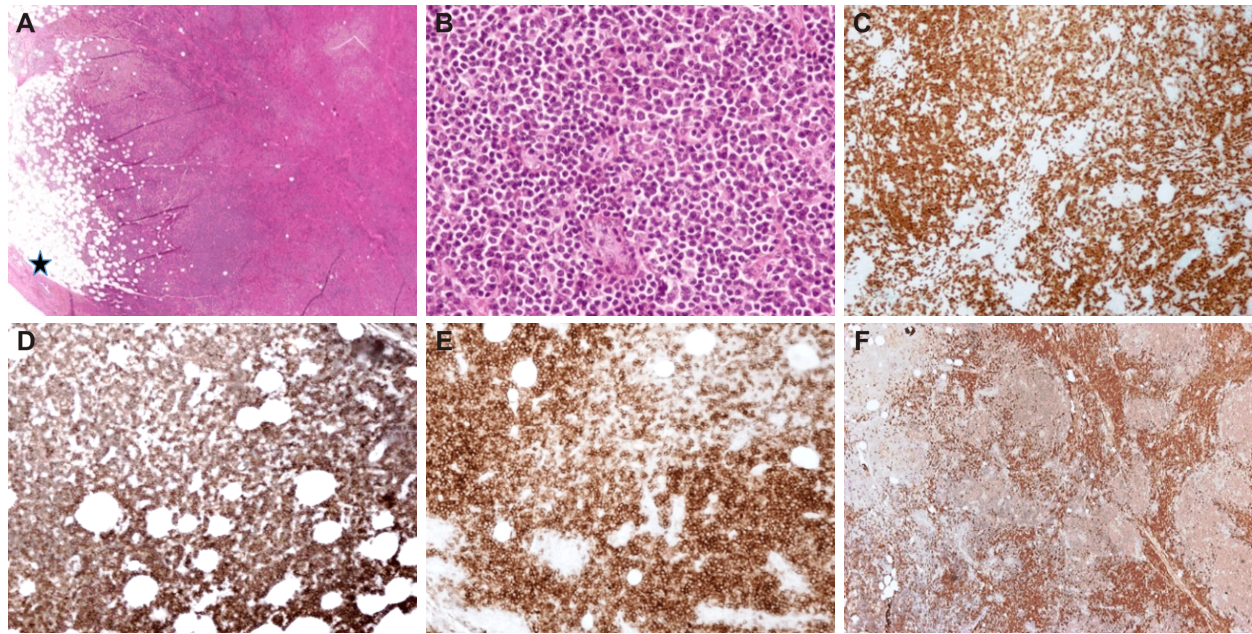
A 78-year-old man, with no medical history of interest, presented an enlargement of the right breast. On physical examination, the enlargement was unilateral, painless, with no skin changes or nipple discharge and no palpable lymphadenopathy. The patient was otherwise asymptomatic and did not complain about loss of weight, sweating or

fever. Chest X-ray did not show any lesion. Routine laboratory investigation revealed remarkable increase of white blood cells 57 640/ $\mu$ L, with 77.2% lymphocytes, 11.9% neutrophils, 10.1% monocytes. There was no anemia, thrombocytopenia, or any lymphadenopathy or hepatosplenomegaly on physical examination. Immunophenotyping of peripheral blood lymphocytes by flow cytometry identified a kappa monoclonal B-cell population. B-cells were expressing cluster of differentiation (CD) 20, CD5, CD23 and were negative for CD79b and FMC7. The patient underwent excisional biopsy, which was preferable to him than the FNA option, since he insisted on the lump surgical removal. A partial mastectomy specimen was sent for histological examination. Immunohistochemistry was performed on serial fresh cut 3- $\mu$ m thick unstained paraffin sections for CD20 (clone L-26, Dako, Glostrup, Denmark), paired box protein 5 (PAX5) (clone DAK-Pax-5, DakoCytomation, Glostrup, Denmark), CD3 (clone NCL-CD3-PS1, Novocastra, Newcastle, UK), CD5 (clone SP19, Spring Bioscience, UK), CD23 (clone SP23, Spring Bioscience), CD10 (clone 56C6, Novocastra), B-cell lymphoma (Bcl) 2 (clone 124, DakoCytomation), Bcl-6 (clone PG-B6p, DakoCytomation), cyclin D1 (clone P2D11F11, Novocastra), CD43 (clone DFT-1, Dako Cytomation), CD138 (clone MI15, DakoCytomation), immunoglobulin (Ig) M (polyclonal, DakoCytomation), IgG (polyclonal, DakoCytomation), IgA (polyclonal, Dako Cytomation),  $\kappa$  (clone kappa light chains, DakoCytomation),  $\lambda$  (clone lambda light chains, DakoCytomation), Ki67 (clone MIB-1, DakoCytomation). The immunostaining was performed on automated immunostainers, namely Bond Max (Leica Microsystems, Wetzlar, Germany) and Dako Autostainer (Dako, Denmark).

The surgical specimen measured 3×2 cm. On cut sections, a 2.5×2 cm tan-white colored lesion, with no well-circumscribed borders was observed within the adipose tissue. Histological examination revealed breast tissue infiltration by large nodular foci of lymphoid cells (Figure 1A). The tumor cells were small to medium-sized with roundish nuclei, indistinct nucleoli and scanty mitotic activity. There were also larger cells with morphological features of prolymphoid lymphocytes and paraimmuno-blasts, singly or in small aggregates similar to proliferation

centers. In addition, large aggregates of cells having plasmacytoid features were found (Figure 1B).

Immunohistochemical analysis revealed positivity of the neoplastic lymphoid cells for CD20, PAX5 (Figure 1C), Bcl-2, CD5 (Figure 1D), CD23 (Figure 1E), CD43, whereas immunostainings for CD3, CD10, cyclin D1, Bcl-6 and CD138 were negative. The proliferation index was approximately 20%. The plasmacytoid cells showed monotypic kappa light (Figure 1F) and IgG heavy chain expression.



**Figure 1 – Breast tissue infiltration by neoplastic lymphoid population (A, asterisk: mammary duct), consisting of small to medium-sized cells (B), some of which present plasmacytoid features (B), immunoreactive to PAX5 (C), CD5 (D), CD23 (E) and kappa light chains (F) antibodies. HE staining: (A) ×20; (B) ×400. Immunohistochemistry: (C–E) ×100; (F) ×40. PAX5: Paired box protein 5; CD: Cluster of differentiation; HE: Hematoxylin–Eosin.**

In summary, histopathological and immunohistochemical findings confirmed the diagnosis of a B-cell chronic lymphocytic leukemia (CLL) with plasmacytoid differentiation and IgG/κ monotypic expression.

The patient underwent computed tomography (CT) scan without any evidence of lymphadenopathy or organomegaly or signs of other organ involvement. According to Rai staging system, the disease was characterized as IAE.

## ☞ Discussions

The peculiarity of this case lies in the fact that a breast lump led to the diagnosis of CLL. The patient had no other symptoms and no other tissue involvement by the lymphoma. Routine laboratory test during breast lump investigation revealed a striking leukocytosis with lymphocytosis. However, in the absence of lymphadenopathy, organomegaly and symptoms, the possibility of breast tissue involvement by lymphoma was unexpected. CLL involvement of the breast is extremely rare in females [4, 5] and this is the first reported case in males.

CLL is a common low-grade B-cell NHL that could be presented at several extranodal anatomical sites. Leukocytosis with lymphocytosis is characteristic finding of the disease. CLL exhibits a male predominance and affects mainly middle-aged to elderly patients [6], who are

commonly asymptomatic at the time of the diagnosis, as observed in our case, as well. An interesting feature of this case is the presence of plasmacytoid differentiation of the lymphoma. CLL cases consisting of lymphocytes with up to 25% or more having a plasmacytoid form [7] are considered a distinct morphological variant of this type of lymphoma, sometimes raising differential diagnostic problems with lymphoplasmacytic lymphoma. However, the distinctive CD5+, CD23+, cyclin D1- immunophenotype and the presence of prolymphocytes and paraimmuno-blasts support the diagnosis of CLL. Whether the micro-environment is responsible for such a differentiation remains to be clarified.

Breast lymphoma is a rare breast malignancy even in females and can be either primary or secondary [8, 9]. The clinical criteria for the classification of PBL include adequate pathological evaluation with mammary tissue in close association with lymphomatous infiltrate, without evidence of disseminated lymphoma or a previous history of lymphoma [10]. According to the literature, secondary breast lymphoma is more frequent than PBL that varies from 0.85% to 2.2% of all extranodal malignant lymphomas [11]. The median age of patients ranges from 60 to 65 years [12]. Bilateral breast involvement occurs in 11% of all breast lymphomas [13]. Diffuse large B-cell lymphoma is the most common histological subtype [10].

The clinical manifestation usually includes a painless breast mass, most often presented in the external superior quadrant. Other symptoms/signs may be palpable lymph nodes, local pain, and inflammation [14]. Skin changes, edema and local pain usually suggest a T-cell lymphoma. As far as the imaging findings are concerned, the lymphoma on mammography appears as a solitary, noncalcified, circumscribed or not, oval or round mass. Ultrasonography is more informative about lesions that present themselves

as diffuse infiltration on mammography or lesions associated with skin thickening or edema. The mass on CT appears circumscribed round or oval while the value of magnetic resonance image (MRI) is not established yet [14].

Lymphoma of the male breast is extremely rare and only 37 cases have been reported or referred in the English literature, so far. Clinicopathological data of the reported cases, including the present one, are summarized in Table 1.

**Table 1 – Clinicopathological characteristics of male breast lymphoma cases**

No.	Age [years]	Size of tumor [cm]	Site of tumor	Clinical information	Lymph nodes	Histology	Primary / secondary	Author(s), year [Ref. No.]
1.	9	N/A	N/A	N/A	N/A	N/A	Primary	Docimo, 1959 [14]
2.	35	N/A	R breast	N/A	N/A	N/A	Primary	Sinner, 1961 [14]
3.	38	N/A	R breast	N/A	N/A	N/A	Primary	Bettini & Saint Omer, 1964 [14]
4.	81	4×4	R breast	N/A	Present	B-cell, DSNC	Primary	Aoi <i>et al.</i> , 1985 [14]
5.	65	4×5×2	L breast	N/A	Absent	B-cell, DLBCL	Primary	Yamamoto <i>et al.</i> , 1986 [14]
6.	74	>2	R breast	N/A, prostatectomy	Present	B-cell, DLBCL	Primary	Kawanisi <i>et al.</i> , 1989 [14]
7.	81	N/A	Bilateral, diffuse	Gynecomastia, suspicious of prostatic nodule, Estrogen TX (9 years)	Present	B-cell, DLBCL	Primary	Hugh <i>et al.</i> , 1990 [15]
8.	65	7×5×5	L breast	N/A	Absent	B-cell, DLBCL	Primary	Kitaoka <i>et al.</i> , 1900 [14]
9.	45	5.6×5×3.5 / 4×3.5×2.2	Bilateral, under nipple	N/A	Absent	B-cell, DLBCL	Primary	Murakami <i>et al.</i> , 1993 [14]
10.	69	11×11×8	R breast	N/A, Estrogen TX (10 years)	Absent	B-cell, DM	Primary	Okada <i>et al.</i> , 1995 [14]
11.	N/A	N/A	N/A	N/A	N/A	DLBCL	Primary	Abbondanzo <i>et al.</i> , 1996 [16]
12.	N/A	N/A	N/A	N/A	N/A	DLBCL	Primary	Abbondanzo <i>et al.</i> , 1996 [16]
13.	76	5.6×5.5×3.5	R breast	Gynecomastia	Absent	B-cell, DLBCL	Primary	Murata <i>et al.</i> , 1996 [17]
14.	65	4×5×2.5	L breast	Elastic-hard mass	Present	B-cell, DLBCL	Primary	Hinoshita <i>et al.</i> , 1998 [18]
15.	69	2.4×3.9	L breast	Palpable mass, bilateral gynecomastia	Absent	B-cell, DLBCL	Primary	Sashiyama <i>et al.</i> , 1999 [14]
16.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Wong <i>et al.</i> , 2002 [19]
17.	44	2	L breast	Palpable mass	Present	B-cell, DLBCL	Primary	Cabras <i>et al.</i> , 2004 [20]
18.	67	6×5×4	R breast	Palpable mass	Present	B-cell, DLBCL	Primary	Mpallas <i>et al.</i> , 2004 [21]
19.	50	4×4×7	R breast	Palpable breast mass, axillary masses	Present	B-cell, DLBCL (ARL)	Primary	Chanani-Khan <i>et al.</i> , 2005 [22]
20.	63	N/A	R breast	Palpable mass	Present	DLBCL	Secondary	Vignot <i>et al.</i> , 2005 [23]
21.	33	N/A	L breast	Breast mass	N/A	TCRBCL	Secondary	Duncan <i>et al.</i> , 2006 [2]
22.	65	3	R breast	Palpable mass	Absent	T-cell, ALCL	Primary	Gualco <i>et al.</i> , 2009 [24]
23.	64	6×7	L breast	Painless growing lump	Absent	B-cell, DLBCL	Primary	Miura <i>et al.</i> , 2009 [25]
24.	62	7×4	L breast	Palpable breast mass	Present	B-cell, MZL	Primary	Duman <i>et al.</i> , 2011 [26]
25.	51	2.3	L breast	Palpable mass	Absent	T-cell, ALCL	Primary	Ko <i>et al.</i> , 2012 [27]
26.	76	N/A	L breast	Palpable lumps	Absent	B-cell, DLBCL	Primary	Mouna <i>et al.</i> , 2012 [28]
27.	48	4.8×4.7	R breast	Painful lump, HIV-positive, ART-induced gynecomastia	Present	B-cell, DLBCL	Primary	Rastogi <i>et al.</i> , 2012 [29]
28.	85	N/A	R breast	Palpable mass	N/A	B-cell lymphoma	N/A	Surov <i>et al.</i> , 2012 [8]
29.	46	3×4	R breast	Palpable mass	Present	DLBCL	Primary	Lokesh <i>et al.</i> , 2013 [30]
30.	60	5×4	L breast	Palpable mass	Present	SLL	Primary	Lokesh <i>et al.</i> , 2013 [30]

No.	Age [years]	Size of tumor [cm]	Site of tumor	Clinical information	Lymph nodes	Histology	Primary / secondary	Author(s), year [Ref. No.]
31.	50	2×2	L breast	Gynecomastia, palpable lump behind nipple	Present	B-cell, DLBCL	Primary	Mukhtar <i>et al.</i> , 2013 [31]
32.	70	N/A	R breast	Bilateral enlargement, R breast induration	Absent	B-cell recurrence of MCL	Secondary	Ikeda <i>et al.</i> , 2015 [3]
33.	56	4×2.5×3.7	R breast	Palpable mass	Present	B-cell, MCL	Secondary	Ruiz Pardo <i>et al.</i> , 2017 [32]
34.	N/A	N/A	N/A	N/A		B-cell, aggressive	Primary	Franco Pérez, 2017 [33]
35.	65	1.7×1.5	R breast	Cervical lymphadenopathy, gynecomastia	Present	B-cell, DLBCL	Secondary	Sharma, 2017 [34]
36.	74	N/A	R breast	N/A	N/A	B-cell, DLBCL	Primary	Tokuyama <i>et al.</i> , 2017 [35]
37.	47	N/A	Bilateral	Gynecomastia	Present	HL	Secondary	Lin & Dalal, 2018 [1]
38.	78	2.5×2	R breast	Breast mass	Absent	CLL	Secondary	Present case

N/A: Not available; R: Right; L: Left; HIV: Human immunodeficiency virus; ART: Antiretroviral treatment; DSNC: Diffuse small non-cleaved cell; DLBCL: Diffuse large B-cell lymphoma; DM: Diabetes mellitus; ARL: Acquired immunodeficiency syndrome (AIDS)-related lymphoma; TCRBCL: T-cell/histiocyte-rich B-cell lymphoma; ALCL: Anaplastic large-cell lymphoma; MZL: Marginal zone lymphoma; SLL: Small lymphocytic lymphoma; MCL: Mantle cell lymphoma; HL: Hodgkin's lymphoma; CLL: Chronic lymphocytic leukemia.

In this review, we collected all primary and secondary breast lymphomas in males with infiltration of mammary gland, excluding those of cutaneous breast lymphoma. According to the information that was available for each case, we found that there was a wide range of age distribution from nine to 85 years, with a median age of 60 years, similar to that described in female breast lymphoma. The majority of the cases occurred in the right breast (18/33, 54.5%) than the left breast (12/33, 36.4%). In three cases (3/33, 9.1%), lymphoma was present bilaterally. Histologically, the vast majority of the cases correspond to B-cell lymphomas (31/34, 91.2%), mainly of diffuse large B-cell lymphoma (DLBCL) type (23/34, 67.6%). Although primary lymphomas seem to be more common (29/36, 80.6%) than secondary (7/36, 19.4%), as mirrored by literature review, we should be cautious to reach a safe conclusion, since PBL cases are more often accepted for publication.

## Conclusions

Given the rarity of male breast lymphoma, as illustrated by this case review, a high level of clinical suspicion is recommended in order to reach early the correct diagnosis. Male breast lymphoma presents a wide variety of morphological characteristics and even in cases of secondary breast lymphoma, the diagnosis can be really challenging, particularly if the first clinical manifestation is a breast lump, without lymph node involvement.

## Conflict of interests

The authors declare that they have no conflict of interests.

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