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ORIGINAL ARTICLE

Primary and Secondary Breast Lymphoma: Focus on Epidemiology and Imaging Features

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Abstract

Aim of this study was to select all the cases of Primary (PBL) and Secondary (SBL) Breast Lymphoma from our breast unit since 01/01/2000, to obtain up-to-date data on the prevalence of this rare pathology and to analyze imaging features, with a special focus on CT. All pathological reports of breast biopsies performed from 01/01/2000 to 01/01/2019 were at first screened. Among them, we performed two different researches, looking for key words suggesting either a diagnosis of lymphoma or any other malignant disease. Using the Wiseman criteria, we identify PBL and SBL. All imaging features of PBL and SBL were analyzed. Prevalence of lymphoma amongst suspicious breast masses and amongst all breast malignancies were calculated. Out of 42,505 histopathology reports from mammary nodule biopsies, we found 19,354 malignancies. We were able to identify 11 patients affected by PBL (0,03% of suspicious breast lesions, 0.06% of breast malignancies), and 23 cases of SBL (0,05% of suspicious breast lesions, 0,12% of breast malignancies). Most common isotype in PBL was DLBC lymphoma, whereas in SBL that resulted Follicular lymphoma. In PBL group, we were able to retrieve images 7 CT or CT-PET study performed at diagnosis 7 US, 1 mammography and and 1 MR. In SBL group, we analyzed 14 CT/CT-PET examinations, 11 US studies and 3 mammography. PBL and SBL are rarer than considered until now. There is no definite imaging characteristic able to distinguish between these two pathologies and among them and breast cancer.

Keywords Breast · Lymphoma · Epidemiology · Imaging

Introduction

Breast is an uncommon extra-nodal site of involvement by lymphoma, apparently due to the small amount of lymphoid tissue in this organ [1]. Lymphomatous involvement of the breast can be distinguished in primary and secondary, but the criteria used to categorize a breast lymphoma as primary are not homogeneous. Following the original description provided by Wiseman [2] and successively modified by Hugh [3], with the term Primary Breast Lymphoma (PBL) is intended a lymphoid neoplasm which, at the time of the diagnosis, is present exclusively at the level of the breast, with or without homolateral involvement of the axillary lymph nodes. Consequently, are included in this definition only patients categorized at Ann-Arbor's stages IE or IIE, without history of lymphoma in other districts. The other forms of lymphoma should be categorized as secondary (SBL). According to the literature, the most typical presentation is the insurgence of a palpable, large and non-painful mass at the level of the breast in patient who lack systemic symptoms. Men are exceptionally involved, with 96% of cases reported affecting women. The mean age at diagnosis is 60–70 years and the most common histotype is Large B-cells lymphoma, reported to represent up to the 80% of cases. There is some discordance in literature regarding the epidemiology of this kind of neoplasm; in particular, PBL is reported to represent between the 0.04% and the 0.5% of all breast malignancies [4, 5], the 0.38–0.70% of Non-Hodgkin lymphomas and the 1.7–2.2% of extra-nodal lymphomas [6–9]. However, there is no consensus if these data regard the prevalence of true PBLs or if

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they also include secondary forms. The clinical outcome of patients is quite good, with an overall survival at 5 years in 80% [10] of cases. Prognostic factors include stage at diagnosis, histologic grade, age and IPI [11]. Most authors agree that a systemic treatment with chemotherapy remains the basis of management of PBL even if there was some debate on the role of surgery in the treatment of this pathology [12–14]. Radiotherapy is prevalently used as a support to surgery. There have been only few attempts in literature to find specific radiological features able to differentiate Breast Lymphomas [1, 15]. Aim of this paper is to analyze the cases of Primary and Secondary Lymphomas diagnosed in our Breast Unit, to provide up-to-date data on the prevalence of this disease and to describe its radiological features, with a special focus on CT findings.

Material and Method

All pathological reports of breast biopsies performed from 01/01/2000 to 01/01/2019 in our hospital database were at first screened. In cases of multiple biopsies performed on the same patient, in order to exclude reports related to the same lesion, we did not consider for each patient more than one biopsy per year. At the end, 42,505 pathological reports from mammary biopsies were included in our study. Among them, we performed two different researches, looking for key words suggesting either a diagnosis of lymphoma or any other malignant disease. Reports of lymphoma were then screened in order to select Primary and Secondary Breast Lymphomas. We used the original criteria by Wiseman to categorize the patients. Therefore, to be accepted in the Primary Lymphoma group, patients had to satisfy the following criteria: no history of previous lymphoma; selective involvement of the breast with or without homolateral axillary lymph nodes (documented with a PET-CT or a CT); a bone marrow biopsy negative for lymphomatous cells. Patient with breast involvement by a relapsing lymphoma, or with a first diagnosis of lymphoproliferative disease with both breast and other districts involved were included in the Secondary Breast Lymphoma group. Cutaneous lymphomas affecting the mammary region were not considered as Breast Lymphomas. We used the Ann Arbor's system for staging the patients. Due to the lack of consensus regarding cases with bifocal breast involvement, we arbitrarily decided to consider these patients in stage IE. For histologic purposes, the neoplasms were categorized according to the World Health Organization (WHO) classification. Data regarding clinical presentation, stage, and radiological findings were collected from our archives. When lesions resulted bifocal or bilateral, they were considered separately: in multifocal lesions, we considered only the larger one in our analysis. Epidemiological analysis on our series were done, calculating prevalence of breast lymphoma and the ratio lymphoma/malignancies in our database. As regards imaging findings, we focused on CT patterns since, being our institution a secondary center, we found few data only about mammography or ultrasound. The margins of lesions at CT were defined as smooth, irregular/spiculate or undefined. Lesions were categorized as solid, colliquated or mixed on the basis of densitometric values or histological reports after radical surgery, when performed. Same criteria were applied to define the presence of calcifications. Densitometric data were compared with the CT features of breast carcinoma available in literature, with a special focus on the most commonly type, the Invasive Ductal Carcinoma. Anyway, we also will also report our findings from Mammography and Ultrasound, when available.

Results

Out of 42,505 histopathology reports from mammary nodule biopsies, we found 19,354 malignancies. Among them, there were 40 cases of breast involvement by lymphoma (0.09% of suspicious breast lesions, 0.21% of breast malignancies). Among them, 6 patients resulted without any data allowing us to classify them as Primary or Secondary Breast Lymphoma and were excluded from our series. We were able to identify 11 patients affected by PBL (0,03% of suspicious breast lesions, 0.06% of breast malignancies), and 23 cases of Secondary Breast Lymphomas (0,05% of suspicious breast lesions, 0,12% of breast malignancies). One patient in the SBL lymphoma group had relapse of a PBL in the contralateral breast.

In the 11 patients of the PBL group, we were able to retrieve images from a CT or CT-PET study performed at diagnosis in 7 (one showed bifocal lesion and we considered the 2 lesions separately). We found data from US in 7 cases, from mammography in 1 and from an MR study in 1.

In the 23 patients with SBL, we analysed 14 CT/CT-PET examinations, 11 US studies and 3 mammographs.

Primary Breast Lymphoma Group All PBLs in our series affected women (mean age at the diagnosis 66 years; range 38–78 years). The most common type resulted Diffuse Large B-cells lymphoma (72,7%), followed by MALT-lymphoma (18,2%) and Follicular lymphoma (9.1%). There were 58.3% of PBL in the left breast and 41.7% in the right. Of them, 50% of PBLs were located in the upper outer quadrant, 25% were in upper inner quadrant, 16,7% were retro-areolar and 8,8% were found in the lower inners. In 36.4% cases there was homolateral axillary lymph-node involvement, and these patients were staged IIE. None of our patients showed bilateral breast involvement at the time of the diagnosis. Mean lesion diameter, measured on CT or CT-PET at diagnosis, was 41,4 mm (range 18-80 mm) and no lesion showed

calcifications. 80% of nodules were reported as solid, the others (20%) presented areas of colliquation and were categorized as mixed lesion. 66,6% of lesion presented smooth and well-defined margins, 16,7% had spiculated/partially defined margins and 16,7% were undefined. At US, lesions appeared nodular or pseudo-nodular/undefined with good correlation with CT findings, always more or less hypoechoic. The lesion seen at mammography presented as a nodular, well-defined mass. MRI showed a breast nodule with strong contrast enhancement (Table 1).

Secondary Breast Lymphoma Group All lesions were found in women. Mean age at the diagnosis was 71 years (range 30-88y). As regards histology, 10/23 lesions (43.5%) resulted Follicular lymphoma, 8/23 (34.8%) were Diffuse Large B-cells lymphoma, 2/23 (8.7%) MALT, 1/23 (4.3%) Mantle cells lymphoma and 1/23 (4.3%) Burkitt Lymphoma. A conclusive histological diagnosis was not possible in 1 case. Lesions were in the right breast in 50% of cases, in the left one in 37.5%, and bilateral in 6.2%; no data on the location of the lesion could be found in one case. A solitary lesion at diagnosis was detected in 73.9% of patients, 8,7% had a bifocal lesion in the same breast, 4.3% had bilateral lesions and 8.7% showed multiple nodules in the same breast which involved also the derma. At CT, mean diameter at diagnosis was 43.4 mm (range 10-156 mm), and one lesion showed a millimetric peripherical calcification. 77.8% of lesions were classified as solid, the others were mixed (22.2%). 43.7% of lesions showed smooth margins, 37.5% had poorly defined margins and 18.8% had spiculated margins. All lesions were hypoechoic at US; in 1 case, the lesion appeared as diffuse ductal ectasia with debris inside the ductal system. Mammography was unable to detect one lesion (seen at US and CT as a solid, hypoechoic and homogeneous nodule); the two other patients showed one nodule each (one had bifocal disease at CT) (Table 2).

Discussion

There are different clinical studies available in literature exploring the prevalence of breast lymphoma, focusing on the clinical features and on the most appropriate management of these patients. A common limitation that can be found in many is lack of homogeneity in the definition of PBL, with some papers accepting as such neoplasms in stage III/IV or undetermined due to the absence of complete investigation [5, 15, 16]. Moreover, there are different case series in the radiological literature describing imaging findings in breast lymphoma but, again, it is not always clear if a bone marrow biopsy had always been performed to distinguish primary from secondary forms [17–22]. The main consequence is that data about the epidemiology of this rare pathology are somewhat misleading. The highest prevalence reported in the

Table 1 Primary breast lymphomas

PBL	TYPE	STAGE	LOCATION	DIMENSION (CT)	BORDERS (CT)	DENSITY	CA	US	MAMMOGRAPHY	MRI
Case1 38y	LARGE B-CELLS	IIE	LEFT U-O	45MM	SPICULATED	MIXED	NO	26 mm, pseudo-nodular undefined, iso-hypoechoic	NO DATA	NO DATA
Case2 55y	MALT	IE	LEFT U-I	NO DATA	NO DATA	SOLID	NO	NO DATA	NO DATA	NO DATA
Case3 78y	LARGE B-CELLS	IIE	LEFT U-O	80MM	NO DATA	MIXED	NO	NO DATA	NO DATA	NO DATA
Case4 79y	LARGE B-CELLS	IE	LEFT R-A	NO DATA	NO DATA	SOLID	NO	28 mm, nodular well defined, hypoechoic	NO DATA	NO DATA
Case5 70y	LARGE B-CELLS	IE	LEFT U-0	32MM	NO DATA	SOLID	NO	NO DATA	NO DATA	NO DATA
Case6 71y	MALT	IE	RIGHT BIFOCAL U-I AND U-O	20MM/50MM	UNDEFINED/ SMOOTH	SOLID/SOLID	NO	Pseudo-nodular, undefined	NO DATA	Both solid hyperintense T1
Case7 62y	LARGE B-CELLS	IE	LEFT R-A	18MM	SMOOTH	SOLID	NO	16 mm nodular well defined hypoechoic	NO DATA	NO DATA
Case8 66y	LARGE B-CELLS	IE	RIGHT U-O	67MM	SMOOTH	SOLID	NO	30 mm (20 days before ct-pet), nodular well defined mixed echogenity	Nodular hyperdense	NO DATA
Case9 64y	FOLLICULAR	IE	RIGHT U-I	19MM	SMOOTH	SOLID	NO	23 mm, nodular well-defined hypo-anechoic	NO DATA	NO DATA
Case10 75y	LARGE B-CELLS	IIE	RIGHT U-O	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Case11 77y	LARGE B-CELLS	IIE	LEFT L-I	NO DATA	NO DATA	NO DATA	NO DATA	53 mm hypoechoic nodular well defined	NO DATA	NO DATA

Table 2 Secondary breast lymphomas

SBL	TYPE	LOCATION	DIMENSION (CT)	BORDERS (CT)	DENSITY	CA	US	MAMMOGRAPHY	MRI
Case1 76y	FOLLICULAR	RIGHT INNERS	70MM	SMOOTH	MIXED	NO	Solid hypoechoic 66 mm polycyclic	NO DATA	NO DATA
Case2 70y	MALT	RIGHT MULTIFOCAL	67MM	UNDEFINED	SOLID	NO	NO DATA	NO DATA	NO DATA
Case3 88y	LNH	BIFOCAL LEFT INNERS	20MM/25MM	SMOOTH/ UNDEFINED	SOLID/SOLID	NO	Diffuse ductal ectasia	Pseudo-nodular opacity	NO DATA
Case4 88y	LARGE B-CELLS	RIGHT MULTIFOCAL	67MM	SPICULATED	MIXED	NO	Hypoechoic 16 mm (3 month before CT)	NO DATA	NO DATA
Case5 86y	LARGE B-CELLS	RIGHT U-O	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Case6 79y	FOLLICULAR	LEFT U-I	14MM	SMOOTH	SOLID	NO	NO DATA	NO DATA	NO DATA
Case7 82y	FOLLICULAR	RIGHT U-O	NO DATA	NO DATA	SOLID	NO	22 mm nodular well-defined	NO DATA	NO DATA
Case8 51y	FOLLICULAR	LEFT U-O	10MM	SMOOTH	SOLID	NO	NO DATA	NO DATA	NO DATA
Case9 83y	LARGE B-CELLS	LEFT DIFFUSE	80MM	UNDEFINED	MIXED	NO	NO DATA	NO DATA	NO DATA
Case10 70y	LARGE B-CELLS	RIGHT LOWERS	NO DATA	NO DATA	SOLID	NO	NO DATA	NO DATA	NO DATA
Case11 30y	BURKITT	BILATERAL U-I	63MM/35MM	UNDEFINED/ UNDEFINED	SOLID/SOLID	NO	Nodular	NO DATA	NO DATA
Case12 78y	FOLLICULAR	LEFT U-I	15MM	SMOOTH	SOLID	NO	NO DATA	Nodular dense, 14 mm	NO DATA
Case13 47y	LARGE B-CELLS	LEFT U-I	26MM	SMOOTH	SOLID	NO	Nodular hypoechoic, well defined	NO DATA	NO DATA
Case14 70y	FOLLICULAR	RIGHT L-O	19MM	SPICULATED	SOLID	YES	Nodular, well defined, Hypoechoic	Undetected	NO DATA
Case15 86y	MANTLE CELLS	RIGHT DIFFUSE	156MM	UNDEFINED	MIXED	NO	NO DATA	NO DATA	NO DATA
Case16 79y	FOLLICULAR	RIGHT DIFFUSE	28MM	SMOOTH	SOLID	NO	NO DATA	NO DATA	NO DATA
Case17 77y	MANTLE CELLS	BIFOCAL LEFT EXTERNALS	19MM/24MM	SPICULATED	SOLID	NO	Pseudo-nodular, undefined 34 mm/35 mm hypoechoic	NO DATA	NO DATA
Case18 70y	LARGE B-CELLS	RIGHT OUTERS	NO DATA	NO DATA	NO DATA	NO DATA	Pseudonodular, undefined inhomogeneous	NO DATA	NO DATA
Case19 61y	LARGE B-CELLS	LEFT U-O	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Case20 57y	LARGE B-CELLS	LEFT	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Case21 77y	FOLLICULAR	RIGHT UPPERS	NO DATA	NO DATA	NO DATA	NO DATA	8 cm polycyclic undefined	NO DATA	NO DATA
Case22 69y	FOLLICULAR	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Case23 58y	FOLLICULAR	RIGHT U-O	NO DATA	NO DATA	NO DATA	NO DATA	12 mm ipo/anaechoic nodular well defined	NO DATA	NO DATA

literature (0.53%) comes from a paper from 1972 [2] and the lowest (0.04%) can be found in a paper from Jernstrom, who reported 3 supposed Primary Breast Lymphoma out of 6300 breast cancer in 1962 [23]. Neither of these works, however, can be considered exhaustive.

Strictly following the Wiseman criteria, we were able to find only 11 PBLs and 23 SBLs over 42,505 breast biopsies in our Breast Unit; that is, respectively, 0.03% PBLs and 0.05% SBLs within suspicious breast masses. Furthermore, considering only breast malignancies, we found 0.06% PBLs and 0.12% SBLs in 19,340 biopsies.

On that basis we can state that breast involvement by Lymphoma is rare. We think that the low prevalence of PBL in our series is due to the strict criteria we used to accept patient in this group. We did not find cases of this pathology affecting men, in accordance with previous studies affirming the exceptionality of this eventuality. As previously reported, also in our series the most common type of lymphoma involving primarily the breast is DLBCL, while secondary breast involvement was more common by Follicular lymphoma, closely followed by DLBCL. Mean age at the diagnosis was similar in the two groups, being both PBL and SBL a condition that most commonly affects women around 70 years. Both PBL and SBL frequently appears as solid, quite large masses, and around 30% of cases can show areas of colliquation or necrosis. Calcification are exceptionally described in literature; in one patient we found a mass associate with a calcific spot at its periphery, but we can't be sure if this was associated with the lymphoma or represented an accessory finding within the adjacent mammary tissue. We had only one case of PBL presenting as a bifocal mass in the same breast, whereas SBL more often presented with multiple masses in one or both breasts. On imaging, there are not definite difference between Primary and Secondary breast Lymphoma which allow to distinguish the two pathologies. Although we noted that PBL appears more commonly like a well-defined nodule than SBL, and this latter form shows more often multiple involvement of the breast, even with a CT-PET not showing the involvement of other districts, it is not possible to diagnose confidently a primary form without a bone marrow biopsy. Therefore, except for the cases where lymphoma involvement appears undeniable in other areas, or when a positive history for lymphomatous neoplasm is present, it is not possible to distinguish between these pathologies only on the basis of imaging. Consequently, other studies including a CT-PET and bone marrow biopsy are essential for this purpose. Previous studies reported that irregular shape, spiculate margin and rim enhancement are the most reliable CT characteristics of breast malignancies, especially found in Invasive Ductal Carcinoma [24]. We can't reasonably say that those characteristics significantly differ from lymphoma's ones. Moreover, in our series, in accordance with other reports in literature, the most common presentation was a palpable mass; therefore, US guided biopsy resulted the most common diagnostic approach to these patients, with PET-CT being the second level exams when the nature of the lesion had been disclosed, making other imaging studies useless. We can speculate that, having these lesions a rapid growth that makes easy for the patient to note the insurgence of the disease, it is rare for the nodules to be discovered in the context of a screening mammograph or occasionally during a CT performed for other purposes. Consequently, it makes little sense trying to differentiate these pathologies with imaging, being aware that the only diagnostic approach for a patient with recent onset of a palpable breast mass is biopsy [25]. On the other hand, older cases of PBL, especially with large masses at the presentation or when the histopathology report misdiagnosed the lesion, were approached with surgery in the suspect of breast cancer, both in our study and in literature. In that view, it results mandatory to help the pathologist to formulate the exact diagnosis performing core-needle instead of fine needle biopsy.

Compliance with Ethical Standards

Conflict of Interest All the Authors declare that they have no conflict of interest.

Ethical Approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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