

REVIEW

Lymphoepithelioma-Like Carcinoma of the Breast Mimicking Granulomatous Mastitis- Case Report and Review of the Literature

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Abstract

Lymphoepithelioma-like carcinoma (LELC) of the breast is an exceedingly rare variant of mammary cancer. To our knowledge, only twenty - one cases have been reported in the literature. Diagnosis of this type of mammary carcinoma may be challenging, owing to its rarity and the histopathological similarity to common inflammatory and malignant lesions of the breast mainly granulomatous mastitis, medullary carcinoma, pleomorphic lobular carcinoma, lymphoma and other hematological malignancies. Our case is the 22nd case of lymphoepithelioma-like carcinoma reported in the breast, presenting with a palpable tender mass in a post-menopausal female. Her clinical picture had been mistaken for inflammatory disease. We present our case, with its detailed clinical history, radiological findings, histopathological and immune-histochemical findings along with a review of the literature. Highlighting this type of tumors may help in appropriate diagnosis. Moreover, studying the behavior of these rare neoplasms is essential to expedite treatment for this tumor type.

Keywords: Lymphoepithelioma- like carcinoma- LELC- breast cancer- medullary carcinoma

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Introduction

Lymphoepithelioma - like carcinoma of the breast (LELC) is a rare mammary neoplasm, morphologically similar to the well-known nasopharyngeal counterpart (Iezzoni et al., 1995). Lymphoepithelioma can also occur in stomach, lung, thyroid, thymus, uterus and salivary gland (Iezzoni et al., 1995). Although LELC of the breast is extremely rare; its prognosis may be favorable like medullary carcinoma (Dinniwell et al., 2012).

The undifferentiated appearance of cells and the prominent lymphocytic infiltration may offer a diagnostic challenge as it may be morphologically similar to medullary carcinoma, lymphomas or granulomatous mastitis (Cristina et al., 2000; Sanati et al., 2004).

Usually histopathological examination reveals sheets and nests of malignant epithelial cells having pale eosinophilic cytoplasm in a background of lymphoid infiltrate. Dense lymphoid aggregates and plasma cells interspersed within fat and surrounded by hyaline material are also seen. Germinal center can be observed in some aggregates (Nio et al., 2012).

It is a very rare tumor, until 2014 we found only 21 reported cases (Cristina et al., 2000; Peştereli et al., 2002).

We report a case of LELC of the breast occurring in 66 years old female and added one more case to the

previously published ones.

Case presentation

A 66 years old postmenopausal woman presented with two months history of right lateral breast pain and a palpable mass. Her past medical history was unremarkable. On general examination, she denied fever, chills, or night sweet. No weight loss was reported and she was asymptomatic apart from right breast tenderness. Physical examination revealed bilateral palpable axillary lymph nodes and a discrete mobile 20 mm breast mass. The examination was otherwise non-contributory.

A diagnostic mammogram, subsequently performed, revealed a 22 mm rounded fairly defined high-density mass with micro lobulated margins at the posterior lateral aspect of the right breast. The mass showed no associated micro calcifications (Figure 1). The mammographic findings were reported - according to the American College of Radiology Breast Imaging Reporting and Data System (Sickles et al., 2013). The mass was reported as: (BI-RADS) 4C: highly suspicious for malignancy.

A Tru-cut needle biopsy was taken and sent elsewhere for pathological examination. The case was reported by the pathology consultant as granulomatous mastitis with epithelioid histiocytes, lymphoid aggregates and multinuclear giant cells of Langhans type admixed with

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polymorph nuclear leukocytic infiltrate.

The patient went for excisional biopsy and the specimen was sent for our institute for pathological evaluation. Gross examination revealed a fibro fatty piece of tissue that weighed 70 gm. and measured 6x4x4 cm. On sectioning, it showed a fairly defined firm gritty grey white mass measured 2.2x2 cm with surrounding margins measured 2 cm laterally, 0.7 cm medially, 0.8 cm superiorly, 0.4 cm inferiorly, and 1cm deeply. Extending deep, inferior, medial and superior margins were received and measured 4x2x0.5 cm, 2x2x0.4 cm, 2x1x0.7 cm and 2x2x1cm respectively. Axillary tissue specimen weighed 110gm. and measured 12x9x3 cm. Its dissection revealed 10 nodules that ranged in diameter between 0.7 cm and 2.5 cm.

Microscopically, sections examined revealed scattered atypical mono and multinucleated bizarre giant cells masked by dense diffuse lymphoid cellular infiltrate associated with wide fibroplasia destructing the normal mammary architecture (Figure 2). The resection margins were free with least clearance 0.8 cm inferiorly. The axillary nodes were all reactive free of atypical cells (0/10).

We decided to implement Immunohistochemical staining to sort out the nature of the atypical cells and to detect their activity. The panel included markers for epithelial/ histiocytic and lymphoid lineages. The selected panel was CK, CD68, LCA, CD20, CD3, Ki67, ER, PR and Her2.

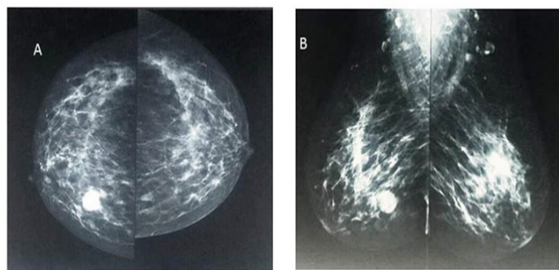


Figure 1. A- Right Mediolateral-oblique (A), craniocaudal (B), mammographic projections demonstrate a 2.2-cm, irregular-shaped, high-density. The mass is hyperdense and has an indistinct margin with no associated microcalcifications. B- The mass was categorized as BI-RADS category 4C: high suspicion for malignancy.

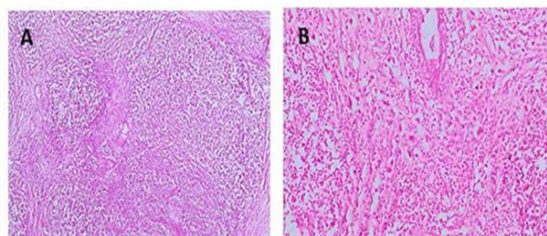


Figure 2. A- Nests of anaplastic neoplastic cells, with scattered tumour giant cells and heavy lymphoid infiltrates (hematoxylin-eosin, original magnification ×200). B- The tumor cells are growing in sheets or are intimately intermingled with the very dense stromal lymphoid cell infiltrates (hematoxylin-eosin, original magnification ×400).

Immunohistochemical results

The scattered atypical giant cells showed positive reaction for CK which also highlighted the invasive patterns of the cells. Few histiocytes expressing weak CD68 positive reaction were seen dispersed in the background. The LCA positive small lymphocytes showed dual CD3 and CD20 positive reaction reflecting their reactive nature. Regarding the hormonal receptor, tumor cells were negative for both ER and PR. They also showed negative overexpression for Her2 (triple negative pattern) (Figure 3). The mitotic activity of the CK positive large neoplastic cells were denoted by 50% positive nuclear reactivity to Ki67 (Figure 3).

Discussion

LELC of the breast has to be differentiated from other mammary neoplastic lesions with prominent lymphocytic infiltrate, mainly medullary carcinoma (Nio et al., 2012), Hodgkin and non-Hodgkin lymphoma (Saleh et al., 2005, Sanati et al., 2004) and other inflammatory conditions (Ikumi et al., 2014). The presented case was preliminary diagnosed as granulomatous mastitis on the initial pathological examination of the Tru cut needle biopsy.

However; the post excisional biopsy pathology provided ample material that revealed features that were obviously different from those of granulomatous mastitis. We found out large cells that were atypical, with few bizarre highly suspicious forms in a background of severe inflammatory reaction rich in lymphocytic infiltrate, that arouse our suspicion for epithelial or non-epithelial neoplasia.

Also we needed to differentiate the present case from

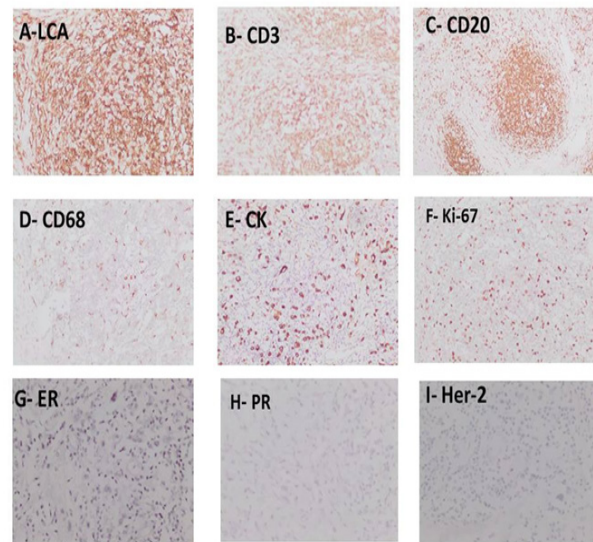


Figure 3. The LCA Positive Small Lymphocytes were Polymorphus with Dual CD3 and CD20 Positive Reaction Reflecting Their Reactive Nature (A, B and C). Few cells with weak CD68 positive reaction were seen scattered in the background (D). The atypical cells showed positive reaction for CK with 50% nuclear reactivity for Ki-67, which also highlighted the invasive patterns of the cells (E and F). Tumor cells showed negative reaction for both ER and PR. They also showed negative overexpression for Her2 (triple negative pattern) (G, H and I).

Table 1. Summarizes the Profiles of the 22 Cases (3-16)

case	Ref	year	age	Presenting problem	Size (cm)	Lymph node (N/Y)	surgery	Chemotherapy (N/Y) agent listed if known	Radiation therapy (N/Y)	Outcome (mo)*	ER status	PR status	Her2 status	EBV
1	Kumar and Kumar (11)	1994	65		2	N	Mastectomy ALND	NR	NR	7	+	+	NR	NR
2	Christina et al (3)	2000	54	Mass	1.5	N	Quadrantectomy ALND	Y	N	6	+	-	-	-
3	Dadmanesh et al(7)	2001	43	NR	1.9	Y	Quadrantectomy	N	N	60	-	-	-	NR
4	Dadmanesh et al(7)	2001	53	NR	2	N	NR	N	N	72	-	-	-	NR
5	Dadmanesh et al(7)	2001	49	NR	1	N	Quadrantectomy	N	N	**	-	-	-	NR
6	Dadmanesh et al(7)	2001	52	NR	2.7	N	Quadrantectomy	N	N	36	+	-	-	NR
7	Dadmanesh et al(7)	2001	64	NR	2	N	Mastectomy	N	N	60	-	-	-	NR
8	Dadmanesh et al(7)	2001	69	NR	2.3	N	Mastectomy	N	Y	48	-	-	-	NR
9	Naidoo et al (14)	2001	50	Mass	2.5	Y	Wide local excision ALND	N	N	3	NR	NR	NR	-
10	Pestereli et al (16)	2002	56	Mass	1.9	Y	Modified radical mastectomy ALND	Y	N	12	+	+	-	-
11	Iivan et al (9)	2004	59	Mass	3.5	N	Wide local excision ALND	Y(Tamoxifen)	Y	52	+	+	NR	-
12	Iivan et al (9)	2004	67	Mass	1.1	N	Quadrantectomy ALND	N	Y	46	+	+	NR	-
13	Sanati et al (5)	2004	62	Mass	3	NR	NR	NR	NR	36	+	-	-	-
14	Kurose et al (13)	2005	47	Mass	2.8		Total mastectomy ALND	Y(CEF)	N	12	+	+	+	-
15	Saleh et al (4)	2005	51	Mass	2	Y	Lumpectomy ALND	N	N	NR	-	-	NR	-
16	Kulka et al (12)	2008	42	Mass	2.5	N	Lumpectomy	N	Y	NR	+	-	-	-
17	O'Sullivan-Mejia et al (15)	2009	55	Abnormal mammo	2	N	Mastectomy	Y (Trastuzumab)	Y	22	-	-	+	-
18	Jeong et al (10)	2010	37	Mass	2.2	N	Modified mastectomy	Y	N	23	-	-	-	-
19	Dinniwel et al (2)	2012	55	Mass, tenderness	4	N	Excisional biopsy	N	Y	36	-	-	-	-
20	Nio et al(6)	2012	45	Mass	3	N	Quadrantectomy ALND	Y	Y	NR	-	-	-	NR
21	Ikumi Suzuki et al (8)	2012	45	Mass, tenderness	2	Y	Partial mastectomy ALND	Y(AC+Paclitaxel)	Y	36	-	-	+	NR
22	Present case	2016	66	Mass, tenderness	2	N	Wild local excision	NR	NR	NR	-	-	-	NR

*Time after initial surgical procedure; ** Contralateral (right) LELC 3 years after initial diagnosis; ALND, Axillary lymph node dissection; NR, Not reported; CEF, Cyclophosphamide, epirubicin hydrochloride, 5FU; AC, Doxorubicin and cyclophosphamide; LELC, Lymphoepithelioma-like carcinoma; ER, Estrogen-receptor; PR, Progesterone-receptor; EBV, Epstein-Barr virus

other types of breast carcinoma as lobular carcinoma and ductal carcinoma.

Anaplastic lymphoma was excluded owing to the negative reaction of the large atypical cells to the lymphoid markers LCA, CD3 and CD20. Moreover, CD15 and CD30 neoplastic R-S cells were also absent. Thus Hodgkin disease was also excluded.

Immunohistochemical staining proved the malignant epithelial nature of the epithelial cells owing to their strong CK reactivity, infiltrative patterns and the high proliferative index.

Medullary carcinoma of the breast is well circumscribed and has pushing border, with dense lymphocytic infiltration. Histologically it can be differentiated by its fairly monomorphic cells and the syncytial pattern of growth. The present case showed infiltrative nests and isolated clusters with frequent isolated giant cells admixed with dense lymphoid cells, resulting in a so-called lymphoepithelial lesion.

Previous studies stated that LELC of the breast should be distinguished from medullary carcinoma by the presence of syncytial growth pattern that must constitute at least 75% of the latter tumor area (Ilvan et al., 2004, Kurose et al., 2005).

Moreover, Kurose et al., (2005) indicated that medullary carcinomas characteristically should be well circumscribed, with pushing; non-infiltrative borders with well demarcated tumor cells arranged in syncytial pattern admixed with dense lymphocytic infiltrate.

Lymphoepithelioma-like carcinoma of the breast may have morphological features similar to the unusual microscopic patterns of lobular carcinoma (Kumar and Kumar, 1994; Peştereli et al., 2002). However, invasive lobular carcinoma is typically characterized by a classic single-file pattern (Lopez and Bassett, 2009).

Cristina et al., (2000) in their reported case mentioned that the neoplastic ductal epithelial cells were disposed either as cohesive nests or as sheets within inflammatory background, predominantly lymphocytes. However the in present case, the large neoplastic cells were dispersed within the lymphoid follicles mimicking granulomatous reaction.

Cases of invasive ductal carcinomas - not otherwise specified (NOS) - with prominent lymphoid cell infiltration may also be considered as one of the differential diagnoses of LELC. However, these neoplasms have infiltrative borders and the lymphoid infiltrate in these cases is not as prominent as in LELC and does not obscure the neoplastic cells (Jeong et al., 2010).

Kumar and Kumar (1994) stated that the intense lymphocytic infiltrate obscuring the neoplastic cells in LELC may lead to an initial differential diagnosis of a pseudo lymphoma, lymphoma, or even leukemia .

Accordingly, we found the immunohistochemical approach using CD20, CD3, and cytokeratin mandatory to rule out the differential diagnosis of these hematologic malignancies (Sanati et al., 2004).

To our knowledge, this is the 22nd case of LELC reported in the breast (Dinniwell et al., 2012; O'Sullivan-Mejia et al., 2009), since the first case was reported by Kumar and Kumar (1994) .

Table 1 summarizes the data reported from the 22 cases; all patients were females, their ages ranged between 37 and 69 (average 53.7) years. Initial clinical presentations were reported in only 15 cases. Fourteen patients (64%) presented with a palpable mass and only three (14%) of them were accompanied with tenderness. Only one patient had abnormal mammographic findings on y. The tumor size ranged between 1 and 4 cm (average 2.26 cm) (Cristina et al., 2000; Peştereli et al., 2002).

Nodal involvement was reported in only five cases, and no distant metastases were reported in any of the cases; in spite of the poor morphological features of this type of neoplasms, such as cellular anaplasia and the high mitotic rate.

The surgeries included eight mastectomies, six quadrantectomy specimens, three wide local excisions, two lumpectomy specimens, only one case was excisional biopsy and in two cases surgery was not reported.

Hormone receptor study was performed in 21 cases: ER showed positive reaction in nine cases (43%), and PR was positive in only five cases (24%). HER2 over-expression was also evaluated by using immunohistochemistry in 17 cases, and it showed strong positive over expression in three of them (18%).

Only one case of recurrence was reported in patients followed up for periods between three and 72 months (average 32 months) (Nio et al., 2012). Thus, its prognosis might be favorable despite the worrisome morphologic features (Jeong et al., 2010).

Ridolfi et al., (1977) suggested that the prominent lymphoid infiltrate might provide an efficient immune-surveillance against tumors. However, the relatively short follow-up duration in the reported cases hinders proving this suggestion (Ridolfi et al., 1977).

The role of EBV in evolution of gastric, pulmonary, thymic and salivary gland LELCs was previously reported (Iezzoni et al., 1995). However, EBV was not detected in any of the mammary LELCs reported cases, as demonstrated in Table I. In the contrary, Kulka et al., (2008) detected human papilloma virus types 18 and 33 in their reported case of mammary LELC .

In Conclusion, we report a case of lymphoepithelioma like carcinoma of the breast occurring in 66 years old female and this report added one more case to the previously published ones. This case and other cases of LELC of the breast represented a diagnostic challenge owing to the morphologic similarities to other inflammatory mammary lesions and neoplasms and the rarity of this neoplasm. Proper diagnosis is the key for optimal management for this particular type of cancer.

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