



Lymphoepithelioma-like carcinoma of the breast: a diagnostic and therapeutic challenge

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ABSTRACT

We present a patient with lymphoepithelioma-like carcinoma (LELC) of the breast whose diagnosis is illustrative of the pathology nuances that must be taken into account to successfully reach correct identification of the disease. We also present an overview of our patient's proposed treatment in the context of 16 other reported LELC cases. Although LELC cases are rare, a sufficient number have been reported to discern the natural history of this pathologic entity and to undertake a review of those cases and of the application of oncologic first principles in their management. Given the potential for locoregional spread and distant metastases in LELC, adjuvant therapy has a role in the treatment of this entity.

KEY WORDS

Lymphoepithelioma-like carcinoma, breast, radiotherapy

1. INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma composed of malignant epithelial cells with an associated background of lymphocytes. Lymphoepithelioma was first described by Schminke¹ and Regaud and Reverchen² in 1921, but not until 1994 was a case of LELC in the breast reported³. Schminke and Regaud and Reverchen each described patterns of growth of the malignant epithelial cells characteristic of this pathologic entity. The cells may be arranged singly (Schminke's pattern) or in syncytial masses, nests, or cords (Regaud's pattern). Since Kumar and Kumar's first reported case in the breast³, another 15 cases of breast LELC have appeared in the English medical literature⁴⁻¹².

Here, we present a patient with LELC of the breast whose diagnosis is illustrative of the pathologic nuances that must be taken into account to successfully reach correct identification of the disease. We

also present an overview of our patient's proposed treatment in the context of the 16 other reported LELC cases.

2. CASE PRESENTATION

A 55-year-old postmenopausal woman originally from Ghana presented with a 4-week history of left breast tenderness and an upper outer quadrant mobile breast mass. She had been mammographically screened, with the most recent mammogram (performed 1 year before her presentation) having demonstrated no abnormalities. Her past medical history was unremarkable, with a surgical history of Cesarean section, tubal ligation, and hernia repair. She was gravida 2, para 2, with menopause having occurred at age 53. On systems review, she denied fevers, chills, or night sweats. No weight loss was reported, and she was asymptomatic but for left breast tenderness.

Physical examination revealed no cervical or axillary adenopathy, but was significant for a diffusely swollen left breast with a discrete, mobile 4-cm mass. The exam was otherwise noncontributory.

Mammography revealed a 3- to 4-cm upper outer quadrant density with spot compression views showing lobulated margins. No evidence of calcifications was noted. Breast ultrasonography showed a 4.3×3.5×2.6-cm lobulated, poorly marginated, hypoechoic solid mass. Computed tomography of the thorax, abdomen, and pelvis showed no evidence of distant metastases and the presence of an 8-cm left breast mass with a uniform low-density component (Figure 1).

Fine-needle aspirate yielded a cellular specimen noteworthy for single and groups of abnormal elongated cells with visible nucleoli presenting together with lymphocytes and plasma cells. A bone marrow biopsy revealed normocellular marrow with no evidence of lymphoproliferative disorder.

An excisional biopsy was followed by 3 successive pathology reviews. The initial consultant

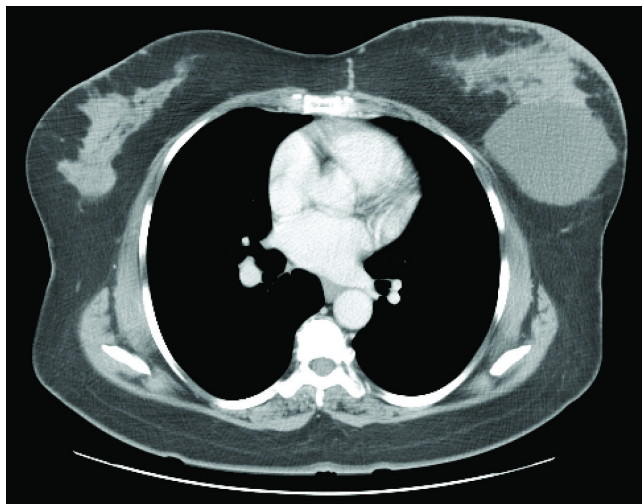


FIGURE 1 Axial slice from computed tomography study of the thorax demonstrating a left breast mass.

described a 6.5-cm mass, well circumscribed in relationship to the adjacent breast parenchyma, of lymphoid infiltrate with irregular germinal-like centres, favouring a diagnosis of non-Hodgkin lymphoma. Given that lymphoma of the breast is a rare clinical entity, a second opinion was sought. The second consultant described a malignant epithelial lesion confirmed by staining for cytokeratins AE1, AE3, and Cam 5.2. The background lymphoplasmacytic population was thought to be reactive, with a diagnosis of medullary carcinoma favored. The need for confirmation of this diagnosis by a breast pathologist resulted in the third and final pathology review.

The third review, by an expert breast pathologist, described dense nodular aggregates of lymphocytes and plasma cells interspersed with and surrounded by fat and hyalinized stroma on microscopic examination. Germinal centers were observed in some aggregates. Microscopy showed sheets of large, loosely cohesive, and highly atypical cells (Figure 2). The cells had pale eosinophilic cytoplasm and moderately pleomorphic nuclei, with inconspicuous nucleoli, in a background of dense lymphoplasmacytic infiltration. The lymphoplasmacytic infiltration overshadowed the epithelioid cells in some areas. There was no *in situ* ductal or lobular carcinoma identified in the specimen. These histologic features led to the suspicion that this entity was a large B-cell lymphoma.

1.1 Immunohistochemistry

Immunohistochemical studies used the avidin–biotin–peroxidase complex method and monoclonal antibodies against low molecular weight cytokeratin, cytokeratin 5/6, cytokeratin 7, estrogen and progesterone receptors, c-Erb-2 (HER2), epidermal growth factor (HER1), CD117 (c-Kit), B-cell marker CD20, and T-cell marker CD3. The stains for lymphoid markers

such as CD20 and CD3 were positive in the lymphoid infiltrate. No skewing in the kappa and lambda light chains ratio was observed, indicating a non-clonal lymphocytic infiltrate. The large epithelioid cells in the center of the lymphoplasmacytic infiltrate were strongly positive for cytokeratin 7, with weak positive staining for low molecular weight cytokeratin and high molecular weight cytokeratins 5 and 6. Tumour cells were negative for both the estrogen and progesterone receptors, HER2, and HER1. Diffuse and strong positivity for CD117 was observed (Figure 3).

1.2 *In-Situ* Hybridization

In situ hybridization with an ISH iView Blue Detection Kit (Ventana Medical Systems, Tucson, AZ, U.S.A.) to detect Epstein–Barr virus (EBV) in tumour epithelial cells and polymerase chain reaction to detect human papilloma virus both yielded negative results.

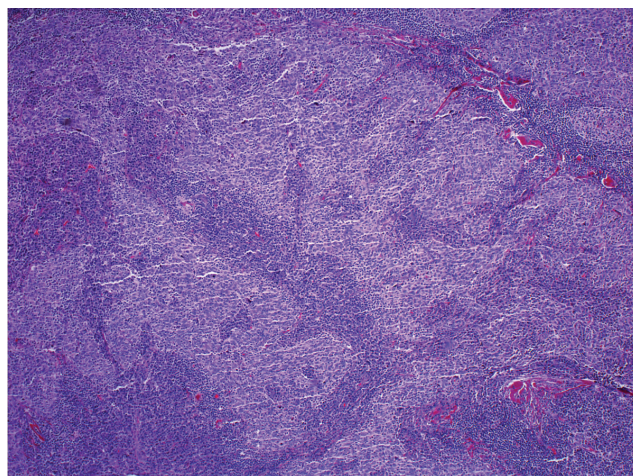


FIGURE 2 Tissue section of lymphoepithelioma-like carcinoma of the breast (hematoxylin and eosin stain).

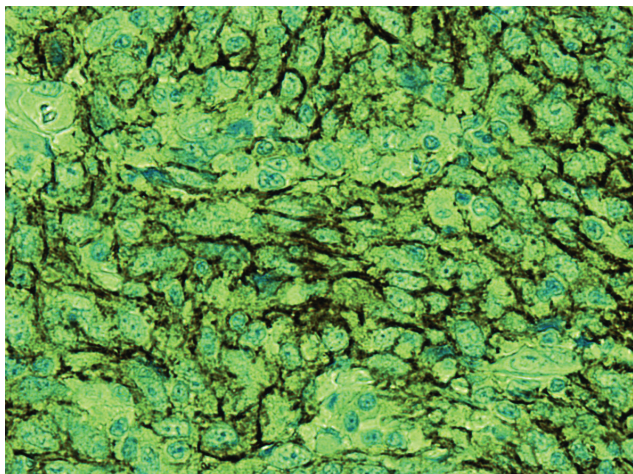


FIGURE 3 Immunohistochemical staining for CD117 (c-Kit) demonstrates strong positivity.

The differential diagnosis included medullary carcinoma, ductal or lobular carcinoma with lymphoid stroma, non-Hodgkin lymphoma, and LELC. Distinguishing the latter tumour from medullary breast carcinoma depends on circumscription and the syncytial growth pattern present in medullary carcinoma. In our case, the tumour demonstrated multinodular lesions without circumscription. Furthermore, in contrast to the features of medullary carcinoma, the margins of the tumour clusters were heavily permeated by numerous lymphocytes, resulting in poor margin definition. However, both tumour types share some features, such as an absence of EBV and negative results for hormone receptors. Although breast carcinomas can be associated with dense infiltration by lymphocytes, obscuring of the neoplastic cells in the lymphocytic background is unusual, in contrast to LELC.

Primary or secondary lymphoproliferative neoplasms of the breast should also be considered in the differential diagnosis. An LELC shows diffuse proliferation of lymphocytes and can mimic non-Hodgkin lymphoma, as in our case. Immunostaining for epithelial markers such epithelial membrane antigen or cytokeratin is very helpful, because the neoplastic epithelial cells within the intense lymphocytic infiltration will be highlighted. Based upon those features, a diagnosis of LELC of the breast was made.

Before management proceeded further, a review of the English medical literature was undertaken.

2. DISCUSSION

Lymphoepithelioma-like carcinomas are tumours arising outside of the nasopharynx with characteristics similar to those of nasopharyngeal lymphoepithelioma. These tumours have been reported in many organs, and 16 cases of LELC of the breast have previously been published. Tables I and II summarize the published cases. As with all of the published cases, our patient showed no evidence of EBV.

Lymphoepithelioma-like carcinomas arising outside of the nasopharynx have morphologic features identical to those of nasopharyngeal lymphoepithelioma. On pathology review, a differential diagnosis of lymphoma and medullary carcinoma in addition to LELC can be generated¹¹. The undifferentiated malignant cells in a background of infiltrating lymphocytes can be mistaken for lymphoma, as occurred with the first reviewer. The application of immunohistochemistry can help to reveal the epithelial nature of the malignant cells and avoid a misdiagnosis. Similarly, the morphology of LELC of the breast is similar to that of medullary carcinoma and requires thorough review. These two entities show differences with respect to circumscription and the syncytial growth patterns of the tumour cells. Medullary carcinomas are reported to be well circumscribed and to displace adjacent breast

tissue rather than invade it. The medullary tumour cells occur in syncytial masses (there is no noted equivalent in LELC of the breast). The stromal infiltrate in LELC has fewer plasma cells than are noted in medullary carcinoma, which manifests a prominent lymphoplasmacytic reaction. Recognition of these potential diagnostic pitfalls will facilitate an accurate diagnosis of this rare condition.

Lymphoepithelioma-like carcinoma has been reported in a variety of anatomic sites that include skin^{13–16}, lacrimal and salivary glands^{17,18}, thyroid gland¹⁹, thymus²⁰, breast³, lung²¹, esophagus²², stomach²³, colon²⁴, hepatobiliary system^{25,26}, renal pelvis^{27–30}, ureter²⁸, kidney²⁷, bladder³¹, prostate²⁷, uterine cervix³², vulva^{33,34}, and vagina³⁵. The foregoing sites typically have better outcomes than are seen with aggressive nasopharyngeal tumours; however, they do demonstrate the potential for local spread, angioinvasion, and metastasis to lymph nodes. The paucity of published literature on both management and long-term follow-up makes recommendations difficult. For each anatomic site, measures to ensure local control (surgery or radiotherapy, or both) need to be combined with systemic therapy for the management of potential distant spread. With additional reports and longer periods of follow-up, improved insight into therapy and prognosis may be obtained.

As with all breast cancers, surgery is the primary therapy for LELC of the breast. Every woman in the published literature underwent an excision, quadrantectomy, or mastectomy. As in the more common breast cancer histologies, the clinical goal should be an assurance of clear margins. The presence of lymph node metastases in 4 of the 14 women who underwent an axillary lymph node dissection (28.6%) lends support to continued use of that procedure or of a sentinel lymph node biopsy. Internal mammary lymph nodes appear at risk of spread, given a notable parasternal recurrence in the case reported by Kurose *et al.*⁸ and attributed to a nodal recurrence. Breast-conserving surgery and mastectomy both appear to be appropriate for primary therapy.

Radiotherapy was administered adjuvantly in 4 of the 13 reported cases in which information on additional treatment after surgery was available. The dose–fractionation and target volume were described in 2 of those 4 cases as 50.4 Gy delivered in 28 fractions to the breast alone. In 3 of the 4 cases, the women had undergone a wide local excision or a quadrantectomy, in which case the use of adjuvant radiotherapy would be consistent with standard breast-conserving therapy³⁶. A therapeutic rationale for the use of radiotherapy after mastectomy in the case reported by Dadmanesh *et al.*⁵ was not provided. None of the women who underwent mastectomy had tumours larger than 5 cm or a burden of regional nodal metastasis, but it would not be unreasonable to consider the use of adjuvant radiotherapy in women

TABLE 1 Characteristics and treatment of reported cases of lymphoepithelioma-like carcinoma (LELC) of the breast

Reference	Age (years)	Side (L/R)	Size (cm)	Lymph node status	Surgery	Systemic therapy	Radiotherapy	Clinical outcome
Kumar and Kumar, 1994 ³	65	R	2	0	Mastectomy, ALND			No evidence of disease at 7 months
Cristina <i>et al.</i> , 2000 ⁴	54	R	1.5	0/19	Wide local excision, ALND		Yes	No evidence of disease at 6 months
Dadmanesh <i>et al.</i> , 2001 ⁵	43 53	L R	1.9 2	1/1	Quadrantectomy, ALND			No evidence of disease at 60 months No evidence of disease at 72 months
	49 52	L R	1 2.7	0/19 0/20	Quadrantectomy, ALND			Contralateral LELC 3 years later No evidence of disease at 36 months
	64 69	R R	2 2.3	0/29 0/19	Mastectomy, ALND		Yes	No evidence of disease at 60 months No evidence of disease at 48 months
Naidoo <i>et al.</i> , 2001 ⁹	50	R	2.5	2/24	Wide local excision, ALND			No evidence of disease at 3 months
Peştereli <i>et al.</i> , 2002 ¹⁰	56	R	2	2/27	Mastectomy, ALND	Chemotherapy		No evidence of disease at 12 months
Ilvan <i>et al.</i> , 2004 ⁶	59	R	3.5	0/20	Wide local excision, ALND	Tamoxifen	Yes, 50.4 Gy	No evidence of disease at 53 months
	67	R	1.1	0/16	Quadrantectomy		Yes, 50.4 Gy	No evidence of disease at 46 months
Sanati <i>et al.</i> , 2004 ¹²	62	L	3.0		Wide local excision			
Kurose <i>et al.</i> , 2005 ⁸	47	L	2.8	0/33	Mastectomy, ALND	Tamoxifen		At 4 months, biopsy-positive parasternal mass; CEF and 40 Gy RT; at 19 months, parasternal mass and lung metastasis
Saleh <i>et al.</i> , 2005 ¹¹	51	L	1.3	1/8	Wide local excision, ALND			
Kulka <i>et al.</i> , 2008 ⁷	42	R	2.5	0/10	Wide local excision ×2			

L/R = left or right; ALND = axillary lymph node dissection; CEF = cyclophosphamide-epirubicin-5-fluorouracil; RT = radiotherapy.

TABLE II Summary of the *in-situ* lobular component and receptor status

Reference	In situ lobular component	Receptor status		
		Estrogen	Progesterone	HER2
Kumar and Kumar, 1994 ³	Positive, infiltrative	Positive	Positive	ND
Cristina <i>et al.</i> , 2000 ⁴	Positive, infiltrative	Positive (42%)	Negative (<10%)	Negative
Dadmanesh <i>et al.</i> , 2001 ⁵	Negative	Negative	Negative	Negative
	Negative	Negative	Negative	Negative
	Negative	Negative	Negative	Negative
	Negative	Positive	Negative	Negative
	Negative	Negative	Negative	Negative
	Negative	Negative	Negative	Negative
Naidoo <i>et al.</i> , 2001 ⁹	Negative	ND	ND	ND
Peştereli <i>et al.</i> , 2002 ¹⁰	Positive, infiltrative	Positive (80%)	Positive (20%)	Negative
Ilvan <i>et al.</i> , 2004 ⁶	Negative	Positive	Positive	ND
	Negative	Weak positive	Weakly positive	ND
Sanati <i>et al.</i> , 2004 ¹²	Atypical lobular hyperplasia	Negative	Negative	Negative
Kurose <i>et al.</i> , 2005 ⁸	Negative	Negative	Negative	ND
Saleh <i>et al.</i> , 2005 ¹¹	Negative	Positive	Negative	ND
Kulka <i>et al.</i> , 2008 ⁷	Negative	Weak positive	ND	Negative

ND = not determined.

who may have those features and to take an approach analogous to that for stage III or locally advanced breast cancer³⁷. Radiotherapy may also have a palliative role, given that a parasternal mass treated with 40 Gy and CEF (cyclophosphamide–epirubicin, and 5-fluorouracil) chemotherapy appears to have had some effect.

Chemotherapy was used in 2 of the reported cases. In the case reported by Peştereli *et al.*¹⁰, it was used in an adjuvant fashion, and in the case of Kurose *et al.*⁸, it was delivered after recurrence. Unfortunately, the Kurose group described only chemotherapy with CEF being given. Assessment of efficacy is confounded by the delivery of radiotherapy, with one of the interventions or their combination having produced a response. However, in LELC arising in other anatomic sites, chemotherapy has demonstrated some potential efficacy and may merit consideration in cases involving the breast were there to be evidence of metastatic spread^{18,21,27,31,38–40}. Unfortunately, the data are insufficient to provide definitive guidance.

Hormonal therapy was used in 2 women, one of whom was negative for the estrogen and progesterone receptors and experienced recurrence. Of the 16 reported patients, hormone receptor status was known for 15, 8 of whom (53%) were strongly or weakly estrogen receptor–positive, with 4 being strongly or weakly progesterone receptor–positive. In reviewing the pathology, receptor status should always be assessed, with consideration given to hormonal therapy in women who are receptor-positive.

Interestingly, the present case is the first to assess the CD117 surface marker in LELC of the breast. The cell-surface marker CD117, a proto-oncogene, is a receptor for cytokine stem cell factor. Cellular signaling through CD117 plays a key role in cell survival, proliferation, and differentiation. CD117 is most commonly associated with gastrointestinal stromal tumours, but it has also been reported in other malignancies^{41,42}. The significance of c-Kit expression in LELC of the breast, with its prognostic and therapeutic implications, needs further investigation⁴³.

In synthesizing the available historical case material and applying the standard oncologic principles of breast cancer therapy, a sentinel lymph node dissection was undertaken. After radiocolloid and patent blue dye injection, 2 sentinel lymph nodes were identified. On pathology review, no evidence of metastatic disease was detected. In the absence of nodal metastatic spread and given the paucity of data, the utility of chemotherapy is uncertain and may not be of benefit. An anthracycline-based regimen was offered to the patient, who declined it. Whole-breast radiotherapy with a dose of 5000 cGy in 200-cGy fractions was delivered over 5 weeks, with no noted adverse sequelae. Since completion of therapy, the patient has been seen for follow-up surveillance with medical history, physical examination, and annual mammography. Three years after primary therapy, she remains well, with no evidence of disease recurrence.

3. CONCLUSIONS

Lymphoepithelial-like carcinoma of the breast is a rare clinical entity. Pathologic diagnosis depends on a thorough histologic and immunohistochemical examination. The known characteristic pathologic features of LELC ensure an appropriate diagnosis. The demonstrated metastatic potential of LELC means that thorough staging, with axillary assessment and imaging is recommended. Breast-conserving therapy appears to be appropriate, although further follow-up is recommended before the use of breast-conserving surgery alone. The role of systemic therapy is unclear given the small series of patients available. In the presence of locoregional or distant metastasis, chemotherapy should be considered. Hormone receptors are noted to be positive (strongly or weakly) in a significant number of women and merit inclusion, where appropriate. The potential for targeted agents merits further consideration and may help to better elucidate the causes of this rare pathology.

4. CONFLICT OF INTEREST DISCLOSURES

The authors have no known financial conflicts of interest.

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