

CASE REPORT

LYMPHOEPITHELIOMA-LIKE BREAST CARCINOMA

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Nasopharyngeal lymphoepithelioma is an undifferentiated carcinoma in a dominated lymphoplasma-histiocyte stroma. Lymphoepithelioma-like carcinoma of the breast is the mammary counterpart of the lymphoepithelioma of the nasopharynx and is characterised by proliferation of poorly differentiated malignant cells within a prominent lymphoid infiltrate. It is a very rare primary carcinoma of the breast first reported in 1994 by Kumar and Kumar. Fewer than 40 cases have been reported in the English literature. In this manuscript a case of lymphoepithelioma-like carcinoma of the breast in a 57-year-old patient is reported along with a literature review on this rare entity.

Key words: lymphoepithelioma-like carcinoma, breast cancer, lymphoepithelioma, Epstein-Barr virus, HPV.

Introduction

Nasopharyngeal lymphoepithelioma is a well-defined entity first described in 1921 by Regaud, Reverchon, and Schminke [1, 2]. Two distinct histological patterns have been described: Schminke pattern, consisting of isolated tumour cells, and Regaud pattern, in which tumour cells are arranged in nests, cords, or syncytial appearance. In both patterns neoplastic cells are associated with a densely infiltrated lymphoid stroma. The type of architectural pattern is not related to prognosis. Lymphoepithelioma-like carcinoma (LELC) is a poorly differentiated carcinoma occurring outside the nasopharynx, which displays identical histological features to its nasopharyngeal counterpart. It has been reported in several anatomic sites including breast [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25], colon [26], esophagus [27], kidney [28], lacrimal gland [29, 30], larynx [31], hepatobiliary system [32, 33],

lungs [34], major and minor salivary glands [35, 36, 37, 38], orbital adnexa [39], prostate [28], skin [40], stomach [41], thymus [42], thyroid [43], trachea [44], ureter [45], urinary bladder [46], uterine cervix [47], vagina [48], and vulva [49, 50]. Epstein-Barr virus (EBV) has been associated with LELC in several anatomic sites, such as nasopharynx, salivary gland, stomach, and thymus, but not in non-foregut derived tissues such as skin, uterine cervix, oral cavity, and urinary bladder [51].

Lymphoepithelioma-like carcinoma of the breast (LELC-B) was first described in 1994 by Kumar and Kumar [3]. In total, 33 cases have been reported in the English literature. The diagnosis may be challenging, especially on frozen sections, due to its morphological similarity to medullary carcinoma, lymphocyte-rich invasive carcinoma of ductal or lobular type, non-Hodgkin's, and Hodgkin's lymphoma. Herein, we review 33 previously reported cases of LELC-B additionally to a case recently encountered

in our pathology department that proved to be diagnostically challenging.

Due to the rarity of this entity no solid evidence regarding the optimal treatment strategy exists. Patients with LELC-B are excluded from randomised controlled trials, and their management is therefore based on anecdotal cases or published case reports [23].

Case report

A 57-year-old patient with no previous history was admitted due to palpable lymphadenopathy of the left axilla. On clinical examination a small palpable breast lump in the upper outer quadrant of the left breast was identified, followed closely by FNAC, which was positive for malignancy. Mammography revealed an asymmetrical mass close to the pectoralis major muscle measuring 15 mm surrounded by microcalcifications. Clinically enlarged lymph nodes were identified by an ultrasound in the ipsilateral axilla. Radiological examination for cancer staging was subsequently performed and showed a multilobulated solid mass in the upper outer quadrant of the breast together with enlarged axillary lymph nodes and a left adrenal gland adenoma. No distant disease was identified. Conn's syndrome and hypertension were also diagnosed during her hospitalisation. The patient underwent a lumpectomy with axillary lymph node excision along with left laparoscopic adrenalectomy at the same surgical procedure.

Grossly, the tumour was relatively well circumscribed, measuring 22 mm, on a cut surface it had a relatively hard consistency. Microscopically, on low-power examination the tumour had a nodular appearance separated by fibrous septa. Higher-power examination revealed small tumour islands, cords, and single cells displaying a moderate degree of atypia and scanty cytoplasm. They were surrounded and

intermingled predominantly by lymphocytes (Fig. 1); lymphoid follicles and occasional plasma cells, eosinophils, and histiocytes were also noticed. Occasionally the tumour sheets were permeated and destroyed by lymphocytes resulting in so-called lymphoepithelial lesions. In situ component, either ductal or lobular, was not identified. Mitotic figures were few.

Metastatic disease was found in 8 of 13 lymph nodes (Fig. 2).

The presentation of the patient with extensive lymphadenopathy and the predominant lymphoepithelial component of the tumour in combination with the absence of in situ structures rendered the suspicion of a lymphoproliferative disorder and hence an experienced hem-pathologist (A.P) consultation was carried out. Therefore, the immunohistochemical staining of the lymphocytic infiltrate demonstrated positivity for lymphoid markers CD20 and CD3, with predominance of T-lymphocytes (CD3+, CD4+ > CD8+). Studies for light chain expression by the B-lymphocytes (CD20+) and plasma cells show polytypic cell population SIg/CIg(κ) \geq SIg/CIg(λ).

Additional immunohistochemical indices revealed positivity of tumour cells for the epithelial markers AE-1/AE-3, Cytokeratin 8/18, EMA, Cytokeratin 7 (Fig. 3), and E-Cadherin. Negativity was noticed for Cytokeratin 20, ER, PR, C-ERB-2, and CD-117. Ki-67 showed positive staining in 80% of the tumour nuclei. Epithelial markers were applied to lymph nodes as well. Tumour cells showed positive staining for AE-1/AE-3 and Cytokeratin 7 (Fig. 4).

In situ hybridisation to detect Epstein-Barr virus (EBV) yielded negative results. Type 16 HPV was detected by PCR and in situ hybridisation techniques.

The diagnosis of LELC-B was made. The patient showed no postoperative complications and was discharged seven days after surgery. She received adju-

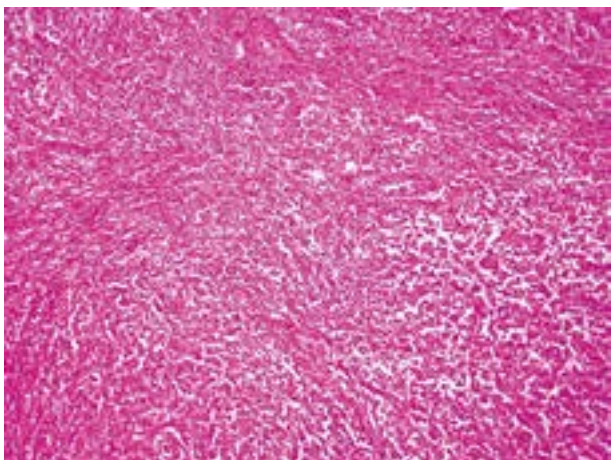


Fig. 1. Low-power photograph displaying small islands embedded in a lymphocyte-rich stroma (HE, magnification 4 \times)

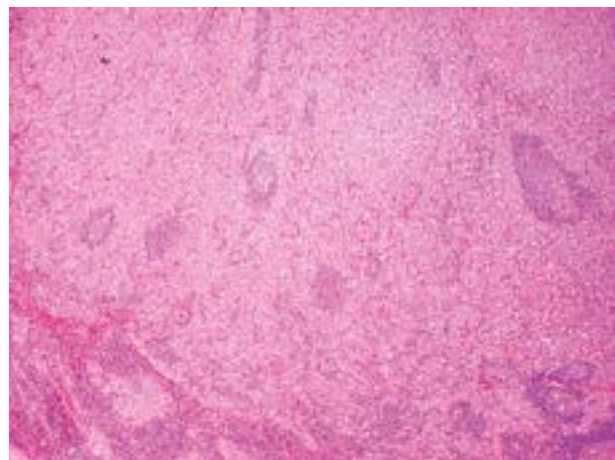


Fig. 2. Low-power photograph showing extensive lymph node infiltration sparing germinal centres

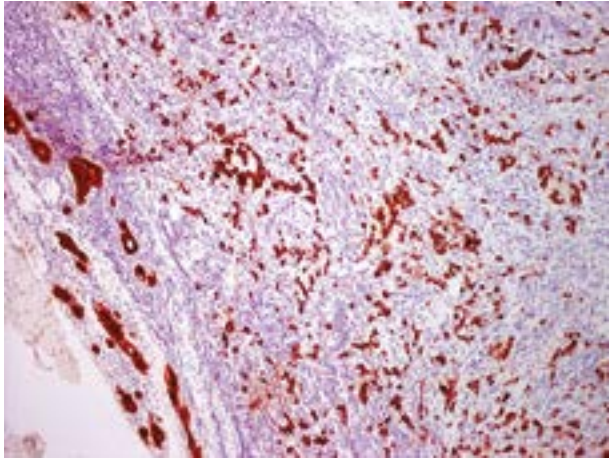


Fig. 3. Cytokeratin 7 highlighting malignant epithelial cells inside the dense lymphoid infiltrate (Cytokeratin 7, magnification 10×)

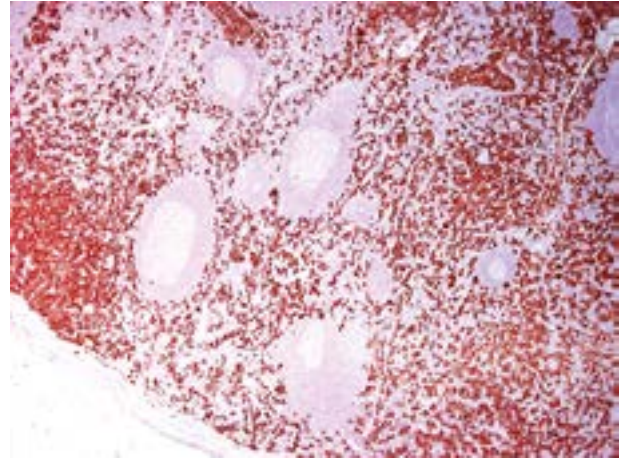


Fig. 4. Lymph node infiltration by tumour cells arranged in islands, cords, and single cells as shown by Cytokeratin 7 (Cytokeratin 7, magnification 4×)

vant therapy with a combination of chemotherapy and RT; 36 months later there is no evidence of recurrence or metastasis.

Discussion

Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma analogous to the nasopharyngeal lymphoepithelial carcinoma. Concerning the breast, it is a rare entity with only 33 cases (32 patients) described in the literature, the majority being single case reports. The clinical characteristics of the previous reports are summarised in Table I. Morphologically, tumour necroses were identified in two patients in the Dadmanesh series as well as in five more cases [5, 10, 15, 19, 24]. A lobular variant of LELC-B has been reported by some authors [3, 4, 7, 9] associated with LCIS [3, 4, 7], pagetoid spread [4], or with atypical lobular hyperplasia [9]. Ductal carcinoma in situ was not identified in any of the previous cases. In three of the cases there was association with sclerosing lymphocytic lobulitis in the surrounding breast parenchyma [6, 19, 20]. Kurose *et al.* reported glandular differentiation on electron microscopy [10]. Dadmanesh *et al.* described in their series one case of familial tumour with established BRCA mutation [5]. Dinniwell *et al.* reported CD-117 positivity in their tumour [18]. There is no evidence of association with EBV either by ISH [4, 5, 8], immunohistochemistry [7], or PCR [4]. Our case was negative for EBV assessed with *in situ* hybridisation. The reviewed literature indicated two cases of LELC-B in association with HPV [12, 17]. The case in hand was examined for low- and high-risk HPV; detection of type 16 virus was evident using PCR and *in situ* hybridisation techniques.

Lymph node metastasis was found in seven of the cases that reported nodal status. Our case was treated

with BCS together with axillary lymph node dissection, and metastatic disease was found in eight lymph nodes, thus being the only case with N2 disease.

In the present case, the infiltration of axillary lymph nodes by the tumour mandated the use of systemic adjuvant treatment. The patient was therefore offered adjuvant chemotherapy based on the AC – T regimen. This regimen consists of four cycles of doxorubicin and cyclophosphamide administered successively with four cycles of paclitaxel administered intravenously every 21 days. After the completion of adjuvant chemotherapy the patient was offered adjuvant radiotherapy. She is currently leading an active life and is free of disease 36 months after diagnosis. We attribute the optimal outcome partly to the incorporation of the taxanes to an anthracycline-based chemotherapy and mainly to the multidisciplinary approach of this rare disease.

LELC-B may be under-diagnosed due to its similarity to lymphocyte-predominant breast carcinoma (LPBC) of ductal or lobular type. In fact, their resemblance is so intense that some authors have debated whether LELC-B is a distinct entity [8].

The differential diagnosis includes medullary carcinoma (MC), atypical medullary carcinoma (AMC), and lymphoproliferative disorders such as non-Hodgkin's lymphoma and Hodgkin's lymphoma.

MC is defined as a special type of breast carcinoma with favourable prognosis. Its histological recognition is based on a number of histological criteria proposed by Ridolfi *et al.*, including syncytial growth pattern in more than 75%, complete microscopic circumscription, moderate to marked lymphoid stromal infiltration, high nuclear grade and numerous mitoses, lack of *in situ* component, or gland formation [54].

AMC diagnosis requires that the tumour fulfils the first two criteria and has the possibility of missing up to two of the remaining criteria. LELC-B may show

Table I.

CASE	REF.	YEAR	AGE	SIZE (MM)	LN (Y/N)	SURGERY	RT (Y/N)	ER	PR	HER2	OUTCOME (MO)
1	Kumar <i>et al.</i> [3]	1994	65	20	N(0)	MS, ALND	NR	+	+	NR	7 ANED
2	Cristina <i>et al.</i> [4]	2000	54	15	N(0/19)	WLE, ALND	Y	+	-	-	6 ANED
3	Dadmanesh <i>et al.</i> [5]	2001	43	19	Y(1/1)	QE	N	-	-	-	60 ANED
4	Dadmanesh <i>et al.</i> [5]	2001	53	20		NR	N	-	-	-	72 ANED
5	Dadmanesh <i>et al.</i> [5]	2001	49	10	N(0/19)	QE, ALND	N	-	-	-	*
6	Dadmanesh <i>et al.</i> [5]	2001	52	27	N(0/20)	QE, ALND	N	+	-	-	36 ANED
7	Dadmanesh <i>et al.</i> [5]	2001	64	20	N(0/29)	MS, ALND	N	-	-	-	60 ANED
8	Dadmanesh <i>et al.</i> [5]	2001	69	23	N(0/19)	MS, ALND	Y	-	-	-	48 ANED
9	Naidoo <i>et al.</i> [6]	2001	50	25	Y(2/24)	WLE, ALND	N	NR	NR	NR	3 ANED
10	Pestereli <i>et al.</i> [7]	2002	56	19	Y(2/27)	MS, ALND	N	+	+	-	12 ANED
11	Ilvan <i>et al.</i> [8]	2004	59	35	N(0/20)	WLE, ALND	Y	+	+	-	52 ANED
12	Ilvan <i>et al.</i> [8]	2004	67	11	N(0/16)	QE, ALND	Y	+	+	-	46 ANED
13	Sanati <i>et al.</i> [9]	2004	62	30	NR	WLE	NR	+	-	-	
14	Kurose <i>et al.</i> [10]	2005	47	28	N(0/33)	MS, ALND	Y	+	+	+	**
15	Saleh <i>et al.</i> [11]	2005	51	20	Y(1/8)	WLE, ALND		-	-	NR	NR
16	Kulka <i>et al.</i> [12]	2008	42	25	N(0/10)	WLE, ALND	Y	+	-	-	NR
17	O'Sullivan Meija <i>et al.</i> [13]	2009	55	20	N(0/2)	Seg. MS, SLND	Y	-	-	+	22 ANED
18	Jeong <i>et al.</i> [14]	2010	37	22	N(0/13)	MS, ALND	N	-	-	+	23 ANED
19	Kucukzeybek <i>et al.</i> [15]	2011	58	30	N(0/24)	MS, ALND	NR	-	-	-	***
20	Trihia <i>et al.</i> [16]	2012	53	15	Y(2/30)	PM, ALND	NR	-	-	-	NR
21	Nio <i>et al.</i> [17]	2012	45	30	N(0/5)	QE, ALND	Y	-	-	-	12 ANED
22	Dinniwell <i>et al.</i> [18]	2012	55	40	N(0/2)	EB, SLND	Y	-	-	-	36 ANED
23	Top <i>et al.</i> [19]	2013	59	30	N(0/23)	MS, ALND	N	-	-	-	9 ANED

Table I. Cont.

CASE	REF.	YEAR	AGE	SIZE (MM)	LN (Y/N)	SURGERY	RT (Y/N)	ER	PR	HER2	OUTCOME (MO)
24	Abdou <i>et al.</i> [20]	2014	45	20	N(0/24)	QE, ALND	NR	-	-	-	
25	Suzuki <i>et al.</i> [21]	2014	64	20	Y(3/23)	PM, ALND	Y	-	-	+	36 ANED
26	Jansari <i>et al.</i> [22]	2015	39	40	-	LE	-	-	-	-	-
27	Nankin <i>et al.</i> [23]	2015	39	27	N(0/5)	WLE, ALND	N	+	-	-	24 ANED
28	Herrera-Goepfert <i>et al.</i> [24]	2016	57	21	N(0/1)	MS,SLND	N	+	+	-	
29	Shet <i>et al.</i> [25]	2016	56	30	Y(1/17)	WLE, ALND	Y	-	-	-	103 ANED
30	Shet <i>et al.</i> [25]	2016	39	20	N(0/18)	MS, ALND	N	-	-	-	****
31	Shet <i>et al.</i> [25]	2016	40	25	ND	WLE	Y	-	-	-	84 ANED
32	Shet <i>et al.</i> [25]	2016	40	35		MS, ALND	N	-	-	-	6 ANED
33	Shet <i>et al.</i> [25]	2016	51	30		MS, ALND	N	-	-	-	24 ANED
34	Present case	2017	57	22	Y(8/13)	LE, ALND	Y	-	-	-	ANED

MS – mastectomy; WLE – wide local excision; PM – partial mastectomy; EB – excisional biopsy; ANED – alive no evidence of disease; ALND – axillary lymph node dissection, NR – Not reported, NCB – needle core biopsy; QE – quadrantectomy; LE – lumpectomy; Seg. MS – Segmental mastectomy

* Contralateral LELC 3 years later.

** Development of parasternal mass after 4 months, metastasis to parasternal lymph node and lung 19 months later.

*** Local recurrence occurred after 18 months. No evidence of distant metastasis was found.

**** Patient developed contralateral breast malignancy after 53 months.

syncytial growth pattern, although not in >75%, usually has an infiltrative pattern lacking circumscription, and its cells are not as pleomorphic as in MC or AMC [5]. Another useful feature is that in MC and AMC the lymphoid infiltrate does not obscure or intermingle with the epithelial cells [8]. It should be noted that in the latest (fourth) edition WHO classification of tumours of the breast, both MC and AMC are collectively termed as carcinoma with medullary features [55].

Lymphocyte-rich invasive breast carcinoma or LPBC is defined as a carcinoma with at least 50-60% inflammatory stroma [56]. The distinction between LELC-B and LPBC lies in the amount of the lymphocytic infiltrate, which in LPBC should not be as intense as in LELC-B, thereby obscuring the neoplastic cells. Also, certain architectural and cytological characteristics may prove helpful in the differential diagnosis [5].

Morphologically it may be difficult to distinguish the Schminke pattern of LELC-B from non-Hodgkin's and Hodgkin's lymphoma. In the literature, in

a number of cases NHL was the main diagnostic challenge on microscopic examination [6, 8], and some cases were initially diagnosed as NHL [5, 18, 25]. Moreover, the presence of binucleated and/or multinucleated cells, thus bearing strong resemblance to Hodgkin's Lymphoma [6, 11], are cases that need further investigation. Nonetheless, the differential diagnosis of LELC-B on morphological bases is mainly from Hodgkin's Lymphoma and NHL, therefore of exclusion diagnosis, a panel of immunohistochemical staining showing positivity for epithelial differentiation AE-1/AE-3, EMA, Cytokeratin 8/18, and Cytokeratin 7 in combination to lymph-marker CD3, CD20, CD15, CD30, and ALK-1 is needed to solve the ambiguity.

Conclusions

LELC-B is a rare disease, considered as the nasopharyngeal lymphoepithelioma counterpart, which pathologists should be aware of. Specific features that help distinguish this entity include nodular mass

dominated by dense inflammatory cells that permeate and destroy tumour cells separated by fibrous septa. Tumour cells display a moderate to high degree atypia, small nucleoli, and scanty cytoplasm. Multinuclear features may be present. The *in situ* component, whenever present, is always of lobular type. Due to the lack of evidence regarding the optimal management of this disease, it is recommended that experience between clinicians be shared in literature and treatment be designed in a multidisciplinary approach.

The authors declare no conflicts of interest.

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