

# Lymphoepithelioma-like Carcinoma of the Breast: A Case Report with a Special Analysis of an Association with Human Papilloma Virus

YOSHINORI NIO<sup>1</sup>, KAZUHIKO TSUBOI<sup>1</sup>, MIKAKO TAMAOKI<sup>1</sup>,  
MASASHI TAMAOKI<sup>1</sup> and RIRUKE MARUYAMA<sup>2</sup>

<sup>1</sup>Nio Breast Surgery Clinic, Kyoto, Japan;

<sup>2</sup>Department of Pathology, Faculty of Medicine, Shimane University, Izumo, Japan

**Abstract.** *Lymphoepithelioma-like carcinoma (LELC) of the breast is a very rare tumor, and fewer than 20 cases have been reported. A recent report suggested the implication of human papilloma virus (HPV) in the pathogenesis of breast LELC. We report a case of LELC of the breast with a review of its relevance to an association with HPV. A 45-year-old female patient presented with a solid mass in the outer-upper part of her left breast, which was diagnosed as malignant (ductal carcinoma) by fine-needle aspiration cytology. The patient underwent a quadrantectomy of the breast and axillary sentinel node biopsy. Pathological examination revealed cohesive sheets or nests of malignant epithelial cells, with unclear circumscription in a background of diffuse lymphoid infiltration; the postsurgical clinical stage was pT1pN0M0, stage I. Immunohistochemistry demonstrated that the tumor was triple negative and basal-like breast cancer. In the present case in situ hybridization demonstrated positive HPV signals in a few tumor cells; however, polymerase chain reaction study failed to detect HPV in tumor cells. Conclusion: To the best of our knowledge, this is the second report on HPV infection associated with breast LELC.*

Lymphoepithelioma-like carcinoma (LELC) is a tumor with histological features similar to those of nasopharyngeal lymphoepithelioma; besides the nasopharynx, this kind of tumor occurs in various organs, including the stomach, salivary glands, lungs, thyroid, thymus and uterus. On the

other hand, LELC of the breast is very rare, and to our knowledge only 19 cases, including the present case, have been reported since the first report by Kumar and Kumar in 1994 (1-12).

The histological features of LELC of the breast are characterized by cohesive sheets or nests of malignant epithelial cells with unclear margins in a background of diffuse lymphoid infiltration. The malignant cells are occasionally permeated by lymphocytes, resulting in separated nests and single cells. These histological features are very similar to those of medullary carcinoma, and LELCs of the breast may be diagnosed as a medullary carcinoma with striking infiltration of lymphocytes.

Epstein-Barr virus (EBV) is known to be associated with the pathogenesis of nasopharyngeal LELC, and previous studies investigated the presence of EBV in malignant cells of breast LELC by using *in situ* hybridization (ISH) or polymerase chain reaction (PCR), but the results were negative (1-10, 12). Recently, Kulka *et al.*, reported that LELC of the breast was tested positively for human papilloma virus (HPV) (10). In this case report, we also investigated the relevance of HPV in LELC of the breast.

## Case Report

**Clinical course.** A 45-year-old female patient presented with a solid mass in the outer-upper part of her left breast, measuring about 3 cm in diameter. Mammography demonstrated a dense irregular shadow, 2.5 cm in diameter (Figure 1). Ultrasonography revealed a low-echoic lesion with a highly echoic central spot (Figure 2), and elastography demonstrated the strain ratio of the tumor was 24.4 in comparison with surrounding normal breast tissue, suggesting that the tumor was very hard. Fine-needle aspiration cytology (FNAC) diagnosis was positive (ductal carcinoma or medullary carcinoma). The tumor in the left breast was demonstrated as an enhanced tumor shadow by a

*Correspondence to:* Yoshinori Nio, MD, Nio Breast Surgery Clinic, Hello-Yuai Bldg. 1&2F, 511 Anenishihorikawa-cho, Nakagyo-ku, Kyoto 604-8264, Japan. Tel: +81 758030111, Fax: +81 758110101, e-mail: nio@star.ocn.ne.jp

**Key Words:** Lymphoepithelioma-like carcinoma, breast cancer, human papilloma virus, *in situ* hybridization, polymerase chain reaction.

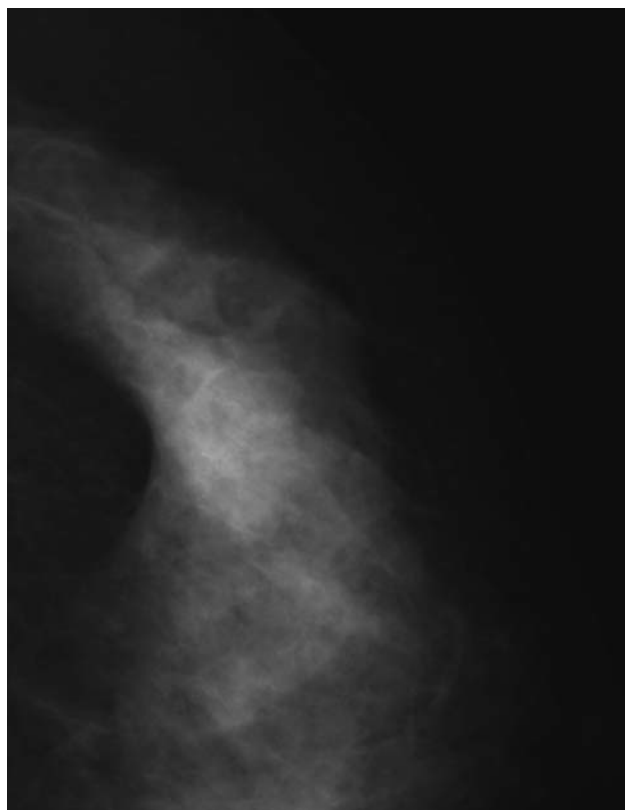


Figure 1. Mammography demonstrated a dense irregular shadow.

contrast medium on computed tomographic (CT) examination (Figure 3). Swelling of the left axillary lymph node (AxLN) was indicated by CT examination, but it was not enhanced by a contrast medium CT examination. Positron emission tomography (PET)/CT examination demonstrated a high accumulation of  $^{18}\text{F}$ -fluorodeoxy glucose (FDG) in the lesion at the left breast (maximum standard uptake value=6.8) (Figure 4), but accumulation of FDG to the swelling AxLN was low. No distant metastases were demonstrated, neither in CT nor in PET/CT examinations. In addition, the patient had no symptoms or signs of gynecologic disease.

The patient underwent a quadrantectomy of the left breast and level-I axillary node dissection. After surgery, she underwent radiotherapy and adjuvant chemotherapy.

**Post surgical pathology.** The post surgical pathological diagnosis was LELC (Figure 5). The histological features demonstrated large and small cohesive sheets and nests of malignant epithelial cells, with striking diffuse lymphoid infiltration in the background of a fibrous matrix. Furthermore, some tumor sheets were solid, but the borders of most tumor sheets and nests were unclear, and they were

occasionally permeated and destroyed by infiltrating lymphocytes, resulting in a so-called lymphoepithelial lesion. The nuclear grade was 3, and immunohistochemical examination demonstrated that the tumor was a triple-negative (TN) breast cancer: negative for estrogen receptor (ER), progesterone receptor (PgR), and human ERBB2 (HER2). Furthermore, subtype analysis demonstrated that the present case was a basal-like subtype breast cancer: positive for epidermal growth factor, but negative for cytokeratin 5/6.

**ISH and PCR.** A recent report suggested an association of HPV in the pathogenesis of LELC of the breast. Accordingly, the present study investigated HPV with ISH using paraffin-embedded specimens and probes (INFORM HPV Probes, Ventana Japan KK, Japan) which recognize the high-risk HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 66. As a result, in a few tumor cells, positive signals were seen, and some were integrated into the nucleus, but others were seen as an episomal pattern (Figure 6). Furthermore, a PCR study was performed using an HPV GenoArray Test Kit (HybriBio Ltd., Hong Kong) to screen for high-risk HPV genotypes, but the results were negative for high-risk HPV, and failed to type HPV.

## Discussion

LELC of the breast needs to be distinguished from breast neoplasms with prominent lymphoid infiltration, such as medullary carcinoma (13), lymphoma or lymphatic leukemia (6, 9). At first, the present case was diagnosed as positive as ductal carcinoma or medullary carcinoma by FNAC, but the post surgical pathology revealed features obviously different from those of medullary carcinoma. Medullary carcinoma of the breast with lymphoid infiltration can be differentiated by its clear cytoplasm, syncytial growth pattern and well-circumscribed and pushing border. However, the present case demonstrated an unclear border of tumor sheets or nests, and they were also destroyed by infiltrating lymphoid cells, resulting in a so-called lymphoepithelial lesion. Furthermore, the tumor cells seemed to be clearly epithelial and different from lymphoma or leukemic infiltration. Judging from these characteristic features, the present case was diagnosed as LELC of the breast.

To our knowledge, 19 cases of LELC of the breast, including the present case, have been reported since the first report by Kumar and Kumar (1-12). Among them, one patient had bilateral metachronous LELCs (3), and 18 patients had 19 LELCs. Tables I and II summarize the profiles of the 19 cases. All patients were female, their ages ranged between 37 and 69 (average 53.7) years and tumors were located in the right breast in 11 cases and in the left breast in eight cases. The tumor size ranged between 10 and 35 mm (average 21.4 mm), and 10 cases were pT1 and nine

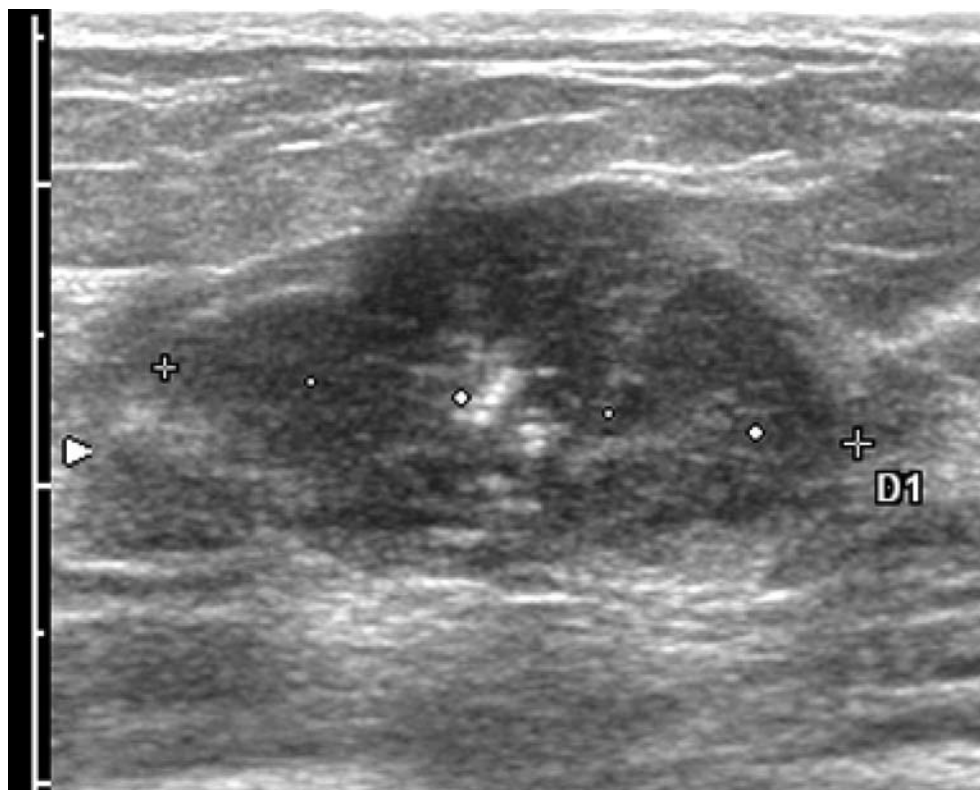


Figure 2. Ultrasonography revealed a low-echoic lesion with a highly echoic central spot.

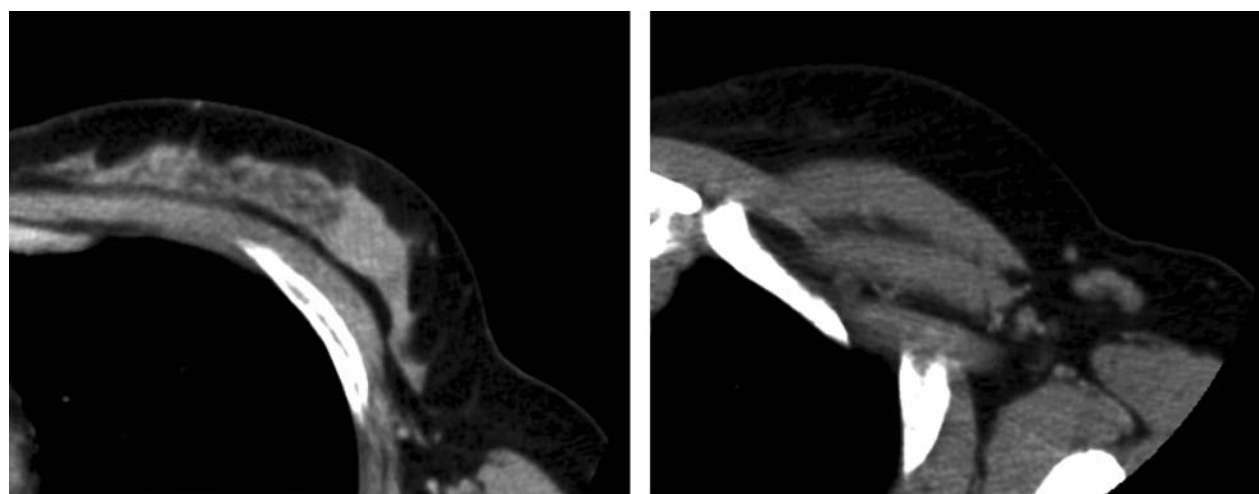


Figure 3. Computed tomography examination demonstrated a tumor in the left breast, which was enhanced by a contrast medium, and a large axillary lymph node was slightly enhanced.

were pT2. Nodal involvement was positive in four cases, and all positive cases were pN1. No distant metastases were seen in any case. pTNM stage was classified as stage I in six cases, IIA in 11 cases, and IIB in eight cases. The surgeries

included six mastectomies, five quadrantectomies, six wide local excisions, and in one case surgery was not reported. The expressions of hormone receptors were evaluated by using immunohistochemistry (IHC) in 18 cases: ER was



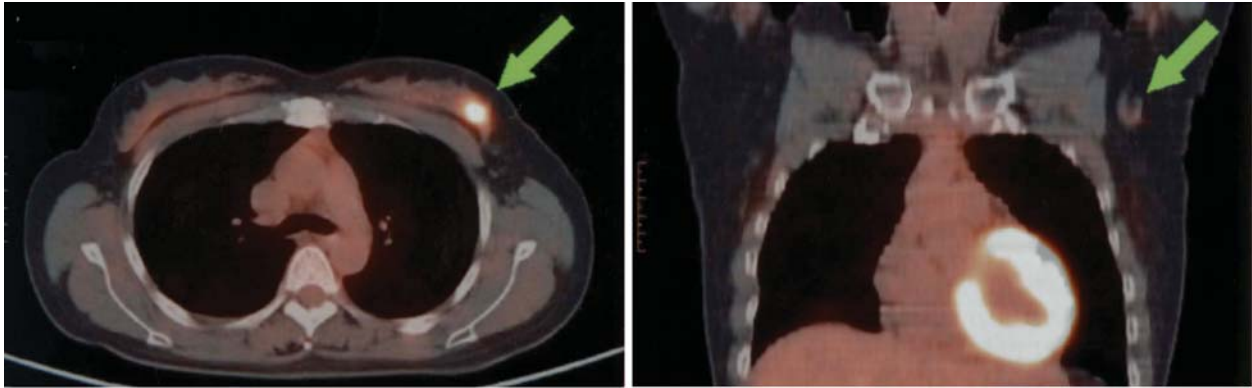


Figure 4. On positron emission tomography/computed tomography examination,  $^{18}\text{F}$ -fluorodeoxy glucose (FDG) was highly accumulated in the lesion in the left breast (maximum standard uptake value=6.8), and a large left axillary lymph node was demonstrated, but the accumulation of FDG to the latter was not significant, and no distant metastases were seen.

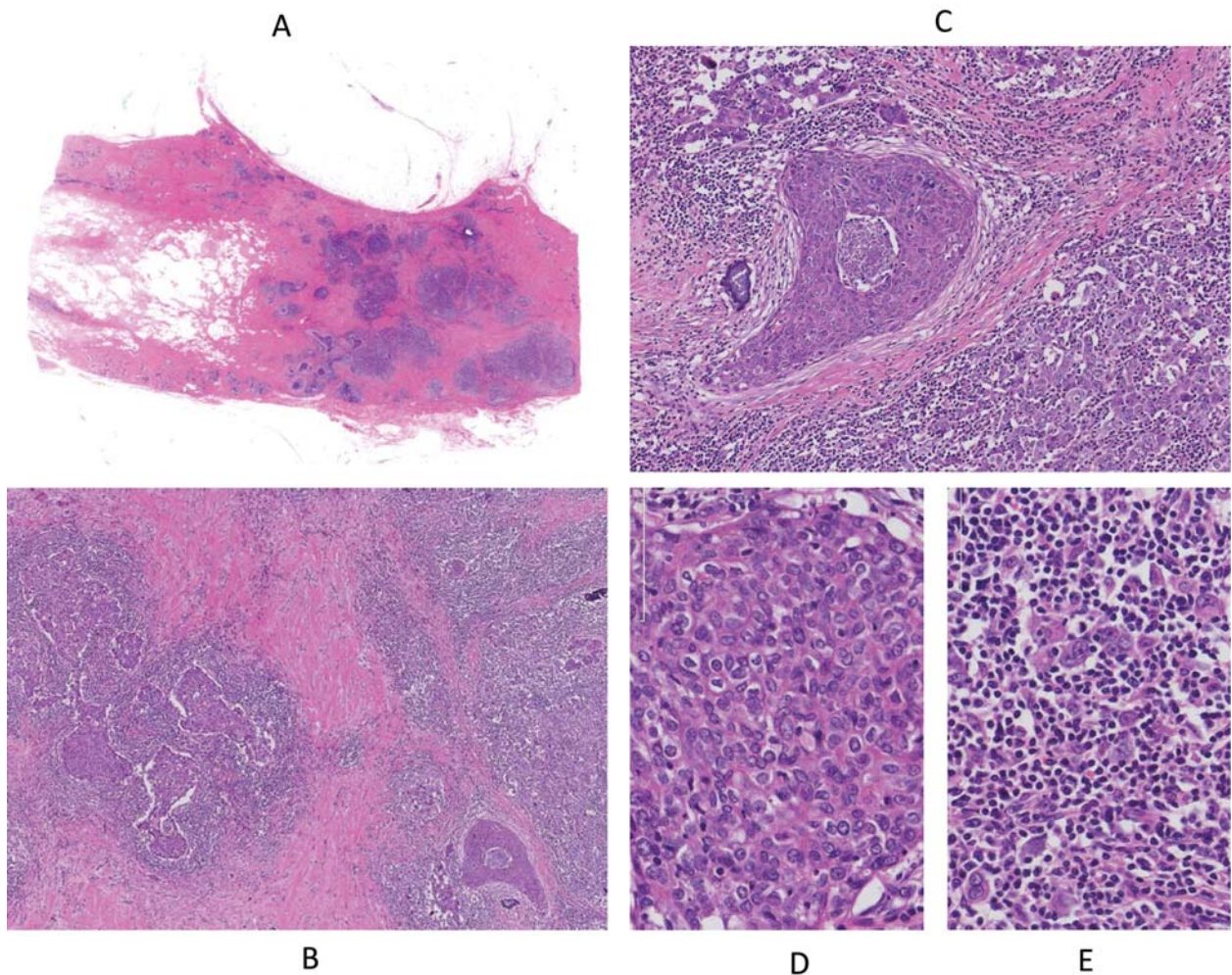


Figure 5. Histological analysis of the lesion. A: Panoramic view of the microscopic features (magnification,  $\times 1$ ). B: Large and small cohesive sheets and nests of malignant epithelial cells can be seen with striking diffuse lymphoid infiltration in the background of a fibrous matrix (magnification,  $\times 50$ ). C: The borders of some tumor sheets and nests were clear, but others were occasionally permeated and destroyed by infiltrating lymphocytes, resulting in a so-called lymphoepithelial lesion (magnification,  $\times 100$ ). D: Tumor cells of a solid tumor sheet (magnification,  $\times 400$ ). E: Tumor sheet destroyed and permeated by infiltrating lymphocytes. Tumor cells have lymphoma-like features (magnification,  $\times 400$ ).

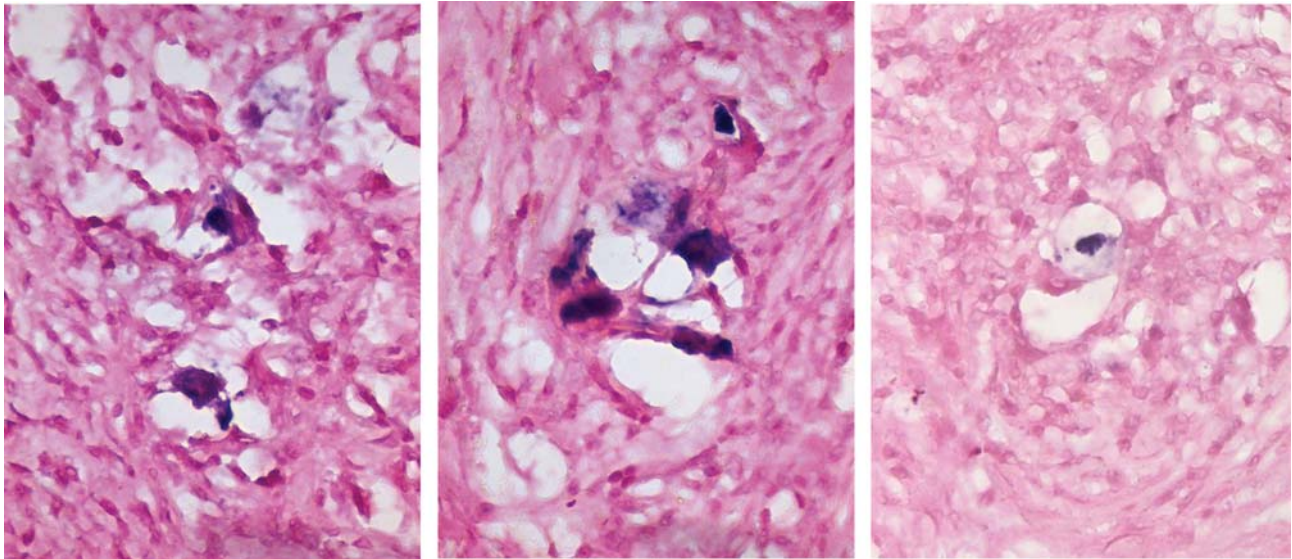


Figure 6. *In situ* hybridization. In a few tumor cells positive signals were seen, and some were integrated into the nucleus, but others were seen as an episomal pattern (magnification,  $\times 400$ ).

Table I. Summary of clinical features of lymphoepithelial-like carcinoma of the breast reported in the literature.

No	Author (ref)	Year	Age (years)	Gender	Side	T	Size (cm)	N	M	Stage	Surgery	Adjuvant therapy	Outcome
1	Kumar and Kumar (1)	1994	65	F	R	1	20	0	0	1	MX+AxDx	None	7m DF
2	Cristina <i>et al.</i> (2)	2000	54	F	R	1	15	0	0	1	WLE+AxDx		6m DF
3	Dadmanesh <i>et al.</i> (3)	2001	43	F	L	1	19	1 (1/1)	0	1	QX+AxDx		60m DF
4			53	F	R	1	20			2A			72m DF
5			49	F	L	1	10	0 (0/19)	0	1	QX+AxDx		36m DF
6			52	F	R	2	27	0 (0/20)	0	2A	QX+AxDx		36m DF
7			64	F	R	1	20	0 (0/29)	0	1	MX+AxDx		60m DF
8			69	F	R	2	23	0 (0/19)	0	2A	MX+AxDx	RT	48m DF
9	Naidoo <i>et al.</i> (4)	2001	50	F	R	2	25	1 (2/24)	0	2B	WLE+AxDx		3m DF
10	Peştereli <i>et al.</i> (5)	2002	56	F	R	1	20	1 (2/27)	0	2A	MX+AxDx	ChT	12mDF
11	Sanati <i>et al.</i> (6)	2004	62	F	L	2	30		0	2A	WLE		
12	Ilvan <i>et al.</i> (7)	2004	59	F	R	2	35	0 (0/20)	0	2A	WLE+AxDx	RT+TAM	53m DF
13			67	F	R	1	11	0 (0/16)	0	1	QX+AxDx	RT	46m DF
14	Kurose <i>et al.</i> (8)	2005	47	F	L	2	28	0 (0/33)	0	2A	MX+AxDx	TAM	19m Rec
15	Saleh <i>et al.</i> (9)	2005	51	F	L	1	13	1 (1/8)	0	2A	WLE+AxDx		
16	Kulka <i>et al.</i> (10)	2008	42	F	R	2	25	0 (0/10)	0	2A	WLE+AxDx		n.d.
17	O'Sullivan-Mejia <i>et al.</i> (11)	2009	55	F	L	2	31	0 (0/2)	0	2A	LE+SNB	RT+ChT+Tr	22m DF
18	Jeong <i>et al.</i> (12)	2010	37	F	L	2	22	0 (0/13)	0	2A	MX+AxDx	ChT	23m DF
19	present case	2011	45	F	L	1	13	0 (0/5)	0	1	QX+SNB	ChT+RT	12m DF

F, Female; R, right; L, left; T, primary tumor; N, nodal involvement; M, distant metastasis; MX, mastectomy; AxDx, axillarydissection; QX, quadrantectomy; WLE, wide local excision; LE, local excision; RT, radiotherapy; ChT, chemotherapy; TAM, tamoxifen; Tr, trastzmad; m, month; DF, disease-free; Rec, recurrence; n.d., no description.

positive in seven cases (39%), and PgR was positive in three cases (17%). The overexpression of HER2 was also evaluated by using IHC in 16 cases, and it was overexpressed in three cases (19%). Finally, seven cases (44%, 7/16) were classed as the TN type. Post surgical adjuvant therapies were

reported in nine cases, and four cases underwent chemotherapy. In summary, LELCs of the breast have several characteristics suggesting poor prognosis, such as undifferentiated histological features, a high mitotic rate, and a high frequency of the TN type. However, nodal



Table II. Summary of IHC, ISH and PCR of lymphoepithelial-like carcinoma of the breast reported in the literature.

No.	Author (ref)	ER	PgR	HER2	p53	CK5/6	CK 7	CK20	CK			EBV			HPV	
									AE1/AE3	EGFR	EMA	IHC	ISH	PCR	ISH	PCR
1	Kumar and Kumar (1)	+	+						+							
2	Cristina <i>et al.</i> (2)	+	+	-	-											
3	Dadmanesh <i>et al.</i> (3)	-	-	-							+					
4		-	-	-							+					
5		-	-	-							+					
6		+	-	-							+					
7		-	-	-							+					
8		-	-	-							+					
9	Naidoo <i>et al.</i> (4)								-		-	-	-			
10	Peştereli <i>et al.</i> (5)	+	+	-	-				+		+	-				
11	Sanati <i>et al.</i> (6)	+	-	-					+							
12	Ilvan <i>et al.</i> (7)	+	+	-	-				+			-	-			
13		-	-	-	-				+			-	-			
14	Kurose <i>et al.</i> (8)	-	-	+	-				+		+	-	-			
15	Saleh <i>et al.</i> (9)	-	-					+	-		+	-				
16	Kulka <i>et al.</i> (10)	+	-	-	+	+			+				-	-	+	+
17	O'Sullivan-Mejia <i>et al.</i> (11)	-	-	+					+							
18	Jeong <i>et al.</i> (12)	-	-	+	+				+				-			
19	present case	-	-	-		-				+					+	-

IHC, Immunohistochemistry; ISH, *in situ* hybridization; PCR, polymerase chain reaction; ER, estrogen receptor; PgR, progesterone receptor; HER2, human ERBB2 receptor; CK, cytokeratin; EGPR, epidermal growth factor receptor; EBV, EB virus; HPV, human papilloma virus.

involvement was not seen in any of the 19 cases reported, the clinical stages were lower than IIB, and the prognosis appeared to be good. After surgery, the patients were followed up for between three and 72 months (average 32 months), and only one case had a recurrence. Striking lymphoid infiltration may be one of the reactions of the immune-surveillance system against tumors. However, the follow-up duration was relatively short, and it is difficult to draw definitive conclusions.

Iezzoni *et al.* reported that EBV was associated with LELCs only in the stomach, salivary glands, lungs and thymus (14). However, EBV has not been shown in LELCs of the breast, as summarized in Table I. Recently, it was reported that HPV types 18 and 33 were demonstrated within the tissue of LELC of the breast (10). This case underwent hysterectomy for cervical carcinoma, and HPV type 33 was shown in a cervical carcinoma specimen. To the best of our knowledge, there is only one report on HPV infection in LELC of the breast, and the present study is the second. Here, we investigated HPV with ISH using a cocktail of probes which recognize genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 66 of HPV. As a result, positive signals were seen in a few tumor cells: some were integrated into the nucleus, but others were seen as an episomal pattern. However, the PCR study using the HPV GenoArray Test Kit was negative for high risk HPV, and failed to type HPV. The

different results between the ISH and PCR assays are not necessarily controversial, and do not eliminate the possibility of HPV infection in the present case. Unger *et al.* reported that in cervical carcinoma, ISH and PCR assays for HPV detection were concordant in about 75% of cases, while ISH<sup>+</sup>/PCR<sup>-</sup> cases accounted for 11% (15). Kelesidis *et al.* also reported that in cervical specimens, including from atypical to high-grade squamous intraepithelial lesions, ISH and PCR assays for HPV detection were concordant in about 78% of cases (16). These authors discussed the reasons for the discordant results between ISH and PCR. Basically, infection with HPV types are not amplified by the primers used, but are still detectable by the ISH cocktail; the ISH assay's sensitivity is determined by the number of copies of HPV per cell, whereas the PCR assay's sensitivity is determined by the number of copies in the assay tube. Regardless, these discordant results may be due to the quantities of mRNA and DNA of the virus, as well as how the specimens are preserved.

## Conclusion

We report a 45-year old female case of LELC of the breast with a special analysis of an association with HPV. To the best of our knowledge, this is the second report on HPV infection associated with breast LELC.

## References

- 1 Kumar S and Kumar D: Lymphoepithelioma-like carcinoma of the breast. *Mod Pathol* 7: 129-131, 1994.
- 2 Cristina S, Boldorini R, Brustia F and Monga G: Lymphoepithelioma-like carcinoma of the breast. An unusual pattern of infiltrating lobular carcinoma. *Virchows Arch* 37: 198-202, 2000.
- 3 Dadmanesh F, Peterse JL, Sapino A, Fonelli A and Eusebi V: Lymphoepithelioma-like carcinoma of the breast: lack of evidence of Epstein-Barr virus infection. *Histopathol* 38: 54-61, 2001.
- 4 Naidoo P and Chetty R: Lymphoepithelioma-like carcinoma of the breast with associated sclerosing lymphocytic lobulitis. *Arch Pathol Lab Med* 125: 669-672, 2001.
- 5 Peştereli HE, Erdogan O, Kaya R and Karaveli FS: Lymphoepithelioma-like carcinoma of the breast. *APMIS* 110: 447-450, 2002.
- 6 Sanati S, Ayala AG and Middleton LP: Lymphoepithelioma-like carcinoma of the breast: report of a case mimicking lymphoma. *Ann Diagn Pathol* 8: 309-315, 2004.
- 7 Ilvan S, Celik V, Ulker Akyildiz E, Senel Bese N, Ramazanoglu R and Calay Z: Lymphoepithelioma-like carcinoma of the breast: Is it a distinct entity? Clinicopathological evaluation of two cases and review of the literature. *Breast* 13: 522-526, 2004.
- 8 Kurose A, Ichinohasama R, Kanno H, Kobayashi T, Ishida M, Nishinari N and Sawai T: Lymphoepithelioma-like carcinoma of the breast. Report of a case with the first electron microscopic study and review of the literature. *Virchows Arch* 447: 653-659, 2005.
- 9 Saleh R, DaCamara P, Radhi J and Boutross-Tadross O: Lymphoepithelioma-like carcinoma of the breast mimicking nodular sclerosing Hodgkin's lymphoma. *Breast J* 11: 353-354, 2005.
- 10 Kulka J, Kovalszky I, Svastics E, Berta M and Füle T: Lymphoepithelioma-like carcinoma of the breast: not Epstein-Barr virus-, but human papilloma virus-positive. *Hum Pathol* 39: 298-301, 2008.
- 11 O'Sullivan-Mejia E, Idowu MO, Davis Masssey H, Cardenosa G and Grimes MM: Lymphoepithelioma-like carcinoma of the breast: diagnosis by core needle biopsy. *Breast J* 15: 658-660, 2009.
- 12 Jeong AK, Park SB, Kim YM, Ko BK, Yang MJ, Kwon WJ, Lee JH and Weon YC: Lymphoepithelioma-like carcinoma of the breast. *J Ultrasound Med* 29: 485-488, 2010.
- 13 Lespagnard L, Cochaux P, Larsimont D, Degeyter M, Velu T and Heimann R: Absence of Epstein-Barr virus in medullary carcinoma of the breast as demonstrated by immunophenotyping, *in situ* hybridization and polymerase chain reaction. *Am J Clin Pathol* 103: 449-452, 1995.
- 14 Iezzoni JC, Gaffey MJ and Weiss LM: The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. *Am J Clin Pathol* 103: 308-315, 1995.
- 15 Unger ER, Vernon SD, Lee DR, Miller DL and Reeves WC: Detection of human papillomavirus in archival tissues. Comparison of *in situ* hybridization and polymerase chain reaction. *J Histochem Cytochem* 46: 535-540, 1998.
- 16 Kelesidis T, Aish L, Steller MA, Aish IS, Shen J, Foukas P, Panayiotides J, Petrikos G, Karakitsos P and Tsiodras S: Human papillomavirus (HPV) detection using *in situ* hybridization in histologic samples: correlations with cytologic changes and polymerase chain reaction HPV detection. *Am J Clin Pathol* 136: 119-127, 2011.

Received February 19, 2012

Revised March 10, 2012

Accepted March 12, 2012