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

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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
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 18F-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...
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 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.
Figure 4. On positron emission tomography/computed tomography examination, $^{18}$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, ×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, ×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, ×100). D: Tumor cells of a solid tumor sheet (magnification, ×400). E: Tumor sheet destroyed and permeated by infiltrating lymphocytes. Tumor cells have lymphoma-like features (magnification, ×400).
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 1. Summary of clinical features of lymphoepithelial-like carcinoma of the breast reported in the literature.

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

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

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, ×400).
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+/PCR– 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


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