Lymphoepithelioma is a distinctive neoplasm of the nasopharyngeal region characterised by a prominent reactive lymphocytic infiltrate, often masking the malignant epithelial component. The counterpart at other sites, lymphoepithelioma-like carcinoma (LELC), has been seen in the salivary glands, lungs, stomach and uterine cervix, but is exceptionally rare in the breast. To our knowledge, there are only two recent case reports in the English literature on its cytological findings. Herein, we demonstrate characteristic cytopathological features of a mammary LELC.

The patient, a 50-year-old postmenopausal Japanese woman, presented with swelling of a left axillary lymph node. Her family history included a grandmother with mammary cancer. Ultrasonography revealed an irregularly shaped, hypoechoic left breast mass showing heterogeneous internal echoes as well as a conspicuously-enlarged regional node. We performed ultrasound-guided, fine needle aspiration (FNA) of this lymph node and the cytological diagnosis was metastatic carcinoma. Subsequently, an ultrasound-guided, core needle biopsy of the breast mass yielded a histological diagnosis of invasive ductal carcinoma.

Intra-operative FNA specimens from the left breast tumour cytologically showed high cellularity with numerous lymphocytes in a haemorrhagic background (Figure 1a). Carcinoma cells with indistinct cell borders were loosely connected in solid clusters (Figure 1b), although single, detached carcinoma cells were also frequent (Figure 1c). There was prominent infiltration of some carcinoma cells by lymphocytes (Figure 1b). These large carcinoma cells had ovoid or irregularly shaped nuclei with a fine granular chromatia pattern and distinct nucleioli (Figure 1b, c). FNA sampling of an involved axillary node yielded similar cytological findings.

The cut surface of the leucoproteus specimen contained a grey-whitish, localised multinodular mass (Figure 2). Histologically, the tumour was composed of polygonal carcinoma cells with relatively clear cytoplasm and large nuclei, accompanied by intratumoural as well as interstitial lymphocytic infiltrates with focal germinal centres (Figure 3a-c). Benign lymphoepithelial-like lesions were also observed at the tumour periphery. Metastasis was identified in one, 29 × 20 mm in size, of the 23 excised axillary lymph nodes (Figure 4). Immunohistochemical examinations revealed carcinoma cells to be positive for cytokeratin (CK) AE1/AE3 (Figure 3d), CK 34BE12 and EMA and focally positive for E-cadherin (Figure 3e), c-kit and CK5/6. In contrast, associated lymphocytes predominantly showed CD3, rather than CD20, reactivity. Carcinoma cells were negative for both oestrogen and progesterone receptors (Allred’s total score: 0 and 0, respectively). The HER2 score was 0, and the Ki67 (MIB-1) labelling index was 70.1%. Epstein-Barr virus-encoded RNA in situ hybridisation was negative.

Postoperatively, the patient received four cycles of 3-weekly fluorouracil (500 mg/m²), epirubicin (100 mg/m²) and cylophosphamide (500 mg/m²), followed by four cycles of 3-weekly docetaxel (75 mg/m²) and adjacent chemotherapy, and subsequent radiation (46 Gy in 23 and 9 Gy in 3 fractions) to the remnant left breast. She remains alive and well, 10 months after surgery, with neither recurrence nor metastasis.

**Figure 1** Cytological findings on a fine needle aspiration smear of lymphoepithelioma-like mammary carcinoma. (a) Clustered and detached cancer cells in the background of abundant lymphocytes with linear nuclear artefact. (b) Malignant pleomorphic carcinoma cells with a focal lymphoid infiltrate and marked lymphocytic penetration. (c) A mixture of small lymphocytes and dissociated carcinoma cells with delicate nuclear chromatin resembling of macrophages.

LELC and medullary carcinoma of the breast share many cytopathological features such as a markedly lymphocytic background, high cellularity, absence of glandular structures, large neoplastic cells and distinct nucleioli. However, lymphoepithelial clusters and fine nuclear chromatin are the two most important cytological clues for diagnosing LELC. Also, complete tumour circumscrition and the dominant synchronal growth pattern of adenocarcinoma cells are clinicopathological characteristics of mammary carcinomas with medullary features. Benign and malignant haematological conditions including lymphoma, leukaemia and various types of marrow should be ruled out especially when singly dispersed histiocyte-like cancer cells are obscured by a dense lymphocytic infiltrate. Binding cell appearances and/or immunoreactivities for epithelial markers allow a definitive carcinoma diagnosis.

Some investigators stress that breast LELC can be regarded as an unusual form of invasive lobular carcinoma based on overlapping morphological and immunohistochemical features. In the present case, intratumoral carcinoma cells were focally positive to negative owing to loss of cell cohesion, whereas 34BE12 was consistently positive in neoplastic cells. Accordingly, these immune-profiles may reflect ductal and lobular features in this mammary counterpart of LELC.

Follow-up data after surgery for LELC (3-72, mean 34.9 months) were obtained from six previously-reported breast cancer cases and there have been no mortalities attributable to this malignancy, although one patient (5%) had distant metastasis to the lung (24 months), and axillary lymph-node involvement was detected in 7 (22%) of 32 cases including our current patient. Tumour-infiltrating lymphocytes (TILs), not only stromal but also intratumoural, have recently been demonstrated to predict a good outcome with increased responsiveness to chemotherapy. The relatively favourable prognosis of patients with LELC, despite frequently having the 'triple negative' subtype with a high MIB-1 index and histological grade 3, could be associated with these TIL immune functions. It is, therefore, worth keeping in mind LELC when pure acinar epithelial lesions are detected in cytological smears.

**Acknowledgments:** Tomonori Kawasaki is supported by Grants-in-Aid for Scientific Research (No. 25460414, No. 16K08748 and No. 16H00668) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and a Grant from the National Hospital Organization (TH5-NHI-156). Chisaka Muramatsu, Jiro Ichikawa, Masao Saitoh are supported by Grants-in-Aid for Scientific Research (No. 16K08748 and No. 16H00668) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and a Grant from the National Hospital Organization.