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Research Article

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Pathohistological and Immunohistochemical Analysis, Differential Diagnosis, Prognosis and Complex Treatment in a Rare Lymphoepithelioma-Like Breast Cancer

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Abstract

We present a 78-year-old woman with a rare neoplasm of the right mammary gland – Lymphoepithelioma-like carcinoma (LELC). Lymphoepithelioma-like carcinoma is an undifferentiated neoplasm, consisting of malignant epithelial cells on the background of lymphocytes. Pathomorphological features and immunohistochemical (IHC) analysis determines the rare pathohistological variant of breast cancer . This clinical case of lymphoepithelioma-like breast cancer is the 34th published in medical literature in English. In the discussion, we emphasize the importance of immunohistochemical analysis to assess the differential diagnosis with other benign and malignant breast tumors . Lymphoepithelioma-like breast cancer is an extremely malignant epithelial neoplasm with an unfavorable prognosis, requiring complex oncological treatment.

Keywords: Lymphoepithelioma-like Breast Carcinoma, Pathohistological Analysis, Immunohistochemical Analysis, Differential Diagnosis, Prognosis, Complex Treatment

Introduction

Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma consisting of malignant epithelial cells on a lymphocyte background (1,2). This rare malignant epithelial tumor was first published in 1921 by Schminke (3), Regaud and Reverchen (4), but the first breast clinical case was first published in 1994 (5). This rare epithelial neoplasm has been reported in several other organs and structures such as the skin, lacrimal and salivary glands, thyroid, thymus, lung, esophagus, stomach, colon, hepatobiliary system, renal pelvis, ureter, kidney, bladder, prostate, cervix, vulva and vagina. (1,6). LELC is a real pathohistological challenge requiring an immunohistochemical panel to prove the epithelial tumor morphology and for differential diagnosis with other benign and malignant breast neoplasms (1,2). Pathomorphological characteristics and immunohistochemical (IHC) analysis determine the rare histological variant of undifferentiated breast cancer (7). In this publication we present the 34th clinical case of those published in medical literature in English.

Clinical Case

We present a 78-year-old woman with a painful lump in her right mammary gland, who noticed that it had been growing for 3 months. After a radical mastectomy with an axillary dissection, a locally advanced triple negative Lymphoepithelioma-like breast carcinoma (LELBC)/pT3N2M0 (G3) was determined.

Preoperative Local Status - Right Mammary Gland

In the upper lateral quadrant there is a visible skin retraction with solutions of 2 cm. A large, hard-elastic formation with dimensions over 5 cm is palpated, which fixes the proper skin. A package of enlarged lymph nodes with a diameter of more than 10 cm is palpated in the right axilla. A radical right mastectomy with an axillary lymph dissection was performed.

Macroscopic Characteristic

In the incision of the breast are found diffuse seals without a tumor formation. A package of fused lymph nodes measuring 18/10 cm from the right axilla was removed.

Microscopic Characteristics

Breast parenchyma with involutional changes, ducts with atrophy, periductal fibrosis, abundant infiltrate of mature lymphocytes, mononuclear inflammatory cells and discochemical atypical cells located singly or in groups among the lymphocyte infiltrate. Tumor cells have a light cytoplasm, the nuclei are moderately polymorphic, rarely with visible nucleoli. Atypical tumor cells infiltrate breast adipose tissue (Fig.1). No tumor infiltration was found in the epidermis of the nipple, and the underlying tissues were covered by the neoplasm described above. Massive metastases are found in the axillary lymph package.

Diagnosis

Diffuse throughout the mammary gland undifferentiated mammary carcinoma without involvement of the skin; packets of fused axillary lymph nodes, all with massive metastases. / pT3 N2 Mx (G3).

Immuno Histo Chemistry (IHC)

Neoplastic cells show diffusely positive expression for epithelial markers - CK7, CK AE1 / AE3, E-cadherin, Mamaglobin, EMA and focal expression of CD 117 (Fig. 2).

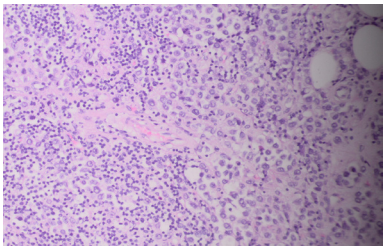

Figure 1: Photomicrography -Pathohistology of lymphoepithelioma-like breast cancer / H&E x 40

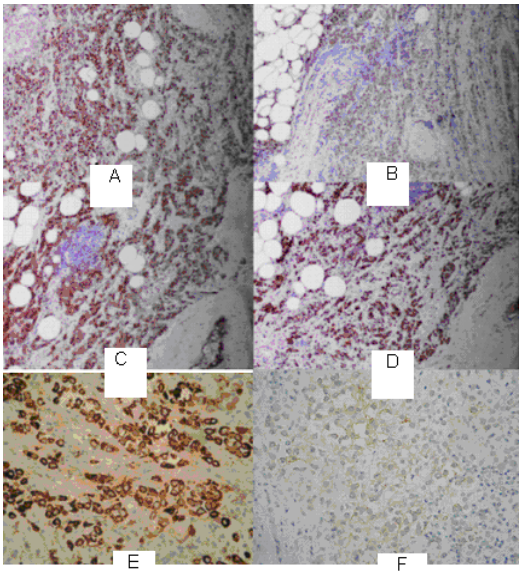

Figure 2: Photomicrography of immunohistochemistry- Diffuse positive expression in tumor cells for: A / CK7; B / SC AE1 / AE3; C / E-Cadherin; D / Mamaglobin, E / EMA and F / focal expression for CD 117 x20

Focal positive expression for CD 3 in mature T-lymphocytes and for CD 20 in mature B-lymphocytes (Fig. 3). High proliferative index Ki 67 of tumor cells over 50% (Fig. 4).

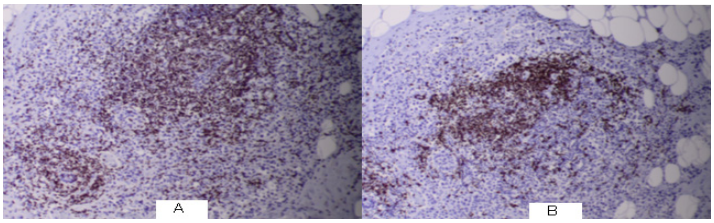

Figure 3: Photomicrography of immunohistochemistry- Focally positive expression for A / CD 3 in mature T-lymphocytes; B / CD 20 in mature B- lymphocytes x20

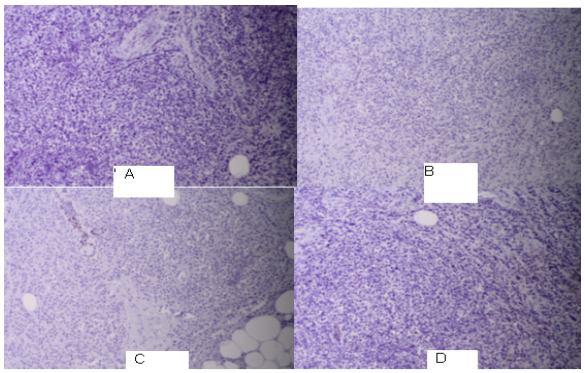

Figure 4: Photomicrography of immunohistochemistry - high proliferative index Ki 67 over 50% x20

In the differential diagnostic plan, negative IHC expression for Melan A, p63, Chromogranin A and CK 20 was reported (Fig.5). Expression is negative for estrogen receptors, progesterone receptors and HER2 (Fig.6).

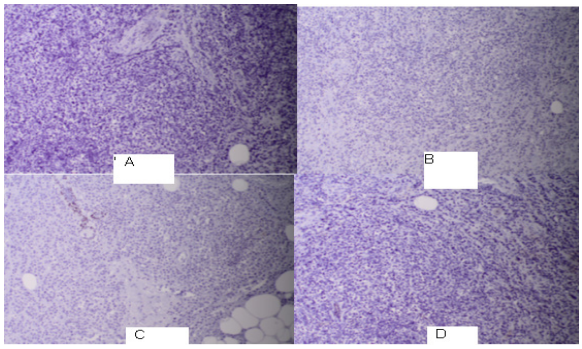

Figure 5: Photomicrography of immunohistochemistry- Negative expression for A / Melan A; B / p63; C / Chromogranin A; D / CK20 x20

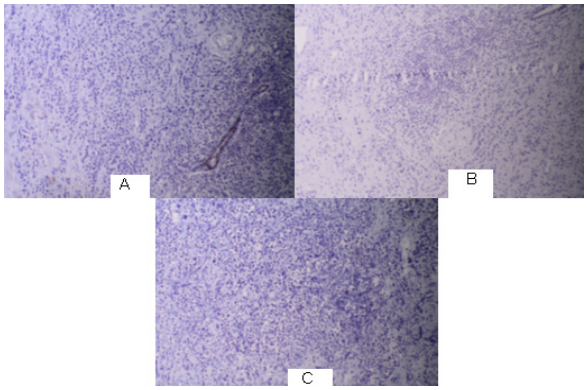

Figure 6: Photomicrography of immunohistochemistry - Negative expression for A / Estrogen receptor; B / Progesterone receptor; C / HER2 x20

Based on the IHC profile and the pathohistological characteristic, it is a rare / nonspecific variant of mammary lymphoepithelioma-like carcinoma. After immunohistochemistry, lobular carcinoma, met-

aplastic carcinoma, melanoma and lymphoproliferative process of the breast were rejected. Following an oncology committee, adjuvant chemotherapy and radiotherapy was recommended. 2 months after the decision for complex treatment the woman died due to rapid progression of the disease with the development of lung metastases (Fig.7).

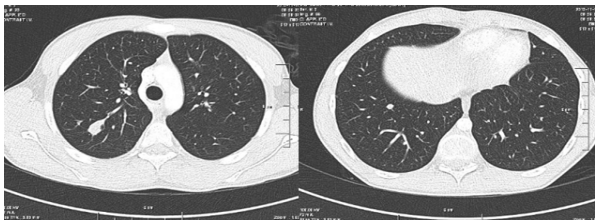

Figure 7: CT of the thorax with venous contrast - There are multiple lung metastases in the parenchyma of both lungs

Discussion

This clinical case presents the oldest patient ever diagnosed with the disease (78 years old). The average age of the already published 33 clinical cases of breast cancer is 52 years (37-69) (7). What is more special in our case is that it is a locally advanced carcinoma / pT3 N2 M0. During examination of the literature of other breast cancer patients, such large and diffuse tumor in the breast as the large packages of metastatic axillary lymph nodes wasn't revealed (1,2,7).

The Pathohistological Verification of Breast Cancer is a real challenge for the pathologist. LELC is an undifferentiated carcinoma with a malignant epithelial component on the background of lymphocytic infiltrate (2,7-9). Large areas of abundant lymphocytic mononuclear inflammatory cells and non-cohesive tumor cells with light cytoplasm, moderately polymorphic nuclei, rarely with visible nucleoli, in the form of either individual cells according to the model of Schminke or, rarely, small groups - nests or chains modeled on Regaud located within fibrous stromal connective tissue (10,1). In the presented clinical case we report accumulations of tumor cells among lymphocytic infiltrate (Fig. 1). Similar to Suzuki I, et al / 2014 the patient's tumor also appeared to have necrotic and abscess-like features on initial pathological examination, which has not been described in other cases of LELC (2). To prove the epithelial origin of tumor cells, IHC with epithelial markers such as EMA or Cytokeratin (1,10,11) is required. Figure 2 shows the diffuse expression of tumor cells to CK7, CK AE1 / CK AE3, E-Cadherin, Mamaglobin and EMA. CD117 is a specific marker for gastrointestinal stromal tumors. This marker is a photo-oncogene receptor for cytokine-cellular factor. Cell staining with CD117 plays a key role in cell survival, proliferation and differentiation (1). Our clinical case is the second of the published breast LELCs in which focal positive expression for CD117 was reported (Fig. 2). Figure 3 shows focal positive expression for CD 3 in mature T-lymphocytes (10) and for CD 20 in mature B-lymphocytes, a finding similar to the 32nd published lymphoepithelioma-like breast cancer (12). IHC of hormonal receptors to Estrogen, Progesterone and HER2 is negative (Fig. 6), which determines a triple-negative hormone-independent breast cancer with an unfavorable prognosis and an increased risk of distant metastases. A similar finding was found in Suzuki I, et al / 2014, where lymphoepithelioma-like carcinoma with stage IIA (pT1c, N1a, M0) with 27% Ki 67 was presented (2). In our clinical case we report a high proliferative index of tumor cells / Ki 67 - over 50% (Fig. 4).

Differential Diagnosis (DD)

In such a rare histological variant of breast cancer, a differential diagnosis with medullary carcinoma is required in the first place (1,2,7,12). Medullary carcinoma (MC) of the breast is described by Rapin and Ridolfi by the following characteristics: syncytial growth of tumor cells> 75% with complete differentiation, presence of diffuse mononuclear stromal infiltrates, moderate to pronounced nuclear pleomorphism and lack of microglandular characteristic (1,13,14). In contrast to the characteristic of MC, in the presented clinical case a diffuse multinodular lesion, consisting of tumor nests strongly penetrated by numerous lymphocytes is demonstrated (Fig.1). In contrast to LELC in MC, clouding of tumor cells from the lymphocyte background is uncommon (1). The stromal infiltrates in LELC contain fewer plasma cells, than those in medullary carcinomas, where a lymphoplasmic reaction is predominant (1). As in our case in LELC, diffuse infiltration of lymphocytes is typical (Fig.1). The pathohistological morphology is similar to primary or secondary Non-Hodgkin's or Hodgkin's lymphoma in the breast (1,7,15). Epithelial immunohistochemical markers EMA or Cytokeratin are used to help the differential diagnosis due to their diffuse expression in epithelial neoplastic cells (Fig.2). In lymphoproliferative neoplastic diseases, epithelial tumor components are absent, however, the differential diagnosis with mononuclear lymphoid cells is difficult (16). Sometimes LELC of the breast can be misdiagnosed as lymphoma (12). For DD with lymphoma, additional IHC of mature T-lymphocytes with CD3 and mature B-lymphocytes with CD20 is required (1). In Fig. 3, diffuse expression to the CD3 and CD20 of the lymphocyte infiltrate without staining the epithelial tumor cells was reported. DD also includes a number of other undifferentiated tumors such as melanoma (via negative IHC expression of tumor cells to Melan A), metaplastic carcinoma (negative expression to p63, a specific nuclear marker for myoepithelial cells), neuroendocrine carcinoma (negative expression to chromogranin A) and adenocracinoma (negative expression to CK 20, which is a specific marker for adenocracinoma in gastric or intestinal epithelium, urothelium, or Merkel cells) (Fig.5).

Despite the small number of observed and published clinical cases of LELC in the breast, the prognosis does not differ from the other more frequently diagnosed histological variants (invasive ductal and invasive lobular) mammary carcinomas. It depends on the stage of the disease, the pT and pN categories, the hormonal status and the result of HER2. Local recurrences have been reported in 3 patients and lung metastases in one (7,17). The average survival of the 33 published cases was 30.59 months, which outlines a good prognosis (7,11), most likely due to lymphocyte infiltrates showing cell-mediated immune responses (8). Breast LELC is a rare tumor with characteristic pathologic properties, which may result in lymph node or distant metastasis (10). For the second time in medical literature in English, we present a progression of the disease with the development of lung metastases after Kurose A, et al / 2005 (17).

Complex Treatment

Although it is an undifferentiated mammary carcinoma (G3), the complex treatment is carried out according to the oncological rules valid for common carcinoma histologies. In the first place, is the surgical treatment, which must achieve clean resection lines (1,10,12,15,17). The most commonly used surgical interventions are conservative surgery or radical mastectomy with axillary dissection. Breast cancer / pT2N0M0 after simple mastectomy with sentinel biopsy, adjuvant chemotherapy (ChT), radiotherapy with TD 45Gy and hormone therapy achieved 17-month disease-free survival (7). In locally advanced patients /Stage III, neoadjuvant ChT is required, which was not performed in the clinical case presented by us, due to concomitant diseases. LELC in the breast pT2N1-2 requires adjuvant complex treatment, including ChT, radiotherapy, hormone therapy, depending on the hormonal status (2,7) and targeted therapy for HER2 positive carcinomas.

Conclusion

The pathohistological verification of LELC in the breast is a real challenge for the pathologist. LELC is a rare mammary undifferentiated carcinoma with a malignant epithelial component on the background of lymphocytic infiltrate. A wide panel of immunohistochemistry to prove this rare pathohistological carcinoma variant is required. The differential pathohistological diagnosis with medullary carcinoma, with primary or secondary lymphoproliferative diseases of the breast, with a number of undifferentiated neoplasms such as melanoma and metaplastic carcinoma is important. Early diagnosis determines a good prognosis. Although it is an undifferentiated mammary carcinoma, the complex treatment is carried out according to the oncological rules valid for the common breast carcinomas.

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