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Case Report

Unilateral Mammary Paget Disease Associated with Underlying Synchronous Breast Tumors: Report of A Case

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Abstract

Observations: *Paget* disease of the breast was described as nipple ulceration associated with underlying breast cancer. A 67-year-old female patient was referred to dermatology outpatient clinic for evaluation of a scaly erythematous 2 cm plaque in the left nipple and nearby areola. The patient was suspected to have *Paget* disease. A retroareolar mass approximately 1 cm in size was found on breast examination performed by a general surgeon. Mammograms demonstrated two masses in the left breast. In the histopathological examination of mastectomy specimen two nodules were detected in the inferolateral breast quadrant compatible with Grade II invasive ductal carcinoma. High grade ductal carcinoma *in situ* and *Paget disease* were detected in the nipple-areola complex. All of the lesions showed similar immunohistochemistry profiles on immunohistochemical examination. The absence of E-cadherin staining in our patient's *Paget* cells implies that E-cadherin mutation may play a role in the development of *Paget* disease.

Introduction

Paget disease of the breast was first described by *Paget* in 1874 as a nipple ulceration associated with underlying breast cancer [**1, 2**]. Mammary *Paget* disease is relatively rare, representing 0.7-4.3 % of all breast cancers [**2**]. The age adjusted incidence rate was found to be 0.64 in 2002 in the USA. The mean age of diagnosis was 62.6 years for women [**1**].

Mammary *Paget* disease is found to be associated with infiltrating ductal carcinoma in 50.4 % of patients and ductal carcinoma in situ in 36.3 % of patients. Mammary *Paget* disease is not associated with any underlying breast lesion in 13.3 % of patients [**1**].

In this report we describe a female patient with mammary *Paget*'s disease associated with three synchronous primary breast lesions showing similar immunohistochemistry profile.

Case Report

A 67-year-old female patient was referred to dermatology outpatient clinic from cardiology clinic for evaluation of a skin lesion of the breast. Her complaint was present for one month and there was no history of pruritus, nipple discharge, spontaneous healing or previous treatment. The lesion became worse with shampoo and got better with use of soap. On dermatologic examination scaly erythematous 2 cm plaque was detected in the left nipple and nearby areola (**Figure 1**). The patient was diagnosed to have probable Paget disease and

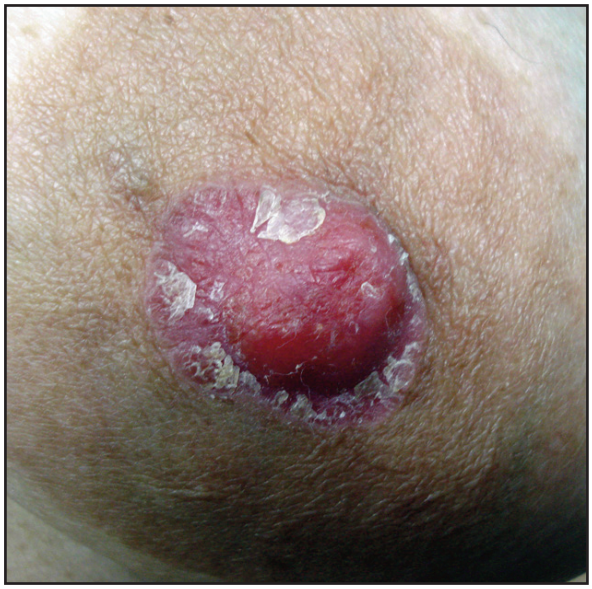

Figure 1. Scaly erythematous plaque in the left nipple and adjacent areola

consulted to general surgery clinic for biopsy and for the evaluation of any underlying breast tumors. A 1 cm retroareolar mass was found at 10 o'clock position on breast examination performed by the general surgery consultant. But there were not any palpable axillary lymphadenopathies in the patient.

Past medical history revealed that the patient was in the period of menopause for 10 years without hormone replacement therapy. She had 4 children that were breast fed for 12-18 months. There was no family history of breast cancer.

Complete blood count, urinanalysis, blood urea nitrogen, liver enzymes and prothrombine time were in normal range. Hepatitis markers were negative. But fasting blood sugar was 125 mg/dl and

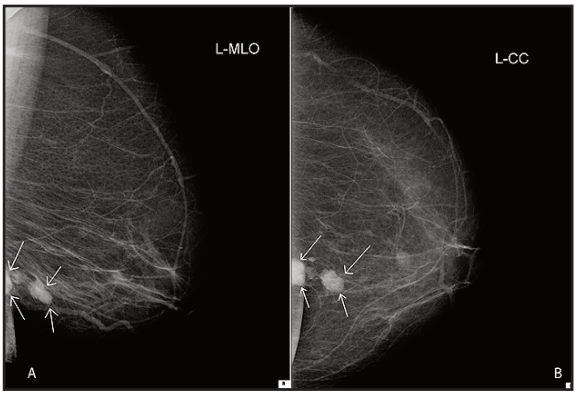

Figure 2. Left mammogram shows high density lobulated noncalcified masses 8 cm from the nipple in inferior breast. BIRADS assesment category 4: lesions suggestive of malignancy (arrows). (**A**-Mediolateral oblique view, **B**-Craniocaudal view).

serum creatinine was 1.16 mg/dl. There were not any suggestive findings of distant metastases.

Mammograms showed two masses; one was 1cm in diameter and the other was 1.2 cm in diameter. There was not any associated skin thickening or nipple and skin retraction or areolar-subareolar abnormalities (**Figure 2**).

An excisional biopsy of one of the intraglandular lesions and incisional biopsy from the skin lesion of the breast were performed. The histopathologic examination of mammary biopsy specimen revealed Grade II invasive ductal carcinoma with relatively well defined tumor borders and the tumor was 1 cm in diameter. Histopathologic examination of the skin biopsy specimen from the nipple showed proliferation of atypical pleomorphic clear cells which formed solid occlusive masses in the lactiferous ducti (DIN II) and the same cells were observed to form nests diffusely in the epidermis. A

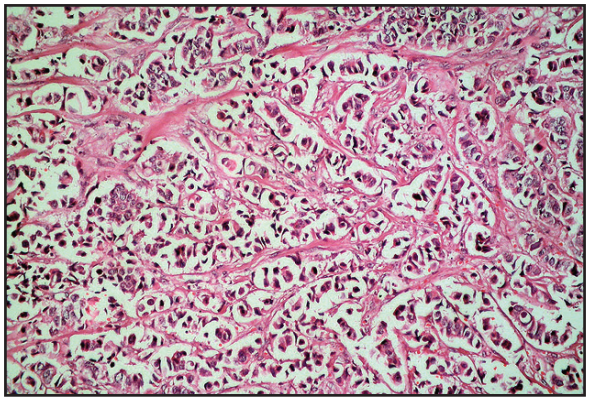

Figure 3. Invasive ductal carcinoma: solid nests, cordons, trabecules and focal gland like structures are located in a hyalinized fibrous stroma and the cells have large hyperchromatic nuclei and eosinophilic cytoplasms and show moderate degree of pleomorphism (*Hematoxylin and Eosin* 10 x 20)

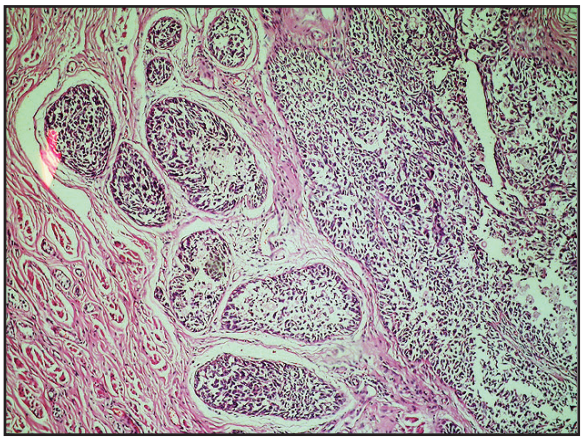

Figure 4. High grade ductal carcinoma in situ, solid occlusive atypical pleomorphic cellular proliferations in the lactiferous ducti (*Hematoxylin and Eosin* 10 x 20).

diagnosis of invasive ductal carcinoma, ductal carcinoma in situ and mammary Paget disease was concluded. The patient underwent modified radical mastectomy after coronary stent placement performed to ameliorate heart circulation before breast surgery. The mastectomy specimen contained 1 x 1.3 x 1.3 cm and 1.5 x 1.3 x 1.3 cm sized two nodules located in inferolateral breast quadrant. Histopathologically these nodules were characterized by solid nests, cordons, trabecules and focal gland like structures located in a hyalinized fibrous stroma with relatively well defined borders of the tumors, and these findings were compatible with Grade II invasive ductal carcinoma. The cells had large hyperchromatic nuclei and eosinophilic cytoplasms and showed moderate degree of pleomorphism. Sparse mitotic activity was also observed (**Figure 3**).

There was no angiolymphatic invasion. Diffuse fat necrosis was observed in the peritumoral areas. There was minimal inflammatory reaction around the tumors. Specimens were taken from the inferomedial quadrant of the resected breast by the pathologist and their histopathological examination revealed solid occlusive patterned atypical monotonous cellular proliferations characterized by round or polygonal shaped pleomorphic cells with well defined cytoplasmic borders that showed central necrosis and microcalcifications in multiple ducti. These findings were interpreted as high grade ductal carcinoma in situ. Histopathologic examination of the nipple specimen showed multiple solid occlusive atypical pleomorphic cellular proliferations in the lactiferous ducti (**Figure 4**). The same cells were observed to form nests diffusely in the epidermis (**Figure 5**). These histopathologic observations were interpreted as high grade ductal carcinoma in situ and *Paget*'s disease of the nipple-areola complex. All of the lymph nodes removed from lower axillary area showed reactive lymphoid hyperplasia.

Immunohistochemical examination was performed for all of the breast lesions. The cells of the two invasive ductal carcinoma lesions were estrogen and progesterone receptor negative but they were positive diffusely for E-cadherin and C-erb-B2 (Figure 6A). *Paget* cells were negative for GCDFP, E-cadherin, S-100, estrogen and progesterone receptors. However they were positive for CK 7, EMA, CEA, HER-2, MUC 1, C-erb-B2 (Figure 6B) and low molecular weight cytokeratins (CAM 5.2, AE 1). Intraductal carcinoma in situ cells were found to be EMA, CEA, E-cadherin, C-erb-B2 positive but they were negative for S-100, progesterone and estrogen receptors.

Discussion

It has been suggested that any chronic dermatosis of the nipple or areola skin should be examined histopathologically for the presence of *Paget* disease. But interestingly, our patient's skin lesion was present only for one month. In mammary *Paget* disease hard breast nodules are found on palpation in 30-50 % of cases [**2**], and mammary *Paget* disease is associated with an underlying breast cancer in 86.7 % of patients [**1**]. If detailed pathological examination of all removed breast tissue is done, then *Paget* disease is associated with an underlying breast carcinoma in 98.5 % of cases [**3**]. Our patient's eczematoid lesion was associated with underlying breast masses but such eczema-like lesions were reported to exist in the absence of any palpable breast tumor more frequently [**2**].

There are two theories explaining the development of *Paget* disease: 1) Epidermatropic theory is the most widely accepted theory of the pathogenesis of *Paget* disease. This theory explains that the paget cells are derived from an underlying breast carcinoma [**1, 2**]. Intraepidermal transformation theory proposes that *Paget* cells arise in situ from multipotential cells or *Toker* cells located in the epidermal basal layer or terminal lactiferous ductus. Most *Paget* disease cases are associated with an underlying breast carcinoma and both of them share the same immunohistochemistry profile and gene expression [**1, 4**]. *Schelfhout* et all. has demonstrated that heregulin-α, a motility factor released by keratinocytes of the nipple, is an essential factor for explaining the epidermatropic theory. They have concluded that heregulin-α plays a central role by attracting breast cancer cells and causing them to spread throughout the nipple epidermis [**5**]. These findings and our case with three underlying breast cancer lesions support the most widely accepted epidermatropic theory.

The tumors associated with mammary *Paget* disease consist of ductal carcinoma in situ or

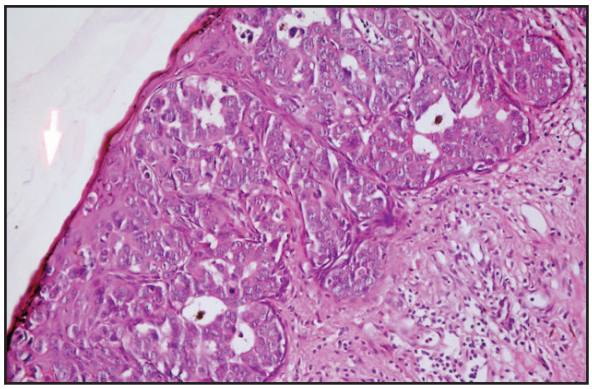

Figure 5. Healing of the lesions over leg by hypertrophic scars. Some lesions have healed by atrophic scars are seen as hypopigmented areas.

invasive ductal carcinomas and they are usually located close to the areola [**1, 2**]. Our patient's invasive ductal carcinoma nodules were located peripherally and close to each other in one breast quadrant. *Kothari* et al. demonstrated that the tumors accompanying *Paget* disease involved the central area in 25% of cases, involved one quadrant of the breast in addition to the central area in 41% of cases and involved more than one quadrant in addition to the central area in 34 % of cases. In other words the tumors are multifocal in 41% of cases and multicentric in 34% of the cases [**3**].

The diagnosis of *Paget* disease is generally made on the basis of clinical findings. Mammograms, although not always positive, should be obtained in all cases suggestive of *Paget* disease to search for any underlying tumor and to determine further treatment. Findings that may be seen at mammography include skin thickening, nipple retraction, subareolar or more diffuse malignant microcalcifications, and a discrete mass or masses. Studies that evaluated the frequency of mammographic findings in *Paget* disease have not demonstrated uniform results [**6**]. *Ikeda* et al reviewed mammograms of 58 patients with pathologically proved *Paget* disease. Of the 34 patients with typical clinical features of Paget disease, only 17 (50%) had positive mammograms. Of the 24 patients without typical clinical features of *Paget* disease, only one had a negative mammogram [**7**]. *Sawyer* and *Asbury* reviewed 17 cases of *Paget* disease; mammograms were positive in 71% of these cases [**8**]. *Burke* et al reviewed the mammograms of 22 patients with a histologically confirmed diagnosis of paget disease. Two of these patients had negative mammograms; but these two patients had nipple changes [**6**]. *Kothari* et al. has demonstrated that the mammography underestimates the extent of the underlying breast carcinoma in about 43% of the cases. They concluded that mammography was of limited value in determination of the appropriate surgical procedure [**3**]. In our case mammography detected discreate masses involving one peripheral quadrant and clinical examination detected the retroa-

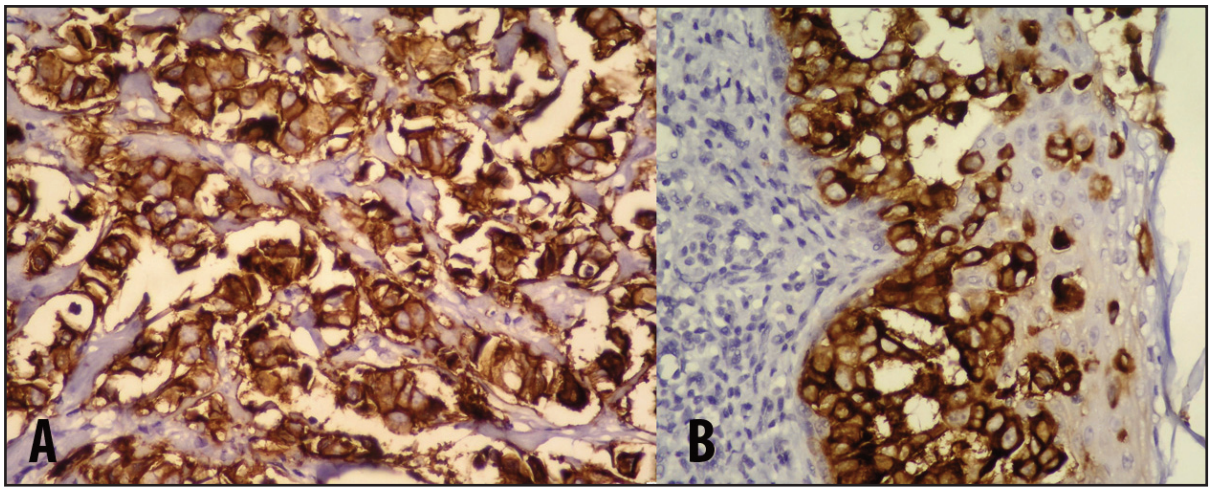

Figure 6. Invasive ductal carcinoma (**A**) and Paget disease (**B**): Membranous staining with C-erb-B2 (immunohistochemistry, 10 x 20)

reolar lesion. So our patient underwent surgical treatment with known 3 lesions.

Immunohistochemistry profiles of *Paget* disease and underlying ductal carcinomas in our patient were in accordance with the literature [**4, 9**]. Our patient's nodules were proven to be ductal in origin because E-cadherin staining was present. E-cadherin is a cell to cell adhesion molecule [**9**]. The absence of E-cadherin staining in our patient's *Paget* cells could imply that E-cadherin mutation plays a role in the development of *Paget* disease by causing the migration of underlying ductal carcinoma cells to the nipple-areola complex.

Patients with *Paget* disease have significantly worse prognosis and this is attributed to higher C-erb-B2 positivity in these cases [**3**]. In our patient two invasive ductal carcinomas, ductal carcinoma in situ and *Paget* disease lesions all showed C-erb-B2 positivity indicating worse prognosis for the patient. Also the absence of estrogen and progesterone receptor in tumor cells indicates that the patient could not benefit from any hormonal therapy.

Invasive ductal carcinomas are usually unifocal lesions compared with invasive lobular carcinomas [**9, 10**]. For ductal carcinoma in situ, multicentricity rate is in 40-80% range. Ductal carcinoma in situ is thought to be an anatomic precursor of invasive ductal carcinoma [**10**]. It could be possible in our patient that all of the tumors are either loco-regional dissemination of one single tumor or all of them are primary lesions. We have concluded that one primary breast tumor disseminated to form two invasive ductal carcinoma tumor nodules, ductal carcinoma in situ lesions in multiple lactiferous ducti and *Paget* disease of the nipple-areola complex in our patient. This conclusion was the result of the fact that all of the breast lesions had similar immunohistochemistry profile. It could be concluded that multifocal breast cancer lesions in *Paget* disease may be the result of spread of one focus throughout the lactiferous ducti to involve one quadrant and the central area and the nipple-areola complex as in our patient. The presence of high grade ductal carcinoma in situ foci in the inferomedial quadrant detected by pathological examination of the resected breast in our patient could be explained by multicentricity of ductal carcinoma in situ of the breast [**10**]. We think that this lesion has not transformed into invasive ductal carcinoma yet. But it is related to the same transformation process causing the ductal carcinoma lesions located in the inferolateral quadrant.

Here we report a case of *Paget*'s characterized by multifocal breast cancer lesions with similar immunohistochemistry profile, supporting the epidermatropic theory. The absence of E-cadherin staining in *Paget* cells implies that E-cadherin mutation could be an important factor in the pathogenesis of *Paget* disease.

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Abbreviations

BI-RADS: Breast Imaging Reporting and Data System Classification
CEA: Carcinoembriyonic Antigen
CK 7: Cytokeratin 7
EMA: Epithelial Membrane Antigen
GCDFP: Gross Cystic Disease Fluid Protein
MUC 1: Human Mucin 1

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