Bilateral Paget Disease of the Nipple Associated With Lobular Carcinoma In Situ

Application of Immunohistochemistry to a Rare Finding

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We report synchronous bilateral Paget disease derived from lobular carcinoma in situ in a 53-year-old woman who underwent bilateral mastectomy. The epidermis of both nipples contained small cells with a moderate amount of pale-staining cytoplasm. The nuclei had fine chromat and identifiable nucleoli. The cells were strongly immunoreactive with cytokeratin 7 and displayed nuclear estrogen receptor reactivity. The underlying mammary gland showed involvement by lobular carcinoma in situ with pagetoid spread into lactiferous ducts, which was confirmed by lack of immunoreactivity for E-cadherin.

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Mammary Paget disease (MPD) occurs in 1% to 4% of patients with breast cancers and is characterized by infiltration of the nipple epidermis by adenocarcinoma cells. Clinically, MPD presents as an eczematous eruption on the nipple and/or areola, often accompanied by pain or pruritus. About 10% to 28% of MPD cases are detected only by histopathologic examination of the nipple in a mastectomy specimen without apparent clinical abnormality. Almost all cases of MPD are associated with in situ or infiltrating ductal carcinoma of the breast. Mammary Paget disease has very rarely been associated with specialized forms of duct carcinoma (eg, papillary and medullary), duct carcinoma arising in florid papillomatosis of the nipple, and lobular carcinoma. A unique case of synchronous bilateral MPD derived from LCIS in a patient without clinical signs of Paget disease is presented.

REPORT OF A CASE

A 53-year-old woman underwent a left breast needle localization biopsy for microcalcifications in 1995. Microscopic examination of the left breast biopsy revealed benign proliferative changes, cysts, and multiple foci of atypical apocrine adenosis with microcalcifications. A single focus of atypical lobular hyperplasia was also present.

In April 2000, follow-up mammography revealed microcalcifications in the right breast for which the patient underwent a needle localization biopsy. Microscopic examination showed microinvasive ductal carcinoma and ductal carcinoma in situ (DCIS), solid type with high nuclear grade and extension into lobules. Immunohistochemical studies demonstrated membranous staining with HER-2/neu protein and nuclear reactivity with estrogen and progesterone receptor in the DCIS areas. The microinvasive carcinoma was depleted on subsequent sections and therefore was not available for hormone receptor studies. Multiple foci of LCIS and atypical duct hyperplasia were also present. Microcalcifications were noted in the proliferative changes.

In October 2000, the patient underwent bilateral mastectomies with excision of right axillary sentinel lymph nodes.

PATHOLOGIC FINDINGS

Gross examination of the right breast revealed a 20.0 × 15.0 × 3.5-cm specimen with a 17.5 × 7.0-cm ellipse of skin showing a 4.5-cm linear scar in the upper outer quadrant. The cut surface of the breast parenchyma revealed fibrosis underneath the cutaneous scar. No other lesion was present. The nipple and areola skin was grossly unremarkable.

Gross examination of the left breast revealed a 20.0 × 15.0 × 3.0-cm specimen with a 20.0 × 7.0-cm ellipse of skin showing a 4.0-cm linear scar in the upper outer quadrant. The nipple and areola were grossly unremarkable. Cut sections of the specimen revealed fibrous breast tissue without a distinct mass.

Microscopic sections of the right breast parenchyma showed atypical ductal hyperplasia and benign proliferative changes associated with microcalcifications.

Microscopic sections of the left breast parenchyma revealed micropapillary apocrine DCIS, widespread LCIS, apocrine adenosis, and columnar cell alteration associated with microcalcifications.

Microscopic sections from both right and left nipples showed LCIS involving lobules with pagetoid spread into lactiferous ducts. No intraductal or invasive duct carcinoma was found in either nipple. The skin of both nipples showed Paget disease characterized by the presence of single and small groups of cells with a moderate amount of pale-staining cytoplasm, nuclei with fine chromatin, and small nucleoli. These cells were similar in morphology to the LCIS in the nipple and in the breast tissue.

Immunohistochemical staining was performed to further characterize the carcinoma cells in the Paget disease using the standard avidin-biotin-peroxidase complex.
method (Table). The carcinoma cells within the epidermis of both nipples showed strong immunoreactivity with CK7 in a background of negatively stained keratinocytes. Immunostaining for estrogen receptor showed nuclear reactivity in the carcinoma cells. The carcinoma cells were negative for carcinoembryonic antigen and HER-2/neu. A similar pattern of staining was observed within the LCIS in nipple ducts and lobules. Lobular carcinoma in situ within the ducts and lobules of nipple showed absence of reactivity with E-cadherin. Interpretation of E-cadherin immunoreactivity was difficult around single neoplastic cells within the nipple epidermis owing to the strong membranous reactivity in the surrounding keratinocytes. However, lack of E-cadherin immunoreactivity was apparent between Paget cells in which aggregates of 2 or more carcinoma cells were present. The in situ carcinoma in the nipple and left breast are depicted in Figure 1, and the nipple skin lesion is shown in Figure 2.

**COMMENT**

Bilateral breast carcinoma is reported to occur in 5% to 10% of all patients with breast cancer. However, synchronous bilateral Paget disease of the nipple is extremely rare. This report describes a unique case of synchronous bilateral Paget disease of the nipple derived from LCIS, which involved underlying lactiferous ducts and lobules in the nipple.

Mammary Paget disease represents the spread of carcinoma cells into the epidermis of the nipple and areola from an underlying mammary adenocarcinoma in almost
In the current case, the left breast contained 1 focus of DCIS in the upper outer quadrant, and the right breast had DCIS and microinvasive duct carcinoma in the upper outer quadrant. No intraductal or invasive duct carcinoma was present in either carefully sampled nipple. However, both nipples had multiple lobules, many of which were involved by LCIS with pagetoid spread into lactiferous ducts. The cytomorphology of the Paget cells, absence of DCIS in the nipples, involvement of the lactiferous ducts by LCIS, and absence of HER-2/neu and E-cadherin staining strongly support the conclusion that bilateral Paget disease derived from LCIS in this instance.

References