Mammary Paget’s disease without underlying malignancy of the breast

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Mammary Paget’s disease (MPD) is usually accompanied by underlying breast malignancy; however, a few cases have been reported as only skin lesions without any evidence of malignancy of the breast on imaging tests and microscopic examination of surgical specimen. Here, we describe a 47-year-old woman who visited our hospital who had an eczematous lesion on right nipple and areola for over 10 years. The lesion was diagnosed as Paget’s disease by punch biopsy; however, imaging studies demonstrated no breast malignancy or lymph node metastasis. The patient underwent surgery of on the nipple and areola including underlying breast tissue. No underlying malignancy was found upon microscopic examination, except for Paget’s disease. Immunohistochemical stains revealed that the tumor cells were positive for cytokeratin 7, and negativity for p63, cytokeratin 5/6, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. We report a case of MPD without underlying malignancy. To the best of our knowledge, this is the third case reported in Korea.

Keywords: Paget’s disease; Breast; Immunohistochemistry

INTRODUCTION

Paget’s disease is an intraepithelial adenocarcinoma that can occur both in the breast and in the extramammary anogenital skin. Mammary Paget’s disease (MPD) is an uncommon breast cancer that is usually associated with underlying malignancy of the breast. Only a few cases of MPD without underlying malignancy of the breast have been reported in English literature [1-9]. We report a case of Paget’s disease in a 47-year-old woman who did not have any clinical or pathological evidence of underlying malignancy in breast parenchyma. To the best of our knowledge, this is the third case in Korea.

CASE

A 47-year-old woman presenting erythematous patches on the right nipple and areola (Fig. 1) visited the department of
dermatology at our hospital. The lesion had been present for 10 years with repeated improvement and deterioration. The patient had only conservative treatment without any further evaluation in local clinics. Based on punch biopsies of the nipple and areola, the lesions were diagnosed as Paget’s disease. Immunohistochemical (IHC) stains were performed and the results in tumor cells were as follows: cytokeratin 7 (+); p63 (-); cytokeratin 5/6 (-).

Consecutively conducted mammography and ultrasonography demonstrated heterogeneous dense breast tissue and several small, oval shaped hypoechoic nodules in the bilateral breast, which indicated benign lesions (Fig. 2A, 2B). Positron emission tomography-magnetic resonance imaging revealed a thin enhancing lesion (1.0×0.4 cm) on the nipple and areola of the right breast, but there was no evidence of regional lymph node metastasis or distant metastasis. The patient underwent breast-conserving surgery of the nipple and areolar skin with sentinel lymph node biopsy.

The resected right breast measured 24.2 g, and was 5.4×4.7×2.1 cm in size. The overlying skin measured 4.0×2.5 cm and the nipple measured 1.5×1.3 cm. The skin contained a 3.5×2.3 cm light red discoloration patch and the nipple was relatively smooth on the surface, except for a previous biopsy site (Fig. 3A). There was no definite mass-like lesion in the breast parenchyma on serial sections (Fig. 3B).

Microscopically, large atypical tumor cells were arranged in
glandular clusters, or small nests within the epidermis. These had abundant basophilic and fine granular cytoplasm with nuclear atypia and pleomorphism. Some tumor cells contained intracytoplasmic mucin. The tumor cells were confined to the epidermis, and no involvement of the lactiferous duct or breast parenchyma by carcinoma was identified. On IHC staining, tumor cells were negative for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), CDX-2, mucin 2 (MUC2) and mucin 5AC (MUC5AC), but positive for MUC1.

DISCUSSION

MPD, which was first described by James Paget in 1874, is usually accompanied by underlying breast malignancy (85-95%), mostly high-grade invasive carcinoma, with no special type or ductal carcinoma in situ [10,11]. MPD without underlying carcinoma is very rare, accounting for 1.4-13% of all MPD [7,12,13]. Sometimes, MPD occurs by pagetoid spread of ductal carcinoma in situ originating from the lactiferous ducts of breast to the epidermis of the nipple. However, it has been suggested that primary MPD can originate from adenocarcinoma, Toker cells, or pluripotent stem cells within the epidermis, rather than from the lactiferous ducts. Secondary MPD indicates the spread of tumor cells from underlying breast carcinoma.

Previous studies analyzed IHC features of primary and secondary MPD and extramammary Paget’s disease (EMPD) [14]. However, it is impossible to distinguish primary from secondary MPD using IHC stains. Interestingly, the results of IHC for HER2 protein showed distinct patterns between MPD and EMPD. HER2 positivity was more commonly observed in MPD (71-100%), but less frequently detected in EMPD (0-55%), which also showed weaker staining for HER2 than the former. Our case represented complete negative immunoreactivity for HER2 (Fig. 4F). The immunostaining results for ER and PR were also negative (Fig. 4D, 4E).

Meissner et al. analyzed HER2 expression in MPD with or without underlying breast carcinoma and in EMPD [15]. In their study, all five MPD cases without underlying malignancy showed positive expression for HER2, similar to the cases of MPD with underlying breast cancer. These findings suggested that the development of MPD and HER2 positive breast carcinoma have common cytogenetic alterations or signaling events.

Fig. 4. Microscopic findings of the nipple and areola. (A) The tumor cells formed nests or showed glandular differentiation within the epidermis. Some of single tumor cells are spreading to the striata (H&E stain, ×200). (B, C) The tumor cells were positive for CK7 and MUC1 (B, ×200; C, ×200). (D-F) The tumor cells were negative for ER, PR, and HER2 (D, ×100; E, ×100; F, ×100). CK7, cytokeratin 7, MUC1, mucin 1, ER, estrogen receptor, PR, progesterone receptor, HER2, human epidermal growth factor receptor 2.
pathways associated with tumorigenesis.

Liu et al. reported that MPD and EMPD are different biological diseases despite their morphological similarity [16]. They evaluated the expression of HER2 and their downstream signaling pathway members, including AKT/pAKT and phosphatase and tensin homologue (PTEN) in MPD and EMPD. They found that HER2 overexpression was more frequent in MPD than in EMPD, and that HER2 negativity associated with AKT and PTEN positivity was present only in EMPD.

Different mucin expression patterns have been reported in MPD and EMPD. Kuan et al. conducted IHC staining of MUC series in 13 cases of MPD and 13 cases of EMPD [17]. MUC1 was generally positive in both MPD and EMPD. In contrast, MUC5AC was negative in all MPD cases, but positive in 10 out of 13 cases of EMPD. Liegl et al. also demonstrated that MUC5AC immunostaining between MPD and EMPD was quite different, as positive staining for MUC5AC was 0% in MPD (0/50), but 42.1% (8/19) in EMPD [14]. In our case, tumor cells were strongly positive for MUC1, but negative for MUC5AC. And it is exclusive of Paget’s disease of extramammary origin, such as metastatic adenocarcinoma from gastrointestinal tract because the tumor cells showed negative immunostaining for CDX-2 and MUC2.

There have been about 20 cases of MPD without underlying breast carcinoma [1-9]. Prognosis of MPD is different depending on whether it is associated with underlying breast carcinoma or not. MPD patients with underlying breast malignancy have poorer prognosis than those without a palpable breast tumor (5-year survival rate, 32-43% vs. 92-94%) [18].

In Korea, two cases of MPD without underlying malignancy of breast have been reported. The first case was reported by Han et al. in 1976 [19]. The patient underwent radical mastectomy and was diagnosed as with Paget’s disease, but did not have any underlying malignancy in breast parenchyma. The second case was reported by Yeo et al. in 1994 [20]. They collected fifteen cases of MPD, including three cases of MPD showing only nipple change, but malignancy of breast parenchyma. Among these, one case had no malignant lesions and the other two cases had invasive carcinoma and intraductal carcinoma, respectively. The follow-up data of each case were not described in those reports.

In our case, the patient was alive without any clinical evidence of recurrence for 8 months after surgery. She also has no malignancies in other organs. We report here the third case of MPD without underlying malignancy of the breast in Korea.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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