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Extramammary Paget's Disease Combined with Squamous Cell Carcinoma *In Situ* of the Vulva: A Case Report and Differential Diagnosis

Eun Jeong Jang, Young Kyung Bae, Dong Hoon Shin[1], Doo Jin Lee[2]

Departments of Pathology, [1]Dermatology, and [2]Gynecology, Yeungnam University College of Medicine, Daegu, Korea

Dear Editor:

A 68-year-old woman presented with itching sensation of the vulva. She had undergone a total hysterectomy with both salpingo-oophorectomy due to squamous cell carcinoma *in situ* (SCIS) of the cervix 23 years ago. After the gynecologic operation, she had experienced local recurrences and underwent radiation therapy and wide excision of the vagina and vulva several times.

On physical examination, the vulvar skin showed a pink, wet glistening lesion with focal erosion. Under clinical impression of vulvar recurrence of SCIS, a partial vulvectomy was performed. Microscopic examination of the specimen showed acanthosis with full thickness cellular atypia, consistent with SCIS (Fig. 1A). Human papillomavirus (HPV) type 16 was detected using a HPV DNA ChipTM kit (AGBIO Diagnostics, Seoul, Korea). Near the resection margin, nests and singly arranged pagetoid cells with pale-staining cytoplasm and hyperchromatic nuclei were identified. The surrounding squamous epithelium showed no atypia (Fig. 1B). The pagetoid cells were diffusely and strongly positive for CK7 and focally positive for carcinoembryonic antigen (CEA), but negative for CK5/6, CK20, p63, and S100 protein (Fig. 2A～D). The tumor cells of SCIS were diffusely positive for CK5/6 and p63, but negative for CK7 and CEA (Fig. 2E～H). This lesion was diagnosed as primary extramammary Paget's disease (EMPD) combined with SCIS.

This case should be differentiated from both pagetoid SCIS and EMPD with bowenoid features histologically. Pagetoid Bowen's disease (pagetoid SCIS) is a histologic variant of SCIS showing nests of pale staining cytoplasmic cells with no immunohistochemical features of Paget's disease. The tumor cells in pagetoid Bowen's disease expressed CK7, CK19, keratin-903 (34betaE12) and CK5/6, but were negative for CK18, CK20, Cam5.2, CEA, GCDFP-15, c-erbB-2, S100 protein, Melan A, and HMB-45[1,2]. Absence of mucin and diffuse positive staining for p63 and CK5/6 support

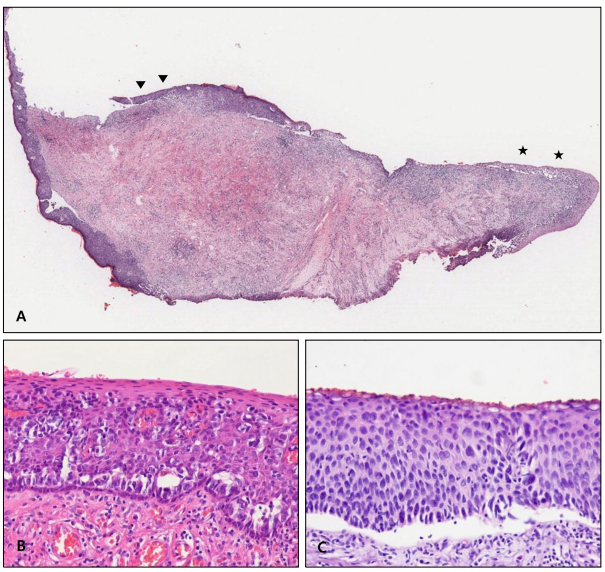

Fig. 1. (A) Scanning view of partial vulvectomy specimen (H&E, ×8). Surface erosion is noted in the right upper portion of the figure. (B) The right side of Fig. 1A (★) represented extramammary Paget's disease (H&E, ×200) and (C) the left side of Fig. 1A (▼) showed squamous intraepithelial lesion including carcinoma *in situ* of the vulva (H&E, ×200).

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Corresponding author: Young Kyung Bae, Department of Pathology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea. Tel: 82-53-640-6755, Fax: 82-53-622-8432, E-mail: ykbae@ynu.ac.kr

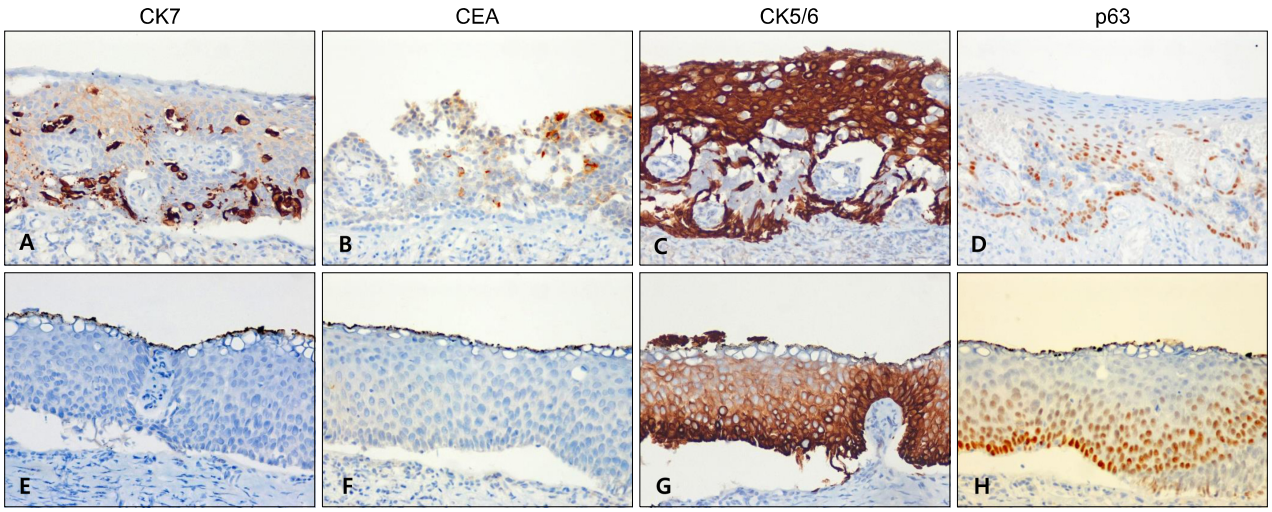

Fig. 2. Immunohistochemical results showed distinct patterns in extramammary Paget's disease (A～D) and squamous carcinoma *in situ* (E～H). Paget's cells were strongly positive for CK7 (A) and focally positive for carcinoembryonic antigen (CEA) (B), but negative for CK5/6 (C) and p63 (D). Non-neoplastic keratinocytes are positive for CK5/6 and p63. The tumor cells of squamous carcinoma *in situ* were totally negative for CK7 (E) and CEA (F), but positive for CK5/6 (G) and p63 (H) (A～H, ×200).

the diagnosis of SCIS[3]. EMPD with bowenoid features has histologic features of both Bowen's disease and EMPD, however, immunohistochemical stains show the same results corresponding to EMPD. In previous studies, immunohistochemical stains for CEA, CK7, and Cam5.2 were strongly expressed in both characteristic Paget cells and in areas with full-thickness atypia, while stains for CK20, HMB-45, S100 protein, and p63 were completely negative[4]. CK7, which has been used as a marker of EMPD, has been expressed in occasional cases of pagetoid SCIS[2]. The date of manufacture or the lot numbers of the antibody, the type of clone (OV/TL 12/30 vs. Ks7.18) and/or the detection method of the laboratory (ABC complex system vs. Envision complex system) were raised as possible causes for the heterogeneity in CK7 expression[2].

Although EMPD and SCIS were closely located in our case, we do not know whether they are coincidental tumors or mixed carcinoma *in situ* exactly. A recent ultrastructural study suggested that pagetoid Bowen's disease and primary EMPD may arise from a common progenitor cell[5].

In conclusion, we report a rare case of vulvar EMPD combined with SCIS. Histologically, differentiation of EMPD combined with SCIS from pagetoid SCIS and EMPD with bowenoid features is difficult, thus immunohistochemistry is required to confirm the diagnosis.

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