Disclosure: The authors have no financial interest to declare in relation to the content of this article.
on the other (Fig. 2A). In the interstice between them, there was a gap of approximately 2 mm in which Paget cells were not found. Immunohistochemical staining revealed the cells to be positive for cytokeratin 7 (CK7), gross cystic disease fluid protein 15 (GCDFP-15), and Mucin 5AC and negative for cytokeratin 20 (CK20), carcinoembryonic antigen, and mammaglobin. The staining pattern of CK7 and CK20 suggests that EMPD originated from the epidermis rather than the skin infiltration of gastrointestinal cancer. There were no other overlapping cancers in the scrotum, axilla, and intestinal tract. Because the stump of EMPD was positive, we made the additional surgery for the remaining EMPD after skin mapping by punch biopsies around the initial surgical wound and around the anus. As a result of the second surgery, no malignant cells, including Paget cell in the epidermis, were found in the surgical specimen. Follow-up observations of the patient have revealed no recurrence for 1 year.

**DISCUSSION**

EMPD is a rare cutaneous carcinoma and diagnosis is frequently delayed because of its unremarkable cutaneous signs. In early EMPD, minor depigmentation spots are observed, followed by irregularly pale red spots like eczema, accompanied by an incongruity and itching. Eventually, irregular induration and nodules appear, often with vice lesions away from the main lesion. The so-called double or triple Paget disease, which occurs frequently in the vulva and axilla where the apocrine gland is distributed.
and GCDFP-15. Differential diagnosis of intraepidermal cells are CK7, carcinoembryonic antigen, anticytokeratin, mon immunohistochemical markers positive for Paget staining and alcian blue pH2.5 staining, and the most common or oval nucleus and bright cytoplasm, grow in the breast cancer, liver cancer, and so on.

of patients with EMPD have malignant tumors, including in the occurrence of the other tumor, and a theory that two co-occur: a theory that one tumor plays a contributing role within EMPD of the vulva was made by Ishizawa et al. in reports where BCC and EMPD occurred simultaneously in when the tumor is secondarily derived from the intestine. expresses the opposite pattern and is negative for GCDFP-15 the epidermis is positive for CK7 and negative for CK20, it Pagetoid phenomenon). Although the tumor derived from EMPD) gastrointestinal cancer (secondary EMPD, so-called immunohistochemical markers positive for Paget cells are CK7, carcinoembryonic antigen, anticytokeratin, and GCDFP-15. Differential diagnosis of intraepidermal Pagetoid neoplasms includes Bowen disease (squamous cell carcinoma in situ) and superficial spreading of malignant melanoma in situ, which can be distinguished by histologic presence using several immunochemical markers. Melanoma in situ is positive for S-100 protein and human melanin black-45 (HMB45), and Bowen disease is positive for AE1AE3 (pancytokeratin), protein 63 (p63), and eventually CK7. Regarding perianal lesion of Paget disease, immunohistochemical staining should be enforced to distinguish whether its origin is the epidermis itself (primary EMPD) gastrointestinal cancer (secondary EMPD, so-called Pagetoid phenomenon). Although the tumor derived from the epidermis is positive for CK7 and negative for CK20, it expresses the opposite pattern and is negative for GCDFP-15 when the tumor is secondarily derived from the intestine.

The literature review by the authors includes 4 case reports where BCC and EMPD occurred simultaneously in the same region. The first report in which BCC occurred within EMPD of the vulva was made by Ishizawa et al. in 1998. Table 1 summarizes the demographic and clinical variables in 5 patients, including our case. There are 2 major opinions on a mechanism by which BCC and EMPD co-occur: a theory that one tumor plays a contributing role in the occurrence of the other tumor, and a theory that 2 tumors arise individually with no causal relevance between them. We believe the latter theory is more likely in our case for the following 2 reasons. First, on histopathological examination, BCC and EMPD are definitely parted from each other by the epithelium with no malignant cells. Second, it was impossible to prove a temporal relationship between the 2 tumors in our case; for example, if the onset of BCC evidently preceded that of EMPD, it can be hypothesized that the occurrence of BCC reduced local immunity in some way and contributed to the occurrence of EMPD; however, in the present case, we could not know which of them first occurred because of the defect of cutaneous signs of EMPD and whether one interferes with the other. In conclusion, we inferred 3 potentialities in the occurrence of EMPD in our case, immunodeficiency due to cirrhosis, complication with underlying internal malignancy (hepatocellular carcinoma), and completely independent occurrence. However, which of them is true could not be proven in just 1 case.

| Reference (Year) | Age/Sex | Location | Clinical Presentation of BCC | Clinical Presentation of EMPD | Immunohistology | Treatment |
|-----------------|---------|----------|-----------------------------|-----------------------------|----------------|-----------|
| Ishizawa et al\(^1\) (1998) | 85/Woman | Vulvar | Ulceration | Erythema | CEA(+) | Wide resection with 3 cm margin from vitiligo lesion |
| Kobayashi et al\(^\ddagger\) (2003) | 52/Men | Scrotum | 14 x 12 mm nodule | Vitiligo | — | Radial vulvectomy |
| Abdelbaqi et al\(^\ddagger\) (2012) | 82/Women | Vulvar | A heaped-up erythema lesion | Erythema (recurrence of EMPD) | — | — |
| Kang et al\(^\ddagger\) (2016) | 73/Woman | Scalp | 20 mm nodule | Alopecia | CAM5.2(+), CK7(+) | Wide local resection |
| This case (2017) | 83/Men | Perianal | 10 mm nodule | None | CK7(+), GCDFP-15(+), MUC5AC(+) | Wide local resection around the last scar |

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CAM5.2, anticytokeratin; CEA, carcinoembryonic antigen; MUC5AC, Mucin 5AC.

is widely known. The incidence of underlying adnexal carcinoma has been reported to vary, for example, Chanda\(^4\) found that 24% of 196 cases from English literature from 1962 to 1982 had an underlying adnexal carcinoma. In a Japanese study, Kamiya\(^5\) reported that in 2008 about 11.3% of patients with EMPD have malignant tumors, including gastric cancer, colon cancer, prostate cancer, lung cancer, breast cancer, liver cancer, and so on.

Histopathological findings of EMPD show that nucleoli are clearly distinct, and characteristic Paget cells, with circular or oval nucleus and bright cytoplasm, grow in the epidermis and sometimes in the epithelium of the appendages. Paget cells are positive in periodic acid schiff (PAS) staining and alcian blue pH2.5 staining, and the most common immunohistochemical markers positive for Paget cells are CK7, carcinoembryonic antigen, anticytokeratin, and GCDFP-15.\(^5\) Differential diagnosis of intraepidermal Pagetoid neoplasms includes Bowen disease (squamous cell carcinoma in situ) and superficial spreading of malignant melanoma in situ, which can be distinguished by histologic presence using several immunochemical markers. Melanoma in situ is positive for S-100 protein and human melanin black-45 (HMB45), and Bowen disease is positive for AE1AE3 (pancytokeratin), protein 63 (p63), and eventually CK7.\(^5\) Regarding perianal lesion of Paget disease, immunohistochemical staining should be enforced to distinguish whether its origin is the epidermis itself (primary EMPD) gastrointestinal cancer (secondary EMPD, so-called Pagetoid phenomenon). Although the tumor derived from the epidermis is positive for CK7 and negative for CK20, it expresses the opposite pattern and is negative for GCDFP-15 when the tumor is secondarily derived from the intestine.\(^5\)

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SUMMARY

We experienced a case of concurrence of BCC and EMPD around the anus; however, the mechanism by which 2 different skin cancers coexisted remains unknown in our case. With the aging of the population in the future, an increase in the number of patients with multiple skin cancers is expected. Attentive immunohistochemical staining may be useful to distinguish a perianal tumor from other conceivable differential diagnoses.

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