Case Series

A Case Report of Familial Extramammary Paget's Disease in Female Siblings

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Keywords

Familial extramammary Paget's disease · Extramammary Paget's disease · Paget's disease of the vulvar

Abstract

Extramammary Paget's disease (EMPD) is a rare intraepithelial neoplasm that occurs in apocrine-bearing areas of skin. Most EMPD patients initially present with chronic pruritic eczematous lesions involving genitalia, perineum and perianal area. Familial form of EMPD is extremely rare. Several genetic mutations have been proposed but specific modes of inheritance are still unknown. This article reports two cases of familial extramammary Paget's disease in female siblings.

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Introduction

Extramammary Paget's disease (EMPD) is a rare intraepithelial neoplasm that occurs in apocrine-bearing areas of skin such as vulva, perineum, penis, scrotum, and perianal area. EMPD commonly occurs in women older than 60 years of age without specific risk factors or

precipitating cause identified to date. Most EMPD patients initially present with pruritic erythematous plaques with scale commonly involving genitalia, perineum, and perianal area. The disease is categorized by its origins into two forms: primary and secondary. Primary EMPD originates in epidermis or adnexal structures, whereas secondary EMPD develops in association with internal malignancy, commonly malignancy in the gastrointestinal or urinary tract. Based on a recent study by Van der Linden [1], however, secondary EMPD does not increase the risk of malignancy compared with the general population. Up until now, not so many familial EMPD cases have been reported. This article reports two cases of familial vulvar EMPD in female siblings.

Case Presentation

Case 1

A 61-year-old Asian woman presented with a 2-year history of chronic pruritic genital lesion slowly progressing to the anus. She visited the Department of Obstetrics and Gynecology and was referred to a dermatologist for evaluation of her genital lesion. The patient had hypertension, hyperlipidemia, and type 2 diabetes mellitus. Physical examination revealed localized well-defined moist, erythematous and whitish eroded plaques on bilateral labia majora, labia minora, clitoris, posterior fourchette, right anterior part of the anus, as well as bilateral perineal and inguinal areas without urethral involvement (Fig. 1). No inguinal lymph node was palpable in both groins. A tissue specimen examination, collected by incisional skin biopsy from the lesion at right inguinal area, showed epidermal proliferation with nests of clear cell neoplasm with pagetoid spreading through the epidermis with flattened basal cell layer lying between clear cell neoplasm and the underlying epidermis (Fig. 2). Immunohistochemical study revealed that the tissue was positive for cytokeratin 7 (CK7), cytokeratin 20 (CK20), but negative for gross cystic disease fluid protein 15 (GCDFP15), CDX2, and PAX8. The diagnosis of EMPD was made. Papanicolaou smear test, chest X-ray, cystoscopy, esophagogastroduodenoscopy, and colonoscopy were normal. The patient underwent wide excision with a cutting margin of 2 cm. Pathological report after surgery revealed EMPD without dermal or subcutaneous invasion. After a 12-month postoperative period, the patient is still on follow-up with no disease recurrence.

Case 2

A 67-year-old Asian woman presented with a chronic pruritic genital lesion similar to her younger sister (case 1) for 2 years. The patient visited the Department of Dermatology for consultation on her present genital lesion. The patient had hypertension, hyperlipidemia, and a 20-year past history of completed left modified radical mastectomy for breast cancer and total abdominal hysterectomy and bilateral salpingo-oophorectomy for uterine tumor. Physical examination revealed localized well-defined erythematous and whitish eroded plaques on bilateral labia majora, labia minora extending to the perianal area (Fig. 3) without urethral, clitoral, and vaginal involvement. No inguinal lymph node was palpable on both groins. An incisional skin biopsy was performed on the lesion at the right labia majora. A biopsy

specimen showed epidermal proliferation with large rounded atypical cells with clear ample-staining cytoplasm scattered through the epidermis with flattened basal cell layer lying between atypical cells and the underlying epidermis (Fig. 4). Immunohistochemical study was positive for CK7, CK20, and GCDP15 but negative for CDX2. The diagnosis of EMPD was established. Papanicolaou smear test, chest X-ray, esophagogastroduodenoscopy, colonoscopy, computed tomography of the whole abdomen and pelvis revealed unremarkable results. The patient underwent wide excision with a cutting margin of 1 cm. Pathological report after surgery revealed EMPD with multiple foci of microinvasion <1 mm. One year after the surgical excision, the patient has no recurrence of the disease and is still on follow-up.

Discussion/Conclusion

EMPD is a rare intraepidermal neoplasm that occurs in apocrine-bearing skin areas such as the vulva, perineum, penis, scrotum and perianal area. Croker [2] described the first case of EMPD in 1889. EMPD commonly occurs in Caucasian women older than 60 years of age without specific risk factors or precipitating causes identified to date. Most cases of EMPD usually present with slowly progressing eczematous skin lesions on the anogenital area with classic strawberries and cream appearance. Ectopic EMPD can occur at any locations such as trunk, scalp, extremities, and face.

A familial form of EMPD was firstly reported by Kuehn et al. [3] in 1973. Up until now, not so many familial EMPD cases have been reported. Most cases were reported from Japan in the Japanese literature. At least five articles were reported in English (Table 1). The age range at diagnosis was 47–83 years. Locations of the tumor were in the genital area in most cases. Lymph node metastasis was found in 4 cases. However, no case of distant metastasis was reported. Only one case had gastric adenocarcinoma concurrent with EMPD. The familial relationships were father and son in 3 reports, brother and brother in 4 reports, and brother and sister in 3 reports. Our cases were the first report of female siblings who had the same skin lesion on the same site of anogenital area. These findings might suggest genetic alterations in the pathogenesis of this disease.

Genetic mutations in various genes affecting epidermal growth factor receptor (EGFR) signaling have been reported for disease pathogenesis, given an example of mutations in RAS/RAF and PIK3CA/AKT pathways such as KRAS, NRAS, BRAF, PIK3CA, and AKT1 genes [4]. Moreover, germline mismatch repair (MMR) genes alterations such as MLH1, MLH3, MSH2, MSH6, and PMS2 have also been implicated in the pathogenesis of EMPD [5]. A recent study by Kiniwa et al. [6] published in 2019 showed recurrent several somatic gene mutations identified by whole exome analysis. For instance, PIK3CA, ERBB2, and TP53 mutations. However, none of these findings could identify a relationship between genetic alterations and mode of inheritance in familial EMPD. Further study is required to demonstrate these relationships. Unfortunately, our patients did not undergo genetic study due to insurance coverage.

Currently, EMPD is categorized into two forms, primary and secondary. In primary EMPD, the tumor arises from intraepidermal parts of apocrine glands or pluripotent stem cells in the

epidermis, whereas secondary EMPD usually associates with several underlying internal malignancy such as gastrointestinal or urothelial tract cancer [7]. In previous case reports of familial EMPD reported by Inoue et al. [8], there is only 1 patient who was found to have associated gastric adenocarcinoma. Screening of associated malignancy in addition to age-appropriate and symptom-directed screening should be performed in EMPD cases. However, Van der Linden et al. [1] suggested that routine screening for primary noninvasive vulvar Paget's disease should not be performed because there was not a significantly increased risk of developing associated malignancy in subgroup analysis.

Biopsy is the standard method for a definitive diagnosis of EMPD. Histopathology of such tumors reveals the intraepithelial proliferation of pagetoid cells spreading throughout the epidermis. These tumor cells usually stain positive for low-molecular-weight cytokeratin such as CK7, anticytokeratin such as CAM5.2, carcinoembryonic antigen, and epithelial membrane antigen. Furthermore, CK20 is commonly positive in secondary EMPD. However, the study of Perrotto et al. [9] showed that CK20 might be positive in 22% of primary EMPD cases. Thus, these data may explain positivity of CK20 in the cases reported in this study.

Currently, there is no standardized guideline for management of EMPD due to rarity of the disease. However, surgery is still the mainstay of treatment [10]. Current alternative and adjunctive treatments in inoperable patients include radiotherapy, photodynamic therapy, topical chemotherapy or immunomodulator, and systemic chemotherapy [11].

In conclusion, familial cases of EMPD are very rare with few reports in the English literature. They demonstrated EMPD in different family relationships. This article presents the first case of familial EMPD which occurred in female siblings. Therefore, history taking of familial disease is essential in EMPD patients. Once the correct diagnosis is made, proper management will be assigned to the patient, preventing spread of tumor.

Statement of Ethics

The patients have given their written informed consent to publish their case including publication of clinical photographs. This case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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Fig. 1. Localized well-defined moist, erythematous and whitish eroded plaques on the anogenital region.

Fig. 2. Epidermal proliferation with nests of clear cell neoplasm with pagetoid spreading through the epidermis with flattened basal cell layer. H&E, 10×.

Fig. 3. Localized well-defined erythematous and whitish eroded plaques on the anogenital area.

Fig. 4. Epidermal proliferation with large rounded atypical cells with clear ample-staining cytoplasm scattered through the epidermis with flattened basal cell layer.

Table 1. Case reports of familial extramammary Paget's disease

Case reports	Patients	Location	Metastasis site	Underlying malignancy
Kuehn et al., 1973 [3]	1. Male 66 yr. (Father) 2. Male 58 yr. (Son)	Scrotum Scrotum	Right inguinal LN No	No No
Sakamoto et al., 1988 [12]	1. Male 57 yr. (Brother) 2. Male 55 yr. (Brother)	Scrotum Scrotum	Right inguinal LN No	NA NA
Amano et al., 1994 [13]	1. Male 59 yr. (Brother) 2. Female 56 yr. (Sister)	Scrotum Labia majora	No No	NA NA
Hashimoto et al., 1995 [14]	1. Male 83 yr. (Brother) 2. Male 72 yr. (Brother)	Scrotum, shaft of penis Scrotum, shaft of penis	NA NA	No No
Nishibo et al., 1996 [15]	1. Male 81 yr. (Father) 2. Male 50 yr. (Son)	Scrotum, shaft of penis Scrotum	NA NA	NA NA
Mochizuki et al., 1998 [16]	1. Male 68 yr. (Father) 2. Male 47 yr. (Son)	Scrotum Scrotum	No No	NA NA
Demitsu et al., 1999 [17]	1. Male 74 yr. (Brother) 2. Female 66 yr. (Sister)	Mons pubis Mons pubis	No No	No No
Inoue et al., 2000 [8]	1. Female 83 yr. (Sister) 2. Male 83 yr. (Brother)	Vulvar Scrotum	No No	No Gastric adenocarcinoma
Zhang et al., 2015 [18]	1. Male 67 yr. (Brother) 2. Male 56 yr. (Brother)	Scrotum Scrotum	Multiple lymph LN No	No No
Rao et al., 2015 [19]	1. Male 56 yr. (Brother) 2. Male 68 yr. (Brother)	Scrotum Scrotum, root of penis	No Left inguinal LN	No No
Cases reported in this study	1. Female 61 yr. (Sister) 2. Female 67 yr. (Sister)	Anogenital Anogenital	No No	No No

LN, lymph node; NA, not applicable; yr, year.