Case Report

Coexisting Vulvar Paget's Disease and Mucinous Carcinoma of the Breast: A Case Report and Review of the Literature

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Vulvar Paget' disease is the most common site of extramammary Paget's disease (EMPD). The disease frequently associated with the underlying invasive skin adnexal carcinoma or representing the migration of underlying internal malignancy, especially anorectal and genitourinary cancer, but the coexisting with primary breast cancer is rare. Herein, the authors report a case of a 46-year-old Thai woman who had vulvar Paget's disease with subsequent development of mucinous carcinoma of the breast. Interestingly, the overexpression of HER-2/neu in vulvar Paget's disease raises the additional option of anti-HER-2/neu antibody therapy in highly aggressive or recurrent disease. In conclusion, primary breast cancer should be of concern in patients with vulva Paget's disease, even though it is an uncommon association.

Keywords: *Vulvar Paget's disease, Co-existing cancer, Breast cancer, Mucinous carcinoma*

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EMPD is a rare intraepithelial adenocarcinoma, usually affects apocrine gland-rich bearing skin in anogenital area[1]. When the disease is present, the associated underlying invasive skin adnexal carcinoma or the underlying internal malignancy must be worked up, especially in anorectal and genitourinary region, but the association of breast cancer is less frequently seen[2].

Case Report

A 46-year-old Thai woman came to the hospital with vulva puritus for 10 years. The physical examination revealed a well-demarcated erythematous patch with minimal lichenification of the left labia majora. The lesion was not improved after the appropriate tropical treatment. Skin biopsy was performed. Histopathologic examination showed pagetoid spreading of large single cells/clusters of Paget's cells with large nuclei, prominent nucleoli, and finely granular cytoplasm involving the entirely epidermal thickness without underlying invasive carcinoma (Fig. 1). The tumor cells were positive for diastase-resistant periodic acid Schiff (PAS) stain. The immunohistochemical study showed positive immunohistochemical stain for low molecular weight cytokeratin (LMWCK), cytokeratin 7 (CK 7) (Fig. 2a), carcinoembryonic antigen (CEA), focally positive gross cystic disease fluid protein-15 (GCDFP-15) (Fig. 2b), and HER-2/neu (Fig. 2c), but negative for cytokeratin 20 (CK20) (Fig. 2d), S-100, HMB-45, estrogen receptor (ER), and progesterone receptor (PR). Simple vulvectomy was performed. Five years later, the patient had a palpable left breast mass. The excisional biopsy revealed mucinous carcinoma (Fig. 3). The tumor size was 2 cm. The mucicarmine stain was positive (Fig. 4a).The immunohistochemical study showed positive ER (Fig. 4b) and PR (Fig. 4c) in 80% and 30%, respectively, but negative HER-2/neu (Fig. 4d). Simple mastectomy with sentinel lymph node biopsy was done. No overlying mammary Paget's disease, residual tumor or metastatic carcinoma were seen in all four axillary sentinel lymph nodes. Tamoxifen was given. Vulva Paget's disease had recurred many times and she was treated by repeated wide-excision and radiation therapy. No recurrent breast cancer was detected in the regularly 5 years follow-up.

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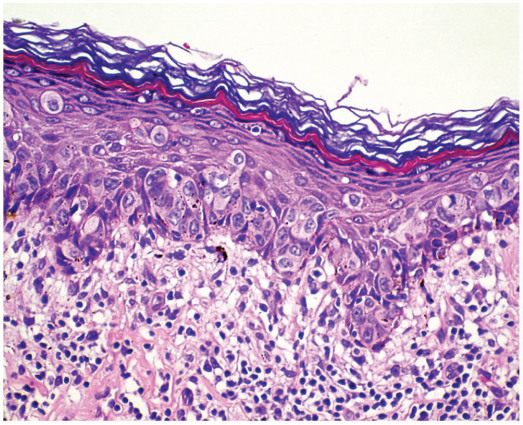

Fig. 1 Histopathology of the vulvar biopsy specimen showed pagetoid spreading of typical Paget's cells within the epidermal layer of the vulvar without underlying invasive carcinoma (H&E, x200)

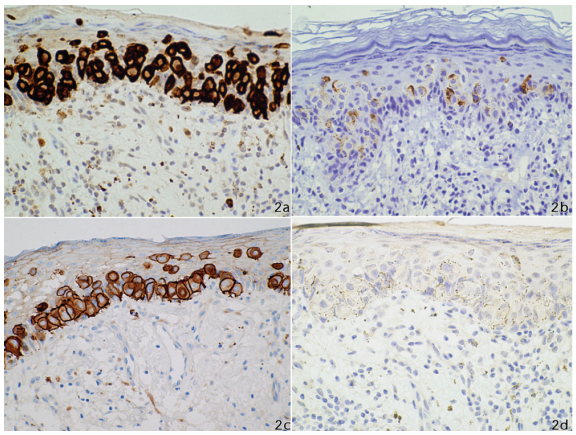

Fig. 2 Immunohistochemical study of vulva Paget's disease showed immunoreactivity for CK 7 (a), GCDFP-15 (b), HER-2/neu(c), but negative for CK20 (d) stain

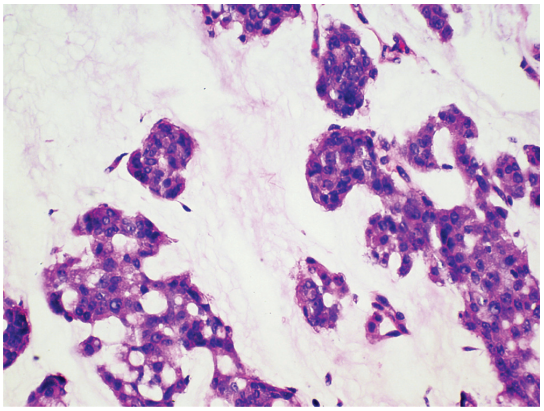

Fig. 3 Histopathology of the left breast mass specimen revealed invasive clusters of small uniform tumor cells floating in the pool of extracellular mucin (H&E, x100)

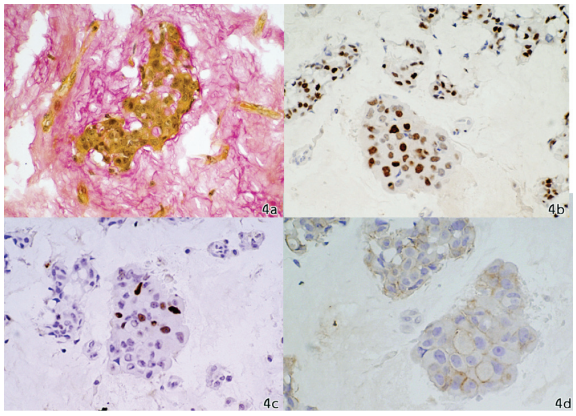

Fig. 4 The breast mass specimen showed positive mucicarmine stain (a) and immunoreactivity for ER (b), and PR (c), but negative for HER-2/neu (d) stain

Discussion

EMPD was first described by Radcliffe Croker in 1889 in penis and scrotum. The lesion is morphologically and histologically identical to mammary Paget's disease, which was described 15 years earlier by James Paget[1]. The common affected sites are apocrine rich areas, mainly in anogenital regions. The other rarer occurring sites in axilla, eyelid, and extraauditory canal have been reported[2]. The most common location is vulva. Vulvar Paget's disease usually occurs in postmenopausal Caucasian women, with median age of 70 years. The patient usually present with chronic vulvar itching with well-demarcated erythematous eczematous scalely patch or plaque[3,4]. The histopathological identification of unique Paget's cells, which show relatively large, having large nuclei, prominent nucleoli, and finely granular amphophillic to basophilic cytoplasm, spreading within the epidermal layer is the diagnostic criteria of Paget's disease[1,2]. The pathogenesis of EMPD has not been clearly understood. It has been recently subclassified into cutaneous and non-cutaneous type, based on the origin of neoplastic cells[4]. In the complete exclusion of spreading from the internal malignancy (noncutaneous type), the disease should be primary cutaneous typed EMPD. The use of special

Table 1. Summary of patients with co-excisting vulvar Paget's disease and breast carcinoma in English literatures

Year/author	Age (at time of vulvar EMPD diagnosis)/sex	The first presenting tumor	The second tumor/ period from the first tumor	Treatment of vulvar Paget's disease	Treatment of breast cancer	Tumor recurrence/metastasis		Outcome
						Vulva	Breast	
1954/ Bowman HE[5]	42/F	Vulvar EMPD	Lt. breast ca/ 7 years	Vulvectomy	MRM with RT	No	No	NED in 13 years
1963/ Helwig EB[6]	N/D	Anogenital EMPD	Breast ca/ 7 months	N/A	N/A	No	Metastasis to the axillary and supraclavicular LN, liver, bone, and head of the pancreas	Death from breast metastasis
	N/D	Anogenital EMPD	Breast ca/7 years	N/A	N/A	No	No	Death from unknown cause
1965/ Gupta RK[7]	56/F	DCIS	Anogenital EMPD/23 years	Wide local excision	MRM	N/A	N/A	Uneventful post-operation
1968/ Koss LG[8]	71/F	Rt. breast ca	Vulvar EMPD/ 8 years	Wide local excision	MRM	No	No	NED in 10 years
1971/ Boehm F[9]	56/F	Lt. MPD	Vulvar EMPD/ 2 years	Vulvectomy	MRM	No	Lt. supraclavicular LN metastasis from breast ca 5 years later	N/A
1971/ Fenn ME[10]	62/F	Breast ca, bcc, melanoma, ileal carcinoid	Vulvar EMPD/ 24 years	Hemivulvectomy	N/A	No	No	Alive
1972/ Fetherston WC[11]	71/F	Rt. breast ca	Vulvar EMPD/ 4 years	Wide simple vulvectomy	MRM	No	No	NED in 1 year
	67/F	Breast ca, bcc	Vulvar EMPD/ 2 years	Wide simple vulvectomy	MRM	No	No	NED in 3 year

bcc = basal cell carcinoma; ca = carcinoma; CMT = chemotherapy; DCIS = ductal carcinoma in situ; EMPD = extramammary Paget's disease; F = female; IDCA = invasive ductal carcinoma; ILCA = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; Lt. = left; MPD = mammary Paget's disease; MRM = modified radical mastectomy; N/A = not available; NED = no evidence of disease; RT = radiotherapy; Rt. = right

Table 1. (cont.)

Year/author	Age (at time of vulvar EMPD diagnosis)/sex	The first presenting tumor	The second tumor/ period from the first tumor	Treatment of vulvar Paget's disease	Treatment of breast cancer	Tumor recurrence/metastasis		Outcome
						Vulva	Breast	
1975/ Tsukada Y[12]	71/F	Rt. DCIS/ Lt. IDCA with MPD	Vulvar EMPD/ 27 years	Electron beam radiotherapy	Rt. mastectomy, Lt. MRM	1.5 year	No	N/A
	73/F	Concurrent Lt. IDCA, MPD and vulvar EMPD		Simple vulvectomy	MRM	No	N/A	NED in 13 months
1975/ Taylor PT[13]	76/F	Breast ca	Vulvar EMPD/ 39 years	Total vulvectomy	MRM	No	No	NED in 13 months
1975/ Friedrich EG[14]	66/F	Concurrent Rt. breast ca and vulvar EMPD		Total vulvectomy	MRM	N/A	N/A	N/A
1998/ Popiolek DA[15]	55/F	Concurrent Lt. IDCA, DCIS with MPD and vulvar EMPD		Rt. partial vulvectomy	MRM, tamoxifen	No	No	NED 2 years
1999/ Farrell AM[16]	57/F	Lt. IDCA, rectal ca	Vulvar EMPD/ 10 years	Simple vulvectomy	Mastectomy	Invasive adenocarcinoma/ 20 years	No	Death 1.5 years after recurrent
	83/F	Lt. IDCA	Anogenital EMPD/10 years	Wide excision	Mastectomy, tamoxifen	No	No	NED in 1.5 years
2009/ Spiliopoulos D[17]	63/F	Lt. IDCA	Vulvar EMPD/ 5 years	Simple vulvectomy	Lumpectomy with LN discussion, RT, CMT, tamoxifen	Recurrent in 4 and 18 months	MPD, DCIS, ILCA, LCIS 7 years from the breast cancer diagnosis	N/A

bcc = basal cell carcinoma; ca = carcinoma; CMT = chemotherapy; DCIS = ductal carcinoma in situ; EMPD = extramammary Paget's disease; F = female; IDCA = invasive ductal carcinoma; ILCA = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; Lt. = left; MPD = mammary Paget's disease; MRM = modified radical mastectomy; N/A = not available; NED = no evidence of disease; RT = radiotherapy; Rt. = right

stains and immunohistochemistry are often necessary to confirm the diagnosis as well as indicating the pathogenesis or cell origin of the disease. In the present case, the tumor cells of the vulva were positive immunohistochemical studies for LMWCK, CK7, GCDFP-15, and diastase-resistant PAS stain, but negative for CK20. Findings are supportive of the primary cutaneous type of EMPD over secondary from adjacent internal malignancy[1,3]. The association of this primary EMPD of the vulva with a coexisting breast cancer has been reported but rarely existing[5-17]. There were 17 cases of coexisting vulvar Paget's disease and carcinoma of the breast in review of the English literatures (Table 1). Three cases were firstly presented with vulvar Paget's disease, 11 cases had breast cancer on the first presentation, and three cases had concurrent tumor. The mean age of patients were 64.60 years old (ranged from 42 to 83 years old). In patients that firstly present with vulvar Paget's disease, the mean time to develop secondary tumor was 4.86 years. One case had breast cancer metastasis and death. In cases that firstly present with breast cancer, the mean time to develop secondary tumor was 13 years. One case had recurrent both vulvar Paget's disease and breast cancer in 4 months and 7 years, respectively. Another one had lymph node metastasis from breast cancer in 5 years. Two cases had only recurrent vulvar Paget's disease in 1.5 and 20 years (this case died 1.5 years after recurrent tumor). The hypothesis of cells of origin in primary cutaneous form is still unsettled, but mostly believed the concept of the intraepidermal cell of apocrine gland that analogous to Toker cells in normal lactiferous duct in origin[1,17]. The other theories include the migration from the underlying adenocarcinoma and the derivative of undifferentiated pluripotent stem cells of epidermis or adnexa[2,12]. Interestingly, the expression of HER2/neu may raise the possibility targeted therapy in these individuals[18]. To the authors' knowledge, even though there were few reported cases of this co-existing tumor, the concurrence of vulvar Paget's disease and mucinous breast carcinoma have not been documented before. In conclusion, primary breast cancer should be of concern in patients of vulvar Paget's disease, even though it is an uncommon association.

Potential conflicts of interest

None.

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โรคพาเจท (Paget's disease) ของปากช่องคลอดเกิดร่วมกับมะเร็งเต้านมชนิดสร้างเมือก (mucinous carcinoma): รายงานผู้ป่วย และทบทวนวรรณกรรม

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โรคพาเจทของปากช่องคลอดเป็นชนิดที่พบได้บ่อยที่สุดของโรคพาเจทที่เกิดนอกบริเวณเต้านม เซลล์เนื้องอกอาจเกิดจากมะเร็งรยางค์ของผิวหนังบริเวณนั้น หรือ ลุกลามจากมะเร็งอวัยวะภายใน โดยเฉพาะอย่างยิ่งมะเร็งของทวาร ลำไส้ใหญ่ อวัยวะสืบพันธุ์ หรือทางเดินปัสสาวะ แต่พบโรคร่วมกับมะเร็งเต้านมได้น้อย ผู้นิพนธ์รายงานผู้ป่วยหญิงไทยอายุ 46 ปี ซึ่งได้รับการวินิจฉัยเป็นโรคพาเจทของปากช่องคลอด ร่วมกับมะเร็งเต้านม สิ่งที่น่าสนใจในผู้ป่วยรายนี้คือ พบการแสดงออกของ HER2/neu เพิ่มขึ้นในชิ้นเนื้อพาเจทของปากช่องคลอด ซึ่งลักษณะดังกล่าวอาจเป็นทางเลือกในการรักษาแบบจำเพาะต่อเซลล์มะเร็งเป้าหมายด้วย anti-HER-2/neu antibody ในกรณีที่โรครุนแรงหรือมีการกลับเป็นซ้ำ โดยสรุป ควรตรวจหามะเร็งเต้านมในผู้ป่วยโรคพาเจทของปากช่องคลอดด้วย แม้ว่าจะเป็นโรคที่พบร่วมกันได้ไม่บ่อย