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Case Report

Cytological diagnosis of patients with extramammary Paget's disease of the vagina

Qijun Chen[1], Yan Qiu[2], Lian Xu[1], Xiao Tang[1], Kaixuan Yang[1], Wei Wang[1]

[1]Department of Pathology, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, West China Second Hospital, Sichuan University, Chengdu, Sichuan, China; [2]Department of Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

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Abstract: Extramammary Paget's Disease (EMPD), also called extramammary eczematoid carcinoma, is classified as primary and secondary EMPD based on the pathogenic mechanism. The origin of the Paget cells of primary EMPD is still controversial. Apocrine or eccrine gland cells, such as Bartholin's gland, and intraepidermal pluripotent keratinocyte stem cells have been considered possible originating cells of primary EMPD. Secondary EMPD usually originates from the malignancies of rectum, cervix, and urinary bladder. We report a case of a 58-year-old woman suffering from intermittent vaginal bleeding for half a year, who was diagnosed as EMPD by vaginal cytology.

Keywords: Vagina, extramammary Paget's disease

EMPD is a rare intraepithelial adenocarcinoma, which accounts less than 2% of all vulvar maliganancies [1]. The majority of EMPD are observed in apocrine glands, including scrotum, penis, labia majora, labia minora, and vagina. Rarely, EMPD may also be found in perianal skin, perineum, axilla, etc. Also, Paget cells of perineum EMPD may infiltrate into peripheral organs, such as cervix, rectum, scrotum, or urinary tract [2].

Case report

A-58-year-old postmenopausal woman complained of intermittent vaginal bleeding and a foreign body sensation for half a year with a history of progression for 2 months. She underwent lesionectomy 2 year ago for eliminating perianal EMPD. On physical examination, significant scar was observed on the perianal skin. The vaginal opening, lower segment (1/3) of anterior vaginal wall, lower segment (1/2) of posterior vaginal wall, and bilateral vaginal walls had poor elasticity and severe contact bleeding. The cervix was smooth. No abnormalities were found in the uterine body and bilateral adnexa. Vaginal fluid-based cytology (LCT) and the conventional Papanicolaou smears of the vagina and HPV-DNA detection were performed.

In this case, tumor cells were detected in the vaginal fluid-based cytology test (LCT) and the conventional papanicolaou smears. The cytologic characteristics of the tumor were as follows: since EMPD is usually susceptible to infections, inflammatory infiltration of neutrophils, or lymphocytes were observed in the smears. Some squamous cells and necrotic debris were also shown in the slides. We also found several Paget tumor cells, which provided direct evidence for diagnosis of this case. Paget tumor cells existed individually or arranged into clusters and nests by microscopy. The tumor cells were usually large, polygonal, or lace-like with one or two round, oval, or irregular medium sized nuclei. Some tumor cells were signet ring-shaped since their nuclei were pushed to the edge of the cell. The nuclei were dark stained and often with nuclear vacuoles. Most nuclei had a single nucleolus while multiple nucleoli were observed in one nucleus occasionally. The cytoplasm of most tumor cells was abundant, light stained, and clear with an irregular edge and often contains vacuoles of varying size, while a small subset of Paget cells had no cyto-

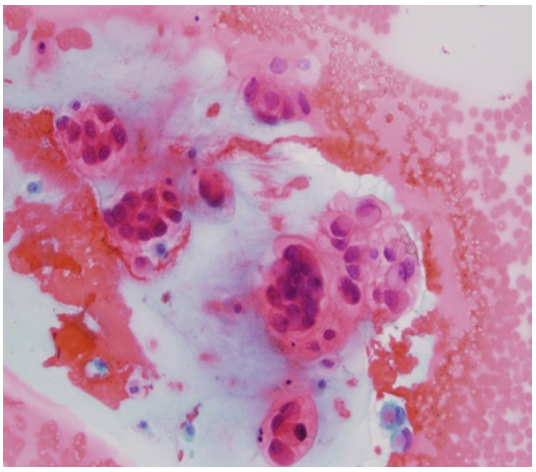

Figure 1. Pap smear. Paget tumor cells exist individually or arranged into clusters and nests. The tumor cells are usually large, polygonal, or lace-like with one or two round, oval, or irregular medium sized nuclei. The nuclei are dark stained. The cytoplasm of most tumor cells is abundant, light stained, and clear with an irregular edge and often contains vacuoles of varying size. Some tumor cells are signet ring-shaped. ×400.

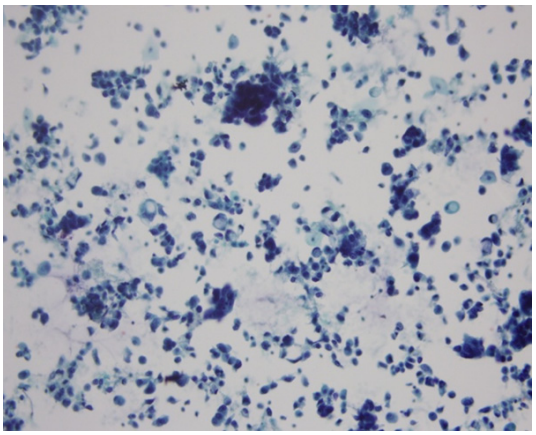

Figure 2. Vaginal fluid-based cytology test (LCT). Inflammatory infiltration of neutrophils and lymphocytes are observed in the smears. Some squamous cells and necrotic debris are also shown in the slides. Paget tumor cells exist individually or arranged into clusters and nests. Some tumor cells are signet ring-shaped. The nuclei are dark. ×200.

plasm but a naked nucleus. In addition, mitosis could be observed at high magnification. (**Figures 1**-**3**). The result of HPV-DNA test was negative. Based on the above cytological features and clinical history, the patient was diagnosed with perianal EMPD involving the vagina.

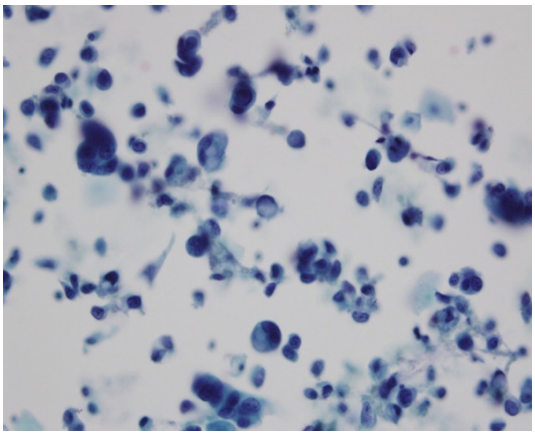

Figure 3. Vaginal fluid-based cytology test (LCT). Paget tumor cells are large, polygonal, or lace-like with one or two round, oval, or irregular medium sized nuclei. Some tumor cells are signet ring-shaped. Nuclei are dark and often have nuclear vacuoles. ×400.

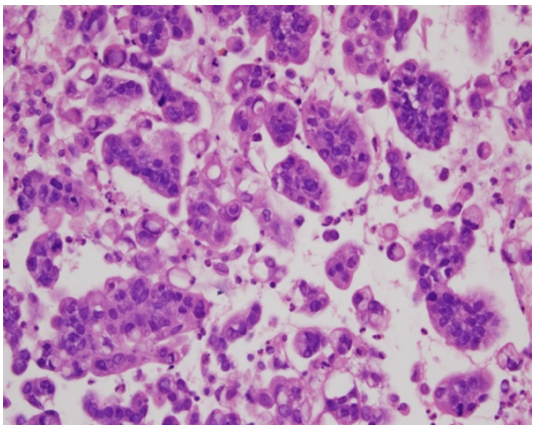

Figure 4. Vaginal biopsy. Paget cells present singly or occur in packed clusters. Most of these cells are large with abundant pale cytoplasm and distinct borders, which present a balloon-like shape. Large darknuclei with prominent nucleoli can be seen. HE ×400.

Subsequently, the patient underwent vaginal posterior wall biopsy. During the surgery, it was found that the posterior wall of the vagina, the perineal body, the lower part of labia majora, and the perianal tissue were firm, congested, and had scattered ulcers. The lesion of posterior vaginal wall was removed for further diagnosis. The texture of removed tissue was firm and the incision was difficult to suture. Clinical primary diagnosis was post-operative EMPD with vaginal involvement. Microscopically, Paget cells presented singly or occurred in packed clusters. Most of these cells were large

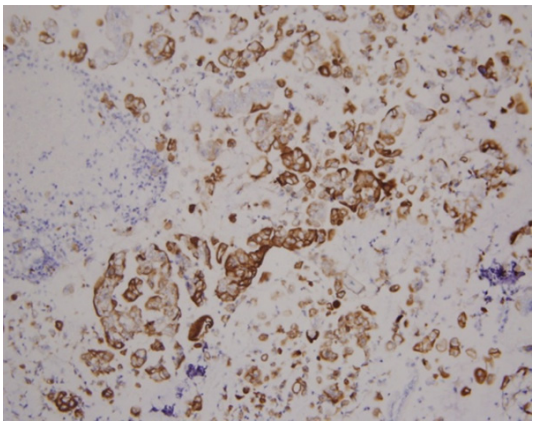

Figure 5. Immunohistochemistry showed the Paget cells are positive for CK7. DAB ×200.

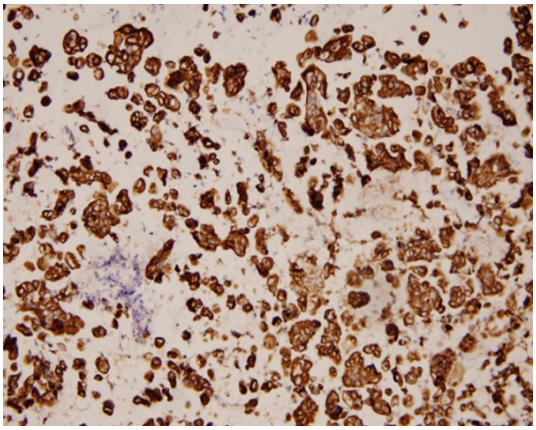

Figure 6. Immunohistochemistry showed the Paget cells are positive for GCDFP-15. DAB ×200.

with abundant pale-stained cytoplasm and with distinct borders, which present a balloon-like shape. Large dark-stained nuclei with prominent nucleoli can be observed microscopically, similar to the features of Paget cells in the cytologic test (**Figure 4**). Immunohistochemical staining demonstrated that Paget tumor cells were focally positive for muc-2, CK7, CEA, GCDFP-15, P16 (**Figures 5**, **6**) and were negative for CK20, P63, CDX2, S-100, ER, PR. The pathological diagnosis of vaginal biopsy was perianal EMPD with vaginal involvement.

We reviewed pathological slides from this patient, which were obtained 2 years ago. Invasion of Paget tumor cells were observed in the epidermis. The tumor cells were large and most of them had a large nucleus and prominent nucleoli. The cytoplasm of tumor cells was

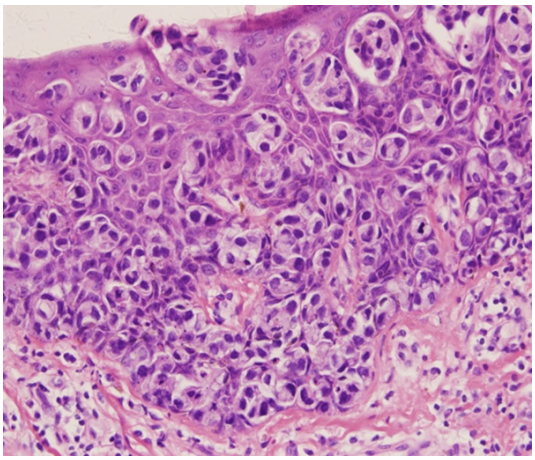

Figure 7. Invasion of Paget tumor cells is observed in the epidermis of perianal EMPD. The tumor cells are large and most of them have large nuclei and prominent nucleoli. The cytoplasm of tumor cells is abundant and light. In some neoplastic cells, the nucleus is peripheral and cells are signet ring-shaped. HE ×400.

abundant and light staining. In some neoplastic cells, the nucleus was squeezed to the side and presented as signet ring-shaped. The borders between tumor sites and the superficial dermis were ambiguous (**Figure 7**).

Discussion

Clinical features and pathogenesis

EMPD most commonly involves regions with distribution of apocrine glands, including scrotum, penis, labia majora, labia minora, and vagina. In a few patients, EMPD may be observed in perianal skin, perineum, axilla, etc. Most EMPD lesions are single while few of them occur multiply. Vulvar EMPD is more common in females than in the corresponding skin in males and almost all female patients are postmenopausal [3] and over 60 years old. Long-term perineal EMPD can invade surrounding organs or tissues of patients, such as vagina, cervix, anus, rectum, or urinary tract. The borders of the lesions usually appear irregular, slightly elevated, and demarcated. EMPD present as a verrucous, nodular, or papillary brown and central flushing plaque with scaling erosion, exudate, superficial scales, or crusts [4]. The most common symptoms are varying degrees of pruritus. The presence of pain and bleeding is reported to be more common in patients with invasive disease.

Most of the patients with EMPD do not have tumors in deep tissue. The recurrence rate after surgery is about 30%, but no metastasis occurs. About 10% of EMPD may develop to invasive carcinoma, then further progress to metastasis [3].

Pathological diagnosis

The cytologic features of this patient were similar to those reported in the previous literature [5-10]. Paget tumor cells existed individually or were arranged into clusters and nests. The tumor cells were usually large, polygonal, or lace-like with one or two round, oval, or irregular medium-sized nuclei. Some tumor cells were signet ring-shaped with nuclei pushed to the edge of the cell. The nuclei are dark-stained and often have nuclear vacuoles. Most nuclei have a single nucleolus while multiple nucleoli are observed occasional cells. The cytoplasm of most tumor cells is abundant, light-stained and clear, with irregular edges and often contains vacuoles of varying size, while small subsets of Paget cells have no cytoplasm but a naked nucleus. In addition, mitosis may be observed at high magnification. Cytologic diagnosis of Paget disease must be combined with a previous history or assistance of immunocytochemistry. On vaginal biopsy Paget cells presented singly or occurred in packed clusters.. Most of these cells were large with abundant pale stained cytoplasm. Large dark stained nuclei with prominent nucleoli can be observed microscopically. Signet-ring like cells and adenoid structure are commonly appeared in EMPD lesions. Paget cells were positive for CK7, CEA, and GCDFP-15 which supports our final diagnosis [11-13] Positive expression of P16 in Paget cells also has been reported in previous literature [14]. In this case, Paget cells were focally positive for P16. The significance of P16 positive expression in Paget cells is still unclear, but we must be wary not to confuse EMPD with squamous epithelial lesions.

The differential diagnoses by cytology includes squamous epithelial high-grade intraepithelial neoplasia (HSIL), endometrial cancer, and endocervical adenocarcinoma. Squamous intraepithelial tumor cells usually present as small, single, scattered with irregular nucleus, high nucleus/cytoplasm ratio and clumped deep staining chromatin, which can help us differentiate EMPD from HSIL. Adenocarcinoma cells of endometrial cancer may also contain clear cytoplasm as in EMPD. EPMD has no three-dimensional balls and eosinophilic cytoplasm. Signet-like cells usually can be observed in endocervical adenocarcinoma but appeared in EMPD commonly [10]. In addition, immunochemistry will be effective for distinguishing EMPD from other disease in clinical practice. Clinical history is also very important for providing an accurate diagnosis. One of main histological differential diagnoses is vaginal VaIN. Immunohistochemistry interpretations for P63, CK7, CEA, and GCDFP-15 are useful to provide a final diagnosis. Additionally, superficial spreading malignant melanoma (SSMM) and immunohistochemistry for S-100, HMB-45, and melan-A will be useful to distinguish EMPD from SSMM [15]. It is also necessary to exclude metastatic poorly differentiated cancer, such as metastatic sites originating from rectal cancer.

Treatment

The treatment and prognosis of vulvar EMPD depends on the types of lesion. Paget cells that are confined to the epithelium or not are important for evaluating the prognosis of EMPD. Primary intraepithelial Paget disease is usually a kind of indolent, painless, and superficial tumor. For intraepithelial lesions, conservative resection (wide excision) with a gross margin 2-3 cm and resection to the fascia is recommended. For vulvar EMPD patients with invasive lesions, or with different histopathological types of skin adnexal or vulvar adenocarcinomas, ipsilateral inguinal lymph node excision should be performed. If Paget cells are observed in the surgical margins microscopically, EMPD lesions have not been completely removed. On this occasion, an enlarged partial vulvectomy or total vulvectomy should be provided [3, 16, 17]. If the recurrence occurs in the surrounding tissue after EMPD surgical excision, and the recurrence is not associated with adenocarcinoma, only conservative treatment is required. Usually, superficial resection or topical therapy is recommended and imiquimod is most commonly used in clinical practice [18, 19]. Other new therapies including radiation therapy, laser ablation, phototherapy, and topical therapy with 5-fluorouracil are also suggested in clinical work [20]. In this case, the patient with perianal EMPD recurred after surgery, and

the lesion was widely distributed. Topical therapy was adopted to control the progression of this disease and the prognosis was acceptable.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei Wang, Department of Pathology, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, West China Second Hospital, Sichuan University, People's South Road, Chengdu 610041, Sichuan, China. Tel: (86)186-0801-9998; E-mail: bearwin2000@126.com

References

[1] Parker LP, Parker JR, Bodurka-Bevers D, Deavers M, Bevers MW, Shen-Gunther J, Gershenson DM. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. Gynecol Oncol 2000; 77: 183-9.

[2] In: Kurman RJ, Ellenson LH, Ronnett BM, editors. Blaustein's pathology of the female genital tract. 6th edition. New York, NY: Springer; 2011. pp. 82Y6.

[3] Fanning J, Lambert HC, Hale TM, Morris PC, Schuerch C. Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, andrecurrence after surgical excision. Am J Obstet Gynecol 1999; 180: 24-7.

[4] Brainard JA, Hart WR. Proliferative epidermal lesions associated with anogenital Paget's disease. Am J Surg Pathol 2000; 24: 543-52.

[5] Costello TJ, Wang HH, Schnitt SJ, Ritter R, Antonioli DA. Paget's disease with extensive involvement of the female genital tract initially detected by cervical cytosmear. Arch Pathol Lab Med 1988; 112: 941-4.

[6] Gu M, Ghafari S, Lin F. Pap smears of patients with extramammary Paget's disease of the vulva. Diagn Cytopathol 2005; 32: 353-357.

[7] Westacott LS, Cominos D, Williams S, Knight B, Waterfield R. Primary cutaneous vulvar extramammary Paget's disease involving the endocervix and detected by Pap smear. Pathology 2013; 45: 426-8.

[8] Clayton EF, Rubin SC, Dumoff KL. Paget cells in endometrial and endocervical curettings in a patient with recurrent vulvar Paget's disease. Int J Surg Pathol 2014; 22: 374-377.

[9] Gilliland K, Knapik J, Wilkinson EJ. Cytology of vulvar/vaginal paget disease: report of a case and review of the literature. J Low Genit Tract Dis 2013; 17: e26-30.

[10] Davis G, Anderson L, Pather S. Extramammary paget's disease mimicking localized malignancy on cervical cytology. Diagn Cytopathol 2016; 44: 931-934.

[11] Goldblum JR, Hart WR. Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. Am J Surg Pathol 1997; 21: 1178-1187.

[12] Crawford D, Nimmo M, Clement PB, Thomson T, Benedet JL, Miller D, Gilks CB. Prognostic factors in Paget's disease of the vulva: a study of 21 cases. Int J Gynecol Pathol 1999; 18: 351-9.

[13] Liegl B, Leibl S, Gogg-Kamerer M, Tessaro B, Horn LC, Moinfar F. Mammary and extramammary Paget's disease: an immunohistochemical study of 83 cases. Histopathology 2007; 50: 439-447.

[14] Sah SP, McCluggage WG. Florid vulval Paget disease exhibiting p16 immunoreactivity and mimicking classic VIN. Int J Gynecol Pathol 2013; 32: 221-227.

[15] Hill SJ, Berkowitz R, Granter SR, Hirsch MS. Pagetoid lesions of the vulva: a collision between malignant melanoma and extramammary Paget disease. Int J Gynecol Pathol 2008; 27: 292-6.

[16] Baehrendtz H, Einhorn N, Pettersson F, Silfverswärd C. Paget's disease of the vulva: the Radiumhemmet series 1975-1990. Int J Gynecol Cancer 1994; 4: 1-6.

[17] Crawford D, Nimmo M, Clement PB, Thomson T, Benedet JL, Miller D, Gilks CB. Prognostic factors in Paget's disease of the vulva: a study of 21 cases. Int J Gynecol Pathol 1999; 18: 351-9.

[18] MacLean AB, Makwana M, Ellis PE, Cunnington F. The management of Paget's disease of the vulva. J Obstet Gynaecol 2004; 24: 124-8

[19] Hatch KD, Davis JR. Complete resolution of Paget disease of the vulva with imiquimod cream. J Low Genit Tract Dis 2008; 12: 90-4.

[20] Feldmeyer L, Kerl K, Kamarashev J, deViragh P, French L. Treatment of vulvar Paget disease with topical imiquimod: a case report and review of the literature. J Dermatol Case Rep 2011; 5: 42-6.