Cytology of Vulvar/Vaginal Paget Disease: Report of a Case and Review of the Literature

Kelly Gilliland, DO, Jacquelyn Knapik, MD, and Edward J. Wilkinson, MD
University of Florida, Gainesville, FL

■ **Abstract**

Objective. We describe a woman with a long-standing history of Paget disease involving the vulva and vagina, who was previously diagnosed with a high-grade squamous lesion, atypical glandular cells, and adenocarcinoma on various different yearly Pap tests.

Materials and Methods. This article is a case report of this patient and a review of the literature concerning the cytology of Paget disease.

Results. By reviewing Pap test cytology findings, Paget cells were identified as atypical cell groups with enlarged nuclei and occasional prominent nucleoli and further characterized by immunoreactivity to carcinoembryonic antigen and gross cystic disease fluid protein that distinguished them from high-grade squamous lesion.

Conclusions. By enabling early diagnosis, regular surveillance, and identification of Paget cells by cytopathology, the Pap test becomes a valuable tool in identifying initial and recurrent Paget disease when it involves the vagina. ■

Key Words: Paget disease, extramammary, carcinoembryonic antigen, gross cystic disease fluid protein, Pap test

Extramammary Paget disease is a rare intraepithelial adenocarcinoma that represents less than 2% of all vulvar neoplasms [1]. The disease may persist for years and is prone to recurrence because of clinically ill-defined areas of extension and multicentric foci of the tumor cells. Vulvar Paget disease may be classified as a primary cutaneous disease or as a secondary disease, associated with a colorectal, bladder, or other adenocarcinomas [2].

The Paget cell of primary cutaneous Paget disease arises from a multipotent cutaneous stem cell with several possible precursor cells. The cells may exhibit features similar to mammary or extramammary Toker cells, apocrine or eccrine gland cells such as from the Bartholin gland, or secondarily colorectal or transitional bladder mucosa [3, 4].

In most Pap tests, immunocytochemistry is not used and not necessary; the lesions are predominantly squamous-derived neoplasms. However, in the rare case of Paget disease, the cells can mimic high-grade lesions; therefore, a clinical suspicion or previous diagnosis make the utilization of immunocytochemistry extremely helpful. Primary cutaneous Paget cells are generally immunoreactive for glandular markers such as carcinoembryonic antigen (CEA), B72.3, and gross cystic disease fluid protein (GCDFP). They are also immunoreactive for cytokeratins CAM 5.2 and cytokeratin 7 (CK-7). Special stains using mucicarmine, periodic acid–Schiff, Alcian blue, and colloidal iron also may prove useful in identifying Paget cells by staining the glycogen and mucin-like material in the cytoplasm [2].

As an important diagnostic differential, superficial spreading malignant melanoma may resemble cutaneous Paget disease. The cells of melanoma are generally immunoreactive for melanoma markers such as HMB45 and melan-A and Paget cells are immunonegative. Melanoma also is generally S-100 immunoreactive; however, in Paget cases, S-100 may also be immunoreactive in the melanocytic and dendritic cell hyperplasia that may be associated with the disease. Cytokeratin 20 (CK-20) is usually negative

Reprint requests to: Kelly Gilliland, DO, University of Florida College of Medicine, Department of Pathology, PO Box 100275, Gainesville, FL 32610-0275. E-mail: kellysgilliland@gmail.com

The authors have declared they have no conflicts of interest.

in primary vulvar Paget disease; however, those secondary cases arising from the colorectal region or bladder can be immunoreactive, in which the colorectal associated cases are CK-20 reactive without CK-7 expression. Paget-like cases, referred to as pagetoid urothelial intraepithelial neoplasia, related to urothelial carcinoma of the bladder and urethra, are often both CK-7 and CK-20 reactive and may express uroplakin III [5, 6].

It is important in Paget disease to relieve the patient's symptoms and exclude invasive disease. The predominantly used invasive treatment for Paget disease is local surgical excision with a 1-cm margin of normal skin. Microscopic foci of disease may be difficult to identify at the time of surgery, therefore, leading to recurrences that are typically only intraepithelial disease and can be treated more conservatively with a superficial excision or topical therapy using imiquimod [7]. Other newer treatments include radiotherapy, laser ablation, photodynamic therapy, and topical use of 5-fluorouracil [8].

CASE REPORT

The patient is a 70-year-old woman with an extensive history of recurrent Paget disease involving both the vulva and the vagina. Her past medical history consists of hypertension, hypothyroidism, gastroesophageal reflux disease, urinary urgency, and mitral valve prolapse. The patient had a total abdominal hysterectomy many years before the Paget diagnosis, secondary to uterine leiomyomata; therefore, no cervical screening Pap tests or colposcopies were performed.

After initial diagnosis at age 61, she underwent a simple vulvectomy and partial vaginectomy for Paget disease that originated in the vulva and extended to the vaginal margins. One year later, she had a recurrence on direct vulvar biopsy and underwent a wide local excision involving both the vulva and the vagina. The diagnosis was Paget disease extending to all margins. The following year, the first vaginal Pap test of record was diagnosed as adenocarcinoma, not otherwise specified, and a follow-up direct vulvar biopsy showed Paget disease for which the patient underwent a repeat wide local excision with rotational flap. The tumor involved 3 separate margins. The next vaginal Pap test from 1 year later was diagnosed as atypical glandular cells – not otherwise specified (AGC-NOS). Another excision followed in a year with Paget disease involving both the vulva and extending to the vagina. The next follow-up vaginal Pap tests were diagnosed as HSIL, then 1 year later AGC – favor neoplastic, and then HSIL again 3 months later. Eventually, the patient underwent 1 more excision with a total of 5 wide local excisions over a course of 7 years. Again, the diagnosis was Paget disease; this specimen had external margins free from Paget disease.

As per the history, the patient was followed up with intermittent vaginal cuff cytology with diagnoses ranging from AGC-NOS, AGC – favor neoplastic, adenocarcinoma to HSIL. Most recently, the patient had a suspicious lesion on the left lateral vulva and left periurethral area, which was directly examined by biopsy. This revealed vulvar Paget disease with surface ulceration. The Paget disease extended to the lateral margin of resection. Because of extensive scarring, a blind vaginal Pap test was done. Atypical glandular cells were identified consistent with the patient's history of Paget disease.

Cytologically, the vaginal cuff Pap test showed atypical glandular cells in clusters and single cells with a high nuclear-to-cytoplasmic ratio, pale cytoplasm, and some prominent nucleoli. Additional ThinPrep Pap slides were ordered and immunocytochemistry was performed to aide in the distinction from a squamous lesion. The cells were strongly immunoreactive to CEA and focally immunoreactive to GCDFP. The immunoprofile and cytologic features supported that the cells were related to her previous diagnosis of vulvar Paget disease. The previous histology specimen and accompanying immunohistochemistry were compared with the cytology findings. Immunohistochemistry had been performed on the previous vulvar and vaginal excision in which the cells were reactive for CEA (essentially all cells), focally for GCDFP and negative for S-100. In addition, studies were performed with CK-7 and CK-20 to enable the distinction of the origin of the Paget disease. The cells were immunoreactive for CK-7 and immunonegative for CK-20, thereby supporting the diagnosis of primary vulvar/vaginal Paget disease (histology only).

The most recent vaginal cuff cytology specimen showed malignant appearing cells located predominantly in loose clusters (see Figures 1A, B). However, it has been noted that cells may appear singly or in glandlike clusters. The atypical enlarged glandular cells had high nuclear-to-cytoplasmic ratios with central to eccentric nuclei. Within the nucleus, the chromatin pattern was fine with prominent nucleoli noted in some of the cells. The abundant cytoplasm was granular with no obvious large vacuoles or pigment. Comparison of the cytology specimen with the previous biopsy revealed similar large cells with enlarged nuclei, prominent nucleoli, and abundant cytoplasm infiltrating the epidermis (see Figures 1C, D).

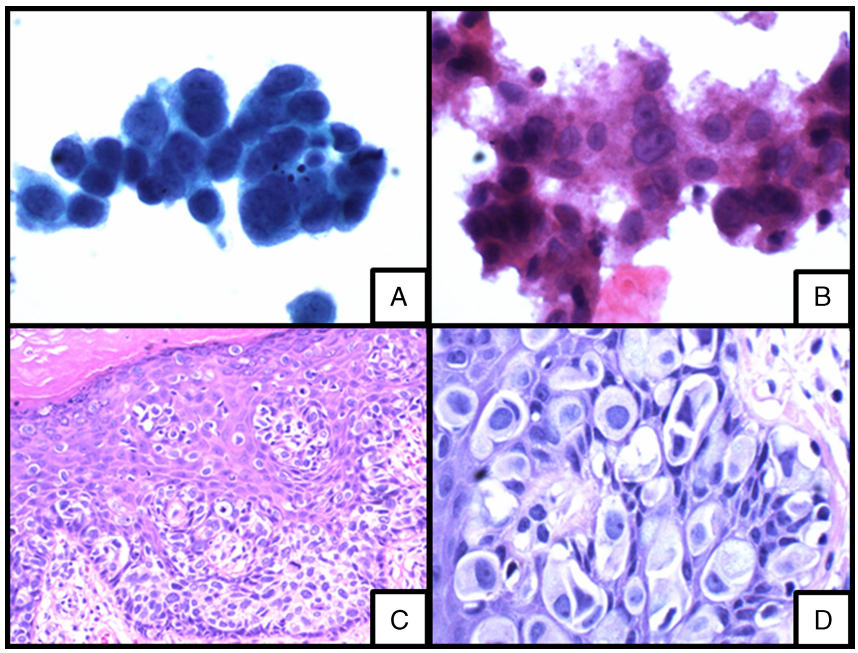

Figure 1. A, ThinPrep Pap test: groups of Paget cells (Pap, ×600). B, ThinPrep Pap test: groups of Paget cells (hematoxylin-eosin, ×600). C, Surgical excision of the vulva with Paget disease (hematoxylin-eosin, ×200). D, Surgical excision of the vulva with Paget (hematoxylin-eosin, ×600).

Immunocytochemical markers were used on the additionally prepared unstained thin-layer Pap slides. The atypical cells were diffusely immunoreactive with CEA, monoclonal and polyclonal (see Figure 2A), and focally reactive to GCDFP (see Figure 2B). Of note, mucicarmine was attempted, and despite published success, we were unable to detect any staining in the Paget cells. The immunoprofile correlated well with the primary tissue excision profile in which polyclonal CEA was immunoreactive in all cells (see Figure 2C) and GCDFP was reactive focally

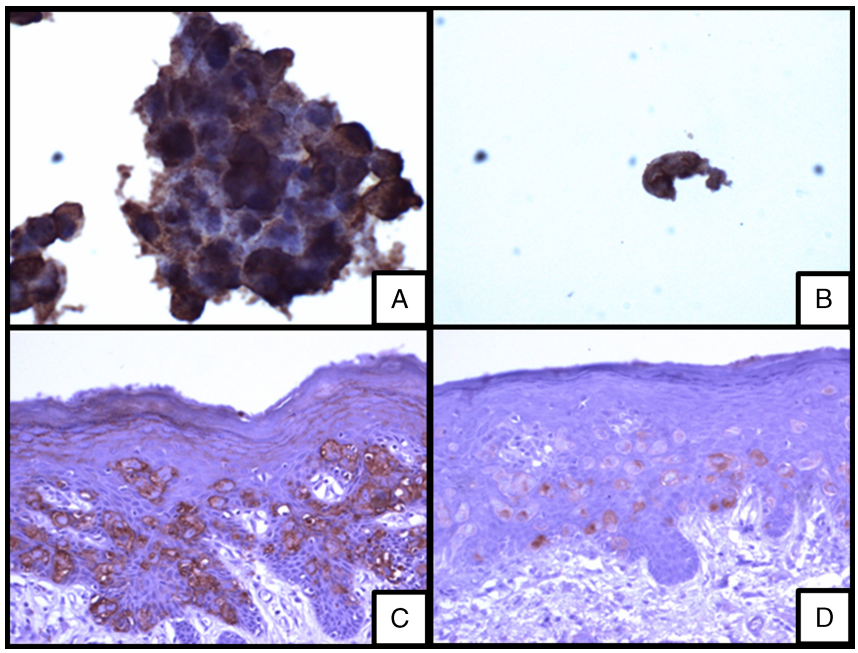

Figure 2. A, ThinPrep Pap test: groups of Paget cells (immunostain CEA, polyclonal, ×600). B, ThinPrep Pap test: Paget cells (immunostain GCDFP, ×600). C, Surgical excision of the vulva with Paget disease (immunostain CEA, polyclonal, ×200). D, Surgical excision of the vulva with Paget (immunostain GCDFP, ×200).

in some cells (see Figure 2D). These findings supported the diagnosis of Paget disease of cutaneous type.

DISCUSSION

Extramammary Paget disease of the vulva is a relative rarity that was first described in 1901 by Dubreuilh [9]. This neoplastic process may be a primary cutaneous neoplasm, originating from the vulva, or a secondary disease, originating from an adenocarcinoma from the anorectum, other glandular site, or bladder. Approximately 70% to 85% of vulvar Paget cases are primary, with no underlying carcinoma, as opposed to Paget disease of the breast, which is associated with underlying ductal carcinoma in situ or invasive carcinomas in most cases [10].

Routine Pap tests are very reliable in detecting squamous lesions, which have markedly irregular nuclear contours, high nuclear-to-cytoplasmic ratios, coarse chromatin, and hyperchromasia. However, glandular lesions can be much more difficult to diagnose; there is some overlap in cytologic features between glandular and squamous lesions. Cytologically, the cells of Paget disease are large, with a high nuclear-to-cytoplasmic ratio, abundant pale cytoplasm, round vesicular nuclei, prominent nucleoli, and no to rare mitotic figures [11]. These rare cases of Paget disease may easily be misdiagnosed as high-grade lesions as in this case. Also, the cessation of routine screening in older patients may necessitate a strong clinical suspicion of Paget disease to initiate cytology or biopsy testing. Noting that the diagnosis is rarely made using a cytology specimen. Instead, a tissue biopsy is a more reliable method with identification of the cells in the deep layers of the epidermis, with clusters and single cells migrating toward the surface, so-called "pagetoid spread." The additional use of cytology screening of the vulva, vagina, and periurethral tissues can be of benefit by supplementing the biopsy diagnosis by determining the extent of spread, particularly as in this patient because of extensive scarring and lack of good visibility.

Review of the literature shows few studies using exfoliative cytology to identify Paget cells in vulvar and vaginal lesions. The first case report of using cytology to detect malignant Paget cells of the vulva was described by Bennington et al. [12] in 1966. The cells were diagnosed as suspicious for malignancy and stained with periodic acid–Schiff to aid with the diagnosis. Masukawa and Friedrich [13] described 5 cases in which abrasive cytology was used to identify cells with increased nuclear-to-cytoplasmic ratio and multiple nucleoli consistent with Paget disease. Guarner and Cohen [14] presented the first case report that used immunocytochemistry to identify Paget cells on a cytology specimen. Their cytology diagnosis from the Pap smear was described as a large cell nonkeratinizing carcinoma. The cells appeared mostly in clusters with high nuclear-to-cytoplasmic ratios, large nucleoli, and clumped chromatin. A mucicarmine stain was positive for mucin, and 4 antibodies were immunoreactive, namely, MAK 6, EMA, CEA, and GCDFP-15, in the Paget cells confirming the diagnosis. Costello et al. [15] describe a case in which pleomorphic Paget cells with vacuolated cytoplasm were detected initially by Pap smear in a patient with extensive disease. Several additional studies have touted the use of cytology as an aide to the diagnosis of Paget disease that may help in preoperative detection and demarcation of the lesion [16–20]. Brown and Wilkinson [21] described a case involving the use of a vaginal cytology specimen to detect a high-grade malignancy consistent with a secondary vulvar Paget disease of urothelial origin. The vulvar resection specimens were immunoreactive for CK-7 and CK-20 and uroplakin III, which supported the diagnosis of urothelial carcinoma. Gu et al. [22] encountered 3 cases of extramammary Paget disease involving the vulva and vagina in which the cells in the cytology were described as enlarged and hyperchromatic with high nuclear-to-cytoplasmic ratio cells, rare signet ring cells, and cells within cells. The cells were both single and within sheets. A case report by Klapsinou et al. [23] recognized the utility of vulvar and vaginal brushings for detecting Paget cells described in their report as moderately enlarged, singly or in loose groups, with vesicular nuclei, clear cytoplasm, and prominent nucleoli. These authors advocate the use of screening cytology with histology specimen biopsies necessary to confirm the diagnosis.

A study by Parker et al. [24] determined that the mean time to follow-up from onset of symptoms was 1.88 years in Paget disease. This delay in receiving treatment may translate to worse outcome, particularly in those patients with an underlying carcinoma or invasive Paget disease. The use of the follow-up Pap tests and vulvar examination with vulvar biopsy as indicated is of value to identify Paget disease initial presentations or recurrences. The use of immunocytochemistry is of additional great value to identify Paget cells on biopsy or cytology specimens in distinction from high-grade squamous lesions.

REFERENCES

1. Parker LP, Parker JR, Bodurka-Bevers D, Deavers M, Bevers MW, Shen-Gunther J, et al. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. *Gynecol Oncol* 2000;77:667–71.

2. Kurman RJ, Ellenson LH, Ronnett BM, eds. *Blaustein's Pathology of the Female Genital Tract*. 6th ed. New York, NY: Springer; 2011:82–6.

3. Willman JH, Golitx LE, Fitzpatrick JE. Vulvar clear cells of Toker precursors of extramammary Paget's disease. *Am J Dermatopathol* 2005;27;185–8.

4. Kuan SF, Montag AG, Hart J, Krausz T, Recant W. Differential expression of mucin genes in mammary and extramammary Paget's disease. *Am J Surg Pathol* 2001;25:1469–77.

5. Goldblum JR, Hart WR. Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. *Am J Surg Pathol* 1997;21:1178–87.

6. Wilkinson EJ, Brown HM. Vulvar Paget disease of urothelial origin: a report of three cases and a proposed classification of vulvar Paget disease. *Hum Pathol* 2002;33:549–54.

7. Hatch KD, Davis JR. Complete resolution of Paget disease of the vulva with imiquimod cream. *J Low Genit Tract Dis* 2008;12:90–4.

8. 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.

9. Dubreuilh W. Paget's disease of the vulva. *Br J Dermatol* 1901;13:407–13.

10. Piura B, Raninovich A, Dgani R. Extramammary Paget's disease of the vulva: report of five cases and review of the literature. *Eur J Gynaecol Oncol* 1999;20:98–101.

11. Koss LG, Melamed MR. *Diagnostic Cytology and Its Histopathologic Bases*. 5th ed. Philadelphia, PA: J. B. Lippincott Company; 2006:482–3.

12. Bennington JL, Smith DC, Figge DC. Detection of cells from extramammary Paget's disease of the vulva in a vaginal smear. Report of a case. *Obstet Gynecol* 1966;27:772–5.

13. Masukawa T, Friedrich EG. Cytopathology of Paget's disease of the vulva: diagnostic abrasive cytology. *Acta Cytol* 1978;22:476–8.

14. Guarner J, Cohen C. Vulvar Paget's disease. Cytologic and immunohistologic diagnosis of a case. *Acta Cytol* 1988;32:727–30.

15. 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.

16. Kashimura Y, Kashimura M, Horie A. Cytologic, histologic, DNA ploidy and electron microscopic analyses of a case of vulvar Paget's disease. *Anal Quant Cytol Histol* 1989;11:413–8.

17. Kuhn W, Kubler HC, Rummel HH. Cytologic diagnosis of Paget's disease of the vulva. *Geburtschilfe Frauenheilkd* 1989; 49:67–9.

18. Yu BK, Lai CR, Yen MS, Tou NF, Chao KC, Yuan CC. Extramammary Paget's disease found by abnormal vulvar brush sampling. *Eur J Gynaecol Oncol* 2002;23:35–6.

19. Castellano Megias VM, Ibarrola de Andres C, Martinez Parra D, Lara Lara I, Perez Palacios C, Conde Zurita JM. Cytology of extramammary Paget's disease of the vulva. A case report. *Acta Cytol* 2002;46:1153–7.

20. Funamoto Y, Haba R, Kobayashi TK, Kushida Y, Matsunaga T, Shiota A, et al. Cytologic diagnosis of vulvar Paget's disease by means of brushing smear: report of a case. *Diagn Cytopathol* 2010;38:127–31.

21. Brown HM, Wilkinson EJ. Cytology of secondary vulvar Paget's disease of urothelial origin. *Acta Cytol* 2005;49:71–4.

22. Gu M, Ghafari S, Lin F. Pap smears of patients with extramammary Paget's disease of the vulva. *Diagn Cytopathol* 2005;32:353–7.

23. Klapsinou E, Terzakis E, Arnogiannaki N, Daskalopoulou D. Paget's disease of the vulva detected in vulvar and vaginal brushing smears: a case report. *Acta Cytol* 2010;54(5 Suppl): 898–902.

24. Parker LP, Parker JR, Bodurka-Bevers D, Deavers M, Bevers MW, Shen-Gunther J, et al. Paget's disease of the vulva: pathology, pattern of involvement and prognosis. *Gynecol Oncol* 2000;77:183–9.