Cytomorphology of cervicovaginal melanoma: ThinPrep versus conventional Papanicolaou tests

Namrata Setia¹, Robert A Goulart², Gladywn Leiman⁴, Christopher N Otis¹, Rukmini Modem¹, Liron Pantanowitz¹,²,⁴,＊

Address: ¹Department of Pathology, Baystate Medical Center, Tufts University School of Medicine, ²New England Pathology Associates, Mercy Medical Center, Sisters of Providence Health System/Catholic Health East, Springfield, MA, ³Department of Pathology, Fletcher Allen Health Care, University of Vermont, Burlington, VT, ⁴Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

E-mail: Namrata Setia - namrata.setia@baystatehealth.org; Robert A Goulart - robert.goulart@sphs.com; Gladywn Leiman - gladwyn.leiman@vtmednet.org; Christopher N Otis - christopher.otis@baystatehealth.org; Rukmini Modem - rukmini.modem@baystatehealth.org; Liron Pantanowitz* - pantanowitzl@upmc.edu

*Corresponding author

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Abstract

Background: Primary cervicovaginal melanoma is a rare malignancy associated with a high risk of recurrence. Prior studies discussing the cytomorphology of cervicovaginal melanoma have been based primarily on review of conventional Papanicolaou (Pap) smears. The aim of this study was to evaluate cervicovaginal melanomas identified in liquid-based Pap tests, in comparison with features seen on conventional Pap smear preparation. Materials and Methods: Cases of cervicovaginal melanoma identified on Pap tests with concurrent or subsequent histopathologic confirmation were collected from the Baystate Medical Center cytopathology files and personal archives of the authors over a total period of 34 years. All cytopathology (n = 6) and the available histology slides (n = 5) were reviewed. Cases were analyzed regarding clinical, histopathologic and cytomorphologic findings. Results: A total of six cases with invasive cervicovaginal melanoma diagnosed on Pap tests were identified. Most patients were postmenopausal with contact bleeding, correlating with surface ulceration (identified in biopsy/excision material in 5/5 cases). Most cases had deeply invasive tumors (5/5: modified Breslow’s thickness > 5 mm and Chung’s level of invasion IV/V). Pap tests included four ThinPrep and two conventional smears. Overall, ThinPrep Pap tests exhibited a higher ratio of tumor cells to background squamous cells. While all Pap tests were bloodstained, tumor diathesis was prominent only within conventional smears. Melanoma cells were present both as clusters and scattered single cells in each Pap test type. Both the preparations contained epithelioid tumor cells, whereas spindled tumor cells were seen in only two ThinPrep cases. Prominent nucleoli and binucleation of tumor cells were seen in both the preparations. Melanin pigment was identified in only ThinPrep (3/4) cases and nuclear pseudo-inclusions in one conventional Pap smear. Cell blocks were made in three ThinPrep cases and immunocytochemistry (S-100, HMB45, Melan-A) performed on additional vial material (one ThinPrep slide and one cell block) was immunoreactive in melanoma cells. Conclusion: Primary cervicovaginal melanoma, a rare malignancy seen predominantly in postmenopausal women, may be successfully diagnosed in either ThinPrep Pap tests or conventional Pap smears. While ThinPrep Pap tests did not demonstrate morphologic advantage over conventional smears, liquid-based cytology specimens did provide additional material for cellblock preparation and immunocytochemical evaluation in a subset of cases.

Key words: Cervix, conventional smear, cytology, melanoma, Pap test, ThinPrep, vagina
INTRODUCTION

Primary cervicovaginal melanoma is a rare malignancy, constituting approximately 9% of all vaginal neoplasms. Melanoma involving the uterine cervix is even more infrequent, with only about 60 cases reported to date. These tumors have a high mortality rate. These patients usually present late with advanced disease. Moreover, the varied cytomorphological spectrum (e.g. epithelioid, spindled, combined patterns, and amelanotic features) that may occur with melanoma (“the great masquerader”) combined with the rarity of these tumors at this site certainly pose a diagnostic challenge to cytopathologists. Most prior studies discussing the cytomorphology of cervicovaginal melanoma have been based primarily on review of conventional Papanicolaou (Pap) smears. There have been only very few case reports describing the findings of cervicovaginal melanoma using liquid-based cytology. The use of liquid-based automated Pap test preparations for the diagnosis of cervicovaginal melanomas has not been evaluated. The aim of this study was to assess the cytomorphological features of cervicovaginal melanomas observed in liquid-based preparations in comparison with conventional Pap tests.

MATERIALS AND METHODS

A retrospective review spanning 34 years of the pathology computer database at Baystate Medical Center and the personal teaching archives of the authors was performed for melanomas involving the vagina and uterine cervix. Data regarding patient demographics (age, gender), clinical findings (presentation, outcome), histopathology (melanoma prognostic features), cytology specimen preparation (direct smear, ThinPrep, cell block), cytomorphology (cellularity, diathesis, tumor cell features including necrosis, epithelioid or spindle cell shape, cohesion, pigmentation, multinucleation, nucleoli, nuclear inclusions) and ancillary studies (immunocytochemistry) were recorded. Detailed clinical history was available in only three cases. All cytology slides and available histopathology and ancillary study slides were reviewed. Accrued data were analyzed using descriptive statistics.

RESULTS

A total of six patients were identified with invasive cervicovaginal melanoma, four from departmental archives and two from the authors’ personal archives.

Clinical findings

Clinical details of the patients are summarized in Table 1. The average patient age was 67 years (range 50–76 years). Five patients were Caucasians and one was African in descent. Most patients presented with postmenopausal bleeding (4/6). Contact bleeding in these patients correlated with the presence of tumor surface ulceration identified in biopsy/excision material in 5/5 cases. Most cases (5/5) had deeply invasive tumors; all were modified Breslow’s thickness > 5 mm with a Chung level of invasion IV/V. The diagnosis of melanoma was confirmed in all cases by biopsy material [Figure 1]. In cases where information was available about where tumors were found, melanomas were located on the anterior (1/4), posterior (1/4), anterior and posterior (1/4) and lateral (1/4) vaginal wall. All patients were treated with surgery and radiation therapy. Local recurrence was noted in two cases and metastases (to the groin and pleura) were seen in two cases. One patient (case 1) had three recurrences with malignant pleural effusions and ascites. Another (case 2) relapsed with multiple liver, pulmonary and external iliac lymph node metastases. Two patients had a prior history of a concomitant malignancy (pulmonary squamous cell carcinoma and papillary transitional cell carcinoma of the urinary bladder). A diagnostic workup performed in all cases did not reveal malignant melanoma at any other location.

Cytopathology findings

The cytological specimens reviewed included four Thinprep Pap tests and two conventional Pap smears. Overall, Thinprep Pap tests exhibited a higher ratio of tumor cells to background squamous cells. While all Pap tests were bloodstained, tumor diathesis was most prominent with conventional smears [Figure 1]. The tumor diathesis obscured some of the tumor cells. Melanoma cells were present both as clusters and dissociated single cells in each Pap test type. Both the preparations contained epithelioid tumor cells, whereas spindled tumor cells were seen in only two Thin-
Prep cases. Prominent nucleoli and binucleation of tumor cells were seen in both the preparations. Melanin pigment was identified in only ThinPrep (3/4) cases and tumor cell nuclear pseudo-inclusions in one conventional Pap smear. Cell blocks were prepared in three ThinPrep cases (two with contributory material and one acellular). Immunocytochemistry (S-100, HMB-45, Melan-A) performed on one additional ThinPrep slide and one cellblock demonstrated immunoreactivity in melanoma cells.

**DISCUSSION**

The overall annual incidence of melanoma of the female genital tract is less than 0.2 per 100,000 women. Of these, the majority arise in vulvar skin, accounting for 3–7% of melanomas in women.\(^1\) Primary cervicovaginal malignant melanomas are uncommon tumors comprising approximately 2–5% of female genital tract melanomas. Fewer than 250 cases of vaginal melanomas and 60 cases of cervical melanomas have been reported to date.\(^1\) Nigogosyan et al. described the presence of melanoblasts in vaginal mucosa in 3% of women, which could theoretically explain the origin of melanomas in this location.\(^1\) Blue nevi in the cervix and vagina have also been described.\(^1\) In our study, most cases had deeply invasive tumors with a mean modified Breslow’s thickness of ≥9.54 mm, which is significantly higher than the 2.91 mm recorded in a series of 19 cases of vaginal melanoma by Chung et al.\(^1\) However, the Chung level of invasion was IV/V in all of our cases, similar to that observed by the authors in their study.\(^1\)

Vaginal melanomas are typically seen in postmenopausal women with a peak incidence in the sixth and seventh decades.\(^1\) Cervical melanomas, on the other hand, have been reported in a wider age distribution at diagnosis, ranging from 20 to 78 years.\(^2\) In our study, the median age at diagnosis for vaginal melanomas was 70 years, and the two patients with cervical melanomas were 50 and 72 years of age. Vaginal melanomas do not appear to exhibit a racial predisposition, in contrast to vulvar melanomas, which preferentially affect Caucasian women.\(^1\) Only one of the patients in this series was of African descent. Similar to previous studies,\(^1\) abnormal vaginal bleeding associated with tumor surface ulceration was the most common presenting symptom. Ulceration in these tumors likely contributes to the bloodstained tumor diathesis identified in the cytopathologic specimens. The presence of ulceration, however, does not necessarily increase the likelihood of obtaining exfoliated tumor cells, as has been suggested by some authors.\(^1\) Medek et al. reported a case of an ulcerated oral melanoma that did not shed melanoma cells in a cytopathologic preparation until the tumor had been traumatized by needle aspiration.\(^2\)

The diagnosis of melanoma was established on concomitant cytologic and biopsy material obtained in most of our cases. However, melanoma in this location may first be detected on a Pap test. Most of the case reports in the literature describing the cytological findings of melanoma in the lower female genital tract were based on conventional Pap smears (Table 2). In fact, the only case series published in 1974 by Masubuchi et al., describing the cytopathology of malignant melanoma of the vagina, involved conventional Pap tests.\(^2\) We intended to compare the cytological features of cervicovaginal melanomas identified in liquid-based Pap tests compared to those seen in conventional Pap smear preparations. The small study size in our series of this rare neoplasm, including previously published cases, makes it difficult to compare the sensitivity and specificity of these two techniques reliably. Nevertheless, we did not find any morphological advantage with ThinPrep Pap tests. Whereas melanoma...
cells are typically described as dyshesive and isolated on smears,\textsuperscript{[19]} in the present study they were also observed forming clusters in each Pap test type. Several clusters with overlapping cells were difficult to interpret. Prominent nucleoli are a well-recognized cytomorphological feature of melanoma cells\textsuperscript{[7,8,21-25]} and were seen in all cases of the present study. Melanin pigment, when present, is a helpful finding in differentiating melanoma from other high-grade tumors such as poorly differentiated carcinoma, sarcoma, and anaplastic lymphoma. However, melanin may be focal and not represented in Pap test material or could be absent in the case of an amelanotic melanoma. It is unclear why melanin pigment was identified in only three of the ThinPrep cases of this study. Nuclear pseudo-inclusions (also called Apitz bodies), considered to be one of the characteristic features of melanoma,\textsuperscript{[21]} were only seen in one conventional Pap smear. Most other investigators have similarly not been able to identify these nuclear inclusions in cytological smears.\textsuperscript{[7,8,23-25]} While ThinPrep Pap tests did not provide a morphological advantage over conventional smears, liquid-based cytology specimens did offer additional material for cell block preparation and immunocytochemical evaluation in a subset of our cases. The advantages of cell block preparation and immunocytochemistry performed on procured cytology material has been demonstrated by several investigators.\textsuperscript{[26]} Cell blocks and immunocytochemistry were utilized as adjuncts to confirm a diagnosis of malignant melanoma in three cases.

In summary, we present to the best of our knowledge the largest cytopathology series of six cervicovaginal melanomas, comparing liquid-based cytology with

| Reference | Year of study | Type of Pap test | Diathesis | Tumor cell type | Tumor cell arrangement | Melanin pigmentation | Tumor cell nucleoli | Tumor cell binucleation | Nuclear inclusions |
|-----------|---------------|-----------------|-----------|----------------|------------------------|----------------------|---------------------|------------------------|---------------------|
| [2] 2001  | Conventional  | Hemorrhagic background | Epithelioid | Single and small groups | Present | Prominent | Present | Present | Present |
| [4] 1988  | Conventional  | Not reported | Spindle only | Small groups and occasional scattered | Absent | Present | Absent | Absent | Absent |
| [5] 1994  | Conventional  | Atrophic with clean background | Epithelioid | Single and loose groups | Present | Present | Absent | Present | Present |
| [6] 1987  | Conventional  | Present | Epithelioid | Single (predominant) with few small clusters | Absent | Present (in pleomorphic cells) | Multinucleated cells present | Absent | Absent |
| [7] 1962  | Conventional  | Not reported | Epithelioid | Single and grouped | Absent | Prominent with a clear halo | Absent | Absent | Absent |
| [8] 1971  | Conventional  | Not reported | Epithelioid and spindle | Not reported | Present | Prominent | Not reported | Absent | Absent |
| [9] 2007  | ThinPrep      | Absent | Nevoid | Small groups and single | Absent | Prominent | Absent | Absent | Absent |
| [21] 1975 | Conventional  | Not reported | Epithelioid and spindle | Single | Present | Prominent | Present | Present | Present |
| [22] 1978 | Conventional  | Not reported | Epithelioid | Single and grouped | Present | Prominent | Absent | Absent | Absent |
| [23] 1974 | Conventional  | Not reported | Epithelioid | Not reported | Present | Not reported | Not reported | Absent | Absent |
| [24] 1974 | Conventional  | Not reported | Epithelioid | Single | Present | Prominent | Present | Present | Present |
| [25] 2000 | Not reported  | Absent | Epithelioid | Single and grouped | Absent | Prominent | Not reported | Absent | Absent |
| Present study 2010 | Conventional | Present | Epithelioid | Single and grouped | Present | Prominent | Present | Present | Present |
| Present study 2010 | ThinPrep | Absent | Epithelioid and spindle | Single and grouped | Present | Prominent | Present | Absent | Absent |
conventional Pap tests. These mucosal melanomas frequently present as ulcerated masses, resulting in high cellularity with characteristic melanoma tumor cells, even on conventional Pap tests. Although the number of cases reported in the series is limited, the type of preparation method (conventional, Thinprep) did not appear to confer a cytomorphological advantage with respect to making a diagnosis of melanoma. ThinPrep cases, however, did impart the advantage of additional material for cell block preparation and immunocytochemistry.

COMPETING INTEREST STATEMENT BY ALL AUTHORS

No competing interest to declare by any of the authors.

AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author acknowledges that this final version was read and approved. All authors qualify for authorship as defined by ICMJE http://www.icmje.org/#author. Each author participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article.

ETHICS STATEMENT BY ALL AUTHORS

The study was undertaken as an Intradepartmental cytology-histology correlation/audit and an academic exercise. IRB approval was obtained. At all times, patient confidentiality was maintained. Authors take responsibility to maintain documentation in this respect.

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