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Metastatic breast cancer diagnosed on cervical cytology

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Keywords: breast cancer, cervical cytology, metastatic, Pap test, Papanicolaou test

1 INTRODUCTION

In 2014, the use of the Cobas HPV test for primary cervical cancer screening for women who are 25 years and older without the need for a concomitant Pap test was approved by the US Food and Drug Administration (FDA). Primary HPV testing will be incorporated into the updated American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in 2020 as a screening option for patients 25 years of age and older. However, because a high-risk HPV infection is not associated with an endometrial or metastatic carcinoma, HPV DNA testing alone would not detect these cancers. We describe here a 64-year-old woman who had a remote history of breast cancer and presented for a routine Pap test. The diagnosis of “atypical glandular cells, favour neoplastic, suggestive of breast origin” was rendered cytologically and supported by the results of cervical and endometrial biopsies. We present detailed cytological and clinical findings of this very rare occurrence, and review literature of reported metastatic breast cancer cases detected on Pap test. Our case underscores the continued relevance and importance of the Pap test in certain patient populations for whom conventional cervical cytology may have added value compared to primary HPV screening.

2 CASE PRESENTATION

A 64-year-old postmenopausal woman with a past medical history of fibroids, gastroesophageal reflux disease, and obesity presented for her annual gynaecological exam. Her pelvic exam was normal, and the patient was asymptomatic. However, the ThinPrep Papanicolaou (Pap) test (Hologic, Inc.) showed multiple small groups of cells with scant cytoplasm, irregular nuclear contours, and inconspicuous small nucleoli. Rare cytoplasmic vacuoles imparting a signet-ring cell appearance were present. The atypical cells were focally arranged in short single-file lines. No tumour diathesis or mitotic activity was identified (Figure 1A,B). Upon review of the patient’s medical record, a remote history of breast cancer was discovered. A cell block was prepared by Cellient Automated Cell Block System (Hologic, Inc.), and immunohistochemistry (IHC) was performed to further clarify the nature of the abnormal cells. The cells were positive for GATA3 (Figure 1C) and negative for PAX8 and oestrogen receptor (ER). The overall cytomorphologic and immunophenotypic findings were suspicious for adenocarcinoma and suggestive of breast origin. Concurrent high-risk HPV testing was negative. The Pap test was signed out as “Atypical glandular cells, favour neoplastic, suggestive of breast origin.”

The patient’s previous breast cancer (diagnosed in 2002) was reviewed and showed infiltrating carcinoma with both ductal and lobular features (Figure 2A). The patient had undergone a partial mastectomy, followed by adjuvant chemotherapy, whole breast radiotherapy, and hormonal therapy; she completed all treatment in 2013.

Following the abnormal cytology, the patient returned to the clinic for colposcopy, and cervical biopsies were obtained. The biopsies showed a microscopic focus of adenocarcinoma consistent with metastatic breast cancer (Figure 2B); the malignant cells were positive for GATA3 (Figure 2C) and negative for p16. The patient also had an endometrial biopsy, which showed metastatic breast cancer with small, dyshesive tumour cells present in the endometrial stroma (Figure 3A). The tumour cells were positive for GATA3 (Figure 3B), ER, and progesterone receptor (PR), and negative for HER2 and E-cadherin (Figure 3C) by IHC. However, her pelvic ultrasound showed a normal-sized uterus with no focal abnormalities. Additionally, the patient’s most recent mammogram, completed one month before the abnormal Pap test, was normal.
FIGURE 1  Cytological and immunocytochemical features of the atypical glandular cells on the Pap test. (A) The ThinPrep Pap test showed small groups of cells with scant cytoplasm, irregular nuclear contours, and inconspicuous small nucleoli. (B) The atypical cells were focally arranged in short single-file lines, and (C) were positive for GATA3 by immunohistochemistry (A, ThinPrep Papanicolaou stain, 400×; B, Cell block H&E, 400×; C, 400×)

FIGURE 2  Previous mastectomy and follow-up cervical biopsy. (A) The patient’s previous breast cancer (17 years prior) was reviewed, and showed infiltrating carcinoma with both ductal and lobular features (H&E, 100×). (B) Subsequent cervical biopsy showed metastatic breast cancer with small, dyshesive tumour cells present in the ectocervical stroma (H&E, 40×). (C) The tumour cells were positive for GATA3 by immunohistochemistry (100×)
Subsequent imaging revealed multiple osseous lesions and the patient was treated for metastatic ER/PR positive breast cancer. The patient tolerated the treatment well, and follow-up imaging showed a complete response, with no residual tumour identified.

3 | DISCUSSION

Screening for cervical cancers with the Pap test has been very effective in reducing the incidence of cervical cancer and mortality in the United States, with an observed decline by more than 70% since the 1950s. However, the Pap test has a lower sensitivity for detecting glandular lesions than for squamous lesions and “atypical glandular cells” (AGC) may be a consequence of benign as well as neoplastic conditions of the cervix, upper endocervical canal or higher in the gynaecological tract. Some cases of ovarian, vaginal, and even colon or breast cancer have been reported after an AGC Pap test interpretation, but the diagnosis of metastatic extragenital malignancy on a cervical smear is rare. In a study of 3007 women with AGC, 433 patients (14.4%) had precancerous or malignant lesions on histologic follow-up and 14 cases (3% of these) were metastatic carcinoma. In another study of 143 glandular epithelial abnormalities, five cases of metastatic lesions to the cervix were identified (3.5%), including three cases of colorectal adenocarcinoma and two cases of serous papillary carcinoma. The majority of patients who were found to have metastatic extragenital malignancy on a cervical smear had undergone cervical smear because of vaginal bleeding, or rarely an incidental finding noted after a routine Pap test. Akhtar et al reported a case of lobular carcinoma of the breast in a 62-year-old postmenopausal female following an abnormal screening mammogram. Similar to our case, a routine Pap test necessitated further workup, revealing synchronous endometrial and cervical metastases. A literature search of patients with cervical (with or without uterine) metastases of breast cancer revealed on Pap test (without or without co-current cervical biopsy) identified a total of twenty-four previously published cases; nine were ductal, and fourteen were lobular (one was not specified). Cases with isolated cervical metastases and cases with disseminated metastatic disease with cervical involvement were reported. The majority of cases had no gross evidence of malignancy on examination. Our case is somewhat unique, as the primary tumour metastasis in the axillary lymph nodes was the ductal component, but the late metastasis was the lobular component seventeen years later (Figure 4).

The discrepancy in ER expression between the cytology and subsequent histology was presumably due to the cell block preparation method that was used in this case. As the cells in the cervical fluid specimen were already fixed in PreservCyt® for ThinPrep, we prepared a cell block using Cellient™ Automated Cell Block System. Correlation with the histology findings in this case demonstrated that ER was expressed in 99% of cells in the endometrial biopsy, suggesting a negative ER status result on cell block material is a false negative. Cellient is a proprietary automated system which produces
a paraffin-embedded cell block from an alcohol-fixed liquid-based sample. The resultant cell block sections show good morphology; however, exposure and fixation with alcohol may potentially interfere with immunoprofiles.24,25 At our institution, when the need of hormone receptor status assessment is anticipated, we use a thrombin clot method to generate a cell block to satisfy the requirement for formalin fixation as our ER/PR IHC has been validated on formalin-fixed paraffin-embedded blocks. However, we occasionally attempt ER on Cellient prepared cell blocks as it is indicated in literature that breast biomarker IHC assays performed on Cellient blocks are reliable and correlate with tissue block results, particularly for ER and HER2.26

In 2014, the use of the Cobas HPV test for primary cervical cancer screening for women who are 25 years and older without the need for a concomitant Pap test was approved by the FDA. Because a high-risk HPV infection is not associated with an endometrial or metastatic carcinoma, HPV DNA testing alone would not detect these cancers. Our case illustrates that the Pap test can detect metastatic cancer from an extraterine source, and clinicians should be aware of some of the limitations of the potential use of the HPV test as the primary screening tool in comparison with the Pap test alone, or co-testing with both Pap and HPV testing. The new ASCCP guidelines are expected to be published in the summer of 2020. The new guidelines will incorporate the patient’s current and past results to create an individualised assessment of a patient’s risk of progressing to pre-cancer or cancer. In addition, primary HPV testing will be incorporated into the updated guidelines as a screening option for patients 25 years of age and older. Healthcare providers should continue to be vigilant in following up on patients with any glandular abnormalities on the Pap test, especially those who are symptomatic (abnormal bleeding) or have a history of cancer. This case underscores the continued relevance and importance of the Pap test in certain patient populations for whom conventional cytology may have added value compared to primary HPV screening.

AUTHOR CONTRIBUTIONS
L. Yuan and K. S. Dyhdalo contributed to data acquisition, report conception, manuscript writing, and editing. A. Sierk, G. Zhang, and O. Oshilaja contributed data acquisition. C. Booth and J. Brainard contributed to editing.

CONFLICT OF INTEREST
None.

DATA AVAILABILITY STATEMENT
Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon request.

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REFERENCES


How to cite this article: Yuan L, Oshilaja O, Sierk A, et al. Metastatic breast cancer diagnosed on cervical cytology. *Cytopathology*. 2020;00:1–5. [https://doi.org/10.1111/cyt.12901](https://doi.org/10.1111/cyt.12901)