

## Case Reports

**Melanoma presenting as atypical glandular cells on cervical cytology****Peter F. Schnatz, D.O.<sup>1-4</sup>; Kristine Pattison, M.D.<sup>5,6,9</sup>; Jessica White, D.O.<sup>1</sup>; Srinivas Mandavilli, M.D.<sup>7</sup>;****Kathryn E. Sharpless, M.D., PhD<sup>8</sup>; James Hoffman, M.D.<sup>9</sup>**

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**Abstract**

**Background:** While most diagnoses associated with atypical glandular cells (AGCs) are localized to the uterus, a small number of extrauterine malignancies have been reported in connection with this finding. The current case report describes a malignant melanoma of the vulva presenting as an AGC Pap.

**Case presentation:** A 50-year-old female presented with localized vulvar symptoms. A biopsy was read as non-specific vulvitis. A Papanicolaou test (Pap) done at the time of that biopsy revealed AGCs. At her follow-up visit to evaluate her AGCs, the vulvar lesion was found to have increased in size. A second biopsy documented that the vulvar lesion was malignant melanoma.

**Conclusions:** All patients with an AGC Pap should undergo colposcopy, endocervical curettage, cervical biopsies (if indicated), and endometrial biopsy in high risk women. Even when the work-up is negative, diligent follow-up is recommended because of the risk of delayed diagnoses and extra-uterine malignancies.

**Keywords:** atypical glandular cells; cervical dysplasia; abnormal cytology; vulvar cancer; malignant melanoma

**Received:** December 5, 2011; **Accepted:** January 14, 2012; **Published online:** March 29, 2012

**Introduction**

Atypical glandular cells (AGCs) on cervical cytology, was defined in 1988 by the National Cancer Institute Workshop. (Originally, this entity was called atypical

glandular cells of undetermined significance.) The designation includes glandular cells (either endometrial or endocervical) with atypical features more severe than would be anticipated from a routine inflammatory process, but not severe enough to qualify for invasive

adenocarcinoma [1]. Approximately 0.3% of all Pap tests are reported as having AGCs [2]. This is a truly important finding on Pap testing, as 29.1% of these patients will have an associated squamous intraepithelial lesion (SIL), glandular abnormality, or a malignancy [2]. Despite this high likelihood of an abnormal finding, many other patients do not have important pathology [3].

A minimum required evaluation, after an AGC Pap test, includes a colposcopy (with cervical biopsies as indicated) along with endocervical curettage (ECC). An endometrial biopsy (EMB) should also be performed in women 35 years of age or older and in women under age 35 who have risk factors for endometrial carcinoma [2]. If the AGC is unspecified (i.e. not read as “favor neoplasia”), HPV testing can be considered [4, 5]. Aside from local inspection of the vulva, vagina, and an adequate pelvic examination, additional testing (ultrasound or other imaging modalities) should be directed based on the patient symptomatology. In cases of AGC favor neoplasia, a diagnostic cone biopsy is recommended [5]. Other indications for a diagnostic cone biopsy may include 1) recurrent AGC Pap smear, 2) concurrent finding of severe squamous dysplasia, and 3) positive HPV testing [4].

While the majority of diagnoses associated with an AGC Pap test are localized to the uterus (including the uterine cervix and uterine corpus); other diagnoses and cancers have occasionally been implicated. These extra-uterine findings have included benign findings, such as endometriosis [6]; and extrauterine malignancies, such as vaginal, vulvar, fallopian tube, ovarian, bladder, breast, and colon cancer [2,7]. Previously reported vulvar findings associated with AGC include vulvar intraepithelial neoplasia and Paget’s disease of the vulva. The current report presents a case of malignant melanoma of the vulva presenting as an AGC Pap result.

## Case presentation

A 50-year-old para 4 white female presented to her primary care gynecologist for a routine annual examination and Pap test in September 2008. She reported a localized area of pruritus just to the right of her clitoris. A small, red, hyperkeratotic lesion was noticed, biopsied, and reported to be non-specific vulvitis. A Pap test at that time showed AGC. She underwent

colposcopy with an ECC and an EMB which were both normal. She was asked to return in approximately 6 months to repeat the Pap test, ECC, and EMB. In May 2009, the Pap, ECC, and EMB were performed and all read as normal; however, the periclitonal lesion was noted to be increased in size. This area was re-biopsied, and this time read as malignant melanoma (superficial spreading pattern with a documented depth of invasion of 0.49 mm). A referral was made for further evaluation and treatment of the malignant melanoma.

On further review, evidence of melanoma was found on the 9/08 biopsy and confirmed on the 5/09 biopsy. Treatment consisted of an anterior radical vulvectomy with bilateral sentinel node dissections. The sentinel nodes were located in the inguino-femoral region. They were identified by azulfidine blue vital dye and technicium 99 isotope. The melanoma grossly measured 2.7 by 2.3 cm with 0.66 mm depth of invasion into the reticular dermis (Clark’s level IV). The surgical margins were widely negative, as were the sentinel lymph nodes. No further treatment was recommended.

The original AGC Pap smear was reviewed at a later date by a separate pathologist, who confirmed the findings; and importantly, identified morphologic similarities to malignant melanoma. Immunocytochemical staining with HMB45 (a marker seen in a vast majority but not all of malignant melanomas), however, performed directly on the Pap smear was negative. As discussed below, it was felt likely that this was a false negative result. The patient was followed for two years from the original Pap. During that time, two colposcopies, two endocervical curettages, and all Pap smears were normal, further suggesting the vulvar melanoma was the original etiology of the atypical glandular cells. There has been no other clinical explanation of her original AGC smear. There has been no evidence of recurrence of her melanoma.

## Discussion

About 1/3 of women with an AGC Pap result have a clinically important condition in their cervix or uterine corpus [2]. Many, however, do not receive an adequate evaluation at the time of their initial cytologic finding [3]. The vast majority (99.6%) of associated, pathologic conditions are localized to the vagina, cervix, uterus, fallopian tubes, or ovaries [2]. This leaves about 0.4% of

the AGC cases which are associated with pathology somewhere other than these locations.

The finding of an AGC Pap test should warrant extreme caution. The work-up of an AGC Pap test is estimated to have a 4.7% false negative rate, even following a comprehensive evaluation [3]. Furthermore, it has been shown that despite a thorough initial evaluation for AGC, approximately 11% of patients will develop a significant delayed diagnosis (12 months or more beyond the initial Pap test). Slightly less than half of those 11% are invasive malignancies [8]. Importantly, when the HPV test, or local evaluation, is negative, the likelihood of an endometrial or extra-uterine malignancy rises [4]. Therefore, in cases where the local evaluation is negative, especially if the patient has an AGC-favor neoplasia or a persistent AGC; the possibility of an extrauterine malignancy should be considered.

Although the immunocytochemical staining with HMB45 was negative, the authors believe there is a high likelihood that this was a false negative result for one of several technical reasons: 1) Immunocytochemical stains are optimally performed on formalin fixed material rather than alcohol fixed smears, as was the case in this Pap smear. 2) Immunocytochemical stains are optimally performed on recently prepared material, which also was not the case in this Pap smear. 3) Additional cytologic material was not available for additional testing using other immunocytochemical markers of malignant melanoma (Melan-A, Tyrosinase, S-100), which could have confirmed the diagnosis.

Each year vulvar carcinomas account for only 4% of all gynecological cancers. Approximately 90% of these cancers are squamous cell carcinomas. The second most common vulvar cancer is vulvar melanoma. In contrast to cutaneous melanoma, which presents in younger women, vulvar melanoma tends to present in older postmenopausal women and has a 5-year survival rate of between 20 to 55% [9]. In light of the relatively rare occurrence of vulvar melanoma, especially given the low incidence of AGC Pap tests (0.3%); diagnosing melanoma from an AGC Pap result will be unlikely to occur often. Certainly, this helps explain why we were unable to find another such case report. This case highlights the extreme variety of conditions which can present as an AGC Pap test.

Anecdotally, the lead author has heard of an AGC Pap smear leading to a diagnosis of disease in the patient's husband. The patient was evaluated by her general gynecologist for the incident AGC Pap result. The provider's initial comprehensive evaluation was negative. When the cytologic and histologic specimens were reviewed with the pathologist, the consensus was that AGCs were present. The unanticipated finding was that the AGCs had the appearance of prostate cells. The gynecologist recommended that her husband be evaluated by an urologist. Her husband was subsequently diagnosed with prostate cancer.

In conclusion, while AGC is a relatively uncommon diagnosis, it can have a wide array of underlying etiologies, many of which can be quite concerning. The diagnosis of melanoma in this case is most probable due to the clear morphologic features suggestive of melanoma, and the lack of any other explanation after a thorough work-up and follow-up. All patients with an AGC Pap result should have local evaluation, colposcopy, ECC and cervical biopsies if indicated, with an EMB in high risk women. If the entire work-up is negative, and the patient has a high risk indicator, a cervical cone biopsy should be offered. Keeping in mind that approximately one out of three women with AGCs have a pathologic diagnosis, if this testing is still negative, especially if HPV testing is negative and/or your pathologist confirms the presence of concerning atypical cells, the consideration of extra-uterine malignancy should be entertained. Finally, we should all be reminded that if a lesion continues to grow or change, even if it is read as benign on biopsy, it should be re-biopsied and followed closely.

#### **Acknowledgements**

The authors would like to thank Heidi Leftwich, D.O. for her assistance with the manuscript preparation.

#### **Disclosure**

There are no real or perceived conflicts of interest.

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