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Atypical glandular cells and adenocarcinoma *in situ* according to the Bethesda 2001 classification: Cytohistological correlation and clinical implications

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Abstract

Background: The objective of this study was to evaluate the correlation between the 2001 Bethesda classification of endocervical glandular abnormalities and histological diagnosis.
Study design: A series of 155 women with endocervical glandular abnormalities on cervical smears were included: 91 with atypical glandular cells (AGC) not otherwise specified (NOS), 15 with AGC-favor neoplastic (FN); 35 with AGC associated with high-grade squamous intraepithelial lesion (HSIL) as combined diagnosis and 14 with adenocarcinoma *in situ* (AIS).
Results: Histological outcome of squamous neoplasias (CIN 2 or worse) and adenocarcinoma were significantly associated with AGC-FN and AIS, taking as reference AGC-NOS, and more associated with AIS than AGC-FN. Similar associations were observed for histological outcome of adenocarcinoma, but no association was observed for only squamous neoplasia. Histological outcome of CIN2 or worse was strongly associated with AGC when HSIL was also present, but no association was observed with only for adenocarcinoma histological outcome.
Conclusions: AGC-NOS, AGC-FN and AIS cytological diagnosis represent a progressively increasing association with neoplastic diagnosis, due to progressively increasing association with adenocarcinoma. Histological outcome of squamous neoplasia is frequent but does not differ with these cytological interpretations. The presence of HSIL associated with AGC represents greater probability of squamous neoplasia but not adenocarcinoma.

Keywords: Uterine cervix; Adenocarcinoma; Cervical intraepithelial neoplasia; Squamous carcinoma; Cervical smear

1. Introduction

The Bethesda System has undergone two revisions to improve the clinical relevance of its diagnostic categories [1,2]. The changes made in the last revision (2001) classified endocervical glandular cell abnormalities less severe than invasive adenocarcinoma into three categories: Atypical glandular cells (AGC) not otherwise specified (NOS), AGC favor neoplastic (FN) and adenocarcinoma *in situ* (AIS). These changes in terminology were introduced with the objective of increasing detection of a significant pathology in women with cytological glandular abnormalities [3–6].

The wide variety of significant histological findings in women with endocervical AGC justifies immediate management and squamous neoplasia is more frequently revealed than glandular neoplasia by histological examination [7–11]. Biopsy-confirmed cervical intraepithelial neoplasia

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(CIN) 2 or CIN 3 have been reported in 9–41% of women with the initial diagnosis of AGC not otherwise specified (NOS), and in 27–96% of women diagnosed with AGC favor neoplastic (FN). In addition, 0–8% of patients receiving a cytological diagnosis of AGC will indeed have biopsy-confirmed adenocarcinoma *in situ* (AIS), and 1–9% will be diagnosed with invasive carcinoma [3,7]. The cytological interpretation of AIS is more frequently associated with the histological diagnosis of glandular neoplasia, either AIS (48–69%) or invasive cervical adenocarcinoma (38%) [3,8].

AGC in cervical smears constitutes a clinical problem due to the lack of well-defined cytomorphological criteria for the interpretation of this finding, the high degree of interobserver variability and the lack of characteristic colposcopic features [8,12,13]. In such cases, the wide variation in the frequency of biopsy-confirmed cervical intraepithelial neoplasia (CIN) 2 or CIN 3 observed among studies is a consequence of this problem. Moreover, cytological AIS cannot specifically differentiate between AIS and invasive adenocarcinoma, which can only be confirmed by histology [1,6,7,14].

There have been different opinions on the usefulness of the subclassification of cytological glandular abnormalities. In this study, we analysed the correlation of glandular abnormalities less severely than invasive adenocarcinoma, associated or not with high-grade squamous intraepithelial lesion (HSIL), with the histological outcome. We aimed at adding some information to the growing body of literature related to the usefulness of the subclassification of glandular cell abnormalities according to the 2001 Bethesda System.

2. Materials and methods

2.1. Case selection

A series of 155 women with cervical smears suggestive of glandular abnormalities of endocervical origin, including AGC and AIS, who attended the Colposcopy Clinic at the State University of Campinas, Brazil between March 2002 and March 2005 were enrolled in this prospective study. The study's protocol was approved by the institution's Internal Review Board and all women selected voluntarily signed an informed consent form prior to enrollment. Prior to study inclusion, the conventional cervical smears of all patients were revised by two observers in accordance with the 2001 Bethesda System – TBS [4,15,16] and the final cytological diagnoses were established by consensus. The women with cervical smears showing glandular abnormalities of origins other than endocervical were excluded, including those cases of endometrial and undetermined origin.

Following enrollment, all patients underwent colposcopy, and a second cervical smear with endocervical sampling (cytobrush) was carried out during the first study visit. Biopsies were performed whenever a suspicious image was found with satisfactory colposcopy. At the same visit, all women were referred to pelvic ultrasound examination for the evaluation of the uterine cavity and ovaries.

Cervical conization was carried out: whenever cervical colposcopy was unsatisfactory with suspicious lesions; whenever cervical biopsy was less than cervical cancer, regardless of referred cervical cytology; whenever the colposcopy was negative or unsatisfactory with any abnormal second cervical smear (with endocervical sampling). Cervical conization was not carried out in women referred for AGC-NOS with satisfactory negative colposcopy and negative cytology. All women with referral cytology AGC-FN or AIS also had abnormal second cervical smears. Women found to have invasive cervical or endometrial carcinoma were given standard care and treatment.

The women underwent uterine curettage when the pelvic ultrasound was suggestive for endometrial abnormalities. In postmenopausal women, the ultrasound abnormalities that indicated an endometrial curettage were endometrial thickness greater than 5 mm and/or homogeneous texture and/or irregular transition between endometrium and myometrium. In premenopausal women, irregular transition between endometrium and myometrium would have been the only ultrasound abnormality to indicate curettage, but no case with that abnormality was found.

Of the 155 women admitted to the study, 126 had histological assessment of their cervical lesions. If more than one biopsy had been performed, the most severe diagnosis was considered for the purposes of this analysis. The remaining 29 women that had been referred for AGC-NOS had satisfactory negative colposcopy evaluation and a negative second cervical smear. These women were scheduled for routine control visits every 4 months and were considered free of neoplasia, being therefore analyzed together with the other 53 cases that received a negative histological diagnosis for neoplasia.

2.2. Histopathology

Biopsy specimens were stained with hematoxilin and eosin (HE), reviewed according to the WHO's criteria [17] and classified as: CIN 1, CIN 2, CIN 3, invasive squamous carcinoma, adenocarcinoma *in situ*, invasive cervical adenocarcinoma, and endometrial adenocarcinoma. All the histological analyses were carried out in the local Laboratory of Pathology, and diagnosis was always established by the same pathologist, who was unaware of the cytological diagnoses.

2.3. Statistical analysis

All statistical analyses were carried out using the SAS software program, version 8.0. Odds ratios (OR) with 95% confidence interval (95% CI) were used to evaluate the magnitude of the association between the cytological diagnosis of the glandular abnormalities and significant histologic diagnosis.