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ORIGINAL ARTICLE

The histological outcome of glandular dyskaryosis - AGUS - reported in Papanicolaou smears

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Summary

Purpose: *The objective of this study was to investigate the prognostic significance of glandular dyskaryosis/ AGUS, reported in Papanicolaou (Pap) smears.*

Materials and methods: *During a 4-year period 26,408 smears were assessed at the Department of Cytology of our hospital. Thirty (0.11%) smears were reported as having glandular dyskaryosis. The studied material was taken by colposcopy, fractional curettage and/or cone biopsy.*

Results: *The final diagnosis included 2 cases of invasive cervical carcinoma (1 squamous cell and 1 adenocarcinoma), 1 case with ovarian cancer, 8 cases with high grade squamous intraepithelial lesion (HGSIL) and 10 cases with other non-malignant pathology (polyps, hyperplasia) of endometrial origin. These findings reflect a 36.7% positive predictive value for significant squamous and glandular pathology.*

Conclusion: *Patients with glandular dyskaryosis require further evaluation because it may hide serious pathology from all internal genital organs. Colposcopy in combination with fractional curettage and/or cone biopsy are proposed as the appropriate diagnostic tools in women with such cytological abnormality.*

Key words: colposcopy, fractional curettage, glandular dyskaryosis, glandular pathology, Papanicolaou smears, squamous pathology

Introduction

Glandular dyskaryosis of the cervical smears is the cytopathological terminology which describes the proportion of the nucleus (*karyon* in ancient greek) vs. the cytoplasm of the glandular cervical cells. It is described as low, moderate or high dyskaryosis, depending on the enlargement of the nucleus in comparison to the cytoplasm and the characteristics of the hyperchromatic nucleus. The incidence of glandular dyskaryosis in cervical smears (Papanicolaou - Pap - test) is rare ranging from 0.05 to 0.1 % [1,2]. Despite its rarity, it is associated with significant pathology in a considerably high percentage of cases with figures varying from 45 to 90% [3-6].

In 1988, the Bethesda classification of cervical cytology introduced 2 new categories of cytological diagnosis, namely atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGUS) [7,8]. This category corresponds to borderline dyskaryosis as described in the classification used in the U.K. [9]. AGUS is a diagnostic category of the Bethesda system encompassing glandular-type cells that show either endometrial or endocervical differentiation and display greater-than-expected atypia for a reactive process but do not meet the criteria for invasive adenocarcinoma [10]. AGUS replaced the term glandular dyskaryosis, although this has not been universally adopted. In the 2001 revision of the Bethesda system AGUS was further sub-classified into 3 categories [7]. These are atypical glandular cells (either endocervical, endometrial, or glandular cells) not otherwise specified (AGC-NOS); atypical glandular cells (either endocervical or glandular cells), favor neoplasia (AGC-favor neoplasia); and endocervical adenocarcinoma *in situ* (AIS) [7].

Due to the limited number of published studies and the significant risk for internal genitalia pathology

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mentioned above, we conducted the present study in order to evaluate our hospital's data and add our findings to the available literature.

Materials and methods

Between January 2002 and December 2005, 26,408 Pap smears were assessed at the Department of Cytology of our hospital. The smears were taken by swab and analysed blinded by more than one qualified cytopathologist. Thirty smears showed glandular dyskaryosis / AGUS and those women were referred to our Colposcopy Unit for further evaluation. Our standard work-up consisted of colposcopic inspection of the cervix, colposcopically directed or blind biopsies –based on whether visual lesions of the ectocervix and/or the transformation zone were noted– and endocervical and endometrial curettage. Curettage was done under general anesthesia and, if necessary, cone biopsies were also performed. These women formed the study population. Microsoft Excel 2002 for Windows XP was used for the evaluation of the above data, while the positive predictive value of the cytological findings were calculated using standard mathematical formula (diseased patients with positive test divided with all patients with positive test).

Results

Thirty out of 26,408 cervical smears (0.11%) showed glandular dyskaryosis / AGUS. After completion of the work-up mentioned above, serious cervical pathology was found in 10 (33.3%) patients. More specifically, we discovered 2 (6.7%) cases of cervical carcinoma, 1 of which was squamous cell and the other one adenocarcinoma, and 8 (26.7%) cases of HGSIL. Furthermore, we found 1 (3.3%) patient with clear-cell ovarian carcinoma who finally proved to be of stage IIC, and 10 (33.3%) cases with non-malignant endometrial pathology (hyperplasia, polyps).

The mean age of our patients was 43.5 years (range 23-78). Nineteen (63.3%) women were premenopausal and 11 (36.7%) postmenopausal. Two out of 19 premenopausal women suffered of cervical carcinoma, 6 of HGSIL lesions, 5 of benign endometrial pathology, while the remaining 6 proved negative. Regarding postmenopausal patients, 1 out of 11 had ovarian cancer, 2 HGSIL, and 5 non-malignant endometrial pathology, while in the remaining 3 we found no pathology.

The above data underline the higher prevalence of cervical cancer and HGSIL in younger patients (8/19 = 42.1% vs. 3/11 = 18.2%) (p=0.01).

Regarding the benign endometrial findings, a marked difference was observed between pre- and postmenopausal women. Among the first, 3 cases with polyps were found and 2 cases with irregular hyperplasia indicating abnormal progesterone activity (PCO syndrome). On the other hand, among postmenopausal women polyp formation was found in 1 patient while in the other 4 hyperplasia was the histological diagnosis (2 simple and 2 complex), though none with atypia. All the above findings are summarized in Table 1.

These findings reflect an overall 36.7% positive predictive value for significant squamous and glandular pathology between the cytological indication and the final histopathological outcome. This figure reaches 70% if both malignant and non-malignant results are to be counted.

Discussion

Detection of dysplasia and carcinoma *in situ* in Pap smears has led to a marked decline in the incidence and mortality of invasive cervical carcinoma in developed countries [11]. Cytological screening has reduced the annual incidence of cervical carcinoma from 17/100000 to 8.5/100000 in the last 20 years in the U.K. [12]. However, the incidence of cervical adenocarcinoma has increased over this time [13]. Up to 30% of HGSIL are associated with equivocal cervical smears, which show borderline or mild dyskaryosis [12].

Although Pap smears identify cervical carcinoma,

Table 1. Papanicolaou smears with glandular dyskaryosis and pathology after colposcopy and fractional curettage

	Patients, n	*Mean age (years)*	*Cervical cancer*		*Ovarian cancer*	*HGSIL**	*Benign endometrial pathology*		*Negative*
			SCC§	*Adeno Ca*		*Hyperplasia*	*Polyps*		
Premenopausal	19	37.3	1	1	–	6	2	3	6
Postmenopausal	11	54.3	–	–	1	2	4	1	3
Total	30	43.5	2		1	8	6	4	9

*high grade squamous intraepithelial lesion §squamous cell carcinoma

their main contribution remains the early detection of women with pre-invasive cervical lesions and of course their follow-up [14].

Cervical cytology showing glandular dyskaryosis is very rare with an incidence ranging between 0.05-0.1% [1,2]. Compared to that, cervical smears showing moderate or severe squamous dyskaryosis are 15-20 times more common and account for 1.5-1.6% of all adequate smears [1].

In our series, glandular dyskaryosis in cervical smears was predictive of genital tract pathology in 70% of the women. This is similar to the findings of Leeson et al. [3]. This predictive value was almost equal (non-statistically significant difference) in premenopausal (68.4%) and postmenopausal women (72.7%). Overall, our data reflect a 36.7% positive predictive value for significant squamous and glandular pathology.

Regarding Pap smears showing glandular dyskaryosis, the new guidelines of the British Society of Colposcopy and Cervical Pathology suggest that women should be offered colposcopy after only one mildly dyskaryotic smear [15]. It is shown that the positive predictive value of a mildly dyskaryotic smear for HG SIL is similar for all age groups [15]. However, Winn and Jones suggested that high-grade abnormalities were twice as prevalent (22 vs. 11%) in women < 35 years rather than in older women [16]. It has been shown that age is a key factor in determining the frequency and type of neoplasia found in women with glandular dyskaryosis. There is a higher risk of HGSIL or endocervical adenocarcinoma *in situ* and a lower risk of endometrial hyperplasia or cancer in premenopausal compared with postmenopausal women. It has been found that the majority of cancers in women with glandular dyskaryosis over the age of 35 are endometrial in origin [17-19]. Similarly, Geier et al. believed that women < 35 years old with cytologically atypical glandular cells of undetermined significance have a higher frequency of histopathologic findings, with most being squamous lesions, whereas those who are >50 years old have more glandular lesions than do younger women [18].

Our results are in full concordance with the latter, supporting the fact that women with a cervical smear showing glandular dyskaryosis are at a significant risk of having gynecological cancer and therefore merit specialist referral, whereas age proved to affect significantly the percentage of patients diagnosed with malignant or premalignant diseases (42.1% in premenopausal and 27.3% in postmenopausal women).

Colposcopy evaluates the ectocervix and the transformation zone but is of limited value for the evaluation of the glandular epithelium of the endocervix. Glandular lesions are often situated high up in the endocervical canal and therefore are not visible colposcopically. Therefore, further investigation of the endocervical canal is mandatory. Nevertheless, glandular lesions are associated with squamous lesions in approximately 50% of the cases [20,21]. In our study, 9 out of 30 women had squamous cervical pathology. Colposcopy-directed biopsy and endocervical curettings provide a firm diagnosis in most patients. Pisal et al. and earlier Gornal et al. proposed that endometrial assessment is mandatory in women with glandular dyskaryosis in their Pap smears [6,21]. In our study, 33.3% of women were found to have endometrial pathology, either polyps or hyperplasia. For patients in whom colposcopy is considered unsatisfactory cone biopsy should be performed. Cone biopsy offers the advantage of fully evaluating the upper endocervical canal, including its glandular divings [3,22]. Finally, if no pathology is found after cone biopsy and endometrial curettage, but the cervical smears continue to show glandular dyskaryosis, then carcinomas of the ovaries, colon, breast or stomach may be considered and investigated according to the literature [6,23,24]. This is the reason why in our series, one woman proved to be free of cervical and endometrial pathology and through further laboratory work-up was finally diagnosed to have stage IIC ovarian cancer.

Glandular neoplasia in cervical screening is meant to detect cervical glandular intraepithelial neoplasia or invasive endocervical adenocarcinoma along with a few endometrial cancers and occasionally extrauterine cancer. Strangely enough, not a single case of cervical glandular intraepithelial neoplasia was detected in our study, neither endometrial hyperplasia with atypia nor endometrial adenocarcinoma. Furthermore, while our study's positive predictive value of the test was 36.7%, others have reported much higher figures (up to 70%) [25-27].

The above difference must be attributed to the relatively small number of patients with glandular dyskaryosis as consequence of the proportionate small overall number of Pap smears evaluated in our cytology laboratory during the study period. Because of its rarity, glandular dyskaryosis/AGUS has the bias of considerable variability of its final diagnoses, a fact that is more obvious in smaller cytological laboratories. However, results similar with our findings were shown in a Hungarian study of comparable size [28].

In conclusion, despite the limitation of the small number of patients, our results indicate that the finding of glandular dyskaryosis on a Pap smear requires further evaluation, since the possibility of significant squamous or glandular pathology is high, reaching 36.7%.

The baseline work-up includes colposcopy, col-

poscopically directed biopsies, endocervical and endometrial curettage. Although many centers propose HPV-DNA testing in this investigation, the current ASCCP Consensus Guidelines do not recommend the use of HPV testing in the management of AGUS [29]. Cone biopsy of the cervix may be also required as well as evaluation of the ovaries (usually with ultrasound and CA-125 levels). More rarely evaluation of the breasts, stomach and colon may be performed.

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