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Review article

Glandular cell abnormalities in cervical cytology: What has changed in this decade and what has not?

Neeta Kumar[a,*,1], Ruchika Gupta[b,1], Sanjay Gupta[b,1]

[a] Department of Pathology, Faculty of Dentistry, Jamia Millia Islamia (Central University), New Delhi, India
[b] Division of Cytopathology, ICMR-National Institute of Cancer Prevention and Research, Noida, India

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ABSTRACT

The relative as well as absolute increase in cervical adenocarcinomas has brought the glandular lesions of cervix into attention of the cytologists and molecular biologists alike. Though the cytologic criteria for diagnosis of these lesions have been refined to a great extent through the evolution of the Bethesda System for reporting cervical smears, still some challenges exist regarding an accurate recognition of glandular cell changes in cervical smears and molecular tests to aid their detection. The present review is a narrative compilation of the current status of identification of cervical glandular abnormalities in the smear, the changing scenario of their histologic outcomes, newer entities within the category of glandular lesions and molecular cytology as relevant to this topic. The script also briefly explores the role of HPV DNA testing, the outcomes of HPV-positive and negative glandular abnormalities and the potential status of glandular lesions in the wake of implementation of HPV vaccination. Though this review is not an exhaustive one, it aims to put the issues pertaining to cervical glandular abnormalities into perspective and to explore the future research directions.

Contents

Introduction

Glandular cells on cervical smears have garnered more attention in the last decade because of the relative as well as an absolute increase in the incidence of adenocarcinoma (ADCA) of cervix, especially in young women. The incidence of ADCA doubled from the early 1970s to the early 1980s [1]. Subsequent data from the United States, Canada and Europe showed that endocervical

* Corresponding author.
E-mail address: kumar_neeta@hotmail.com (N. Kumar).
[1] Equal contribution.

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ADCA comprised up to 25% of all cervical cancers compared to about 10%–15% three decades ago [2–4]. Liu et al (2001) from Canada reported that the incidence of cervical ADCA among women increased by three-fold in the age group of 20–34 years and twofold in the age group of 35–49 years [4].

Many contributing factors have been identified for this change such as a higher prevalence of human papillomavirus (HPV) infection and/or a change in the distribution of HPV types coupled with a better recognition of glandular lesions by the pathologists due to improved sampling devices and better processing techniques of cervical samples along with a relative reduction in cases of squamous lesions [5]. The rate of squamous cell carcinoma has been showing a declining trend in most of the developed world as well as many regions of India as a result of organized or opportunistic screening and HPV vaccine implementation [2]. In addition, prevalence of endometrial ADCA is on the rise that contributes to a proportion of AGC diagnosed on cervical smears [6].

In view of the better understanding of the biology of glandular lesions and their increased recognition on the cervical smears, The Bethesda System (TBS) has been revised three times for reporting of glandular lesions. Since then, significant knowledge and experience has accumulated in the identification of precursor neoplastic lesions of glandular origin on cervical smears, and their outcome on biopsy. This paper discusses some of the issues related to identification of glandular cell abnormalities on cervical smear and traces the changing facets in the journey of glandular lesions from AGUS to AGC.

Evolution of reporting glandular lesions in The Bethesda System (TBS)

The cytopathologists have been struggling to interpret changes in glandular cells on cervical smears ever since the beginning of cervical smear screening. The outcome of reporting glandular cell abnormality in cervical smear ranged from reactive changes to underlying significant lesions, which were either squamous or glandular in origin. In order to highlight this well identified problem, a category of "Atypical Glandular Cells of Unknown Significance (AGUS) was created in the TBS 1988, the first standardized approach to reporting cervico-vaginal cytology [7].

In view of the evidence that cytodiagnosis of atypia in glandular cells was more frequently associated with detection of high grade lesions on a subsequent biopsy and was not really of undetermined significance (unlike atypical squamous cells, ASCUS), the term AGUS was replaced with Atypical Glandular Cells (AGC) in TBS 2001 revision. This category included subcategory qualifiers according to risk of malignancy as not otherwise specified (NOS) and favor neoplasia (FN) and cellular origin as endocervical or endometrial [8]. Both the subcategories warrant further work-up to exclude high grade lesions. The most recent update of this system, TBS 2014, did not make any significant change to the classification of glandular cell abnormalities, except that the age criteria for reporting of benign-appearing endometrial cells in cervi**co-**vaginal smears has been increased from ≥40 years in TBS 2001 to ≥45 years in 2014 [9]. Glandular dysplasia as specified in the WHO classification (2003) has not been adopted in the TBS 2001 and TBS 2014 [8].

Diagnostic challenges of atypical glandular cells: intra and inter-observer reproducibility in AGC diagnosis

The rate of reporting of AGC in cervical smears varies between 0.08 and 2.5% in the literature. This wide variation may be attributed to the inconsistencies in application of the diagnostic criteria, differences in the sample collection and smear preparation (conventional versus liquid-based cytology) methods, the scale of screening (primary or referred), and the population screened [10,11]. Identification and interpretation of AGC has been a diagnostic challenge to the cytopathologists due to non-familiarity with cytomorphology of glandular abnormalities and the frequent morphological overlap with squamous lesions particularly those with crypt invasion, reactive atypia, metaplasia well as benign glandular lesions lining the endocervix and endometrium that have been highlighted in numerous publications [9,12,13]. The cytological criteria are better defined for the diagnosis of high grade glandular abnormalities like adenocarcinoma in situ (AIS) and ADCA leading to good inter-observer agreement for these diagnosis as compared to AGC-NOS and AGC-FN categories which represent equivocal glandular atypia [14].

There is limited literature regarding intra and inter -observer reproducibility and variability in the diagnosis of AGC. The Bethesda Inter-observer Reproducibility Study (BIRST), which evaluated the inter-observer concordance for TBS 2001, included only five images for AGC and 11 for high grade glandular lesions. The concordance of participants with the TBS panel was less than 30% for AGC compared to 60% for high grade lesions [15]. The BIRST-2 study published in 2017 showed only 33% concordance for AGC diagnosis between participants and the TBS panel [16]. Hence, there is a need for emphasis on educational notes on the interpretative challenges in borderline glandular lesions. Lepe M et al evaluated the inter-observer variability in AGC diagnosis as per the guideline-specified management and categorization as glandular or squamous lesions. There was a fair to moderate agreement on AGC diagnosis as per clinical management guidelines and only a fair agreement for categorization of cases as glandular, squamous or both. The authors suggested that this variability is likely to have a real effect on the patient management and should be taken into account by both the pathologists and clinicians [17]. Robust well-designed studies are needed to understand the reasons of inter-observer variability in AGC diagnosis for further refinement of criteria for diagnosis of AGC in cervical smears.

Impact of changing sampling devices on pick up of glandular lesions

The initial major challenge in cytologic diagnosis of AGC was the scanty glandular cell component on smears due to the use of sampling devices not designed or suitable to sample the endocervix. This was compounded by the fact that the glandular lesions usually occur high up in the cervix or deep within the glands leading to difficulty in obtaining an adequate and representative sample. The sampling problem often resulted in missed opportunities for early diagnosis of premalignant and malignant glandular lesions on cervical smears [18]. This challenge has been circumvented to a large extent by the availability of improvised endocervical sampling devices such as endocervical brush and broom made of high quality microfibre and having soft bristles causing minimal trauma and pain to the patient. These devices have facilitated collection of a good number of glandular cells, which had been earlier difficult with the traditional Ayre's spatula. A systematic review and meta-analysis confirmed that the use of cytobrush along with spatula led to a 3.33-times increased number of cervical smears having endocervical cells than spatula alone and led to increased detection of dyskaryotic cells by 10.7%. The authors also mentioned that cervical sample collection devices with improvised endocervical sampling were likely to result in improved detection of glandular abnormalities [19]. A more recent comparison of cervex-brush and extended-tip wooden spatula for conventional cytology reported an increase in glandular abnormality detection from 0.5% using spatula to 1.1% using cervix

brush and returning to 0.3% when the smear takers again started using spatula [20].

Impact of modifications in processing techniques (liquid based cytology and cell block) on cytodiagnosis of AGC

Liquid based cytology (LBC), introduced in cervical screening about two decades ago, has resulted in reduction of unsatisfactory cervical cytology specimens. Initial reports showed higher rates of detection of glandular abnormalities in LBC smears [21,22]. This was attributed to better endocervical sampling with improvised cell transfer in liquid medium and improved morphology mainly due to improved quality of smears with a clean background, minimal overlapping of cells, lesser obscuration by blood and inflammatory cells and reduced cell loss [22]. However, a few subsequent studies have not corroborated this finding [23–25]. Kituncharoen et al found a similar detection rate of AGC in conventional and LBC preparations [22]. A Turkish study reported similar rates of AGC-NOS diagnosis on conventional cytology and LBC smears [24]. Patel et al reported similar accuracy in conventional smears and Sure Path LBC for detection of endometrial cancer [26]. Although randomized controlled trials (RCTs) and systematic reviews did not show any significant difference between conventional and LBC for squamous intraepithelial lesions [27,28] RCTs specifically focusing on evaluation of sensitivity of AGC in CS and LBC are not yet available.

Recently, there has been an interest in improving the cytological diagnosis of AGC using cell blocks prepared from LBC samples. Risse et al, in their study of 26 cases of AGC with cell blocks, showed that immunohistochemistry for $p16^{INK4a}$, Ki67, CD10 and CD45 helped in detecting the benign mimics of AGC and avoiding unnecessary colposcopy in these cases. This approach improved the diagnostic accuracy of clinically significant glandular lesions by LBC [29]. George et al evaluated cell blocks in cases of ASCUS and AGC and reported that of the 20 cases of AGC on cervical smear, one was diagnosed as LSIL and another as ADCA on cell block. Though the difference was not statistically significant due to low number of cases in their study, the authors concluded that cell blocks prepared from LBC pellets can be used as an adjunctive aid for improving the cytological diagnosis of both ASCUS and AGC [30]. However, it must be mentioned that cell blocks can only be prepared from LBC samples and are likely to incur additional costs for preparation and time to reporting. Since LBC is not being practiced on wide scale in many low and low middle-income countries, the utility of cell blocks cannot be adequately assessed in these regions. A detailed cost-benefit analysis of the utility of cell blocks in increased detection of cervical glandular lesions needs to be undertaken in large multicentric trials.

Histological outcome on follow up of AGC: past and current scenario

Majority of the earlier studies published in the last two decades have shown that the most frequent significant histologic outcome of AGC diagnosis on cervical smear was high grade squamous intraepithelial lesions (HSIL) or CIN 2-3 [12,13,31–33]. However, more recent articles on this topic demonstrate a significant shift with predominance of glandular abnormality on a subsequent biopsy. A study by Boyraz et al reported clinically significant pathology in 33.8% of AGC cases with endometrial neoplasms being the most frequent. In their study, colposcopy-directed biopsies and endocervical sampling was performed in all patients with AGC diagnosis while endometrial sampling was done in all females more than 35 years of age as well as those with risk factors if they were younger than 35 years [34]. Another report by Kim et al demonstrated cervical ADCAs in 33% of patients after AGC diagnosis on cytology. In their study, the histological outcome varied depending on the cytologic subcategorization of AGC. Squamous intraepithelial lesions were more frequently detected after AGC-NOS diagnosis on smears while glandular lesions of cervix, endometrium and metastatic ADCA were predominant on follow-up of AGC-FN [35]. However, there still remains a significant variation in the histologic outcome after cytologic AGC diagnosis reported in the literature. This may be attributed to the non-uniformity in histologic evaluation after AGC diagnosis. Cervical biopsy, if employed alone, has significant limitation especially in histologic detection of premalignant and malignant glandular lesions. Studies including comparison with surgical specimen (conization or hysterectomy) diagnoses demonstrate higher detection of significant lesions with frequent pickup of glandular premalignant or malignant lesions [11]. The American Society for Colposcopy and Cervical Pathology guidelines recommend colposcopy with endocervical sampling in the initial management of AGC categories except atypical endometrial cells where endometrial sampling is mandatory [36]. Hence, the real frequency of various histologic outcomes can be known only with large-scale studies comparing the cytologic AGC diagnosis with uniformly applied histologic evaluation. In addition, it is important to remember that the presence of a concurrent SIL may be masked or ignored by the atypia in the glandular cells [13,37]. Hence, smears showing glandular cell lesions should always be diligently scrutinized to look for a coexisting SIL keeping in mind that atypical squamous cells may be few and scattered in such smears.

Long term outcome of AGC diagnoses on cervical smears

Chhieng et al reported that 12.7% of patients among high-risk population with clinically significant lesions were diagnosed after a mean interval of 3 years from their initial AGC diagnosis, suggesting that patients with AGC should be followed up for longer periods [38]. A population-based screening study from Taiwan showed a 18-fold higher risk of cervical cancer along with about 6-fold risk for uterine cancer and 2-fold risk enhancement for ovarian cancer in women with a cytological diagnosis of AGC and an average follow-up of 6 years [39]. In a more recent landmark cohort study in Sweden, Wang et al reported that the risk of detection of cervical ADCA was higher after a cytologic diagnosis of AGC and remained at a high level even up to 15 years, especially for women in the age group of 30–39 years at the time of AGC diagnosis. These findings call for immediate histologic evaluation and close surveillance of women with cytodiagnosis of AGC over a long period and not let them be lost to follow-up [40]. Further large-scale studies are also warranted with risk stratification for the subcategories of AGC-NOS and AGC-favoring neoplasia in order to monitor the long-term outcomes in these qualifiers.

Cyto-histological correlation of AGC cases: impact of the American Society of Cytopathology (ASC) 2017 recommendations

There are numerous reports in the literature on cervical cyto-histological correlation as a measure of quality assurance in a gynecologic pathology laboratory. However, majority of these discussed their results only for squamous lesions. There has been some degree of ambiguity in the way a pair of cytologic AGC and its histologic diagnosis should be dealt with. For instance, variance was observed in categorizing a pair of AGUS/ AGC-NOS and CIN2 as major or minor discrepancy on cyto-histological correlation [41,42]. ASC has recently, in 2017, put forth recommendations for cervical cyto-histological correlation in an effort to bring about uniformity in the correlation results [43]. These recommendations include a discrepancy assessment grid depicting possible

combinations of cytological and histological diagnosis, including the categorization of glandular cytology and corresponding histology. We conducted a cyto-histologic correlation exercise at our centre utilizing the ASC 2017 guidelines and found a 33.3% agreement, 50% minor discrepancy and 16.7% major disagreement in pairs with cytological diagnosis of AGC (including AGC-NOS and FN) (unpublished results). Wider application of these guidelines and the discrepancy assessment grid shall help in delineating the concordance rate for glandular lesions and refining the cytomorphologic diagnostic criteria for these entities.

Role of HPV DNA testing, impact of HPV vaccination and HPV negative glandular lesions

The relative rarity of AGC diagnosis in cervical smears has been a limiting factor in the evaluation of utility of testing for high-risk HPV (hrHPV) in these cases. A high sensitivity and specificity of HPV testing for CIN2+ lesions in patients with cytologic diagnosis of AGC has been reported in a few studies [44,45]. A large follow-up study of 1857 cases of AGC with HPV testing and histological evaluation showed the highest HPV positivity in the group of AGC with concomitant squamous lesions and lowest in cases with atypical endometrial cells. A significant difference was noted in the rate of detection of clinically significant lesions in HPV-positive AGC group compared to HPV-negative cases with NPV of 99.2% [46]. Research has established that most of the glandular lesions are associated with HPV18 followed by HPV16 and 45 [47]. Hence, there appears to be a role of reflex HPV testing in the further evaluation and management algorithm for AGC cases and more such studies would provide the evidence to allow the policy makers to incorporate HPV testing in the management guidelines for AGC. In 2016, the National Institute of Cancer, France adopted reflex HPV-testing for triage of cytologically-detected cervical glandular abnormalities before being referred for colposcopy [48]. The results of impact of this management approach on clinical outcome of women with glandular lesions are awaited.

HPV-based tests are gradually being approved for primary screening of cervical cancer [49]. This approach has raised concerns regarding the status of HPV-negative lesions, especially in the glandular category. It is important to note that some variants of cervical ADCA such as clear cell, serous, mesonephric ADCA and gastric-type, majority of endometrial carcinomas and carcinomas of other sites like ovary (that may be detected rarely on cervical smear) are negative for HPV [50–52]. Though cytology is evidently better than HPV testing for detection of these variants, the issues with endocervical sampling and the low frequency of representation of endometrial and extra-uterine malignancies in cervical smear need to be kept in mind while reporting on studies evaluating the efficacy of one or the other screening modality for cervical cancer screening.

Increasing implementation and uptake of HPV vaccination as a primary preventive measure for cervical cancer is likely to lead to a significant reduction in the HPV-associated cervical precancers and cancers, as is already being observed in Australia, the first country to include HPV vaccination in its national program [53]. Researchers predict that the reduction in HPV-related cervical neoplasms shall be associated with a relative increased prevalence of HPV-negative ADCA and its precursors. In such a scenario, primary HPV-based screening with reflex cytology only in HPV-positive females shall practically eliminate the chances of detection of these HPV-negative glandular lesions [54]. Hence, alternative strategies to address the issue of detection of HPV-negative glandular lesions need attention. In this regard, a commercially available latex agglutination test using HIK1083 (marker for pyloric gastric mucin) has been shown to detect gastric-type mucin in cervical discharge. This test is highly sensitive and specific for detection of gastric-type glandular lesions of the cervix [55]. However, more such tests or modalities need to be evaluated to enhance the pickup of HPV-negative atypical glandular lesions.

Molecular approach to detection of glandular malignancy: role of biomarkers

The 2014 World Health Organization classification listed 19 types of primary malignant cervical glandular tumors [56]. As mentioned earlier, HPV DNA can be detected in a majority of cervical ADCAs and AIS while certain histotypes are unrelated to HPV [57]. Similar to the squamous precancerous lesions of the cervix, there has been interest in identification of immunohistochemical expression of biomarkers for better delineation of glandular lesions. However, the literature on biomarkers in glandular lesions is still limited. A recent systematic review and meta-analysis of immunohistochemical biomarkers in malignant glandular lesions concluded that p16, dual p16/Ki67, ProExC, CEA, epithelial specific antigen (ESA), HIK1083 and loss of ER expression were sensitive and specific for differentiation between select malignant versus benign lesions. However, the meta-analysis was limited by the lack of standardized definition of expression of certain biomarkers such as p16 and scant literature on estimates for all malignant lesions for a single marker [58]. Thus, there is a need for evaluation of biomarkers in distinction of various grades of glandular lesions from each other along with standardized criteria for scoring and algorithms of sequential testing [58]. Biomarkers found useful in such studies must also be tested on cervical smears to improve the accuracy of sub- categorization for glandular lesions according to TBS2014.

Since endometrial and ovarian cancers can also shed cells in the cervical canal, these tumors may occasionally be picked up in the cervical sample as AGC. The cytomorphologic distinction between cervical ADCA and those of endometrial or ovarian origin may not always be possible. Moreover the diagnostic cells may be few or poorly preserved considering the long path traversed by them in cervical canal. Molecular techniques have been investigated for better recognition of these malignancies and to provide an advantage over morphology. One such test, PapGene test performs multiplex testing of 12 genes and has been shown to accurately detect mutations in one or more of these genes in endometrial and ovarian cancers while no mutation was detected in samples from females without cancer [59]. Another test named PapSEEK combines assays for mutations as well as aneuploidy and has been demonstrated to have nearly 99% specificity for endometrial/ovarian cancer including early stage cancers [60]. These molecular tests need to be validated before being offered for clinical use and more studies are awaited.

Role of computer-assisted screening in detection of glandular lesions

The last two decades have witnessed the introduction of automated computer-assisted screening of LBC preparations in an effort to improve the efficiency by filtering cytopathologists' workload. The initial studies demonstrated up to 10% of cases of atypical glandular cells not being flagged for cytopathologists' review [61,62]. A recent study evaluating the BD Focalpoint slide profiler reported that all the cases of AGC with abnormalities on follow-up biopsy were classified for review by cytopathologist. However, only one-third of these cases were ranked in quintile 1, ie most likely to contain abnormality [63]. The current evidence regarding utility of automated screening in detection of glandular lesions is limited and suggests that the algorithms of such

systems need to be refined further to improve the efficacy and clinical application.

Summary

1 Increasing use of LBC has significantly reduced unsatisfactory smear rate and improved adequacy thereby enhancing the ability to detect glandular disease compared to conventional smear.
2 New sampling devices such as endocervical brushes have improved collection and detection of endocervical cells and in turn, glandular lesions.
3 HPV co-testing has also supplemented pick up of endocervical glandular lesions with augmented sensitivity.
4 Overall efficacy of cervical smear for detection of endometrial malignancy has risen to 38% from 30% over the past decade.
5 Histologic follow-up of glandular lesions detected on cytology is now more often glandular rather than squamous abnormality due to improved accuracy of cytodiagnosis of glandular features, overall increased prevalence of malignant glandular lesions and studies including recommended histologic evaluation of AGC diagnosis.
6 Recognition of HPV-negative glandular lesions like clear cell, gastric-type, mesonephric has necessitated development of newer biomarkers for their identification in the wake of shift to primary HPV-based cervical cancer screening.
7 Molecular approach employing PAPgene or PapSEEK test for endometrial and ovarian carcinomas based on identification of characteristic oncogenic DNA mutations in the cervical samples has added a new dimension to aid diagnosis of non-endocervical cancers through cervical sample collection.

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