Indian Journal of Public Health Research and Development
Volume 14 No. 2, April-June 2023

Clinicopathologic Significance of Atypical Glandular Cells in Cervical Cytology Smears: A five years Retrospective Study in a Tertiary Care Hospital

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How to cite this article: Rajashree Pradhan, Sharmistha Debnath, Somsubhra Chattopadhyay. Clinicopathologic Significance of Atypical Glandular Cells in Cervical Cytology Smears: A five years Retrospective Study in a Tertiary Care Hospital. Indian Journal of Public Health Research and Development 2023;14(2).

Abstract

Introduction: Cervical cancer is the fourth most common cancer among women. Recently the incidence of cervical adenocarcinoma has been increased significantly on the contrary to the decreasing incidence of cervical squamous cell carcinoma. Routine screening of cervical cancer by cervical smear cytology study to detect the pre-invasive lesions carries a significant role in reducing the incidence and mortality rate of cervical cancer.

Objective: The aim of our study was to analyze the prevalence of Atypical Glandular Cells (AGCs) detected in cervical smear screening, the follow up histopathological outcome and their clinical significance.

Materials and Methods: This was a retrospective study done in College of Medicine and Sagore Dutta Hospital, Kolkata over a period of 5 years from June 2017 to June 2022. Patients detected with Atypical Glandular cells (AGCs) in cervical smears and having records of follow up histopathology reports were included in this study. The cases of AGCs in which the follow up histopathological reports were not available were excluded from the study.

Result: The prevalence of atypical glandular cells were 0.57%. Out of the total 10,950 cervical smears examined AGCs were found in 63 cases (0.57%). Out of 63 cases of AGCs subcategorization was done(according to TBS 2015) which showed AGC not otherwise specified (AGC-NOS) in 46 cases (0.43%) and AGC Favoring Neoplasia (AGC-FN) were seen in 15 cases (0.13%). Both AGC -NOS and AGC-FN showed various pathology ranging from reactive, metaplastic, benign to, in situ/Invasive carcinomas.

Discussion: One of the major concern of AGC is that the cytological findings which characterize it have poor reproducibility between observers leading to interobserver variability. Due to the reported risk of premalignant and malignant lesions in AGCs it bear a great clinical significance and need for further histopathological correlation.

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Conclusion: Due to very low incidence of AGCs and the risk of malignancy associated with it multiple histological evaluation methods required for earlier diagnosis and management of the malignancies detected on histologic follow up.

Key Words: Cervical smear, Atypical Glandular Cells, histologic follow up, Bethesda System.

Introduction

Cervical cancer is the fourth most common cancer among women globally, with an estimated 6,04,000 new cases and 3,42,000 deaths in 2020. [1] The incidence of cervical cancer has been reduced in many countries due to the widespread cervical cytology screening. The mean annual % decrease in the average age adjusted range from 1.81% to 3.48%. [2] The risk of cervical cancer due to squamous cell abnormalities as detected on cervical cytology is widely accepted. [3] The risk of cervical cancer associated with the abnormalities of cervical glandular cells are still uncertain. [4]

On the contrary to this the incidence of cervical adenocarcinomas have significantly increased where as cervical squamous carcinomas show a decreasing incidence. [5] The decreasing incidence of SCC is probably related to its early recognition at its precursor stage (Squamous intraepithelial lesions) by effective screening programs .

In the new 2001 Bethesda system the term Atypical Glandular Cells of undetermined significance has been replaced by the term Atypical Glandular Cells (AGC) [6] with the subclassification of AGC not otherwise specified (AGC NOS), AGC – favor neoplasia(AGC- FN), Adenocarcinoma In situ (AIS) and adenocarcinoma. AGCs are uncommon diagnosis with a screening incidence between 0.08 to 2.1%. [7] Now a days one of the major challenge in gynecologic cytopathology is accurate interpretation of AGC in cervical PAP smears for early detection of glandular neoplasia of the female genital tract.[8] AGC in cervical cytology include conditions ranging from reactive, inflammatory to dysplasia and malignancy. Due to this, the presence of AGCs in cervical cytology smear are very important and carries a great clinical significance.

AIMs & Objectives

The aim of our study was to analyze the clinicopathologic significance of AGCs detected in cervical smears and their various histopathologic follow up outcomes.

Materials and Methods

Study design and place of study

This was a retrospective study done in a tertiary care hospital college of Medicine and Sagore Dutta Hospital, Kolkata.

Duration

The study was conducted over a period of 5 years (June 2017 to June 2022).

Case Definition

(AGCs in cervical cytology smears were subcategorized according to the Bethesda System 2014.

(a) Definition of AGC NOS

Cells resembling endocervical cells with nuclear atypia, that exceeds a reactive or reparative process but lack unequivocal features of endocervical adenocarcinoma in situ or invasive adenocarcinoma.

(b) Definition of AGC, FN

Glandular cells with morphology either quantitatively or qualitatively falls short of interpreting as endocervical adenocarcinoma in situ or invasive adenocarcinoma.

Inclusion Criteria

The women whose cervical cytology smears show AGC(NOS, FN) (Categorized according to the Bethesda 2014) along with available histopathology follow up reports were included in this study.

Exclusion Criteria

The women whose cervical cytology smears show AGCs but follow up histopathology reports not available were excluded from this study.

→ Cases interpretated as AGC on PAP test in cervical smear from June 2017 to June 2022 were retrieved from cervical cytology records of our department of pathology.

→ All the documented histologic follow up such as endocervical curettages, cervical biopsies cervical excisional biopsy, endometrial curettage and biopsies were collected from the histopathology record of our department.

→ The parameters retrieved from medical records in the obstetric and Gynecologic department of our institution included the patients age at the AGC interpretation, follow up procedures, the time interval from the PAP smear study to the colposcopic examination and cervical biopsy, HPV testing.

Ethical Consideration

The study was approved by the Institutional Ethics Committee (IEC) of our institute.

Statistical Analysis

All the data were analyzed and represented as number and percentage by using software SPSS version 20. 0 . P-value < 0.05 was considered statistically significant.

Result

The total numbers of cervical smears examined over the period of 5 years in our hospital were 10,950. Out of this AGCs were detected only in 63 cases (0.57%) . Out of the 63 cases of AGC, 48 cases were diagnosed as AGC NOS (0.43%) and 15 cases were diagnosed as AGC,FN (0.13%). Subcategories of AGC along with their clinical presentations were described in Table- 1.

Histologic follow up of patients with AGC NOS and AGC FN were described in Table-2 and Table-3 respectively. Various interventions such as colposcopy, USG, HPV testing which the women detected with AGCs had undergone was described in Table-4.

Table-1: revalence of AGCs subcategories in different age groups and their clinical presentation.
n-63

		AGC NOS (n=48, 76.19%)	**AGC FN (n=15, 23.8%)**
A)Age group			
i)	30-39 years	28 (58.33%)	3 (4.76%)
ii)	40-49 years	11 (17.46%)	4 (6.34%)
iii)	>= 50 years	9 (14.28%)	8 (12.69%)
B) Clinical presentation			
i)	Abdominal pain	11 (17.46%)	6 (9.52%)
ii)	Vaginal discharge	34 (53.96%)	9 (14.28%)
iii)	Spotting/vaginal bleeding	3 (4.76 %)	12 (19.04%)

Table 2: Histologic Follow up Results of 48 patients with AGC-NOS.

n=48

Sl. No	Histology	Number	Percentage
1	CIN-1	6	12.5%
2	CIN-2 & CIN-3	4	2.4%
3	AIS	2	0.8 %
4	AC	1	0.6 %
5	Endometrial hyperplasia	1	0.6%
6	Ovarian Malignancy &	0	0 %
	Metastatic Carcinoma		
7	Endometrial carcinoma	0	0%
8	Benign	31	64.58%
9	Difficulty in diagnosis	3	6.25%

Table 3: Histologic follow up of 15 cases of AGC, FN.

Sl. No	Histology	Number	Percentage
1	CIN-1	1	6.6%
2	CIN-2/CIN-3	2	13.3%
3	AIS	5	33.3 %
4	AC	3	20 %
5	Endometrial Carcinoma	1	6.6 %
6	Metastatic Carcinoma	1	6.6 %
7	Benign	2	13.3 %

Table 4: Various other interventions the patients detected with AGC had undergone.

n=63

Interventions	Number	Percentage
1.Colposcopy	Abnormal findings seen in 26 cases	41.26%
2.Abdominal USG	Endometrial pathology – 2 cases Adnexal SOL -1 case	3.17% 1.58%
3.HPV testing	3 (Available)	4.76 %
4.Repeat cervical smear study	3	4.76%

Discussion

The Bethesda system of reporting of cervico -vaginal cytology was initiated at the National Institute of Health in Bethesda Maryland.[9,10] In December 1988. Recently an update has come up that is TBS-2014 update.[10] In our study all the cases of AGC were studied and categorized according to the TBS-2014 guidelines.

Atypical Glandular Cells (AGC) in cervical cytology smears (PAPs) are diagnosed when the glandular cells show nuclear atypia that exceeds reactive or reparative changes but do not exhibit the characteristic features of Adenocarcinoma In situ(AIS) or Invasive Adenocarcinoma (AC) .[11]

AGC are classified into the following Sub categories.[10]

- Atypical Endocervical cells (NOS or Specify in comments).
- Endometrial cells (NOS or specify in comments).
- Glandular cells (NOS or specify in comments).
- Atypical Endo cervical cells favor neoplastic
- Glandular cells favor neoplastic.

One of the major concern of AGC is that the cytological findings which characterize if have poor reproducibility between observers leading to interobserver variability . [12]

According to SF Derchian et al there is a poor correlation between initial Pap smear results of AGC with that of final histopathology report, which might be because of various factors affects the histopathological outcomes of AGC on pap test. [13]

The incidence of AGC has been reported to be 0.48%.[3] The malignancy rate of AGC have been reported to be 2.8-9.7%.[3] Due to the reported risk of precancerous and malignant lesions of AGC in cervical cytology, if bears a great clinical significance and need for further histopathological correlation. [14]

Following the Bethesda System guideline 2014 in our study all the cases were categorized as follows.

In our study out of 10950 cases AGC detected in 63 cases (0.57%). The sub-categorization of AGC in our study were AGC-NOS (n=48, 0.43%) and AGC-FN (n=15, 0.13%).

In our cases majority of the patients subcategorized under AGC-FN were > 50years age, with the complain of vaginal discharge. 34 cases from AGC-NOS patients and 12 cases from AGC-FN patients complained of vaginal discharge with a percentage of 53.96% and 19.04% respectively.

According to the guidelines of the American Society for colposcopy and cervical pathology (ASCCP) 2019[15] Women diagnosed with atypical glandular cells (AGC) on cytological smears have to undergo a series of interventions for proper clinical management, such as –

Colposcopy for abnormal clinical findings.

Colposcopy guided cervical biopsy.

Endocervical curettage

Since the precise discrimination of the cells of AGC (endocervical or endometrial) endometrial sampling along with colposcopy guided cervical biopsy and endocervical curettage is recommended in women aged >= 35 years. (According to the guidelines of the ASCCP). [15]

In our study all women aged >=35 years detected with AGC has undergone cervical biopsy & endocervical curettage along with pelvic examination, USG and endometrial biopsy.

In women < 35 years if AGC detected a repeat cervical smear testing done before any further investigation.

On cervical biopsy and endocervical curettage if the histopathology report show any one of the following features such as reactive, metaplastic, inflammatory lesions if needs no further evaluation. If the histopathology report shows presence of SIL (LSIL or HSIL) or AIS they have to undergo a standard established protocol for follow up (after conization) such a colposcopy, repeat PAP smear testing, HPV testing with an interval of 6 months. In our study on histopathology follow up the 48 cases of AGC-NOS shows the following diagnosis as – CIN 1 (6,12.5%), CIN 2 &3(n=4, 2.4%), AIS (n=2, 0.8%), AC(n=1, 0.6%), endometrial hyperplasia (n=1, 0.6%), benign (Reactive, metaplasia) (n=31, 64.58%) and in 3 cases (6.25%) there were difficulty in diag. Out of 15 cases of AGC –FN show the following diagnosis. [IN 1 (n=1, 6.6 %)], CIN 2/3 (n=2, 13.3%), AIS (n=5, 33.3%), AC (n=3, 20%). Endometrial Ca (n=1, 6.6%), metastatic carcinoma (n=1, 6.6 %) and benign lesions (n=2, 13.3%).

Since the glandular abnormalities have a tendency to extend high into the cervical canal and to develop skip lesions, identification and accessibility of these lesions on colposcopy is a critical challenge.[16]

In our study the abnormal finding on colposcopy was seen in 26 cases (n=26, 41.26%). This is due to the co-existence of HSIL with AGC which is similar to the study by KE Sharpless et al which stated that it is the abnormalities of the squamous component which is identified on coloscopy. [17]

HPV testing

Result of HPV testing is available only in 3 cases (4.76%).

Limitation of the study

One of the important limitation of the study was small sample size due to low incidence of AGCs on pap test.

There were very low number of results of HPV testing available.

The ancillary studies like high risk HPV testing and cell block preparation of cervical cytology specimens were not available, which might help to improve diagnostic accuracy of AGC specially in the cases of associated squamous abnormalities & could be helpful in better clinical management of these women. [18,19]

Conclusion

Since AGCs include a wide variety of conditions which range from reactive conditions to dysplasia to carcinoma and due to very low incidence of AGC multiple histological evaluation methods required(following PAP test) for earlier diagnosis and management of the malignancies detected on histologic follow up.

Conflict of Interest– None.

Funding – No financial support received.

Contribution of the authors– All authors having equal contribution.

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