



Original Article

# Atypical glandular cells: Help or hindrance

Narang Sanjeev<sup>1</sup>, Dargar Parul<sup>1</sup>, Singh Anjali<sup>1</sup>, Malhotra Apurva<sup>1</sup>

<sup>1</sup>Department of Pathology, Index Medical College, Indore, India

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## ABSTRACT

**Background:** A typical glandular cell is still a rare diagnosis despite refinement of the cytomorphologic criteria. This study aims to evaluate the follow up biopsies of cases diagnosed as atypical glandular cells on pap smears and to correlate with histological findings.

**Materials and Methods:** This is a retrospective study over a period of 7 years based on cyto-histopathological correlation of AGC diagnosed cases.

**Results:** Cytodiagnosis of atypical glandular cells was given in 212(0.05%), and 140 (0.66%) patients underwent biopsy. Among these 74(52%) were benign and 66(47%) neoplastic. Of the 39 cases reported as AGC favor neoplastic, 24(61%) showed malignancy with a positive predictive value of 61.5% and of the 101 cases classified as AGC-NOS on cytology, 59 (58%) cases showed benign features with a negative predictive value of 58.4%.

**Conclusion:** Our study highlights the immediate need of histological follow up of patients diagnosed with AGC. It is important because the range of diseases associated is very variable and includes benign as well as malignant conditions.

## Correspondence:

Dr Parul Dargar, MBBS, DNB

Assistant Professor, Department of pathology,

Index medical college and research centre, Nemawar road, Indore, Madhya Pradesh, India

Email: parulmaheshwari2009@gmail.com

ORCID ID: orcid.org/0000\_0009/97135363



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## INTRODUCTION

Atypical glandular cells is still a rare diagnosis despite refinement of the cytomorphologic criteria. Although continuous efforts over the last two decades has led to a better understanding of cervical glandular carcinogenesis, leading to an increase in sensitivity and precision in diagnosis of such lesions, still cervical cytology is contributing as a screening test for squamoid neoplastic lesions only. Diagnosing glandular lesions has been cumbersome due to both inefficient sampling and subtle features on microscopy.<sup>1</sup> Relative sensitivity of Pap smear reporting, regarding glandular pathology needs enhancement, so that appropriate treatment can be implemented. AGC (atypical

glandular cells) is the newer term by Bethesda group for the original category of AGUS “atypical glandular cells of undetermined significance”. This amendment was made to avoid the overlap with ASCUS (atypical squamous cells of undetermined significance). Secondly, in 2014 they have emphasized that the site of origin (endometrial or endocervical) be mentioned whenever feasible, since the follow up and treatment approach varies. However if diagnostic clues are limited then use of the term “atypical glandular cells” (AGC) would be appropriate. Next they have emphasized on the use of “favor neoplastic” and at the same time “favor reactive” has been considered as misleading and so has been dropped off, instead not otherwise specified (NOS) is the favorable terminology.<sup>2</sup>

AGC is an infrequent diagnosis, reported ten times less than the atypical squamous cells<sup>3</sup> and previous studies say that it represents less than 1% of cervical smears.<sup>4,5</sup> At the same time diagnosing AGC on cytology is crucial in view of the possibility of underlying high grade lesions which are seen more than in ASCUS.<sup>6</sup> The present study is an endeavor to evaluate the relative frequency of patients being diagnosed as AGC and to assess the significance of this diagnosis on follow up biopsies.

## MATERIAL AND METHODS

It was a longitudinal and retrospective study, based on analysis of results from pap smears and histopathological examinations carried out at a tertiary care centre of central India during January 2008 –January 2017. The study protocol had been approved by the institute's committee on human research. The cases considered for evaluation in this study are only those which underwent biopsies in the subsequent two years of cytological diagnosis of AGC on conventional PAP smears including both ‘NOS’ and ‘favor neoplastic’ categories. The next step involved classifying results of histopathological examinations into two main types of benign and malignant lesions. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) was calculated.

## RESULTS

Of the 35 TNBCs, there were 13 cases (37.1%) of IDC- During the period of study, out of a total of 4,22,514 Pap smears, 212 (0.05%) cases were diagnosed as AGC. Out of these 140 (0.66%) patients had undergone follow up biopsy within next two years. One hundred one (72%) cases were classified as AGC- NOS and 39 (27%) were classified as AGC- favor neoplastic. Histopathological assessment revealed 74 cases (52%) as benign and 66 (47%) cases as neoplastic.

Among the 101 cases classified as AGC-NOS on cytology; 59 (58%) cases showed benign features and 42 (41%) cases showed neoplastic changes on biopsy. On the other hand

among 39 cases reported as AGC favor neoplastic; 24 (61%) cases showed malignancy and 15 (38%) cases showed benign features on histopathological examination. Further PPV evaluated for the diagnosis of AGC-favor neoplastic was as 61.5% as shown in table 1. The NPV for AGC-NOS was 58.4 percent.

## DISCUSSION

Reporting atypical glandular cells on cyto-smears is challenging yet important since this diagnosis leads to a more significant disease process and is related to a spectrum of lesions ranging from benign to malignant.<sup>7,8</sup> A follow up biopsy becomes important after AGC diagnosis and the practice of just repeating pap smear like in case of ASCUS should be omitted.<sup>9</sup> Evidences from previous studies evaluating histological results in women with a diagnosis of AGC have shown that it includes a range of benign changes as well as cervical precursor lesions of glandular and/or squamous origins to invasive cervical cancer and other gynaecological cancers.<sup>10</sup> In the present study, the prevalence of diagnostic category of AGC was 0.05% which is comparable with study by Loos et al<sup>11</sup>, quoting 0.06 % prevalence of AGC among cervical smears. In our study 53% of cases were benign diagnoses on subsequent biopsy and 47% had malignancy. This finding also corroborated with previous studies which state that 50 to 80 % of AGUS diagnosed cases have only subtle histologic changes while 20 to 50 percent show significant features of cervical intraepithelial neoplasia, adenocarcinoma in situ or adenocarcinoma.<sup>12</sup> Another study by Mood et al in Iran concluded that 52.4% of patients with AGC had preneoplastic and neoplastic morphology on histopathology examination.<sup>13</sup> Similarly Loos et al revealed 46.9% malignant lesions on histological follow up of AGC diagnosis.<sup>11</sup> In the present study histopathological correlation revealed 39 out of the 66 malignant cases (in situ and invasive) to be of glandular origin (59%) while the remaining 27 (40%) cases to be of squamous origin. The proportion of adenocarcinoma is higher as compared to previous studies which quote higher percentage of invasive squamous cell carcinoma diagnosed through a histopathological analysis in patients with AGC as mentioned in six articles,<sup>15-20</sup> of which five were published from 2003 to 2009. Another study by Marques et al<sup>14</sup> carried out in 2011 states 12% to 46% of cases to be of glandular origin. As mentioned by these authors the incidence of clinically significant lesions ranged from 1.43% to 4.4 percent.<sup>17</sup> The diagnosis of cervical adenocarcinoma in these all articles, ranged from 1.4%<sup>14</sup>-18%.<sup>16</sup> A relatively higher percentage of confirmed cases of glandular origin on histopathology in our study is probably due to a high index of suspicion while screening pap smears and also because of stringent adherence to the cytological criteria for AGC diagnosis given by the Bethesda group. Another probable reason could be the rise in number of cervical adenocarcinoma in the last two decades.<sup>9</sup> One of the limitations of our study has been low

**Table 1: PPV and NPV of AGC diagnosis**

AGC	NEOPLASTIC BIOPSIES	BENIGN BIOPSIES	TOTAL	PPV	NPV
FAVOR NEOPLASTIC	24	15	39	61.5%	-
NOS	42	59	101	-	58.4%
<b>TOTAL</b>	<b>66</b>	<b>74</b>	<b>140</b>	<b>-</b>	<b>-</b>

PPV (61.5%) because of low prevalence and rarity of AGC as a cytologic diagnosis. AGC is a diagnostic challenge for other researchers also specially because of inter-observer variability and low PPV.<sup>21</sup> Another limitation comes from restricted period of follow up i.e. two years from cytological to histological assessment, despite knowing that the period of evolution of an initial cervical lesion into a distinct invasive form may be up to 20 years.<sup>22</sup>

The high rate of malignancy associated with AGC diagnosis, as in present study (47%) and also concluded in previous studies emphasizes the need to adopt an aggressive assessment strategy for AGC.<sup>13,23,24</sup>

## CONCLUSION

The result highlights importance of improving diagnosis as well as reinforces immediate histological follow up of patients diagnosed with AGC. Secondly a close surveillance for many years is also recommended. This will go a long way in treatment of this dreaded disease early in the course and thus serve to significantly reduce the morbidity and mortality associated with advanced disease.

**Conflict of Interest:** None

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