Glandular Atypia In Cervical Smear: Cytohistologic And Clinical Correlation

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Citation

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Abstract

The purpose of this study was to audit and analyse all the cases of Glandular Atypia reported by cervical cytology. The cytological features were correlated with histopathology diagnosis and subsequent follow up of these patients.

Design: A retrospective case note based study from January 1995 through December 1999, identifying all patients with cervical smears reported as Glandular Atypia. Their subsequent colposcopic examination, treatment, final diagnosis and follow up were retrieved from the notes.

Results: Of the 78 women with Glandular Atypia reported in their cervical smear, the mean age was 38.6 years and 21 (27%) were nulliparous. The median follow up of these women was 18 months. On further investigation 4 cases were diagnosed to have endocervical adenocarcinoma, three cases of squamous cell carcinoma of the cervix and three cases of endometrial adenocarcinoma. One case of microinvasive adenocarcinoma of the cervix was diagnosed. Collectively 11 cases (14%) were malignant in 78 cases.

Seven cases (8.9%) were diagnosed as Cervical Glandular Intraepithelial Neoplasia (CGIN) and 38 cases (48.7%) of cervical intraepithelial Neoplasia (CIN) with or without involvement of the cervical glands. Eight cases (10.2%) were diagnosed as chronic cervicitis and two cases of cervical endometriosis. Three cases (3.8%) only were normal following investigations.

Conclusion: This retrospective study suggested that a diagnosis of Glandular Atypia in the cervical smears correlated with clinically significant lesions in the majority of cases.CIN and CGIN were the most common lesions identified. Close follow up with Colposcopy and both cytobrush and spatula cytology is recommended in-patients where CGIN has been diagnosed and treated by local ablation or excision without hysterectomy.

INTRODUCTION

The incidence of cervical adenocarcinoma is increasing in both relative and absolute terms over the past two decades (Singleton et al, 1981). Until now there are no standard guidelines for the clinical management of women with abnormal glandular cytology.

The natural history of cervical glandular intraepithelial neoplasia (CGIN) is less understood than that of squamous intraepithelial neoplasia (CIN), with which it is often associated. It affects the surface epithelium and the endocervical crypts and in some cases is discontinuous or multifocal.

Based on the NHSCSP publication No 10 (1999) for histopathology reporting in cervical screening, there is, as yet, no agreed nomenclature or system of grading for CGIN. It is preferable, in the present state of knowledge, to recognize only two grades of CGIN, High grade CGIN (CGIN 3 or adenocarcinoma in situ) and low-grade CGIN encompassing cellular abnormalities of a lesser degree. The term low grade CGIN should not necessarily be taken to indicate that there is a lesser chance of progression of the disease. It is recommended that the clinical management of low grade and high grade CGIN should be the same.

The diagnosis, evaluation and treatment of glandular neoplastic lesions of the cervix present challenges to both the cytopathologist and clinician because of their rarity, lack of characteristic colposcopic findings and usually inaccessible endocervical location (Kumar and Howell, 2000). In response to this dilemma, this study seeks to

investigate the type of lesion found with glandular dyskaryosis and attempts to form a management plan when a clinician is confronted with such a problem.

PATIENTS AND METHODS

A retrospective review of the records of the regional cytology laboratory, Department of Pathology, Stirling Royal Infirmary identified 78 patients who had cervical glandular abnormality, detected on cytological examination of cervical smears over a period of five years from January 1995, through December 1999. Ethical assessment for this work was sought and no ethical issues were found.

All the seventy-eight patients were referred to the Colposcopy clinic at Stirling Royal Infirmary, Forth Valley Acute Hospitals Trust. The case notes of these women were reviewed to obtain the following data: age, parity, smear result at referral, symptoms (IMB, menorrhagia, discharge, PCB & PMB), medications, contraception, smoking status, previous cervical smear abnormality, previous cervical surgery or treatment, colposcopic findings, histological diagnosis and treatment as well as the duration and outcome of follow up.A chi square test is used to correlate presence of significant disease (dysplasia or worse) with age, use of exogenous hormones and colposcopic findings. $P < 0.05$ was taken as significant.

RESULTS

The mean age of patients at cytological examination was 38.6 (range 18-69 years). Twenty-one patients (27%) were nulliparous. All patients were referred because of an abnormal smear detecting glandular atypia with or without squamous dyskariosis. All patients had colposcopic directed biopsy except for one patient who was pregnant at the time of colposcopic examination. In some cases additional histopathlogical examination was performed on the specimens obtained by LLETZ, cone biopsy, pipelle endometrial sampling or hysterectomy. The results of final histopathologic diagnosis are listed in Table1.

Figure 1

Table 1: Results Of Final Biopsy (N= 78)

CIN1 + HPV	8
CIN2 + HPV	8
CIN3 + HPV	18
CIN3 + HPV + Involvement of the glands	4
High grade CGIN	3
Low grade CGIN	1
High grade CGIN + CIN1	1
High grade CGIN + CIN2	1
High grade CGIN + CIN3	1
cervical microinvasive adenocarcinoma	1
Cervical adenocarcinoma	4
Cervical squamous cell carcinoma	3
Endometrial adenocarcinoma	3
Benign Cervical polyp	3
Endometrial glandular atypia in a cervical polyp	1
Cervical tuboendometriod metaplasia	1
Cervical endometriosis	2
Non-specific cervical inflammation	8
Viral Atypia only	3
No pathology	3
Biopsy not done (patient pregnant)	1

Regarding contraception, 15 women (19.2%) were on combined OCP. One woman was on minipills. Two were using Depo provera injections and two were on progestagen implants. Four were sterilized and two were using copper IUCD. The remaining 52 women were using either no contraception, condoms or their partners had been sterilized. There was no correlation between the type of contraception and the diagnosis of a significant disease.

Regarding symptoms, 60 women (76.9%) were asymptomatic. Two had IMB. One had menorrhagia. Five women had excessive vaginal discharge. Six women were complaining of PCB and one had PMB. The remaining three women had a combination of more than one of the above symptoms.

In total, 11 (14%) cases of cancer were diagnosed in our series. Five (6.4%) were cervical adenocarcinoma one of these was microinvasive. Three (3.8%) were cervical squamous cell carcinoma and another three were endometrial adenocarcinoma. The average age for the cancer cases was 46.5 (Range 32-69). Four cases were asymptomatic, one with PMB, five with PCB and one with PCB and menorrhagia. These four asymptomatic cases were cervical cancers (One microinvasive, two adenocarcinoma and one squamous cell carcinoma). Four of these 11 cases were postmenopausal. Two cases of the three diagnosed as endometrial adenocarcinoma were using local vaginal estrogen to treat atrophic vaginitis for an average of 10 months.

Mean follow up was for 18 months (range 12- 24 months). The seven cervical cancers diagnosed in the series were treated with radical hysterectomies and pelvic lymphadenectomies (Table 2). Two of the three patients with endometrial adenocarcinoma were treated with TAH+BSO. The remaining case had in addition lymph node sampling that was positive and subsequently had external radiotherapy to the pelvis. One patient had microinvasive adenocarcinoma of the cervix discovered on loop excision. Her loop excision was shown to have completely removed the microinvasive lesion. She completed 18 month of cytologic and colposcopic follow up successfully.

Figure 2

Table 2: Treatment of the patients with abnormal glandular smear (n =78)

Treatment Procedure	Number	Percentage
LLETZ	37	51.4
Cone Biopsy	15	20.9
Hysterectomy	4	1.4
Radical hysterectomy with pelvic lymphadenectomy	7	9.7
Radiotherapy	1	1.3
Cold coagulation	4	1.4
cervical polypectomy	1	1.4
No treatment	9	12.5

One of the rare findings was cervical tuboendometrioid metaplasia. This change seems to occur more likely in women who have had previous treatment to their cervix. This is characterized by replacement of the endocervical surface or crypt epithelium by cells of typical tubular or endometrioid type. In cervical smears, endometrial stromal cells may be misinterpreted as severe dyskariosis. Large endometrial cell fragments of glandular and/or stromal cells or the glandular cells of tuboendometrioid metaplasia may be misinterpreted as CGIN.

Figure 3

Figure 1: Atypical glandular cells showing the typical three - dimensional structure and feathered edge.

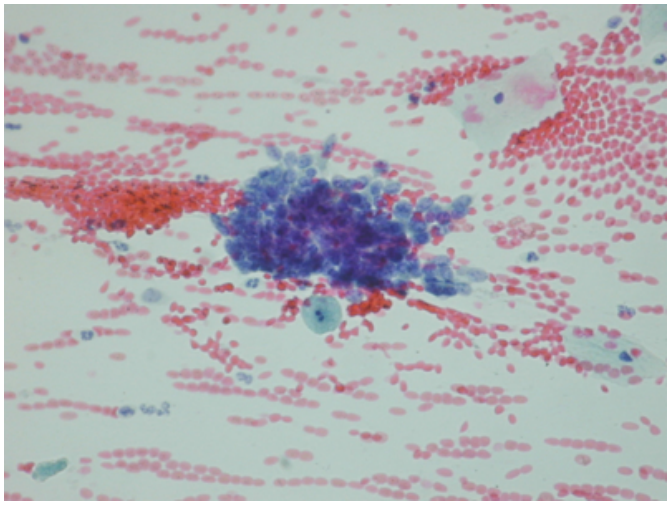
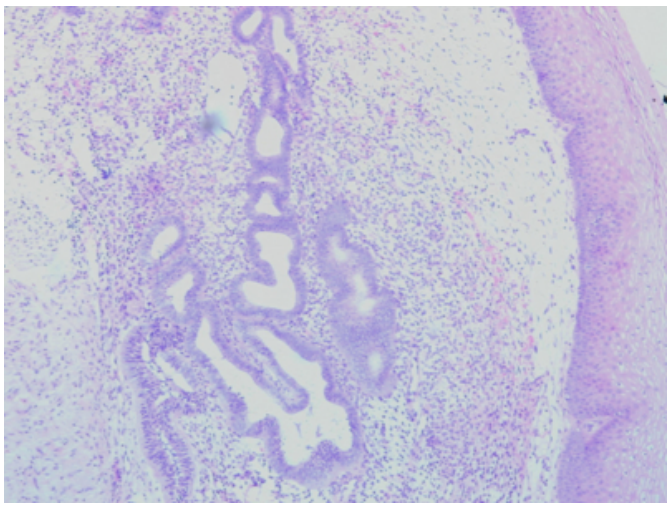


Figure 4

Figure 2: Histological picture of glandular dysplasia. One gland at the middle of the slide shows both normal and dysplastic epithelium.



DISCUSSION

Glandular dysplasia, although apparently less common than squamous dysplasia, is almost certainly an underdiagnosed lesion (Luesley et al, 1987). Clinically significant lesions were found in high proportion of cases, just over half of these were found to be squamous cervical lesions. Mohamed et al (2000) in their clinical review of borderline glandular cells on cervical cytology found 57% of cases had clinically significant lesions: 16% invasive disease, 33% CIN and 7% high grade CGIN. Earlier reported studies have also shown high proportion (50-83%) of significant histological lesions when glandular abnormalities have been reported in the

cervical smears (Bose et al, 1994. Goff et al 1992).

In our review 89% of cases had clinically significant lesions. Fourteen percent (14%) invasive disease, 52% CIN and 7% CGIN. This high incidence of CIN is not surprising giving the more frequent occurrence of squamous intraepithelial neoplasia relative to cervical glandular epithelial neoplasia (Goff et al 1992. Burja et al 1999). The common occurrence of coexistent squamous neoplastic lesion with glandular neoplastic lesion of the cervix has also been reported by Jaworsky et al, 1990. This observation is most likely explained by the common aetiologic factors associated with both lesions.

A high proportion of CGIN lesions test positive for human papilloma virus (HPV). HPV DNA has been frequently detected (40-70 %) in high-grade CGIN lesions but in only a few cases of low grade CGIN (Tase et al, 1989). We found histologic features of human papilloma virus infection in isolation or in combination with other cervical neoplastic lesion in 34% cases.

Benign lesions, which can be detected in association with abnormal glandular cytology, include microglandular hyperplasia, inflammation, tuboendometrial metaplasia, cervical endometriosis, isolated HPV or endometrial hyperplasia. (Goff et al, 1992. Buckley et al 1994. Jackson et al 1996).

In our series chronic cervicities was diagnosed in 10% of cases and Isolated HPV in 4%. We found two cases of cervical endometriosis and one case of tuboendometrial metaplasia. The case of tuboendometrial metaplasia had had loop excision of the cervix for CIN 3 lesion two years prior to her glandular atypia smear. She had repeat of her loop excision that revealed complete removal of the metaplastic cells. The subsequent smears including endocervical cytobrush were negative up to completed 2 years of follow up.

One of the two cases of cervical endometriosis had had cervical cautery in 1986 for postcoital bleeding. She was complaining of recurrence of her PCB and had cervical smear showing glandular atypia. Cervical biopsy at the colposcopy clinic diagnosed cervical endometriosis. She was treated with knife cone biopsy and her PCB subsequently stopped. Her cervical smear follows up were negative up to one year following her treatment.

In pregnancy, Arias Stella changes similar to that in the endometrium may also occur in the cervical crypt epithelium. The nuclei are large and hyperchromatic with vacuolated cytoplasm. This Arias Stella change in the cervical smear can sometimes give rise to diagnostic difficulties (NHSCSP working party, 1999). We had one case of glandular atypia during pregnancy. She had had loop excision for CIN 2 lesion two years prior to her abnormal smear. Colposcopic examination was satisfactory and repeat of her smear together with endocervical cytobrush was negative and showing normal endocervical cells. Her postnatal smears were negative including the use of cytobrush up to one year follow up.

Overall, management of patients with cervical glandular atypia should be individualized. Colposcopy should be performed and loop excision or cone biopsy considered. Pipelle endometrial sampling or hysteroscopy D&C should be considered in symptomatic patients with IMB, menorrhagia, or PMB. The sensitivity of a punch biopsy to detect glandular intraepithelial abnormality is poor due to lack of criteria for colposcopic recognition and to the finding that lesions may be confined to small area in the endocervix (Luesley et al, 1987). Local ablation is not an ideal form of treatment.

CONCLUSION

This retrospective study suggests that a diagnosis of cervical glandular atypia correlated with a clinically significant lesion in the majority of cases. In addition to malignant lesions, cervical squamous intraepithelial neoplasia and cervical glandular intraepithelial neoplasia were the most common lesions identified. Close follow up with colposcopy and both cytobrush and spatula cytology is recommended for patients where CGIN has been diagnosed and treated without hysterectomy.

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