Uterine Cervix: Benign Histomorphological Spectrum With Emphasis On Pseudoneoplastic Lesions

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Abstract

Background: Non-neoplastic lesions of cervix constitute a wide variety of lesions in the hysterectomy or cervical biopsy specimen. Most of these lesions are commonly seen in women of reproductive age group. The aim of the current study is to determine the incidence and to categorize the histological types of various non-neoplastic lesions of the cervix with emphasis on pseudoglandular lesions.

Materials And Methods: The present prospective study includes 282 specimens from either hysterectomy or cervical biopsy specimens. The study was conducted in the Department of Pathology, RajaRajeswari Medical College and Hospital over a period of one and a half year. All the lesions were categorized after routine tissue processing and staining.

Results: The study includes 682 non-neoplastic cervical lesions. The most common lesion was inflammatory, reactive or reparative 459(67.3%) cases followed by glandular hyperplasia in 41(6.0%) cases, metaplasia and ectopias in 167(24.4 %) cases and benign neoplasm in 15(2.3 %) cases.

Conclusion: The spectrum of cervical lesions is vast and categorization can provide the basis for identifying the etiology and their clinical presentations. Recognition of the pseudo-neoplastic entities is of crucial importance in preventing overtreatment and thereby reducing the morbidity.

Introduction

Non neoplastic lesions of the cervix forms a large proportion of diagnosis, obtained from small biopsy or hysterectomy specimens. They are seen across all women with peak in reproductive age group. Some of these can mimic in situ and invasive neoplastic lesions and many precursor lesions and malignant neoplasms may mimic benign conditions.Non neoplastic glandular lesions such as deep nabothian cyst, diffuse laminar hyperplasia, tunnel clusters, microglandular hyperplasia (MGH), and mesonephric hyperplasia can mimic neoplastic lesions.Endometrial adenocarcinoma with mucinous differentiation or a microglandular pattern can closely mimic MGH, often resulting in a diagnostic dilemma in a cervical biopsy specimens. Deep glands and cysts are common non-neoplastic lesion of the cervix that is important to distinguish from adenocarcinoma in small biopsy specimens. Tunnel clusters, which are also usually an incidental microscopic finding and microglandular hyperplasia which, when florid, may be misdiagnosed as neoplastic conditions. "Florid deep glands" (FDG) can be mistaken for adenoma malignum of the cervix (minimal deviation adenocarcinoma of mucinous type).Familiarity with these pseudoneoplastic entities by the pathologists is

needed to avoid over diagnosis and hence inappropriate treatment.

This article is an attempt to know more about the clinic morphologic aspects of glandular hyperplasias of uterine cervix.

Materials And Methods

The present prospective study was undertaken in the department of pathology at RajaRajeswari Medical College and Hospital during a period from January 2021-June 2022. The study included both cervical punch biopsy and hysterectomy specimens. A detailed clinical history including age, parity, clinical findings and provisional diagnosis were collected from the case files. All the specimens were received in the histopathology section. The gross findings of the specimens were examined and recorded, followed by fixation in 10% formalin for 24 hours and the specimens were submitted for processing. After routine processing, sections were cut at 3-5 µ thickness and stained routinely using Hematoxylin and Eosin stain. These stained sections were analyzed by light microscopy. All the benign lesions of the uterine cervix involving ectocervix and endocervix were included. Inadequate biopsy specimens without lining epithelium and stromal fragment and specimen diagnosed as malignant were excluded from the study. The non-neoplastic lesions of the uterine cervix were categorized based on the etiology and histomorphological examination.

Results

A total of 282 cervical specimens were received,of which 244 were hysterectomy specimens and 38 cases were cervical biopsy specimens.Non-neoplastic lesions were analyzed and 682 lesions were identified as in (Table-1).Multiple coexisting lesions was observed in many specimens. The common lesions encountered were inflammatory lesions,459(67.3%) cases and the least were benign neoplasms, 15(%) cases.

The first category; inflammatory, reactive or reparative lesions, 459(67.3%) cases were identified. 223cases, were seen in age group between 41-50years, followed by 116 cases in 31-40years and least in the age group of <30 years, as seen in (Table-2).Under this category, chronic non-specific cervicitis was the commonest lesion comprising of 357 (52.34%) cases.Nabothian cysts were seen associated in 84(49.41%)cases. Koilocytic changes; which is categorized as low grade squamous intraepithelial lesions in Papanicoloau smear; were seen in 31(4.54%) cases. Papillary endocervicitis was seen in 69(10.11%) cases and Follicular cervicitis in 2(3.22%) cases as seen in (Table 3).

The 2nd category Glandular hyperplasia ,were seen in 41cases (6.0%) as seen in (Table-4).In the present study, Diffuse laminar endocervical glandular hyperplasia, was frequently seen in 21(3.07%) cases,Microglandular hyperplasia was seen in 15 (2.19 %%) cases, Tunnel clusters in 10 (1.46%) cases, Florid deep glands in 4 (0.58%)cases and 1(0.14) case of endometriosis. Age wise distribution of Glandular hyperplasias of uterine cervix encountered in the present study showed highest number of cases of 16 in the age group of 40-49 years, followed by, 15 in 30-39, 6 in 20-29, and 3 in 50- 59years as seen in (Table 5).

Excessive vaginal bleeding and pain abdomen were the most common presenting complaints seen in 12 and 9 cases each, followed by mass per abdomen in 3 cases, white discharge per vagina in 11 , Irregular vaginal bleeding in 4 cases and dysmenorrhoea in 2 as seen in (Table-6).

The 3rd category metaplasia and ectopies, were observed in 167(43.17%) cases and was seen in the mean age group between 31-60 years. Squamous metaplasia was the commonest finding seen in 163(23.9 %) cases followed by tuboendometrial metaplasia in 1(0.14 %) case. Mesonephric rests was seen in 1(0.14%) case and tubal metaplasia was seen in 2(0.29 %) cases respectively. (Table 7).

The 4th category, benign neoplasm, cervical polyps consisted of 15(2.1%)cases and was frequently seen in age the group of 30-50 years.2(0.29) cases of Leiomyomatous polyp was seen in the study as documented in (Table-1).

TABLE 1: Diagnostic Category of Non-neoplastic Uterine Cervical Lesions

Diagnostic Category	Diagnosis	Frequency %
Inflammatory, reactive and reparative lesions(Category-1)	Chronic cervicitis Papillary endocervicitis Koilocytic changes Follicular cervicitis	67.3%
Glandular hyperplasia (Category-2)	Nabothian cyst Diffuse laminar endocervical glandular hyperplasia(DLEGH) Tunnel clusters Microglandular hyperplasia Endometriosis	6.0%
Metaplasia and Ectopias,(Category-3)	Squamous metaplasia Tubal metaplasia Tubuoendometrial metaplasia Mesonephric rests	24.4%
Benign neoplasm ,(Category-4)	Endocervical polyp Leiomyomatous polyp	2.3%

TABLE 2: Age wise Distribution of Uterine Cervical Lesions

Age Group	Inflammatory	Glandular hyperplasia	Metaplasia and ectopias	Benign neoplasm
<=30	15	5	2	1
31-40	116	15	55	4
41-50	223	17	76	5
51-60	85	3	21	3
>61	20	0	13	2

TABLE 3: Distribution of Inflammatory, Reactive and Reparative Lesions of Uterine Cervix

Diagnosis	Frequency %
Chronic cervicitis	357(52.34%)
Koilocytic changes	31 (4.54%)

Papillary endocervicitis	69(10.11%)
Follicular cervicitis	2(3.22%)

TABLE 4: Distribution of Glandular Hyperplasias of Uterine Cervix

Sl.no	Lesions	Frequency
1	Diffuse laminar endocervical glandular hyperplasia	21(3.07%)
2	Microglandular	15(2.19%)
3	Florid deep glands	4(0.58%)
4	Tunnel clusters	10(1.466%)
5	Endometriosis	1(0.14%)

TABLE 5: Age wise distribution of Glandular Hyperplasias of uterine cervix

Age Range	No. of Cases
20-29	6
30-39	15
40-49	16
50-59	3

TABLE 6: Distribution of presenting complaints of the Glandular hyperplasias

Presenting complaints	No.of cases
Excessive vaginal bleeding	12
Pain abdomen	9
White discharge per vagina	11
Irregular vaginal bleeding	4
Mass per abdomen	3
Dysmenorrhoea	2

TABLE 7: Prevalence of Metaplasia and Ectopias

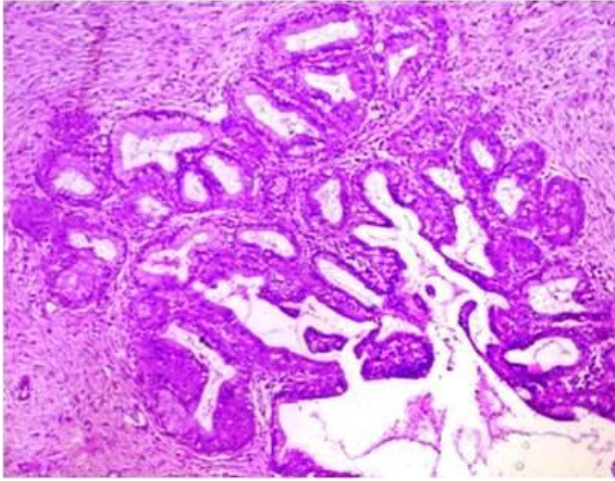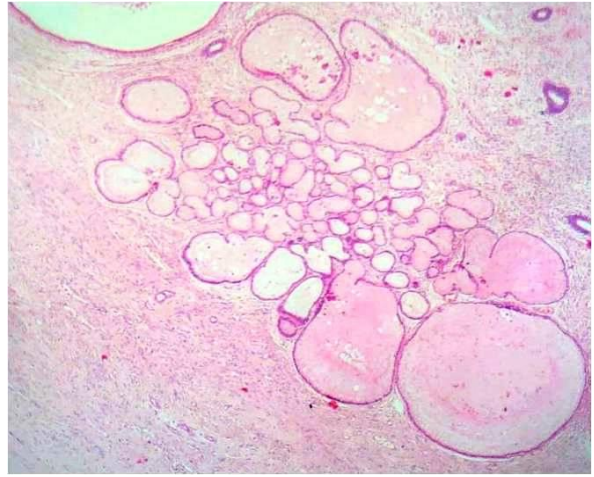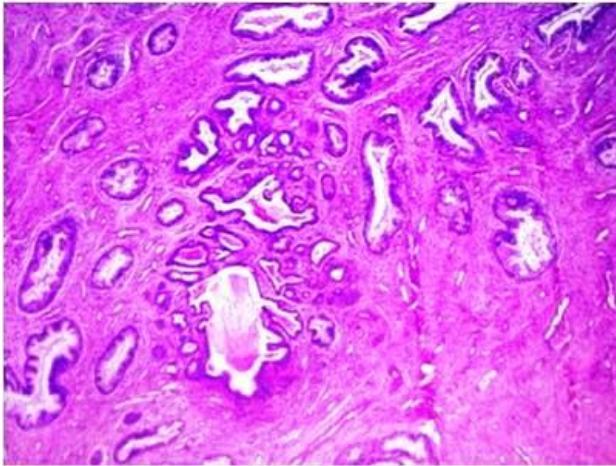| Diagnosis	Frequency
Squamous Metaplasia	163 (23.9%)
Tubal Metaplasia	2(0.29%)
Tuboendometroid metaplasia	1(0.14%)
Mesonephric rest	1(0.14%)

Fig (A)   **Fig (B)**

Photomicrograph in Fig(A) shows Tunnel cluster of Type A-Composed of small closely packed glands in a lobular architecture and Fig(B) -Tunnel cluster of Type B- Cystically dilated glands with mucin secretions in H&E,40x

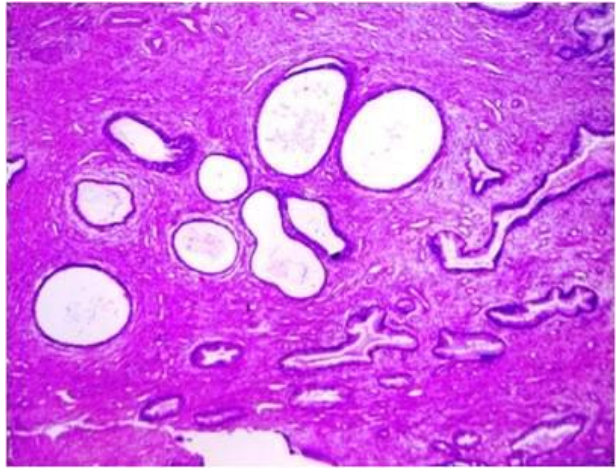**Fig(C)**   **Fig(D)**
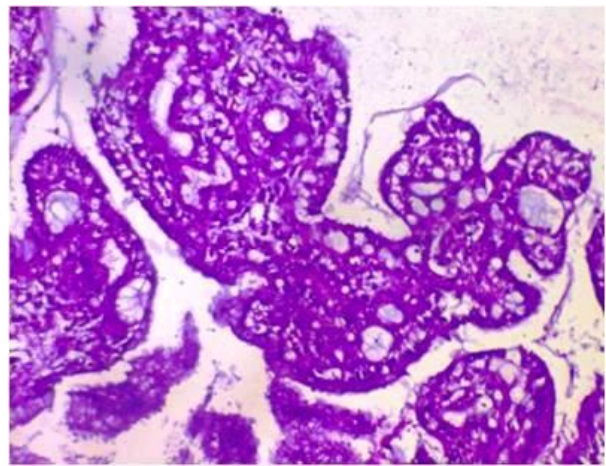
Photomicrograph in Fig(C) shows Diffuse proliferation of glands limited to inner third of cervical wall and Fig(D) shows tightly packed glands with subnuclear vacuolation,H&E,40x

Fig (E)   **Fig (F)**

Photomicrograph of Fig(E) shows multiple cystically dilated Nabothian cysts with secretions and Florid proliferation of glands extending to a depth of more than 9 mm in Fig(F),H&E,40x

Discussion

Cervical biopsies constitute the major bulk of specimens received in the department of pathology and benign lesions were encountered in vast number. Many of these are rare, not given much importance but can mimic neoplastic lesions. A variety of pseudoneoplastic lesions may occur in the cervix and create problems in differential diagnosis. Failure to differentiate them from well-differentiated adenocarcinoma can result in potentially major adverse consequences for the patient in the form of inappropriate therapy[1].

Reports have considered non-neoplastic lesions of the uterine cervix as cervical inflammatory lesions which may be acute or chronic and they occur as a result of infective or non infective etiology.Most of the other non-neoplastic lesions like tunnel clusters, mesonephric hyperplasia, and microglandular endocervical hyperplasia are not given much importance even though they mimic insitu or malignant neoplasm.

Inflammatory reactive and reparative lesions were the most common lesion encountered in our study. Chronic non-specific cervicitis,357 (52.34 %) cases were the most common finding. It was seen associated with other lesions like squamous metaplasia, koilocytosis and pseudoglandular lesions like nabothian cyst, tunnel clusters, florid glands,

DLEGH and microglandular hyperplasia. Paaronen J et al has stated that the etiology of chronic non-specific cervicitis is variable and is of importance because it may lead to endometiritis, salpingitis and pelvic inflammatory disease through ascending intraluminal spread, and it may also play a role in the initiation or promotion of neoplasm[1,2].

Other lesions encountered in the category were papillary endocervicitis in 69(20.7%) cases, Koilocytic changes in 31(9.19 %) cases and Follicular cervicitis in 2(0.59%) cases. Papillary endocervicitis comprises papillae of various sizes which are filled with inflammatory cells. This is not really a mimic unless florid when the main differential diagnosis to consider is a villoglandular adenocarcinoma[1,2,4].

Koilocytic changes are the morphologic hallmark of HPV infection of the cervical squamous epithelium. In our study it was observed in 31 (9.19%) cases which correspond with the findings of Basnet et al. Normal basket weave hyperkeratosis should not be confused with koilocytosis, as the diagnosis of koilocytosis has important therapeutic implications on the patient. Many studies have also proven that HPV infection (koilocytosis) in association with HIV infections have predisposed to cervical intraepithelial carcinoma and malignancy[2,3].

Follicular cervicitis was seen in 2(0.59%) cases. The presence of lymphoid follicle is often associated with chlamydial infection. They do not mimic any particular neoplasia. However, high-grade CIN present above any lymphoid follicles can be spongiotic or thin and easily overlooked[2,4] .

The second group, glandular hyperplasias were seen in 41(6.0 %) cases. Diffuse laminar endocervical hyperplasia (DLEGH) was seen in 21(3.07%) cases, which corresponded with the finding of Naveen kumar B.J who had observed it in 7/124 (5.65%) of cases[4].

DLEGH comprises of tightly packed, small to medium-sized glands present usually in the upper one third of the wall generally accompanied by chronic inflammation. No lobulation is seen but instead there is a sharp demarcation by a straight line between the hyperplastic glands and the underlying stroma. At low power it may mimic adenoma malignum or cervical glandular intraepithelial neoplasia (CGIN) [2] .

Microglandular hyperplasia was seen in 15(2.19 %) cases. Basnet et al observed 13 cases of MEH, of which more than half the patients had given a history of the use of oral contraceptives. Microglandular hyperplasia is a benign proliferation of endocervical glands and is often an incidental finding. It occurs in the reproductive age group and particularly in women who are either pregnant or are taking progesterone. Microscopically, it comprises small, closely packed glands with mixed inflammatory cells in the intervening stroma. The most characteristic feature of MGH is cytoplasmic vacuolation rendering a lace-like pattern. It is frequently accompanied by squamous metaplasia and endocervical polyps. As a result, this can mimic clear cell carcinoma or the microglandular variant of adenocarcinoma (especially endometrial carcinoma) [2,5].

Tunnel clusters was found in 10 (1.46%) cases. All the tunnel clusters were incidental findings in cervix as observed by Manek et al and and Naveen kumar B.J.Tunnel clusters are of two types, Type A which is non-cystic, comprises of small closely packed glands often in a lobular architecture and Type B are cystic and usually occurs near the surface and not deep in the stroma.However,when they do have glands reaching deep into the stroma, they can mimic the microcystic variant of usual endocervical adenocarcinoma[4,6].

Four cases of florid deep glands of the uterine cervix were noted in the present study in the age group of 35years (3cases) and 38years (1 case) .In a study by D Daya and R H Young, 2 cases were noted in the age of 43 and 62years respectively[5,8].

Nabothian cyst was seen in 84(49.41%) cases. Our results found in the study were slightly less than the study conducted by Naveen Kumar B.J, 70(3.14%) cases. Nabothian cyst is thought to arise due to blockage of endocervical glands and associated changes. Grossly they appear as cystic spaces filled with mucin and microscopically lined by flattened epithelium which when extend deep into the endocervical wall may be mistaken for malignancy [4,5] .

Endometriosis comprises of ectopic endometrial glands and stroma anywhere in the cervix but usually in the superficial one third of the wall. It can be cystic or may even form a circumscribed mass when in the form of an endometrioma.The pathogenesis is either by implantation at surgery or trauma or true metaplasia like tubal and tubo-endometrioid metaplasia. It can mimic CGIN[5,7].

The third group metaplasia and ectopies were observed in 167(43.17% %) cases with mean age group being 41-50 years. Squamous metaplasia was seen in 163(23.9%) cases and was the commonest finding similar to the study observed in the Basnet et,al and Deepa et al. Squamous metaplasia is by far the most commonest metaplasia of the cervix occurring at the transformation zone. Immature squamous metaplasia can also mimic a stratified mucinous intraepithelial lesion (SMILE).Tubal and Tuboendometrial metaplasia affect the glandular epithelium of the endocervix.Tubal metaplasia is diagnosed when the specimen from the endocervix contains all three cell types found in fallopian tube(ciliated, secretory and intercalated). Tubal metaplasia when combined with features of endometrial mucosa, the term Tuboendometrial metaplasia is used.Tubal metaplasia is often found following conization, therefore it has been suggested that it represents aberrant differentiation following injury. In our study each of these lesions were encountered.Mesonephric rests were seen in 1(0.14%) case. This was in concordance with the studies of Basnet et,al [2,4,5,6,8].

Among the fourth category,endocervical polyp was seen in the study, accounting for 15 (2.1 %) cases.Endocervical polyps are not true polyps but are thought to be associated with chronic inflammatory changes (polypoid cervicitis). Polyps with branching papillary configurations are termed papillary endocervicitis and occur mainly in the 4th to 6th decades of life .Endocervical polyp can be vascular, fibrous or heavily inflamed and there were often microglandular hyperplasia. Within these polyps, there can be CIN or CGIN[4.7].

Conclusion

Non-neoplastic lesions of the cervix are frequently encountered in women of reproductive age group. The categories emphasized can provide the basis for identifying the etiology and their clinical presentations. Glandular hyperplasias of the cervix are mostly due to hormonal stimulation either during pregnancy or due to consumed pills. Missing out these lesions or over diagnosing it as malignancy; can have potentially adverse consequences, for the patient.

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