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Original Article

Uterine Cervix - Benign Histomorphological Spectrum

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ABSTRACT

Introduction: Non neoplastic lesions of cervix form a wide variety of lesions in the cervical biopsy specimen or hysterectomy specimens. Chronic cervicitis is the commonest finding; but can be associated with other underlying pathologies. In our study we aim to study and categorize the morphology of non neoplastic lesions of cervix in cervical biopsy specimen or hysterectomy specimens into inflammatory, reparative or reactive lesions, glandular hyperplasia, metaplasia and ectopies and benign neoplasm.

Materials and Methods: This is a retrospective study that consisted of 520 slides retrieved from the records of department of histopathology KIST medical college. Whenever required block were retrieved and recut sections were made. All the benign lesions were included in the study.

Results: The commonest lesions diagnosed were inflammatory, reparative or reactive changes 513 (98.6%) cases, followed by metaplastic changes 311 (59.8%) and glandular hyperplasia in 44 cases (8.4%). Benign neoplasms were seen in 33(6.3%) cases.

Conclusions: Cervix is a target organ for varieties of neoplastic and non neoplastic diseases. There are many benign mimics of malignant cervical lesions. It may be difficult to interpret adequately in a small biopsy specimen however it is necessary to distinguish between these benign lesions and their mimics to prevent unnecessary inappropriate treatment to the patient.

Keywords: Benign; Cervicitis; Endocervical polyp; Hyperplasia; Mesonephric rest ; Microgalndular; Nabothian cyst; Squamous metaplasia; Tubal metaplasia; Tunnel cluster

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INTRODUCTION

Cervix is a gateway to varieties of neoplastic and non-neoplastic lesions.[1] 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. Histopathologic studies of the cervix is very important for early diagnosis of the cervical diseases as they have advantage of being readily available, relatively cheap, and technically easy.[2]

The reports are often interpreted as "chronic cervicitis" which is of no significant relevance to the treating physicians. Inflammatory lesions are the commonest among the non-neoplastic lesions.[1] A wide variety of non neoplastic lesions occurs in the uterine cervix in the background of inflammation. Recognition of these pseudoneoplastic entities is of crucial importance in preventing overtreatment of such lesions that often occur in young women of reproductive age.[3] Early recognition of Human papilloma virus (HPV) related cervical changes can prevent progression to cervical carcinoma. In the small biopsy specimens early

diagnosis of these lesions might be of help to the clinicians for appropriate treatment. Non neoplastic glandular lesions such as deep nabothian cyst, diffuse laminar hyperplasia, tunnel clusters, microglandular hyperplasia (MGH), and mesonephric hyperplasia can mimic neoplastic lesions.[4] Endometrial adenocarcinoma with mucinous differentiation or a microglandular pattern can closely mimic MGH, often resulting in a diagnostic dilemma in a small biopsy specimens.[5] Deep nabothian cyst are an uncommon non-neoplastic lesion of cervix that is important to distinguish from adenocarcinoma[6] in small biopsy specimen. Tunnel clusters, which are also usually an incidental microscopic finding, show lobular clusters of glands rather than the diffuse scattering of glands seen in florid deep glands.[7] Tunnel clusters[8,9] and mesonephric[10] microglandular hyperplasia[6] which, when florid, may be misdiagnosed as neoplastic conditions. "Florid deep glands" (FDG) can be mistaken for an aggressive neoplasm, specifically adenoma malignum of the cervix (minimal deviation adenocarcinoma of mucinous type).[7] Over diagnosing as malignant can have potentially adverse consequences for the patient in the form of inappropriate treatment.[7]

Thus, categorization and familiarity of the cervical non neoplastic lesions with their histo-morphologic findings are essential in their recognition.[4]

MATERIALS AND METHODS

The present retrospective study of the hysterectomy specimen and biopsy of cervix was conducted in the Department of Pathology, Kist Medical College & Hospital, Lalitpur, Nepal. Permission from institutional review board has been obtained. A total of 520 cases submitted for routine histopathologic investigations were considered for this study. All the slides of cervix were retrieved from histopathology slide records and were reviewed. Whenever required the blocks were retrieved and recut of the sections were done.

All the benign lesions of the uterine cervix involving ectocervix and endocervix were included. Inadequate biopsy specimens without lining epithelium and inadequate stromal fragment and specimen diagnosed as malignant was excluded from the study.
The non-neoplastic lesions of the uterine cervix were divided into 4 categories (Table.1) based on the etiology and histomorphological examination[11]

Category 1: Inflammatory, reactive and reparative lesions
Category 2: Glandular hyperplasias
Category 3: Metaplasias and ectopies
Category 4: Benign neoplasms

RESULTS

A total of 520 cervical specimens with benign lesion were included in the study received as a part of hysterectomy or cervical biopsy. A closer study of the pathology of the uterine cervix revealed a number of non-neoplastic lesions of local origin.

Out of 520 specimens, 901 lesions were noted (Table 2). Multiple coexisting lesions were observed in many specimens. The common lesion encountered was inflammatory lesion 513(98.6%) and the least was benign neoplasm 33(6.3%) cases.

Table 1: Diagnostic category and various disease conditions

S.N	Diagnostic category	Diagnosis
1.	**Inflammatory, reactive and reparative lesions**	Chronic cervicitis
		Papillary endocervicitis
		Koilocytic changes
		Follicular cervicitis
2.	**Glandular hyperplasia**	Nabothian cyst
		Diffuse laminar endocervical glandular hyperplasia(DLEGH)
		Tunnel clusters
		Microglandular hyperplasia
3.	**Metaplasia and ectopies**	Squamous metaplasia
		Tubuloendometrial metaplasia
4.	**Benign neoplasm**	Endocervical polyp Leiomyomatous polyp

Table 2: Various diagnostic categories and its prevalence

Diagnostic category	Frequency (%)
Inflammatory	513 (98.6%)
Metaplasia	311(59.8%)
Glandular hyperplasia	44 (8.4%)
Benign neoplasm	33 (6.3%)
Total	**901(100%)**

The mean age of the patient was 45.5 years, the youngest being 23 years-old and the oldest 76 years-old. (Table 3)

The first category; inflammatory, reactive or reparative lesions was seen in 513 cases (98.6%) and 388 cases (74.6%) was seen in age group between 31-50years (Table 3). Under this category chronic nonspecific cervicitis comprised 394 (75.7%) cases being the commonest lesion identified. Koilocytic changes; which is categorized as low grade squamous intraepithelial lesions in Papanicoloau smear; were seen in 33 (6.3%) cases. (Table 4)

The 2nd category "Glandular hyperplasia" was seen 44 cases (8.4%) with the mean age 31-50 age group except one case seen in age less than 30 years. Nabothian cyst was seen in 70(13.4%) cases, Diffuse laminar endocervical hyperplasia in 33(6.3%) cases, tunnel clusters and microglandular hyperplasia in 10(1.9%) cases respectively. (Table 5)

The 3rd category "metaplasia and ectopies" were observed in 311(59.8%) cases. Two hundred eighty eight cases were seen in between 31-60 years age group. Squamous metaplasia was the commonest finding (n=212; 40.7%) and tuboendometrial metaplasia17(3.2%) cases. Mesonephric rest was seen in 3 (0.5%) cases. (Table 6)

The 4th category benign neoplasm, endocervical polyp was included and consisted of 33(6.3%) cases. Benign neoplasm was commonly seen in age group between 30-50years.

DISCUSSION

A vast number of benign lesions in the cervix are encountered in

Table 3: Age wise distribution of various cervical lesions

Age Group (years) Inflammatory	Frequency (%)				Total
	Inflammatory	Metaplasia and Ectopies	Glandular Hyperplasia	Benign Neoplasm	
<=30	17	3	1	2	23
31-40	133	72	15	7	227
41-50	255	151	28	16	450
51-60	80	65	0	6	151
>61	28	20	0	2	50

Table 4: Prevalence of various disease conditions in Inflammatory, reactive and reparative lesion category

Diagnostic	Frequency (%)
Chronic cervicitis	394 (75.7)
Follicular cervicitis	7 (1.3)
Koilocytic changes	33 (6.3)
Papillary endocervicitis	79 (15.1)

Table 5: Prevalence of various disease conditions in glandular Hyperplasia category

Diagnostic	Frequency (%)
DLEGH	33 (6.3)
MGH	10 (1.9)
Tunnel cluster	10 (1.9)
Nabothian Cyst	70 (13.4)

Table 6: Prevalence of various disease conditions in Metaplasia and Ectopies category

Diagnostic	Frequency (%)
Squamous Metaplasia	212 (40.7)
Tuboendometrial Metaplasia	17 (3.2)
Mesonephric Rest	03 (0.5)

day to day practice.
Many of these are rare, not given much importance but can mimic in situ and invasive neoplastic lesions.[11]

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.[4] 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.[4]

Inflammatory reactive and reparative lesions were the most common lesion encountered in our study. Chronic non specific cervicitis 394 (75.7%) cases were the most common finding. It was seen associated with other lesions like squamous metaplasia and koilocytosis. It was also seen accompanying nabothian cyst, tunnel clusters, DLEGH and microglandular hyperplasia. Paaronen J et al[12] 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.
Other lesion encountered in the category were papillary endocervicitis 79 cases (15.1%) Koilocytic changes 33(6.3%) cases and Follicular cervicitis 7(1.3%) cases. Papillary cervicitis 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.[11]

Koilocytic changes are the morphologic hallmark of HPV infection of the cervical squamous epithelium.[13] In our study it was observed in 33 (6.3%) cases which corresponds with the findings of Prathima KM and Ramdas Naik et al.[9,13]. These koilocytes are squamous epithelial cells that contain an acentric hyperchromatic nucleus that is displaced by a large perinuclear vacuole. It is important to not confuse the normal basket weave hyperkeratosis with koilocytosis, as the diagnosis of koilocytosis has important therapeutic implications on the patient.[4,14] Many studies have also proven that HPV infection (koilocytosis) in association with HIV infection and lower CD4 counts have predisposed to cervical intraepithelial carcinoma and malignancy.[15] Hence, the positive identification of koilocytosis goes a long way in preventing malignancies in such HIV positive patients.[16]

Follicular cervicitis was seen in 7(1.3%) 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.[11]

The second group, glandular hyperplasia were seen in 44(8.4%) of the cases. Diffuse laminar endocervical hyperplasia (DLEGH) was seen in 33(6.3%) cases, which corresponded with the finding of Naveen kumar BJ[14] who had observed it in 7/124 (5.65%) of cases. 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. At low power it may mimic adenoma malignum or cervical glandular intraepithelial neoplasia (CGIN) but it generally does not have any atypia.[11]

Microglandular hyperplasia was seen in 10(1.9%) cases. Nichols et al[13] observed 31 cases of MEH (24%), 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.[11] Microscopically, it

comprises small, closely packed glands with mixed inflammatory cells in the intervening stroma. It is frequently accompanied by squamous metaplasia. As a result, this can mimic clear cell carcinoma or the microglandular variant of adenocarcinoma (especially endometrial carcinoma).[11]

Tunnel clusters was found in 10 (1.9%) cases. All the tunnel clusters were incidental findings in cervices which were removed for unrelated causes, and was in correlation as observed by Aravind pallipady et al[16] 2.7%, and Fluhman et al.[9,17] Tunnel clusters are two types of type A which is non-cystic, comprises of small closely packed glands often in a lobular architecture and Type B are cystic and usually near the surface and not deep in the stroma.[11] However, when they do have glands reaching deep into the stroma, they can mimic the microcystic variant of usual endocervical adenocarcinoma.[11]

Nabothian cyst was seen in 70(13.4%) cases. Our results found in the study were slightly higher than the study conducted by Krishna Dubey et al[18] where it was seen in 49(19.7%) cases. Nabothian cyst is thought to arise due to blockage of endocervical glands and associated changes. They appear grossly cystic spaces filled with mucin and microscopically lined by flattened epithelium which when extend deep into the endocervical wall may be mistaken for malignancy.[6]

The third group metaplasia and ectopies were observed in 311(59.8%) cases with mean age group being 41-50 years. Squamous metaplasia was seen in 212(40.7%) cases and was the commonest finding. Study conducted by Aravind Pallipady et al[16] showed squamous metaplasia, in (73.20%) which was slightly higher than our study and similar findings was observed in the studies of Prathima KM and Bhattacharya S et al[18,19] 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).[11] Tubal, tuboendometrial metaplasia affect the glandular epithelium of the endocervix.[20] 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.[20] Tubal metaplasia is often found following conization therefore it has been suggested that it represents aberrant differentiation following injury.[20] Mesonephric rest were seen in 3(0.5%) cases.

Among the fourth category endocervical polyp was seen in the study accounting for 33 (6.3%) cases. A study conducted by Barut et al[21] revealed that endocervical polyps occurred in 2 to 5 percent. These occur mainly in the 4th to 6th decades of life which correlated with our findings. Endocervical polyp can be vascular, fibrous or heavily inflamed and there were often microglandular hyperplasia. Within these polyps, there can be CIN or CGIN.[11] 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.[21]

CONCLUSIONS

Varieties of non-neoplastic lesions of cervix are commonly encountered in cervical biopsy specimens. Women of reproductive age group are more prone to acquire such conditions. Early detection and management can prevent further complications. Missing out these lesions; in small biopsies or over diagnosing it as malignancy; can have potentially adverse consequences, for the patient.

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