Clinico-Pathological Study of Non-Neoplastic Lesions of Uterine Cervix with their Histopathological Categorization

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Abstract: The non-neoplastic lesions of the uterine cervix are frequently seen in the histopathology departments. Of the 821 cervical specimens received, 909 non-neoplastic lesions were evaluated. Most of the patients' presented with vaginal bleeding, mass per vagina and white discharge. Based on histomorphology, the non-neoplastic lesions were divided into 3 categories i.e. Non-Infective Non-Adaptative lesions [76.79%], Adaptative lesions [13.64%] and Infective lesions [9.57%]. These lesions have overlapping symptoms and were clinically misdiagnosed to be malignant neoplasm. Therefore, familiarity regarding histopathological examination of these non-neoplastic cervical lesions with categorization can assist in appropriate management and prevent complications. Hence, the present study was undertaken.

Keywords: Cervicitis, Metaplasia, Infections, Histopathology, Non-neoplastic lesions.

1. Introduction

The major proportion of specimens in most of the histopathology departments usually belong to the gynaecopathology [1]. Among various gynaecological specimens, the commonest are non-neoplastic lesions affecting the uterine cervix.

Although, there is accessibility of the cervix to direct examination, clinical diagnosis still remains obscure. The diagnostic procedures like cervical cytology have an advantage to screen for cervical diseases. However, there is poor correlation in cervical cytology findings with their subsequent cervical biopsy reports. Therefore, histomorphological examination of the cervical lesions still remains gold standard for the diagnosis of non-neoplastic lesions of the uterine cervix [2].

Of the non-neoplastic various lesions, cervical inflammations due to non-infective and infective causes were common. The term chronic cervicitis may indicate only the duration of the symptoms, which becomes very difficult for the gynaecologist to correlate with clinical diagnosis. Other lesions like tunnel clusters, mesonephric hyperplasia, endometriosis and microglandular endocervical hyperplasia may be misinterpreted as malignant [3]. Thus, categorization and familiarity of the cervical non-neoplastic lesions with their histomorphological findings are essential in their recognition and could improve the approach towards better management of the patient. Also, early detection of these non-neoplastic lesions can prevent further complications.

2. Methods

The present prospective cross-sectional study was conducted over a period of 2years in the histopathology division, department of Pathology at 2 tertiary health centers in Pondicherry and Telangana. The study included 821 specimens of uterine cervix obtained either in the form of biopsies or hysterectomy specimens. Inadequate biopsy specimens and specimens diagnosed as benign, in-situ and invasive malignant neoplasms of uterine cervix were excluded from the study. Clinical details of the patient including age, parity, clinical findings and provisional diagnosis were collected from the gynecology department.

All the specimens received at histopathology division were fixed in 10% formalin. The macroscopic findings of the hysterectomy specimens were examined and recorded, followed by fixation in 10% formalin for 24 hours. The hysterectomy specimen was later sampled carefully and tissue pieces were processed. The entire tissue piece of the biopsy specimen was submitted for processing and sections were cut at 4-6 μ thickness followed by Hematoxylin and Eosin stain. These stained sections were analyzed by light microscopy. Special stains like Ziehl Neelsen stain, Periodic Acid Schiff stain were performed wherever required.

3. Results and Discussion

Among 1,052 cervical specimens received during the study period, 830 specimens were non-neoplastic and remaining 222 specimens belonged to neoplastic lesions of the uterine cervix. Nine specimens were excluded from the study due to inadequate tissue biopsy. Out of 821 non-neoplastic specimens, 909 lesions were noted. In 72 [8.77%] specimens, more than one co-existing lesion was observed, whereas in 05 [0.61%] specimens there were more than 2 lesions. The non-neoplastic lesions of the uterine cervix were divided into 3 categories [Table.I] based on the etiology and histomorphological examination:

Category.1: Infective Lesions,

Category.2: Adaptative Lesions and

Category.3: Non-Infective Non-Adaptative [NINA] Lesions.

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 Table 1: Categorization of non-neoplastic lesions of uterine

 cervix

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Categories	No. of lesions	%		
Infective lesions	87	9.57%		
Adaptative lesions	124	13.64%		
NINA lesions	698	76.79%		
Total	909	100%		

The most common category was NINA lesions [76.79%] followed by Adaptative lesions [13.64%] and Infective lesions [9.57%].

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Clinical details	Cervicitis [n=678]	Mesonephric remnants	Endometriosis [n=1]	Decidual Change [n=1]	Dysplasia
		[<i>n</i> =3]			[n=15]
Age group	40-49	40-49	40-49	20-29	40-49
Bleeding per vagina	310	01	01	01	03
Painful Menstruation	53	00	00	00	00
White discharge	116	00	00	00	03
Mass per vagina	216	02	00	01	05
Pain Abdomen	138	00	00	00	02
Urinary problems	32	01	00	00	01
Constipation	4	00	00	00	00
Fever	1	00	00	00	00
Post coital bleeding	6	00	00	00	00

Of the various NINA lesions [Table.II], chronic cervicitis [678/698, 97.13%] was the predominant lesion followed by dysplasia [15/698, 1.01%] and Mesonephric remnants [3/698, 0.43%]. The commonest age group affected was between 40-49 years. Among patients with cervicitis, excessive vaginal bleeding was the most common symptom followed by mass per vagina, pain abdomen and white

discharge. Among the other NINA lesions like mesonephric remnants, dysplasia; mass per vagina was the clinical symptom observed. Patients' with endocervical glandular dysplasia presented with vaginal bleeding and white discharge. Only one case each of endometriosis and decidual change were seen with excessive vaginal bleeding.

 Table 3: Clinicopathological correlation in Adaptative lesions of uterine cervix

Clinical Details	Tubo-endometrial	Microglandular	Tunnel clusters	Diffuse Laminar	Florid Hyperplasia
	metaplasia [n=81]	hyperplasia [n=12]	[n=20]	Hyperplasia [n=7]	[<i>n</i> =4]
Age group	40-49	40-49	40-49	20-29	40-49
Bleeding per vagina	48	07	11	04	00
Painful menstruation	07	00	02	00	01
White discharge	16	02	03	03	02
Mass per vagina	18	03	05	01	02
Pain Abdomen	25	04	09	04	02
Urinary symptoms	01	01	03	00	00
Constipation	01	00	01	00	00

Among the adaptative lesions [Table.III], tubo-endometrial metaplasia [81/124, 65.32%] was frequently observed followed by tunnel clusters [20/124,16.13%]. microglandular hyperplasia [12/124, 9.68%], diffuse laminar endocervical glandular hyperplasia [7/124, 5.65%] and florid endocervical glandular hyperplasia [4/124, 3.23%] were seen. The commonest age group affected with adaptative lesions was between 40-49years where as in patients' with diffuse laminar hyperplasia, the age group were 20-29years. The most frequent clinical symptom observed among patients' with adaptative lesions was bleeding per vagina and pain abdomen.

 Table 4: Clinicopathological correlation in Infective lesions of uterine cervix.

Clinical Details	Chlamydia	Subclinical HPV	Tuberculosis		
	Infection [n=48]	Infection [n=38]	Infection		
			[<i>n</i> =1]		
Age group [yrs]	40-49	40-49	30-39		
Bleeding per vagina	23	21	1		
Painful menstruation	2	2	0		
White discharge	21	10	0		
Mass per vagina	10	12	0		

Pain abdomen	13	8	2
Urinary symptoms	4	1	0
Constipation	2	0	0

In the present study, chlamydial infection [48/87, 55.17%] and subclinical Human Papilloma Virus infection [38/87 specimens, 43.68%] were the most frequently seen infective lesions. The commonest affected age group was between 40-49 years. In chlamydial infections, bleeding per vagina and white discharge were the commonest symptoms whereas bleeding per vagina and mass per vagina were observed in HPV infections [Table.IV]. Only one case of tuberculosis was seen; presenting with irregular vaginal bleeding and abdominal pain.

4. Discussion

Non-neoplastic lesions of the uterine cervix form the majority of the gynaecological specimens in histopathology departments [3]. There are various numbers of non-neoplastic lesions, which are of great importance to the clinician and the pathologist. The diagnosis and approach towards these lesions are greatly neglected [3, 4]. Previous

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 [5]. Most of the other non-neoplastic lesions like tunnel clusters, mesonephric hyperplasia, endometriosis and microglandular endocervical hyperplasia are not given much importance even though they mimic insitu or malignant neoplasm [6,7]. Hence, a new categorization of these non-neoplastic lesions of uterine cervix into Infective lesions, Adaptative lesions and NINA lesions was introduced in our study.

NINA lesions constituted 76.79% of all the non-neoplastic lesions. Chronic non-specific cervicitis is a frequently encountered lesion both clinically and in histopathological specimens [4]. It is diagnosed by histology based on chronic inflammatory cell infiltrates consisting of lymphocytes, plasma cells and histiocytes. In our study among NINA lesions, chronic cervicitis [97.13%] was the commonest lesion and occurred more frequently between 40-49years. This may be due to the fact that most of these women are having children and still are sexually active. Thus, they are more prone to use chemical irritants like intrauterine contraceptive devices, tampons, diaphragms, etc. Also, it is well known that inflammatory process of the cervix is the "gate-way" not only to ascending infection but also to the risk of ectopic pregnancy and tubal infertility [8,9]. The other NINA lesions like dysplasia [Figure.1] need to be identified early, as they may progress to malignant neoplasm if not treated [10]. Also, literature mentions that the mesonephric rests [Figure.2] not only mimic adenocarcinoma but can advance to mesonephric carcinoma [11]. Endometriosis and decidual change type of lesions presents with excessive vaginal bleeding resulting in severe anemias and its complications.



Figure 1: [H&E, X200], Mild dysplasia



Figure 2: [H&E, X200], Mesonephric remnants.

Cellular adaptation is the body's method for dealing with stressors to maintain homeostasis. Most of the adaptative lesions of the uterine cervix were frequently seen between 20 - 49years age group, probably suggesting use of oestrogen – progesterone treatments [12, 13].

Among the adaptative lesions of the uterine cervix, tuboendometrial metaplasia [65.32%] [Figure.3] was the commonest. It is characterized by the presence in the endocervix of epithelia resembling tubal and endometrium. These lesions were observed in patients with conisation and are been interpreted as an aberrant differentiation after cervical trauma [14]. In our study, microglandular hyperplasia, diffuse laminar hyperplasia and florid hyperplasia corresponded to complex proliferation of the epithelium of endocervical glands[12], circumferential glandular hyperplasia in the stroma[15] and florid pattern of glandular proliferation[16] respectively. All these glandular hyperplasias mimic cervical adenocarcinoma but nuclear atypia, atypical mitosis and stromal invasion solves the diagnosis. Most of the tunnel clusters [Figure.4] belonged to type B consisting of cystic tunnel clusters and two cases were of type A i.e. non-cystic. The commonest clinical symptom in most of the patients' with adaptative lesions was bleeding per vagina except patients' having florid hyperplasia presented with mass per vagina and white discharge.



Figure 3: [H&E, X200], Tubo endometrial metaplasia.



Figure 4: [H&E, X100], Tunnel clusters.

In the present study, infective cervical lesions were seen only in 9.57% cases. Of these lesions, chlamydial infection and subclinical HPV infection constituted 55.17% and 43.68% respectively. Both these infections were seen commonly in patients' with age group 40 – 49years. The histopathological findings of infection with chlamydia species [Figure.5] are sub-epithelial lymphoid follicles with germinal centres, fibrosis and scarring [17]. The hallmark of infection with Human Papilloma Virus [Figure.6] was koilocytic change in the epithelial cells, which correlates well with HPV nucleic acid by in-situ hybridisation. Infection with HPV is thought to be the initiating event; other factors like co-existing microbial infection and cigarette smoking also contribute to cervical carcinogenesis [18,19].



Figure 5: [H&E, X200], Subepithelial lymphoid follicles with germinal centres



Figure 6: [H&E, X200], Koilocytosis.

5. Conclusion & Future Scope

The present study emphasizes the spectrum of nonneoplastic lesions of uterine cervix, which can be divided under various categories. These categories can provide the basis for identifying the etiology and their clinical presentations. Early detection and management of the NINA lesions and Infective lesions prevents further complications; thereby reducing the amount of morbidity. Most of the Adaptative lesions mimicking cervical adenocarcinoma are reversible and minor surgical interventions are required for their correction. Furthermore clinicopathological studies involving non-neoplastic lesions of uterine cervix on a community basis may eliminate the fraction of undiagnosed conditions.

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