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Immunohistochemical expression of Ki 67 in low grade lesions of cervix diagnosed by colposcopy.

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Abstract :
The basic elements in the development of cancer including cervical cancer and its precursors are uncontrolled cell proliferation and malignant transformation. Precancerous lesions of cervix are easily detectable and treatable. Population based cervical screening with the help of Pap smear, colposcopic screening with biopsies and LLETZ procedure for treatment has substantially reduced the incidence of cervical cancer. Many a time low grade lesions diagnosed clinically does not correlate with morphology. Ki67 a proliferative index marker is a useful tool in identifying the proliferation of cells at an early stage. Hence this study aimed at finding out the utility of Ki67 a proliferative index marker in clinically discordant cases where the colposcopy diagnosis was LSIL and histopathology was chronic cervicitis with squamous metaplasia. In our study 834 cases reported as chronic cervicitis with squamous metaplasia over a period of 6months had a high proliferative index score with Ki67 indicating that around 23.5 of cases go unnoticed on routine light microscopy.
This inference from our study stresses the importance of running a proliferative index marker on a routine basis in clinically suspected low grade lesions even in population based screening to reduce the cancer burden.
Keyword : Ki67, LSIL, Colposcopy.

INTRODUCTION:
Cancer cervix is the third most common malignancy in females worldwide (1). It is a leading cause of cancer associated death in developing countries.
The screening procedures to bring down the incidence of carcinoma cervix in reproductive age group females include Pap smear, colposcopy and colposcopy directed biopsy. In developing countries Pap smear screening followed by colposcopy and colposcopy guided biopsies have proven useful as long term regular follow up of patients pose a significant problem(3). Morphological features of cervical neoplasia in biopsies include loss of polarity, abnormal mitotic figures and cellular atypia .Many a time low grade lesions are missed as basal and suprabasal mitosis is not clearly evident on

sections under light microscope. Therefore the aim of this study is to assess the proliferative activity by using Ki 67, a proliferative index marker in cases where there was a disagreement between low grade lesions diagnosed clinically.

MATERIALS AND METHODS:

This is a retrospective study where cases diagnosed by colposcopy as low grade lesion from July 2010 to December 2010 were selected from archives of Pathology. Cases reported as high grade lesion, carcinoma in situ, invasive malignancies and sections with very little material were excluded.

After obtaining due Institute Ethical Committee clearance, the blocks were retrieved and colposcopic findings were taken from the medical record Department. Hematoxylin and Eosin stained slides were analysed. Ki67 (Biogenix clone no 297, using HRP technique), a proliferative index immunohistochemical marker was run on all these cases with appropriate control. The scoring system was assigned according to the intensity of nuclear staining and the percentage positivity of staining as in Table I. (4), (5). This was then compared with morphology.

Table I: Scoring System for Ki67

RESULT:

912 patients were screened by Pap smear technique over the period of 6 months. Out of these 912 cases reported 78 cases were biopsied under colposcopy for atypia / LSIL lesions. 50 cases were selected for our study using the exclusion criteria as mentioned above. Out of 50 cases of suspected low grade lesions in colposcopy only 16 cases were morphologically confirmed as LSIL/CIN I and the rest 34 cases were reported as chronic cervicitis with squamous metaplasia. On all these 50 blocks retrieved, Ki67 was run (biogenix clone 297) using HRP technique and the results were analysed. 16 cases reported as LSIL morphologically had a proliferative score of 2 to 3 (Fig 1). 8 out of 34 cases reported as chronic cervicitis with squamous metaplasia had a proliferative index score of 2 to 3 and the rest 26 cases had a score of 0 to 1 (Fig2).

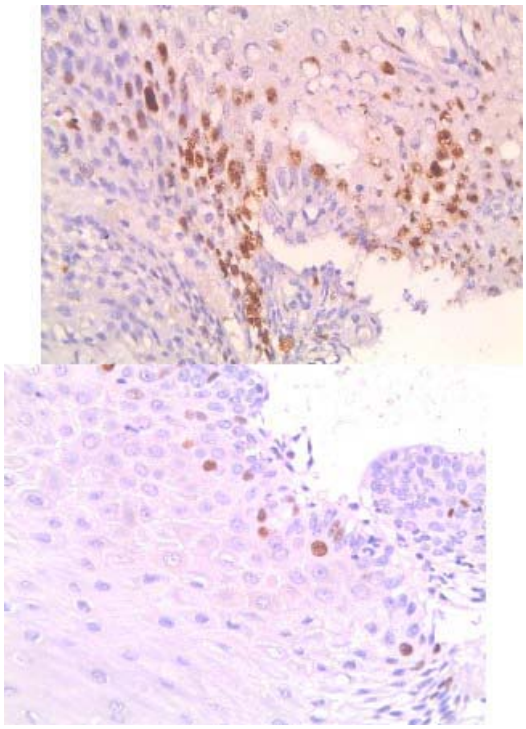

Fig1:Ki67 Score of 2-3 (IHC , 400x)
Fig2: Ki 67 Score of 0-1 (IHC , 400x)

DISCUSSION AND CONCLUSION:

Cancer cervix is associated with HPV infection and is related to sexual activity. Carcinoma cervix is preceded by precursor lesions which evolve over a period of time to squamous cell carcinoma. These lesions were defined as CIN and classified as CINI, II and III. These lesions were redefined as LSIL and HSIL for treatment purposes. LSIL includes CIN I, HSIL includes CIN II and CIN III (2).

The histopathological features of LSIL include atypical, immature squamous cells that are confined to lower one third of the epithelium ,increase in suprabasal mitosis and / or kiolocytosis.

HSIL ranges from progressive atypia and immature basal cells expansion above the lower third of epithelial thickness to diffuse atypia and expansion of immature basal cells to the epithelial surface.

Carcinoma cervix is one of the preventable and a slowly progressive cancer, the screening methods like Pap smear, colposcopy and colposcopic directed biopsy helps to detect the precursor and early stage lesions which could be treated thereby reducing the cancer burden and incidence.

The basic element in the development of cervical cancer is uncontrolled cellular proliferation. Therefore proliferative markers are useful in assessing the proliferative index in morphologically difficult cases .One such proliferative index marker is Ki67 .It is a non-histonic protein and expressed in all phases of cell cycle except in Go(6). It has a function of growth in cancer; therefore the Ki67 expression suggests the proliferative activity of the lesion.

Ki67 is normally expressed in the parabasal layer. A high positivity in the basal and in the mid third layer of cervix indicates a proliferative lesion. (7)

From our study, we found that Ki67 was significantly high in cases diagnosed and reported as LSIL / CINI (Score of 2-3) and was present in basal layer upto mid third. Ki67 score was low in cases of Chronic Cervicitis with Squamous metaplasia (Score of 0-1) and was seen mainly in suprabasal layer.A few cases reported as Chronic cervicitis with Squamous metaplasia (8/34) had a relatively high index of Ki67 indicating the difficulty in assessing the activity morphologically under light microscopy. From this preliminary study we infer that around 23.5% of cases might not be reported as CIN I morphologically as mitosis may not be evident under light microscopy though there was a high clinical suspicion of LSIL/CINI.

These 23.5% of the cases screened and biopsied may come with high grade lesions of cervix /invasive malignancies in later years. Therefore using a proliferative index marker like Ki 67 on a routine basis is necessary to detect the proliferative activity in clinically suspected cases of LSIL/ CINI for accurate diagnosis.

From this preliminary study of ours we infer that, on clinically suspected cases of LSIL/CINI a proliferative marker like Ki67 when used as an adjunct to histopathology as a routine diagnostic tool will go a long way in reducing the cancer burden especially in population based screening. However a larger prospective study is essential to prove the utility of Ki67 as a routine diagnostic marker for suspected low grade lesions of cervix under colposcopy.

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Table I: Scoring System for Ki67

Scores	Staining intensity (Nuclear Staining)	% positivity	Result
0	No staining	0	Negative
1	Weak	<10	Negative
2	Strong	10-50	Positive
3	Strong	>50	Positive

Total number of cases :50

Histopathological Diagnosis	No. of Cases		Ki67 Score
LSIL/CIN I	16		2-3
Chronic cervicitis with Squamous metaplasia	34	26	0-1
		8	2-3