Biological Behaviour of Squamous Intraepithelial Lesion of Cervix Under Rural Conditions in Western Lucknow, India

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Abstract: Objective: The biological behavior of squamous intraepithelial lesions (SIL) is uncertain as most of the lesions regress, and only some of them progress to higher grades or persist. This varied behavior is common under rural conditions due to the lack of progression-promoting agents like Human papillomavirus (HPV). Methods: Rural cervical cancer screening has been in progress for the last 8 years in the villages of West Lucknow through a camp approach, and to date, 2980 women have undergone cytological examination. Among them, 499 women were diagnosed with SIL, and 310 of these cases were followed. The details of follow-up findings in these 310 cases have been analyzed. Results: Of the 310 SIL cases followed, 242 showed regression of the lesions (78.1%), 3 showed progression from low-grade SIL to high-grade SIL (0.9%), while the remaining 65 (21%) showed persistence of SIL. Among the 65 persistence cases, 35 showed regression of the lesion (53.8%) on further follow-up, while the remaining 30 cases could not be followed. Both regression and persistence of SIL were observed more frequently in younger women (21-30 years), while there was a low trend with increasing age. Conclusion: Most of the SIL cases on follow-up showed regression of the lesion. Even those SIL cases that showed persistence regressed to normal in more than 50% of cases upon further follow-up. Progression of the lesion is not common (only 3 cases). Attempts are underway for the follow-up of the remaining persistence cases and also those initial SIL cases who could not be followed up during the first attempt.

Key Words: SIL, persistence, progression, regression, rural women, process.

I. INTRODUCTION

Squamous intraepithelial lesions of the cervix (SIL) are precancerous manifestations in the human female lower genital tract, which may exhibit varied behavior after diagnosis in cervical smears. SIL can progress to higher grades of SIL (HSIL) from low-grade SIL (LSIL) and eventually lead to carcinoma of the cervix, or it may persist as LSIL or HSIL. On the other hand, these precancerous lesions of the cervix often regress to normal. This regression is a common finding under rural conditions in India due to a lack of progression-promoting agents like HPV infection, the use of contraceptives such as Intrauterine devices (IUD) or hormones, and a lower number of changing sexual partners. These factors are more prevalent in urban areas of the country. In a 35-year hospital-based study (1971-2005) at K.G. Medical University, Lucknow, we observed a SIL prevalence of 7.8%. However, the follow-up was poor in these women due to the challenges of conducting follow-ups in a large city compared to small villages where the patients are localized [1].

Although cervical cytology has been found very effective in controlling the incidence and associated morbidity due to carcinoma of the cervix, the biological behavior of SIL, particularly LSIL, remains a problematic issue, as the majority of LSIL cases regress spontaneously [2]. Even high-grade lesions (HSIL) regress in 40% of cases [3]. In our series, out of 310 SIL cases followed, 242 showed regression (78.1%), 65 showed persistence (21%), and the remaining 3 cases displayed progression from LSIL to HSIL (0.9%).

HPV infection, mainly oncogenic HPV types, has been found to shorten the duration of progression from LSIL to HSIL compared to cases with no HPV infection. Similarly, regression of HSIL to LSIL and LSIL to normal takes longer with oncogenic HPVs [4]. The authors of [4] stated that SIL persists longer and progresses more quickly in women with oncogenic HPV than in those with non-oncogenic HPV or without HPV. Hence, testing for oncogenic HPV may help identify SIL cases that are likely to progress rapidly.

Matsumoto et al. [5] found a mean follow-up period of 40
months in Japanese women, in which SIL regressed to normal in 362 cases and progressed to CIN-3 in 96 cases. They observed that women with multiple HPV infections are more likely to have persistent lesions and found that type-specific HPV testing for LSIL cases is useful for identifying an increased or decreased risk of disease progression. Trimble et al. [6] found that high-risk HPV testing, such as HPV-16, is less likely to regress than with other types. Apiwattanasevee et al. [7] found 66.2% regression in 154 LSIL cases followed for 2 years, with 31.8% showing persistent cytology and 2.0% progressing to high-grade SIL.

Aydin et al. [8] observed that the remarkable decrease in the prevalence and mortality rate due to cervical cancer may be associated with a more effective screening program. This is closely related to the progression of SIL to malignancy [8]. The spontaneous regression of LSIL may simplify the follow-up program, reducing unnecessary visits and patient anxiety [9]. Annual cytology is sufficient for the majority of LSIL patients. Melnikow et al. [10] and Moscicki et al. [1] observed that 61% of LSIL patients regressed to normal over 1 year of follow-up [11, 10].

In this communication, we present the details of follow-up findings in 310 SIL cases who were followed (out of 499 detected) over an 8-year duration.

II. MATERIALS AND METHODS

The outcome of this study has been the result of 8 years of Rural cancer cervical screening in the villages of western Lucknow in the blocks of Malihabad, Kokori, and Mall. The study was carried out through camp approach by organizing camps for screening in the villages. Prior to this, women were counselled and motivated to attend the camp apprising them about the ill hazards of cervical cancer and utility of early detection of the disease in its preinvasive phase by cytology examination. In all, 189 camps have been organised till date and 5339(28.2%) women attended camp and 2980 (55.8%) of them have undergone Pap smear examination.

Cytological studies of cervical smears in 2980 women revealed SIL in 499 cases. Of the 499, only 22 were high grade SIL (HSIL) while remaining 477 were low grade SIL (LSIL). Follow-up was planned in these SIL cases by calling them at Era’s Hospital for repeat Pap smear examination after 1 year in case of LSIL and after 3 months and also for cervical biopsy in 22 cases of HSIL. As none of these women turned up to the Hospital due to poor financial status of patients and lack of transport, home visits were planned in these cases by telling them the importance of follow-up through counselling and motivation and asking them to come next day to the venue (Primary school) for repeat smear examination where the camp was held initially.

In all, follow-up has been possible in 310 of the 499 SIL cases (62.1%). The remaining 189 SIL cases could not be followed and attempts are underway to follow 164 of them except 26 (who have either undergone hysterectomy or expired or left the village). In all women in whom Pap smear was examined, the cervical smear was collected from smegocolumnar junction of cervix, by the gynaecologist attending the camp and sent to the cytology lab of the Department of Pathology of the college (after immediately fixing them in absolute alcohol) where it was stained according to the Papanicolaou’s technique. The cytological changes in cervical smears were screened by the cytologist of the project and graded according to the Bethesda system of classification [11].

III. RESULTS

The cytological examination of cervical smears in 2980 women revealed squamous intraepithelial lesions (SIL) in 499 cases (16.7%). The distribution of the two grades of SIL in these 499 cases was as follows:

- LSIL - 477 (16.2%)
- HSIL - 22 (0.8%)

The majority of SIL cases were found to be low grade (LSIL - 16.2%). The difference in the incidence of the two types of SIL was statistically highly significant ($\chi^2 = 49.9, p > .0001$). Follow-up after 1-8 years was possible in 310 SIL cases (298 LSIL and 12 HSIL cases). Regression of SIL to normal was seen in 242 SIL cases (239 LSIL and 3 HSIL cases), while in 3 SIL cases, LSIL progressed to HSIL. The remaining 65 cases (56 LSIL and 9 HSIL) showed persistence of SIL (78.1% vs. 21%). Among the 9 HSIL cases showing persistence, 1 case showed persistence of HSIL, while regression of SIL from HSIL to LSIL was seen in 8 of these 9 cases. The percentage of cases showing regression was very highly significant compared to the persistence of SIL ($\chi^2 = 95.47 : p = .0001$).

The SIL rate was significantly higher in rural women (16.7%) compared to their urban counterparts (7.8%). This disparity may be attributed to the fact that rural women, who are mostly poor, illiterate, and financially weak, have poor personal genital hygiene, leading to persistent vaginal infections that remain undiagnosed and untreated due to a lack of medical amenities [12].

The present study showed persistence of SIL in 21% of cases and progression in only 0.9% (3 cases). It appears that progression-promoting agents like HPV infection are very low, the use of family planning procedures like IUD and hormones is minimal, and changes in sexual partners are very rare in a rural setup. In the present study, HPV-DNA estimation was carried out in 130 SIL cases, of which only 17 cases were positive for HPV. Among these 17 cases, 8 showed persistence and progression of SIL (47.1%), while the remaining 9 cases were seen with regressed cases out of 113 HPV-negative cases (7.9%). The HPV types observed in the study were high-risk HPV-18 and low-risk types HPV-31, 33, and 35 [13].

The period of follow-up when regression of SIL to normal was seen in 242 SIL cases ranged from 1 to 7 years, with the
majority of LSIL cases (239) and 3 cases of HSIL regressing after 2 years. Persistence of SIL was observed in 65 SIL cases, with 56 LSIL and 9 HSIL cases showing persistence. The period when persistence was observed in these 65 SIL cases ranged from 1 to 7 years, with the majority of these cases being observed after 2 years.

1st follow-up: was possible in 7 of the 9 HSIL cases, while the remaining 2 cases could not be followed. Among the 7 cases followed, two showed regression to normal 1 year later, while in the remaining 5 cases, persistence of LSIL was seen after 1-2 years. In 56 LSIL cases, the first follow-up revealed regression to normal in 22 cases after a period ranging from 1 to 5 years, persistence of LSIL was seen in 17 cases after 1-3 years, and the remaining 17 cases could not be followed. The total cases showing persistence, regression, and not followed were found to be as follows:

- Total persisted - 17 LSIL + 5 HSIL = 22 (33.8%)
- Total regressed - 22 LSIL + 2 HSIL = 24 (34.7%)
- Not followed - 17 LSIL + 2 HSIL = 19 (27.7%)

The difference in the incidence of regression and persistence on the first follow-up was statistically insignificant ($\chi^2 = 0.08$, $p = 0.98$).

2nd Follow-up: was possible in 22 SIL persistent cases (17 LSIL + 5 HSIL). Of these 22, 9 still showed persistence (5 LSIL + 4 HSIL) 1-2 years later, while regression of SIL was seen in 5 cases after 1-2 years (4 LSIL + 1 HSIL). The remaining 8 SIL cases could not be followed. The findings are shown below:

- Total persistence - 9 (34.6%)
- Total regression - 5 (19.2%)
- Not followed - 8 (46.1%)

The difference in the incidence of persistence and regression of SIL on the 2nd follow-up has been insignificant ($\chi^2 = 0.60$, $p = 0.74$). Of the total 9 persistent cases left on the 2nd follow-up, 3rd follow-up was available in only 6 SIL cases (4 HSIL and 2 LSIL), and all 6 showed regression in the lesion to normal. The remaining 3 cases could not be followed.

More than 50% of the 65 persistent cases regressed on follow-up, extending up to 3 repeat smears (35 cases, 53.8%), while the remaining 30 (46.2%) could not be followed. Attempts are underway to follow 25 cases, except for those where hysterectomy was done (4 cases) or had left the village (1 case). It is encouraging that all the 35 cases followed showed regression to normal, and none progressed to a high grade. Attempts are also in process to follow 3 cases of LSIL showing progression and 1 case of HSIL showing persistence to find out their future behavior.

The relationship between the biological behavior of SIL and age was also investigated (Table 1). The persistence of SIL was found to be highest in young women between the ages of 21-30 years (52.3%), after which this tendency showed a decline with increasing age. Interestingly, 2 out of the 3 LSIL cases showing progression to HSIL were between the ages of 31-40 years, suggesting that progression rates rise with increasing age within this age group.

On further analysis of the regression of LSIL, it was observed that the highest regression rate was seen in the young age group of 21-30 years (52.8%), after which it gradually declined, being lowest in older women above the age of 40 years.

The findings suggest that young women between 21-30 years exhibit both higher rates of regression and persistence of SIL, while women between 31-40 years may be at a higher risk of progression to higher-grade lesions. The age-related trends in SIL behavior observed in this study may have implications for the management and follow-up of SIL cases based on age groups.

IV. DISCUSSION

The present study revealed a 16.7% prevalence of squamous intraepithelial lesions (SIL) among 2980 rural women screened, with the majority being of low grade (LSIL - 16.1%) and only 22 cases classified as high grade SIL (HSIL - 0.7%). Follow-up was available for 310 out of 499 SIL cases (62.1%) over a period of 1-7 years. Regression of SIL was observed in 242 cases (77.8%), while persistence of SIL was seen in 65 cases (22.2%). Only 3 LSIL cases showed progression from LSIL to HSIL after 1-2 years (0.9%). These findings are consistent with previous studies, where a high regression rate of SIL has been reported.

Matsumato et al. [5] observed a high regression rate in Japanese women followed for 40 months. Similarly, Apiwattanasevee et al. [7] reported 66.2% regression of SIL cases over a 2-year follow-up, with only 39.8% showing persistence of the lesion. In contrast, progression of the lesion from LSIL to HSIL was seen in 2.0% of cases in their study, while this was seen in only 0.9% of cases in the present series. Another study by authors in [4] found that the regression of LSIL was longer with oncogenic HPV infection, and persistence of SIL was longer, while progression of HSIL was shorter with these HPVs. In the present study, HPV-DNA testing was performed in 131 rural women, and 17 of them were found to be HPV-positive. Among these 17 positive cases, 8 showed persistence or progression of SIL (47.1%), which is consistent with the reports of other investigators. Additionally, 5 out of the 8 HPV-positive cases showing persistence or progression of SIL were related to high oncogenic HPV-18, as reported in [4].

Other studies have also shown similar findings. Aydin et al. reported 68% regression, 22% persistence, and 9% progression in their series. Trimble et al. [6], Melnikov et al. [10], and Moscicki et al. [14] found regression of SIL in more than 60% of cases over a period of 2 years of follow-up. Similar findings were also reported by Aydin et al., who recommended that annual cytology is sufficient for studying the regression or persistence of SIL, and unnecessary visits should be avoided. The authors of the present study adhered to WHO recommendations on the follow-up of SIL cases and tried to follow LSIL cases after 1 year and HSIL after 3 months.
The present study also revealed that the regression, persistence, and progression of SIL were higher among younger women between the ages of 21-30 years. This finding is consistent with the study conducted by Zhang and Lu [15], who found considerable spontaneous regression of CIN-2 in younger women. Hertzberg et al. [11] also observed LSIL and HSIL occurring more frequently in the age group of 21-25 years, while the progression trend was not as visible in older women.

Currently, biomarkers that can identify lesions with a higher risk of progression than shown with a high probability of spontaneous regression could be immensely useful in managing these cases. Although high-risk HPV infection may be associated with the occurrence of these lesions, it does not aid in decision-making for treatment. An assay combining P-16 and Ki-67 has been found to have higher specificity than HPV for detecting HSIL in women with LSIL [16]. Additionally, chromosomal aberrations, such as hTERC, a human telomeres RNA gene, have been associated with the progression of SIL to frank cancer [12]. C-myc is another potential marker predicting the risk of disease progression in cervical cytology and is involved in a large number of pathways influencing proliferation and tumorigenesis [17]. Applying FISH technique (Fluorescence in situ hybridization) to diagnose these markers from liquid-based cytology samples and carrying out FISH assays combining probes from HPV, TERC, and myc shows promise as a prognostic marker for risk stratification in LSIL cases [18].

V. CONCLUSION

The findings of this study suggest that all diagnosed squamous intraepithelial lesion (SIL) cases in young women should be closely followed up after 1 to 2 years to determine whether there is regression or persistence of SIL. While biomarkers may be expensive and not easily applicable in a rural setup, the emphasis on diligent follow-up in untreated women is important [19].

REFERENCES


TABLE 1. Relationship between biological behaviour of SIL with age.

<table>
<thead>
<tr>
<th>Behaviour of SIL</th>
<th>Age Group</th>
<th>Persistence of SIL (65 cases)</th>
<th>Progression of SIL (3 cases)</th>
<th>Regression of SIL (242 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16-20 years</td>
<td>21-30 years</td>
<td>30-40 years</td>
<td>Above-40 year</td>
</tr>
<tr>
<td>Persistence of SIL</td>
<td>2 (3.1%)</td>
<td>34 (52.3%)</td>
<td>20 (30.7%)</td>
<td>9 (13.8%)</td>
</tr>
<tr>
<td>Progression of SIL</td>
<td>-</td>
<td>1 (33.3%)</td>
<td>2 (66.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Regression of SIL</td>
<td>1 (0.4%)</td>
<td>128 (52.8%)</td>
<td>75 (30.9%)</td>
<td>38 (15.10%)</td>
</tr>
</tbody>
</table>
Myc/Max/Mad network and the transcriptional control of cell behavior.
Annual Review of Cell and Developmental Biology, 16(1), 653-699.