



SPECTRUM OF NILM CHANGES IN CERVICAL PAP SMEAR A TERTIARY HOSPITAL EXPERIENCE

Pathology

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ABSTRACT

Background: Cervical cancer is a major cause of morbidity and mortality among women in India. The PAP smear is an effective screening tool for early detection of cervical lesions. Although Negative for Intraepithelial Lesion or Malignancy (NILM) smears are considered non-neoplastic, associated inflammatory and infectious changes may predispose to future epithelial abnormalities. **Aim:** To study the cytomorphological spectrum of NILM cervical PAP smears and correlate them with clinical and demographic profiles. **Materials And Methods:** This retrospective descriptive study included 200 cervical PAP smears reported as NILM according to the 2014 Bethesda System, collected between July 2023 and August 2024. Clinical details were retrieved from records and data were analyzed using descriptive statistics. **Results:** The mean age was 37.5 years, with most women in the 31–40 years age group. The commonest complaint was white discharge per vagina (35.5%). Inflammatory smear 87 (43.5%) is the one of the frequent patterns of NILM in the study. The other patterns include- 58 (29%) were of shift in flora suggestive of Bacterial Vaginosis, 17 (8.5%) Repair Reaction, 11 (5.5%) Candida species, 8 (4%) Metaplasia, 06 (3%) Trichomonas Vaginalis, 4 (2%) Herpes Simplex Virus, 4 (2%) cases no other specific findings, 2 (1%) Actinomyces, 2 (1%) Granulomatous cervicitis and 1 (0.5%) Parakeratosis cases. **Conclusion:** Inflammatory and infectious conditions form a significant component of NILM PAP smears. Early detection and treatment, along with regular screening, may help prevent progression to cervical epithelial abnormalities.

KEYWORDS

Negative for Intraepithelial Lesion or Malignancy, PAP Smear

INTRODUCTION-

In India and worldwide, cervical cancer is the second and fourth most commonly diagnosed cancer in females respectively and one of the leading causes of cancer death. In India, cervical cancer is the second most common cause of cancer death [1]

The natural history of cervical cancer allows early detection of cervical epithelial lesions by simple and effective screening tool known as PAP smear, discovered by George Papanicolaou [2]. PAP is a universal stain for gynecologic and non-gynecologic cytology smears and is commonly used for oral and cervical cancer screening[1]. The Bethesda System for Reporting Cervical Cytology at 1988 proposed a standard reporting terminology which are reproducible across different pathologists and communicates relevant information to the health care provider. The subsequent Bethesda workshops were conducted at 1991, 2001 and recently at 2014, during the course, TBS has undergone various refinements.[2]

This study aims to explore the use of conventional PAP smear for the diagnosis of various cytomorphological spectrum of cervical PAP smear reports using TBSRC 2014, to analyze the clinical and demographic data of the patients, and also to characterize the age pattern of various PAP smears findings/results and prevalence of abnormal PAP smears as well. This would probably help to find the target group in the study population[2]. Even though LSIL, HSIL and ASCUS are known precursor to cervical malignancy but NILM, which is often associated with longstanding cervical infection, may act as a cofactor in the development of epithelial abnormalities. So, awareness can be raised about genital hygiene and other measures to prevent infection and subsequent risk of neoplastic transformation.

Due to effective primary (human papilloma virus [HPV] vaccination) and secondary (screening) preventive measures, cervical cancer is considered a largely preventable disease.[1]

The World Health Organization made a call for the global elimination of cervical cancer in 2018 using the triple-intervention approach of (a) vaccination, (b) screening of women, and (c) treating all the precancerous lesions detected during screening. A cervical PAP smear examination is an easy, non-invasive, and effective screening method for cervical carcinoma.[1]

AIMS AND OBJECTIVES

We undertook this study to find out the Negative for Intraepithelial Lesion or Malignancy (NILM) spectrum of the cervical smear pattern along with the clinical profiles of patients who underwent cervical PAP smear evaluation.

Methodology-

Study Design- Retrospective Descriptive study.

Criteria for inclusion- All the women more than 21 years attending the OPD with various gynaecology symptoms such as pain abdomen, white discharge, bleeding p/v and also who come for routine screening, who had undergone PAP smear test and are diagnosed as case of Negative for Intraepithelial Lesion or Malignancy (NILM) are included in the study. Institutional ethical committee clearance was obtained.

Criteria For Exclusion- Women who were pregnant, known or treated cases of Epithelial cell abnormality including cancer cervix, unmarried women and diagnosis other than Negative for Intraepithelial Lesion or Malignancy (NILM) were excluded from the study.

Study Period- July 2023- August 2024

Sample Size- 200 cases retrospectively diagnosed as cases of NILM (as per the 2014 Bethesda system for reporting cervical cytology (TBSRC 2014)) after conventional PAP smear analysis were included in the study. The medical records of the study participants are analyzed and complete clinical history including chief complaints, personal and marital history are noted. Reactive cellular changes associated with Bacteria vaginosis, Trichomoniasis, Candidiasis, Inflammatory smear, Metaplasia, Parakeratosis, Repair reaction, Herpes Simplex Virus, Actinomyces and granulomatous cervicitis are included in Negative for intraepithelial lesion/Malignancy (NILM). The data were tabulated and analyzed, with descriptive statistics expressed as frequencies and percentages.

MATERIALS AND METHODS

A retrospective analysis was performed of all the women more than 21 years attending the OPD with various gynaecology symptoms such as pain abdomen, white discharge, bleeding p/v and also who came for routine screening, who had undergone PAP smear test are included in

the study over the past 1 year (July 2023- August 2024). A total of 200 PAP smears received. PAP smear slides stained by the Papanicolaou method were retrieved and reviewed. Clinical history and physical examination findings were recorded from available medical records. The initial diagnosis was based on the presumptive clinical diagnosis. The final diagnosis was made after incorporating the PAP smear report. Diagnostic cytopathological findings suggestive of Negative for Intraepithelial Lesion or Malignancy (NILM) were noted in every individual case. The cytological interpretation was reported according to the 2014 Bethesda System for reporting cervical cytology.

RESULTS-

Table 1- Clinico- Demographic Details (n=200)

Age Group	21-30 years	36 (18%)
	31-40 years	92 (46%)
	41-50 years	42 (21%)
	51-60 years	18 (9%)
	>60 years	12 (6%)

Parity	Nulliparous	04 (2%)
	Living 1	49 (24.5%)
	Multiparous	147 (73.5%)
Marital (Age at marriage)	<21 years	06 (3%)
	>21 years	194 (97%)
Chief complaints	White discharge P/V	71(35.5%)
	Bloody discharge P/V	02 (1%)
	Itching	08 (4%)
	Abnormal uterine bleeding	63 (31.5%)
	Post coital bleeding	04 (2%)
	Lower abdominal pain	20 (10%)
	Cervical erosion	02 (1%)
	Genital ulcer	01 (0.5%)
	Prolapse uterus	05 (2.5%)
	Routine screening	10 (5%)
	Post menopausal bleeding	14 (7%)

Table 2- Age Pattern Of Pap Results-

Age group	Bacterial vaginosis	Trichomonas	Candida	Inflammatory smear	Metaplastic Change *	Parakeratosis	Repair reaction	Herpes simplex virus	Actinomycosis	Granulomatous Cervicitis	No specific finding	Total
21-30	18 (9.0%)	2 (1.0%)	5 (2.5%)	6 (3.0%)	0 (0%)	0 (0%)	3 (1.5%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	35 (17.5%)
31-40	22 (11.0%)	2 (1.0%)	4 (2.0%)	38 (19.0%)	4 (2.0%)	1 (0.5%)	9 (4.5%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	3 (1.5%)	88 (44.0%)
41-50	12 (6.0%)	1 (0.5%)	2 (1.0%)	22 (11.0%)	3 (1.5%)	0 (0%)	4 (2.0%)	1 (0.5%)	1 (0.5%)	0 (0%)	1 (0.5%)	47 (23.5%)
51-60	6 (3.0%)	1 (0.5%)	0 (0%)	10 (5.0%)	1 (0.5%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (9.5%)
>60	0 (0%)	0 (0%)	0 (0%)	11 (5.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (5.5%)
Total	58 (29.0%)	6 (3.0%)	11 (5.5%)	87 (43.5%)	8 (4.0%)	1 (0.5%)	17 (8.5%)	4 (2.0%)	2 (1.0%)	2 (1.0%)	4 (2.0%)	200 (100%)

* [Squamous Metaplasia- 5 (2.5%), Tubal Metaplasia- 2 (1%), Intestinal Metaplasia- 1 (0.5%)]

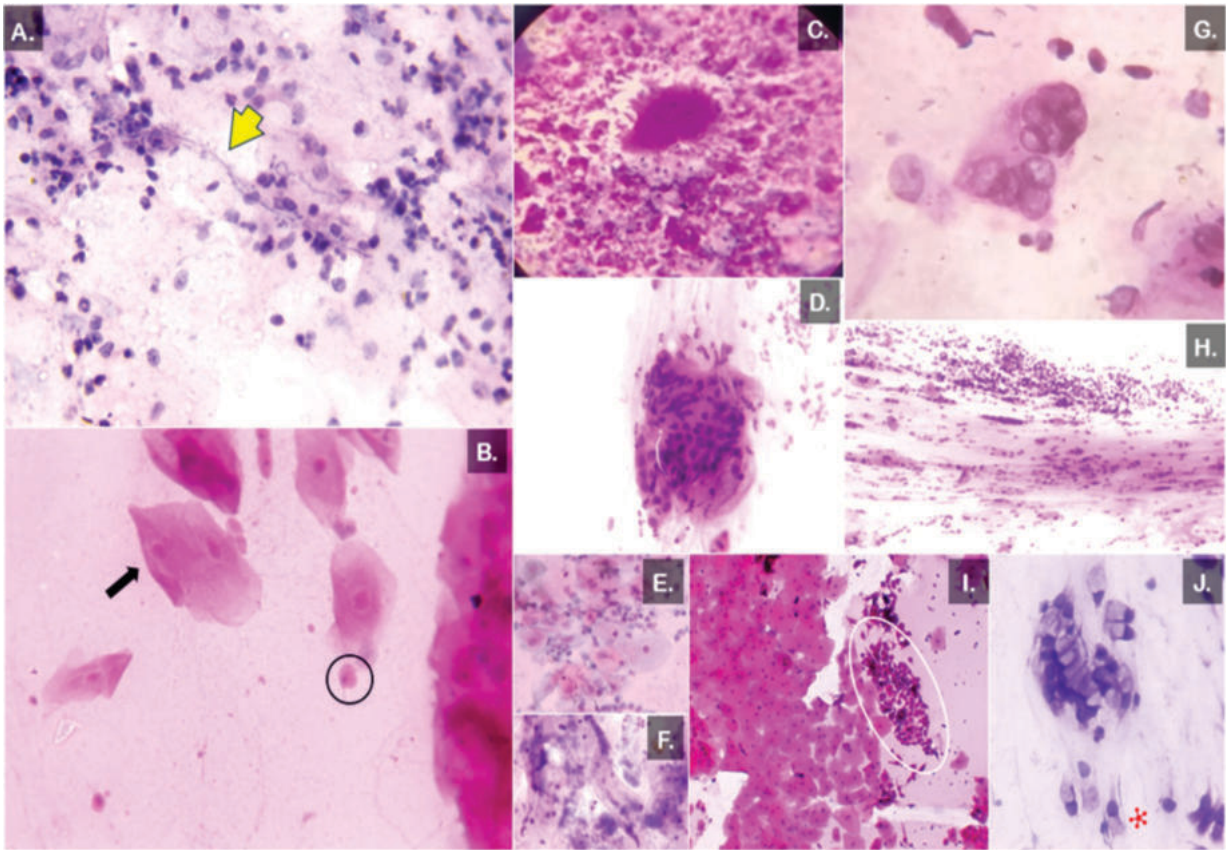


Figure Description:

- A. Candida Hyphae (yellow arrowhead)
- B. Trichomonas vaginalis (black circle) with squamous epithelial cells showing 'trich halo'
- C. Actinomycosis
- D. Epithelioid granuloma in a case of Granulomatous Cervicitis
- E. Candida spores
- F. Bacterial Vaginosis with 'Clue Cell'
- G. HSV Cytopathic Effect- molding, margination, multinucleation (3Ms)
- H. Repair Reaction - "Fish-in-stream" appearance
- I. Parakeratosis & Squamous Metaplasia (white oval)
- J. Intestinal & Tubal Metaplasia (red asterisk)

A total of 200 women between the age of 21-70 years are included in the study with the mean age of 37.5 years. Majority (46%) of women were in age group of 31-40 years followed by 41-50 years age group (21%). Out of 200 women, 04(02%) were nulliparous and 147(73.5%) were multiparous and rest had one living child. The most common chief complaints of women in our study were white discharge 71(35.5%) followed by abnormal uterine bleeding 63 (31.5%), lower abdominal pain 20(10%), post-menopausal bleeding 14(7%), prolapsed uterus 05(2.5%), post coital bleed 04(2%), and 10(5%) had come for routine screening. Out of 200 Negative for intraepithelial lesion/Malignancy (NILM) confirmed pap smears cases, which were satisfactory according to TBSRC 2014, Inflammatory smear 87 (43.5%) is the one of the frequent patterns of NILM in the study involving predominantly 31-40 years age group. The other patterns include- 58 (29%) were of shift in flora suggestive of Bacterial Vaginosis, 17 (8.5%) Repair Reaction, 11 (5.5%) Candida species, 8 (4%) Metaplasia, 06 (3%) Trichomonas Vaginalis, 4 (2%) Herpes Simplex Virus, 4(2%) cases no other specific findings, 2 (1%) Actinomyces, 2 (1%) Granulomatous cervicitis and 1 (0.5%) Parakeratosis cases were identified.

DISCUSSION-

Cervical cancer remains a major public health concern in India, accounting for a significant proportion of cancer-related morbidity and mortality among women, particularly in rural and low-resource settings [3]. The long preinvasive phase of cervical carcinogenesis enables effective secondary prevention through cytological screening using the Papanicolaou smear [3]. The introduction and subsequent refinements of the Bethesda System for Reporting Cervical Cytology, culminating in the 2014 edition, have standardized reporting terminology and improved reproducibility and clinicocytological correlation [1,2].

Although PAP smears reported as Negative for Intraepithelial Lesion or Malignancy (NILM) are categorized as non-neoplastic, they frequently reveal inflammatory, infectious, and reactive epithelial changes that may have clinical significance [1,2]. Recognition of the NILM spectrum is important, as persistent cervical inflammation and infection can alter the epithelial microenvironment and may indirectly contribute to cervical disease progression [4].

In the present study, the mean age of women with NILM was 37.5 years, with the majority belonging to the 31–40-year age group, followed by the 41–50 year age group. A similar age distribution has been reported by Sethy et al., who observed a predominance of NILM and inflammatory smears in women aged 36–45 years [1]. Priyadharisini and Bharathi also reported that women in the third and fourth decades constituted the largest proportion of NILM cases in their tertiary care study [2]. This age group is epidemiologically important, as precursor cervical lesions generally develop several years before the peak incidence of invasive carcinoma [4].

Multiparity was common among women in the present study, which aligns with previously published Indian data identifying multiparity as an established risk factor for cervical cancer [4]. Senapathy et al. described that repeated cervical trauma during childbirth, hormonal influences, and prolonged exposure to oncogenic human papillomavirus (HPV) contribute to increased cervical cancer susceptibility in multiparous women [4]. Early age at marriage, although less frequent in the present cohort, remains a relevant epidemiological factor in the Indian population due to early sexual debut and extended duration of HPV exposure [3].

Clinically, white discharge per vagina was the most frequent presenting complaint in the present study, followed by abnormal uterine bleeding [7]. Sachan et al. similarly reported vaginal discharge as the most common presenting symptom among women undergoing PAP smear screening [7]. Sharif demonstrated a strong clinicocytological correlation between vaginal discharge and inflammatory PAP smear findings, emphasizing the importance of evaluating symptomatic women even in the absence of epithelial abnormalities [8].

Among the NILM spectrum, inflammatory smear was the most common cytological pattern observed in the present study [1]. This finding is consistent with studies by Sethy et al. and Priyadharisini et al., both of whom reported inflammatory smears as the predominant NILM subtype [1,2]. Chronic cervical inflammation is clinically

relevant, as it can disrupt epithelial integrity and impair local immune responses, thereby facilitating persistence of oncogenic HPV strains [4].

Bacterial vaginosis (BV) was the second most frequent NILM finding in the present study [5]. Patel et al. and Babu et al. reported comparable findings, highlighting Bacterial vaginosis as a common cause of chronic cervicitis detected on PAP smear examination [5,6]. Alteration of the normal vaginal flora and increased vaginal pH associated with Bacterial vaginosis may promote epithelial irritation and contribute to HPV persistence [4].

Infectious etiologies such as candidiasis and trichomoniasis were also identified among NILM smears in the present study [7]. Sachan et al. reported similar infectious patterns in symptomatic women undergoing cervical cytology screening [7]. Sharif further highlighted the importance of correlating such infections with clinical symptoms, as they contribute significantly to chronic cervicitis and patient morbidity [8]. Herpes simplex virus (HSV) infection was identified in a small proportion of NILM smears in the present study [8]. Although HSV is not directly oncogenic, Sharif reported that HSV-associated cervicitis contributes to chronic inflammation, and is an important associated risk factor for development of HSV-associated Cervical Cancer [8], a fact corroborated by Dubey et al. [11] and other sources [13].

Actinomyces is an uncommon but clinically significant finding detected on PAP smear and was identified in the present study. Increased incidence was observed among IUCD users, similar to observations reported by Babu et al. [6] and Dubey et al. [12]

Granulomatous cervicitis, though rare, represents an important NILM finding requiring further clinical correlation to exclude infectious etiologies such as tuberculosis, particularly in endemic regions like India [3,6]. Babu et al. highlighted the importance of recognizing granulomatous inflammation on PAP smears to guide appropriate diagnostic evaluation [6].

Metaplastic changes formed an important component of the NILM spectrum in the present study [1,2]. Squamous metaplasia represents a physiological or reactive replacement of columnar epithelium by stratified squamous epithelium at the transformation zone [1,2]. Sethy et al. and Priyadharisini et al. described squamous metaplasia as a common benign NILM finding requiring careful interpretation to avoid confusion with epithelial abnormalities [1,2]. Senapathy et al. emphasized that the transformation zone, where squamous metaplasia occurs, is biologically active and particularly susceptible to oncogenic HPV infection [4].

Tubal metaplasia, characterized by the presence of ciliated columnar cells resembling fallopian tube epithelium, is a less common metaplastic variant encountered in cervical cytology [1,2]. According to the Bethesda System, tubal metaplasia is classified under NILM in the absence of cytological atypia [1,2]. Its occurrence has been attributed to hormonal influence and regenerative changes following inflammation or repair [2].

Intestinal metaplasia is a rare metaplastic finding in cervical cytology and is characterized by goblet cell–like mucin-containing cells [1,2]. When identified without atypia, intestinal metaplasia is considered a benign metaplastic response and included within the NILM category [1,2]. Babu et al. noted that such unusual metaplastic patterns require careful cytomorphological evaluation and clinicocytological correlation to exclude glandular neoplasia [6].

Repair reaction constituted an important NILM subtype in the present study [2]. Priyadharisini and Bharathi emphasized that repair reaction represents reactive epithelial regeneration following inflammation or trauma and may mimic epithelial atypia if not carefully interpreted [2]. Accurate recognition of repair reaction is therefore essential to avoid overdiagnosis and unnecessary clinical intervention [2].

The coexistence of multiple inflammatory, infectious, and metaplastic changes within NILM smears emphasizes that cytological negativity for malignancy does not equate to absence of disease [1]. Skapinyecz et al. demonstrated an association between pelvic inflammatory disease and increased cervical cancer risk, attributing this relationship to higher HPV prevalence in chronically inflamed cervixes [10].

Therefore, identification and appropriate management of NILM-associated changes play a crucial role in comprehensive cervical cancer prevention strategies [3,10].

CONCLUSION-

In conclusion, the present study highlights the significance of the NILM spectrum in identifying inflammatory and infectious cervical changes, particularly among multiparous women aged 30–50 years presenting with vaginal discharge. Previous studies indicate that chronic inflammation and persistent infections may facilitate human papillomavirus persistence and increase susceptibility to cervical epithelial abnormalities rather than directly causing neoplastic transformation [3,4,10]. The effectiveness of the PAP smear as a screening tool, supported by its correlation with colposcopic findings, reinforces the importance of routine screening and targeted preventive strategies, especially in rural populations [1,2,5,7,9]. TBSRC 2014 allows crisp reporting format and helps clinicians to appropriately manage through consensus guidelines. Awareness regarding vaginal hygiene practice and about PAP smear test should be implicated to every woman through mass screening programmes and campaigns to prevent infection and subsequent risk of neoplastic transformation. Timely screening of pre-invasive lesion allows prevention from invasive cervical cancer.

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