

# The prolapse pitfall: differentiating reactive cytologic changes in uterine prolapse from squamous intraepithelial lesions

## Abstract

**Background:** Cervicovaginal cytology is a cornerstone of cervical cancer screening, but its interpretation can be confounded by benign changes, leading to diagnostic pitfalls and potential medicolegal consequences. This study addresses the potential for marked reactive changes associated with uterine prolapse to mimic squamous intraepithelial lesions (SIL), or cervical dysplasia, in cervicovaginal (Pap) smears.

**Methods:** We prospectively collected and studied cervicovaginal smears from 39 patients (age range: 34-75 years; parity range: 4-14, with uterine prolapse. All patients subsequently underwent simple hysterectomy for prolapse symptoms. Cytomorphologic features were evaluated, and Human Papillomavirus status was determined using Polymerase Chain Reaction on cervical swabs. Resected cervical tissue was examined for corresponding histopathologic changes, including HPV/p16 immunohistochemistry.

**Results:** All 39/39 cases demonstrated cytological features concerning for dysplasia, including an increased nuclear-to-cytoplasmic (N/C) ratio, nuclear contour irregularities, and perinuclear halos. However, they also uniformly exhibited changes not typically seen in SIL: frayed cytoplasmic borders (39/39 cases), neutrophilic debris in the background (39/39 cases), and the presence of vesicular nuclei (at least focally, 39/39 cases). All cases were negative for HPV by PCR and negative for HPV/p16 immunostaining on resected tissue. Histopathology of the resected cervix revealed basal cell hyperplasia (34/39), transitional cell metaplasia (32/39), and parakeratosis/koilocyte-like changes (39/39).

**Conclusion:** Cytomorphologic changes in cervical smears from patients with uterine prolapse frequently mimic SIL. Key differentiating cytological features are frayed cytoplasmic borders, abundant neutrophilic debris, vesicular nuclei. Pathologist awareness of this specific reactive entity, supported by clinical history and ancillary HPV testing, is crucial to prevent misdiagnosis and unnecessary patient intervention.

**Keywords:** uterine prolapse, cervicovaginal cytology, pap smear, reactive cellular changes, squamous intraepithelial lesion (sil) mimic, cervical dysplasia, cytomorphology, human papillomavirus (hpv), polymerase chain reaction (pcr), p16 immunohistochemistry, basal cell hyperplasia, transitional cell metaplasia, parakeratosis, koilocyte-like changes, diagnostic pitfalls.

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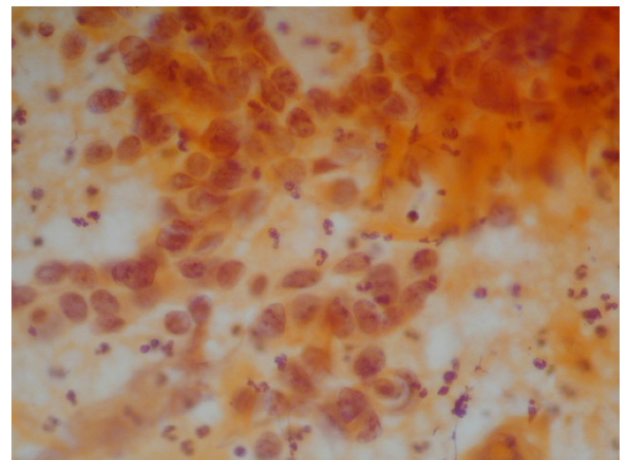
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## Introduction

Uterine prolapse, defined as the descent of the uterus into or beyond the vagina, is a common pelvic floor support defect, with prevalence increasing with age and parity.<sup>1-4</sup> While some studies suggest a lower risk in African Americans and a higher risk in Hispanic women, the condition predominantly affects multiparous and postmenopausal women.<sup>1,5-7</sup> The descent of the cervix exposes the exocervical epithelium to the external environment, leading to chronic irritation, friction, and secondary reactive changes.<sup>8,9</sup> These reactive cytological alterations, which can include increased cellularity, nuclear enlargement, and cytoplasmic changes, often become a source of diagnostic uncertainty when interpret cervicovaginal smears (Pap smears).<sup>1,2,10,11</sup> The potential to mistakenly classify these changes as squamous intraepithelial neoplasia (SIN), also known as cervical dysplasia, is a significant diagnostic pitfall that carries substantial medicolegal implications. This study aims to characterize the specific cytomorphologic profile of reactive changes associated with uterine prolapse and identify key features that reliably distinguish them from true SIL (Figure 1).



**Figure 1** Sheaths of highly atypical squamous cells observed in cervicovaginal smear (pap stain).

## Materials and methods

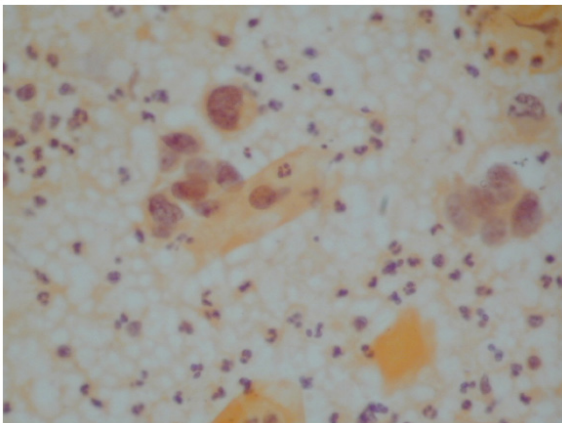
### Study design and patient population

This prospective study investigated thirty-nine (n=39) cases of cervicovaginal smears collected from patients diagnosed with uterine prolapse over a 14-year period. All patients subsequently underwent simple hysterectomy for symptomatic prolapse. Patient ages ranged from 34 to 75 years, and parity ranged from 3 to 14 children.

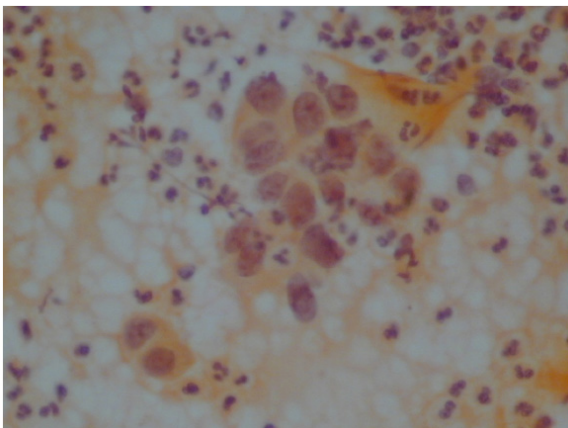
### Cytomorphologic assessment

Cervicovaginal smears were stained with the Papanicolaou method and systematically evaluated by a single blinded pathologist for the following cytological features: (Figure 2a-2d),

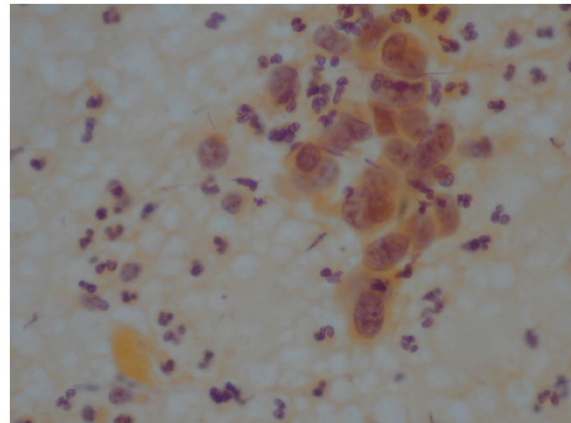
- Increased nuclear-to-cytoplasmic (N/C) ratio
- Nuclear contour irregularities
- Nuclear hyperchromasia
- Discohesiveness of squamous cells
- Perinuclear halos (koilocyte-like changes)
- Nuclear molding
- Loose (frayed) cytoplasmic borders
- Neutrophilic debris in the background
- Presence of vesicular nuclei (at least focally)
- Prominent nucleoli



Figures 2a



Figures 2b



Figures 2c

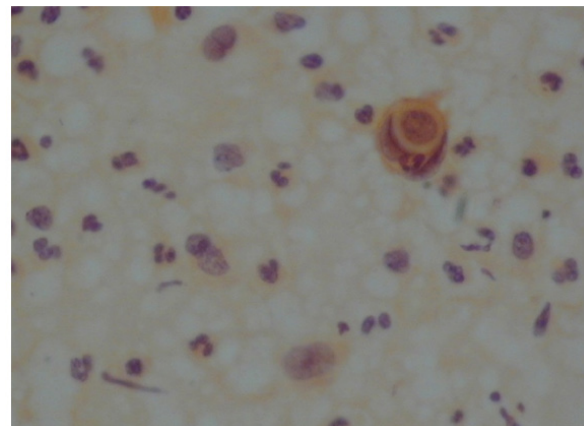


Figure 2d

**Figures 2a-2d** Atypical squamous cells with high Nuclear-to-Cytoplasmic (N/C) ratio and irregular nuclear contours, characteristic of the reactive changes associated with uterine prolapse. Note the presence of prominent nucleoli in some cells and the nuclear debris in the background (Pap stain)

### Ancillary studies

Human Papilloma Virus (HPV) status was determined for all cases. Polymerase Chain Reaction (PCR) was performed on cervical swabs. Additionally, HPV and p16 immunohistochemical (IHC) staining was performed on the corresponding formalin-fixed, paraffin-embedded (FFPE) cervical tissue from the hysterectomy specimen. (Figure 3a–3d)

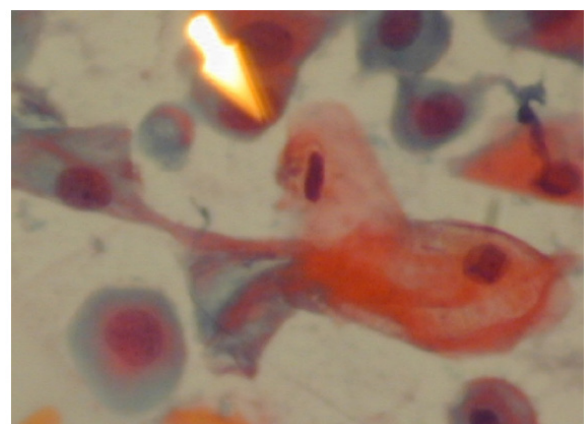


Figure 3a

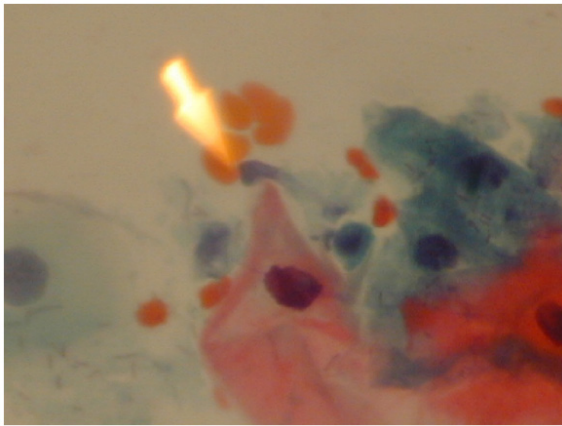


Figure 3c

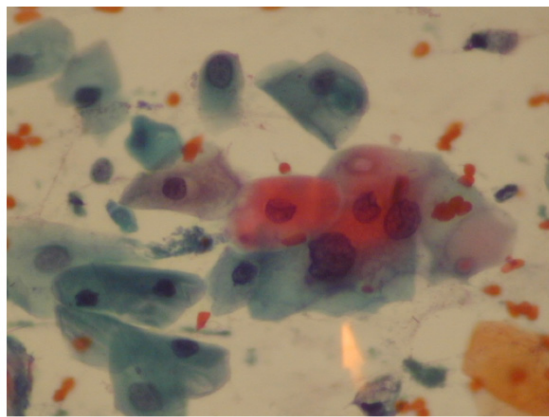


Figure 3d

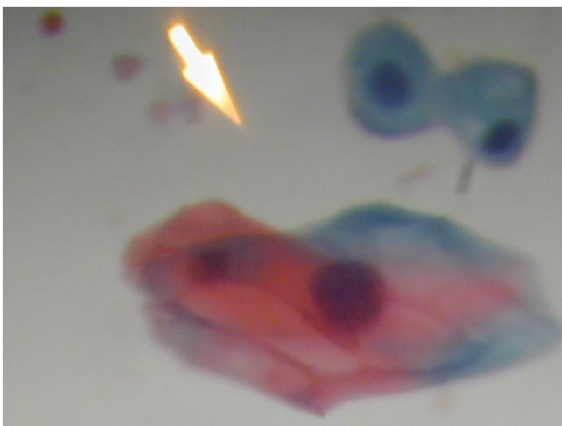


Figure 3e

**Figure 3a-3d** Large nuclei, nuclear hyperchromasia, perinuclear halos, and irregular nuclear contours, which are changes highly similar to koilocytes seen in Human Papilloma Virus (HPV) infections (Pap stain).

### Histopathologic correlation

All resected uterine cervix specimens were examined to correlate the observed cytological changes with underlying tissue histopathology, specifically noting the presence of basal cell hyperplasia, transitional cell metaplasia, and parakeratosis.

## Results

### Cytological findings

Cervicovaginal smears consistently exhibited two groups of findings:

#### I. Features mimicking SIL:

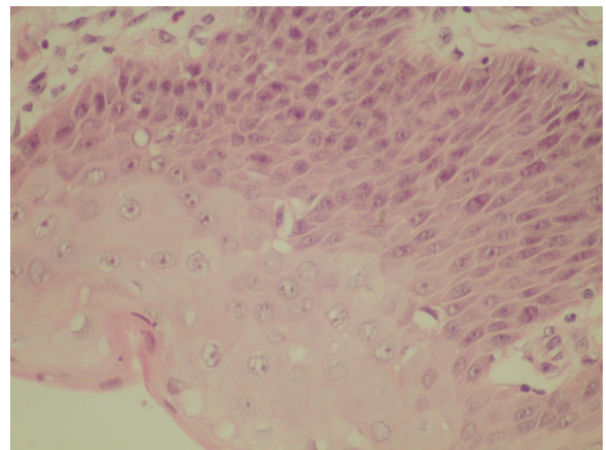
- Increased N/C ratio: 39/39 cases (100%)
- Nuclear contour irregularities: 39/39 cases (100%)
- Perinuclear halos: 39/39 cases (100%)
- Discohesiveness of cells: 29/39 cases (74%)
- Nuclear molding: 28/39 cases (72%)
- Nuclear hyperchromasia: 22/39 cases (55%)

#### II. Features not typically seen in SIL (Reactive Prolapse Changes):

- Loose/frayed cytoplasmic borders: 39/39 cases (100%)
- Abundant neutrophilic debris in the background: 39/39 cases (100%)
- Vesicular nuclei (at least focally): 39/39 cases (100%)
- Prominent nucleoli: 21/39 cases (53%)

### HPV and p16 status

All 39/39 cases demonstrated a negative result for HPV by PCR on the cervical swab. Correspondingly, HPV and p16 immunohistochemical staining was negative in all cases on resected cervical tissue. (Figure 4)



**Figure 4** Histopathology of the resected cervical tissue showing basal cell proliferation extending more than one-third of the epithelial thickness, mimicking cervical intraepithelial neoplasia grade I (CIN I) (H&E stain).

### Histopathologic correlation

The resected cervical specimens showed consistent reactive changes:

- Basal cell hyperplasia (mimicking CIN 1): 34/39 cases
- Transitional cell metaplasia (with umbrella-like cells): 32/39 cases
- Parakeratosis and koilocyte-like changes: 39/39 cases (Figure 5a & 5b)

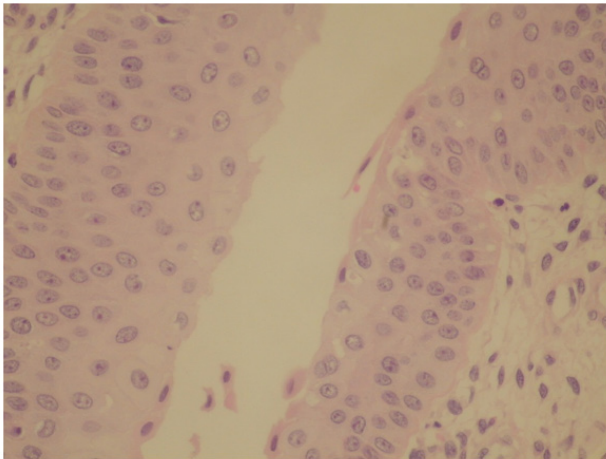


Figure 5a

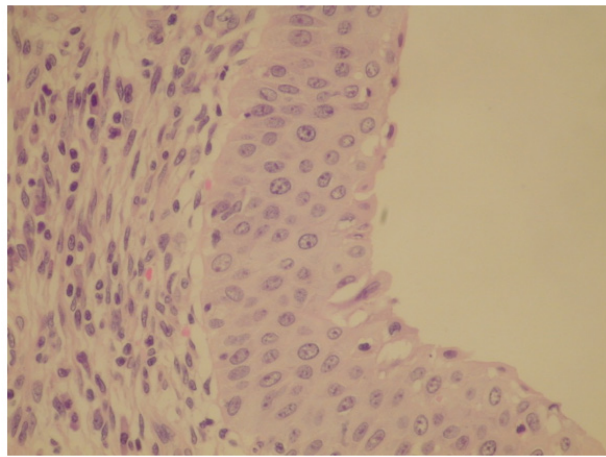


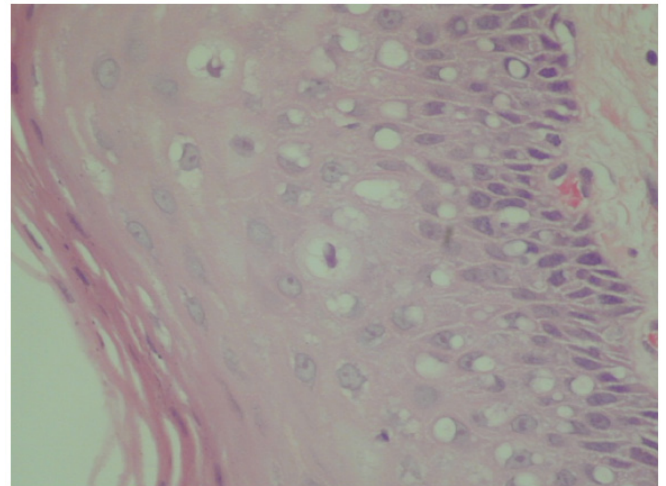
Figure 5b

**Figure 5a and 5b** Histopathology showing Pseudo transitional cell metaplasia with characteristic umbrella-like cells seen in the superficial cervical epithelium of the uterine prolapse specimen (H&E stain, Original Magnification  $\times$ ).

## Discussion and conclusion

The results demonstrate that the chronic frictional irritation associated with uterine prolapse induces marked reactive atypia in the cervical epithelium, which translates to a highly suspicious appearance on cervicovaginal smears, characterized by high N/C ratio and nuclear irregularities, mimicking true SIN.<sup>12,13</sup> However, the consistent presence of four key features—frayed cytoplasmic borders, abundant neutrophilic debris, vesicular nuclei, and occasional prominent nucleoli—serves as a crucial diagnostic clue to differentiate this benign reactive process from a true premalignant lesion. The histopathological findings of basal cell hyperplasia, transitional cell metaplasia, and parakeratosis support the notion of a defensive, proliferative, and frictional response rather than a neoplastic one.<sup>14-16</sup>

The definitive evidence for the benign nature of these changes is the universal negative result for HPV by PCR and the lack of p16 overexpression.<sup>17</sup> This underscores the importance of a comprehensive approach: the clinical history of uterine prolapse, the specific cytomorphological pattern (particularly the reactive markers), and the strategic use of ancillary HPV testing should raise the threshold for a definitive diagnosis of dysplasia (Figure 6).



**Figure 6** Histopathology showing koilocyte-like changes with basal layer increase, mimicking HPV changes with CIN I (mild dysplasia) (H&E stain).

## Summary

Awareness of the “prolapse pitfall” is paramount for pathologists to ensure accurate diagnoses, prevent over-calling benign changes as SIN, and ultimately avoid unnecessary colposcopy, biopsy, and patient anxiety, which can lead to medicolegal complications.

## Acknowledgement

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## Conflict of interest

No potential conflict of interest was reported by the author.

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