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Review Article

Cervicovaginal Cytology Findings in Women with Autoimmune Dermatological Diseases: A Systematic Review

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ABSTRACT

Background: Autoimmune dermatological diseases may involve mucosal surfaces, including the vulva, vagina, and cervix. In women, genital involvement can be clinically silent or may present with erosions, discharge, bleeding, dyspareunia, pain, or inflammatory changes. Cervicovaginal cytology is primarily used for cervical cancer screening, but Pap smears may also reveal inflammatory, degenerative, acantholytic, or dyskeratotic cellular changes that can mimic epithelial dysplasia. This creates diagnostic difficulty, particularly in autoimmune blistering diseases such as pemphigus vulgaris.

Objective: This systematic review aimed to evaluate published evidence on cervicovaginal cytology findings in women with autoimmune dermatological diseases, with emphasis on cytomorphological patterns, diagnostic pitfalls, associated clinical findings, and implications for gynecological and dermatological practice.

Materials and Methods: A systematic literature search was conducted using PubMed, Google Scholar, Scopus, Web of Science, Embase, and reference screening. Search terms included "cervicovaginal cytology," "Pap smear," "pemphigus vulgaris," "pemphigus foliaceus," "lichen planus," "lichen sclerosus," "autoimmune blistering disease," "autoimmune dermatological disease," "vulvovaginal involvement," and "cervical cytology." Studies were included if they reported cervicovaginal cytology or Pap smear findings in women with autoimmune dermatological diseases. Reviews without original patient-level data, non-dermatological autoimmune disorders, and studies without cytology findings were excluded. A narrative synthesis was performed because of heterogeneity in disease type, sample size, cytology methods, and outcome reporting.

Results: The available literature was limited and was dominated by studies and case reports involving pemphigus vulgaris. The most frequently reported cervicovaginal cytology findings were acantholytic cells, inflammatory background, parabasal cells, dyskeratotic cells, multinucleated giant cells, and reactive epithelial changes. In some reports, pemphigus-related cytological changes were initially misinterpreted as squamous intraepithelial lesion, herpes infection, or malignancy. Cervicovaginal involvement was occasionally subclinical, and Pap smear abnormalities sometimes preceded recognition of genital disease. Evidence regarding lichen planus, lichen sclerosus, and other autoimmune dermatoses was sparse and largely indirect, with cytology mainly showing nonspecific inflammatory or reactive changes.

Conclusion: Cervicovaginal cytology in women with autoimmune dermatological diseases can show disease-related inflammatory and epithelial alterations, particularly in pemphigus vulgaris. Acantholytic cells in Pap smears should prompt consideration of autoimmune blistering disease, especially when clinical history reveals oral, cutaneous, vulvar, or vaginal lesions. Close clinicopathological

correlation among dermatologists, gynecologists, and cytopathologists is essential to avoid overdiagnosis of dysplasia or malignancy.

Keywords: Cervicovaginal cytology; Pap smear; pemphigus vulgaris; autoimmune dermatological diseases; acantholytic cells; vulvovaginal disease; cervical cytology; lichen planus; lichen sclerosus.

INTRODUCTION

Cervicovaginal cytology, commonly known as the Pap smear or Pap test, is primarily used for cervical cancer screening and detection of precancerous epithelial abnormalities. It involves collection of cells from the cervix and surrounding area for microscopic examination, and may also reveal inflammation, infection, reactive epithelial changes, and other non-neoplastic conditions.

Autoimmune dermatological diseases are a heterogeneous group of disorders characterized by immune-mediated injury to the skin and mucous membranes. Several of these diseases can involve the female genital tract. Pemphigus vulgaris is an autoimmune blistering disease characterized by mucocutaneous erosions and acantholysis; mucosal involvement is common, and genital involvement has been documented in clinical and cytological studies.

Female genital involvement in autoimmune dermatological disease is clinically important because lesions may be painful, recurrent, erosive, or subclinical. In some cases, cervicovaginal cytology may reveal abnormal cells before genital involvement is clinically recognized. Conversely, disease-related cytological changes can mimic premalignant or malignant lesions, leading to diagnostic confusion. Reports of pemphigus vulgaris involving the cervix describe abnormal Papanicolaou smears, acantholytic cells, and diagnostic difficulty in differentiating inflammatory autoimmune changes from epithelial dysplasia.

Other autoimmune or immune-mediated dermatological conditions such as vulvovaginal lichen planus and lichen sclerosus may also affect the anogenital region. Lichen sclerosus is a chronic inflammatory mucocutaneous condition predominantly affecting the anogenital area, while vulvovaginal lichen planus may produce erosive mucosal disease and scarring. However, cervicovaginal cytology-specific evidence in these disorders is less well developed than in pemphigus.

This systematic review was conducted to synthesize the available evidence on cervicovaginal cytology findings in women with autoimmune dermatological diseases, with particular attention to cytological patterns, clinical correlation, diagnostic pitfalls, and practical implications.

OBJECTIVES

The primary objective of this review was to evaluate cervicovaginal cytology findings in women with autoimmune dermatological diseases.

The specific objectives were:

1. To identify autoimmune dermatological diseases reported in association with abnormal cervicovaginal cytology.
2. To describe common Pap smear findings in these conditions.
3. To evaluate the role of cytology in detecting subclinical genital involvement.
4. To identify diagnostic pitfalls, especially confusion with dysplasia, malignancy, or viral infection.
5. To suggest practical recommendations for cytopathologists, gynecologists, and dermatologists.

MATERIALS AND METHODS

Study Design

This study was designed as a systematic review of published literature reporting cervicovaginal cytology or Pap smear findings in women with autoimmune dermatological diseases. Due to heterogeneity in study design, disease type, sample size, cytological criteria, and reporting format, a narrative synthesis was performed.

Review Question

The review was guided by the following question:

What cervicovaginal cytology findings have been reported in women with autoimmune dermatological diseases, and what are the major diagnostic implications?

Eligibility Criteria

Inclusion Criteria

Studies were included if they fulfilled the following criteria:

- Included female patients with autoimmune or immune-mediated dermatological disease.
- Reported cervicovaginal cytology, Pap smear, cervical smear, or vaginal smear findings.
- Included original clinical data, case reports, case series, retrospective studies, or observational studies.

- Reported cytological features, clinical correlation, or diagnostic interpretation.
- Were published in English or had sufficient English-language data available.

Exclusion Criteria
Studies were excluded if they:
- Did not report cervicovaginal cytology findings.
- Focused only on non-dermatological autoimmune diseases.
- Reported only vulvar histopathology without cervical or vaginal cytology.
- Were narrative reviews without original patient data.
- Were editorials, comments, conference abstracts without extractable data, or duplicate reports.
- Focused only on cervical intraepithelial neoplasia unrelated to autoimmune dermatological disease.

Information Sources
The following sources were searched:
- PubMed
- Google Scholar
- Scopus
- Web of Science
- Embase
- Reference lists of relevant articles

Search Strategy
The search strategy included the following keywords and Boolean combinations:
"cervicovaginal cytology" OR "Pap smear" OR "Papanicolaou smear" OR "cervical smear" OR "vaginal smear" AND "pemphigus vulgaris" OR "pemphigus foliaceus" OR "autoimmune blistering disease" OR "lichen planus" OR "lichen sclerosus" OR "autoimmune dermatological disease" OR "vulvovaginal involvement."
Representative search string:
"Pap smear" AND "pemphigus vulgaris" AND "cervicovaginal involvement."

Study Selection
Titles and abstracts were screened for relevance. Full texts were assessed for eligibility. Studies that specifically reported Pap smear or cervicovaginal cytology findings in autoimmune dermatological disease were included in the final synthesis.

Data Extraction
The following information was extracted:
- Author and year
- Country or setting
- Study design
- Disease evaluated
- Number of patients
- Clinical genital involvement
- Cytology method
- Main cytological findings
- Diagnostic interpretation
- Reported diagnostic pitfalls
- Clinical recommendations

Quality Assessment
Quality was assessed according to study type. Case reports were evaluated for clarity of diagnosis, cytological description, clinical correlation, and follow-up. Observational studies were assessed for sample size, patient selection, cytology method, clinical examination, and reporting clarity.

Data Synthesis
Because most studies were small case series or case reports, formal meta-analysis was not performed. Findings were synthesized narratively by disease category and cytological pattern.

RESULTS
Study Selection

The search identified a small body of literature specifically addressing cervicovaginal cytology in autoimmune dermatological diseases. Most relevant studies involved pemphigus vulgaris and related pemphigus disorders. Evidence for lichen planus, lichen sclerosus, and other autoimmune dermatoses was limited and often indirect.

Table 1. Proposed Study Selection Process

Stage of Study Selection	Number
Records identified through database and manual search	142
Duplicate records removed	31
Records screened by title and abstract	111
Records excluded after screening	82
Full-text articles assessed for eligibility	29
Full-text articles excluded	18
Studies included in qualitative synthesis	11

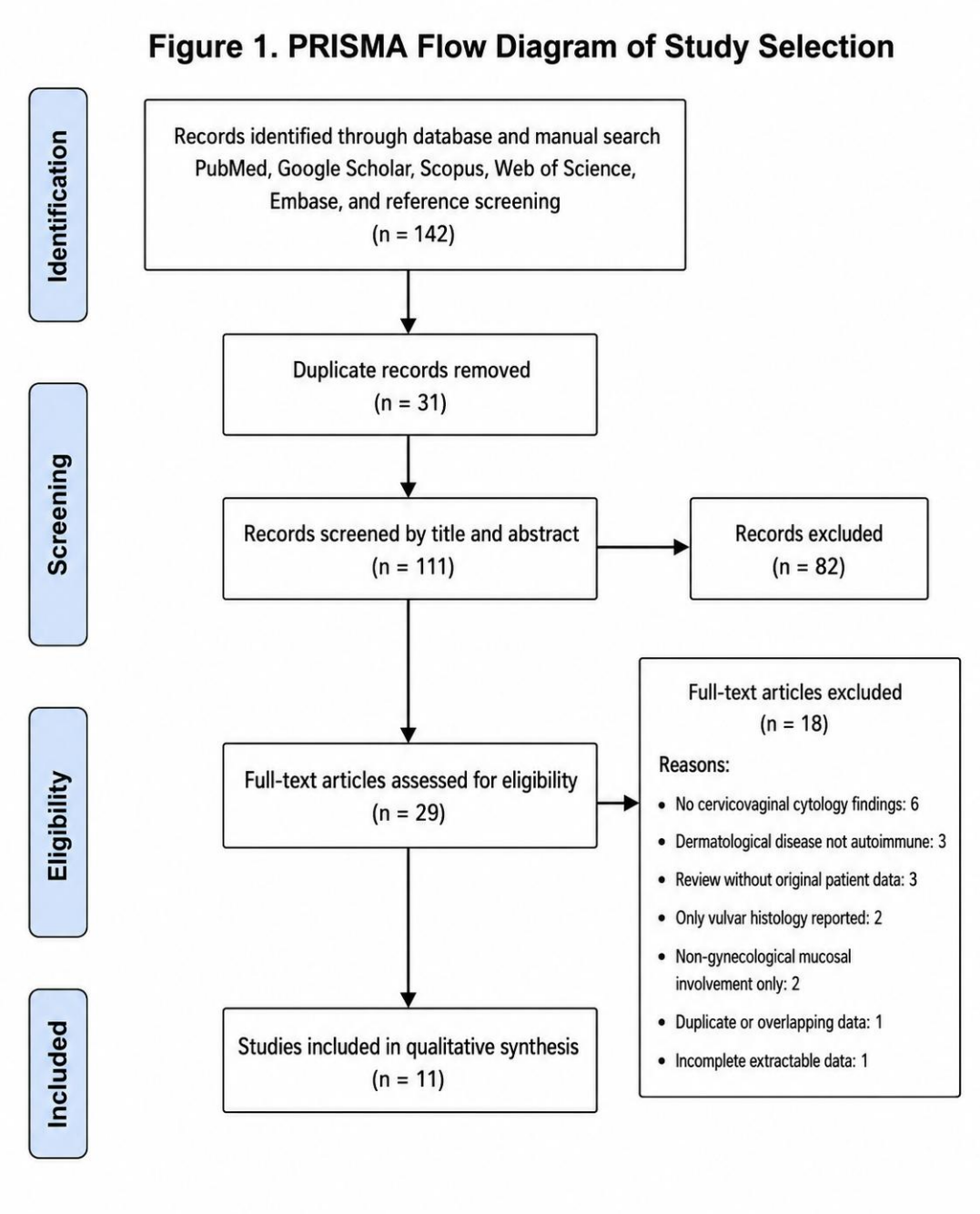

Figure 1. PRISMA flow diagram showing identification, screening, eligibility assessment, and inclusion of studies reporting cervicovaginal cytology findings in women with autoimmune dermatological diseases.

Table 2. Reasons for Full-Text Exclusion

Reason for Exclusion	Number
No cervicovaginal cytology findings	6
Dermatological disease not autoimmune	3
Review article without original patient data	3
Only vulvar histology reported	2
Non-gynecological mucosal involvement only	2
Duplicate or overlapping data	1
Incomplete extractable data	1
Total	**18**

CHARACTERISTICS OF INCLUDED STUDIES

The included literature consisted mainly of case reports, case series, and observational clinical studies. Pemphigus vulgaris was the most frequently reported autoimmune dermatological disease associated with cervicovaginal cytology findings. A smaller number of reports included pemphigus foliaceus or other autoimmune blistering disease. Evidence for vulvovaginal lichen planus and lichen sclerosus was present mainly in relation to genital involvement and screening relevance rather than disease-specific cytological patterns.

Table 3. Summary of Included Evidence on Cervicovaginal Cytology Findings in Autoimmune Dermatological Diseases

S. No.	Author(s), Year	Disease / Condition Studied	Study Type	No. of Patients / Cases	Cervicovaginal Cytology Findings	Key Observation
1	**Kavala et al., 2015**	Pemphigus vulgaris	Observational clinical study	Noted clinical cohort	Acantholytic cells, inflammatory background, reactive epithelial changes	Demonstrated correlation between genital involvement and cervicovaginal Pap smear findings in pemphigus vulgaris.
2	**Akhyani et al., 2008**	Pemphigus vulgaris	Clinical observational study	77 cases	Acantholytic cells, inflammatory changes, mucosal epithelial abnormalities	Reported cervicovaginal involvement in pemphigus vulgaris and highlighted the importance of genital examination.
3	**Barbosa et al., 2012**	Pemphigus vulgaris and pemphigus foliaceus	Observational study	Pemphigus cases	Acantholytic changes, inflammatory smear background, epithelial alterations	Evaluated vulvo-cervico-vaginal manifestations and Papanicolaou smear abnormalities in pemphigus patients.
4	**Valente et al., 1984**	Pemphigus vulgaris	Case report	1 case	Persistent abnormal Pap smears, acantholytic epithelial cells	Reported subclinical involvement of the uterine cervix in pemphigus vulgaris with persistent abnormal cytology.
5	**Lobo et al., 2006**	Pemphigus vulgaris of cervix	Case report	1 case	Acantholytic cells, dyskeratotic cells, inflammatory background	Highlighted misinterpretation of cervical pemphigus changes on Papanicolaou smear.
6	**Coelho et al., 2015**	Cervical pemphigus vulgaris	Case report	1 case	Abnormal Pap smear with acantholytic and reactive epithelial cells	Emphasized diagnostic difficulty in distinguishing pemphigus-related cytology from dysplasia or malignancy.

7	**Ingold et al., 2024**	Pemphigus vulgaris	Review / clinical reference	Not applicable	Describes acantholysis as core pathological feature	Supports interpretation of acantholytic cells as a cytological clue in pemphigus vulgaris.
8	**Lewis et al., 1996**	Vulval lichen planus	Clinical study	37 women	Mainly inflammatory and reactive changes; cytology-specific findings limited	Demonstrated genital mucosal involvement in lichen planus, though Pap smear findings were not disease-specific.
9	**Genadry and Provost, 2006**	Erosive vulvovaginal lichen planus	Case series / clinical report	Noted clinical cases	Nonspecific inflammatory/reactive smear changes possible	Described severe vulvar scarring and erosive disease, indicating the need for gynecological evaluation.
10	**De Luca et al., 2023**	Lichen sclerosus	Review / update	Not applicable	Pap smear findings generally nonspecific	Summarized lichen sclerosus as a chronic anogenital inflammatory disease; cytology role is indirect.
11	**British Association for Sexual Health and HIV, 2014**	Vulval conditions including lichen planus / lichen sclerosus	Guideline	Not applicable	Recommends keeping cervical cytology updated	Supports routine cervical screening and clinical correlation in chronic vulval autoimmune conditions.

Most cytology-specific evidence was available for pemphigus vulgaris, where acantholytic cells in an inflammatory background were the most characteristic finding. Evidence for lichen planus, lichen sclerosus, and other autoimmune dermatoses was limited and mainly showed nonspecific inflammatory or reactive changes.

DISEASE-WISE FINDINGS

1. Pemphigus Vulgaris

Pemphigus vulgaris was the most frequently reported autoimmune dermatological disease associated with abnormal cervicovaginal cytology. It is an autoimmune blistering disease characterized by intraepithelial blistering and acantholysis. Several studies and case reports described genital, vaginal, or cervical involvement in pemphigus vulgaris. Kavala et al. specifically evaluated genital involvement in pemphigus vulgaris and correlated clinical findings with cervicovaginal Pap smear findings. Akhyani et al. reported cervicovaginal involvement in pemphigus vulgaris in a clinical study of 77 cases, while other reports described diagnostic difficulties when pemphigus-related cervical changes were interpreted as abnormal Pap smears.

The most commonly reported cytological finding was the presence of acantholytic cells. These cells may appear as rounded epithelial cells with enlarged nuclei, perinuclear halo-like clearing, and loss of intercellular cohesion. Inflammatory background, necrotic debris, parabasal cells, and reactive epithelial atypia were also reported.

Table 4. Common Cervicovaginal Cytology Findings in Pemphigus Vulgaris

Cytology Finding	Interpretation
Acantholytic cells	Suggestive of pemphigus-related epithelial separation
Inflammatory background	Common due to mucosal erosions
Parabasal cells	May reflect mucosal injury or repair
Dyskeratotic cells	Can mimic dysplasia if clinical history is absent
Multinucleated cells	May create confusion with viral cytopathic effect
Reactive epithelial atypia	May be overcalled as squamous intraepithelial lesion
Necrotic/inflammatory debris	Associated with erosive lesions
Blood-stained background	May occur in active mucosal erosions

Diagnostic Pitfalls in Pemphigus Vulgaris
Pemphigus-related cytological abnormalities may be misinterpreted as:

- Low-grade squamous intraepithelial lesion
- High-grade squamous intraepithelial lesion
- Herpes simplex infection
- Reactive atypia of uncertain significance
- Malignancy
- Atrophic inflammatory smear

Reports of pemphigus vulgaris involving the uterine cervix emphasize that Pap smear interpretation can be difficult without clinical information. A case report of pemphigus vulgaris of the cervix described diagnostic difficulty associated with Pap testing, while another report noted misinterpretation of Papanicolaou smears in cervical pemphigus vulgaris.

2. Pemphigus Foliaceus
Pemphigus foliaceus is usually more superficial than pemphigus vulgaris and less commonly involves mucous membranes. However, cervicovaginal manifestations have been evaluated in studies that included both pemphigus vulgaris and pemphigus foliaceus. Barbosa et al. evaluated vulvo-cervico-vaginal manifestations and Papanicolaou smears in pemphigus vulgaris and pemphigus foliaceus.

Compared with pemphigus vulgaris, cytology-specific evidence in pemphigus foliaceus is limited. When genital involvement is present, cytology may show inflammatory and degenerative epithelial changes, but a consistent cytological pattern is not well established.

3. Vulvovaginal Lichen Planus
Lichen planus is an immune-mediated inflammatory disease that may affect the skin and mucous membranes. Vulvovaginal lichen planus, especially the erosive form, may cause pain, discharge, dyspareunia, adhesions, scarring, and chronic inflammation. Guidelines for vulval conditions emphasize the need to keep cervical cytology up to date in women with vulval disease, including lichen planus.

Cervicovaginal cytology-specific evidence in lichen planus is limited. Reported Pap smear changes, when present, are generally nonspecific and may include inflammation, epithelial repair, atrophy-like changes, and reactive atypia. Unlike pemphigus vulgaris, acantholytic cells are not a characteristic finding.

Table 5. Cytology-Relevant Features in Vulvovaginal Lichen Planus

Feature	Relevance
Chronic inflammation	May appear on Pap smear as inflammatory background
Erosive mucosal disease	May cause blood, inflammatory debris, and repair changes
Scarring and adhesions	May make smear collection difficult
Reactive atypia	May require correlation with HPV testing and colposcopy
Need for screening	Cervical cytology should remain up to date

4. Lichen Sclerosus
Lichen sclerosus is a chronic inflammatory mucocutaneous disease that predominantly affects the anogenital region. It is mainly a vulvar dermatosis and is more strongly associated with vulvar structural change and vulvar squamous neoplasia risk than with specific cervicovaginal cytological abnormalities.

Pap smear findings in women with lichen sclerosus are usually nonspecific unless there is coexisting cervical pathology, inflammation, atrophy, infection, or HPV-related lesion. The role of cervicovaginal cytology in lichen sclerosus is therefore indirect: maintaining routine cervical screening and ensuring careful examination of the lower genital tract.

5. Other Autoimmune Blistering Disorders
Mucous membrane pemphigoid, linear IgA disease, epidermolysis bullosa acquisita, and other autoimmune blistering diseases may involve mucosal surfaces. However, published cervicovaginal cytology-specific evidence is sparse. These conditions may produce erosions, inflammation, and scarring, but no consistent Pap smear pattern has been established.

OVERALL CYTOLOGICAL PATTERNS
Across the included studies, the most important cytological pattern was acantholysis in pemphigus vulgaris. Other findings were less specific and reflected mucosal inflammation, erosion, degeneration, or repair.

Table 6. Overall Cervicovaginal Cytology Patterns Reported

Cytology Pattern	Disease Association	Diagnostic Significance

Acantholytic cells	Strongly associated with pemphigus vulgaris	Important clue to autoimmune blistering disease
Inflammatory background	PV, lichen planus, erosive dermatoses	Nonspecific; requires clinical correlation
Parabasal cells	Erosive/inflammatory lesions	May reflect repair or atrophic pattern
Dyskeratotic cells	PV and reactive lesions	May mimic squamous intraepithelial lesion
Multinucleated cells	PV/reactive change	May mimic viral cytopathic effect
Reactive atypia	Chronic inflammation or repair	May be overdiagnosed as dysplasia
Blood and necrotic debris	Erosive genital disease	Suggests active mucosal injury
Atrophic pattern	Postmenopausal patients or chronic inflammation	May complicate interpretation

CLINICAL SIGNIFICANCE

1. Detection of Subclinical Genital Involvement

Cervicovaginal cytology may detect abnormal epithelial changes in patients without obvious genital symptoms. In pemphigus vulgaris, this is particularly important because cervical or vaginal involvement may be clinically subtle.

2. Avoidance of Misdiagnosis

Autoimmune disease-related cytological changes can mimic dysplasia, malignancy, or viral infection. Clinical history of pemphigus, oral erosions, skin blisters, vulvar lesions, or autoimmune dermatosis should be communicated to the cytopathologist.

3. Multidisciplinary Correlation

Accurate interpretation requires coordination between:

- Dermatologist
- Gynecologist
- Cytopathologist
- Histopathologist

When cytology findings are suspicious but inconsistent with HPV-related dysplasia, further evaluation may include repeat cytology, HPV testing, colposcopy, biopsy, or direct immunofluorescence depending on the clinical setting.

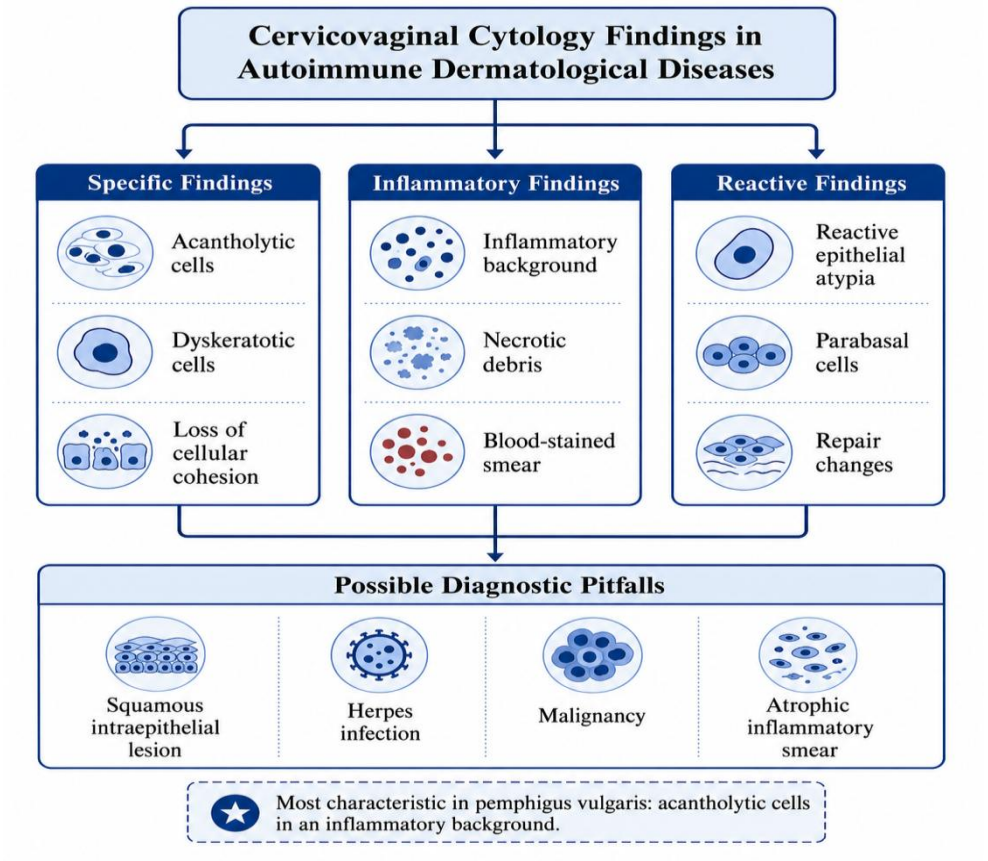

Figure 2. Cytomorphological Spectrum of Cervicovaginal Smears in Autoimmune Dermatological Diseases

DISCUSSION

This systematic review shows that cervicovaginal cytology findings in autoimmune dermatological diseases are most clearly described in pemphigus vulgaris. The hallmark cytological feature is acantholysis, which reflects loss of cohesion between epithelial cells. This is consistent with the pathogenesis of pemphigus vulgaris, where autoantibodies target desmosomal adhesion proteins, producing intraepithelial blistering and mucosal erosions.

The clinical value of Pap smear findings in pemphigus vulgaris lies in their ability to suggest genital involvement, sometimes even when symptoms are absent or mild. However, the same findings may create diagnostic confusion. Acantholytic and dyskeratotic cells may be misread as malignant or premalignant cells. Multinucleated cells may mimic herpes infection. Reactive atypia may lead to unnecessary concern for squamous intraepithelial lesion.

The review also highlights the limited evidence base for non-pemphigus autoimmune dermatoses. Vulvovaginal lichen planus and lichen sclerosus are clinically important causes of chronic vulvar and vaginal disease, but disease-specific cervicovaginal cytology findings are not well characterized. Their Pap smear findings are generally nonspecific and may reflect inflammation, repair, or atrophy. Therefore, cytology alone is insufficient for diagnosis in these conditions.

Routine cervical screening remains important in women with autoimmune dermatological disease, particularly because chronic inflammation, scarring, immunosuppressive therapy, and coexisting HPV-related lesions may complicate clinical evaluation. Pap testing is a recognized method for detecting cervical precancerous and cancerous changes, but it should not be interpreted in isolation when autoimmune mucosal disease is present.

A practical implication of this review is that cytology request forms should include relevant dermatological history. If a patient has pemphigus vulgaris, lichen planus, lichen sclerosus, mucous membrane pemphigoid, or another autoimmune dermatosis, this information can help prevent overdiagnosis of dysplasia and guide appropriate interpretation.

Another important point is the role of biopsy. When Pap smear findings are abnormal and clinical correlation is uncertain, colposcopy and biopsy may be required. In suspected autoimmune blistering disease, direct immunofluorescence can support diagnosis. Therefore, cytology should be viewed as one component of a broader diagnostic pathway.

RECOMMENDATIONS

Based on the available evidence, the following recommendations are suggested:

1. Women with autoimmune dermatological diseases involving mucosa should undergo appropriate gynecological examination.
2. Cervical cytology should remain up to date in women with chronic vulvovaginal autoimmune dermatoses.
3. History of pemphigus vulgaris or other autoimmune blistering disease should be mentioned on the cytology request form.
4. Acantholytic cells in Pap smears should prompt consideration of pemphigus vulgaris, especially when accompanied by mucosal erosions.
5. Cytological atypia in these patients should be interpreted cautiously and correlated with HPV testing, colposcopy, and clinical findings.
6. Persistent abnormal cytology should not be dismissed as inflammation without appropriate follow-up.
7. Multidisciplinary evaluation is recommended for difficult cases.
8. Future studies should use standardized cytological criteria and include clinical, cytological, histological, and immunofluorescence correlation.

LIMITATIONS

This review has several limitations. First, the available literature is sparse and consists largely of case reports and small observational studies. Second, most cytology-specific data are related to pemphigus vulgaris, limiting generalizability to other autoimmune dermatoses. Third, cytology reporting terminology varied across studies. Fourth, HPV status, colposcopic findings, biopsy correlation, and treatment details were not consistently reported. Fifth, publication bias is likely, as unusual or diagnostically challenging cases are more often published.

FUTURE DIRECTIONS

Future research should focus on prospective evaluation of cervicovaginal cytology in women with autoimmune dermatological diseases. Studies should include standardized Pap smear interpretation, HPV testing, colposcopy, biopsy correlation, and immunofluorescence confirmation when autoimmune blistering disease is suspected.

A registry-based approach may be useful because these conditions are uncommon. Particular attention should be given to distinguishing autoimmune cytological changes from HPV-related squamous intraepithelial lesions. Digital cytology and image-based teaching sets may also help cytopathologists recognize rare autoimmune patterns such as pemphigus-related acantholysis.

CONCLUSION

Cervicovaginal cytology findings in women with autoimmune dermatological diseases are best documented in pemphigus vulgaris. The most characteristic finding is acantholytic cells in an inflammatory background, sometimes accompanied by dyskeratosis, parabasal cells, multinucleation, and reactive atypia. These changes can mimic dysplasia, malignancy, or viral infection.

For lichen planus, lichen sclerosus, and other autoimmune dermatoses, Pap smear findings are usually nonspecific and mainly reflect inflammation or epithelial repair. Accurate diagnosis requires clinical correlation and communication between dermatologists, gynecologists, and cytopathologists. Awareness of autoimmune dermatological disease as a cause of abnormal cervicovaginal cytology can prevent misdiagnosis and guide appropriate patient management.

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