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Research Article

Cervical Endometriosis: An Unrecognized Mimic of HPV-Related Koilocytic Changes.

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Abstract

Context: *Koilocytic changes in the cervical squamous epithelium are commonly associated with human papillomavirus (HPV) infections. However, rare non-HPV-related causes, such as uterine prolapse, have been documented. This study explored an unusual association between koilocytic changes and cervical endometriosis, a finding that has not been previously reported.*

Design: *We retrospectively analyzed six cases of cervical endometriosis from our institutional archives (2000–2024). Patients aged 34–51 years (median age: 48 years) presented with vaginal bleeding as the primary symptom. All patients underwent hysterectomy. Three of the six patients were virgins with intact hymens at the time of surgery. Histopathological examination revealed endometriosis extending to the exocervix in all patients. Cervicovaginal smears were not performed in any case. Histopathological evaluation, including HPV immunostaining, was performed on cervical tissue.*

Results: *Histopathological analysis revealed koilocytic changes in all patients with no evidence of dysplasia. Endometriosis was observed in the exocervix in all cases. Acute and chronic inflammation were minimal. Serum CA-125 levels were elevated in all patients (range, 65–380 units/ml). HPV immunostaining of cervical tissue was negative in all cases. Follow-up data indicated no development of vulvar warts or HPV-related lesions.*

Conclusion: *Although koilocytic changes are traditionally used to diagnose HPV infection, they are not pathognomonic. This study demonstrated that koilocytic changes can occur in the context of cervical endometriosis, independent of HPV infection. These findings highlight the importance of considering non-HPV etiologies, such as endometriosis, in the differential diagnosis of koilocytic changes, particularly in patients without HPV risk factors.*

Introduction

Koilocytes are squamous epithelial cells characterized by a distinct perinuclear halo and an atypical, hyperchromatic nucleus (1). Their presence is widely regarded as a pathognomonic feature of a productive Human Papillomavirus (HPV) infection (2). This cellular change is the cornerstone for diagnosing low-grade squamous intraepithelial lesions (LSIL) in both cervicovaginal cytology (Pap smears) and cervical biopsy (3). The diagnostic significance of koilocytosis is rooted in its strong association with oncogenic HPV types, which

are the primary causative agents of cervical cancer (4).

Although the link between koilocytosis and HPV is robust, emerging evidence suggests that this cellular change may not be exclusively viral in origin. Rare reports have described "koilocyte-like" changes in non-infectious contexts, such as in uterine prolapse, where chronic irritation and epithelial stress are believed to induce similar morphological features (5, 6). However, the list of known nonviral mimics remains exceedingly short.

Endometriosis, defined by the presence of ectopic endometrial glands and stroma outside the uterine cavity, is a common hormone-dependent inflammatory condition affecting women of reproductive age (7). While most frequently found in the ovaries and peritoneum, endometriosis can also involve the cervix. Cervical endometriosis can present with symptoms such as abnormal uterine bleeding and dyspareunia or as an incidental finding (8). To date, the histopathological changes in the cervical epithelium overlying endometriotic foci have not been well characterized, and an association with koilocytosis has not been described in the medical literature (8).

This study presents a case series of six women with histologically confirmed cervical endometriosis who demonstrated prominent koilocytic changes in the overlying squamous epithelium in the complete absence of detectable HPV. This article aims to describe this novel association, explore potential underlying mechanisms, and discuss the critical diagnostic implications for pathologists and gynecologists.

Materials and Methods

Study Design and Case Selection

A retrospective search of the institutional pathology archives from January 2000 to December 2024 was conducted to identify cervical endometriosis cases. The inclusion criteria for this study were as follows: (1) a definitive histopathological diagnosis of endometriosis (presence of both endometrial glands and stroma) within the cervical tissue from a hysterectomy specimen and (2) the presence of koilocytic changes in the overlying exocervical squamous epithelium. Patients with concurrent cervical dysplasia (cervical intraepithelial neoplasia), invasive carcinoma, or insufficient tissue for further analysis were excluded. This search yielded six qualifying cases.

Data Collection and Clinical Information

Clinical data for each patient were retrieved from electronic medical records and pathology reports. The collected information included patient age, surgical procedure performed, serum Cancer Antigen 125 (CA-125) levels at the time of diagnosis, and virginity status. Follow-up data were obtained to assess the subsequent development of HPV-related lesions.

Histopathological and Immunohistochemical Analysis

All hysterectomy specimens were fixed in 10% neutral buffered formalin and processed for paraffin embedding. Hematoxylin and Eosin (H&E)-stained slides were examined by a single pathologist to confirm the diagnosis of cervical endometriosis and to characterize the epithelial changes. Koilocytosis was defined as the presence of squamous cells with significant perinuclear cytoplasmic clearing (halos) accompanied by nuclear atypia, including hyperchromasia and irregular, wrinkled nuclear membranes.

To exclude the presence of HPV, immunohistochemical staining was performed on cervical tissue sections exhibiting koilocytosis. A monoclonal antibody targeting the HPV L1 capsid protein (a marker of productive HPV infection) was used according to standard laboratory protocols. The results were interpreted as positive or negative based on the nuclear staining of squamous cells.

Patient Demographics and Findings

The clinical and pathological findings of the six patients are summarized in table below.

Patient	Age (Years)	Site of Endometriosis/Adenomyosis	CA-125 Level (U/mL)	Virginity Status
1	34	Cervix, Endometrium, Uterine Serosa	65	Virgin
2	51	Cervix, Endometrium, Ovaries	380	Not Virgin
3	47	Cervix, Endometrium, Uterine Serosa	125	Virgin
4	41	Cervix, Endometrium, Ovaries	220	Not Virgin
5	48	Cervix, Endometrium, Ovaries	256	Virgin
6	50	Cervix, Endometrium, Peritoneum	360	Not Virgin

Results

Clinical and Laboratory Findings

The six patients ranged in age from 34 to 51 years (median age: 48 years). The universal presenting symptom was abnormal vaginal bleeding. All patients had extensive endometriosis involving the cervix and other pelvic sites and underwent total hysterectomy. Notably, three of the six patients (50%) were virgins with intact hymens at the time of surgery. Serum CA-125 levels were elevated in all patients, with values ranging from 65 to 380 U/mL (normal value < 35 U/mL).

Histopathological and Immunohistochemical Results

Histopathological examination revealed definitive evidence of endometriosis located within the cervical stroma and extending to the exocervix (Figure 1, D). The overlying exocervical squamous epithelium in all

cases displayed prominent koilocytic changes (Figure 1, A–C). These cells exhibited large perinuclear halos and enlarged, hyperchromatic, and often wrinkled nuclei. No evidence of high-grade dysplasia or invasion was observed. The surrounding stromal tissue showed minimal or no significant acute or chronic inflammation.

Crucially, HPV immunostaining for the L1 capsid protein was negative in all six cases, confirming the absence of productive HPV infection in areas exhibiting koilocytosis. Follow-up data, available for all patients for a minimum of three years, showed no development of vulvar, vaginal, or cervical HPV-related lesions, such as warts or dysplasia.

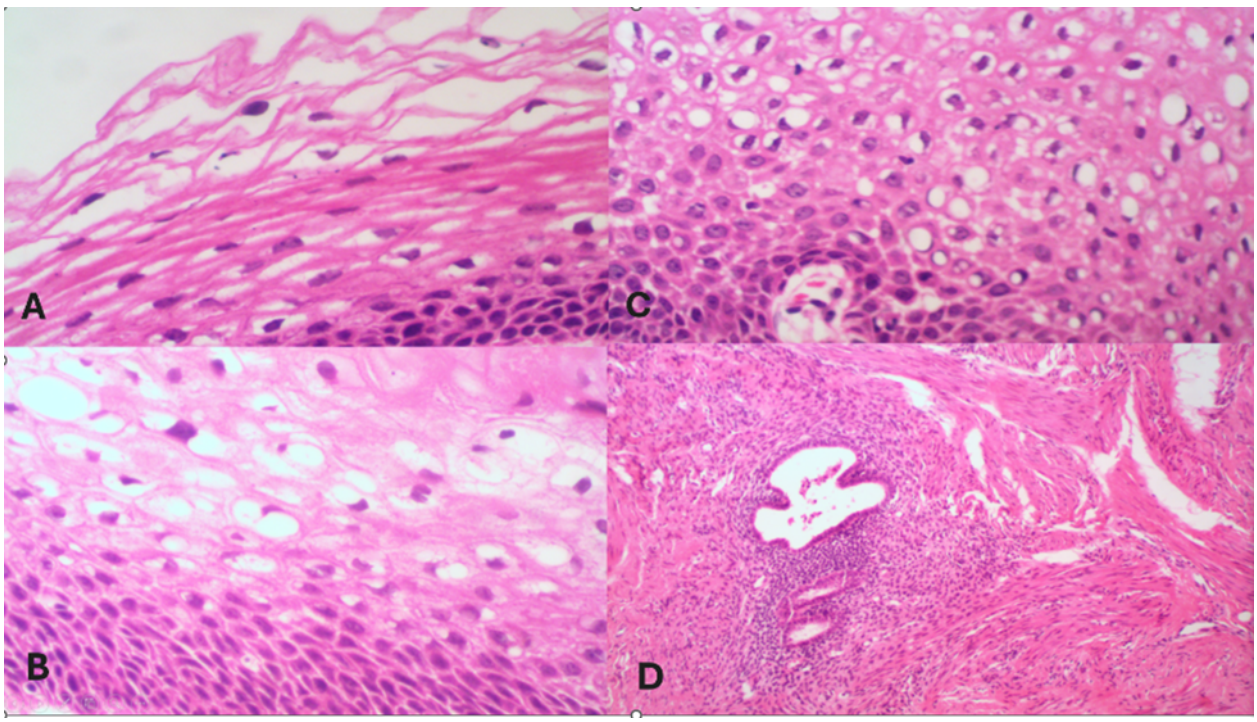

Figure 1: (A, B, C) H&E staining showing prominent koilocytic changes in the exocervical squamous epithelium, characterized by perinuclear halos and atypical nuclei. (D) H&E staining showing a focus of endometriosis (endometrial glands and stroma) within the cervical wall, underlying the affected epithelium.

Discussion

This study is the first to document a compelling association between cervical endometriosis and HPV-negative koilocytic changes in the overlying squamous epithelium. For decades, koilocytic changes have been considered the morphological hallmark of HPV infection. Our findings challenge this long-held dogma and introduce cervical endometriosis as a novel entity in the differential diagnosis of koilocytic lesions.

The mechanism by which endometriosis induces these cellular changes is likely multifactorial. We propose

several hypotheses. First, ectopic endometrial tissue is hormonally active and serves as a source of localized inflammation, producing cytokines, prostaglandins, and growth factors. This altered biochemical microenvironment can induce metabolic stress or degenerative changes in adjacent squamous epithelial cells, leading to glycogen accumulation or cytoplasmic vacuolization, which manifests as a perinuclear halo (9-11). Second, the nuclear atypia observed in these cells may represent a reactive, non-specific response to this chronic underlying inflammatory and proliferative stimulus, rather than a true viral cytopathic effect. This process could be analogous to the reactive atypia observed in epithelial cells overlying other stromal lesions (12).

The clinical context of our cases provides strong evidence against HPV etiology. The fact that 50% of the patients in our series were virgins makes a sexually transmitted HPV infection improbable. Furthermore, the uniformly negative HPV immunostaining and the lack of any subsequent HPV-related disease at follow-up provided definitive evidence to exclude the role of HPV in causing the observed koilocytosis.

The implications of these findings for diagnostic pathology are significant and far-reaching. A pathologist encountering koilocytes in a cervical biopsy may automatically diagnose an HPV-related lesion (LSIL). Such a diagnosis carries significant consequences for the patient, including the psychosocial stress of a sexually transmitted infection diagnosis, the need for more frequent surveillance (colposcopy and HPV testing), and potential anxiety regarding cancer risk. Our study highlights a critical diagnostic pitfall: in a patient with clinical signs of endometriosis (e.g., abnormal bleeding, pelvic pain, elevated CA-125) or in patients with a low pre-test probability for HPV infection (e.g., virgins), the presence of koilocytosis should prompt consideration of an alternative etiology. In these cases, ancillary testing, such as HPV immunohistochemistry or molecular testing, is essential to avoid misdiagnosis.

This study has some limitations. Its retrospective nature and small sample size mean that larger prospective studies are needed to validate these findings. Furthermore, cervicovaginal smears were not available, which could have provided a cytological correlation to the histological changes.

Conclusion

In conclusion, koilocytosis of the cervix, although strongly associated with HPV, is not pathognomonic. This study demonstrates that cervical endometriosis can induce HPV-negative koilocytic changes in the squamous epithelium, representing a previously unrecognized mimic of LSIL. Pathologists and clinicians should be aware of this association to prevent misdiagnosis and ensure appropriate patient management, particularly in clinical scenarios where HPV infection is unlikely. This finding underscores the timeless principle of integrating clinical history with morphological findings and utilizing ancillary tests to arrive at the most accurate diagnosis.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Kurman RJ, Ellenson LH, Ronnett BM, eds. Blaustein's Pathology of the Female Genital Tract. 7th ed. Springer; 2019.

2. Kumar V, Abbas AK, Aster JC. Robbins & Cotran Pathologic Basis of Disease. 10th ed. Elsevier; 2021.

3. Nayar R, Wilbur DC, eds. The Bethesda System for Reporting Cervical Cytology. 3rd ed. Springer; 2015.

4. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of Pathology. 1999;189(1):12-19.

5. Isotalo PA, Hameed A, Kirk ME, et al. Koilocytotic atypia in genital prolapse: a potential diagnostic pitfall. International Journal of Gynecological Pathology. 2005;24(4):394-398.

6. Abu-Farsakh H, Al-Jalad M. Cytopathological Changes of Cervical Smears in Patients with Uterine Prolapse: A Major Pitfall for Squamous Intraepithelial Neoplasia (Cervical Dysplasia). Modern Pathology. 2009;22(S2):25A. [Abstract]

7. Zondervan KT, Becker CM, Missmer SA. Endometriosis. Nature Reviews Disease Primers. 2020;6(1):41.

8. Poblete MT, Cararach M, Mestre-Fusco A, Gitas G, Zavala-Rosas E, Agusti N. Primary cervical endometriosis—a review. Archives of Gynecology and Obstetrics. 2021;303(5):1131-1136.

9. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertility and Sterility. 2012;98(3):511-519.

10. Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. Endocrine Reviews. 2019;40(4):1048-1079.

11. Isotalo PA, Hameed A, Kirk ME, et al. Koilocytotic atypia in genital prolapse: a potential diagnostic pitfall. International Journal of Gynecological Pathology. 2005;24(4):394-398.

12. Goldblum JR, Lamps LW, McKenney JK, Myers JL, eds. Rosai and Ackerman's Surgical Pathology. 12th ed. Elsevier; 2022.