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Case Report

Endocervical adenocarcinoma with non–block-type p16 staining mimicking an endometrial primary: A Case Report

Non-block-type p16 in endocervical adenocarcinoma

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Abstract

Introduction: p16 immunohistochemistry is widely used as a surrogate marker for human papillomavirus (HPV)-associated cervical carcinoma. Non–block-type staining may complicate interpretation, particularly in resource-limited settings without molecular HPV testing.

Case Presentation: A 51-year-old woman presented with abdominal pain, contact bleeding, and vaginal spotting. Cervical biopsy showed invasive adenocarcinoma with endometrioid-like morphology. Tumor cells were carcinoembryonic antigen (CEA)-positive and estrogen receptor (ER)-, vimentin-, and Napsin A-negative, supporting a cervical origin. Supplementary p16 showed weak, patchy, non–block-type staining, while Ki-67 showed a high proliferative index. Molecular HPV testing was unavailable.

Conclusion: This case highlights the importance of integrated morphologic and immunophenotypic assessment when interpreting non–block-type p16 staining to avoid misclassification as an endometrial primary.

Keywords

adenocarcinoma, immunohistochemistry, human papillomavirus, Ki-67, p16 protein

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Introduction

Cervical carcinoma remains a major cause of cancer morbidity and mortality worldwide, particularly in low- and middle-income regions. Accurate histopathologic diagnosis is essential for appropriate classification and clinical management.[1] While evaluation of hematoxylin and eosin (H&E)-stained sections remains the diagnostic cornerstone, immunohistochemistry is widely used as an adjunct in morphologically challenging cases.

Current classification systems recognize both human papillomavirus (HPV)-associated and HPV-independent pathways of endocervical adenocarcinoma; therefore, p16 immunostaining should be interpreted in that context. Among ancillary markers, p16 immunohistochemistry is routinely applied as a surrogate marker for high-risk HPV-associated cervical carcinoma, with diffuse block-type nuclear staining regarded as characteristic. However, reduced or non–block-type p16 expression may occur in invasive cervical carcinomas and represents a recognized diagnostic challenge when interpreted in isolation.[2,3]

This case report aimed to present an invasive cervical adenocarcinoma with non–block-type p16 expression and to emphasize a practical diagnostic approach based on integrated morphologic and immunophenotypic assessment in routine pathology practice.

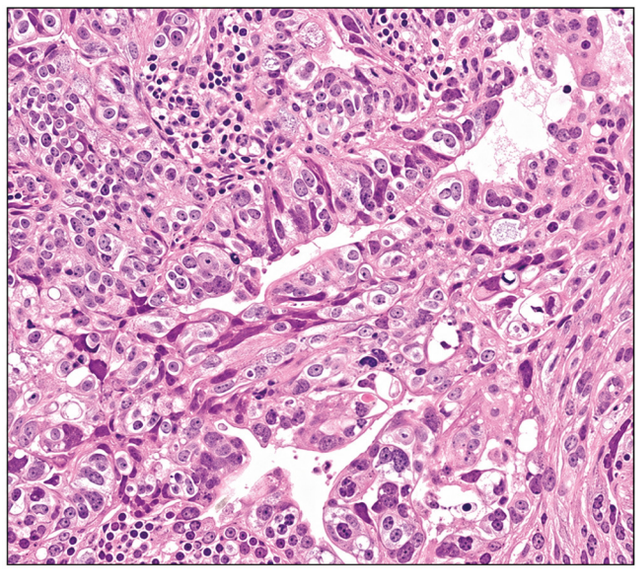


Figure 1. *Histopathologic Appearance of Cervical Adenocarcinoma*

Hematoxylin and eosin staining shows infiltrative malignant glands with endometrioid-like morphology. Scale bar: 50 μm

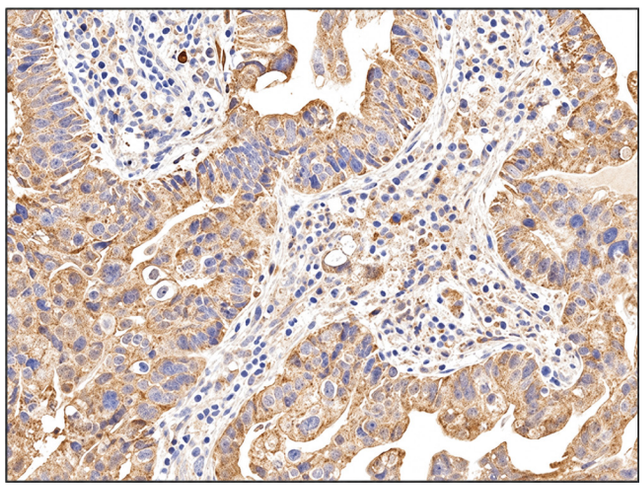


Figure 2. *Hp16 Immunohistochemical Ataining of cervical Adenocarcinoma*

Showing weak, patchy cytoplasmic staining without block-type nuclear positivity. Scale bar: 50 μm.

Case Presentation

A 51-year-old woman presented with abdominal pain, contact bleeding, and vaginal spotting. She was initially referred with a clinical impression of a 3 × 3 cm uterine fibroid. Pelvic imaging showed a thin endometrium measuring approximately 3 mm and a posterior intramural uterine fibroid, with no findings suggestive of an endometrial primary malignancy. However, subsequent clinical evaluation revealed a cervical mass. A cervical biopsy was obtained and submitted for histopathologic evaluation.

Histological examination of H&E-stained sections revealed an invasive malignant glandular neoplasm composed of irregular infiltrative glands with an endometrioid-like architectural pattern (Figure 1). The glands were lined by atypical columnar cells with eosinophilic cytoplasm and enlarged, pleomorphic, hyperchromatic nuclei, with increased mitotic activity. A focal solid growth pattern raised concern for poor differentiation; however, definitive squamous differentiation was not identified. The tumor was associated with a prominent lymphocytic inflammatory infiltrate.

To distinguish a cervical primary from an endometrial mimic, an initial immunohistochemical panel was performed. The tumor cells were positive for carcinoembryonic antigen (CEA) and negative for estrogen receptor (ER), vimentin, and Napsin A, supporting a cervical primary. Based on the integrated histomorphologic findings and site-of-origin markers, a diagnosis of invasive cervical adenocarcinoma, grade II, was made. After the diagnosis, we referred the patient to a specialized oncology service for staging and definitive management. Because our facility served only as the initial diagnostic center, we did not have long-term clinical follow-up or survival outcomes.

To further characterize the case in a resource-limited setting, supplementary immunohistochemical evaluation using available surrogate markers was subsequently performed. Additional histopathological review was performed on formalin-fixed, paraffin-embedded cervical biopsy tissue stained with H&E. Immunohistochemistry for p16 and Ki-67 was performed according to routine laboratory protocols. These markers were available in our laboratory but were not included in the initial routine diagnostic

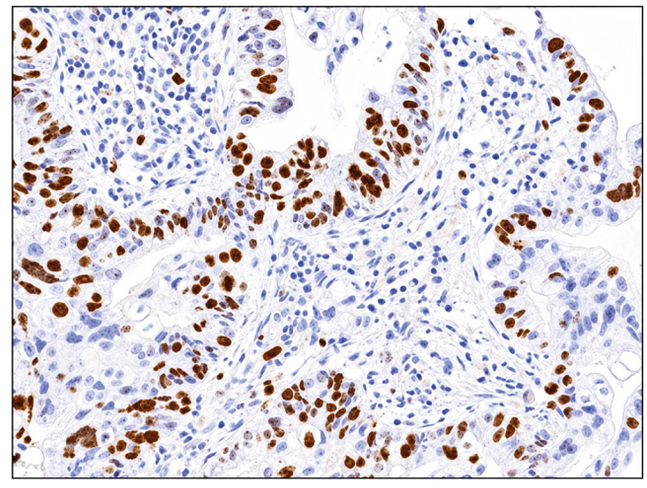


Figure 3. *Ki-67 Immunohistochemical Staining of Cervical Adenocarcinoma*

Showing a high labeling index. Scale bar: 50 μm.

workup. p16 showed a non–block-type pattern characterized by weak, patchy, predominantly cytoplasmic staining and absence of diffuse block-type nuclear positivity (Figure 2), findings not supportive of HPV-associated block-type staining. Ki-67 showed a high labeling index with numerous positively stained tumor nuclei, consistent with high proliferative activity (Figure 3). The detailed data are provided in Supplementary Table 1.

We did not perform molecular HPV testing because it was unavailable in the institutional diagnostic workflow; therefore, HPV status remained unconfirmed. These supplementary findings provided additional interpretive context; however, they were obtained after sign-out as part of an internal diagnostic evaluation, and no amended report was issued.

Ethical Approval

The study was approved by the Ethics Committee of King Faisal Medical Complex, Taif, Saudi Arabia (Date: 19.02.2024, Decision No: 2024-E-10).

Statistical Analysis

Not applicable.

This case report was prepared and reported in accordance with the CARE guidelines.

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Discussion

The 2020 WHO classification of female genital tumors classifies endocervical adenocarcinomas into HPV-associated and HPV-independent pathways. Diffuse block-type p16 staining is widely accepted as a useful surrogate marker supporting HPV-associated lesions. In contrast, negative, patchy, or non–block-type p16 staining patterns may be encountered in HPV-independent tumors and can complicate interpretation when p16 is used in isolation.[2,4,5]

Molecular HPV testing was not available; HPV status remains unconfirmed. However, the absence of diffuse block-type p16 staining, together with the morphology and immunoprofile, excluded an endometrial primary and raised consideration of an HPV-independent pathway in this case, particularly in a resource-limited setting. Similar discordant p16 staining patterns have been reported in HPV-independent cervical carcinomas, underscoring the limitations of p16 as a standalone diagnostic marker.[1,6]

Navigating this atypical immunophenotype requires a structured diagnostic approach to avoid clinically significant misclassification. Because the tumor exhibited an endometrioid-like appearance and the patient had a documented intramural fibroid, distinguishing the lesion from an endometrial primary mimic was a critical first step. The immunohistochemical profile, CEA-positive and ER- and vimentin-negative, supported a cervical origin.

This case demonstrates the diagnostic value of expanding immunohistochemical assessment beyond basic site-of-origin markers in resource-limited workflows. In routine practice, diagnosis may conclude at a broad category such as grade II adenocarcinoma. In this case, supplementary use of p16 and Ki-67, both available in our facility but not included in the initial workup, provided additional interpretive context. The non–block-type p16 pattern did not support HPV-associated block-type staining and raised consideration of an HPV-independent pathway in the differential diagnosis, while Ki-67 supported high proliferative activity. This distinction may be clinically relevant because HPV-independent cervical carcinomas have been associated with less favorable outcomes and more aggressive behavior in published studies. However, definitive pathway assignment requires molecular confirmation.[7]

Reduced p16 expression may reflect true biological mechanisms, including HPV-independent oncogenic pathways, partial disruption of the retinoblastoma pathway, tumor heterogeneity, or tumor dedifferentiation.6 In this case, Ki-67 immunohistochemistry confirmed high proliferative activity, supporting the malignant nature of the lesion, although it was not used as a surrogate marker for HPV status.[8]

Limitations

This case report has several limitations. First, the unavailability of molecular HPV DNA or RNA testing precluded definitive confirmation of the tumor's biologic pathway. Additional markers, including p53 and gastric differentiation markers, were also unavailable in our laboratory workflow. Second, because our institution served solely as the primary diagnostic center, we lacked long-term clinical follow-up and details of the patient's oncologic management.

Conclusion

Despite these limitations, this case highlights a practical diagnostic approach for navigating complex cervical pathology in a resource-limited setting. Awareness of atypical non–block-type p16 staining patterns and their potential association with HPV-independent pathways is important to avoid diagnostic misclassification, particularly confusion with endometrial mimics, in routine pathology practice.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed Consent

Written informed consent was obtained from the patient.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons, but are available from the corresponding author on reasonable request.

Conflict of Interest

The author declare no conflict of interest.

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Author Contributions (CRediT Taxonomy)

Conceptualization: H.J.B.
Methodology: H.J.B.
Validation: H.J.B.
Investigation: H.J.B.
Resources: H.J.B.
Data Curation: H.J.B.
Writing – Original Draft Preparation: H.J.B.
Writing – Review & Editing: H.J.B.
Visualization: H.J.B.
Supervision: H.J.B.
Project Administration: H.J.B.

AI Usage Disclosure

AI-assisted language tools (ChatGPT, OpenAI) were used to edit and refine the manuscript's grammar. The author takes full responsibility for the accuracy, interpretation, and integrity of the content.

Abbreviations

CARE: Case report guidelines
CEA: Carcinoembryonic antigen
ER: Estrogen receptor
H&E: Hematoxylin and eosin
HPV: Human papillomavirus

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