ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J)

December 2025;12(3):130-137

OLGU SUNUMU / CASE REPORT

DOI: 10.56941/odutip.1787102

Premalignant and Early Invasive Lesions of the Endometrium: Case Presentations in the Light of Current Classifications

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Received: 19 September 2025, Accepted: 26 November 2025, Published online: 31 December 2025

Abstract

Accurate classification of premalignant and early invasive lesions of the endometrium is of critical importance for the prevention of endometrial carcinoma and for the development of effective treatment strategies. The 2020 World Health Organization (WHO) classification offers an up-to-date framework for the terminology and diagnostic criteria of these lesions. In this context, we evaluated the diagnostic processes and differential criteria of three distinct endometrial lesion cases based on their morphological and immunohistochemical features. Three cases diagnosed in our pathology clinic were retrospectively analyzed. These included non-atypical endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN), and FIGO Grade 1 endometrioid adenocarcinoma. All cases were histologically examined on hematoxylin and eosin (H&E)-stained sections, and immunohistochemical markers (PAX2, p53, p16, ER, PR, vimentin) were used to support the differential diagnosis. In the first case, benign morphology, preserved gland-to-stroma ratio, and absence of cytologic atypia were observed, supporting a diagnosis of endometrial hyperplasia without atypia. The second case exhibited focal glandular crowding, cytologic atypia, and loss of PAX2 expression, consistent with EIN. In the third case, pronounced nuclear atypia, cribriform glandular architecture, and increased proliferative activity supported a diagnosis of FIGO Grade 1 endometrioid adenocarcinoma. The findings suggest that the combined use of morphological assessment and immunohistochemical analysis enhances diagnostic accuracy in evaluating endometrial lesions. The WHO 2020 classification reinforces this multifaceted approach, enabling the early recognition of precancerous lesions and guiding appropriate therapeutic strategies.

Keywords: Endometrial hyperplasia, Endometrial intraepithelial neoplasia, Endometrioid adenocarcinoma, İmmunohistochemistry, WHO 2020 classification

Endometriumun Premalign ve Erken İnvaziv Lezyonları: Güncel Sınıflamalar Işığında Olgu Sunumları

Özet

Endometriumun premalign ve erken invaziv lezyonlarının doğru sınıflandırılması, endometrial karsinomların önlenmesi ve etkin tedavi planlaması açısından kritik öneme sahiptir. 2020 yılı Dünya Sağlık Örgütü (WHO) sınıflaması, endometrial lezyonların tanımlanması ve terminolojisinin standartlaştırılması açısından güncel bir kaynak niteliği taşımaktadır. Bu çalışmada, farklı morfolojik özellikler gösteren üç endometrial lezyon olgusu, immünohistokimyasal verilerle birlikte değerlendirilerek tanısal süreçler ve ayırıcı tanı ölçütleri irdelenmiştir. Retrospektif olarak yürütülen bu araştırmada, kurumumuzda tanısı konulmuş üç ayrı endometrium olgusu ayrıntılı biçimde incelenmiştir. Bu olgular sırasıyla atipisiz endometrial hiperplazi, endometrial intraepitelyal neoplazi (EIN) ve FIGO Grade 1 endometrioid adenokarsinom tanılarını temsil etmekteydi. Tüm olgular hematoksilen-eozin (H&E) ile boyanmış kesitlerde mikroskobik olarak incelendi, ayrıca ayırıcı tanı amacıyla immünohistokimyasal belirteçler (PAX2, p53, p16, ER, PR, Vimentin) kullanıldı. İlk olguda benign morfolojiye sahip, gland-stroma oranı korunmuş, atipi içermeyen bir hiperplazi izlendi. İkinci olguda sınırlı alanda glandüler sıkışma, sitolojik atipi ve PAX2 ekspresyon kaybı saptanarak EIN tanısı desteklendi. Üçüncü olgu ise belirgin nükleer atipi, kribriform glandüler mimari ve artmış proliferatif aktivite bulgularıyla FIGO Grade 1 endometrioid adenokarsinom olarak değerlendirildi. Elde edilen bulgular, endometrial lezyonların ayırt edilmesinde yalnızca morfolojik değil, aynı zamanda moleküler ve immünohistokimyasal verilerin birlikte değerlendirilmesinin tanısal doğruluğu artırdığını göstermektedir. WHO 2020 sınıflaması, bu çok boyutlu yaklaşımı destekleyerek prekanseröz lezyonların erken evrede tanımlanmasını ve uygun tedavi stratejilerinin belirlenmesini mümkün kılmaktadır.

Anahtar kelimeler: Endometrial hiperplazi, Endometrial intraepitelyal neoplazi, Endometrioid adenokarsinom, İmmünohistokimya, WHO 2020 sınıflandırması

Suggested Citation: Turk Alkan M, Erdem H and Canak O. Premalignant and Early Invasive Lesions of the Endometrium: Case Presentations in the Light of Current Classifications. ODU Med J, 2025;12(3): 130-137.

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INTRODUCTION

The endometrium is a dynamic tissue with a high sensitivity to hormonal stimulation, which makes it susceptible to various proliferative and neoplastic processes. Endometrial carcinoma, the most common malignancy of the female genital tract in developed countries, is frequently preceded by precursor lesions such as endometrial hyperplasia and intraepithelial neoplasia . Therefore, accurate classification and early identification of premalignant endometrial lesions play a critical role in preventing malignant progression (1).

Contemporary classification systems have been developed to address this need. According to the 2020 World Health Organization (WHO) classification, endometrial hyperplasia is divided into two main categories: non-atypical hyperplasia and EIN. While non-atypical hyperplasia generally reflects benign proliferative changes secondary to reactive hormonal stimulation, EIN represents a clonal proliferation characterized by cytologic atypia and an increased gland-tostroma ratio, and is regarded as a true precancerous lesion (2). EIN is particularly significant, as it is recognized as the precursor of estrogen-dependent (type I) endometrioid endometrial carcinoma and, therefore, must be clearly distinguished in the diagnostic setting (3).

Relying solely on morphological features during diagnosis may be insufficient, especially in limited biopsy specimens. Consequently, the systematic application of immunohistochemical markers has gained prominence. Markers such as PAX2, PTEN, p53, p16, and Ki-67 are valuable in distinguishing EIN from carcinoma and in objectively differentiating EIN from nonatypical hyperplasia (4). In particular, the loss of PAX2 expression has emerged as a sensitive and reliable indicator for EIN, aiding in its distinction from non-atypical hyperplasia (5).

In this study, three endometrial cases diagnosed in our pathology clinic were analyzed from a histopathological perspective. Each case represented a different stage within the spectrum of endometrial lesions and was evaluated according to the morphological and immunohistochemical characteristics described in the current literature and in the WHO 2020 classification (2).

CASE REPORTS

Case 1

A 45-year-old patient presented with abnormal uterine bleeding. Examination of the endometrial curettage specimen revealed a mild increase in glandular structures with limited architectural complexity. The stromal distribution between glands was preserved (Figure 1). Histologically, the gland-to-stroma ratio was within normal limits, and the glandular structures exhibited a benign architectural pattern. No significant nuclear atypia was observed. These findings were consistent with a diagnosis of non-atypical endometrial hyperplasia, and no immunohistochemical evaluation was deemed necessary.

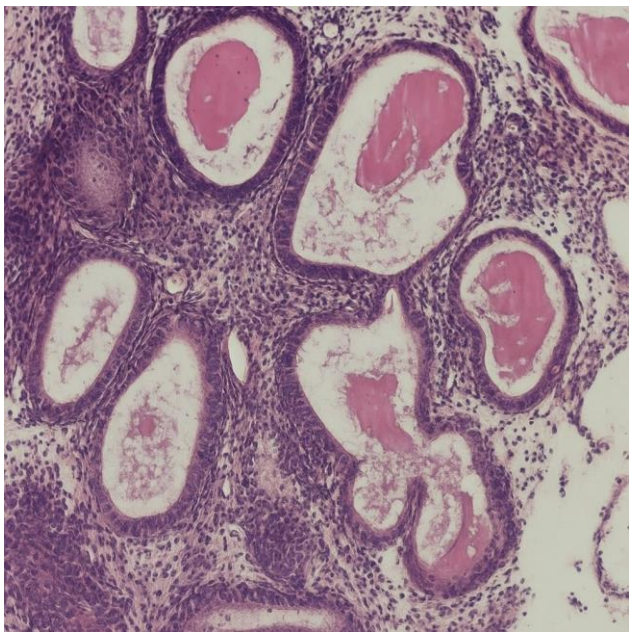

Figure 1. Non-atypical endometrial hyperplasia. Mild glandular complexity with well preserved stromal distribution (H&E, ×200).

Case 2

A 49-year-old perimenopausal patient presented with irregular vaginal bleeding. Endometrial biopsy revealed a significant increase in glandular density, with focal areas showing glandular crowding and cytologic atypia relative to the background endometrium. On hematoxylin and eosin staining (Figure 2), a marked reduction in stromal area, along with mild nuclear enlargement and pleomorphism, was observed. The lesion measured approximately 2 mm in diameter, fulfilling the minimal size requirement for EIN diagnosis. Immunohistochemical analysis demonstrated a loss of PAX2 expression in the lesional glands (Figure 3), supporting the diagnosis of EIN.

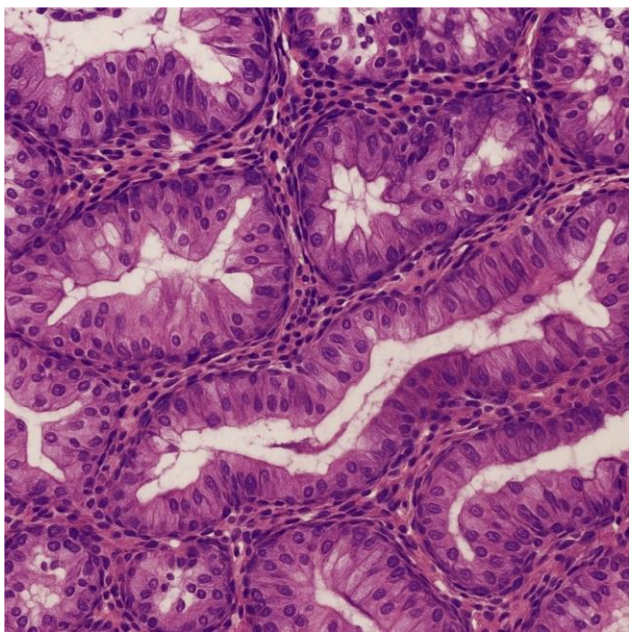

Figure 2. Endometrial intraepithelial neoplasia. Glandular crowding, cytologic atypia, and reduced stromal area without stromal invasion (H&E, ×200).

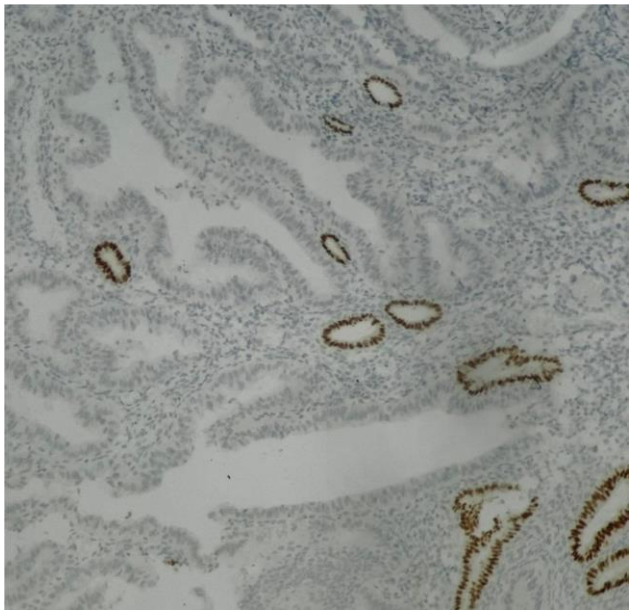

Figure 3. PAX2 immunohistochemical staining showing loss of PAX2 expression in the lesional glands (DAB, ×200).

Case 3

A 62-year-old postmenopausal woman presented with vaginal bleeding. The initial curettage material suggested an endometrial polyp. Due to persistent symptoms despite medical treatment, the patient underwent a total laparoscopic hysterectomy. Histopathological examination of the hysterectomy specimen revealed regions where glandular structures almost completely replaced the stroma, forming areas of cribriform architecture and marked complexity (Figure 4). Nuclear enlargement, hyperchromasia, and pseudostratification were prominent. Immunohistochemical evaluation showed patchy p53 expression (Figure 5), mosaic p16 positivity (Figure 6), diffuse nuclear positivity for ER and PR (Figures 7 and 8), and diffuse cytoplasmic positivity for vimentin (Figure 9). These findings confirmed the diagnosis of FIGO Grade 1 endometrioid adenocarcinoma.

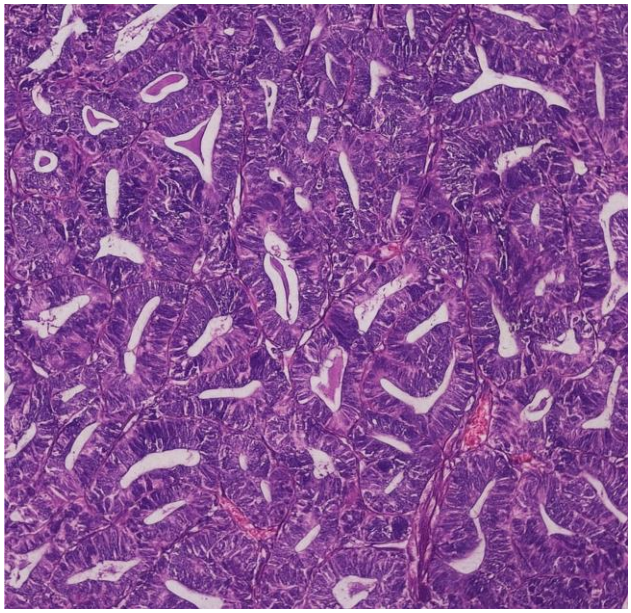

Figure 4. FIGO Grade 1 endometrioid adenocarcinoma. Closely packed neoplastic glands with minimal stroma (H&E, ×100).

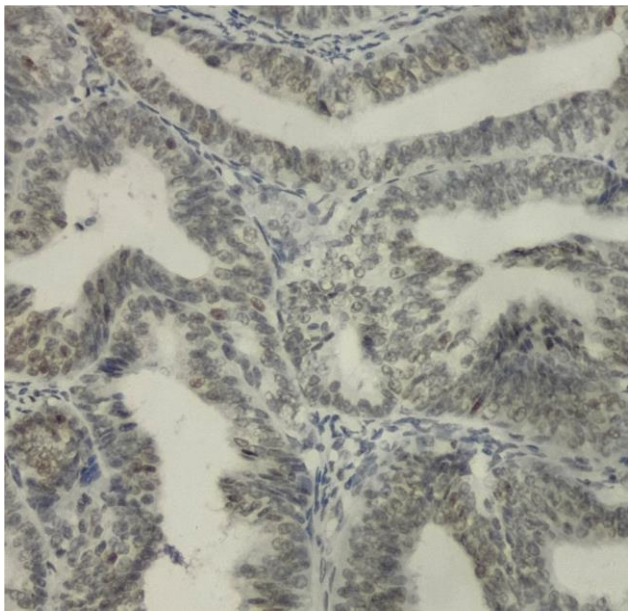

Figure 5. p53 immunohistochemistry. Patchy nuclear staining not supporting mutant-expression (DAB, ×200).

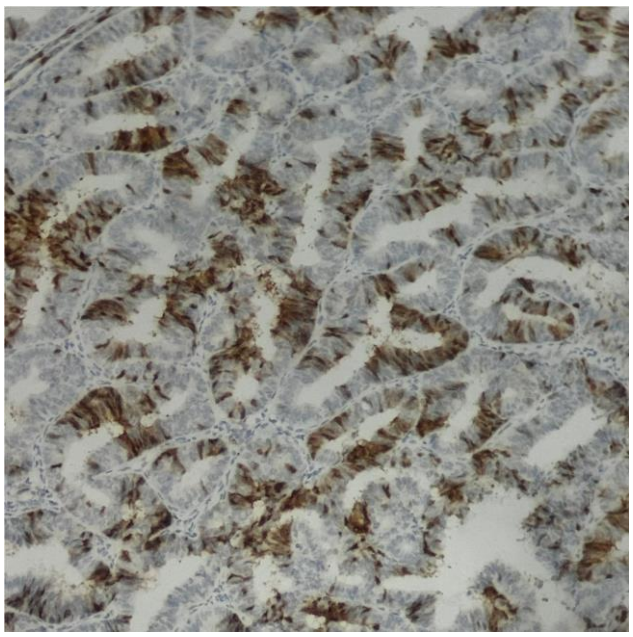

Figure 6. p16 immunohistochemistry. Mosaic pattern of positivity (DAB, ×200).

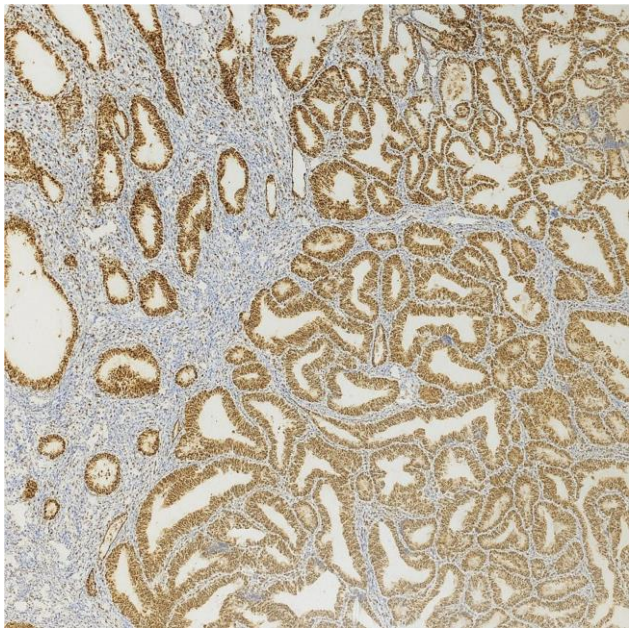

Figure 7. ER immunohistochemistry. Strong, diffuse nuclear staining in tumor cells (DAB, ×200).

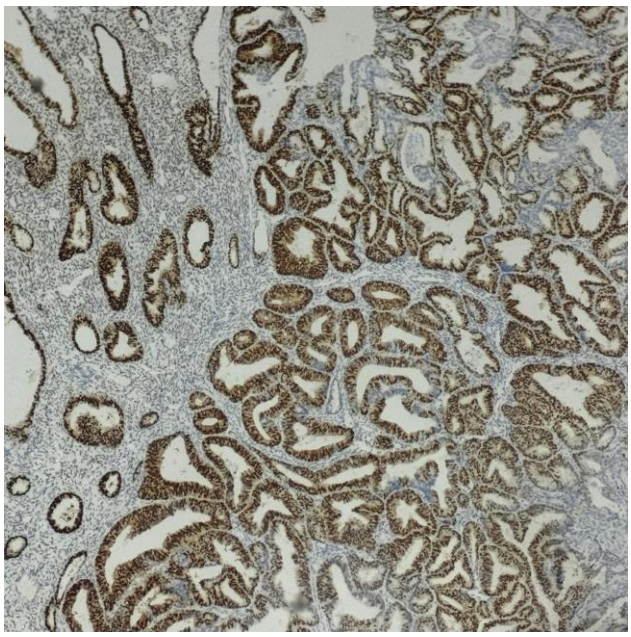

Figure 8. PR immunohistochemistry. Diffuse and strong nuclear positivity in the glandular epithelium (DAB, ×200).

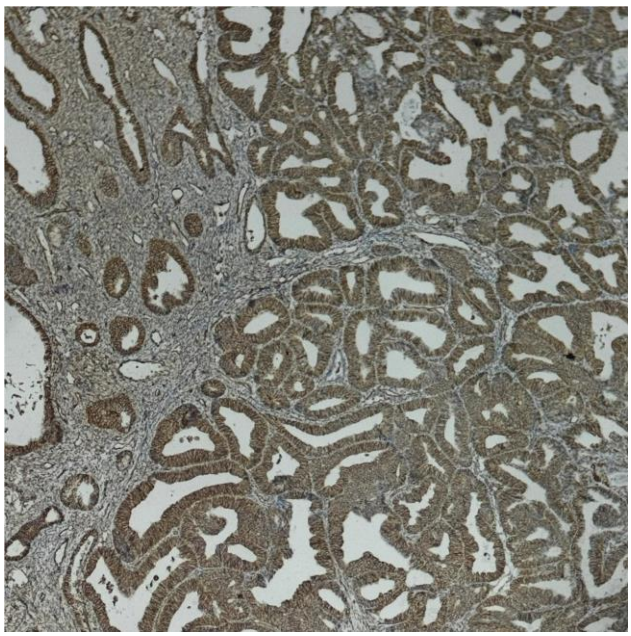

Figure 9. Vimentin immunohistochemistry. Diffuse cytoplasmic positivity in glandular structures (DAB, ×200).

DISCUSSION

Proliferative and neoplastic lesions of the endometrium represent a wide morphological spectrum ranging from benign hyperplasias to invasive carcinomas. Accurate classification and diagnosis of these lesions are essential not only for appropriate clinical management but also for determining prognosis. According to the 2020 World Health Organization (WHO) classification, endometrial intraepithelial neoplasia is recognized as the defined precancerous lesion of estrogen-dependent (type I) endometrioid endometrial carcinoma (1).

EIN is characterized by clonal glandular proliferation, cytologic atypia, and an increased glandto-stroma ratio. These features reflect its potential for malignant progression [4]. However, the distinction between EIN and well-differentiated endometrioid adenocarcinoma (FIGO grade 1) can be challenging in limited or fragmented biopsy specimens. Features such as stromal invasion, cribriform or confluent architecture, and extensive nuclear atypia serve as key distinguishing elements (6).

Morphologic evaluation alone may be insufficient for this distinction. Therefore, immunohistochemical markers have gained significant diagnostic importance. In cases of EIN, loss of PTEN and PAX2 expression is commonly observed, whereas endometrioid adenocarcinomas may demonstrate aberrant p53 staining patterns, heterogeneous or diffuse p16 positivity, and an increased Ki-67 proliferation index (5).

In our study, the first case was diagnosed as non-atypical hyperplasia based on a preserved gland-to-stroma ratio, minimal nuclear atypia, and benign histological features, with no need for further immunohistochemistry. This reflects a reactive, polyclonal proliferation typically associated with hormonal stimulation (7).

In the second case, histopathologic features indicated EIN, with focal glandular crowding and cytologic atypia. The decisive diagnostic marker was the loss of PAX2 expression, a sensitive and specific feature for EIN that supports clonal proliferation and neoplastic transformation (5).

The third case showed distinct morphological and immunohistochemical characteristics compatible with FIGO grade 1 endometrioid adenocarcinoma, including cribriform architecture, nuclear pleomorphism, and an increased proliferation index. Immunohistochemical findings particularly p53 heterogeneity and p16 mosaicism supported the interpretation of an early invasive neoplastic process (8).

Importantly, the WHO 2020 classification clearly differentiates non-atypical hyperplasia typically associated with hormonal imbalance

and benign behavior from EIN, which represents a clonal, neoplastic proliferation with malignant potential. These two lesions differ significantly in their management. While non-atypical hyperplasia may be treated with hormonal therapy and close follow-up, EIN often requires surgical intervention due to its premalignant nature (3).

Our findings underline the diagnostic value of integrating immunohistochemistry into routine histopathologic evaluation. The systematic use of markers such as PTEN, PAX2, p53, p16, Ki67, ER, PR, and vimentin improves diagnostic accuracy, particularly in fragmented or limited specimens, and facilitates the early identification of lesions with malignant potential (4).

CONCLUSION

Accurate diagnosis and classification of premalignant and early invasive lesions of the endometrium are crucial for preventing progression to carcinoma and for guiding appropriate treatment strategies. The 2020 World Health Organization (WHO) classification provides an updated framework for distinguishing among non-atypical hyperplasia, EIN, and welldifferentiated endometrioid adenocarcinoma.

The three cases presented in this study illustrate the histopathologic and immunohistochemical spectrum of endometrial lesions. In particular, the integration of immunohistochemical markers such as PTEN, PAX2, p53, p16, Ki-67, ER, PR, and vimentin into routine diagnostic protocols enhances diagnostic precision, particularly in limited biopsy specimens. These markers contribute substantially to distinguishing reactive processes from true neoplastic proliferations and to identifying lesions with invasive potential.

The distinction among non-atypical hyperplasia, EIN, and low grade carcinoma is not merely academic but carries significant clinical implications. Accurate classification enables individualized management strategies, ranging from conservative hormonal therapy to definitive surgical intervention.

In summary, a systematic approach that integrates morphological evaluation with immunohistochemical analysis enables the early detection and accurate classification of endometrial lesions, thereby preventing malignant progression and improving patient outcomes.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.
Author Contributions: Conception - Meltem Türk Alkan, Havva Erdem, Orhan Çanak; Design - Havva Erdem; Supervision - Meltem Türk Alkan, Havva Erdem, Orhan Çanak; Data Collection and/or Processing - Meltem Türk

Alkan, Havva Erdem, Orhan Çanak; Literature Search - Meltem Türk Alkan, Havva Erdem, Orhan Çanak; Writing - Orhan Canak, Meltem Türk Alkan

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could affect the work reported in this article.

Financial Disclosure: There is no financial disclosure between authors. This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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