https://doi.org/10.48047/AFJBS.6.2.2024.2994-3000

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Histological types and Molecular basis of Endometrial Hyperplasia

Rana Ahmed Ghareeb, Eman Taher Nour-Eldeen, Samar Mosaad Abd El-raouf, Hanaa Mohamed Ibrahim

Department of Pathology, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Rana Ahmed Ghareeb

Email: raghareb@zu.edu.eg, ranaghareeb336@gmail.com

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi:10.48047/AFJBS.6.2.2024.2994-3000

Abstract: Background: The incidence of endometrial hyperplasia (EH) has been estimated to be twice the number of cases of endometrial carcinoma (EC) worldwide. It is thought to be a precursor to endometrial cancer. In the normal menstrual cycle, the endometrium shows proliferative and secretory changes under the effect of estrogen and progesterone. Normal endometrial tissue shows no glandular crowding, and the ratio of glands to stroma is less than 50%. In the secretory phase, the normal endometrial glands may show features such as minimal crowding and a small increase in gland-to-stroma ratio. Endometrial hyperplasia is microscopically characterized by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity and a 2:1 ratio is used as the threshold for diagnosis by many pathologists, although in some systems a glandular contribution exceeding 55%, which corresponds to a gland to stroma ratio just barely above 1:1.

Introduction

The incidence of endometrial hyperplasia (EH) has been estimated to be twice the number of cases of endometrial carcinoma (EC) worldwide [1]. It is thought to be a precursor to endometrial cancer [1].
The presence of atypia in an endometrial biopsy increases the risk of EC up to 9-fold [2].
A large study conducted on the epidemiology of EH reported that women who received the diagnosis of hyperplasia without atypia were in the range of 50-54 years while those with atypia were most commonly seen in the age group of 60-64 years, and the disease was quite rare below the age of 30 years [1].
There are many factors which lead to the development of EH, some of them are modifiable while others are non-modifiable.

A. Modifiable risk factors:
1.Chronic oestrogen exposure

Endometrial hyperplasia is the result of chronic exposure to estrogen which has a proliferative effect on endometrium along with a relative deficiency of progesterone which counteract the estrogenic effect. The causes of estrogen excess could be endogenous or exogenous [3].

Cases with endogenous estrogenic exposure such as; Anovulatory cycles-PCOS and Ovarian tumors- granulosa cell tumors. While exogenous estrogenic exposure most commonly seen in cases who are receiving Tamoxifen as an anti-estrogenic treatment in cases with cancer breast which has an estrogenic effect on endometrium and post-menopausal women who are receiving estrogen only hormone replacement therapy [1].

2. Obesity, physical inactivity

Increase the risk of EH by the conversion of androgens to estrogens within fatty tissue [4].

3. Diets

High fat and high sugar diets seem to increase the risk of EH development by increasing the body fat and which in turn increase endogenous estrogen by androgen conversion in fatty cells [5].

b. Non modifiable factors:

Aging

The risk of EH increases with old age. Although it could happen with young age, it's much more common after age 50 [4].

Familial

Women with family history of EH are at a greatly increased risk of endometrial hyperplasia [3].

3.Racial and ethnic background

African Americans have the highest EH incidence of all racial groups in the US [4].

Others

Women with hereditary nonpolyposis colorectal cancer or Lynch syndrome are associated with increased risk of endometrial hyperplasia [3].

Histological types and Molecular basis of Endometrial Hyperplasia

In the normal menstrual cycle, the endometrium shows proliferative and secretory changes under the effect of estrogen and progesterone. Normal endometrial tissue shows no glandular crowding, and the ratio of glands to stroma is less than 50%. In the secretory phase, the normal endometrial glands may show features such as minimal crowding and a small increase in gland-to-stroma ratio [6].

Endometrial hyperplasia is microscopically characterized by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity and a 2:1 ratio is used as the threshold for diagnosis by many pathologists, although in some systems a glandular contribution exceeding 55%, which corresponds to a gland to stroma ratio just barely above 1:1 [6].

Endometrial hyperplasia subdivided into:

Non atypical hyperplasia (benign endometrial hyperplasia).

Atypical hyperplasia (also known as endometrial or endometrioid intraepithelial neoplasia 'EIN').

[6].

Non atypical hyperplasia (benign endometrial hyperplasia):

Microscopically, nonatypical hyperplasia is characterized by closely packed crowded glands with minimal intervening stroma, the ratio of the gland to stromal is more than 50% but without atypia.

The glands are variable in size with cystic dilatation or irregular luminal contours, lined by elongated columnar epithelium similar of normal proliferative endometrium but with pseudostratification and mitotically active mild nuclear enlargement with smooth nuclear contours and without distinct nucleoli [7].

Hyperplasia without atypia exhibit no relevant genetic changes. They are benign changes and will regress again after the endocrine milieu (physiological gestagen levels) has normalized. In a few cases (1–3%), progression to invasive disease may occur if the endocrine disorder (long-term estrogen dominance or relative or absolute gestagen deficiency) persists over the long term [6].

2.Atypical hyperplasia (EIN):

Microscopically, atypical hyperplasia is characterized by further increase in the gland to stroma ratio.
The glands are markedly crowded disorganization with luminal outpouching lined by stratified cells demonstrating loss of polarity with markedly mitotically active enlarged nucleus with irregular nuclear contour and coarse chromatin with distinct nucleoli [7].
Because the line between atypical hyperplasia and low-grade endometrioid carcinoma can be particularly difficult on small and fragmented samples, pathologists may occasionally interpret biopsy and curettage samples as "at least atypical hyperplasia," which suggests an elevated concern for a carcinoma diagnosis on resection.
Atypical endometrial hyperplasia exhibit many of the mutations typical for invasive endometrioid endometrial cancer (will discussed later). When compared with nonatypical hyperplasia, atypical hyperplasia bears a markedly elevated risk of malignant transformation in up to 60% of cases, patients have coexisting invasive cancer or are at extremely high risk of developing invasive cancer [7].
*Endometrial intraepithelial neoplasia (EIN) classification
A group of gynecologic pathologists suggested endometrial intraepithelial neoplasia (EIN) classification. This system utilized a computerized morphometric analysis. D-score is an important part of this classification. It can be calculated as stromal volume over total tissue volume. The total tissue volume is comprised of the epithelium, gland lumen, and stromal volume [8].
The endometrial tissue is categorized as benign if D is more than one and EIN if D is less than 0 while if D-score is more than 0 and less than 1, it is categorized as indeterminate [6].

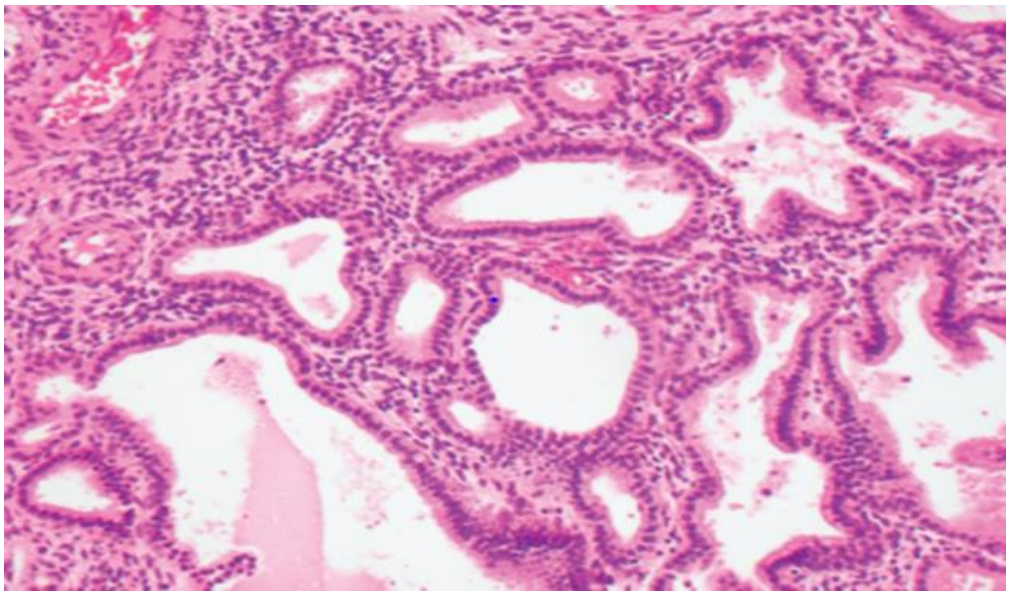

Fig1. Non atypical hyperplasia
Comprised of crowded glands lined by cells similar to those seen in normal proliferative endometrium, with a glands/stroma ratio of approximately 2:1 representing the lower limit of requisite crowding for diagnosis for many pathologists [6].
Fig2. Atypical hyperplasia–endometrial intraepithelial neoplasia shows both glandular crowding and obvious cytologic atypia, including more prominent nuclear enlargement with prominent basophilic nucleoli [6].

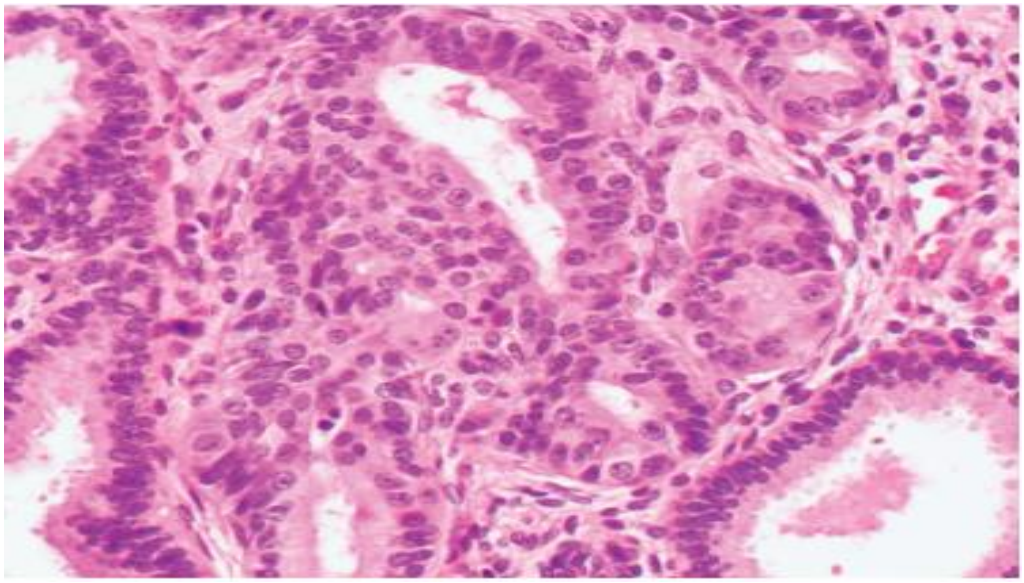

Fig2. Atypical hyperplasia–endometrial intraepithelial neoplasia shows both glandular crowding and obvious cytologic atypia, including more prominent nuclear enlargement with prominent basophilic nucleoli [9].

Prognostic factors of endometrial hyperplasia

While endometrial hyperplasia can progress to endometrial cancer, the rate of progression depends on many factors such as:

The degree of architectural abnormality and the presence or absence of nuclear atypia:

Now it is well established that progression to endometrial cancer is higher in women with atypical compared with non–atypical endometrial hyperplasia with annual risk of progression about 8.2% in nontreated atypical hyperplasia and about 2.6% in non atypical [9].

Mode of treatment:

Studies have found high rates of disease regression in patients who are managed medically. Progestogens induce secretory changes in the endometrium and counterbalance the stimulatory effects of estrogen. Oral, intrauterine, and combined modes of progestine administration are effective [1].

A systematic review of outcomes in patients with atypical endometrial hyperplasia demonstrated a complete response to progestins of 66% and 82% after 6 months of treating these conditions with the levonorgestrel IUD [10].

The differential diagnosis for endometrial hyperplasia includes conditions that can result in focal or generalized thickening of the endometrium as follows:

A. Benign conditions:

Compression artifact:

Pseudocompression of glands due to processing artifact may create appearance of packed and back to back glands but absence of peripheral stromal elements to is a clue to artificial density [7].

Cystic atrophy:

Can have similar low power appearance to EH with closely apposed and cystically dilated glands but these glands do not have the irregular contours of hyperplasia and lined by low cuboidal to flattened without mitotic activity [7].

Endometrial polyp:

Endometrial polyps can show focal glandular crowding and the glands may appear different from the native endometrium. features favoring polyp include: polypoid configuration, dilated thick-walled blood vessels,

compact or fibrotic stroma, and glands oriented parallel to surface endometrium. If the crowded glands show nuclear enlargement, nuclear pseudostratification and loss of polarity, the diagnosis of atypical endometrial hyperplasia can be made [10].

4. Disordered proliferative endometrium:

Histologically considered as degree below hyperplasia without atypia showing

cystic glandular dilation with focal or diffuse loss of spatial organization. Changes are secondary to excess estrogenic influence on the endometrium and should prompt pathologist to search carefully for EIN [7].

B. Malignant condition:

.Endometrioid adenocarcinoma, FIGO grade 1:

The degree of atypia between Endometrioid adenocarcinoma, FIGO grade 1and EIN is usually similar. Features favoring carcinoma are AH / EIN should not have Cribriform confluent glands with intraluminal connections, areas of purely solid epithelium and desmoplastic stroma suggesting invasion or necrosis [10].

According to the classification system which is proposed by The Cancer Genome Atlas (TCGA), endometrial cancer is divided into four categories based on molecular stratification:

Polymerase epsilon DNA polymerase (POLE) ultra-mutated pathway:

Polymerase epsilon DNA polymerase is a DNA replicase that plays a critical role in maintaining a low mutation rate in eukaryotic DNA replication due to its proofreading domain [12].

Polymerase epsilon DNA polymerase ultra-mutated is characterized by somatic mutations in the polymerase epsilon DNA polymerase (POLE) exonuclease proofreading domain and its mutation results in a remarkably high mutation rate hence its name [12].

Five common mutations that make up 95.3% of known POLE variants: P286R, V411L, S297F, A456P, and S459F.

The POLE gene mutation is responsible for approximately 7%–9% of all endometrial cancers and up to 22% of Stage III endometrial cancers, irrespective of tumor grade cancers in the ultra-mutated subgroup, showed excellent prognosis with no recurrences resulting from the possible hypersensitivity to adjuvant treatment [13].

2) Microsatellite Instability (MSI) pathway:

Also known as Mismatch repair deficient (MMRd), which is caused by defects in DNA mismatch repair proteins (MSH2, MLH1, PMS1, PMS2, MSH6, or MSH3). It manifests as an abnormal (increased or decreased) length of microsatellite repeats [14].

The National Cancer Institute guidelines for MSI testing recommend a panel of five microsatellite loci, including three dinucleotide repeat markers (D2S123, D5S346, D17S250) and two mononucleotide repeat markers (BAT 25 and BAT 26). This panel is known as the Bethesda panel [15].

High-frequency MSI (MSI-H) is defined as instability in two or more of the five markers, and low-frequency MSI (MSI-L) is defined as instability in one unstable marker. Microsatellite stable (MSS) status is established when none of the markers shows instability [16].

Endometrial carcinomas of this pathway typically have an intermediate prognosis [16].

Mutations in the oncogene TP53 pathway (p53abn):

Also known as (somatic copy number-high) owing to the high numbers of somatic copy number alterations [17].

This pathway is characterized by TP53 gene mutations, such as nonsense mutations, missense mutations, insertions, deletions, and cleavage.

The TP53 gene consists of all exon regions and adjacent cleavage sites, and the expression of the p53 protein can be used to assess the status of the TP53 gene. Conversely, scattered positive expression in the nucleus is considered normal while abnormal protein expression can indicate complete negativity, diffuse strong positive expression in the nucleus, or cytoplasmic expression [17].

Endometrial cancers of this type are the most aggressive and lethal subtypes with poor prognosis [18].

A subgroup known as p53 wild type (p53wt) was discovered and it is different as tumors at this pathway usually express estrogen and progesterone receptors and are mainly of the endometrioid subtype [19].

No Specific Molecular Profile (NSMP) pathway:

No Specific Molecular Profile pathway are endometrial cancers without POLE mutations, MMRd, and TP53 mutations, also known as (copy-number low tumors) because they are characterizing by low cell mutation and low copy number variation [20].

This pathway is characterized by changes in the PI3K/AKT and Wnt/β-catenin signaling pathways, and the third exon mutation of the β-catenin gene (CTNNB1). Tumors at this type have an intermediate prognosis.[21].

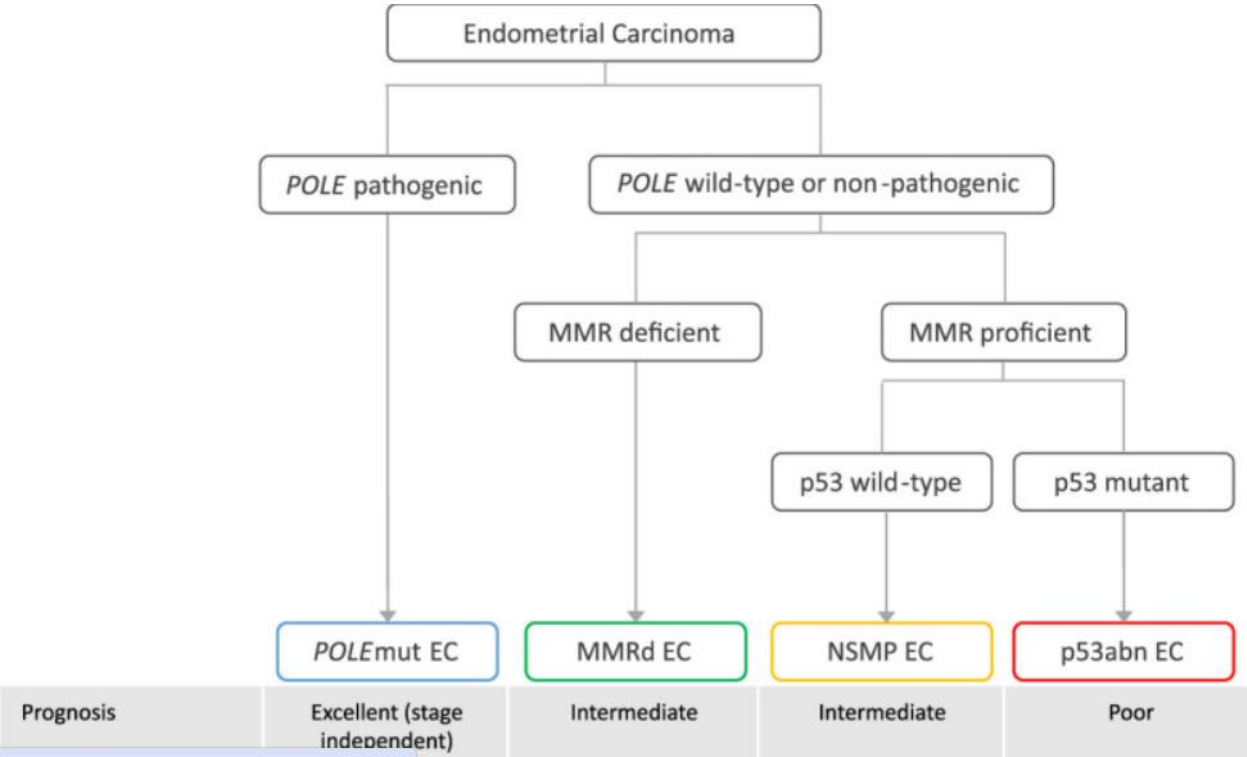

Figure 3: The diagnostic algorithm of the molecular classification of endometrial cancer, associated prognosis [20].

References

1. Singh G, Puckett Y. Endometrial hyperplasia. Obstet Gynecol. 2022;75(1):140-1061.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
3. Giannella E, Santoro A, Palomba S. Endometrial Hyperplasia. In: Endometriosis and Endometrial Disorders. StatPearls Publishing; 2020.
4. Singh G, Puckett Y. Endometrial Hyperplasia. Treasure Island (FL): StatPearls Publishing; 2023.
5. Owuor TO, Reid M, Reschke L, et al. Maternal obesogenic diet induces endometrial hyperplasia, an early hallmark of endometrial cancer, in a diethylstilbestrol mouse model. PLoS One. 2018;13(5).
6. Sanderson KV, Jones MB, Fraser H, et al. Benign and Atypical Endometrial Hyperplasia. In: Comprehensive Gynecologic Pathology. Elsevier; 2017.
7. Travaglino A, Raffone A, Saccone G, et al. Congruence between 1994 WHO Classification of Endometrial Hyperplasia and Endometrial Intraepithelial Neoplasia System. Am J Clin Pathol. 2020;153(1):40-48.
8. Auclair H, Tavassoli FA, Clement PB. Endometrial intraepithelial neoplasia: a new classification system. Int J Gynecol Pathol. 2019;38(1):114-22.
9. Doherty MT, Abu-Rustum NR, Barakat RR, et al. Atypical Endometrial Hyperplasia: A NCCN Clinical Practice Guideline in Oncology. J Natl Compr Canc Netw. 2020;18(10):1267-1278.
10. Singh G, Cue L, Puckett Y. Endometrial Hyperplasia. Treasure Island (FL): StatPearls Publishing; 2024.

11. Travaglino A, Raffone A, Saccone G, et al. Congruence between 1994 WHO Classification of Endometrial Hyperplasia and Endometrial Intraepithelial Neoplasia System. Am J Clin Pathol. 2020;153(1):40-48.
12. Bosse T, Nout RA, McAlpine JN, et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 2018;42(5):561-568.
13. Creutzberg CL, Leon-Castillo A, Boer S, et al. LBA63Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on adjuvant therapy. Ann Oncol. 2019;30.
14. Hause RJ, Pritchard CC, Shendure J, et al. Salipante SJ. Classification and characterization of microsatellite instability across 18 cancer types. Nat Med. 2018;24(4):525.
15. Makker V, MacKay H, Ray-Coquard I, et al. Endometrial cancer. Nat Rev Dis Primers. 2021;7(1):88.
16. George P, Makker V, Oaknin A, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(3):453-470.
17. Hampel H, Pearlman R, Beightol M, et al. Assessment of tumor sequencing as a replacement for lynch syndrome screening and current molecular tests for patients with colorectal cancer. JAMA Oncol. 2018;4(6):806-813.
18. Brett MA, Atenafu EG, Singh N, et al. Equivalent survival of p53 mutated endometrial endometrioid carcinoma grade 3 and endometrial serous carcinoma. Int J Gynecol Pathol. 2021;40(2):116-123.
19. Karnezis AN, Leung S, Magrill J, et al. Evaluation of endometrial carcinoma prognostic immunohistochemistry markers in the context of molecular classification. J Pathol Clin Res. 2017;3(4):279-293.
20. Oaknin A, Bosse TJ, Creutzberg CL, et al. ESMO Guidelines Committee. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877.
21. Paleari L, Pesce S, Rutigliani M, et al. New Insights into Endometrial Cancer. Cancers (Basel). 2021;13(7).