Endometrium at Menopause: The Pathologist’s View

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INTRODUCTION

Endometrium undergoes cyclical modifications under hormonal influence during reproductive life. While the endometrium normally atrophies and remains inactive after menopause, a plethora of disorders affect the endometrium at this stage. In this pictorial review, we highlight these morphologic aspects.

EMBRYOLOGY AND ANATOMY

Endometrium is formed secondary to fusion of the Müllerian (paramesonephric) ducts between the 8th and 9th postovulatory weeks. After the 20th week, the surface epithelium invaginates into the underlying stroma, forming glandular structures that extend toward the underlying myometrium. At birth, the endometrium measures less than 0.5 mm in thickness, and the surface and glands are lined by a low columnar-to-cuboidal epithelium devoid of either proliferative or secretory activity, which resembles the inactive endometrium of postmenopausal women.[1]

The endometrium during the reproductive period undergoes cyclical morphologic changes, which are particularly evident in the superficial two-thirds, the functionalis layer. Morphologic alterations are minimal in the deeper one-third, the basalis layer [Figure 1].[2]

PROLIFERATIVE PHASE

An understanding of the normal proliferative phase endometrium is essential to appreciate menopausal and atypical changes. In the proliferative phase, the endometrial glands are uniform, and evenly spaced, and appear tubular on cross-section [Figure 2a]. An occasional mildly dilated gland is a normal feature and of no significance. Mitotic figures are easily identified within the glands [Figure 2b] and are necessary to label an endometrium as proliferative. The glandular epithelium is composed of pseudostratified cuboidal or low columnar cells with moderate, basophilic cytoplasm and ovoid nuclei, sometimes showing small nucleoli.[3]

DISORDERED PROLIFERATIVE ENDOMETRIUM

Focally evident cystically dilated glands with intervening tubular proliferative phase glands are characteristics of disordered proliferative endometrium [Figure 3]. Disordered proliferation is a pattern that is neither normal nor diffusely hyperplastic, resulting from sustained estrogenic stimulation.[4]

ATROPHY

Atrophy is an important cause of abnormal and recurrent uterine bleeding in postmenopausal patients, found in 25%–48% or more of menopausal women coming for a biopsy.[4,5]

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In the absence of an estrogenic drive, the endometrium is thin on gross examination [Figure 4a]. The functionalis is absent, and only a basalis layer, similar to the basalis of the reproductive years and of the premenarchal endometrium [Figure 4b], is seen.

Biopsy specimens are characteristically scanty, showing only fragmented wisps and detached strips of cuboidal to low columnar epithelium [Figure 4c], along with compact stromal balls. This paucity of tissue does not represent an “insufficient” sample as the scant tissue may be all that is present and therefore is completely representative of the lining of the uterine cavity.[4]

**POSTMENOPAUSAL ENDOMETRIUM**

The histological appearance of the postmenopausal endometrium is variable. The endometrium is usually thin, and this is best appreciated in hysterectomy or endometrial resection specimens [Figure 5a]. The glands vary from small, widely spaced atrophic tubules to cystically dilated glands throughout, an appearance called cystic atrophy or senile cystic atrophy [Figure 5b]. A mixture of small tubules and cystically dilated glands may occur. An absence of proliferative and mitotic activity [Figure 4b] distinguishes it from proliferative endometrium.[1] This cystic change may not be observed in endometrial biopsies because tissue fragmentation during the procedure disrupts the glands, imparting the characteristic appearance described above.

The stroma may be densely cellular and composed of ovoid-to-spindle–shaped cells [Figure 4b] or more fibrous appearance than in premenopausal women [Figure 5a]. This fibrous change may be the direct cause of the cystic change because of blockage of the glands [Figure 5b].

Postmenopausal endometria are similar to those of atrophic endometrium due to other causes, such as exogenous hormones, premature ovarian failure, or radiotherapy.

**ENDOMETRIAL POLyps**

Endometrial polyps have been identified in between 2% and 23% of patients undergoing endometrial biopsy for abnormal uterine bleeding and are more common in the postmenopausal age group.[6] They are thought to be related to hyperestrogenism, possibly originating as localized hyperplasia of the endometrial basalis, secondary to hormonal influences. The stromal component is clonal and shows genetic alterations such as 6p21–22 rearrangements. The glands are polyclonal and appear to be induced through as yet undefined stromal–epithelial interactions.[7,8]

Tamoxifen is also associated with an increased risk of the development of endometrial polyps. Tamoxifen-related polyps may be multiple and large.[7] Histologically, these are indistinguishable from the other common polyps. Some may have staghorn glands with periglandular stromal condensation but lack mitoses, unlike the stroma of adenosarcoma.[8]

Gross examination shows polypoidal outgrowths in the endometrial cavity [Figure 6a]. On histomorphology, the polyps are characterized by a smooth outer contour with epithelium lining the surface on all three sides [Figure 6b], and architecturally abnormal, cystically dilated, and branching glands set in a typically fibrous and sometimes hyalinized stroma showing collections of thick-walled stromal vessels [Figure 6c]. Both glands and stroma must appear different than the nonpolypoidal, uninvolved endometrium.
ADENOMYOMATOUS POLYPS

These polyps show similar glands [Figure 7a] but have smooth muscle in their stroma, usually as irregular bundles and strands in proximity to thick-walled vessels [Figure 7b]. Although smooth muscle is present, the glands are invested by stroma, sometimes resembling a focus of adenomyosis. These polyps usually have proliferative/hyperplastic or functional gland pattern.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an associated increase in the gland/stroma ratio compared with proliferative endometrium.

In 1994 and 2003, the World Health Organization (WHO) and the International Society of Gynecologic Pathologists promoted a system for endometrial hyperplasia classification, which subdivided hyperplasia into four groups according to their nuclear alterations (atypia vs. without atypia) and degree of architectural crowding defined by the extent of back-to-back glandular crowding (complex vs. simple). Although this approach to endometrial hyperplasia diagnosis was better, subsequent studies showed poor-to-moderate interobserver agreement (kappa = 0.337–0.60). Accordingly, the 2014 WHO Classification of Female Genital Tumours (4th edition) simplified the four-tier system into two groups based on the presence of atypia while ignoring the extent of glandular crowding.

Endometrial hyperplasia (WHO 2020) is now subdivided into two broad categories:
1. Endometrial hyperplasia without atypia
2. Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (EAH/EIN).

Endometrial hyperplasia without atypia

This is characterized by an increased gland/stroma ratio and a variety of abnormal architectural patterns. Glands typically vary in size and shape. Dilatation and outpouching of glandular epithelium characterize the architectural abnormalities [Figure 8a]. In other
instances, the glands are only minimally dilated but focally crowded. Increased gland-to-stroma ratio is a characteristic of this entity [Figure 8b]. The atypical glands must be distributed throughout the tissue sampled.

This term now also includes the earlier entity of complex hyperplasia which is characterized by increasing glandular architectural complexity, but without nuclear atypia and a lesser risk of progression to malignancy. Progression to endometrial carcinoma occurs in 1%–3% of women with hyperplasia without atypia.[8]

**Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia**

EAH/EIN is characterized by a crowded glandular architecture distinct from surrounding endometrium or entrapped glands, with atypical nuclear features distinct from the background endometrium or entrapped normal glands [Figure 9].[8] The abnormal focus should have a linear dimension more than 1 mm for making a diagnosis on endometrial biopsies and would translate to half the size of a low-power (×10) magnification.[13]

Initially termed “endometrial intraepithelial neoplasia” (2000), the term was modified to “endometrioid” in the WHO 2014 to better reflect its specific association with endometrioid carcinoma (EC).[13]

The European Working Group (EWG) had also developed a classification for endometrial proliferative lesions. According to the EWG classification, simple and complex hyperplasia without atypia was referred to as “hyperplasia,” while atypical hyperplasia and well-differentiated ECs were combined into a single category designated “endometrial neoplasia.”[13] One-quarter to one-third of EAH/EIN will have cancer at immediate hysterectomy or during the 1st year of follow-up.[8]

**Endometrioid carcinoma**

EC is characterized by increasing glandular complexity with glandular, papillary, and solid architecture of endometrioid glands. On biopsies, EC is differentiated from EIN by (1) stromal invasion defined by a confluent glandular, cribriform, or maze-like pattern, (2) a desmoplastic stroma, or (3) a complex papillary/villoglandular architecture [Figure 10].[8] A size criterion has also been described, the confluent growth being extensive enough to involve at least one-half of a low-power (×4) field, a distance of 2.0 mm [Figure 10a]. Brisk mitotic activity is generally seen in the atypical glands [Figure 10b].[14] In resection specimens, invasion into the underlying myometrium is usually seen [Figure 11].

In the recent WHO classification, a two-tier grading system has been recommended, where grades 1 and 2 are labeled as low grade while grade 3 is high grade.[8]

Four molecular subtypes with distinct prognoses are described: (1) POLE ultramutated, (2) mismatch repair–deficient, (3) p53 mutant [Figure 12], and (4) no specific molecular profile EC [Table 1].[8] A limited panel of immunohistochemistry and POLE mutation analysis is useful in assessing prognosis in the grade 3 ECs. Molecular signatures also show carcinosarcoma to be an aggressive variant of endometrial carcinoma arising from epithelial–mesenchymal transition, rather than a mixed epithelial and
mesenchymal neoplasm, and are included as a type of endometrial carcinoma in the new WHO 2020 [Figure 13].[8]

Other types of endometrial carcinoma
Serous carcinoma (10%) [Figure 14], clear cell carcinoma (<10%), undifferentiated and dedifferentiated carcinomas, mixed carcinoma, carcinosarcoma, rarer types such as mesonephric adenocarcinoma, squamous cell carcinoma, and primary gastric type mucinous carcinoma are also encountered in the postmenopausal endometrium. Immunohistochemistry with a panel of antibodies is helpful in typing.

To summarize, the endometrium at menopause may be inactive but is home to a myriad of neoplastic

| Table 1: Molecular subtypes of endometrioid carcinoma |
|-----------------------------------------------------|
| **Features** | **POLE ultramutated EC** | **MMR-deficient EC** | **p53-mutant EC** | **NSMP EC** |
| Associated clinical features | Younger age at presentation | Association with Lynch syndrome | Advanced stage at presentation | High BMI |
| Associated histologic features | Often high-grade; scattered tumor GC; TILs | Often high grade; TILs; invasion | High grade with nuclear atypia | Low grade, frequency squamous differentiation |
| Diagnostic tests | Sequencing | MMR IHC; MSI assay; NGS | P53 mutant patterns on IHC | Exclusion of other categories |
| Associated molecular features | >100 mutations/Mb; microsatellite stability | >100 mutation/mb; MSI | <10 mutations/mb; somatic copy number alterations | 30%-40% show CTNNB-1 mutations |
| Prognosis | Excellent | Intermediate | Poor | Intermediate to excellent |

EC: Endometrioid carcinoma, NSMP: No-specific molecular profile, BMI: Body mass index, IHC: Immunohistochemistry, MSI: Microsatellite instability, MMR: mismatch repair, GC: giant cells, TILs: tumor-infiltrating lymphocytes, NGS: next-generation sequencing, CTNNB-1: Catenin beta 1 gene
and nonneoplastic pathologies. Therefore, a careful, thorough histopathological examination in correlation with clinical evaluation is essential for proper diagnosis and management of these conditions.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. McCluggage GW. Benign diseases of the endometrium. In: Kurman RJ, Ellenson LH, Ronnett BM, editors. Blaustein’s Pathology of the Female Genital Tract. 6th ed. New York: Springer; 2011.
2. Hapangama DK, Bulmer JN. Pathophysiology of heavy menstrual bleeding. Womens Health (Lond) 2016;12:3-13.
3. Dallenbach-Hellweg G, Schmidt D, Dallenbach F. Atlas of Endometrial Histopathology. 3rd ed. Berlin Heidelberg: Springer-Verlag; 2010. Chapter 3, normal endometrium. p. 7-12.
4. Murdock TA, Veras EF, Kurman RJ, Mazur MT. Diagnosis of Endometrial Biopsies and Curettings. 3rd ed. Switzerland AG: Springer Nature; 2019. Chapter 5, abnormal uterine bleeding. p. 132-3.
5. Smith PP, O’Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: A prospective cohort study. J Minim Invasive Gynecol 2014;21:799-803.
6. Dreisler E, Stumpe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009;33:102-8.
7. Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. SAGE Open Med [2050312119848247]. 2019;7:[about 12 p.]. Available from: https://journals.sagepub.com/doi/10.1177/2050312119848247. [cited 2021 Dec 19].
8. Matias-Guiu X, Oliva E, McCluggage WG, Nucci MR, Olivia E. Tumours of the uterine corpus. In: WHO Classification of Tumours Editorial Board. Female Genital Tumours (WHO Classification of Tumours). 5th ed., Vol. 4. Lyon (France): International Agency for Research on Cancer (IARC); 2020.
9. Murdock TA, Veras EF, Kurman RJ, Mazur MT. Diagnosis of Endometrial Biopsies and Curettings. 3rd ed. Switzerland AG: Springer Nature; 2019. Chapter 8, polyps. p. 207.
10. Kendall BS, Ronnett BM, Isacson C, Cho KR, Hedrick L, Diener-West M, et al. Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. Am J Surg Pathol 1998;22:1012-9.
11. Bergeron C, Nogales FF, Masseroli M, Abeler V, Duvillard P, Müller-Holzner E, et al. A multicentric European study testing the reproducibility of the WHO classification of endometrial hyperplasia with a proposal of a simplified working classification for biopsy and curettage specimens. Am J Surg Pathol 1999;23:1102-8.
12. Zaino R, Carinelli SG, Ellenson LH, Eng C, Katabuchi H, Konishi I, et al. Epithelial tumours and precursors. In: Kurman RJ, Carcangiu ML, Herrington S, Young RH, editors. WHO Classification of Female Genital Tumours. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2014.
13. Murdock TA, Veras EF, Kurman RJ, Mazur MT. Diagnosis of Endometrial Biopsies and Curettings. 3rd ed. Switzerland AG: Springer Nature; 2019. Chapter 9, precursors of endometrial carcinoma. p. 225-60.
14. Murdock TA, Veras EF, Kurman RJ, Mazur MT. Diagnosis of Endometrial Biopsies and Curettings. 3rd ed. Switzerland AG: Springer Nature; 2019. Chapter 10, endometrial carcinoma. p. 261-320.

Figure 14: (a) Serous carcinoma characterized by a papillary growth pattern with fibrovascular cores (blue arrow) and hierarchical, complex branching (yellow arrow) (HE stain, ×2). (b) Myometrial invasion (arrow) in a case of serous carcinoma (HE stain, ×5). (c) The papillae are lined by markedly atypical cells showing hyperchromatic and pleomorphic nuclei with multiple mitoses, including atypical ones (arrows) (HE stain, ×40)