Pictorial Review

Endometrium at Menopause: The Pathologist's View

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Abstract

Endometrium at menopause is inactive and free of cyclical changes that are characteristics of the reproductive age. At the same time, menopausal endometrium is subject to a variety of disease processes, the most sinister of which are the endometrial malignancies. In the present pictorial review, we briefly discuss the various morphologic patterns of diseases affecting the menopausal endometrium. With an aim to provide insights from the pathologists' point of view, multiple pictures for each of the disorders are shared. We highlight the finer points a pathologist looks for, to ensure proper treatment and welfare of postmenopausal women.

Keywords: *Atrophy, endometrial malignancies, endometrium, menopause*

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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].

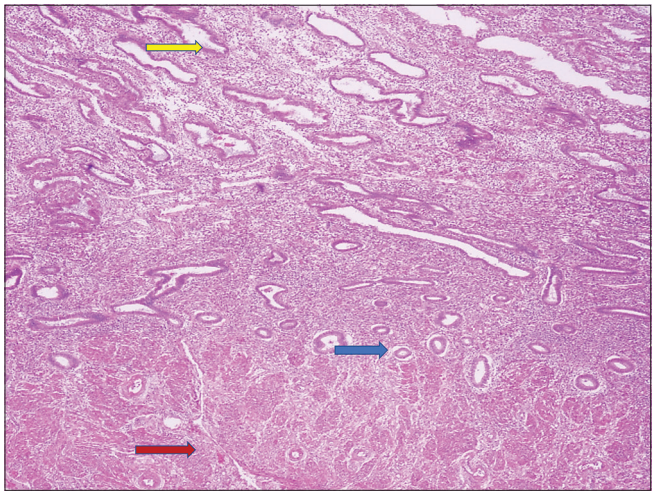

Figure 1: Layers of the endometrium. The stratum functionalis occupies the upper two-thirds and is showing secretory phase appearance in this photomicrograph (yellow arrow). The lower one-third of the stratum basalis shows tubular glands with minimal morphologic alterations (blue arrow). The underlying myometrium (red arrow) shows fascicles of smooth muscle (HE stain, ×5)

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.

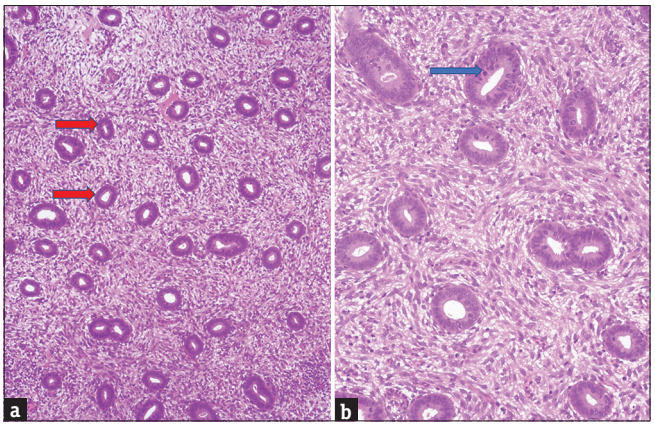

Figure 2: (a) Proliferative phase endometrium composed of evenly spaced tubular glands (red arrow), with compact, cellular surrounding stroma (HE stain, ×5). (b) Glands showing mitoses (blue arrow) help differentiate from inactive atrophic glands (HE stain, ×20)

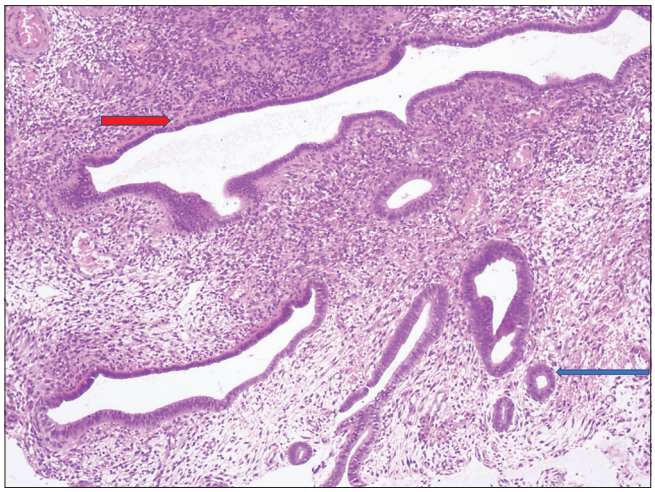

Figure 3: Disordered proliferative endometrium characterized by few dilated and cystic (red arrow) glands amid tubular proliferative phase glands (blue arrow) (HE stain, ×10)

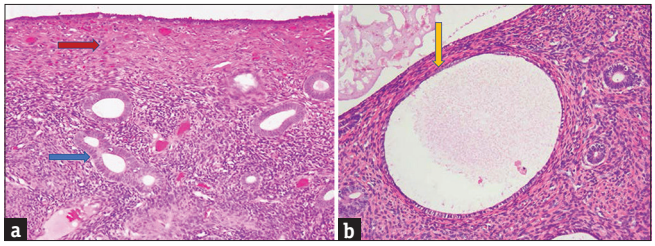

Figure 5: (a) Atrophic endometrium from a hysterectomy showing thinned out endometrium with atrophic, tubular glands (blue arrow) and a fibrous stroma (red arrow) (HE stain, ×10). (b) A case of senile cystic atrophy with cystic glands (yellow arrow) lined by cuboidal cells (HE stain, ×10)

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].[9] 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

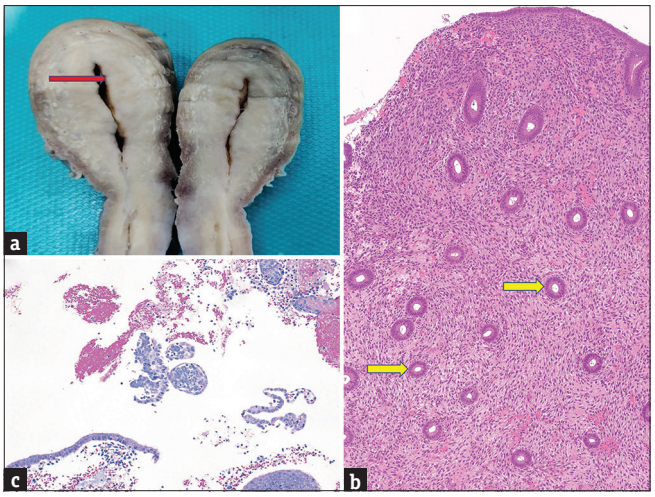

Figure 4: (a) Gross photograph of a cut-opened postmenopausal uterus showing a thinned-out atrophic endometrium (red arrow). (b) Photomicrograph showing inactive glands (yellow arrows) lacking mitoses with surrounding spindle-celled stroma (HE stain, ×5). (c) Photomicrograph of an endometrial biopsy showing strips and fragments of endometrial glands and stroma consistent with atrophic endometrium (HE stain, ×5)

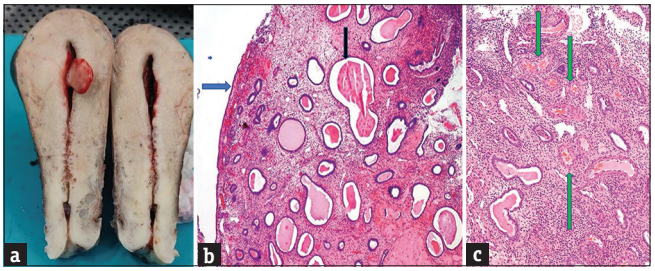

Figure 6: (a) Gross photograph of a cut-opened uterus with a fundal polyp. (b) Photomicrograph of the polyp showing a rounded contour lined by a surface epithelium (blue arrow) and tubular and cystic glands (black arrow) in a fibrous stroma (HE stain, ×5). (c) Stroma with a leash of thick-walled vessels (green arrows) (HE stain, ×10)

this approach to endometrial hyperplasia diagnosis was better, subsequent studies showed poor-to-moderate interobserver agreement (kappa = 0.337–0.60).[10,11] 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.[12]

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]

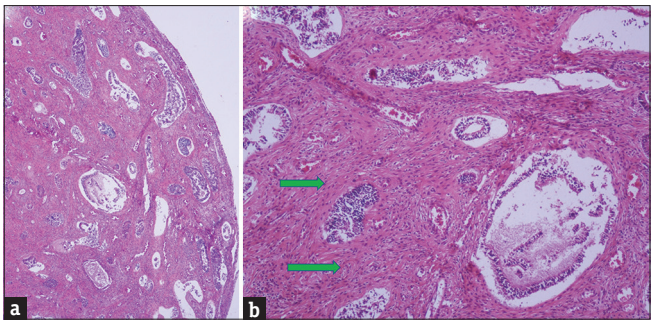

Figure 7: (a) Adenomyomatous polyp showing dilated and tubular endometrial glands with surrounding smooth muscle (HE stain, ×5). (b) Smooth muscle (green arrows)-rich stroma in an adenomyomatous polyp (HE stain, ×10)

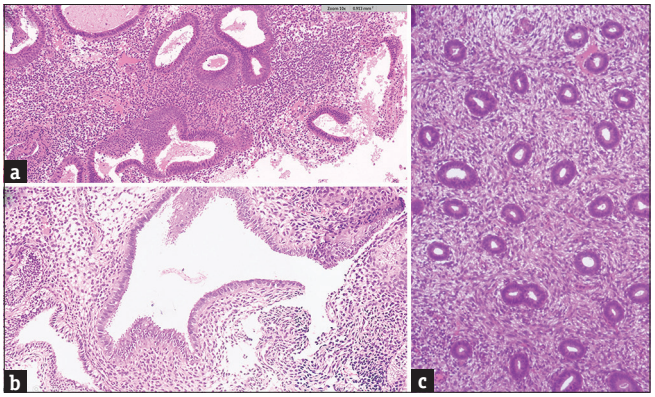

Figure 8: (a) Endometrial hyperplasia without atypia showing a "Swiss-cheese" appearance. An increased gland-to-stroma ratio is seen, with dilated and branching glands (HE stain, ×10). (b) Cystic glands seen throughout the field (HE stain, ×20). (c) Normal proliferative endometrium for comparison (HE stain, ×5)

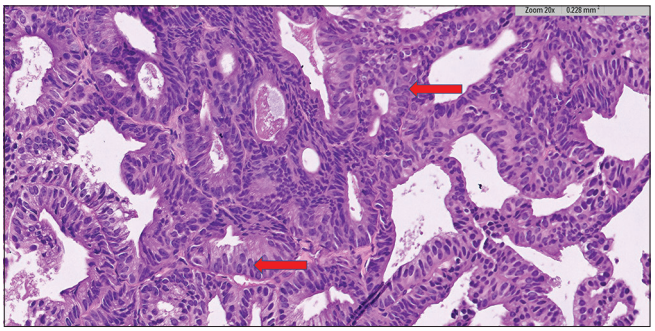

Figure 9: Endometrial hyperplasia with atypia (endometrioid intraepithelial neoplasia) showing closely packed, back-to-back glands with scant intervening stroma. The cells show atypical and rounded nuclei with prominent nucleoli (red arrow) (HE stain, ×20)

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.[8]

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

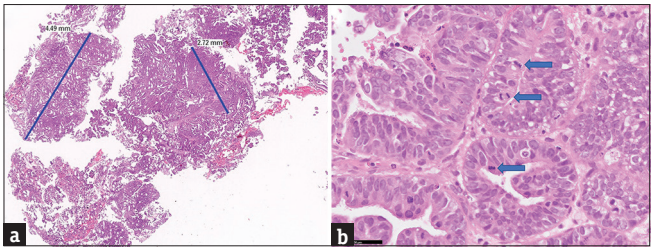

Figure 10: (a) Endometrial biopsy showing confluent glandular proliferation. This confluent growth measured more than 2 mm (HE stain, ×0.5). (b) Atypical glands showing brisk mitoses (blue arrows) (HE stain, ×20)

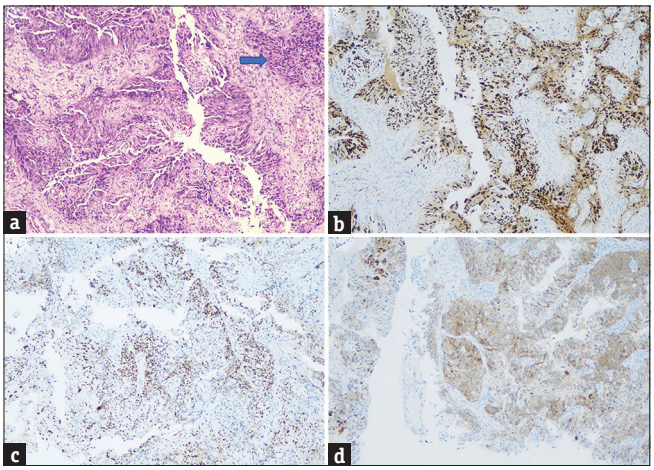

Figure 12: (a) Photomicrograph of a case of endometrioid carcinoma showing high-grade features, characterized by solid nests (blue arrow) with surrounding desmoplastic stroma (HE stain, ×10). (b) On immunohistochemistry, this tumor showed a diffuse, strong nuclear positivity for ER (IHC, ×20 for ER). (c) p53 also showed strong nuclear positivity in more than 75% of cells, consistent with mutant phenotype (IHC, ×10 for p53). (d) p16 showed a patchy positivity (IHC, ×10 for p16). This immunohistochemical pattern is diagnostic of an endometrioid carcinoma, p53-mutant molecular subtype

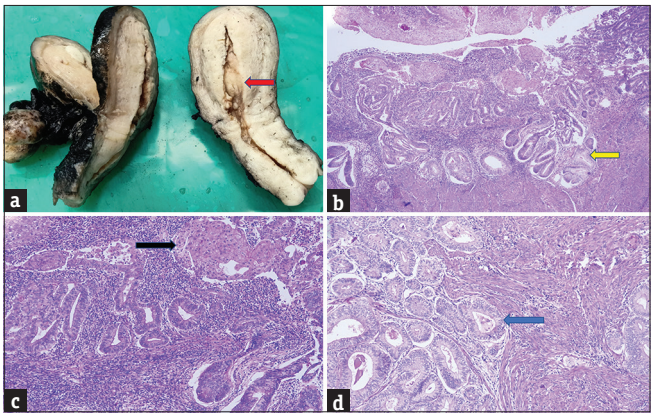

Figure 11: (a) Gross photograph of a hysterectomy showing an endometrial growth on the right lateral wall (red arrow). (b) Endometrioid carcinoma showing myometrial invasion (yellow arrow) (HE stain, ×5). (c) Squamous morules (black arrow) in a case of endometrial carcinoma are metaplastic and not considered while grading the tumor (HE stain, ×10). (d) Neoplastic endometrial glands invading the myometrium (blue arrow) (HE stain, ×10)

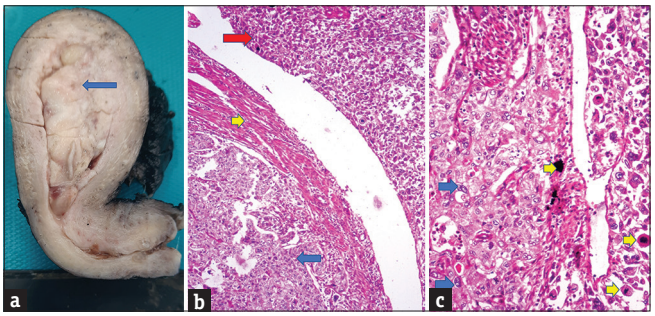

Figure 13: (a) Gross photograph of a hysterectomy showing a fleshy polypoidal growth entirely filling the cavity (blue arrow). (b) Photomicrograph from the same case showing carcinomatous (blue arrow) and sarcomatous elements (red arrow), infiltrating the myometrium indicating a carcinosarcoma (HE stain, ×10). (c) The tumor shows marked nuclear pleomorphism (blue arrows). Abnormal and brisk mitoses are seen in the tumor (yellow arrows) (HE stain, ×20)

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

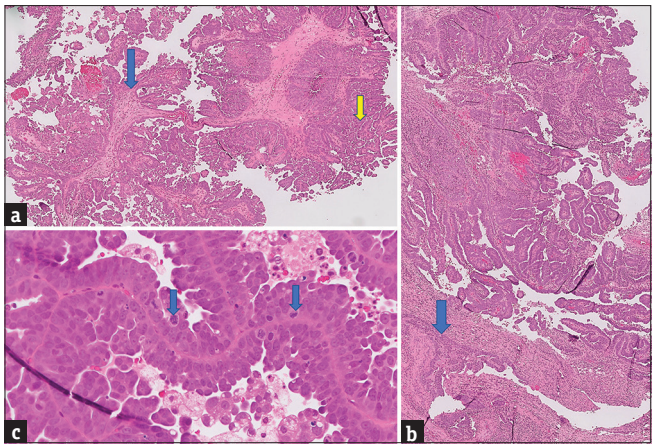

Figure 14: (a) Serous carcinoma characterized by a papillary growth pattern with fibrovascular cores (blue arrow) and hierarchical, complex branching (yellow arrow) (HE stain, ×2). (b) Myometrial invasion (arrow) in a case of serous carcinoma (HE stain, ×5). (c) The papillae are lined by markedly atypical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

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.

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