Classification of endometrial hyperplasia

The classification system used by the World Health Organization (WHO) and the International Society of Gynecological Pathologists designates four different types with varying malignant potential. Hyperplasia is classified as simple or complex based on the absence or presence of architectural abnormalities such as glandular complexity and crowding. Most important, hyperplasias are further designated as atypical if they demonstrate cytologic atypia. Only atypical endometrial hyperplasias are clearly associated with the subsequent development of adenocarcinoma. Simple atypical hyperplasia is a relatively uncommon diagnosis. In general, most atypical hyperplasias have a complex architecture (Tab.1)[12] .

Table (1): World Health Organization classification of endometrial hyperplasia.

Types	Progressing to Cancer (%)
Simple hyperplasia	1
Complex hyperplasia	3
Simple atypical hyperplasia	8
Complex atypical hyperplasia	29

Although endometrial hyperplasias are formally classified into these four different groups, they tend to be morphologically heterogeneous both within and between individual patients. This histologic diversity explains why only a small number of conserved features are useful as diagnostic criteria. As a result, reproducible scoring of cytologic atypia is often challenging, particularly with a small amount of tissue from a biopsy sample [13] .

Endometrial Intraepithelial Neoplasia

Recently, the term endometrial intraepithelial neoplasia (EIN) has been introduced to more accurately distinguish the two very different clinical categories of hyperplasia: normal polyclonal

endometria diffusely responding to an abnormal hormonal environment, and intrinsically proliferative monoclonal lesions that arise focally and confer an elevated risk of adenocarcinoma. This nomenclature emphasizes the malignant potential of endometrial precancers, in keeping with similar precedents in the cervix, vagina, and vulva. Using this system, non atypical anovulatory or prolonged estrogen-exposed endometria generally are designated as endometrial hyperplasias. In contrast, endometrial intraepithelial neoplasia is used to describe all endometria delineated as premalignant by a combination of three morphometric features. These features reflect glandular volume, architectural complexity, and cytologic abnormality. The EIN classification system is a more accurate and reproducible way of predicting progression to cancer but has not been implemented universally [(14)] .

Transvaginal sonography of endometrial thickness is a feasible method for predicting endometrial hyperplasia.In postmenopausal women with endometrial measurements of 5 mm or less, sonographic pathologic studies have demonstrated that bleeding can be attributed to endometrial atrophy.Those with a thicker endometrium warrant biopsy. Alternatively, Pipelle office biopsy or outpatient dilatation and curettage (D&C) may be selected initially. Grossly, hyperplastic endometrium is not distinctive, and thus direct visual identification using hysteroscopy is inaccurate [(15)] .

Treatment

Management of women with endometrial hyperplasia depends mainly on the patient's age and the presence or absence of cytologic atypia. However, non surgical therapy is inherently risky due to the inconsistency of diagnosis and uncertainty in predicting the natural history of individual lesions. In addition, there is no way to anticipate which types will involute with progestin therapy. However, as long as an endometrial sample is representative and a provider has no reason to suspect a coexisting invasive carcinoma, the decision to treat endometrial hyperplasia through hormonal or surgical means relies on clinical judgment [(16)] .

Non atypical Endometrial Hyperplasia

Premenopausal Women:

Premenopausal women with non atypical endometrial hyperplasia typically require 3 to 6 month course of low-dose progestin therapy. Cyclic medroxyprogesterone acetate (MPA) given orally for 12 to 14 days each month at a dose of 10 to 20 mg daily is commonly used. Another frequently used option is to initiate a combination oral contraceptive pill. Progesterone-containing IUDs are also effective. In some patients, hysteroscopic endometrial ablation can be curative, but post treatment surveillance is more difficult, and subsequent hysterectomy rates are high. Although lesions may regress spontaneously without therapy, progestins generally are used to address the underlying etiology, i.e., chronic anovulation and excess estrogen. If no residual hyperplastic endometrium is found during surveillance biopsy, then patients should be continued on progestins and be monitored until menopause. An additional endometrial biopsy is required for new bleeding. In general, biopsies should be avoided when a patient is taking progestins because this hormone confounds the pathologic diagnosis through modification of endometrial morphology. Endometrial shedding during a withdrawal bleed is also an integral component of medication induced ablation and should be completed before assessing persistence. Waiting 2 to 6 weeks after hormone withdrawal before biopsy solves these problems [17] .

Postmenopausal Women:

Postmenopausal women with non atypical endometrial hyperplasia also may be treated with low-dose cyclic MPA or a continuous 2.5mg/day regimen. However, it is particularly important in older women to be confident that an adequate sample has been obtained to exclude cytologic atypia. D&C may be indicated in some circumstances. For instance, occasionally, tissue volume with Pipelle sampling is scant, or bleeding symptoms are more prominent than expected. In practice, postmenopausal patients with simple hyperplasia often are followed without therapy. Complex hyperplasia without atypia usually is treated with progestins. Office endometrial biopsy is performed annually to surveil these women [18] .

Response of non atypical endometrial hyperplasia to progestins:

The overall clinical and pathologic regression rates of progestin therapy exceed 90 % for non atypical endometrial hyperplasia. Patients with persistent disease on repeated biopsy should be switched to a higher-dose regimen such as MPA 40 to 100 mg orally daily or megestrol acetate, 160 mg daily. Again, the clinician must confirm that hormonal ablation has occurred by resampling the endometrium after a suitable therapeutic interval. Hysterectomy also should be reconsidered for lesions that are refractory to medical management [19] .

Atypical endometrial hyperplasia:

Hysterectomy is the best treatment for women at any age with atypical endometrial hyperplasia because the risk of concurrent subclinical invasive disease is high. Premenopausal women who strongly wish to preserve fertility are the main exception. High-dose progestin therapy may be most appropriate for highly motivated patients. Poor surgical candidates also may warrant an attempt at hormonal ablation with progestins. Resolution of the hyperplasia must be confirmed by serial endometrial biopsies every three months until response is documented. Otherwise, hysterectomy should be recommended. Following hyperplasia resolution, surveillance should continue long term due to the potential for eventual progression to carcinoma [20] .

Endometrial carcinoma:

Endometrial cancer is a biologically and histologically diverse group of neoplasms characterized by a dualistic model of pathogenesis. Type I endometrioid adenocarcinomas comprise 75% of all cases.They are estrogen dependent, low grade, and derived from atypical endometrial hyperplasia. In contrast, type II cancers usually have serous or clear cell histology, no precursor lesion, and a more aggressive clinical course. The morphologic and clinical differences are paralleled by genetic distinctions in that type I and II tumors carry mutations of independent sets of genes. (tab.2)

Table (2): Type I and II endometrial carcinoma: distinguishing features.

Feature	Type I	Type II
Unopposed estrogen	Present	Absent
Menopausal status	Pre- and perimenopausal	Postmenopausal
Hyperplasia	Present	Absent
Race	White	Black
Grade	Low	High
Myometrial invasion	Minimal	Deep
Specific subtypes	Endometrioid	Serous, clear cell
Behavior	Stable	Aggressive

The two pathways of endometrial cancer pathogenesis obviously have significant overlap and result in a spectrum of histologic features. However, this dualistic view has therapeutic ramifications for novel treatment strategies that target high-risk disease [21] .

Diagnosis and screening

Clinical Features:

Symptoms:

90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly postmenopausal bleeding. Intermenstrual bleeding or heavy prolonged bleeding in perimenopausal or anovulatory premenopausal women should arouse suspicion. The diagnosis may be delayed unnecessarily in these women because the bleeding is usually ascribed to “hormonal imbalance.” A high index of suspicion also is needed to make an early diagnosis in women younger than 40 years of age. Occasionally, vaginal bleeding does not occur because of cervical stenosis, particularly in thin, elderly, estrogen-deficient patients. In

some patients with cervical stenosis a hematometra develops, and a small percentage have a purulent vaginal discharge resulting from a pyometra [22] .

Signs:

Physical examination commonly reveals an obese, hypertensive, postmenopausal woman, although approximately 35% of patients are not obese and show no signs of hyperestrogenism. Abdominal examination is usually unremarkable except in advanced cases when ascites may be present and hepatic or omental metastases may be palpable. Occasionally, a hematometra appears as a large, smooth midline mass arising from the pelvis. On pelvic examination, it is important carefully to inspect and palpate the vulva, vagina, and cervix to exclude metastatic spread or other causes of abnormal vaginal bleeding. The uterus may be bulky, but often it is not significantly enlarged. Rectovaginal examination should be performed to evaluate the Fallopian tubes, ovaries, and cul-de-sac. Endometrial carcinoma may metastasize to these sites or, alternatively, coexistent ovarian tumors such as a granulosa cell tumor, thecoma, or epithelial ovarian carcinoma may be noted [23] .

Screening of Asymptomatic Women:

The ideal method for outpatient sampling of the endometrium has not yet been devised, and no blood test of sufficient sensitivity and specificity has been developed. Therefore, mass screening of the population is not practical. However, screening for endometrial carcinoma or its precursors is justified for certain high-risk people, including those shown in Table [3]

Table (3): Patients for Whom Screening for Endometrial Cancer Is Justified

1.	Postmenopausal women on exogenous estrogens without progestins
2.	Women from families with hereditary nonpolyposis colorectal cancer syndrome
3.	Premenopausal women with anovulatory cycles, such as those with polycystic ovarian disease

Only approximately 50% of women with endometrial cancer have malignant cells on a Papanicolaou (Pap) smear [(24)].However,compared with patients who have normal cervical cytologic findings, patients with suspicious or malignant cells are more likely to have deeper myometrial invasion, higher tumor grade, positive peritoneal cytologic findings, and a more advanced stage of disease [(25)].

Various strategies have been used to screen for endometrial cancer in women with Lynch syndrome, but the efficacy of endometrial screening in these women remains unproven. The main modalities used include TVS and endometrial sampling. The latter has been used both alone and in combination with hysteroscopy. However, available data are limited, and the evidence to recommend any particular method of screening is lacking. Interval cancers occur despite screening, and the impact of screening on morbidity and mortality is unknown.Although TVS has been used as a first-line screening tool, there is lack of consensus on an appropriate cutoff value for endometrial thickness (ET) in asymptomatic premenopausal women, and interval cancers are known to occur [(26,27)]. Pipelle endometrial biopsy is a well-established method for endometrial sampling and is well tolerated by women as an outpatient procedure. However, it has a tissue yield and procedure failure rate of approximately 10% [(28,29)]. and inadequate samples are more common in the postmenopausal age group. The diagnostic accuracy of pipelle is higher in postmenopausal women. A large meta-analysis of the use of pipelle reported a 99% sensitivity for the diagnosis of endometrial cancer and 81% for the diagnosis of hyperplasia in

postmenopausal women. In premenopausal women, the sensitivity for endometrial cancer was 91% with a specificity of >98% [28].

Morphological Markers:

The most commonly used tumor marker is endometrial thickness, which is measured using transvaginal ultrasound. It is defined as the distance from the proximal to the distal interface of the hypoechoic halo that surrounds the more echogenic myometrium. It is conventional to measure double thickness (thickness of both endometrial layers) at the thickest point in the midsagittal view. Cutoffs of 12 mm in premenopausal women and 5 mm in postmenopausal women have been used in earlier trials, but there is no consensus on this, and interval cancers have been known to occur. Any abnormality such as a polyp should be investigated irrespective of endometrial thickness.In symptomatic patients with postmenopausal bleeding who are not on hormone replacement therapy (HRT), a cutoff for endometrial thickness of >4.0 mm has a sensitivity for detection of endometrial cancer of 98% and a negative predictive value of 99% [30]. The Postmenopausal Estrogen and Progestin Interventions trial found that a ET threshold of 5 mm yielded a PPV of 9%, NPV of 99%, sensitivity of 90%, and specificity of 48% for detecting endometrial hyperplasia or cancer [31].Asubsequent meta-analysis suggested an endometrial thickness of 5 mm as a cutoff for investigating postmenopausal bleeding. A negative test would reduce the likelihood of endometrial cancer to 2.5% [32]. Even though these cutoffs effectively exclude endometrial atrophy, they fail to differentiate between hyperplasia and carcinoma [33]. The endometrial thickness for women using sequential HRT is greater than that for those using a continuous combined preparation. The Scottish Intercollegiate Guidelines Network recommends using 3 mm as a cutoff for women in the following circumstances: (i) those on continuous combined HRT, (ii) those who have not used HRT for a year, and (iii) those who have never taken HRT. They recommend a cut off of 5 mm in women on a sequential preparation [34].

As a tumor marker in asymptomatic postmenopausal women, endometrial thickness has the same poor positive predictive value but high negative predictive value for the detection of serious endometrial disease [31]. Screening studies using conventional and color Doppler ultrasonography in apparently healthy postmenopausal women have established that endometrial carcinomas can be detected at a preclinical stage [35,36] and that transvaginal ultrasonography is more sensitive than blind endometrial biopsy [37]. However, in the absence of symptoms, repeat sampling is not warranted in patients with a thickened endometrium and negative findings at initial biopsy [38]. Endometrial fluid accumulation is detected in 12% of asymptomatic elderly postmenopausal women and is rarely a sign of malignancy [36]. Other techniques that are under investigation and not part of routine protocols include 3-D ultrasonography for the measurement of endometrial volume and power Doppler analysis [39,40,41] and saline infusion sonohysterography [42,43]. The ability of 3-D sonography to distinguish between hyperplasia and cancer is still limited. Saline-infusion sonohysterography may be better than standard TVS at evaluating intrauterine pathology such as polyps or fibroids, but it has limited value in diagnosing hyperplasia or carcinoma [44].

Women on tamoxifen are more prone to develop endometrial polyps or hyperplasia and have 4 to 5 fold higher risk of endometrial cancer. In asymptomatic women on long-term tamoxifen, abnormal ultrasonographic findings are common in the absence of underlying endometrial pathology. The apparent increase in thickness observed on ultrasound probably results from tamoxifen-induced changes in endometrial stroma and myometrium [45,46]. The sensitivity and specificity of TVS as a screening tool is therefore considerably reduced, and the ideal endometrial thickness cutoff for women on tamoxifen is not known [34]. Prompt investigation of abnormal vaginal bleeding rather than screening is probably the best option in this group[47,48]. There may be a role for pretreatment assessment of the endometrium before tamoxifen therapy, though this needs further investigation. Limited data suggest that women at risk for severe atypical hyperplasia can be identified on the basis of hyperplastic

lesions detected on endometrial biopsy before starting tamoxifen [49]. No development of atypical lesions has been reported on subsequent follow-up of lesions treated before tamoxifen therapy[50].

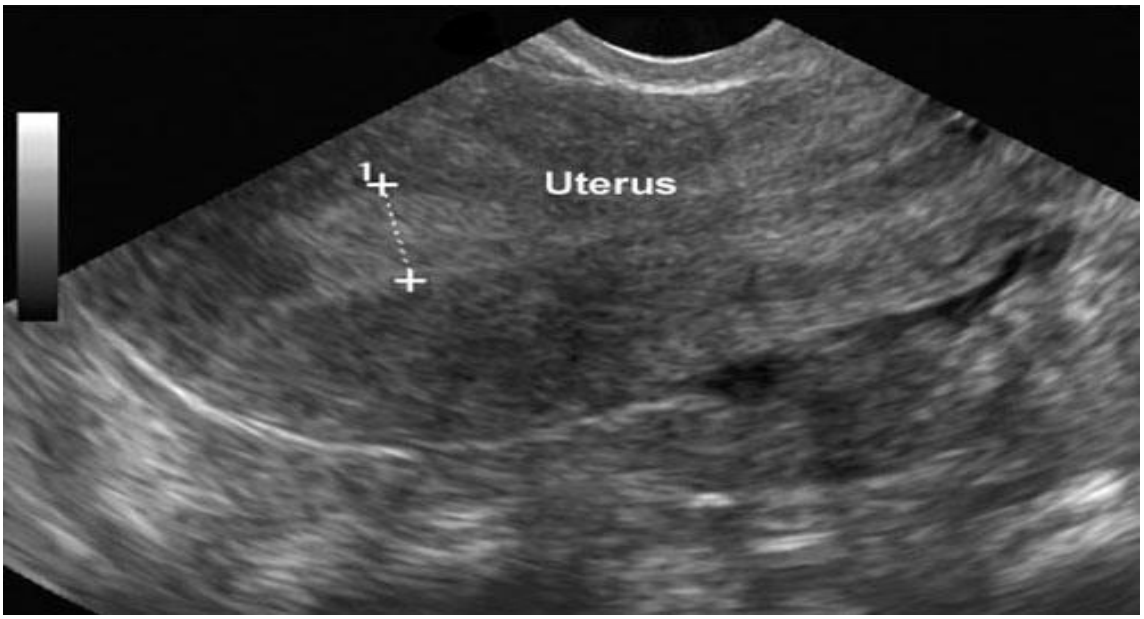

Figure (1): Measurement of uterine size and endometrial thickness by transvaginal ultrasound.

Cytological Markers:

Although the Papanicolaou stained cervical smear was designed to detect cervical cancers, it can detect the presence of malignancy in women with endometrial malignancy. The presence of normal as well as abnormal-looking endometrial cells in cervical smears in the second half of the menstrual cycle or in postmenopausal women should alert the clinician to the possibility of underlying endometrial disease. In a retrospective analysis, 13.5% of postmenopausal women with normal endometrial cells on routine smear, 23% of those with atypical cells, and 77% of those with suspicious cells had either endometrial hyperplasia or carcinoma [51].

The low sensitivity of cytology using conventional Pap smears that indirectly sample the endometrium can be improved by directly sampling the endometrial cavity using a variety of commercially available sampling devices. Although these techniques are simple

and have low risk and good yield, they are associated with technical difficulties because of cervical stenosis and varying degrees of patient discomfort. Their use in screening asymptomatic women is probably best limited to those with a positive result on first-line ultrasonic screening [52]. However, they have a low positive predictive value and a lower diagnostic accuracy than pipelle biopsy [53].

Molecular Markers :

Polymerase-chain-reaction-based technology has made possible the detection of mutations and other key events in small numbers of cancer cells scattered among large numbers of normal cells. Mutations in oncogenes and tumor suppressor genes have been used as molecular markers to detect endometrial carcinoma from cervical smears. K-ras mutations were found to be present as many as 5 months before the diagnosis of endometrial cancer. In addition to K-ras mutations, which may be present in 10% to 30% of tumors, mutations have also been found in p53 (20% cancers) and PTEN/MMACI genes (34% cancers) [54,55]. However, some of these may be late events in endometrial carcinogenesis and may not be suitable for screening. Telomerase is expressed by normal cycling endometrium [56] and preferentially expressed in most malignant tissues, including endometrial carcinoma [57,58]. It has been cited as a possible marker for endometrial hyperplasia and carcinoma in postmenopausal women because activity is normally absent or weak in postmenopausal atrophic endometrium [57,59].

Microsatellite instability (MSI) and immunohistochemistry are other molecular markers that may have potential in predicting the development of endometrial cancer in HNPCC-positive women[60,61]. MSI may occur in as many as 75% of HNPCC- and LS-related [62] and 33% of sporadic endometrial tumors [63]. DNA methylation has also been implicated in sporadic endometrial cancer and is the cause of MSI in these tumors [64]. Endometrial hyperplasia has been shown to demonstrate MSI and to precede endometrial cancer [61]. MSI was demonstrated in cases of endometrial cancer but not in women with normal endometrium in a pilot study [65].

Laboratory Testing:

Prolactin (PRL) is a 23 kD protein that has a dual function as a circulating hormone and as a cytokine. PRL is reportedly involved in more than 300 separate functions including development of the mammary gland, lactation, implantation and pregnancy, angiogenesis, and regulation of immune function[66]. PRL is secreted by the pituitary gland and by multiple non-pituitary sites including human ovarian follicular cells, decidualized stromal cells of the human endometrium, and normal peripheral blood lymphocytes [67]. The synthesis of extrapituitary PRL is driven by a different promoter than its pituitary counterpart[68] although the amino acid structure of pituitary and extrapituitary PRL appears to be identical [69].

PRL is asingle chain protein closely releated to growth hormone and is the strongest discriminative biomarker for endometrial carcer with high diagnostic poweor for early stage disease,although previous case reports suggested that PRL may be an endometrial tumor marker for recurrent disease[70].

Most of PRL comes from the pituitary gland,but some stromal cells of endometrium produce PRL during secretory phase,as well.significantly elevated levels of PRL in endometrial cancer could be due to increased PRL secretion by stromal cells in response to growth and differentiation.the main function of PRL is to control breast development and lacatation in women.however, PRL also act as a cytokine and play an important role in immune and inflammatorty responses[71,72]in addition, PRL can act as a circulating hormone and as a paracrine/autocrine factor to either stimulate or inhibit various stages of the formation and remodeling of new blood vessels[73,74]. The formation of new blood supply, angiogenesis, is an essential component of carcinogenesis and unrestricted tumor growth. therfore, increased level of serum can play an important role in growth and progression of endometrial and other cancer [75].

Measurement of a serum CA125 level. Preoperatively, an elevated titer indicates the possibility of more advanced disease. In practice, it is most useful in patients with advanced disease or serous subtypes to assist in monitoring response to therapy or during posttreatment surveillance. However, even in this setting, it has limited utility in the absence of other clinical findings. [76]

HE4 was demonstrated to provide 46% sensitivity for endometrioid adenocarcinoma of the endometrium in all stages at 95% specificity [77].

Imaging Studies:

In general, for women with a well-differentiated type I endometrioid tumor, chest radiograph is the only required preoperative imaging study. All other preoperative testing is directed toward general surgical preparation. Computed tomographic (CT) scanning or magnetic resonance imaging(MRI) usually is not necessary. However, MRI occasionally can help to distinguish an endometrial cancer with cervical extension from a primary endocervical adenocarcinoma. Moreover, women with serous features or other high-risk histology on preoperative biopsy and those with physical examination findings suggesting advanced disease are most appropriate for abdominal pelvic CT scanning. In these cases, advance knowledge of intra-abdominal disease may be helpful in guiding treatment [78] .

Pathology:

There is a broad spectrum of aggressiveness within the histopathologic types of endometrial cancer. Most patients have endometrioid adenocarcinomas that behave indolently. However, some will have an unfavorable histology that portends a much more aggressive tumor. In addition, the degree of tumor differentiation is an important predictor of disease spread. Tumors that arise following pelvic radiation differ from sporadic endometrial cancers by having a preponderance of high-stage, high-grade, and high-risk histologic subtypes. Effectively managing women with endometrial cancer requires an understanding of these interrelated clinical features (Tab.4)[79] .

Table(4): World Health Organization histologic classification of endometrial carcinoma.

A-Endometrioid adenocarcinoma
1- Variant with squamous differentiation
2- Villoglandular variant
3- Secretory variant
4- Ciliated cell variant
B-non endometrioid adenocarcinoma
1-Mucinous carcinoma
2-Serous carcinoma
3-Clear cell carcinoma
4-Squamous cell carcinoma
C-Mixed cell carcinoma
D-Undifferentiated carcinoma

Histologic Grade:

The most widely used grading system for endometrial carcinoma is the three-tiered International Federation of Gynecology and Obstetrics (FIGO) system. Grade One lesions typically have a good prognosis. Grade Two tumors have an intermediate prognosis. Grade Three cancers frequently have a poor prognosis and are associated with an increased potential for myometrial invasion and nodal metastasis (tab.5) [80] .

Table(5): Histopathologic criteria for assessing grade.

Grade	Definition
1	5% of a non squamous or non morular solid growth pattern
2	6–50% of a non squamous or non morular solid growth pattern
3	> 50% of a non squamous or non morular solid growth pattern

Histologic grading primarily should be determined microscopically by the tumor's architectural growth pattern. However, there are a few exceptions, and the optimal method for determining grade is somewhat controversial. Nuclear atypia that is inappropriately advanced relative to the architectural grade raises a grade one or two tumor by one level. For example, a grade two lesion based on architectural features may be increased to a grade three lesion if significant nuclear atypia is present. In an effort to improve the reproducibility and prognostic importance of the FIGO system, a binary architectural grading system has been proposed recently. The simplicity of dividing tumors into low- and high-grade lesions based on the proportion of solid growth (50 % or >50 %, respectively) is attractive and appears to have value. This approach, however, has not been implemented widely in clinical practice [(81)] .

Histologic Type:

Endometrioid Adenocarcinoma

The most common histologic type of endometrial cancer is endometrioid adenocarcinoma, accounting for more than 75 % of cases. This tumor characteristically contains glands that resemble those of the normal endometrium. The concomitant presence of hyperplastic endometrium typically correlates with a low-grade tumor and a lack of myometrial invasion. However, when the glandular component decreases and is replaced by solid nests and sheets of cells, the tumor is classified as a higher grade. In

addition, an atrophic endometrium is associated more frequently with high-grade lesions that are commonly metastatic. In addition to the characteristic appearance described, endometrioid adenocarcinomas may display variant forms. These include endometrioid adenocarcinoma with squamous differentiation and villoglandular, secretory, and ciliated cell variants. In general, the biologic behavior of these variant tumors reflects that of classic endometrial adenocarcinoma [82] . (fig.2)

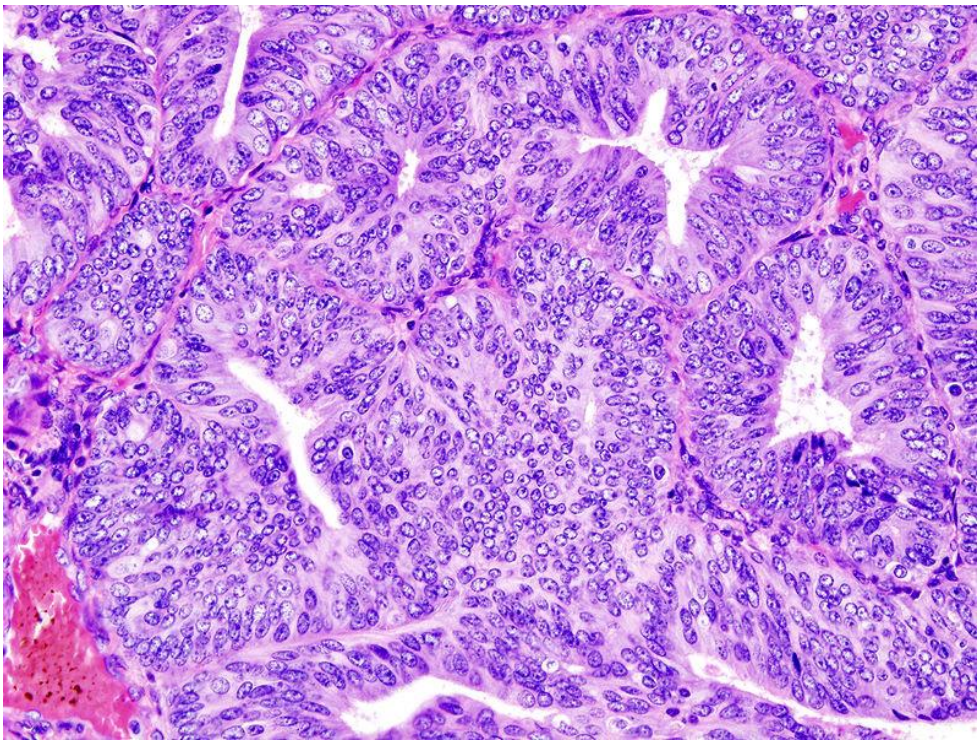

Figure (2): low grade Endometrioid adenocarcinoma by H&E stain.

Serous Carcinoma

Accounting for about 5 to 10 % of endometrial cancers, serous carcinoma typifies the highly aggressive type II tumors that arise from the atrophic endometrium of older women. There is typically a complex pattern of papillary growth with cells demonstrating marked nuclear atypia. Commonly referred to as uterine papillary serous carcinoma (UPSC), its histologic appearance resembles

epithelial ovarian cancer, and psammoma bodies are seen in 30 % of patients. Grossly, the tumor is exophytic with a papillary appearance emerging from a small, atrophic uterus. These tumors occasionally may be confined within a polyp and have no evidence for spread. However, UPSC has a known propensity for myometrial and lymphatic invasion. Intraperitoneal spread, such as omental caking, which is unusual for typical endometrioid adenocarcinoma, is also common even when myometrial invasion is minimal or absent. As a result, it may be impossible to distinguish UPSC from epithelial ovarian cancer during surgery. Similar to ovarian carcinoma, these tumors usually secrete CA125, and serial serum measurements are a useful marker to monitor the disease postoperatively. Uterine papillary serous carcinoma is an aggressive cell type, and women with mixed endometrial cancers containing as little as 25 % of UPSC have the same survival as those with pure serous carcinoma [83] . (fig.3)

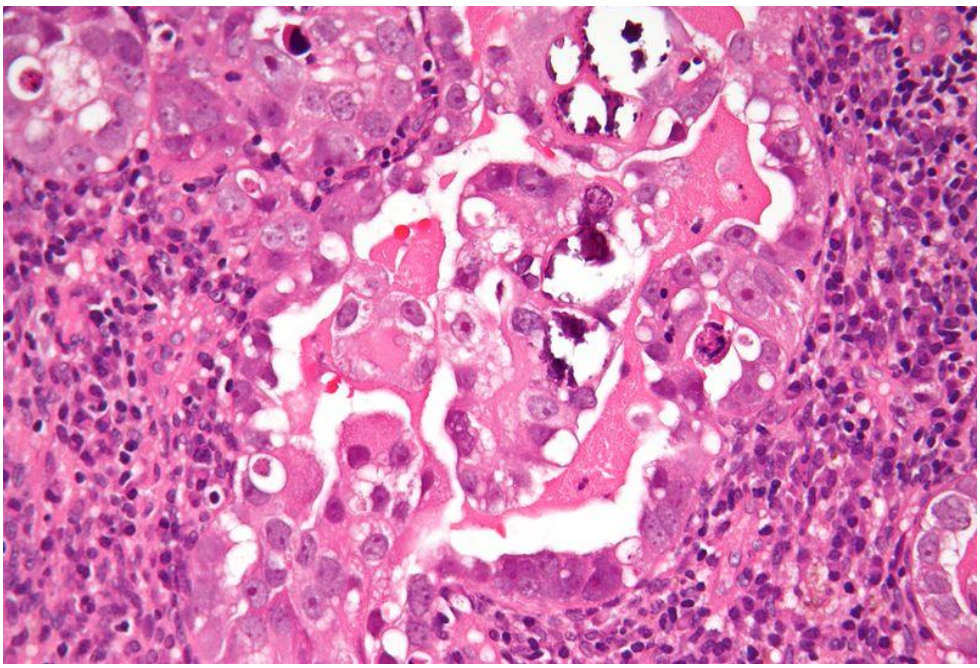

Figure (3): low grade endometrial serous carcinoma by H & E stain.

Clear Cell Carcinoma

Fewer than 5 % of endometrial cancers are clear cell variants, but this is the other major type II tumor. The microscopic appearance may be predominantly solid, cystic, tubular, or

papillary. Most frequently, it consists of a mixture of two or more of these patterns. Endometrial clear cell adenocarcinomas are similar to those arising in the ovary, vagina, and cervix. Grossly, there are no characteristic features, but like UPSC, they tend to be high-grade, deeply invasive tumors. Patients often are diagnosed with advanced disease and have a poor prognosis [84] . (fig.4)

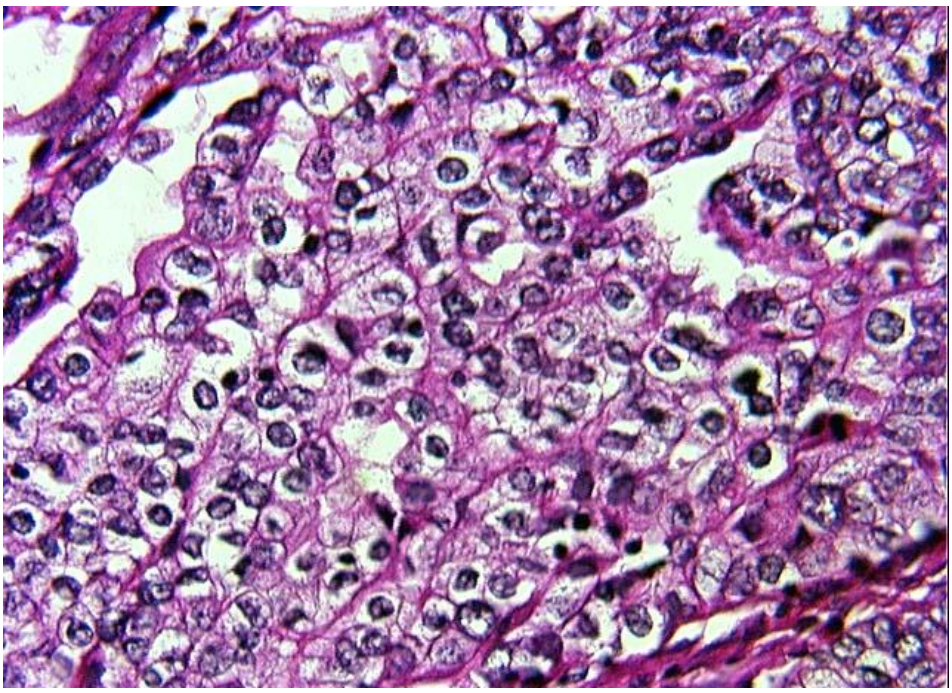

Figure (4): High grade Clear cell carcinoma of the endometrium by H&E stain.

Mucinous Carcinoma

About 1 to 2 % of endometrial cancers have a mucinous appearance that comprises more than half the tumor. However, many endometrioid adenocarcinomas will have a focal component.Typically,mucinous tumors have a glandular pattern with uniform columnar cells and minimal stratification.Almost all are stage I,grade 1, lesions with a good prognosis.Since endocervical epithelium merges with the lower uterine from a primary cervical adenocarcinoma.In this situation segment, the main diagnostic dilemma is differentiating this tumor, immuno-staining may be helpful, but preoperative MRI may be required to further clarify the most likely site of origin [85] . (fig.5)

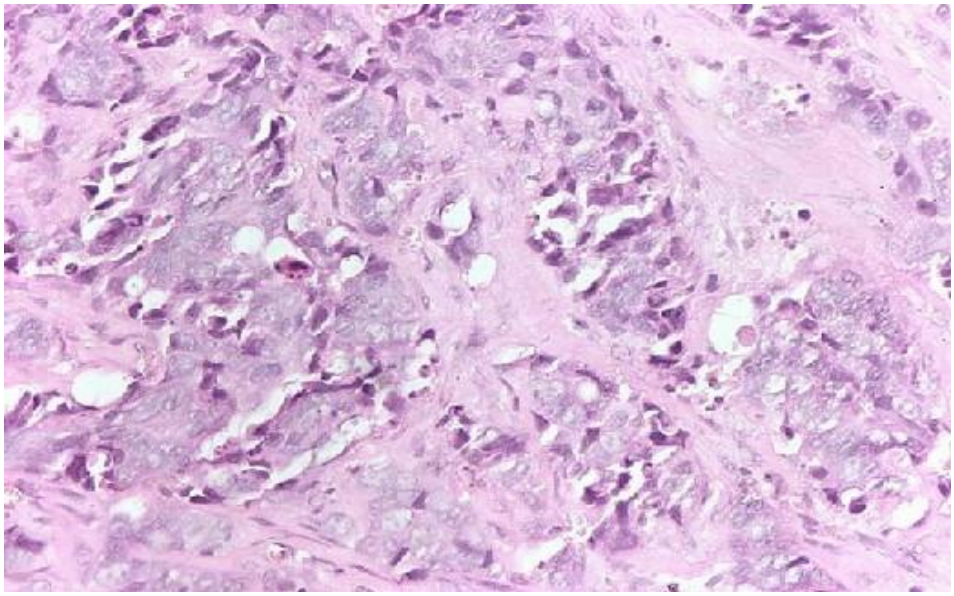

Figure (5): Mucinous carcinoma of the endometrium by H &E stain (grade 2).

Mixed Carcinoma

An endometrial cancer may demonstrate combinations of two or more pure types.To be classified as a mixed carcinoma, a component must comprise at least 10 % of the tumor. Except for serous and clear cell histology, the combination of other types usually has no clinical significance. As a result, mixed carcinoma usually refers to an admixture of a type I (endometrioid adenocarcinoma and its variants) and type II carcinoma[(86)] . (fig.6)

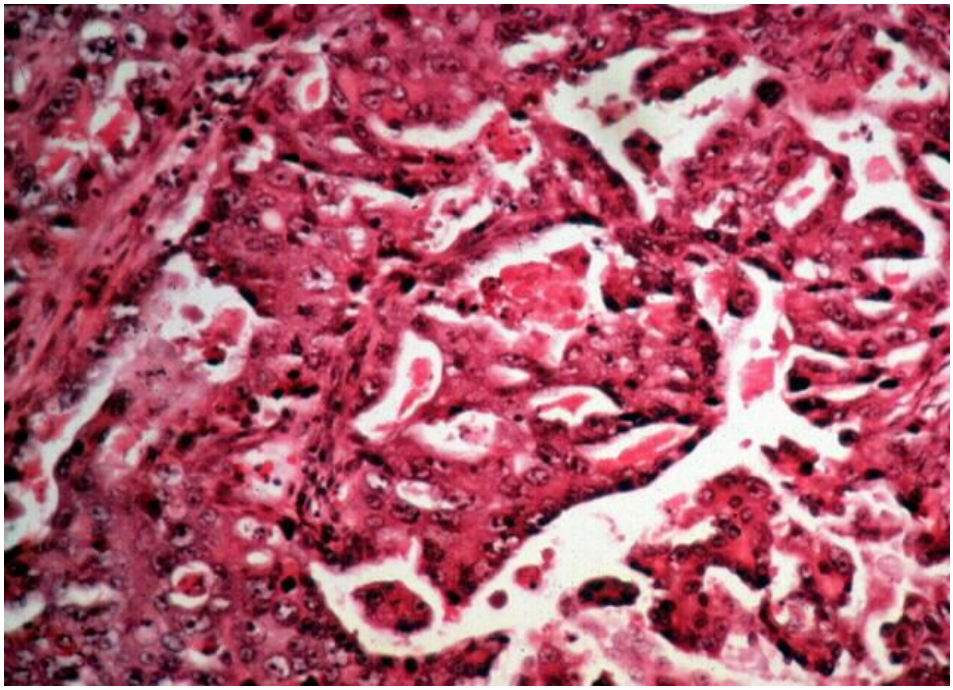

Figure (6): Mixed carcinoma of the endometrium by H &E stain (grade 2).

Undifferentiated Carcinoma

In 1 to 2 % of endometrial cancers,there is no evidence of glandular, sarcomatous,or squamous differentiation.These undifferentiated tumors are characterized by proliferation of medium-sized, monotonous epithelial cells growing in solid sheets with no specific pattern. Overall, the prognosis is worse than in women with poorly differentiated endometrioid adenocarcinomas[87] .

Rare Histologic Types

Fewer than 100 cases of squamous cell carcinoma of the endometrium have been reported. Diagnosis requires exclusion of an adenocarcinoma component and no connection with the squamous epithelium of the cervix. Typically, the prognosis is poor. Transitional cell carcinoma of the endometrium is also rare and metastatic disease from the bladder and ovary must be excluded during diagnosis [87] .

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