PATHOLOGY OF THE UTERUS

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PRESENTACION

El curso de Patología del Utero, que presentamos ahora en 6 horas, ha sido impartido anteriormente en la Escuela Europea de Patología de Turín, Italia (1994 y 2004) y de Cracovia, Polonia (2006) en formato de 3-4 días. Por tanto, el curso actual será completo pero no exhaustivo. Las conferencias serán cortas (20-35 minutos) y en ellas se presentarán mecanismos de enfermedad con los datos más relevantes de la genética molecular y, sobre todo, criterios diagnósticos, diagnósticos diferenciales mas importantes e impacto del diagnóstico en el tratamiento. La integración de los rasgos clínicos, macroscópicos, histológicos, inmunohistoquímicos y, si ha lugar, de las alteraciones genéticas, permitirá obtener en cada caso una instantánea fotográfica de la lesión o de la enfermedad. El curso será de utilidad para patólogos tanto en formación como postgraduados.

Prof. Jaime Prat
Director del Curso
Barcelona, Diciembre, 2006

PATOLOGIA DEL UTERO

Viernes 9 de Febrero, 2007

PROGRAMA DEL CURSO

1ª Parte: Moderador: Dr. Francesc Alameda

10:30 – 10:40	**Presentación** *Dr. Jaime Prat*
10:40 – 11:00	**El virus del papiloma humano (hPV) en la carcinogénesis cervical** *Dr. José Palacios*
11:00 – 11:20	**Lesiones precursoras del carcinoma escamoso cervical: colposcopía, histología y citología** *Dr. Silvestro Carinelli*
11:20 – 11:40	**Carcinoma escamoso microinvasivo** *Dr. Jaime Prat*
11:40 – 12:10	**Carcinoma escamoso invasivo: patología y factores pronósticos** *Dr. Xavier Matias-Guiu*
12:10 – 12:15	**Discusión**
12:15 – 12:45	**Adenocarcinoma in situ e invasivo: diagnóstico diferencial** *Dr. Jaime Prat*
12.45 – 13:05	**Lesiones no-neoplásicas del cervix** *Dra. Esther Oliva*
13:05 – 13:10	**Discusión**
13:10 – 13:30	**Patología endometrial disfuncional** *Dr. Silvestro Carinelli*
13:30 - 13:55	**Hiperplasia endometrial** *Dr. Xavier Matias-Guiu*
13:55 - 14:00	**Discusión**
14:00 – 16:00	**Almuerzo**

2ª Parte. Moderador: Dr. Xavier Matias-Guiu

16:00 – 16:10	**Adenocarcinoma de endometrio: clasificación y aspectos generales** *Dr. Jaime Prat*
16:10 - 16:30	**Adenocarcinoma de endometrio: Patologia molecular** *Dr. José Palacios*
16:30 - 16:55	**Adenocarcinoma de endometrio: Patologia y factores pronósticos** *Dr. Jaime Prat*
17:55 – 17:00	**Discusión**
17:00 – 17:30	**Café**
17:30 – 17:50	**Tumores del estroma endometrial** *Dra. Esther Oliva*
17:50 - 18:20	**Tumores del músculo liso** *Dr. Jaime Prat*
18:20 - 18:40	**Tumores mixtos** *Dra. Esther Oliva*
18:40 – 19:00	**Lesiones misceláneas del útero** *Dr. Silvestro Carinelli*
19:00 - 19:15	**Discusión y conclusiones**

PRECANCEROUS SQUAMOUS LESIONS OF THE CERVIX

Silvestro G. Carinelli, M.D.

GENERAL FEATURES

Both cervical cancer and its precursors have been studied at different levels following the development of pathogenetic theories and diagnostic methods; consequently, different treatment strategies have been applied to patients over the last century.

The concept of cervical cancer precursor dates back to the end of the 19th century. Noninvasive lesions adjacent to and resembling invasive cancer were first noted by Williams in 1888 (1) and defined by Cullen in 1900 (2). At that time, they were interpreted as the source of invasive carcinoma and in 1908 Schauenstein (3) expressed the opinion that the designation "carcinoma" was appropriate. The term "carcinoma in situ", firstly suggested by Schottlander and Kermauner (4), was introduced by Broders in 1932 (5) and subsequently widely accepted.

Following Schiller's (6,7) statement that cervical cancer can be diagnosed histologically in its preinvasive form, several retrospective studies demonstrated that invasive carcinoma develops from precancerous lesions including carcinoma in situ and less atypical changes designated as dysplasia (8). The application of these concepts to the cells exfoliated from the cervix (9-11) opened the possibility to detect the cervical precancer in the population, resulting in a progressive segregation of early steps of cancerization (12). The Papanicolaou (Pap) cervico-vaginal smear became the most successful cancer prevention screening technique available today and demonstrated that screening can theoretically eradicate cancer (13-15).

Unlike most invasive carcinomas, precancerous anomalies of the cervical mucosa may become visible on clinical examination only after magnification. The colposcope, a microscope which allows the ectocervix to be viewed at 6 to 40-fold magnification, was developed by Hinselmann (16) in the 1920s as an alternative diagnostic method to the extensive application of cervical biopsy (17). It rapidly gained popularity in Europe and after some decades also in North America. Proximally to the original squamo-columnar junction the endocervical epithelium undergoes metaplastic changes and the area where these changes occur is designated "transformation zone". When the epithelium of the transformation zone becomes atypical, it may be recognized as such and the abnormalities can be classified and accurately biopsied or excised. However, in some cases the transformation zone is not everted or not fully visible, limiting the efficacy of colposcopy as a screening method. Colposcopy still remains the most useful tool for the study of the dynamic changes occurring in cervix and for conservative treatment of cervical precancer (18).

The existence of a transmissible etiologic agent involved in the development of cervical cancer has long been suspected. Among others, Rigoni Stern (19), an Italian physician, reported in the mid 19th century that cervical cancer was more frequent in married women and widows than in unmarried women including nuns. Following the application of newer molecular technologies, a close relationship between certain types of human papillomavirus (hPV) and cervical cancer was demonstrated (20,21). Since hPV is now considered the most important etiologic agent (21), hPV DNA detection has been introduced in clinical practice and vaccination against hPV epitopes is currently in the early stages of experimental clinical application (22,23). Moreover, within the last few years the sequence of molecular events occurring from infection to neoplastic transformation became progressively clear allowing the application of molecular tests for diagnostic strategies.

Currently, the strategies for detection and treatment of cervical precancer are well established and mortality for cervical cancer has been dramatically reduced in Western countries. However, some problems still remain on the ground, particularly for rare types of cervical cancer including adenocarcinoma. Unlike squamous cell carcinomas, adenocarcinomas are not easily detected by screening and although a relationship between adenocarcinoma and hPV has been demonstrated in most cases, the pathogenesis of adenocarcinoma in situ and its progression are less clear than those of squamous cell carcinoma. Presently, the model under study still remains as squamous cell precancer.

COLPOSCOPIC FEATURES

Early squamous cancerization typically occurs in the transformation zone (TZ), the endocervical mucosa cranial to the original squamo-columnar junction (OSCJ), where metaplastic (squamous) changes occur (18,24-25). After puberty, and usually after delivery, the TZ may be everted on the portio vaginalis (ectropion), more frequently and more extensively on the anterior lip, but extension varies upon time; rarely, the ectropion can be congenital or detected in young nulliparous women and in some cases the OSCJ extends as lower as the fornix and even the upper vaginal wall ("DES-like lesions"). After the menopause, the OSCJ tends to return around the external cervical orifice (ECO) and in rare cases may enter into the cervical canal (entropion).

TZ seems to be more susceptible to injuries than the vaginal lining epithelium and undergoes changes ranging from reparative to inflammatory and neoplastic (18, 24-25). The development of atypical changes in the epithelium and superficial stroma can be detected and classified as atypical transformation zone (ATZ). Like physiologic squamous metaplasia or TZ, precancerous lesions or ATZs expand superficially and cranially from the OSCJ; they may also enter the mucosa of the endocervical canal and, rarely, in late postmenopause reach the endometrium and even the endosalpinx. The precancerous lesions may also involve the endocervical crypts. Width of the ATZ and crypt involvement are directly proportional to increasing severity of dysplasia.

HISTOLOGIC FEATURES

The histologic features of squamous precancer represent a diagnostic continuum characterized by varying degrees of altered maturation, nuclear atypia, and mitotic activity of the squamous epithelium of the TZ which were thought to represent different steps of the neoplastic process (18, 24). According to current histologic terminology, there are 3 grades of severity for squamous precancer, including mild, moderate, and severe dysplasia-carcinoma in situ or CIN 1 to 3 (24-27). In the 1994 WHO Classification (26), the extent of dysplasia was the major diagnostic criterion, with the grade paralleling the thirds of squamous epithelium involved, while in the recent 2003 edition (27) the degree of maturation was considered more appropriate. Atypical features of basal reserve cells or immature squamous metaplasia also are designated CIN, but grade cannot be assessed.

Severity in a single lesion is frequently heterogeneous (28) and classification may be difficult, particularly at the ends of the spectrum. Late in the 60s, distinction between severe dysplasia and carcinoma in situ was not considered reproducible and a single unifying category, CIN3, is uniformly accepted (24-27). Moreover, high-grade CINs are better differentiated on the portio than along the canal and within the crypts, precluding the application of a subclassification in keratinizing, non keratinizing, and small cell types similar to that of invasive cancer (25).

In the late 50s, the typical mild changes of condyloma acuminatum were found to be cytologically and histologically indistinguishable from those of flat lesions, previously considered low-grade dysplasia and confusingly referred as "flat condylomas" (29,30). Such changes, occurring in mature

keratinocytes of the upper half of the squamous epithelium, consisted of enlarged, hyperchromatic, wrinkled nuclei, clear perinuclear haloes, thick cell membranes, and frequent multinucleation. They were defined as koilocytosis or koilocytic atypia and are still classified as descriptive (non diagnostic) terms in CIN1 (26,27).

The Bethesda System (TBS) for cervico-vaginal cytology introduced the term "lesion" (squamous intraepithelial lesion, SIL) with two grades, low-grade SIL (LSIL) and high-grade SIL (HSIL), grouping together CIN 2 and CIN 3 (31). A similar approach was previously suggested for histologic CIN (LCIN and HCIN) (32), but was never universally adopted. The other TBS designation, atypical squamous cells of undetermined significance (ASCUS) has no counterpart in the histologic classification. Using a binary system, efforts (29,30) were renewed to maintain two separate categories, condylomas and cancer precursors, emphasizing koilocytosis (33) or shifting well differentiated lesions with atypia and atypical mitoses in the lower third of the epithelium from CIN 1 to CIN2 (34) without consistent results.

Although stimulating, the various shifts in nomenclature over the last 50 years neither improved diagnostic accuracy nor patient management, and caused duplication of terminologies used in additive fashion. Moreover, the proposed systems have been criticized on the basis of high intra- and inter-observer variability (35-37); as expected in a system with reduced choices, reproducibility is increased and higher degree of concordance obtained (36-37), but the information derived from borderline cases is lost.

CYTOLOGIC FEATURES

Although originally devised as a class system of risk of cervical cancer (12) the Pap test became a classification system paralleling the histologic classification of dysplasia-carcinoma in situ or CIN (15). Following the public critique of poor cervical cytology practice in the United States (15,38) a workshop was held in Bethesda in 1988 for the standardization of the procedures and reporting of the results, known as The Bethesda System (TBS) for cervico-vaginal cytology (31). The proposal included rules for a judgement of adequacy, guidelines for reporting, and a new cytologic classification which introduced the new term "lesion". Squamous intraepithelial lesions (SIL) has two grades, low grade SIL (LSIL) and high grade SIL (HSIL).

On smears, dysplastic squamous cells exhibit varying degrees of differentiation (39). Superficial or intermediate cells with uniform chromatin and small chromocenters correspond to mild dysplasia or CIN 1. Parabasal and small intermediate cells with dense chromatin and enlarged chromocenters correspond to severe dysplasia (CIN 3); the finding of high degree of (squamous) differentiation in cells with pronounced nuclear and cytoplasmatic abnormalities also warrant the designation of carcinoma in situ (CIN 3). Traditionally, moderate dysplasia has been a diagnosis of exclusion (39).

In TBS, LSIL includes the cellular changes of CIN1 and koilocytotic atypia; besides traditional criteria, such as high degree of cell maturity and mild degree of atypia, increased nuclear/cytoplasmic ratio was defined as the nuclear enlargement at least 3 times the area of normal intermediate nuclei. Features previously defined as moderate, severe dysplasia, and CIS, or CIN 2-3, were included in the HSIL. Cell size is usually smaller in HSIL than in LSIL; in some cases, nuclear size is in the range of LSIL, but the nuclear/cytoplasmic ratio is increased. Cells exfoliated from mature CIN3 may show nuclear enlargement less than LSIL, but they exhibit prominent atypia and cytoplasmic keratinization; cells from immature CIN3 are usually arranged singly or in syncytial aggregates. Guidelines for practical application of TBS are available on the Web (40).

TBS also explored the area of so-called "borderline" Paps. Cells showing cellular pleomorphism, or increased nuclear size, or hyperchromasia, but not fully expressed as in SIL were classified in the

new category of ASCUS, which was further divided into ASC-US (undetermined significance) and ASC-H (cannot exclude HSIL). Q-probe assurance measures to close monitor the ASC: SIL ratio and the rate of the SIL positivity in ASCUS cases are essential to validate the appropriate use of this category. Besides all the confusion and managing problems, both for pathologists and gynecologists, derived from the introduction of the new concept and terminology, ASCUS further emphasized the limits of Pap test resulting from sampling and interpretation (41). Although serious considerations were given to abolish it, the ASC terminology remains practical for cytologists. The diagnosis of "LSIL, cannot exclude HSIL" is an example of this philosophy (42).

Athough, the Pap test, was originally devised as an inexpensive, widely accessible, and somewhat imprecise test, over the last 50 years, achieved a stronger diagnostic component and became a feature of medical consultation. However, the goal of every laboratory, i.e., a satisfactory performance is difficult to achieve because of its complexity (15). There are at least 2 major causes for poor performance: sampling and screening. The sampling and collection techniques are crucial, as the result of optimal screening is dependent from the extent of the number of cells and in particular of the atypical cells present on the smear (43,44). Moreover, given an optimal smear there is no way to prevent screening errors. The tools commonly employed for quality assurance, such as the 5-year look back and review of at least 10% of negative smears, do not reflect the actual sensitivity of screening, as they allow only a small fraction of errors to be detected (45).

Liquid-based thin-layer preparations are among the most promising innovations in cytology. Results of several clinical trials have demonstrated that interpretation is more accurate and is associated with less screening errors than interpretation with conventional smears; however, even after training some difficulty may exist in recognizing the target cells, particularly in the HSIL-carcinoma spectrum (46). Another advantage of liquid-based thin-layer preparation is the application of automation which is thought to allow rapid pre-screening and automated screening with a reduction of overall errors (45-47).

In spite of advances, cytology has important limitations. One is reproducibility, particularly in the lower spectrum of atypicality (48), just like histology. The most important limitation, however, is the inherent false-negative rate as the Pap test is highly effective in a population with regular screening, but it is an imperfect test and many laboratories now include a disclaimer-like educational note regarding limitations in the report (49).

MOLECULAR AND IMMUNOHISTOCHEMICAL DATA

Over the last three decades, several epidemiologic studies have clearly demonstrated that almost all cervical cancers are associated with hPV (21). Among the mucosal or genital hPVs, some types, particularly types 6 and 11, are associated with genital condylomas and are designated low-risk hPVs (LRhPV). The 15 known types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) which are associated with carcinoma and severe precursor lesions are designated high-risk hPVs (HRhPV); the types 16 and 18 are considered the prototypes of the group as they have been responsible for about 70% of cervical cancers worldwide with a higher prevalence of type 16 (50%). Those hPVs designated of intermediate risk (types 26, 53, and 66) are frequently included in the latter category (50,51).

While hPV emerged as the etiologic agent of precursor lesions, early studies suggested a causal relationship between LRhPV and LCIN and HRhPV and HCIN; however, comparison of CINs with hPV typing did not demonstrate any constant correlation between histologic features and hPV type (52). Recent studies have shown a predominance of HRhPVs in all grades of CIN, particularly LCIN, mostly in the episomal form, indicating that low grade lesions caused by HRhPV may regress. Unlike lesions produced by LRhPVs, those associared with HRhPVs when persistent may

eventually progress to more severe forms (50,53). Progression occurs when HRhPV becomes integrated in the host cell and this transformation is particularly frequent for hPV16 (53).

Integration of even a few copies of HRhPV in the DNA of the host cell is followed by loss of transcription of most viral genes with the exception of those genes which have transforming and immortalizing properties on the host cells, namely E6 and E7. E5, another viral gene, is probably involved in the early phase, but is no longer expressed when the process of integration is completed. The effect of E6 and E7 is synergistic, as E7 promotes uncontrolled cell proliferatin and E6 inhibits apoptosis resulting in segregation of an immortalized cell clone. The different levels of association with cancer shown by different types of hPV result from the binding potential of the oncoproteins encoded by E6 and E7 hPV genes to the host regulatory proteins (54). The E6 and E7 genes of the LRHPVs (HPV 6-11) are not able to deregulate significantly the cell cycle.

E6 oncoprotein is involved in the degradation of p53 tumor suppressor gene product, which regulates apoptosis. E6 is the ligand of numerous regulatory transcription factors, including CBP/p300 with consequent inhibition of p53 activity and E6AP (associated protein) which mediates p53 destruction, and other still unclear factors. E6AP is a ligand of ubiquitin (E3) and the E6-E6AP complex takes the p53 (ubiquitinization) to the proteasomes for its degradation. Loss of the p53 apoptotic activity results in genomic instability.

E7 oncoprotein (phosphoprotein) inactivates the hypophosphorylated pRB tumor suppressor gene product which acts at the restriction point of the cell cycle controlling the correct G1/S transition. The pRb-E2F complex is the regulator of the G1 phase of the cell cycle; normally, under mitogenic stimulation, phosphorylation by the cyclin D-Cdk4/6 dissociates (inactivates) the complex with release of E2F a (family of) transcription factor which activates the G1/S–phase progression. E2F also leads to production of the cyclin kinase inhibitors (CKI) that decelerates the cell cycle by inactivating the cyclin-dependant kinases (CDKs) that phosphorylates pRb (55,56). hPV16-E7 oncoprotein also binds (inactivates) pRb tumor suppressor gene which becomes independent by the mutagenic and antimutagenic factors and the free E2F is constantly active (uncontrolled mutagenic effect).

Experimental studies have shown that p16, a CKI that decelerates the cell cycle by inactivating the CDKs (D1,2,3-CDK4 and 6 complexes), is strongly upregulated by E7 of hPV16 and other HRHPVs (56,57). In normal cells, the increase of p16 is followed by an increase of pRB and consequent cell cycle arrest. In infected cells, with uncontrolled proliferation, the high cell levels of p16 represent a defense mechanism without results. Although the association with the entire spectrum of high risk hPV types has not been fully demonstrated, p16 is immunohistochemically positive in almost all HCINs (57-60), endocervical type adenocarcinomas and small cell carcinomas.

Activation of factors deregulating the cell cycle favors the production of mitogens such as Ki-67, Cyclin E (61,62), topoisomerase II alpha, and others. The biomarkers associated with abnormal expression of the proteins involved in the cell cycle regulatory mechanisms, such as Ki-67, Cyclin E and p16, may be useful to resolution of the clinical problems identifying precancerous lesions and distinguish them from non neoplastic alterations on biopsy material. Ki-67 staining in the upper two thirds of the squamous epithelium is a strong indicator of HSIL and is useful for the differential diagnosis with atrophy (63). Cyclin E expression is also upregulated in CINs but, similarly to Ki-67 its expression varies in low-grade lesions. Unlike Ki-67 and Cyclin E, which may be positive in either LCIN and HCIN, inflammatory cells and proliferating cells in general, p16 has emerged as one of the most promising immunohistochemical biomarkers for the diagnosis of CINs associated with high-risk hPV types. Available data indicate that when positive, p16 is a strong indicator of HSIL (58-60) and the overall reproducibility of grading is by far better than that on conventional

stained H&E slides (59). Moreover, P16 is a powerful tool for differential diagnosis between HSIL and its imitators, particularly immature squamous metaplasia and atrophy in histologic and eventually in cytologic material (64).

hPV TYPING

While of limited value on histologic material (65), hPV detection and typing, has recently been shown to be a sensitive tool in the triage of abnormal Paps and screening of cervical precancer on swabs. It has long been known that reduction in cervical cancer incidence results from programmed Pap test programs including repetition of the test at regular intervals, ranging from every year or every few years in women with a history of normal Paps. However, in spite of the success of extensive cytology-based screening programs, the sensitivity of Pap test is in the order of 50% to 60% and many women still develop cervical cancer (66). The rationale for the use of the adjunctive hPV DNA testing is based on the accepted concept of causality and the high sensitivity of the new tests.

Polymerase chain reaction (PCR) is the most sensitive method for the detection of hPV DNA and has almost replaced all the previous methods used in research. Unlike PCR, which is not FDA approved, Hybrid Capture (HC) has become the most popular commercial hPV DNA test for routine clinical use. Sensitivity is higher than conventional cytology as well as than liquid based cytology, whereas, as expected, specificity and positive predictive value are lower since HRhPV DNA is an indicator of risk for HSIL (or worse), but not the equivalent for it. Obviously, combination of both tests was more sensitive than either test alone, detecting almost 100% of HSIL, with a further reduction of the overall specificity. The three major uses of hPV detection include: a) triage of women with borderline cytological findings, ASCUS and LSIL); b) follow-up of women after treatment; and c) screening programs in conjunction with Pap test.

Several studies conducted for ASC-US triage have formally validated hPV DNA testing demonstrating that it is highly sensitive and specific for detecting HCIN or HSIL and, with few exceptions, better than repeated Pap test. In The ASCUS LSIL Triage Study (ALTS) (67-69), which is the only randomized controlled trial to understand the application of hPV DNA test, sensitivity was 96.3%, specificity 49% for HPV DNA testing while the corresponding values for Thin Prep liquid based cytology were 85.3% and 45%. A meta-analysis extracted from articles published between 1992 and 2002 (70) also showed an improved accuracy (higher sensitivity, similar specificity) of hPV DNA testing than repeated Pap smear using the threshold of ASCUS for an outcome of CIN 2/3 among women with “borderline” cytologic results. The sensitivity of triage at higher cytologic cutoffs was poorer.

All the studies using hPV DNA testing as a marker for cure (70) were too small and not homogeneous in design; particularly, performance data regarding Pap test were not included in all the studies. Cumulative data indicate sensitivity for CIN 2/3 post treatment as 96.5% and specificity as 77.3%. Moreover, there is an increasing interest for hPV testing as a screening method alone or together with Pap test (71-72). In spite of these promising results, a major problem of hPV typing is cost. For such reason, some limitations to its universal use have been proposed. Unlike women older than 30-35 years who may really benefit from hPV testing, a still unresolved issue is the utility of HPV typing in the young age group in which hPV infection is dramatically high. Moreover, considering the relatively low reproducibility of ASCUS and LSIL on cytologic smears, more stringent criteria should be used for ASCUS in order to select only those equivocal for hSIL (73) and other markers such as p16 are under study as screening test (74).

CLINICAL FEATURES

From the clinician's viewpoint, cytology is just one method to arrive at a cross road where colposcopy and histopathology are complementary for the optimal diagnosis and management of CIN (27). When follow-up was not the choice, numerous destructive or excisional procedures have been used for conservative treatment, from cryotherapy and diathermy to cold knife conization, depending upon the clinical findings, grade and extent of the lesion, involvement of the crypts and extension into the cervical canal, without significant differences in success or morbility (18). More recently, laser vaporization and loop excision (the loop electro-surgical excision procedure or LEEP) have become standard in developed countries; it is easy and practical and allows the possibility of "see and treat".

There is strong evidence that CIN3 should be treated and, consequently, data regarding progression and persistence are obviously artifactual. In a group of 65 women with CIS (CIN3), inadequate treatment was followed by invasive carcinoma in 22% of cases, and persistent CIN in 69% in a period of 1 to 19 (mean 6) years (75); there is no reason to repeat such an unfortunate experience. Among women with lower degree of dysplasia or CIN the option of watching and waiting is ethically justifiable and is a common practice. Some studies have shown that there is a decrease in regression, paralleled by an increase in persistence and progression from lower atypia (CIN 1) to higher atypia (CIN 2 and 3) (76,78). Clinically, however, the main issue continues to be the best system for selecting patients who need treatment from those who may benefit from simple follow-up; although less important from a cancer prevention standpoint, under- or overdiagnosis of a biopsy may cause unnecessary discomfort and/or emotional trauma to the patient.

Until recently the most popular way for making this selection was morphology (cytology and histology). All the proposed classifications and terminologies apply to artificial categories on a spectrum of changes, or so-called "continuum", with no obvious lines of demarcation, and grading of CIN remains dependant on the application of subjectively applied criteria. Some biomarkers associated with abnormal expression of the proteins involved in the cell cycle regulatory mechanisms such as Ki-67, Cyclin E, and p16 may be useful to resolve these problems.

HPV is the most common sexually transmitted viral infection occurring in about 70% of women and HRhPVs are the most frequent types. The distribution of hPV types found in women from different countries is quite heterogeneous and there are at least 5 phylogenetic lines known as European (E), Asiatic (A), Asiatic-American (AA), African, and North American (NA); moreover, there are subclasses and the importance of all these differences is still unclear. In most of the infected women clinical manifestations are not detected and the virus is cleared in about 6 months to one year. In a relatively small number of cases LCIN develops, but not all of them progress while the immune system is efficient.

There is wide agreement that hPV infection alone is not sufficient for the development of cancer and persistence of infection for a certain period of time (5 to 20 years) is required for accumulation of progressive genetic defects escaping the control mechanisms which allow immortalization and cancerization of neoplastic clones. Molecular data parallel the clinical observations that long-term persistent infection is required for progression. Factors possibly affecting persistence include HLA class I antigens, HLA class II haplotypes polymorphism in certain genes, viral variants, loss of heterozygosity, and events compromising the immune system, such as HIV infection, and other clinical cofactors.

Age is the greatest determinant of clearance of hPV, which is maximum in the first three decades, and infection in young women is notoriously transient in spite of its frequency. In this regard,

clearance is also more frequent and shorter for LRhPV than hPV16, but the explanation for persistence of the infection is unknown.

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MICROINVASIVE CARCINOMA OF CERVIX

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Invasive carcinoma

According to the 2003 World Health Organization (WHO) classification, carcinomas of the cervix are separated into 3 general categories: a) squamous cell carcinoma (60-80%); b) adenocarcinoma (15-20%); and c) "other" epithelial tumors.

The most universally accepted staging system for tumors of the cervix is that of the International Federation of Obstetricians and Gynecologists (FIGO) (1994), which divides invasive carcinomas into 4 stages. Stage I includes all tumors confined to the cervix and is divided into 2 categories:

IA: Carcinomas that invade 5 mm or less into the stroma and are macroscopically not visible.
IB: Carcinomas that either invade more than 5 mm or are macroscopically visible.

Microinvasive carcinoma

Microinvasive carcinoma (MIC) (Mestwerdt, 1847) is a small cancer that has invaded the cervical stroma to a limited extent. It is considered a preclinical stage in the progressive spectrum from CIN/SIL to invasive carcinoma. However, the most appropriate definition of MIC remains controversial. The main points of contention are: a) maximum depth of stromal invasion; and b) significance of vascular invasion, tumor volume, and confluency of tumor epithelium, as related to the frequency of lymph node metastasis, recurrence, and survival. Most patients who die of disease have either tumors that invade more than 5 mm into the cervical stroma (>2.5 cm^3 in volume) or vascular invasion. Thus, FIGO has defined stage IA tumors as those invading to a depth of 5 mm or less taken from the base of the epithelium (surface or glandular) from which it originates. A second dimension, the horizontal spread, must not exceed 7 mm.

Stage IA tumors are further subdivided into 2 subcategories:

IA1: Carcinomas that invade 3 mm or less into the cervical stroma.
IA2: Carcinomas that invade more than 3 mm, but no more than 5 mm into the stroma.

In the United States, the Society of Gynecological Oncologists (SGO) (1974) has proposed a more restricted definition of MIC. According to SGO, MICs are tumors invading to a depth of 3 mm or less below the basement membrane and without evidence of vascular invasion. Such tumors have virtually no potential for either metastasis or recurrence. Because the tumor cannot be visualized on gross inspection, the diagnosis of MIC should be based on microscopic examination of at least a cone biopsy that includes the entire lesion and shows free surgical margins.

Clinical Features

Most MICs occur in women 35-46 years of age. The frequency of MIC in patients with SIL varies from less than 1% to more than 50%, which reflects differences in definitions and methods. Serial sections of specimens (cold knife cones) with SIL (usually high-grade) have revealed a 4% prevalence of MIC. The prevalence of MIC in a population-based registry (British Columbia, Canada) was estimated to be 4.8 per 100,000 women screened. In this same registry, the prevalence of carcinoma in situ was 316 per 100,000 women screened.

Most patients with MIC are asymptomatic and the tumors are discovered on routine cervical smears. Grossly, the cervix may appear normal or exhibits nonspecific findings; i.e., cervicitis or erosion. The diagnosis of MIC is made on a conization or hysterectomy specimen. Recent cytologic studies have failed to accurately predict the presence of MIC (only 27.3% prediction rate).

Colposcopically, MIC is characterized by dense acetowhitening (like high-grade SIL) and may show one or more foci of abnormal surface braching vessels. MIC cannot be accurately detected by colposcopy when the tumor invades less than 1mm into the cervical stroma. Therefore, most colposcopists treat high-grade SIL by excisional methods such as loop electrosurgical excision procedure (LEEP). Diagnosis of MIC requires conization in order to rule out more advanced disease.

Pathology

The cone is completely and serially sampled for microscopic examination and the pathologist evaluates the surgical margins, depth of stromal invasion, greatest horizontal extent of the tumor, and whether vascular invasion is present.

The earliest invasive changes ("early stromal invasion", ESI) have the appearance of tiny irregular tongues of neoplastic epithelial cells projecting through the basement membrane into the cervical stroma, usually beneath an area of carcinoma in situ. The cells at the interface between infiltrating epithelium and stroma appear more differentiated, have abundant cytoplasm, and are often degenerated. Small foci of keratinization are seen within the microinvasive foci. The adjacent stroma is infiltrated by lymphocytes and plasma cells and, usually, there is a desmoplastic response. The irregular contour of the invading nests is the most reliable criterion for the diagnosis of MIC. No regional lymph node metastases or deaths from ESI have been reliably documented.

The incorporation of ESI (formerly stage IA1) - a very low-risk (0.2%) subcategory easy to recognize microscopically as epithelial "tongues" (? 0.5 mm) arising from the base of CIN III - into the new stage IA1, has resulted in a loss of prognostic precision; not surprisingly, about 80% of the cases redefined as stage IA1 correspond to ESIs. Furthermore, after excluding ESIs from the current IA1 subcategory, the death-risk for patients with stage IA1 (1-3 mm) and IA2 (3-5 mm) tumors is about the same (1.2% vs 1.7%).

Lymphatic-space invasion is characterized by endothelial-lined spaces containing tumor cells. Identification of vascular invasion may be difficult and is often hampered by technical artifacts. Immunostaining of endothelial cells using antibodies against factor VIII or with *Ulex* may be helpful.

The depth of neoplastic projections should be measured from the initial site of invasion, either from the basal lamina of the surface epithelium or from endocervical glands replaced by SIL. In some cases, however, a direct histologic continuity between the invasive foci and SIL cannot be demonstrated. In such cases, it is assumed that invasion originated from the basal cells of the overlying SIL. The most accurate method to measure the depth of stromal invasion is with a calibrated slide or ocular micrometer.

Although immunostaining against basement membrane constituents such as laminin or type IV collagen have been used for enhancing the recognition of early stromal invasion, normal cervical epithelium and SIL lacking microinvasion frequently exhibit basement membrane disruptions particularly in areas with severe inflammation. Thus, IHC appears to be of limited value.

Differential diagnosis

MIC is frequently overdiagnosed. Of a series of 265 cases submitted to SGO, 132 (50%) were rejected. Recently biopsed conization specimens showing nests of neoplastic epithelium buried within the cervical stroma are very often misinterpreted as exhibiting microinvasion. Both SIL and immature squamous metaplasia with extensive gland involvement should also be distinguished from MIC.

Risk factors

Factors that increase the individual risk for lymph node metastases, recurrence, and death are:

1. Depth of stromal invasion (1 to 5 mm).
2. Vascular invasion.
3. Tumor volume
4. Status of resection margins.

1. Depth of stromal invasion (major factor)

Invasion 1 mm or less: No residual carcinoma found at hysterectomy
Invasion 3 mm or more: Residual carcinoma usually detected

Depth of stromal invasion is related to the presence of lymph node metastases.
3 mm or less: Uncommon (<1%)
3.1-5 mm: 5.8%
6-10 mm (stage IB): 15.8%
11-15 (stage IB): 23.5%

Depth of stromal invasion is related to recurrence.
1 mm or less: Infrequent
3 mm or less: 1% recurrence
3.1-5 mm: 5%

Confluency of neoplastic epithelium does not influence clinical outcome

2. Vascular invasion

Its prognostic value is less clear than that of depth of invasion. Vascular invasion occurs in 0-8% of carcinomas invading <1mm and in 9-29% of tumors invading 1-3 mm. The frequency of vascular invasion increases with depth of stromal invasion. Its clinical significance, however, remains controversial. In patients with less than 5 mm or less invasion, several studies found no relationship between vascular invasion and lymph node metastases. On the other hand, 3 of 4 patients who developed recurrent disease after simple hysterectomy or cone biopsy had vascular invasion. When vascular invasion was present in the cone biosy, invasive carcinoma has been found in 80% of subsequent hysterectomy specimens. Thus, according to SGO, the presence of vascular invasion excludes a diagnosis of MIC.

3. Tumor volume

Patients of cancers 420 mm^3 or less do not develop pelvic node metastases.
Cumbersome and time-consuming method. Unlikely to become a routine method.

4. Surgical margins

The most important contribution of the pathologist and the most important single parameter in deciding treatment. Involvement of the cone margin by invasive carcinoma or even by high grade SIL precludes a diagnosis of microinvasive carcinoma, because deeper invasion may exist higher in the endocervix.

Treatment

Carcinomas with 3 mm or less invasion and without vascular invasion have virtually no risk of lymph node metastases and can be treated conservatively. Tumors invading 3 mm or less but with vascular invasion may rarely metastasize (3.5%).

Most frequent treatment for MIC is hysterectomy. Women who like to preserve their fertility can be managed with conization and periodic follow-up.

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INVASIVE SQUAMOUS CELL CARCINOMA OF THE CERVIX

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Cancer of the cervix is the second most common cancer in women. The incidence has been declining in the last three or four decades in most developed countries. Squamous cell carcinoma is by far the most common tumor of the cervix, although its relative frequency has dropped in comparison with that of invasive adenocarcinoma.

Definition: Squamous cell carcinoma of the cerix is an invasive carcinoma composed of squamous cells of varying degrees of differentiation.

Gross Features: The gross appearance of a squamous cell carcinoma of the cervix may be either predominantly exophytic (growing as a polypoid excrescence) or endophytic (infiltrating into the surrounding structures without much surface growth). Ulceration may be common. A distinctive gross presentation of the tumor is the so-called barrel-shape appearance, in which the tumor infiltrates diffusely the cervical wall.

Microscopic Features: Squamous cell carcinoma of the cervix may show a variety of pathological features. Coexistent areas pf cervical intraepithelial carcinoma are occasionally present.

A variety of **histological types** have been described:

1. Keratinizing

It accounts for 30% of the cases. Tumor cells infiltrate the stroma and show keratin pearl formation. In some cases keratinisation may be very focal. The nuclei are usually large and hyperchromatic with coarse chromatin.

2. Large-cell non-keratinizing

This type accounts dor 60% of cases. The tumor is composed of large groups of cells with abundant cytoplasm, and polygonal shape. Cell borders are distinct, and intercellular bridges are sometimes obvious. Occasionally tunor cells may exhibit a clear appearance secondary to glycogen accumulation.

3. Basaloid squamous cell carcinoma

This type of tumor is composed of grups of immature epithelial cells, showing scanty cytoplasm, and a basaloid appearance, similar to what is seen in basaloid carcinomas of the upper respiratory tract. Tumor cells may resemble the small cells that are seen in carcinoma in situ of the cervix.

4. Verrucous carcinoma

This infrequent type of tumor is characterized by an exophytic, warty, growth pattern, composed of well-differentiated squamous cells with pushing borders. Tumor cells usually show minimal atypia.

5. Warty type

This is an squamous cell carcinoma with a warty architectural pattern, that usually shows prominent features of HPV infection.

6. Papillary

This is a peculiar type of squamous cell carcinoma, with broad papillae, which are lined by epithelium showing features similar to cervical intraepithelial carcinoma. The tumor lacks cellular features of HPV infection, although it is usually positive for HPV 16.

7. Lymphoepithelioma-like

The tumor shows features similar to nasopharyngeal carcinoma. It is characterized by the presence of large nests of poorly-differentiated cells, accompanied by a prominent lymphocytic infiltrate. The islands of tumor cells show a typical syncytial appearance. Epstein-Barr virus DNA sequences have been identified in tumors from patients from Asia, but infrequently in patients from Europe or USA.

8. Squamotransitional carcinoma

This type of tumor show a prominent papillary arrangement, and features very similar to transitional carcinomas of the urinary bladder. No clear relationship has been proposed between this type of tumor and preexisting transitional metaplasia.

PROGNOSTIC FACTORS

Tumor size

Size of the tumor is a good predictor of outcome, and is an important parameter in staging. Measurement of tumor volume was introduced by Burghardt and coworkers. Tumors with a volume less than 2 cm^3, have a five-year survival rate of about 90%, in contrast to those with volumes of more than 30 cm^3, with less than 65% survival. Tumor volume can now be measured with great accuracy using magnetic resonance imaging.

Depth of invasion

Depth of invasion is proportional to the volume of the tumor, and shows strong correlation with survival, and disease-free interval. It is also an independent prognostic factor in node-negative patients with stage Ib and II cervical cancer. In stage I tumors, depth of invasion correlates with positive lymph nodes and five year survival.

Histologic grade

Several histological grading systems have been proposed for squamous cervical carcinoma. Broder system subdivides squamous cell carcinoma into three categories: grade 1 (well-differentiated with pearl formation, intercellular bridges); grade 2: (moderately differentiated), grade 3,(poorly differentiated). Two thirds of the tumors fall into the category of grade 2. Some controversy exist with regard to the prognostic significance of grade.

Lymphovascular space invasion

Lymphovascular channel involvement has been frequently associated with adverse prognosis. In some series it correlates with the presence of lymph node metastasis, and also with the site of positive nodes. The frequency of lymph node metastasis is approximately 25% higher if lymphatic channels are involved. Even in the absence of lynph node metastasis, lymphovascular invasion is a

strong prognostic factor, and correlates with stage. It is also a good predictor of local recurrence in stage I and II tumors (32% versus 3%).

Stage

Stage is the most important prognostic parameter. It is very important in stage I tumors. An important role of histopathology in staging is the identification of parametrial invasion in surgically treated stage I tumors, since parametrial involvement is a poor prognostic factor in early stage cervical cancer, regardless of lymph node status.

Lymph node metastasis

The primary lymphatic drainage of the cervix is to the paracervical and parametrial lymph nodes, and then to the obturator, external iliac, and the internal iliac (hypogastric) lymph nodes. The incidence of pelvic lymph node metastasis increases with stage, and survival rates decrease with increasing number of involved nodes. Extrapelvic disease recurrence has also been associated with positive nodes, even when there is no difference in local recurrence rates, attributable to adjuvant radiotherapy that is given node-positive patients. Lymph node metastasis correlates with other adverse prognostic factors, such as lymphovascular space involvement, tumor size, stage, and parametrial involvement. The site of involved nodes is also important; paraaortic lymph node involvement is associated with lower survival rates than pelvic lymph node involvement alone.

Margins

The prognostic relevance of surgical margins is under debate, but some studies have shown a significant association with reccurrence.

Molecular alterations

Several types of molecular alterations have been associated with adverse prognosis in cervical carcinoma. For example p53 immunoreactivity has been related to poor prognosis. C-erb B2 activation has also been associated with poor prognosis and recurrence post-radiotherapy. Also, c-myc amplification has been related with poor prognosis in early stage cervical carcinoma. The expression of the fragile histidine triad (FHIT) has also been related to nodal status, parametrial invasion and vaginal involvement. Other molecular alterations that may have a potential prognostic value are CD44, cyclin D1, EGFR.

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ADENOCARCINOMA OF THE UTERINE CERVIX

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Adenocarcinomas currently account for 15-20% of all invasive carcinomas of the uterine cervix in developed countries.[1-3] Prior to 1970, they represented only 5% of cervical carcinomas. The relative frequency has been increasing due to a decrease in the frequency of invasive squamous cell carcinomas, which are much more readily identified in their preinvasive stages by cytologic examination than adenocarcinomas. Nevertheless, some studies have indicated that an absolute increase in frequency has also occurred.[1-3]

Almost 60% of cervical adenocarcinomas are associated with squamous intraepithelial lesion (SIL) or invasive squamous cell carcinoma.[4,5] Also, several reports have suggested that the human papillomavirus (hPV) 16, 31, and particularly 18 may have a significant role in the causation of cervical adenocarcinomas. These hPV types have been identified in adenocarcinomas and adenosquamous carcinomas with a frequency of 80% or more.[6-11] An association with prior use of oral contraceptive (OC), particularly those with a strong progestational component, has been described but it has not been totally proved. It is noteworthy that the introduction of OC in the 1960's was followed a few years later by the recognition of *microglandular hyperplasia*, a proliferative cervical lesion that develops in women using OC.[12] Although the similar temporal association suggested the possibility of a causal relationship between OC and cervical adenocarcinoma,[13-15] the association was diminished when adjusted for hPV.

Intrauterine exposure to DES (administered in the 50's and 60'to pregnant women in the U.S. and Western Europe) resulted in a subset of young patients developing clear cell adenocarcinomas of the cervix and upper vagina several years later. The occurrence of these tumors has decreased following the withdrawal of DES from the market about 30 years ago.

Patients with adenocarcinoma of the cervix, particularly those with minimal-deviation mucinous adenocarcinoma, tend to develop mucinous tumors of the ovary[16, 17] and some of them have the Peutz-Jeghers syndrome.

Adenocarcinoma of the cervix is almost always a tumor of adult life; it is rare in the first decade and uncommon in the second decade.[18, 19] The average age ranges from 47 to 53 years.[20, 21] The patients present with abnormal uterine bleeding in 80-90% of the cases. Occasional patients complain of vaginal discharge or pain. The tumor is asymptomatic in up to 20% of the cases[5, 22] and is usually discovered in such cases because of an abnormal Pap smear.[22] In one report, 51% of the patients with cervical adenocarcinoma had normal cytologic findings and only 20% of the patients without a grossly visible lesion had a positive result.[20]

Preinvasive Glandular Lesions

The WHO classification of tumors of the cervix includes glandular atypia, glandular dysplasia (atypical hyperplasia), and adenocarcinoma in situ (AIS) among the preinvasive cervical tumors; however, their morphologic distinction remains unclear.[23]

Adenocarcinoma in situ (AIS)[24, 25, 26] is characterized by replacement of glandular epithelium by cytologically malignant epithelial cells with preservation of the glandular architecture. Involvement of more than one gland is required for the diagnosis. The evidence in favor of AIS being a precursor lesion for invasive adenocarcinoma includes the following: a) Patients with AIS are about 10-15

years younger than those with invasive adenocarcinoma; b) AIS is commonly found in the vicinity of invasive adenocarcinoma; c) similar hPV types are identified in both AIS and invasive adenocarcinoma; and d) occasional cases of AIS have been documented to progress to adenocarcinoma. AIS represents 10-20% of cervical adenocarcinomas.[27] Most AIS are asymptomatic and found in patients with abnormal cervical smears. SIL or invasive squamous cell carcinoma coexists with AIS in almost 60% of the cases and the exfoliated atypical cells lead to clinical investigation helping to identify AIS.

Microscopically, AIS spreads along the surface of the endocervix and does not extend below normal glands. There is neither stromal invasion nor desmoplasia. Part or all of the epithelium lining the glands shows nuclear enlargement, coarse chromatin, increased mitotic activity, and nuclear stratification. Based on cytoplasmic features, four subtypes of AIS have been described: 1) Endocervical or mucinous type (resembling the normal endocervical epithelium); 2) Intestinal type (containing goblet cells and argyrophilic cells); 3) Endometrioid type (without apparent intracellular mucin); and 4) Adenosquamous type. Although these histologic types do not have biologic significance, their distinction helps the pathologist to recognize AIS.

Glandular dysplasia (atypical hyperplasia) closely resembles AIS but differs in that the nuclei are not cytologically malignant and mitoses are less numerous. Because diagnostic reproducibility has not been established, it has been suggested that the entire spectrum of preinvasive glandular lesions including AIS be considered as a single lesion.

AIS should be distinguished from glandular atypia due to inflammation or irradiation (single layer of epithelial cells showing nuclear pleomorphism, hyperchromatism, and lack of polarity), viral infections (nuclear inclusions), microglandular hyperplasia (polypoid lesion composed of small and uniform glands with bland nuclei and without mitotic activity), endometriosis (endometrial glands lined by uniform, occasionally ciliated, cells and surrounded by endometrial-type stroma), tubal metaplasia (ciliated, clear and dark epithelial cells), and mesonephric remnants (deep location, lobular pattern, intraluminal eosinophilic secretion, absence of cytoplasmic mucin or cilia, and bland unstratified nuclei) .

AIS is treated either by conization or hysterectomy. Because of the multicentric distribution of AIS, recurrence occurs more often after conization than hysterectomy (particularly if the lesion involves the margins of the cone).[28, 29]

Microinvasive adenocarcinoma

In contrast to microinvasive squamous cell carcinoma, the glandular counterpart, microinvasive adenocarcinoma (MIA), has received little attention in the literature. The ideal definition of MIA should guarantee the safety of conservative therapy; it should describe an invasive adenocarcinoma small enough not to be associated with metastasis. The main diagnostic problems are: first, to distinguish MIA from AIS; and second, how to measure the depth of invasion[30].

The criteria for microinvasion are: 1) obvious stromal invasion to 5 mm or less; 2) obliteration of the normal endocervical crypts; 3) extension below the deep margin of normal endocervical glands; and 4) stromal desmoplasia[30]. Not all of these features are present in every case. The depth of invasion is usually measured from the surface epithelium (tumor thickness) rather than from the point of origin. This is due to the difficulty to determine where AIS ends and stromal invasion begins.[30]

The diagnosis of MIA cannot be made on punch biopsy alone, but requires either a cone biopsy or hysterectomy specimen. Loop excision procedures are contraindicated in the management of

glandular lesions, as the state of the margins cannot be assessed adequately due to fragmentation or diathermy artifact.[30]

It appears that MIA behaves in the same way as its squamous counterpart. When MIA does not invade beyond 5 mm, the margins are free, and the conization specimen has been totally embedded, conservative treatment is acceptable.[30] A recent review of the literature has revealed that only five (2%) of 219 patients with MIA invading less than 5 mm were found to have metastasis after pelvic lymph node dissection[30].

Invasive Adenocarcinoma

The gross appearance of invasive adenocarcinoma of the cervix varies greatly from polypoid or papillary, nodular, or sessile and ulcerated. Some tumors present as a barrel-shaped cervix. In as many as 20-30% of the cases, the cervix may appear normal.

Although older studies suggested that the prognosis for adenocarcinomas of the cervix was worse than that for squamous cervical cancer, more recent studies adjusting for depth, stage, and therapy have not found a significant difference.[1, 31]

Histologic Types of Invasive Adenocarcinoma

Although less common than squamous cell carcinomas, adenocarcinomas generally cause greater diagnostic difficulty because of their relative rarity, their varied patterns, and the potential for confusing them with several nonneoplastic lesions. Some variants are associated with a distinctive biologic behavior. A classification of these tumors is presented in Table 1.

ENDOCERVICAL (MUCINOUS) TYPE

This is the most common type of adenocarcinoma accounting for almost 70% of all cervical adenocarcinomas. The tumor cells resemble those lining the endocervical glands and contain cytoplasmic mucin. They range from well differentiated to poorly differentiated. Most of these tumors are moderately differentiated mucinous adenocarcinomas. Papillae may be present, but are rarely conspicuous. The tumors are usually associated with a desmoplastic or a prominent fibromatous stroma.

The distinction of endocervical adenocarcinomas from endometrial adenocarcinomas may be difficult particularly when a fractional curettage has not been performed or when tumor is present in both samples of the curettage. The presence of abundant intracellular mucin favors an endocervical origin, but most endometrial adenocarcinomas show focal mucinous differentiation and some of them are largely mucinous. The stroma of the tumor may be helpful; in cervical tumors it is typically fibrous whereas endometrial carcinomas usually contain very little stroma. Carcinoembryonic antigen (CEA) is not a reliable discriminatory feature. Hysteroscopy is often helpful in identifying the site of origin of the tumor.

VARIANTS OF ADENOCARCINOMA, ENDOCERVICAL TYPE

Minimal Deviation Adenocarcinoma (MDA)

This unusually well-differentiated adenocarcinoma has also been designated as *adenoma malignum to* reflect a bland histologic appearance in spite of its highly malignant behavior.[32-36] It is a rare

tumor accounting for only 1-3% of adenocarcinomas of the cervix. A minority of cases are associated with the Peutz-Jeghers syndrome.

Grossly, the cervix is often firm or indurated. Microscopic features include glands lined by columnar cells with mucinous apical cytoplasm and basal uniform nuclei. Features that help in arriving at the correct diagnosis are: 1) variability in gland shape and size, often with large branching glands; 2) a desmoplastic stroma; 3) an irregular, angulated gland contour; and 4) mitotic figures. Near diploid DNA values are present[32]. Areas of clearly malignant glands, vascular invasion, or perineural invasion confirm the diagnosis and are present in approximately half of the cases. In most cases the tumor deeply invades the cervical wall (deeper than normal glands) and spreading to the parametrium is seen in approximately 40% of them. Minimal deviation "endometrioid" adenocarcinomas, some with retention of cilia or apical snouts, have also been described, and appear to have a much better prognosis.[33,36] Benign lesions which must be distinguished from MDA include tunnel clusters, deep Nabothian cysts, diffuse laminar endocervical glandular hyperplasia, microglandular hyperplasia, and mesonephric hyperplasia.

The results of a recent study[34] support the conclusion that this tumor has a poor prognosis. Thirteen of the 22 patients with adequate follow-up information died of tumor and four additional patients were alive with recurrences.[34] Only three patients were disease-free after 2 years.

Villoglandular Papillary Adenocarcinoma

Well-differentiated papillary cervical adenocarcinoma found in young women and characterized by complex branching papillae.[37] Often occurring in women less than 40 years of age, this clinically distinctive variant of cervical adenocarcinoma usually appears as a broad-based cervical polyp. Microscopically, it is characterized by surface papillae and branching with variable amounts of stroma. The stroma often contains many acute and chronic inflammatory cells. The tumors are generally well circumscribed with only small foci of stromal invasion beyond the main tumor mass. The papillae and glands are frequently lined by stratified nonmucinous columnar cells. The tumor cells typically exhibit mild to moderate nuclear atypicality and contain scattered mitotic figures. Lymphatic or vascular invasion is rarely observed. AIS of the endocervix frequently occurs in association with this neoplasm.

Other papillary carcinomas (serous, mucinous and clear cell) exhibit smaller and thinner papillae and frequently show a more complex architecture. The differential diagnosis of villoglandular papillary adenocarcinoma also includes benign lesions such as chronic endocervicitis, mullerian papilloma, villoglandular papillary adenoma, and müllerian adenofibroma.

The young age of the patients and the excellent prognosis of these tumors suggest that it may be managed by a cone biopsy and careful follow up, if the tumor is superficial and well-differentiated, without vascular space invasion or involvement of resection margins. [37,38] Two cases of "villous adenoma" of the uterine cervix associated with underlying invasive adenocarcinoma have been reported.[39] The presence of an underlying invasive carcinoma in these cases indicates that the finding of a villoglandular lesion of the cervix, even if it is lined by only slightly atypical cells, should warrant investigation to exclude an underlying adenocarcinoma.

ENDOMETRIOID ADENOCARCINOMA

These tumors account for 17% of cervical adenocarcinomas.[20,40,41] They are histologically similar to endometrioid adenocarcinomas of the uterine corpus and may even contain squamous morules. Endocervical extension from an adenocarcinoma of the corpus has to be ruled out. Endocervical-type adenocarcinomas that contain relatively little intracytoplasmic mucin may resemble

endometrioid adenocarcinomas of endocervical origin. The features helpful for distinguishing them have been previously mentioned. The presence of vimentin in the neoplastic cells favors the diagnosis of endometrioid carcinoma of the endometrium[42]. The "minimal deviation adenocarcinomas of endometrioid type" have been discussed in the section on adenoma malignum.

CLEAR CELL ADENOCARCINOMA

During the past 30 years, most of the clear cell carcinomas of the cervix diagnosed in the United States have been in young women exposed to DES in uterus. The withdrawal of DES from the commercial market over 25 years ago has resulted in a reduction in these tumors and redistribution, with preponderance of new cases in older women. Presently, less than 5% of cervical adenocarcinomas are of the clear cell type. The characteristic microscopic patterns include tubulocystic, papillary, and solid, containing hobnail cells with either clear or eosinophilic cytoplasm.

Clear cell adenocarcinomas are easily distinguishable from other types of cervical adenocarcinoma; however, in a small biopsy specimen, it may be difficult to distinguish clear cell adenocarcinoma from microglandular hyperplasia; even then, the cytologic atypia found in clear cell carcinoma, the lack of intracellular mucin, and the absence of the typical patterns of microglandular hyperplasia facilitate the differential diagnosis. Rarely, the Arias-Stella reaction or the clear cell glandular hyperplasia of pregnancy involves the endocervix and the cells of these processes may be confused with the hobnail cells and clear cells of clear cell adenocarcinoma. However, in the former lesion the association with pregnancy is usually evident, and the nuclei tend to be dark and homogeneous, exhibiting no mitotic activity. In young children, the very rare yolk sac tumor of the cervix, which may contain clear cells, may be confused with clear cell adenocarcinoma. The presence of a reticular pattern with Schiller-Duval bodies, the positivity of ? -fetoprotein, and the primitive appearance of the tumor cells facilitate the diagnosis. Finally, the rare primary alveolar soft part sarcoma of the cervix should not be confused with a clear cell carcinoma. The distinctive architecture of the former tumor and its characteristic PAS-positive intracytoplasmic crystals help in the differential diagnosis.

More than 85% of clear cell carcinomas are stage I or II when diagnosed.[43] Treatment is either radical hysterectomy and vaginectomy or radiation. Metastasis occurs in about 18% of patients with stage I disease, but in nearly 50% in stage II tumors. Survival of patients with stage I disease is about 90%. Metastasis to distant sites (lung or supraclavicular nodes) occur more frequently (36%) than with squamous cell carcinoma (10%). Features associated with a better prognosis include small size of the tumor, shallow depth of invasion, and older age (19+ years) of the patient.[43]

SEROUS PAPILLARY ADENOCARCINOMA

Carcinomas histologically identical to serous papillary carcinomas of the endometrium or ovary seldom occur in the cervix[44] The diagnosis of primary serous carcinoma of the cervix should be made only after spread from the ovary, fallopian tube or endometrium has been excluded.

MESONEPHRIC ADENOCARCINOMA

Mesonephric adenocarcinoma is one of the rarest subtypes of cervical adenocarcinoma, with less than 40 well-documented cases in the literature.[45-48] Indeed, most of the "mesonephric carcinomas" reported in the older literature are examples of clear cell adenocarcinoma.

Microscopic examination usually reveals a tubuloglandular pattern. The tubules and glands are small and round and typically contain bright pink or red hyaline material, which is negative on

mucin staining. Mesonephric carcinomas usually invade the cervical wall and mesonephric hyperplasia is often present at the periphery of the tumor.[45-48] In two recently reported series, the prognosis of mesonephric carcinomas was better than that of mullerian carcinomas at the same stage.[46,48] Nine cases of malignant mixed mesonephric tumors (MMMT) have also been reported.[46,48] They are aggressive tumors that may present in advanced stage, similar to malignant mixed mullerian tumors.[48]

The most difficult differential diagnosis of mesonephric carcinoma is with mesonephric hyperplasia. Hyperplastic tubules may extend deeply into the cervical wall and even into the uterine corpus.[45] However, in cases of carcinoma, a back-to-back pattern of tubular glands is present, along with significant cytologic atypia and mitotic activity. Mesonephric carcinoma must be distinguished from other adenocarcinomas of the cervix such as adenoma malignum, endometrioid carcinoma and clear cell carcinoma.[45-48]

INTESTINAL-TYPE AND SIGNET-RING ADENOCARCINOMAS

Some cervical adenocarcinomas exhibit unequivocal intestinal features The *intestinal type* mimics the colonic epithelium, and is characterized by glands lined by malignant appearing cells some of which have the appearance of goblet cells. *Signet-ring* cell carcinomas may be pure or mixed with either endocervical or intestinal mucinous adenocarcinoma. The cell nucleus appears displaced eccentrically by mucinous vacuoles. An intestinal-type adenocarcinoma obviously has to be distinguished from an adenocarcinoma of the intestine that has extended directly into the cervix or metastasized to it. Pure or almost pure signet-ring cell carcinomas are exceedingly rare and are less common than metastatic signet-ring cell carcinoma of gastric or breast origin.

ADENOSQUAMOUS CARCINOMA

Approximately one-third of all cervical adenocarcinomas contain malignant-appearing squamous elements (*mixed carcinoma*) which usually represent the predominant component.[40,49] They occur in both old and young women, often in association with pregnancy. The risk factors are more like those of squamous cell carcinoma of the cervix than those of adenocarcinoma. The glandular component is usually poorly differentiated, showing only focal mucinous differentiation. The squamous component is also poorly differentiated exhibiting little keratinization. In some cases, mucin stains may help to demonstrate poorly formed glandular spaces or intracellular mucin. Nevertheless, several studies have shown that almost 60% of ordinary squamous cell carcinomas may show intracellular mucin when special stains are done. Barrel-shaped adenosquamous carcinomas have been stated to have a poor prognosis.[50,51]

GLASSY CELL CARCINOMA

Glassy cell carcinoma, the undifferentiated form of adenosquamous carcinoma of the cervix, accounts for only 1-2% of all cervical carcinomas.[50,52,53] This tumor occurs in younger patients (mean age 31-41 years) than those with ordinary squamous cell or adenocarcinoma of the cervix. Microscopically, these tumors are characterized by large cells with abundant eosinophilic or amphophilic, ground glass cytoplasm, prominent cell borders, large nuclei with prominent nucleoli, a high mitotic rate. A striking inflammatory infiltrate composed predominantly of eosinophils and plasma cells is present. Rare foci of squamous or glandular differentiation and intracellular mucin may be seen. The main differential diagnosis is with large cell nonkeratinizing squamous cell carcinoma. The latter tumor lacks a ground glass appearance of the cell cytoplasms, does not exhibit the prominent nucleoli, and shows more than a minor degree of squamous differentiation. In a recent study, large cell nonkeratinizing squamous cell carcinomas were found to have a prognosis similar to that of glassy cell carcinoma.

ADENOID BASAL CARCINOMA

Adenoid basal carcinoma and "adenoid cystic" carcinoma of the cervix have usually been grouped together in the older literature because of overlapping pathologic features. The two neoplasms, however, are distinct both clinically and pathologically and should be kept separate.[54] One shared feature is a higher frequency in black patients. Adenoid basal carcinoma usually occurs in postmenopausal patients, with a median age of 60 years. The patients are usually asymptomatic and the tumor is often discovered as a result of an abnormal cytological smear. The cervix is normal on pelvic and gross pathologic examination in most of the cases. Microscopic examination reveals widely separated small, round, oval, or lobulated nests of uniform basaloid cells with peripheral palisading. Squamous differentiation occurs centrally, with the squamous cells surrounded by smaller rounded basal cells. Mitotic figures are infrequent and there is no stromal reaction. Squamous dysplasia or carcinoma in situ is usually present in the overlying epithelium, and is responsible for the occasional abnormal cytologic smears. The cells of adenoid basal carcinoma stain immunohistochemically for cytokeratin, but do not stain for S-100 protein.

This tumor has a favorable prognosis and could be treated by hysterectomy or even conization. In a recent study, 10 of 13 patients with follow-up data were alive and well 2 to 10 years after the diagnosis.[54] Adenoid basal carcinoma should be distinguished from adenoid cystic carcinoma and squamous cell carcinoma with basaloid features, both of which have a worse prognosis.

ADENOID CYSTIC CARCINOMA

Patients with adenoid cystic carcinoma are usually postmenopausal, with an average age of 72 years. They usually present with abnormal uterine bleeding and an obvious cervical mass on pelvic examination. Microscopic examination shows the characteristic cylindromatous pattern resembling that seen in adenoid cystic carcinoma of the salivary glands. Unlike the salivary gland tumors, the cervical tumors rarely contain myoepithelial cells and S-100 protein stains are negative. The glandular lumens may contain hyaline or mucinous material. The neoplastic cells are larger than those of adenoid basal carcinoma and have more pleomorphic nuclei. The mitotic rate is generally high and necrosis is typically present and may be extensive. An additional difference from adenoid basal carcinoma is the presence of a hyaline stromal response. Adenoid cystic carcinomas are typically immunoreactive for cytokeratin Adenoid cystic carcinoma has a much worse prognosis than adenoid basal carcinoma. Only four of 12 patients with follow-up data were alive and free of disease at the time of the last follow-up. The other patients had either died of their tumor or had recurrent tumor when last seen.[54]

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Table 1. **Classification of Cervical Adenocarcinoma and Related Tumors**

1. Adenocarcinoma
   a. Endocervical type
      Variants
      (1) Adenoma malignum (minimal deviation adenocarcinorna)
      (2) Villoglandular
   b. Endometrioid
   c. Clear cell
   d. Serous
   e. Mesonephric
   f. Intestinal-type
   g. Signet-ring cell
2. Adenosquamous carcinoma
3. Glassy cell carcinoma
4. Adenoid basal carcinoma
5. Adenoid cystic carcinoma
6. Adenocarcinoma, mixed (specify subtypes)
7. Adenocarcinoma and carcinoid/small cell carcinoma
8. Metastatic adenocarcinoma

NON-NEOPLASTIC LESIONS OF THE CERVIX

Esther Oliva, M.D.

Glandular lesions of the cervix represent an important challenge in daily practice as lesions frequently occur in reproductive age women, specimens to be analyzed may be small and because a diagnosis of malignancy will drive a completely different therapy in patients that frequently want to preserve fertility. The goals of this talk are to delineate criteria to separate benign endocervical glandular proliferations from malignant endocervical processes either in situ or invasive, emphasizing problematic aspects and focussing on helpful histologic and immunohistochemical features.

TUNNEL CLUSTERS

Fluhmann first introduced the term "tunnel cluster" for this common lesion that is usually an incidental microscopic finding but when florid may cause a striking gross abnormality that may simulate a neoplasm. Tunnel clusters are seen in 10% of adult women, and they may be rarely associated with mucinous discharge.

Pathologic features

Type A tunnel clusters are characterized by elongated glands closely packed together frequently arranged around a central primary or secondary endocervical cleft showing a fairly well-defined margin. This variant may be problematic as the small closely packed glands can be irregular and, on occasion, can show pseudostratification, degenerative type nuclear atypia, and cellular crowding. Thus, if all these features are present, the lesion may cause the pathologist to consider the possibility of a malignant neoplasm, most specifically the minimal deviation cervical adenocarcinoma (adenoma malignum).

Type B clusters are typically discrete, usually very small (mean 2.4 mm) rounded foci composed of usually oval to round, closely packed cystic glands. They seem to be more common in the posterior lip of the cervix. Cysts are observed grossly in approximately 40% of the cases and not infrequently significant distortion of the cervical wall occurs. Grossly they may involve the entire length of the endocervical canal and deeply penetrate the cervical wall. On microscopic examination multiple foci are present in about 80% of the cases, and occasionally the tunnel clusters are confluent. The cysts are lined by single cuboidal to low columnar mucinous endocervical type epithelium with neither cytologic atypia nor mitotic activity and typically contain inspissated mucin and sometimes may rupture and have extravasated mucin. They are separated by scanty connective tissue, and the lobulated tunnel cluster is surrounded by normal endocervical stroma. This type of tunnel clusters is frequently associated with Nabothian cysts and are considerably more common than type A but in routine practice it is not infrequent to see both types merging imperceptibly.

Differential diagnosis

? **Adenoma malignum** ("minimal deviation adenocarcinoma"). *It is important to remember that tunnel clusters always represent an incidental finding.* Type A tunnel clusters are more frequently confused with adenoma malignum especially in those cases that show some degree of cytologic atypia. The following combination of features can help in this differential diagnosis:

- Most type A tunnel clusters are associated with a type B tunnel clusters.

- Lobulation and circumscription is also a typical feature of both types of tunnel clusters. The glands are closely packed and do not become widely separated as in adenoma malignum.

- Absence of mitotic activity or overt cytologic atypia as seen somewhere in adenoma malignum.

- The desmoplastic reaction seen in adenoma malignum is lacking in tunnel clusters.

-CEA staining show only luminal positivity in tunnel clusters in contrast to cytoplasmic positivity in adenoma malignum.

? **Endocervical adenocarcinomas with cystic glands or even cystic clear cell carcinoma** may be confused with tunnel clusters, particularly on low power examination, although invasive characteristics are usually seen in these cases elsewhere. On high power, cytologic features of malignancy are identified in these malignant tumors and hobnail and clear cells are not a feature of tunnel clusters although it must be noted that cystic clear cell carcinoma may have a dominant lining of deceptively benign flattened cells.

DEEP GLANDS AND CYSTS

Otherwise *typical endocervical glands* or their cystic counterpart (nabothian cysts) sporadically extend deep in the cervical stroma (outer third). However, the former are usually beneath normal superficial endocervical glands, they are usually few in number and normal in size and shape, they lack cytologic atypia and are unassociated with any stromal alteration, indicating their benign nature. Other benign glandular lesions (tubal metaplasia, tunnel clusters) are commonly present in the same specimen.
Nabothian cysts may also extend deep into the wall, a finding that may cause concern.

Pathologic features

Numerous mucin-filled cysts measuring up to 1 cm in diameter replacing the endocervical wall and they can reach as deep as 1.5 cm. Histological examination shows cysts lined by benign columnar, cuboidal to flattened endocervical epithelium devoid of mitotic activity.

Differential diagnosis

? **Cystic adenocarcinoma**. Glands of cystic cancers are more irregularly distributed, are lined by cytologically malignant cells and may have an associated stromal reaction. In florid cases, CEA may be helpful in this differential diagnosis as benign glandular lesions show typically luminal positivity in contrast to cytoplasmic CEA positivity seen in cervical adenocarcinomas.

LOBULAR ENDOCERVICAL GLAND HYPERPLASIA, NOT OTHERWISE SPECIFIED

This entity is characterized by a distinct lobulation of the hyperplastic endocervical glands. The lesion was described at the same time by one american and one japanese groups, however, the japanese used the name of florid endocervical glandular hyperplasia with intestinal and pyloric gland metaplasia. These lesions are typically an incidental microscopic finding in women of reproductive age or postmenopausal women, but patients may present with atypical glandular cells seen in Pap smear, mucoid discharge or increased discharge or even with a visible gross cervical abnormality. No relationship has been shown with the use of hormones.

Pathologic features

Grossly the cervix may be unremarkable or show multiple cysts, but it may be thickened and fibrotic with numerous, variable sized cysts present throughout the wall and rarely a mass may be noted. On microscopic examination there is an increased number of closely packed endocervical glands with a very striking lobular architecture. The glands are rounded and small to medium size, often present around a large central gland. The lobules are typically well demarcated and most of the times present within the inner half of the cervical wall. The glands are composed of columnar mucin-rich cells with bland, basal, round to oval nuclei with indistinct nucleoli similar to those of the normal endocervix and up to 2 mitoses /10 HPFs may be encountered. The intervening stroma is unremarkable or may show edema or mild inflammation. There is striking similarity of these cells to pyloric type glands of the stomach, and japanese investigators have emphasized that these lesions represent pyloric metaplasia as their immunohistochemical profile shows positivity for combined PAS/Alcian Blue stain (red stain) and HIK1083 indicating the presence of neutral mucin as seen in pyloric type glands. In contrast, normal endocervical glands are HIK1083 negative and show a purple/violet staining with a combined PAS/Alcian Blue stain. The cytokeratin profile is CK7+/CK20- and they are estrogen receptor negative.

Differential diagnosis

? **Tunnel clusters** also show lobulated architecture. In occasional cases it may be difficult to know where to place a given lesion, but in this lesion there is not the particular cystic change of type B tunnel clusters or the small much more irregular glands of type A tunnel clusters.

? **Adenoma malignum**. In addition to the striking orderly lobular arrangement of the glands in lobular endocervical gland hyperplasia, this lesion lacks the irregular stromal infiltration, desmoplastic stromal response, the widespread distribution of the glands and even the focal malignant cytologic features seen in adenoma malignum. Ishii and colleagues have proposed that lobular endocervical gland hyperplasia represents possibly an in situ phase of adenoma malignum as they have found that these lesions frequently coexisted. This issue has engendered some controversy, but most authors favor lobular endocervical gland hyperplasia being a benign lesion.

MICROGLANDULAR HYPERPLASIA

This distinctive proliferation of endocervical glands was first described by Taylor and Norris in 1967 as "atypical endocervical hyperplasia". Shortly thereafter Kyriakos and colleagues designated this atypical hyperplasia as "microglandular" hyperplasia. In the past this lesion was frequently misinterpreted as carcinoma and still today may be a diagnostic challenge. Microglandular hyperplasia is often related to oral contraceptive use or pregnancy but recently this assumption has been questioned. The lesion typically occurs in women of reproductive age, *however, approximately 6% of cases occur in postmenopausal women*. Microglandular hyperplasia is typically an incidental microscopic finding but occasionally the patient may present with vaginal bleeding or discharge.

Pathologic features

Sometimes the lesion is visible as an erosion or a polyp, or, uncommonly, is friable and suspicious for carcinoma. On microscopic examination it is characterized by closely packed glands showing irregular shapes and sizes, often with cystic dilatation, with little intervening stroma showing acute and chronic inflammatory cells, and there may be mucin extravasation into the stroma. The glands usually contain a basophilic or eosinophilic mucinous secretion that often contains many acute inflammatory cells. The glands are lined by mucinous cells, which typically have subnuclear or

supranuclear vacuoles. There is often associated squamous metaplasia that is typically immature and reserve cell hyperplasia. The cells themselves generally show minimal to absent cytologic atypia and at most 1 mitosis/10 HPFs. ***Unusual histologic features*** that may be seen in microglandular hyperplasia that increase the concern for the diagnosis of carcinoma include reticular and solid growths, mucin positive signet-ring cells, hobnail cells, small nests of cells within myxoid stroma imparting a pseudo-infiltrative pattern, and hyaline stroma.

Differential diagnosis

? **Clear cell carcinoma** (CCC) is the cervical adenocarcinoma most likely to be confused with this benign proliferation because both lesions may have tubular, cystic and solid patterns and hyalinized stroma. In CCC the cells have abundant, clear, glycogen-rich cytoplasm with mucin only present in the lumen of the glands whereas the cells in microglandular hyperplasia contain mucin. In addition, the atypia and mitotic rates seen in CCC always exceed those found in microglandular hyperplasia including atypical forms. Finally, CCC shows a definitive invasive growth in contrast to microglandular hyperplasia.

? **Endocervical adenocarcinomas of the usual type** may have focally a microglandular-like pattern, but they usually show malignant cytologic features. As a rule, luminal positivity for CEA supports a diagnosis of a benign cervical glandular lesion, with the caveat that adenocarcinomas are occasionally negative or only focally positive for CEA. It is important to remember that in general a diagnosis of benign versus malignant should not be rendered solely on the basis of immunohistochemical results. Other studies have shown no expression of Bcl-2 or p16 in microglandular hyperplasia while endocervical adenocarcinoma is p16 positive with a high MIB-1 index.

? **Endometrioid, mucinous or mixed endometrioid and mucinous endometrial adenocarcinomas with a microglandular pattern**. These carcinomas may have a combination of focal microglandular-like patterns, extensive acute inflammation, and glands filled with mucin, creating a striking resemblance to microglandular hyperplasia in some instances. This is especially problematic when dealing with a curettage specimen as fragments of an endometrial tumor of this type may be present in a specimen thought to be endocervical in origin or fragments of microglandular hyperplasia may be present in an endometrial curettage. Vimentin staining may be of help as all cases of microglandular hyperplasia tested to date were negative. MIB-1 index may also be helpful as it was 11% in mucinous adenocarcinomas of the endometrium while MIB-1 index was < 0.5% in cases of microglandular hyperplasia in the study conducted by Qiu and Mittal. Finally, estrogen and progesterone receptors are of no help in this differential diagnosis.

✍ *The diagnosis of microglandular hyperplasia should be made with caution in a postmenopausal patient, particularly if there is cytologic atypia greater than usual and the morphologic appearance is not typical of microglandular hyperplasia.*

MESONEPHRIC HYPERPLASIA

Mesonephric remnants, which are present in the lateral walls of the cervical wall in as many as 10-20% of women, are an incidental microscopic finding in reproductive and postmenopausal age groups.

Pathologic features

Although it is almost always an incidental microscopic finding, it is rarely associated with a gross abnormality. They consist of one to several small, well-circumscribed, lobular aggregates of

mesonephric tubules, with or without a mesonephric duct. The cells lining the tubules are typically cuboidal to low columnar and non ciliated with no cytologic atypia, and eosinophilic PAS+ secretions are present in the glandular lumens. Criteria to allocate a proliferation in the remnant or hyperplasia category are arbitrary. A size cut off of 6 mm. is recommended. Although distinguishing among the different categories has no clinical relevance, it is important to be aware of their different histologic appearances in order to avoid confusion with in situ or invasive carcinomas of the cervix or even secondary involvement by endometrioid endometrial carcinoma.

- **Lobular mesonephric hyperplasia (most common)**. It is characterized by round to oval, often focally dilated, tubules that are arranged in at least a vaguely lobular arrangement. The tubules characteristically contain bright, colloid-like, PAS + material in their lumens.

- **Diffuse mesonephric hyperplasia**. It is characterized by an irregular distribution of small to variable sized and focally cystic tubules. Sometimes they may be conspicuous in number, and present deep in the cervical wall. In about one-third of both types of non-ductal hyperplasia, tubules extend to within 1 mm of the endocervical surface, and in sometimes they may reach the mucosa. In those cases the histologic low-power appearance may be diagnostically challenging suggesting transmural involvement by adenocarcinoma. Other features described in mesonephric hyperplasia by Seidman and Tavassoli have included interanastomosing slit-like (retiform) tubules (32%), an endometrioid-like appearance that was likened to epididymal differentiation (14%) and resemblance to seminal vesicle epithelium with lipofuscin pigment. Three-quarters of mesonephric hyperplasia cases with tubules have an additional component of ductal hyperplasia.

- **Ductal mesonephric hyperplasia**. It is the least common subtype of mesonephric hyperplasia. It is characterized by one or more large round or elongated ducts, depending on the plane of section, lined by pseudostratified epithelium that often forms small papillae. In the pure form it has a minimal or absent tubular component. Ductal hyperplasia, particularly when occurring in pure form, is *usually misdiagnosed as a premalignant glandular lesion such as endocervical glandular dysplasia or adenocarcinoma in situ*, because of the papillary architecture, tufting and nuclear pseudostratification. The elongated form of the ducts and lack of an association with endocervical glands are initial clues to their nature, and high power reveals no significant cytologic atypia. Finally, the micropapillae seen in pure ductal hyperplasia are distinctive and usually not a feature of premalignant glandular lesions.

Differential diagnosis

? **Mesonephric adenocarcinoma**. This is a very rare lesion that should be diagnosed only after florid mesonephric hyperplasia has been excluded. In contrast to mesonephric hyperplasia, mesonephric carcinoma is more likely to produce a grossly visible abnormality. On microscopic examination, mesonephric carcinomas are typically associated with irregular destructive invasion with a stromal reaction by the malignant glands including back to back and cribriforming, features not seen in hyperplasia. High degree of atypia and brisk mitotic activity favor a malignant lesion although these features are not always present in all carcinomas. Typically mitotic rate in hyperplasia does not exceed one per 10 high power fields. Immunohistochemistry is not helpful.

? **Adenoma malignum**. In this entity the glands are much more irregular in size and shape than the tubules of mesonephric hyperplasia. In addition they are lined, at least in some areas, by tall columnar mucinous cells that show at least focally significant cytologic atypia in contrast to the cuboidal non-mucinous epithelial cells of mesonephric tubules. They are often surrounded by a desmoplastic stromal reaction or show perineural invasion, features that are absent in mesonephric hyperplasia. From the immunohistochemical point of view, it is important to remember that

mesonephric lesions are frequently positive for CD10 and calretinin and negative for CEA in contrast to endocervical carcinomas, which show the opposite immunohistochemical profile. Although endocervical adenocarcinomas may show CD10 positivity, adenoma malignum is typically negative.

? **Clear cell adenocarcinoma**. In contrast to mesonephric hyperplasia, at least some of the cells lining the glands and cysts of clear cell carcinoma have conspicuous clear, glycogen-rich cytoplasm or are of hobnail type. Additionally, clear cell carcinomas with a pure tubular pattern are uncommon; solid sheets of clear cells and papillary patterns incompatible with a diagnosis of mesonephric hyperplasia are also usually present at least in minor amount.

? **Secondary involvement by endometrioid endometrial carcinoma** may have a similar histologic appearance to that of isolated tubules of mesonephric hyperplasia without associated stromal response. However, in all these instances there is an associated endometrial adenocarcinoma with similar histologic appearance and more cytologic atypia of the neoplastic cells.

✍ *It is important to keep in mind that although as mentioned earlier CD10 and calretinin have been reported to be helpful in the diagnosis of mesonephric lesions, however, it has recently been shown that endometrial adenocarcinomas may also be CD10 and calretinin positive.*

? **Metastatic adenocarcinoma**. For example, metastatic breast carcinoma may consist of small tubular glands and have an appearance somewhat reminiscent of mesonephric hyperplasia. However, they usually focally contain cords of cells and single cells, and malignant cytologic features inconsistent with mesonephric hyperplasia.

SUPERFICIAL ENDOMETRIOSIS AND TUBO-ENDOMETRIOID METAPLASIA.

Cervical endometriosis is divided in two major categories: superficial and deep. Superficial endometriosis typically consists of endometriotic glands and stroma, but occasionally glands are sparse or absent (stromal endometriosis). Deep cervical endometriosis is usually seen in patients with clinical evidence of pelvic endometriosis, and the endometriotic foci within the deep cervical stroma are easily observed on microscopic examination. In contrast, superficial endometriosis can be more diagnostically challenging, especially in small biopsy specimens.

Superficial endometriosis has been reported in 2.4% of patients undergoing colposcopic evaluation. Most superficial endometriotic foci are thought to occur in areas of prior trauma in patients who have had a surgical procedure (curettage, biopsy, cautery), abortion, or vaginal delivery and may be seen after 2-24 months (mean 11) after the procedure. The frequent association with previous trauma has led most investigators to favor menstrual implantation as the most likely pathogenetic mechanism, but a single explanation is likely not valid in all cases and in the absence of antecedent of trauma a metaplastic or developmental process is also postulated by some investigators. Patients range in age from 20 to 53 (average 37 to 38) years. In most instances superficial cervical endometriosis is an incidental finding, but it may present associated with abnormal bleeding, which may be postcoital or spontaneous and it is often premenstrual and brown in color.

Pathologic features

Sometimes these lesions may be seen as a gross abnormality. Regardless of their gross appearance, they typically enlarge, become congested, and are most visible before or during menses, often becoming invisible later in the cycle. On microscopic examination, they are seen immediately beneath the surface epithelium or present at the surface, which sometimes may be ulcerated. The

size of the endometriotic foci as well as the morphology of the endometrial glands changes within the same specimen. Most frequently they are small to medium in size comparable with normal proliferative endometrial glands, but they may be dilated or show a secretory pattern. The endometrial glands may show variable degrees of architectural abnormalities as seen in the endometrium, including back-to-back glands and papillary infoldings. The cells lining the glands are usually cuboidal to columnar and show varying degrees of nuclear pseudostratification. The nuclei are round to elongated, slightly hyperchromatic with slightly coarse chromatin and the number of mitotic figures may range from 0 to 2, but in some cases up to 3 mitoses per gland have been reported. As the glands may have complex architecture, the cells themselves may show variable degrees of cytologic atypia. Apoptotic bodies are rarely seen. The stroma when well developed is composed of small, uniform, dark cells, with scant cytoplasm and oval to round nuclei that often show condensation around glands and it also contains at least focally small thin-walled blood vessels. In many cases there is recent blood extravasation and/or chronic inflammation that may obscure the nature of the stroma. In some occasions the stroma may be found only focally within the lesion and in other occasions the stroma may be the only component to the lesion (*stromal endometriosis*). It is important to perform serial sections in order to reduce the number of false negative diagnosis. Finally as happens in the uterine corpus as well as in extrauterine sites, the endometriotic glands may induce smooth muscle metaplasia. Perineural invasion by the endometriotic glands and stroma has been described.

Differential diagnosis

? **Endocervical glandular dysplasia and adenocarcinoma in situ (AIS)**. In AIS the glands show more architectural complexity and mitotic activity tends to be far more numerous in AIS than in endometriosis. Biscotti and Hart found 1-53 MFs/10 HPFs in their cases with a mean count of 18 MFs/ 10 HPFs. Abnormal mitotic figures are common in AIS. Furthermore, apoptotic bodies occur almost universally in endocervical AIS and this is an important feature of this diagnosis. However, apoptotic bodies can occur in hormonally responsive endometrium and they have also been reported occasionally in cervical endometriosis. Finally, there is usually an abrupt transition from the normal to the abnormal epithelium in AIS while this has only been described in one case in the series reported by Baker and coworkers. Evaluation of endometriosis in cytology may be even more difficult as cells of superficial endometriosis appear as abnormal cells in cytology smears.

? **Tubo-endometrioid metaplasia**. The glands of endometriosis and tubo-endometrioid metaplasia may appear very similar and tubal metaplasia has been associated with the presence of stromal alterations. In fact in many instances one can see both processes side by side. Ismail found tubo-endometrioid metaplasia in 26% uteri after conization. Ten of the 20 cases of cervical endometriosis reported by Baker and coworkers also contain tubo-endometrioid metaplasia. Some authors postulate that endometriosis may arise from metaplasia of the endocervical glands with subsequent induction of the cervical stroma to become endometriotic.

✍ *It is important to keep in mind that endometriosis as well as tubal or tubo-endometrioid metaplasia may undergo malignant transformation.*

ENDOCERVICOSIS

This process refers to the presence of ectopic, benign appearing endocervical-like glands involving the outer aspect of the uterine cervical wall. This lesion may simulate a well-differentiated endocervical adenocarcinoma, more specifically adenoma malignum.

A history of caesarian section may be obtained and a gross abnormality of the outer cervix may be noted. The process typically involves the anterior wall of the cervix or bladder. The lesions are

firm rubbery masses 1 to 2.5 cm. in greatest dimension and may have associated cysts. *Microscopic examination* shows glands of variable size and shape, some of them cystically dilated, lined by mucinous endocervical-type epithelium that range from columnar to flattened with bland cytologic features. Only a periglandular stromal reaction is seen when there is mucin extravasation.

- ✍ *To make the correct diagnosis it is important to be aware that the process is centered in the outer cervical wall and often involves the paracervical tissues.*
- ✍ *A helpful feature to exclude a deeply invasive endocervical adenocarcinoma of the adenoma malignum type is the presence of a zone of uninvolved wall between the glands of this lesion and the normal endocervical glands.*
- ✍ *When involving the bladder, there is no associated stromal response and frequently is accompanied by endometriosis or endosalpingiosis (mullerianosis).*

ARIAS-STELLA REACTION

The Arias-Stella reaction is seen within endocervical glands in about 10% of gravid uteri. It typically involves only a few glands and only part of the glands. Superficial glands are more commonly involved than deep glands and polyps may also be affected. The architectural patterns include intraglandular tufts, delicate filiform papillae and cribriform pattern. Cytologic features include stratified cells with abundant vacuolated cytoplasm simulating hobnail cells, oxyphilic cells and enlarged, pleomorphic and hyperchromatic nuclei and rare mitosis. Optically clear nuclei may also be seen.

Differential Diagnosis

The most common entities in the differential diagnosis include adenocarcinoma in situ or more frequently with clear cell carcinoma; such diagnoses should therefore be made with caution in a pregnant patient.

- ? **Clear cell carcinoma** will often be associated with a mass and histologic examination will reveal features including presence of invasion and tubular and solid patterns. It does not preserve the normal glandular architecture and there is no partial involvement of the glands as seen in Arias-Stella reaction.
- ? **Adenocarcinoma in situ**, in contrast to the Arias-Stella reaction, usually exhibits uniformly atypical nuclei and relatively frequent mitotic figures, and usually lacks marked cytoplasmic vacuolization, hobnail cells, and optically clear nuclei.

CERVICAL ADENOMYOMA

These tumors are frequently an incidental finding in women of reproductive age or postmenopausal. These are benign tumors but if excision is incomplete they may recur.

Pathologic features:

They are polypoid masses growing into the endocervical canal and sometimes protruding into the external os. On gross examination the tumors are well circumscribed and grey-white or tawny and frequently contain multiple mucin-filled cysts: On microscopic examination the glandular component forms glands and cysts lined by a single layer of endocervical-type mucinous epithelium. The glands have frequently a lobular architecture with a large irregular gland surrounded by smaller glands. One can also see tubal or endometrioid-type epithelium. The smooth muscle represents the mesenchymal component of the tumor and it is admixed with the glandular component. Both epithelial and mesenchymal components are uniformly bland.

Differential diagnosis

? **Adenoma malignum** is the main differential diagnosis because of the finding of bland appearing endocervical glands admixed with muscle, this differential being even more difficult in biopsy specimens. The gross circumscription of the adenomyomas, their polypoid appearance, the frequent lobular arrangement of the glands, the absence of invasive glands with a desmoplastic stromal reaction, and lack of even focal atypia are helpful in this differential diagnosis.

Treatment and prognosis

These are benign tumors that may only recur if they are not completely excised.

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NON-NEOPLASTIC ENDOMETRIUM

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NORMAL ENDOMETRIUM

The fetal endometrium consists of columnar epithelium surrounded by myometrium. By the fifth month, a fibroblastic stroma progressively differentiates in between, and invaginations into the surrounding myometrium form primitive glands. Meanwhile, radial arteries arising from the plexus of arquate arteries of the mid myometrium, penetrate into the endometrium forming a basal plexus from which vertical branches, the spiral arteries, originate. Venous and lymphatic systems also develop. At birth, epithelium and vascularized stroma are clearly recognizable.

Development and differentiation of the endometrium are induced by classes of steroid hormones and mediated by steroid hormone receptors (SHR) concentrated in the nucleus of endometrial cells. Estrogens are necessary for growth, and in absence of estrogenic stimulation the endometrium remains atrophic. During the reproductive age, following activation of the hypothalamic-pituitary-ovarian axis, the endometrium responds the cyclical release of estradiol (E2) and progesterone (P) by the ovary with a series of physiologic changes mediated by estrogen receptors (ER) and progesterone receptors (PR). Moreover, other steroids may induce varying degrees of response because of the affinity shown by SHR to closely related classes of steroid hormones in general. They include endogenous hormones, such as estrone (E1), as well as those molecules obtained by synthesis, such as diethylstilbestrol, progestogens and many other endocrinologically active steroids developed for the treatment of gynecologic disorders and contraception. Changes simulate those occurring during the menstrual cycle or pregnancy.

THE MENSTRUAL CYCLE

Menstrual cycles occur after menarche and cease with the menopause. At the end of each cycle the fall of hormonal stimulation determines endometrial degeneration or menstruation; the day of onset of uterine bleeding, when 50% of the endometrium is expelled, is designated day 1 of the new cycle as it can be easily recorded by any woman.

Although cyclic bleeding is normal in the childbearing age, there are variations, either physiologic and pathologic. The menstrual cycles are usually irregular after menarche and around menopause; in between, they are thought to be “regular” and deviations from the expected timing and quantity of blood, even small, are noted and subjectively evaluated. In particular, an abnormal uterine bleeding is an alarming symptom, which influences the emotional status, and one of the leading causes of gynecologic consultation.

Evaluation of the cycles is based on the length and type of bloody discharge and uterine bleeding is considered abnormal in the following cases:

- frequent menstruations or **polymenorrhea** (less than 21 days between menstruations)
- prolonged menstruation or **hypermenorrhea** (more than seven days of bleeding)
- abundant menstrual bleeding or **menorrhagia** (blood loss exceeding 80 ml)

Menometrorrhagia is a comprehensive term describing irregular and/or excessive bleeding during menstrual or intermenstrual days; other practical terms are **intermenstrual bleeding** (vague) and **spotting** (minimal and of short duration). **Amenorrhea** is the absence of menstruations and can precede heavy bleeding.

The diagnostic process for the identification of the cause of the bleeding includes the evaluation of the entity and cronicity of the bleeding, clinical data, laboratory tests, transvaginal ultrasound, hysteroscopy, and endometrial biopsy. Moreover, the symptoms may be caused by something wrong in adjacent organs such as cervix and vagina and other diagnostic procedures may be necessary. In any case, causes should be identified before any blind therapy is given causing delayed diagnosis.

Depending on the age of the patient, endometrial biopsies are required to interpret uterine bleeding or menstrual irregularities and less frequently for infertility and amenorrhea accounting for at least 20% of gynecologic specimens. The old method, dilatation and curettage (D&C), has been progressively replaced by less traumatic procedures, particularly vabra curettage. Cytology needs great experience and caution. Moreover, following the introduction of hysteroscopy, endometrial biopsy is no longer performed blindly, and visible lesions can be precisely evaluated with improvement of the quality of sampling. In some cases ablation is diagnostic and curative.

Historically, the classification of the causes of abnormal uterine bleeding consists of two main groups of lesions and is still valid. There are 1) organic disorders, including all possible causes which may interfere with the function of endometrium (Table 1); and 2) functional disorders, which represent an impairment of the function of the endometrium as a sensitive indicator of the hypothalamic-pituitary-ovarian axis.

Dysfunctional uterine bleeding is an inappropriate clinical designation indicating all types of abnormal uterine bleeding not attributable to organic causes, systemic diseases, or therapies. In the past, endometrial biopsy was the main (or single) method for the evaluation of the function or dysfunction of the endometrium; today, with the advent of sophisticated hormonal test and non invasive diagnostic methods, endometrial biopsy is evaluated in a more broad context and clinicopathologic correlation is more precise.

In the childbearing age, bleeding cannot be easily explained by the morphology of the endometrium alone. Particularly in perimenopausal women, a great variety of histological patterns can be observed depending upon the levels of circulating estrogens and the effects of blind hormonal treatment to control heavy bleeding. In the postmenopause, things become easier as the most frequent type of endometrium associated with bleeding is atrophic endometrium, but any episode of bleeding is suspicious for the presence of abnormal endometrial proliferation, including hyperplasia and carcinoma. Anovulation, which is the main cause of bleeding, is associated with atypical changes in less than 5% of the cases biopsied.

Endometrial cycle

The morphologic events occurring in the endometrium under steroid hormone stimulation by the ovarian cycle are referred as the **endometrial cycle** and are schematically divided into proliferative phase, secretory phase, and menstruation. Regeneration after menstruation from the socalled “basalis” (the layer which is not expelled by menstruation) is not hormonally mediated, but the subsequent changes, proliferation and differentiation of the socalled “functionalis”, are dependent on steroid hormones.

Proliferative phase

The rising plasma levels of E2 during the preovulatory and early postovulatory phases are followed by a corresponding increase of the concentrations of E2R and PR in the endometrial cells and the resulting endometrial proliferation is mediated by a series of polypeptide growth factors E2R dependant.

Proliferation results in increasing thickness of the endometrium, and mitotic activity is the main feature in glandular epithelium and stromal cells. In the early proliferative phase, the glands are straight but, by the second half, they become progressively tortuous in deeper portions. The epithelial cell lining glands are columnar with indistinct cell borders; the nuclei are basal, elongated, and typically pseudostratified. The stroma is immature and the stromal cells have inconspicuous cytoplasms. Spiral arteries are not prominent and have a thin wall.

Secretory phase

After ovulation, the increasing plasma levels of P inhibit the concentration of E2R and convert the E2 primed endometrium into a more differentiated tissue or secretory endometrium. In the absence of pregnancy, the endometrium is no longer sustained and undergo degeneration; differentiation may persist and continue only under proper stimulation by the corpus luteum of pregnancy and placenta with formation of decidua of pregnancy.

Differentiation occurs firstly in the glands and later in the stroma and blood vessels. Unlike the proliferative phase, the secretory phase is characterized by daily changes which permit the so called "endometrial dating" and the "postovulatory days" (POD) are traditionally numbered with the exclusion of POD 1 when the endometrium is still proliferative.

Secretory glycogen vacuoles appear in the subnuclear region of glandular epithelial cells in POD 2, and in POD 3 they reach the maximum of size the cells and extension throughout the endometrium. In POD 4, vacuolization is either subnuclear or supranuclear with the result of nuclear "palisading" in between. In the two following days secretion migrates to the luminal portion, protrudes into the lumen, and progressively detaches from the rest of the cell (apocrine secretion). Since then (POD 7), any secretory activity is lost and the epithelial cells, from columnar and amphophilic become cuboidal and eosinophilic. The nuclei remain in the basal portion and are no longer pseudostratified.

Edema and decidualization are the two typical changes occurring in the stroma. Edema develops since POD 6-7 and reaches a maximum at POD 8; it is associated with increasing coiling of the glands and spiral arteries which become prominent for the thickening of their walls. Since POD 8, stromal cells surrounding arteries enlarge becoming predecidualized; they have abundant eosinophilic cytoplasm and rounded central nuclei. Predecidualization progressively extends to the superficial stroma (POD 11) leading the endometrium to be divided into two portions, predecidualized or "compacta", and deep or "spongiosa". At this time, the coiling of the glands is at the maximum and the luminal borders become markedly irregular ("ferning"). By POD 12 and 13 a polymorphonuclear infiltrate appears perivascularly and progressively becomes diffuse at POD 14, when early fissuration develops in the endometrium.

Premenstrual endometrium is characterized by predecidual transformation which includes hypertrophy of the spiral arteries, secretory exhaustion of the glandular epithelium, epithelioid shape of the surrounding stroma cells, and numerous inflammatory cells.

MENSTRUATION AND ABNORMAL UTERINE DESQUAMATION

Menstruation

Menstruation is the result of the autolysis and collapse of the endometrium following the fall of E2 and P (after involution of the corpus luteum) and is favored by the release of lysosomal enzymes including the fibrinolytic agents which prevent clotting formation. The expulsion of menstrual endometrium, which is most prominent during the first two days, is enhanced by myometrial contractions and the

control of the bleeding is mediated by vasoconstriction of the basal arteries which, unlike those of the functionalis, have the ability to contract.

Diffuse fissuration is associated with rapid collapse of the stroma and disgregation the glands and the shedding of the endometrium is complete in about two days. The menstrual fluid consists of autolyzed tissue, including fragmented glands and masses of loose stroma infiltrated by inflammatory (polymorphonuclear exudates) and blood.

Abnormal uterine desquamation

Any type of derangement of the hypothalamic-pituitary-ovarian axis during childbearing age influences steroid secretion by the ovary with corresponding alterations in production of SHRs by endometrial cells. Anovulatory cycles are common in young women with the Stein-Leventhal syndrome (PCOD) and related disorders. They are also frequent in the perimenopausal period but may occur during the reproductive age. Endogenous or exogenous hormonal stimulation also modifies the programmed or the expected changes.

FUNCTIONAL DISORDERS OR DYSFUNCTIONAL UTERINE BLEEDING

From a clinicopathologic viewpoint, there are 3 major diagnostic patterns associated with dysfunctional uterine bleeding in the childbearing age:

? Glandular and stromal breakdown (estrogen breakdown bleeding).
? Irregular shedding.
? Inadequate luteal phase (luteal phase defect).

Glandular and stromal breakdown (estrogen breakdown bleeding) (anovulatory cycle)

Estrogen breakdown bleeding is a clinical term which indicates endometrial desquamation secondary to inadequate estrogenic stimulation. Typically it occurs in anovulatory cycles in which none of the developing follicles matures to trigger ovulation and subsequent corpus luteum formation. In such cases, the integrity of the endometrium depends entirely on estrogen levels since progesterone, which promotes endometrial maturation or differentiation, is not produced. Increasing estrogen levels may prolong endometrial growth and cause amenorrhea until their progressive or abrupt decrease is followed by focal or extensive breakdown of the endometrium. In estrogen replacement therapy, stimulation is mild but constant and a discrepancy between required hormone levels and therapeutic levels may develop. An abrupt desquamation of the endometrium usually follows a rapid decrease of high levels of estrogens after a period of amenorrhea.

The endometrial changes depend on several factors, i.e., time elapsed from the onset of the bleeding and biopsy, degree of estrogenic stimulation, and modality of the decrease of estrogen levels. The material removed can be predominantly hemorrhagic, with numerous blood clots and few endometrial fragments, or well preserved. These changes are different from menstrual endometrium and include:

? Fragments of proliferative endometrium (from few to numerous or large size) featuring:
    a) Normal proliferative endometrium.
    b) Disordered proliferative endometrium with dilated glands and metaplastic changes, including ciliated and oxyphilic metaplasia.
    c) Cystic (or simple hyperplasia) which is similar to disordered proliferative endometrium but is more abundant and shows higher degree of changes.

? Condensed closely packed hyperchromatic stroma cells with scanty cytoplasm distributed in:
  a) Clusters of varying size.
  b) Characteristic "balls".

? Epithelial changes in the lining of proliferative or condensed stroma showing:
  a) Stratification with hob nail features (syncytial changes).
  b) Eosinophilic cytoplasm (eosinophilic syncytial change).

? Vascular changes within the proliferative type endometrium and condensed stroma including:
  a) Dilated thin walled ectatic venules.
  b) Fibrin thrombi.

Irregular shedding

Under prolonged progesterone stimulation the endometrial integrity cannot be maintained. Corpus luteum, which ceases quite abruptly to function leading to menstruation, may occasionally persist for some days or become a corpus luteum cyst and menses are typically prolonged and abundant. In such cases irregular shedding may be clinically suspected and diagnosis can be made if a biopsy is performed after at least five days of bleeding. Another type of irregular shedding is secondary to abortion and similar changes may occur in polyps and endometritis. The basic changes include:

? Admixture of proliferative and secretory changes, in particular:
  a) Post-secretory or exhausted glands (dilated glands lined by cuboidal cells which have released their cytoplasmic secretion).
  b) Proliferative type glands (tubular glands with columnnar cells with pseudostratified nuclei and pale eosinophilic cytoplasm suggesting some type of secretion).
  c) Edematous to predecidual stroma.
? Glandular and stromal breakdown.

Inadequate luteal phase (luteal phase defect)

The effects of progesterone stimulation can be insufficient due to a primarily deficient follicle or corpus luteum or secondary to several conditions including elevated prolactinemia, hyperandrogenism, receptor defect, stress, fatigue and weight loss. The resulting inadequate luteal phase is not usually associated with abnormal bleeding, but severe dyssynchrony may be seen in symptomatic women. Evaluation is difficult and controverted as inadequate luteal phases have been found in parous women with regular cycles, cycles may be vary in a given woman, and endometrial changes are not uniform throughout the uterine cavity.

In women under investigation for infertility, the diagnosis of luteal phase defect requires correlation with clinical and laboratory data, including basal body temperature, serum progesterone levels, and follicle diameter on ultrasound. By definition, dyssynchrony between the expected day of the cycle and dating of the secretory endometrium (on biopsy) should be more than two days. The accuracy of the test is influenced by the lack of widely accepted criteria for diagnosis (dating is more precise in the early luteal phase, but late secretory endometrium is easier to be recognized) and the uncertain reproducibility. Although widely used in the past, evaluation of a luteal phase defect requires well trained gynecologic pathologists.

Luteal phase defect is characterized by:
? Endometrial dyssynchrony with the day of the cycle.
? Discordance between the degree of maturity of glands and stroma.
? Endometrial disgregation simulating glandular and stromal breakdown.

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TABLE 1. ORGANIC DISORDERS CAUSING UTERINE BLEEDING

Between ages 20 to 50 the most frequent lesions are:

? Leiomyomas, particularly submucosal leiomyomas.
? Endometrial polyps.
? Diffuse adenomyosis.

Other common uterine causes are:

? Secondary to contraception, including oral contraceptive use and intrauterine device.
? Secondary to known or unrecognized pregnancy, including abortion, ectopic pregnancy, trophoblastic disease.
? Inflammation, acute and chronic endometritis including those associated with pregnancy and intrauterine adhesions.
? Endometrial hyperplasia and carcinoma.
? Benign and malignant uterine tumors.

Systemic diseases and therapies associated with bleeding:

? Blood dyscrasias.
? Therapies related to coagulation.
? Functional thyroid diseases.
? Other systemic diseases.

ENDOMETRIAL HYPERPLASIA

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In a broad sense, the term endometrial neoplasia encompasses the spectrum of morphologic alterations that range from endometrial hyperplasia to the different types of endometrial carcinoma. Hyperplasia and carcinoma represent only two different points along the spectrum of endometrial cell proliferations.

Endometrial hyperplasia is defined by WHO (2003) as a spectrum of morphologic alterations ranging from benign changes, caused by an abnormal hormonal environment, to premalignant disease; these lesions display increasing degrees of architectural complexity and nuclear atypia.

A group of investigators has used an alternative approach to define precancerous lesions of the endometrium. They have proposed the term "endometrial intraepithelial neoplasia" to describe monoclonal lesions that share molecular alterations with endometrial carcinoma, and exhibit characteristic morphologic features.

In this presentation, both classification systems with their advantages and disadvantages will be discussed. A third type of noninvasive neoplastic proliferation named "intraepithelial carcinoma", which is currently considered the precursor lesion of serous carcinoma will also be discussed.

Clinical features

Endometrial hyperplasia is a frequent disease. In western countries, it is estimated that 150,000-200,000 new cases are diagnosed every year. It usually occurs around the menopause. However, it may also occur in young women and adolescents. The most frequent etiological factor of endometrial hyperplasia is unopposed estrogen excess (endogenous or exogenous), which may occur in different circumstances: 1) successive prolonged periods of anovulation; 2) estrogen administration; 3) peripheral conversion of androgens to estrone in adipose tissue in either obese women or patients with the polycystic ovarian syndrome; and 4) estrogen-secreting ovarian tumors. Abnormal bleeding is the most frequent presenting symptom, yet, a significant percentage of patients are asymptomatic.

Pathologic features

Gross findings

Endometrial hyperplasia is characterized by the presence of an abundant, irregular endometrial tissue, white to tan in color. It may be diffuse or polypoid, and protrudes into the endometrial cavity.

Microscopic findings

1. WHO System (2003)

The classification proposed by the International Society of Gynecological Pathologists (ISGP) and formulated by the World Health Organization (WHO) in 1994 and 2003, breakdowns endometrial hyperplasia into 4 subtypes, according to the degree of architectural complexity, and the nuclear features. Although application of this system may appear easy, it is sometimes difficult to apply in routine practice. Some studies have demonstrated that there is considerable lack of reproducibility

in the diagnosis and classification of endometrial hyperplasia, particularly in the recognition of cytologic atypia.

Simple hyperplasia without atypia (SH)

SH is characterized by increased endometrial volume and qualitative differences with normal cycling endometrium. There is balanced proliferation of both glands and stroma. The glands may exhibit marked variation in size and shape. Many of them are round and tubular, but others are tortuous, and cystically dilated (so-called cystic or Swiss cheese hyperplasia). They may exhibit irregular outlines and limited epithelial budding. The lining is pseudostratified. The cells are similar to those seen in the mid to late proliferative phase. Secretory changes are rarely present. Tubal metaplasia and ciliated cells are frequently seen. The epithelial cells contain oval nuclei with evently dispersed chromatin and inconspicuous nuclei. Mitotic figures are common. Cells undergoing apoptotic cell death are also present. Nuclear atypia is absent. The stroma is abundant and cellular, as it is seen in the mid to late proliferative phase. There is also dilatation and thrombosis of blood vessels. Although occasional irregular glandular outpouching can occur in simple hyperplasia, if these outpouchings are numerous enough to produce a complex glandular pattern, the diagnosis of complex hyperplasia is justified.

Complex hyperplasia without atypia (CH)

CH is characterized by an increased glandular crowding in comparison with simple hyperplasia. The glands have irregular profiles, and show outpouchings and papillary intraluminal infoldings. The glands usually show back-to-back crowding, with irregular outlines and structural complexity. Cell stratification and cellular polarity is generally maintained. Metaplastic changes of different types (squamous, ciliated, clear cell) may be present. Cytologic features are similar to simple hyperplasia. Mitotic figures and apoptotic bodies are frequent. Nuclear atypia is absent. The intervening stroma is dense, cellular and compact. There is a shift in the gland to stroma ratio in favour of the glands. Complex hyperplasia may be localized, and restricted to a few fragments in an endometrial biopsy showing a disordered proliferative endometrium, or simple hyperplasia.

Simple hyperplasia with atypia (SAH)

SAH is a rare disorder. It is characterized by the presence of the architectural features of simple hyperplasia, and atypia (see below)

Complex hyperplasia with atypia (CAH)

CAH is characterized by the presence of architectural features of complex hyperplasia, but the epithelial cells show nuclear atypia (see below).

Atypical hyperplasias (SAH and CAH) are characterized by the presence of nuclear atypia in the cells lining the glands, as well as by loss of axial polarity (Figure 5). The nuclei are usually large and round, in contrast with the elongated nuclei that are characteristic of SH and CH. There is nuclear pleomorphism, anisonucleosis, nuclear hyperchromasia, and increased nuclear to cytoplasmic ratio. Nucleoli are large and irregular. The chromatin may be either evenly or irregularly dispersed. Mitosis and apoptotic bodies are common. The cytoplasms may be abundant and eosinophilic. It is important to take into account that nuclear atypia may be focal.

2. The "Endometrial Intraepithelial Neoplasia" (EIN) approach

The EIN concept has been proposed as an alternative approach to the WHO classification system. The rationale for the development of this alternative scheme comes from the poor reproducibility attributed to the WHO classification system in several reports.

The EIN system is based on integrated morphological, molecular, morphometrical and prognostic studies. According to this approach, the true precancerous lesions are monoclonal proliferations that derive from polyclonal normal cycling endometrial glands by mutations, which confer small increases in growth advantage. Although genetically abnormal, these lesions may exhibit a benign growth pattern. Accumulation of sufficient genetic damage allows malignant transformation, a stage in which hormonal support is no longer required for survival. Morphometric analysis has suggested that the architecture of these lesions (glandular crowding) may be as important a diagnostic feature as atypia. Three different categories are recognized: 1) Benign hyperplasia; 2) Endometrial intraepithelial neoplasia; and 3) Cancer.

EIN is defined as the histopathologic presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric, and clinical outcome data.

One fundamental aspect of EIN is the correlation with the so-called morphometric, endometrial D-Score, which quantifies specific architectural patterns associated with increased clinical cancer risk. The 3 essential features that are contained in the D-score reflect architectural gland changes (volume percentage stroma, and outer surface density of glands) and nuclear size variation (standard deviation of the shortest nuclear axis).

From the molecular viewpoint, EIN is defined as a proliferative lesion that frequently exhibits monoclonality and similar molecular alterations to endometrial carcinoma (mutations in PTEN, microsatellite instability). Central in the concept of EIN is inactivation of *PTEN* tumor suppressor gene, which is hormonally regulated in the normal endometrium and mutated in EIN. As the abnormal glands clonally proliferate, they generate cohesive radiating clusters of PTEN negative glands that can be diagnosed as focal lesions by their altered cytology and architecture. The role of PTEN seems so relevant that it has been proposed that PTEN immunostaining could be used in the future, as an important tool to identify EIN. However, although PTEN immunohistochemistry can delimit many EIN, it is not currently appropriate for routine clinical use in patient diagnosis of EIN because of poor sensibility and specificity.

The diagnostic criteria of EIN are:

1) Maximun linear dimension exceeds 1mm in size, a scale that usually encompasses more than 5 – 10 glands.
2) Gland area exceeds that of stroma (volume percentage stroma < 55%)
3) Cytology difers between architecturally crowded focus and the background.
4) Mimics should be excluded (basal endometrium, hypersecretory endometrium, true endometrial polyps, regenerative endometrium)
5) Cancer should be excluded (maze-like patterns, cribriform growth pattern, solid areas)

Endometrial lesions, which do not meet these diagnostic criteria, should be classified as "benign hyperplasia".

Most EIN correspond to the lesions termed complex atypical hyperplasia in WHO (2003). Compared to WHO, 2% of simple hyperplasias, 44% of complex hyperplasias and 79% of atypical hyperplasias are EIN.

The risk of confusion when using the word ***neoplasia*** in a preneoplastic lesion is one of the main disadvantages of the EIN approach. Moreover, additional follow-up studies are required to fully validate this scheme.

Endometrial Intraepithelial Carcinoma (EIC)

EIC is the precursor lesion of the serous carcinoma of the endometrium. The lesion is characterized by the presence of highly malignant cells, resembling those of invasive serous carcinoma, which are restricted to the lining of the endometrial surface and glands, without any evidence of stromal invasion. Tumor cells show prominent pleomorphism, lack of polarity, large and atypical nuclei with prominent nucleoli, and frequent mitotic figures, many of them clearly aberrant. The cells show increased Ki-67 (MIB-1) immunostaining, and prominent p53 immunoreaction, which may be helpful in differential diagnosis.

EIC typically occurs in postmenopausal women, in the setting of an atrophic endometrium. It is sometimes restricted to a small area of an otherwise normal endometrial polyp. Rare examples of EIC restricted to polyps have been associated with extrauterine spread.

Differential Diagnosis:

Endometrial Hyperplasia versus non-neoplastic endometrial lesions

Endometrial hyperplasias are frequently overdiagnosed. The most commonly overgraded lesions include polyps, variations of the normal cycling endometrium (artifacts), anovulatory cycles, disordered proliferative endometrium, postmenopausal cystic atrophy, metaplasia, and endometritis. Hyperplasia is almost always a diffuse endometrial lesion whereas polyps, artifacs, and metaplastic changes are focal. An important fact that should be taken into account is that endometrial hyperplasia usually generates abundant material in curettage specimens, while the material obtained in other type of lesions is scanty.

The distinction between simple hyperplasia and disordered proliferative endometrium is often difficult to make since one may arise from the other and mixed lesions are frequent.

The glands in postmenopausal cystic atrophy are lined by a single layer of non-proliferative low cuboidal cells, and the stroma is generally atrophic.

The distinction between simple hyperplasia and endometrial polyps is sometimes difficult, because hyperplasia may occur within polyps. However, endometrial polyps usually have a polypoid configuration, dilated thick-walled blood vessels, and stromal fibrosis.

Distinction between endometrial hyperplasia and chronic endometritis is made by the absence of plasma cells, granulomata and stromal spindling.

Atypical Hyperplasia versus Well Differentiated (Grade 1) Adenocarcinoma

In most endometrial biopsies, distinguishing hyperplasia from adenocarcinoma is easy. Sometimes, however, CAH may be difficult to be distinguished from well differentiated adenocarcinoma in small biopsies or curettages, simply because some of the diagnostic criteria may be absent in a given case.

Kurman and Norris tried to elaborate criteria for making this differential diagnosis. They used as their primary criterion for adenocarcinoma the presence or absence of stromal invasion which was

defined by the presence of at least one of the following features: 1) desmoplastic stromal response in the vicinity of infiltrating glands, 2) confluent or cribriform glandular pattern, 3) extensive papillary pattern, and 4) replacement of stroma by squamous epithelium. To qualify as invasion, the last three changes were required to occupy at least half (2.1 mm) of a low power microscopic field 4.2 mm in diameter.

Using these criteria, when stromal invasion was absent in the endometrial curettage, invasive adenocarcinoma was present in the hysterectomy specimen in 17% of the cases. The carcinomas in these cases were well differentiated and confined to the endometrium or had invaded the myometrium but only superficially. In contrast, when stromal invasion was present in the curettings, residual carcinoma was identified in the uterus in 50% of the cases and, of these, one third were moderately or poorly differentiated and one quarter deeply invaded the myometrium.

The most useful feature for distinguishing CAH from well differentiated carcinoma is stromal disappearance between adjacent glands, because of the presence of confluent, back to back, villoglandular or cribriform glandular patterns. However, additional important findings are the presence of stromal desmoplastic response, tumor cell necrosis, and marked nuclear atypia. The presence of mucinous differentiation has also been regarded as an indirect indicator for invasive adenocarcinoma.

It is important to emphasize that some cases of well-differentiated endometrioid adenocarcinoma may show significantly less cellular atypia than examples of complex atypical hyperplasia. However, when a hysterectomy is performed in these patients, the myometrium may appear invaded by such indolent-looking neoplastic glands. On the other hand, approximately 25% of patients with CAH in curettings are found to have coexisting adenocarcinoma in the hysterectomy specimens.

In peri- and postmenopausal patients, distinction between complex atypical hyperplasia and well-differentiated carcinoma may not be important, since both lesions are treated similarly by hysterectomy. However, evaluation of premenopausal women should be made with great care. In young patients with complex atypical hyperplasia, the results of conservative therapy have revealed a 25% risk of recurrent carcinoma.

Prognosis and Treatment

Because of problems of terminology and lack of follow-up data, it has been difficult to determine the malignant potential of the various types of endometrial hyperplasia. If we follow the WHO approach, overall, it appears that about 1 –10% of the simple or complex hyperplasias and more than 25% of complex atypical hyperplasias progress to carcinoma after 1 to 20 years. There is not enough follow-up information in the literature about simple atypical hyperplasia to indicate that it is precancerous.

It is important to emphasize that, when complex atypical hyperplasia is diagnosed in a biopsy specimen, a well-differentiated adenocarcinoma is discovered in the hysterectomy specimen in 15-20% of the cases, or the lesion will eventually be followed by carcinoma in approximately 30% of the patients who did not undergo hysterectomy.

Kurman et al. reported that the progression rate to carcinoma was significantly higher among premenopausal patients with atypical hyperplasia (23%) than in those who had endometrial hyperplasia without atypia (1.6%). Thus, hyperplasia without atypia appears to be a highly reversible lesion (80%), whereas atypical endometrial hyperplasia seems to represent the immediate precursor of endometrioid carcinoma and is occasionally found in its proximity.

The premalignant potential of hyperplasias is also influenced by age, since 80% of simple hyperplasias occurring in women younger than 31 years of age will likely regress.

Endometrial hyperplasia may be treated with progestins. Response rates vary from less than 40% to 100%. Hyperplasia with atypia is less likely to respond to hormonal therapy. For that reason, peri and postmenopausal women with complex atypical hyperplasia are usually treated by hysterectomy. The treatment of choice in premenopausal women with complex atypical hyperplasia is controversial.

If the EIN approach is considered, the following therapeutic decision scheme is recommemded:

1. Benign hyperplasias (D-score> 1): short-term progesterone ablative treatment, followed by ultrasonographic and clinical surveillance.
2. EIN: hysterectomy is recommended.

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ADENOCARCINOMA OF THE ENDOMETRIUM

Jaime Prat, M.D.

Endometrial carcinoma is the most common malignant tumor of the female genital tract in the Western world. After an increase in the 1970s that resulted from the unrestricted use of estrogen replacement therapy in postmenopausal women, the incidence rates has become stable over the last two decades at 10-20 per 100,000 person-years. Recently, the progressive use of tamoxifen - a non-steroidal estrogen agonist and antagonist - for the treatment of breast cancer has been associated with increased risk of endometrial cancer although there is not complete agreement among different studies.

Approximately 80% of cases of endometrial carcinoma are well to moderately differentiated (*endometrioid*) adenocarcinomas, which are confined to the uterine corpus at diagnosis and therefore, most can be cured. Conversely, high-grade carcinomas (clear cell and serous carcinomas) only account for 15% to 20% of cases and show marked nuclear atypia. These tumors usually invade the myometrium, and may extend beyond the uterus at the time of hysterectomy. In addition to clinical and morphologic differences, these two groups of endometrial carcinomas differ in their pathogenesis. Whereas prognosis in the latter group is generally poor, the pathologist's role in establishing the outcome in the former group is crucial. Furthermore, it has become progressively apparent that both groups overlap to an extent, consequently making the dualistic model a guideline at best. Over the last two decades, several studies have demonstrated the prognostic importance of various key surgical and pathologic parameters, including histologic type, histologic grade, surgical-pathologic stage, depth of myometrial invasion, vascular invasion, and cervical involvement. This review presents the most important prognostic factors of endometrial carcinomas from the pathologist's viewpoint, and attempts to clarify existing conflicts in the classification and diagnosis of these tumors.

Two Types of Endometrial Carcinoma

A dualistic model of endometrial carcinogenesis has been proposed.[1-3] Over the last 15 years, and based on Bokhman's[1] clinical model for explaining the pathogenesis of endometrial carcinomas, these tumors have been classified into two types: type I tumors (about 80%) are *endometrioid* carcinomas frequently preceded by complex and atypical hyperplasia and associated with estrogenic stimulation. Type I tumors occur predominantly in pre- or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility, and late menopause. Typically, most endometrioid carcinomas are confined to the uterus and follow a favorable course. In contrast, type II tumors (about 20%) are *nonendometrioid* (largely serous and clear cell) carcinomas, occasionally arising in endometrial polyps or from precancerous lesions (endometrial intraepithelial carcinoma) in the vicinity of atrophic endometria.[45-54] Type II tumors are usually not associated with estrogen stimulation or hyperplasia, readily invade the myometrium and vascular spaces, and carry a high mortality rate (Table 1).

Although the dualistic model appears applicable to paradigmatic cases at both clinicopathological and molecular levels, there is often overlap in the clinical, pathological, immunohistochemical, and molecular characteristics of the tumors.[4] For instance, it has been shown that some nonendometrioid carcinomas (type II) may develop from preexisting endometrioid carcinomas (type I) as a result of tumor progression.[4] Obviously, these tumors may share the pathologic and molecular features of types I and II endometrial carcinoma. Therefore, even if the dualistic model is conceptually tempting, it is somewhat artificial and mixed tumors are frequently seen in routine practice.

Epidemiology

Most epidemiologic studies have regarded endometrial carcinoma as a single homogeneous disease and have not related risk factors with specific pathologic subcategories. Since *endometrioid* carcinomas predominate, it is not surprising that the reported risk factors are largely associated with endometrioid carcinomas. Consequently, almost all risk factors are thought to promote estrogen excess and protective factors are considered anti-estrogenic. Nevertheless, it has been recognized that some patients with endometrioid carcinomas do not exhibit the classic risk factors for these tumors and their development may be estrogen independent[21].

Risk Factors	**Protective Factors**
- Estrogen (10x after 10 yrs); (low risk)	-Oral contraceptives progesterone)
- Estrogenic tumors	-Smoking (? serum estrogens)
- Polycystic Ovarian Disease (? LH ? Androstenedione ? E3)	
- Nulliparity	
- Obesity (aromatization A? E)	
- Tamoxifen (E agonist and antagonist; controversial)	

Classification (WHO)

The new classification[25] of endometrial carcinomas proposed by the WHO in 1994 is based primarily on the cell type of the tumor, reflecting the fact that tumor cell type, as well as histologic grade, and degree of myometrial invasion,[37-39] has an important effect on biologic behavior. The recent 2003 WHO classification is essentialy similar.

Endometrioid carcinoma: Over 80% of endometrial adenocarcinomas are composed of tubular glands lined by stratified non-mucin-containing epithelium[40,41]. In the rare cases in which basal vacuolization or supranuclear vacuolization are present, a diagnosis of *secretory* endometrioid adenocarcinoma is appropriate. Separation of adenoacanthomas and adenosquamous carcinomas has been based on whether the squamous component of the tumor is cytologically benign or cytologically malignant and invasive of the stroma, independently of the glandular component. The WHO committee concluded that such a distinction was not reproducible because of the frequency of tumors in an intermediate category.[25] The term "adenocarcinoma with squamous differentiation", modified by the grade of the tumor, has been recommended.[42] Villoglandular adenocarcinomas are also thought to represent another variant of endometrioid endocarcinoma with no significant difference in behavior.[25] A granulomatous response may be encountered in the pelvic peritoneum, secondary to keratin exfoliation in cases of adenocarcinomas with squamous differentiation[43]. These granulomas have no prognostic significance. High-grade endometrioid carcinomas may contain a trophoblastic component and are associated with production hCG.

Mucinous adenocarcinoma: This rare type of adenocarcinoma is characterized by the presence of a significant amount of intracellular mucin in a significant number of the tumor cells.[25,44] Minor quantities of mucinous elements in an otherwise typical endometrioid adenocarcinoma do not warrant a diagnosis of mucinous adenocarcinoma.[25,44] Mucinous adenocarcinoma of the endometrium may be difficult to distinguish from mucinous adenocarcinoma of the endocervix in a curettage specimen. In the endometrial tumor there is usually an admixture with endometrioid neoplastic glands, whereas in the endocervical tumor there is often a dense fibrous (desmoplastic) stroma. A prominent papillary pattern favors an endometrial origin. Furthermore, endometrial carcinomas are characterized by a vimentin-positive, ER-positive, and carcinoembryonic antigen (CEA)-negative immunoprofile, whereas endocervical adenocarcinomas are characterized by the

opposite findings.[55,56] Mucinous carcinomas tend to be low-grade and minimally invasive tumors and, therefore, have an excellent prognosis.[44]

Serous papillary carcinoma: Microscopically, this high-grade carcinoma resembles papillary serous carcinoma of the ovary.[45,46] It is characterized by a coarse and irregular papillary pattern with cellular budding, marked nuclear pleomorphism (grade 3), macronucleoli, slit-like and irregular glandular spaces, intraluminal papillary tufting, and occasionally psammoma bodies.[45,46] Clear cell differentiation is found in about one third of the cases. Solid growth and necrosis may be present. Deep myometrial and vascular invasion are frequent. Grading serous carcinomas is useless, since all of them are high grade by definition. The discordance between well differentiated architecture (glands and papillae) and nuclear anaplasia is the morphologic hallmark of serous carcinoma.[45,46] The papillary pattern of the serous carcinoma is to be distinguished from the typical villoglandular papillary pattern that is sometimes found in endometrioid carcinomas (Type I). The latter do not show severe nuclear atypia, solid growth, necrosis, or abnormal mitotic figures. The differential diagnosis is important because the serous carcinoma is associated with a poor prognosis related to the frequency of deep myometrial invasion and peritoneal dissemination, whereas the villoglandular endometrioid carcinoma is associated with a good prognosis, similar to that of the non-papillary endometrioid adenocarcinoma. Multicentric carcinogenesis may play an important role in the intraabdominal spread of serous carcinoma.

A significant percentage of serous carcinomas may be mixed with other patterns of differentiation, such as endometrioid carcinoma or arise within benign endometrial polyps. When at least 25% of the neoplasm is serous, the behavior of these tumors resembles that of pure serous carcinoma.

Vascular invasion is common in serous carcinoma and is associated with a higher frequency of extrauterine disease. Unlike in endometrioid carcinomas, depth of myometrial invasion in serous carcinomas is not a reliable predictor of stage. Several studies have demonstrated that serous carcinomas that have not invaded the myometrium can be associated with extrauterine disease or recur after the initial treatment.[47,48] Lymph node metastases have been identified in 36% of serous carcinomas without myometrial invasion[48]. Six of 10 serous carcinomas that were associated with polyps had little or no myometrial invasion, although all six tumors recurred.[49]

The uninvolved endometrium adjacent to serous carcinoma is atrophic in 76% of the cases and hyperplastic in only 5% (usually mixed tumors; probable sequence: hyperplasia ? endometrioid ca ? serous ca).[2] In contrast, endometrioid carcinomas are associated with atrophy in 29% of the cases, and hyperplasia in 46%.[2,50]

Recent studies suggest that serous carcinoma develops from malignant transformation of the surface epithelium. The precursor lesion designated e*ndometrial intraepithelial carcinoma* (EIC) has been described in the atrophic endometrium adjacent to the tumor; endocervix; tubal mucosa; and ovarian, intestinal, or other peritoneal surfaces.[2,46] The finding of this precursor lesion would explain that serous carcinomas that have not invaded the myometrium or appear confined to endometrial polyps can be associated with peritoneal disease or recur after the initial therapy.[46,51] P53 overexpression, c-erbB-2 immunoreactivity, and aneuploidy are more common in serous than in endometrioid carcinomas, which is consistent with the aggressive behavior of the former tumors.[52,53]

The behavior of serous carcinomas is significantly worse than grade 3 endometrioid carcinomas. Serous carcinomas are associated with five times the number of expected recurrences for clinical stage I tumors[45].

Clear cell carcinoma: This tumor again is identical histologically to the clear cell carcinoma of the ovary. It may be characterized by clear cells filled with glycogen, hobnail cells protruding into glandular lumens or both. It may be highly papillary. Like the serous carcinoma, the tumor tends to occur in older women and it is associated with a poor prognosis.[25,54]

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FIGURE 1: **The two types of Endometrial Carcinoma**.

	Type I	**Type II**
Age	Pre- and Perimenopausal	Postmenopausal
Unopposed Estrogen	Present	Absent
Hyperplasia-Precursor	Present	Absent
Grade	Low	High
Myometrial Invasion	Minimal	Deep
Specific Subtypes	Adenocanthoma	Adenosquamous
		Clear cell
		Papillary Serous
Behavior	Stable	Progressive
Genetic alterations	Microsatellite instability	P53 mutations, LOH

FIGURE 6: **Histologic Classification of Endometrial Carcinoma**

Endometrioid
  Typical
  Variants
  With squamous differentiation
  Secretory carcinoma
  Ciliated carcinoma
Serous papillary adenocarcinoma
Clear cell adenocarcinoma
Mucinous adenocarcinoma
Squamous cell carcinoma
Mixed carcinoma*
Undifferentiated carcinoma

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* A carcinoma containing greater than 10% of a second cell type

PROGNOSTIC PARAMETERS OF ENDOMETRIAL CARCINOMA

Jaime Prat, M.D., F.R.C.Path.

In patients with endometrial carcinoma, the pathologist plays an important role in establishing the prognosis and the need for postoperative adjuvant treatment. Over the past two decades, several pathologic features, which clearly separate two or more groups of these patients with different outcome (disease-free survival or recurrence), have been described and confirmed. Prognostic parameters are considered useful when they achieve statistical value, are reproducible, and show significance in multiple investigations.

Several studies done by the Gynecologic Oncology Group (GOG) have shown that the prognostic parameters for endometrial carcinoma can be separated into uterine and extrauterine factors.[1-4] Uterine factors include (1) histologic type, (2) histologic grade, (3) depth of myometrial invasion, (4) vascular invasion, (5) presence of atypical endometrial hyperplasia, (6) cervical involvement, (7) DNA ploidy and S-phase fraction, and (8) hormone receptor status. Extrauterine factors include (1) positive peritoneal cytology, (2) adnexal involvement, (3) pelvic and paraaortic lymph node metastasis, and (4) peritoneal metastasis.

Patients with extrauterine disease, cervical involvement, and vascular invasion constitute a high risk group (with approximately 65% frequency of recurrence).[4] Alternatively, patients whose tumors are confined to the corpus uteri (without cervical involvement) and have no evidence of vascular invasion have a lower overall risk of recurrence. Their prognosis, however, varies significantly depending upon three main pathologic parameters: (1) histologic type, (2) histologic grade, and (3) depth of myometrial invasion.[2-6] In this group, accurate pathologic evaluation is crucial for establishing the appropriate therapy.

Histologic type

The cell type has consistently been recognized as an important predictor of the biologic behavior of endometrial carcinoma. Over the last 15 years, and based on Bokhman's[7] clinical model for explaining the pathogenesis of endometrial carcinomas, these tumors have been classified into two types: type I tumors (about 80%) are *endometrioid* carcinomas (Fig. 1) frequently preceded by complex atypical hyperplasia and associated with estrogenic stimulation. Type I tumors occur predominantly in pre- or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility, and late menopause. Typically, most endometrioid carcinomas are confined to the uterus and follow a favorable course. In contrast, type II tumors (about 20%) are *nonendometrioid* (predominantly serous and clear cell) carcinomas (Fig. 2), occasionally arising in endometrial polyps or from precancerous lesions (endometrial intraepithelial carcinoma) in the vicinity of atrophic endometria.[8,9] Type II tumors are usually not associated with estrogen stimulation or hyperplasia, readily invade the myometrium and vascular spaces, and carry a high mortality rate (Table 1).

Furthermore, it has been found that the molecular alterations involved in the development of endometrioid (type I) carcinomas differ from those of serous (type II) carcinomas.[10,11] The former tumors often show microsatellite instability (MI) (20-30%)[12,13] and *PTEN* mutations (30-50%),[14,15] and only rarely exhibit p53 mutations (?10%).[16] In contrast, the vast majority of serous carcinomas show p53 mutations, loss of heterozygosity (LOH) on several chromosomes, and only occasionally have microsatellite instability[16,17] (Table 1). Although the dualistic model appears applicable to paradigmatic cases, there is often overlap in the clinical, pathological, immunohistochemical, and molecular characteristics of the tumors.[11,13] Indeed, it has been shown that some nonendometrioid carcinomas (type II) may develop from preexisting endometrioid carcinomas (type I) as a result of

tumor progression.[18] In such cases, the resulting tumors may share the pathologic and molecular features of types I and II endometrial carcinoma. Therefore, even if the dualistic model is conceptually tempting, it is somewhat artificial, and mixed carcinomas are frequently seen in routine practice.

Adenocarcinoma with squamous differentiation (which occurs in about 25% of endometrial cancers) is considered a variant of endometrioid carcinoma and the grade of the glandular rather than the squamous component is a better prognostic indicator for these tumors.[19, 20] Otherwise typical and well differentiated endometrioid carcinomas may exhibit secretory or ciliated differentiation, focally or predominantly. The presence of such histologic components does not change the overall favorable prognosis of these tumors.[21-23] Villoglandular adenocarcinomas (Fig. 3) are also thought to represent another variant of endometrioid adenocarcinoma with no significant difference in behavior.[24,25] The rare mucinous carcinomas tend to be low-grade and minimally invasive tumors and, therefore, have an excellent prognosis.[26] In contrast, serous, clear cell, squamous, and undifferentiated carcinomas are frequently lethal tumors with overall 5-year survival rates from 30% to 70%.[18,24,27-30]

Histologic grade

Whereas nonendometriod carcinomas are considered high-grade tumors by definition and there is no need to grade them, grading of endometrioid carcinomas is prognostically very important. These tumors span the spectrum from very well differentiated to almost completely undifferentiated, and probably merge at the higher end of the spectrum with undifferentiated carcinomas.[31] The prognostic value of grading endometrial adenocarcinomas has been recognized for many years.[6,32] The 1988 International Federation of Gynecology and Obstetrics (FIGO) grading system is based primarily upon architectural features.[33] Tumors that are 5% or less solid are grade 1 (Fig. 4), those that are 6% to 50% solid are grade 2 (Fig. 5), and those that are greater than 50% solid are grade 3 (Fig. 6). Areas of squamous differentiation are not accepted as evidence of solid tumor growth; solid growth is based only on the non-squamous (glandular) component. The presence of grade 3 nuclear features, however (i.e., marked nuclear pleomorphism, coarse chromatin, prominent nucleoli), in architecturally grade 1 or 2 tumors increases their grade by one.[6] Most endometrioid carcinomas are architecturally grade 1 and assessment of whether the nuclear features are grade 3 is quite subjective. As previously stated, in serous carcinoma, clear cell carcinoma, and squamous cell carcinoma, nuclear grading takes precedence over architecture.

The value of the FIGO grading system was demonstrated by Zaino and coworkers in a univariate analysis of over 600 patients with clinical stage I or occult stage II endometrioid carcinomas. The 5-year relative survival was 94% for the patients with grade 1 tumors, 84% for grade 2, and 72% for grade 3.[19]

Subsequent modifications to the FIGO grading scheme have been suggested but not formally adopted. Taylor et al.[34] have proposed a two-tiered grading system (based on the FIGO system) in which low-grade tumors have 20% or less nonsquamous solid areas, whereas high-grade tumors exhibit more than 20% nonsquamous solid areas. They found that this system had higher reproducibility and same or better prognostic significance than the three grade FIGO system. Recently, Lax et al.[35] also proposed a binary architectural grading system based on the presence of greater than 50% solid growth (without distinction of squamous from glandular epithelium), a diffusely infiltrative growth pattern, and tumor cell necrosis. High grade tumors should exhibit at least two of the three previous criteria. This system stratified patients in three prognostic and therapeutic groups: (a) patients with low-stage (IA or IB) low-grade tumors had a 100% 5-year survival rate; (b) patients with higher stage (IC and II-IV) low-grade tumors, and those with high-grade tumors confined to the myometrium (IB and IC) had a 5-year survival rate of 67% to 76%;

and (c) patients with advanced stage high grade tumors had a 26% 5-year survival rate.[35] The first group of patients requires no further treatment. Those patients in the second group with stage IC tumors (confined to the corpus), either low-grade or high-grade, should be considered for postoperative radiation therapy. The subset of patients with advanced stage low-grade tumors, with a 5-year survival rate of 76%, has not been previously recognized. Although progestin therapy is usually not effective in patients with advanced-stage disease, it appears to be effective in young women with well differentiated endometrial carcinomas, even if they are at advanced stage. In contrast, advanced stage high-grade tumors require adjuvant chemotherapy.[35]

Since histologic grade correlates with other prognostic factors such as age, stage, and depth of myometrial invasion, it would seem that histologic grade is not an independent prognosticator. Indeed, its significance decreases after adjustment for these other factors.[32, 36] Nevertheless, as suggested by the results of Lax et al., even for patients with advanced stage disease, histologic grade carries prognostic value.[35]

FIGO Stage

Although not perfect, FIGO stage is the single strongest prognostic parameter for women with endometrial carcinoma.[37-40] The 1971 FIGO clinical staging system (based upon sounding of the uterus, fractional curettage, and pelvic examination) proved to be less accurate than histologic evaluation of the hysterectomy specimen.[37-39] Determination of spread of tumor to the cervix (stage II) based on fractional curettage had an error rate of approximately 50%.[37, 39] Decrease in preoperative radiotherapy practice caused FIGO in 1988 to change from a clinical to a surgical-pathologic staging system (Table 2).[33] The new staging system requires hysterectomy as well as assessment of pelvic and paraaortic lymph nodes, adnexae, and peritoneal fluid cytology. Pathologic evaluation includes histologic grade, depth of myometrial invasion, and determination of cervical involvement. All this information should be included in the surgical pathology report.

Endometrial carcinomas are divided into 4 stages: (I) confined to the uterine corpus; (II) extension to the uterine cervix; (III) involvement of pelvic organs (true pelvis); and (IV) spread beyond the true pelvis. The vast majority of patients have tumors limited to the uterus. Stage I disease has 3 subdivisions based on the extent of tumor invasion into the uterine wall: IA (tumor confined to the endometrium); IB (invasion limited to the inner half of the myometrium); and IC (tumor invasion to the outer half of the myometrium). Stage II is also subdivided into IIA (only endocervical gland involvement) and IIB (cervical stromal invasion). Stage III tumors are subclassified into three groups: IIIA, when the tumor invades the uterine serosa, and/or the adnexae, and/or there is a positive peritoneal cytology; IIIB, if there is vaginal involvement or metastasis; and IIIC, when the tumor metastasizes to the pelvic and/or paraaortic lymph nodes. Finally, Stage IVA tumors are those that have invaded the bladder and/or rectal mucosa, whereas Stage IVB tumors have extended beyond the pelvis and metastasize to intraabdominal or inguinal lymph nodes (Table 2).[33]

The 5-year disease free survival has been reported as 90% for stage I, 83% for stage II, and 43% for stage III.[41] Univariate analysis reveals that 5-year survival for patients in stage IA is 93.8%, in stage IB, 95.4%, and in stage IC, 75% (Table 3).[39]

Intraendometrial carcinoma (Stage IA)

Endometrial stromal invasion is manifested by various architectural and cytologic features, some of which may be absent in individual cases, leaving the final decision to the overall evaluation of the lesion. In most cases, there is confluent arrangement of clearly malignant glands, which may result in either a cribriform pattern or extensive papillary growth into glandular lumina. Rarely, however, the invasive glands lack significant nuclear atypia and the diagnosis of stromal invasion relies

exclusively upon architectural features. Occasionally, invasion is manifested within the endometrium by the presence of a desmoplastic stroma around the tumor glands[42] (Fig. 7). Recently, a diagnostic test to predict myoinvasion based on glandular complexity and severe cytologic atypia (nuclear pleomorphism and nucleolar prominence) have been proposed.[43]

Myometrial invasion

In low-stage endometrial carcinomas, myometrial invasion is an independent predictor of outcome.[3,4,32,36,44-46] Recognition of myometrial invasion is straightforward when glands that are irregularly shaped, randomly distributed, and surrounded by a desmoplastic stroma, infiltrate the myometrium (Fig. 8). Occasionally, however, a carcinoma that has not invaded the myometrium shows an irregular endomyometrial junction in which rounded nests of tumor seem to protrude into the inner myometrium, and are misinterpreted as evidence of superficial myometrial invasion (Fig. 9). In fact, myoinvasion is frequently overdiagnosed in routine practice in as much as 25% of the cases. In contrast, failure to diagnose true myoinvasion by the referring pathologist is extremely rare.[31] The clue to this problem is the frequent failure to recognize that the normal endomyometrial junction is often not a straight line, but rather a series of hills and valleys with shorter and longer tongues of endometrium dipping down into the myometrium. Similarly, irregular tongues of endometrial carcinoma are often seen and do not represent true invasion of the superficial myometrium.[31] (Fig. 9). An extension of this concept is the involvement of foci of adenomyosis by carcinoma (Fig. 10). Adenomyosis is really a "diverticulosis" of endometrium deep into the myometrium, and carcinoma can extend deeply into these foci without invading the myometrium.[31] Tumor involvement of adenomyotic foci occurs in about 25% of the cases and is not associated with an adverse prognosis. According to three reports,[47-49] comprising a total of 50 patients, criteria used for distinguishing adenomyotic involvement by carcinoma from true myometrial invasion include: a) presence of endometrial stroma; b) presence of benign endometrial glands; and c) absence of inflammatory response and desmoplasia.[47-49] In older women, in whom the adenomyotic stroma is often atrophic, the distinction may be difficult, and CD10 immunostaining can be helpful in the identification of the adenomyotic stromal cells (Fig. 10D). Alternatively, truly myoinvasive tumors may show an expansile or pushing border and may be interpreted as noninvasive. This problem is usually resolved by including a block of the tumor with the adjacent normal endomyometrial junction. Rare carcinomas of the uterine corpus arise within adenomyosis without involvement of the ectopic endometrium. Such tumors, which can be of an unfavorable histologic subtype, may be associated with a delay in diagnosis resulting in a more advanced stage at presentation.[50]

The pattern of myometrial invasion may vary considerably from widely scattered glands and cell nests throughout the myometrium, frequently associated with stromal retraction that simulates vascular invasion (Fig. 11), to more crowded glands with varying degrees of differentiation. When the invasive glands are well differentiated and associated with little or no stromal response, the term "*adenoma malignum*" pattern has been applied[51] (Fig. 12). Two studies have suggested that this pattern may have an adverse prognostic significance[46,52] but, more recently, a larger study did not confirm this suggestion.[51] More often, however, myoinvasion is accompanied by a fibromyxoid stromal reaction, a lymphocytic infiltrate, or both. Whereas the latter finding is associated with a favorable outcome, the presence of a host stromal reaction correlates with a higher frequency of death or recurrence. Occasionally, myoinvasive endometrioid carcinomas with prominent fibromyxoid stromal reaction contain microcystic or slit-like glands lined by flattened epithelial cells that can be easily overlooked or misinterpreted as blood vessels.[46,53] According to a recent report, these distinctive glandular changes (microcystic, elongated, or fragmented glands), which are likely degenerative, are associated with an adverse effect on prognosis, probably because of a greater frequency of vascular invasion.[53]

In addition to the three subdivisions proposed in the 1988 FIGO staging system, several other methods have been effectively used for measuring myometrial invasion, including division of myometrial thickness by thirds, depth of tumor invasion in mm, or distance between the tumor and the uterine serosa in mm. Nevertheless, the best method for assessment of depth of myometrial invasion has not been established. It has been found that the risk of extrauterine extension for intraendometrial tumors is only 8%; tumors invading the inner third have a 12% risk, and those invading the full myometrial thickness, 46% risk.[2] There are, however, some exceptions. Serous carcinomas apparently confined to a polyp may occasionally be associated with extrauterine disease. In such cases, either myometrial or vascular space invasion have been missed, or the carcinomas have developed multicentrically.[9,54]

As previously stated, myometrial invasion is an independent predictor of outcome. In the GOG experience, recurrence developed in only 1% of patients with no myometrial invasion compared with 7% with inner 1/3, 14% with middle 1/3, and 15% with outer 1/3 invasion (Table 4).[4] A study of over 400 patients with clinical stage I endometrioid carcinomas revealed that the 5-year survival was 94% when the tumor was confined to the endometrium, 91% when the tumor involved the inner third of the myometrium, 84% when the tumor extended into the middle third, and 59% when the tumor infiltrated the outer third of the myometrium (Table 5).[19]

The decision to perform pelvic and para-aortic lymph node sampling/dissection is largely based on depth of myometrial invasion (also on cell type and histologic grade). Intraoperatively, the pathologist may be requested to assess these features by frozen section.[55,56] A pilot study revealed a usable algorithm for a reasonable likelihood of finding metastatic disease: for tumors confined to the endometrium (all histologic grades) the risk was negligible; for superficial myometrial invasion, the risk was substantial only for grade 3 carcinomas; for middle third invasion, the risk was substantial for grade 2 and grade 3 tumors; and for deep myometrial invasion, all grades of tumor had substantial risk (20-45%) (Table 6).[1]

Vascular invasion

The presence of tumor cells within endothelial lined spaces is a strong predictor of recurrence and death from tumor, independent of histologic grade or depth of myometrial invasion.[57-59] As stated earlier, stromal retraction is a frequent artifact which may simulate vascular invasion. Immunoperoxidase staining of endothelial cells (factor VIII or CD31) may facilitate recognition of vascular channels.[46] Also, a perivascular lymphocytic infiltrate is often associated with vascular invasion. Vascular invasion is infrequent in endometrioid carcinomas. The frequency of vascular invasion increases with unfavorable cell types, high histologic grade, and deep myometrial invasion. Nevertheless, the presence of vascular invasion, independent of grade and depth of myoinvasion is highly suggestive of lymph node metastases.[36,59] Vascular invasion occurs in 35-95% of serous carcinomas.[18,27,28]

Endometrial hyperplasia

Endometrioid carcinomas that are accompanied by atypical endometrial hyperplasia and exhibit various metaplasias, particularly ciliated and eosinophilic metaplasia, are associated with a favorable prognosis. These tumors are frequently low-grade carcinomas and lack myometrial invasion.[60-61] Alternatively, high-grade tumors are often accompanied by an atrophic endometrium.

Cervical involvement (Stage II)

Cervical involvement in endometrial carcinoma, a finding present in 6% to 20% of the cases, usually results from direct surface or stromal extension, although it may be secondary to implantation or lymphatic spread.[39,62-64] Implantation occurs in the denuded endocervix following fractional curettage in about 5% of the cases.[62,64] As stated earlier, histologic diagnosis of cervical involvement on the basis of the findings within an endocervical curettage can be difficult.[37,39,64] The diagnosis of cervical involvement (stage II disease) in the 1988 FIGO staging system is based on examination of the hysterectomy specimen.[33]

The two subdivisions of stage II (A: endocervical gland involvement; and B: cervical stromal invasion) may be difficult to distinguish and the prognostic value of such distinction has been questioned.[62,63] Nevertheless, it seems quite logical that the prognosis of a stage IIA carcinoma with exclusively glandular involvement (Fig. 13), should be better than that of a stage IIB carcinoma with destructive stromal invasion (Fig. 14). In fact, FIGO data document that the outcome of stage IIA G1 tumors is significantly better than that of stage IC G3 tumors (invasion > 1/2 of the myometrium without cervical involvement).[65] Alternatively, an adenocarcinoma involving the cervical glands may only represent a separate adenocarcinoma in situ primary in the endocervix. Most likely, patients with stage IIA tumors are currently overtreated and additional survival studies should be done to compare cases with various degrees of cervical involvement.

Occasionally, grade 1 or 2 endometrial carcinomas invade predominantly within the deep endocervical stroma, undermining the normal endocervical glands and rising the possibility of an independent primary endocervical carcinoma.[66] Additional sections that show continuity between the tumor glands in the cervix and those in the corpus may facilitate the correct diagnosis.[66] Furthermore, endometrial carcinomas are characterized by a vimentin-positive, ER-positive, and carcinoembryonic antigen (CEA)-negative immunoprofile, whereas endocervical adenocarcinomas are characterized by the opposite findings.[67,68]

Serosal invasion, peritoneal cytology, and adnexal involvement (Stage IIIA)

In the view of many gynecologic oncologists, the criteria used for classifying an endometrial carcinoma as stage III tumor (6% of cases) are somewhat artificial.[65] The adverse prognostic significance of stage IIIA tumors (based on tumor involvement of the uterine serosa or positive peritoneal cytology) (Fig. 15) has not been universally confirmed.[69] Serosal invasion represents the extreme of deep myometrial invasion of stage I disease. It is quite different from adnexal spread and, according to some authors, the two should not be lumped.[65] In the ovarian carcinoma staging system, surface involvement of the ovary is classified as stage I, whereas in the endometrial carcinoma system serosal involvement of the uterus is classified as stage III; again, according to some authors, the former seems appropriate whereas the latter does not.[65]

Positive peritoneal cytology is often associated with other risk factors such as high tumor grade, deep myometrial invasion, and extrauterine spread.[69-71] Nevertheless, some investigators have found a statistically significant difference in survival between patients with clinical stage I and II disease with and without positive peritoneal cytology.[46,70] (32% versus 7% recurrence rate). Between 5% and 15% of patients have positive peritoneal cytology as their only manifestation of extrauterine spread.[3] Presently, it is unclear whether patients with positive peritoneal cytology in the absence of known extrauterine disease should be treated.

It seems possible that many of the tumors classified as stage IIIA, based on the presence of "adnexal involvement", are indeed independent primary ovarian carcinomas, particularly endometrioid carcinomas and, naturally, the prognosis of these cases would be as favorable, if not even better,

than that of stage IIIA endometrial carcinomas with serosal involvement or positive peritoneal cytology.

Lymph node metastasis (Stage IIIC)

Endometrial carcinomas associated with pelvic and/or paraaortic lymph node metastasis are classified as stage IIIC tumors[33] (Fig. 16). Almost a third of patients with positive pelvic lymph nodes have positive paraaortic nodes. Prognosis with positive pelvic lymph nodes seems more favorable than with positive paraaortic lymph nodes.[4] In fact, in a GOG study, only 36% of patients with positive aortic nodes were free of tumor at 5 years compared with 85% with negative aortic nodes;[4] and yet these two findings are both considered as stage IIIC in the FIGO staging system.

In clinical stage I carcinomas, the frequency of lymph node metastasis is related to depth of myometrial invasion. Inner third myometrial invasion is associated with a 5%, middle third with a 23%, and outer third with a 33% rate of lymph node metastasis.[19] When grade and myometrial invasion are considered together, grade 1 tumors invading the inner third are not associated with pelvic node metastasis, but with outer third invasion, pelvic metastases occur in 25% of the cases (Table 7).[19]

Ploidy

Approximately two thirds of endometrioid carcinomas are diploid by flow or static cytometry. In contrast, 55% of the non-endometrioid carcinomas (serous, clear cell or undifferentiated carcinomas) exhibit non-diploid DNA patterns. Diploid tumors are usually low-grade endometrioid carcinomas with only superficial invasion, and are associated with longer survival than aneuploid carcinomas.[72-75] Differences in disease-free survival for stage I tumors have been as significant as 94% for diploid versus 64% for aneuploid carcinomas.[76-78] Therefore, DNA content is thought to be a useful prognostic parameter.

Steroid receptors

Most endometrioid carcinomas contain cells with both estrogen (ER) and progesterone receptors (PR) as a sign of differentiation. Currently, assessment of ER and PR is largely performed by immunohistochemistry. Characteristically, endometrioid carcinomas exhibit marked heterogeneity in ER and PR distribution. The presence and quantity of steroid receptors correlate with FIGO stage, histologic grade, and survival.[79-82] There is also correlation between ER and PR and *bcl-2*, absence of mutant *p53*, and low intratumoral angiogenesis. Nevertheless, because of great variation in reported data, ER and PR are not routinely measured in hysterectomy specimens. In contrast, measurement of steroid receptors in metastases may be helpful for establishing appropriate treatment.

Bcl-2

bcl-2 is a proto-oncogene that inhibits programmed cell death or apoptosis. The immunohistochemical expression of Bcl-2 protein varies during the menstrual cycle: it is highly expressed in the proliferative phase, with downregulation during the secretory phase. High levels of Bcl-2 are found in endometrial hyperplasia, with decreased expression in adenocarcinoma. Loss of Bcl-2 has been associated with poorer prognosis, increased depth of invasion, higher FIGO stage, and aggressive cell types,[83] and also with a higher probability of lymph node metastasis.[84,85]

c-erb-B2 (*HER-2-neu*) and *P53*

Amplification or overexpression of the c-erb-B2 (HER-2-neu) oncogene occurs in about 20-40% of endometrial carcinomas (Fig. 17) and has been associated with other adverse prognostic factors, including advanced stage, higher grade, and worse overall survival;[86,87] however, some studies have found that c-erb-B2 is not independently associated with adverse prognostic factors, although it does seem to have an influence on overall survival.[88,89] Currently, c-erb-B2 is thought to be a parameter of only potential utility. In contrast, mutation or overexpression of *p53* (Fig. 18) has been constantly associated with lower survival, particularly in serous carcinomas, in which it correlates with other strong adverse prognostic factors such as advanced stage and absence of PR.[77,87] In multivariate analysis, *p53* status has shown an independent effect on survival.[89] Increased expression of cyclin A occurs in high-grade endometrial carcinomas associated with p53 expression. Positive staining for cyclin A has recently been described in 31% of endometrial carcinoma cases as an indicator of unfavorable prognosis.[90]

Markers of proliferation

Mitotic count, S-phase fraction by flow cytometry, and proportion of proliferating cells by immunohistochemistry (PCNA, Ki-67, MIB-1) are the methods most commonly used. Ki-67 and MIB-1 identify cells in most of G1, S, G2, and M phases of the cell cycle.[91-93] PCNA and Ki-67 expressions in stage I endometrial carcinoma correlate with histologic grade, depth of myometrial invasion, and risk of recurrence. Most endometrioid carcinomas express low-Ki-67 proliferation index and have a favorable prognosis, whereas most serous and clear cell carcinomas show high Ki-67 proliferation index and have poor outcome.

Microsatellite instability (MI)

Microsatellites are repetitive DNA sequences that are widely distributed throughout the genome. Because of their repetitive structure, microsatellites are particularly susceptible to replication errors, resulting in insertion or deletion mutations (MI).[94] The genes responsible for MI encode proteins involved in DNA mismatch repair such as MLH1, MLH6, MSH2, MSH3, and PMS2. Mutations of these genes alter the ability of the cells to repair replication errors. Although MI was initially found in cancers from patients with the hereditary nonpolyposis colon cancer (HNPCC) syndrome,[95] it has also been encountered in sporadic tumors as well. Affected individuals in HNPCC families carried germline mutations in the DNA repair genes, primarily MLH1 or MSH2. In contrast, most sporadic endometrial carcinomas with MI do not have acquired mutations in mismatch repair genes; MI in these cancers is thought to be caused by hypermethylation of the MLH1 promoter, leading to epigenetic inactivation of this DNA repair gene.[96] MI has been found in up to 30% of endometrial carcinomas, particularly of the endometrioid type,[13] and is associated with favorable outcome.[97] Although most studies have not found a correlation between MI and age, race, histologic grade, stage, or depth of myometrial invasion, the 5-year survival rate of endometrioid endometrial carcinomas with MI has been described to be about 20% better than that of cases without it.[97] The association of MI with endometrioid histology explains the favorable prognosis and suggests that the pathway of molecular carcinogenesis characterized by inactivation of mismatch repair genes results in a less aggressive clinical phenotype. Endometrial carcinomas with MI are more likely to have PTEN mutations (see below) and less likely to have p53 overexpression, a molecular abnormality frequently found in nonendometrioid carcinomas.[97]

PTEN

The tumor suppressor gene *PTEN* (phosphatase and tensin homologue deleted from chromosome 10), also called *MMAC1* (mutated in multiple advanced cancers) is mutated in 30-60% of endometrial carcinomas.[98,99] *PTEN* is located on chromosome 10q23.3 and encodes a phosphatidylinositol phosphatase. The product induces apoptosis and G_1 cell cycle arrest through antagonizing the phosphatidylinositol 3'-kinase/Akt-mediated cell growth pathway.[100] *PTEN* mutation occurs almost exclusively in endometrioid (type I) carcinomas, most of them with MI and absence of p53 overexpression.[15,101] Although initial investigations reported that *PTEN* mutation was associated with early stage, nonmetastatic disease, and prolonged survival,[101] more recent studies have suggested that mutation only outside exons 5-7 of *PTEN* might represent a molecular predictor of favorable survival, independent of clinical and pathological characteristics of tumors.[102] In another investigation, promoter methylation of *PTEN* was associated with advanced stage in endometrial carcinoma.[103] Furthermore, a recent report has indicated that PTEN-positive staining is a significant prognostic indicator of favorable outcome for patients with advanced endometrial cancer who undergo postoperative chemotherapy.[104]

Beta-catenin

Beta-catenin is involved in the maintenance of tissue architecture and cell polarity and also plays a role in transcriptional activation. Cytoplasmic levels of beta-catenin are regulated by the opposing actions of Wnt-1 and APC. An increase in Wnt-1 stimulation or a decrease in beta-catenin degradation results in nuclear accumulation of beta-catenin and transcriptional activation. Beta-catenin gene (*CTNNB1*) mutations have been reported in approximately 15-40% of low-grade endometrioid carcinomas.[105-107] It has been suggested that beta-catenin mutations occur in a subset of less aggressive tumors with low metastatic potential.[108] Similarly, nuclear expression of beta-catenin, which has been reported in 73% of the *CTNNB1* mutated tumors,[107] mainly occurred in low-grade endometrioid carcinomas.[109]

K-ras

Mutations in codon 12 of *K-ras* occur in approximately 20% of endometrial carcinomas, mostly of the endometrioid type with MI. In most series the *ras* mutations have not been related to stage, grade, depth of myometrial invasion, or survival.[110]

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Table 1. **The two types of Endometrial Carcinoma**

	Type I	**Type II**
Age	Pre- and Perimenopausal	Postmenopausal
Unopposed Estrogen	Present	Absent
Hyperplasia-Precursor	Present	Absent
Grade	Low	High
Myometrial Invasion	Minimal	Deep
Specific Subtypes	Endometrioid carcinoma	Serous carcinoma
		Clear cell carcinoma
Behavior	Stable	Progressive
Genetic alterations	Microsatellite instability, PTEN mutations	P53 mutations, LOH

Modified from Bokhman JV (7).

Table 2: **Staging of endometrial adenocarcinoma. FIGO 1988 (1989)[33]**

Stage	Definition
IA	Tumor limited to endometrium
IB	**Invasion to < 1/2 myometrium**
IC	Invasion to > 1/2 myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumor invades serosa and/or adnexae and/or positive peritoneal cytology
IIIB	Vaginal involvement or metastasis
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastasis including intra-abdominal and/or inguinal lymph nodes

Table 3. **Endometrial Carcinoma**

(5-year-Survival)

Stage I	90%	IA 93.8% IB 95.4%
Stage II	83%	IC 75.0%
Stage III	43%	

(Wolfson AH, et al. Ref. 39)
(Maneschi M, et al. Ref. 41)

Table 4: **Endometrial Carcinoma**

Depth of myoinvasion	**Recurrence**
None	1.0%
Inner 1/3 myo	7.7%
Middle 1/3 myo	14.5%
Outer 1/3 myo	15.0%

(Morrow CP, et al. Ref. 4)

Table 5: **Endometrial Carcinoma**

(5 yr survival)

Endometrium	94%
Inner 1/3 myometrium	91%
Middle 1/3 myometrium	84%
Outer 1/3 myometrium	59%

(Zaino RJ, et al. Ref. 19)

Table 6: **Risk Features for Lymph Node Metastasis**

	Negligible risk
Myometrial invasion	None, G1, G2, G3 Inner one-third, G1, G2 Middle one-third, G1
Vascular invasion	None
Occult spread to cervix and/or adnexae	None
Cell type	Endometrioid
	Substantial risk
Myometrial invasion	Inner one-third, G3 Middle one-third, G2, G3 Outer one-third, G1, G2, G3
Vascular invasion	Present
Occult spread to cervix and/or adnexae	Present
Cell type	Endometrioid G3; serous; clear cell

Modified from Boronow RC, et al (1)

Table 7: **Endometrial Carcinoma**

(Stage I)

Depth of invasion	**Lymph node metastasis**
Inner 1/3 myometrium	5%
Middle 1/3 myometrium	23%
Outer 1/3 myometrium	33%
Grade 1 – Inner 1/3	None
Grade 1 – Outer 1/3	25%

(Zaino RJ, et al. Ref. 19)

ENDOMETRIAL STROMAL TUMORS

Esther Oliva, M.D.

Endometrial stromal tumors are the second most common category of mesenchymal tumors of the uterus. They are typically composed of neoplastic cells that resemble the endometrial stromal cells of the proliferative endometrium. In the uterus they are divided into two main categories, endometrial stromal nodule and low-grade endometrial stromal sarcoma while outside the uterus these tumors are classified as endometrioid stromal sarcomas.

- ENDOMETRIAL STROMAL NODULE (ESN)

These tumors are rare and they have a non-specific clinical presentation.

? **Gross features**: Well-circumscribed, nonencapsulated tumor with a soft, tan to yellow cut-surface.

? **Microscopic features**: The most important single criterion for its diagnosis is the finding of a non-infiltrative border of the tumor on microscopic examination. It is allowed the presence of focal irregularities in the form of lobulated or finger-like projections into the adjacent myometrium that do not exceed 3 mm. ***No vascular invasion should be seen***.

- LOW-GRADE ENDOMETRIAL STROMAL SARCOMA (ESS)

Low-grade ESS accounts for 10-15% of uterine malignancies with a mesenchymal component. Extrauterine pelvic extension at presentation is found in up to 1/3 of the patients. Rarely, the patient presents with tumor at a metastatic site such as the ovary.

? **Gross features**: There is a nodular or diffuse permeation of the myometrium, including worm-like plugs of tumor in myometrial or parametrial veins. The cut surface is soft, fleshy, bulging, and tan to yellow.

? **Microscopic features**: The tumor permeates the myometrium as irregular tongues and myometrial as well as extrauterine veins and lymphatics are frequently invaded. The tumors are cellular with uniform, oval to spindle-shaped cells of endometrial stromal-type. Significant degrees of nuclear atypia are absent. Mitotic rates are usually ?3/10HPFs but higher rates do not exclude this diagnosis. Mitoses are no longer used to differentiate between low-grade and high-grade ESSs. **Tumors with the typical morphology of endometrial stromal tumors (EST) and characteristic tongue-like growth should be classified as low-grade ESSs regardless of their mitotic counts because the prognosis in these tumors is similar to ESSs with low mitotic counts**. In contrast tumors with an endometrial origin but lacking endometrial stromal differentiation should be classified as undifferentiated endometrial sarcomas.

Low-grade ESSs have a low malignant potential but are characterized by late recurrences.

DIFFERENTIAL DIAGNOSIS

1. ENDOMETRIAL STROMAL NODULE VS ENDOMETRIAL STROMAL SARCOMA

The differential diagnosis between ESN and ESS is not possible in a curettage specimen except in the rare case in which the former is completely curetted during the procedure such that the pathologist can appreciate the margins of the lesion. ***Distinction between an ESN and an ESS is primarily based on the presence of infiltrative margins or vascular permeation in the latter, which in most cases can only be established in a hysterectomy specimen***. Only small ESNs are likely to be diagnosable with confidence on a curettage, an important issue when the patient is in her reproductive age and desires to preserve her uterus. In these women a combination of diagnostic imaging and hysteroscopy may be useful in monitoring the growth of the lesion. In occasional cases local excision has been successful. The same rules apply when fragments of tumor seen in the curettage specimen are predominantly composed of sex cord-like elements. In those cases the differential diagnosis includes a uterine tumor resembling an ovarian sex cord tumor and a conventional EST with sex cord-like differentiation. Although the former in most cases is well circumscribed, the pathologist needs to evaluate margins in order to properly subclassify the tumor and for this reason a hysterectomy is usually the treatment of choice.

Recently, Dionigi and colleagues reported a series of 50 ESNs including 3 tumors that did not fulfill the criteria for ESN but still did not have the typical permeative growth of an ESS. These tumors have been descriptively referred to as "endometrial stromal tumors with limited infiltration" until more information is obtained regarding their prognosis.

2. ENDOMETRIAL STROMAL TUMOR VS CELLULAR ENDOMETRIAL POLYP

Endometrial polyps may be fragmented in curettage specimens and some of the fragments may consist of cellular stroma only. Although ESTs may arise in endometrial polyps, in such cases one sees an expansile growth of endometrial stroma with the typical vascular network, which contrasts with the more compact, atrophic appearance of the endometrial stroma of the polyp in which vessels, if prominent, tend to be larger, thick-walled, and irregularly distributed.

3. ENDOMETRIAL STROMAL TUMOR VS ADENOMYOSIS WITH SPARSE GLANDS AND INTRAVASCULAR ADENOMYOSIS

Adenomyosis with a scant glandular component or in which adenomyotic foci are present in vascular spaces or associated with intravascular endometrial tissue may cause concern for a low-grade ESS. On gross examination adenomyosis occurs as an incidental finding, produces an ill-defined nodularity or asymmetric thickening of the uterine wall but not a mass. There is a zonation phenomenon within the adenomyotic foci with a less cellular central area surrounded by a more cellular periphery composed of a rim of endometrial stroma, smooth muscle or both, and the atrophic appearance of the stromal nests and cells that lack nuclear atypia and mitotic activity are in contrast with the expansile growth of the stromal nests and proliferative appearance of the cells in ESS. The absence of other morphologic features of ESS, the presence of typical areas of adenomyosis elsewhere, and the postmenopausal age of the patients helps in establishing the correct diagnosis.

4. ENDOMETRIAL STROMAL TUMOR VS INTRAVASCULAR ENDOMETRIAL TISSUE, AND MENSES-ASSOCIATED CELLULAR STROMA

Intravascular menstrual endometrium if composed of only stromal cells may cause problems in the differential diagnosis with ESS. The stromal cells form tight clusters of small spindle cells with

hyperchromatic nuclei and a high nuclear/cytoplasmic ratio. Some of the nests may have a necrotic appearance and in other areas they may be surrounded by a cuff of larger cuboidal to low columnar epithelial cells with more abundant eosinophilic cytoplasm. These clusters of cells are frequently associated with neutrophils and lymphocytes.

5. ENDOMETRIAL STROMAL TUMOR VS HIGHLY CELLULAR LEIOMYOMA (HCL)

Many highly cellular leiomyomas have a somewhat different consistency and color from that of conventional leiomyomas, on average being softer and having a tendency to be yellow or yellow-tan, closely resembling the gross appearance of endometrial stromal tumors. On microscopic examination as their definition implies they are as cellular as endometrial stromal tumors and they may have prominent vascularity as well as irregular margins with the surrounding stroma. Findings that help in the differential diagnosis with an endometrial stromal neoplasm are:

- ✍ Focal merging of the highly cellular areas with typical fascicular areas of smooth muscle neoplasia in most of the cases.
- ✍ Finding large thick muscular wall blood vessels in contrast to the arterioles of an endometrial stromal neoplasm.
- ✍ Presence of cleft-like spaces, some apparently representing compressed vessels, others apparently the result of edema.
- ✍ Strong and multifocal or diffuse immunoreactivity for smooth muscle markers including desmin and h-caldesmon.

6. ENDOMETRIAL STROMAL SARCOMA VS INTRAVENOUS LEIOMYOMATOSIS (IVL)

IVL may cause confusion with an ESS mainly because of its prominent intravascular growth. The marked cellularity of some cases of IVL resembling a HCL may increase confusion with ESSs. Helpful features include a clefted or lobulated contour of the intravascular masses, a focal fascicular architecture, cells with blunt-ended nuclei, prominent thick-walled vessels and hydropic change. Finally, if a tumor shows vascular permeation, a useful diagnostic feature of some cases of IVL is that the tumor cells may be seen not only in vascular lumina but also beneath the vascular endothelium and "colonizing" the walls of veins. Although cardiac involvement is seen in up to 40% of cases of IVL, low-grade ESSs may also have it although infrequently.

7. FIBROUS-MYXOID ENDOMETRIAL STROMAL TUMORS VS OTHER MESENCHYMAL TUMORS

ESTs may undergo extensive fibrous and or myxoid change. The most frequent and problematic differential diagnosis pertains to smooth muscle tumors including myxoid leiomyomas, the rare myxoid variant of IVL and myxoid leiomyosarcomas. Helpful features in establishing the diagnosis of myxoid/fibroblastic EST are a frequent presentation as an endometrial polypoid mass, a prominent multinodular or tongue-like pattern of myometrial infiltration, the focal presence of typical endometrial stromal neoplasia with characteristic arterioles, and the absence or minimal staining for muscle markers in most cases.

8. MISCELLANEOUS OTHER PROBLEMS IN THE DIFFERENTIAL OF PURE ENDOMETRIAL STROMAL TUMORS

If tissue sample is small and shows crush artifact, metastatic breast cancer or lymphoma may be in the differential. The history as well as immunohistochemistry will facilitate the diagnosis.

UNUSUAL VARIANTS OF ENDOMETRIAL STROMAL TUMORS

- ENDOMETRIAL STROMAL TUMOR WITH SMOOTH MUSCLE DIFFERENTIATION (EST-SMD*)*

In general it is required that the smooth muscle component occupy at least 30% of the neoplasm to merit this categorization.

? **Gross features**: Some of these tumors contain one or more tan to yellow, soft nodules alternating with firm, white whorled nodules or they are embedded in or at the periphery of paler, firmer tissue.

? **Microscopic features**: The endometrial stromal component has the characteristic cell type and arterioles. The smooth muscle component may show nodules with central hyalinization ("starburst" pattern) that merge with disorganized short fascicles of smooth muscle or long mature fascicles of smooth muscle. An unusual pitfall in the evaluation of these tumors is posed by the irregular interdigitation of both components, particularly when the smooth muscle is mature and relatively well organized. If the latter is misconstrued as myometrial muscle, a well-circumscribed tumor may be misinterpreted as an invasive EST and hence an ESS. It is crucial to appreciate that in such cases one is examining regions with divergent differentiation within the mass itself rather than invasion.

Recurrences may show an EST, smooth muscle or both components. For prognostic purposes these tumors should be reported as ESNs or ESSs with smooth muscle differentiation (depending on the margins) with the designation mixed endometrial stromal-smooth muscle tumor given in parentheses with any other unusual features of either component recorded in a notation. We do not use the term “stromomyoma” because this term implies a benign tumor.

- ENDOMETRIAL STROMAL TUMORS WITH MYXOID AND/OR FIBROUS BACK-GROUND.

As discussed earlier these tumors show a prominent myxoid and/or fibrous background, although in most cases one can identify areas of conventional endometrial stromal neoplasia. As with endometrial stromal tumors with smooth muscle differentiation, these tumors may cause problems when they metastasize, more frequently in the lungs as they can also have this prominent myxoid/fibrous appearance. It is important to notice that in some instances this appearance will be seen for the first time at metastatic sites.

- ENDOMETRIAL STROMAL TUMOR WITH SEX CORD-LIKE DIFFERENTIATION.

This finding does not have any prognostic significance.

- ENDOMETRIAL STROMAL TUMORS WITH ENDOMETRIOID GLANDULAR DIFFERENTIATION

The epithelial component may resemble endometrioid glands, either benign or malignant. The origin of the glands has been attributed to entrapment of non-neoplastic endometrial or adenomyotic glands or epithelial differentiation in these neoplasms. These rare neoplasms should be distinguished from adenomyosis and endometriosis, and indeed some (perhaps most) cases of "aggressive endometriosis" in our opinion probably represent ESSs with endometrioid gland differentiation. Mullerian adenosarcoma should also be included in the differential diagnosis. The latter, however, shows a more uniform distribution of the glands within the stromal component as

well as intraglandular polypoid stromal projections and periglandular stromal condensation. In addition adenosarcomas are more circumscribed and less often have vascular invasion.

UTERINE TUMOR RESEMBLING OVARIAN SEX-CORD TUMOR (UTROSCT)

The term "uterine tumor resembling ovarian sex-cord tumor" was applied by Clement and Scully to a heterogeneous group of uncommon neoplasms characterized by pure or prominent microscopic patterns that resemble those of ovarian sex-cord tumors. Several tumors reported in the older literature as "granulosa cell tumors" of the uterus belong in this category. The histologic appearance of some of these neoplasms merges imperceptibly with that of ESTs exhibiting less than predominant sex cord-like differentiation. The designation UTROSCT should be restricted to tumors with prominent sex cord-like differentiation in which there is no conspicuous endometrial stromal background.

Patients are in the reproductive and postmenopausal age groups, with an age range of 16 to 73 (mean, 47) years. The presenting clinical manifestations are usually abnormal vaginal bleeding or uterine enlargement and occasional patients are asymptomatic.

Pathologic findings

? **Gross features**: They are generally solid, round, well-circumscribed myometrial masses that range from 0.7 cm to 20 cm in diameter (mean, 6 cm); rare tumors have been predominantly cystic. UTROSCTs are usually mural, but are occasionally submucosal or subserosal. Rare tumors have been located predominantly within the endometrium or endocervix. The cut surfaces are often yellow, but occasionally gray to tan, and are soft, fleshy and homogeneous without the whorled pattern of a leiomyoma.

? **Microscopic features**: The cardinal features are a variety of epithelial and stromal patterns that create a resemblance to those of ovarian sex-cord tumors, especially granulosa cell and Sertoli cell tumors, alone or in combination. Anastomosing cords, broad trabeculae, small nests, sertoliform or retiform tubular structures, Call-Exner-like bodies, and diffuse sheets of uniform cells reminiscent of a diffuse adult granulosa cell tumor may be seen. The epithelial-like cells vary from small, round, and regular with scanty cytoplasm to large with abundant eosinophilic, clear, or foamy cytoplasm that is often lipid-rich. The nuclei are generally small and regular with little pleomorphism and indistinct nucleoli. Nuclear grooves are rare or absent and mitotic figures are typically scarce. The fibrous stroma ranges from scanty to abundant and from moderately cellular to hypocellular and hyalinized. An occasional striking feature in some cases of UTROSCT is the presence of conspicuous mature smooth muscle between the sex cord-like elements. The nature of this smooth muscle component has not been extensively studied. It is possible that in some cases it is metaplastic but in the majority of cases, in our opinion, it has an appearance indistinguishable from that of normal myometrium, which it probably represents in many, perhaps most, cases. Although this, therefore, presumably represents “myometrial invasion” by the tumor, it does not have any significant adverse prognostic implications and it is our practice when this muscle is incorporated within an otherwise typical UTROSCT to consider it part and parcel of the neoplasm and not to use terminology such as “with myometrial invasion” which might be confusing and sound ominous to the treating physician

Differential Diagnosis

Epithelioid smooth muscle tumors may have a sex cord-like pattern, although generally not as strikingly as in tumors of probable endometrial stromal cell derivation. The extent to which desmin and caldesmon positivity is allowable in uterine tumors resembling ovarian sex-cord tumors is still a matter of debate. We, and others allow its presence in such tumors, but this finding must be evaluated in the light of conventional light microscopic and other immunohistochemical findings. Further studies are indicated to establish the appropriate boundary between the classification of an epithelial-like tumor of the uterus as a uterine tumor resembling an ovarian sex-cord tumor and an epithelioid smooth muscle tumor.

Endometrial stromal tumor with sex cord-like differentiation. If any areas of conventional endometrial stromal neoplasia are present in the tumor it should be classified as an endometrial stromal neoplasm, either a nodule or a low-grade sarcoma.

Treatment and prognosis

Assessing the prognosis of these tumors from the literature is difficult because most of the reported series include circumscribed tumors and infiltrating tumors with the features of ESSs without distinction between them. UTROSCTs should be considered tumors of low-malignant potential unless small and well circumscribed in which instance, for practical purposes, they are benign.

- OTHER UNUSUAL MORPHOLOGIC FEATURES IN ENDOMETRIAL STROMAL NEOPLASMS

1- Epithelioid appearance
2- Granular change
3- Clear cell change
4- Rhabdoid appearance
5- Skeletal muscle differentiation
6- Adipose differentiation
7- Bizarre nuclei

- UNDIFFERENTIATED ENDOMETRIAL SARCOMA

The lack of specific evidence of endometrial stromal cell origin in most cases precludes their placement in the endometrial stromal group of uterine tumors. Myometrial invasion is common but the intravascular worm-like plugs characteristic of low-grade ESS are usually absent. They have marked cellular pleomorphism, brisk mitotic activity and carry a very bad prognosis. These tumors should be diagnosed only after extensively sampling has excluded smooth or skeletal muscle differentiation or even small foci of carcinoma as that would result in a diagnosis of MMMT. Occasional tumors have a component of low-grade ESS indicating that in those cases at least the high-grade component presumably is truly of endometrial stromal derivation.

IMMUNOHISTOCHEMICAL PROFILE

Although in most instances the diagnosis of endometrial stromal neoplasia is based on morphologic grounds alone, immunohistochemical stains may be helpful in the diagnosis of problematic cases. The neoplastic endometrial stromal cells are typically immunoreactive for vimentin, muscle-specific and smooth muscle actin, and keratin. This panel of antibodies, however, is not very sensitive in distinguishing ESTs from smooth muscle tumors, the commonest and most problematic

group of tumors in the differential diagnosis. Desmin staining has been of help in our experience, but the frequency of desmin staining in ESTs and percentage of desmin positive tumor cells varies among studies. In the study by Franquemont et al., two of two ESNs were strongly and diffusely positive and 7 of 12 ESSs were immunoreactive for desmin, although the staining was diffuse in only four of them, and limited to scattered cells in the other three. Similarly, normal endometrial stromal cells were desmin positive in 9 of 10 cases. The staining was confined to scattered cells in 8 cases, but it was diffuse in the ninth. In some studies the sex cord-like elements in ESSs and UTROSCTs have been desmin/caldesmon-positive suggesting smooth muscle differentiation. More recent studies, however, have suggested that these elements represent sex cord differentiation as discussed below. Other studies have shown a frequency of desmin positivity ranging from 0 to 30% in typical ESS. In our laboratory, desmin has been focally positive in only 3 out of 29 ESTs studied, a finding we consider consistent with smooth muscle differentiation in ESTs as discussed earlier. In recent years, a few other antibodies have been tested in ESTs.

CD10, initially described as tumor-specific antigen in acute lymphoblastic leukemia, was strongly and diffusely positive in 5/5 ESSs in a recent study. The normal endometrial stromal cells were also positive. In the study just cited only one of 16 malignant smooth muscle tumors including one from the uterus was positive for CD10. However, more recent studies have shown that smooth muscle tumors as well as mixed mullerian tumors (including adenosarcoma and malignant mixed mullerian tumor) or even rhabdomyosarcomas may be positive for CD10. For this reason this antibody should not be used in isolation when evaluating the origin of a mesenchymal tumor of the uterus. In the ovary, CD10 is positive in sex-cord stromal tumors, the latter usually showing weak and focal staining. For that reason, although CD10 is not widely used in the diagnosis of sex-cord stromal tumors, it is important to be aware of this finding.

h-caldesmon is also helpful in the differential diagnosis of ESTs versus smooth muscle tumors. h-caldesmon is a calcium, calmodulin, and actin-binding protein widely distributed in smooth and non-smooth muscle cells and is thought to regulate cellular contraction. Its isoform, high-molecular-weight caldesmon, is specific for smooth muscle cells and smooth muscle tumors and is never expressed in myofibroblasts. In a study of 9 ESTs and 15 benign and malignant smooth muscle tumors, Nucci et al found that all ESTs were negative for this antibody. In contrast all leiomyomas and leiomyosarcomas were positive, although staining was focal or confined to isolated cells in three leiomyosarcomas. Others have confirmed these findings.

Inhibin is a gonadal hormone that acts as a suppressor in the synthesis and secretion of pituitary follicle stimulating hormone. It is a very useful marker for sex cord stromal tumors of the ovary although not pathognomonic Inhibin has been negative in 20 ESSs of the ovary reported in different series from the literature. In the uterus, Baker and colleagues studied the expression of inhibin in 10 ESTs with sex cord-like differentiation. It was positive in 3/10 of these tumors usually being focal and weak and confined to sex cord-like areas. Additionally, 5 of 5 UTROSCTs were positive for inhibin, although the staining varied from weak and punctate to diffuse and strong and was generally much stronger and more extensive in areas with prominent foam cells. Krishnamurthy and colleagues found that 3 of 7 UTROSCTs were inhibin positive, ranging from focal (1) to extensive (2). The authors concluded that the inhibin staining in certain areas of these tumors was indicative of true sex cord-like differentiation rather than smooth muscle diferentiation. In the same study, 4 of seven UTROSCTs stained for Mart-1, an antigen expressed by normal melanocytes and melanocytic neoplasms, and steroid producing cells and tumors composed of such cells located in the adrenal cortex, ovary, and testis. The positive staining for Mart-1 in UTROSCTs is consistent with the presence of steroid-producing cells and is supportive of their specialized gonadal stromal nature**. Inhibin** is the paramount marker for sex cord-stromal tumors of the ovary, however, remember that inhibin is not totally specific for sex cord-stromal tumors and that

mesonephric tumors frequently show focal and weak positivity and that a minority of ovarian carcinomas have been reported to be also positive for a-inhibin.

Calretinin has been shown to be highly sensitive but not as specific marker as inhibin for sex cord - stromal tumors. Some sex cord-stromal tumors that are negative for inhibin may be calretinin positive. Calretinin is also positive in fibromas of the ovary. This antibody is expressed in non-neoplastic ovarian sex cord-stromal cells, but also in secretory endometrial stromal cells. There is limited experience with ESTs at the moment, although some ESTs have reported to be calretinin positive. Morover, other tumors may stain for calretinin including leiomyosarcomas, mesonephric tumors as well as endometrioid carcinomas of the ovary and endometrium and for that reason positive calretinin immunoreactivity should be used in the appropriate context.

CD99 was initially described as a marker for Ewing's sarcoma as well as primitive neuroectodermal tumors, but it also stains normal sex-cord elements as well as tumors derived from them. Loo and colleagues studied 5 ESSs, one of which had sex cord-like differentiation; positive staining for CD99 was confined to the sex-cord-like areas. In the series reported by Baker and colleagues, only three of ten ESTs with a sex cord-like component were positive for CD99, with weak and focal positivity confined to the sex-cord areas. CD99 was positive in all 5 UTROSCTs in that series, ranging from weak and slightly punctate to intense and diffuse. In the series by Krishnamurthy and colleagues, all 7 UTROSCTs were positive for CD99, ranging from one to three in intensity. In contrast, smooth muscle tumors have been negative for inhibin as well as for CD99 with the exception of one epithelioid smooth muscle tumor that showed weak positivity for this antigen. The combination of positive staining for keratin, desmin, and CD99 has been documented in granulosa cell tumors of the ovary and the same findings in ESSs with sex-cord-like differentiation and UTROSCTs support true sex-cord rather than smooth muscle differentiation. CD99 reacts with normal sertoli and granulosa cells and it is marker for sex-cord stromal tumors. The degree of expression may be related to the degree of tumor differentiation and the staining may be membranous or cytoplasmic. It has been shown that CD99 is much less sensitive and less specific than inhibin in the diagnosis of sex cord-stromal tumors.

Mart-1 (Melan A, A103) is typically positive in steroid cell tumors but also in other sex cord - stromal tumors, including Sertoli-Leydig cell tumors, adult and juvenile granulosa cell tumors, and even in the fibroma-thecoma category of ovarian tumors, although experience is very limited. Endometrial/ioid stromal tumors have been shown to be negative for Mart-1, with the exception of sex-cord areas that may be positive.

CD34, a myeloid progenitor cell antigen present in endothelial cells and some other mesenchymal cells, including perivascular and periadnexal dermal fibroblasts, has been found to be present in the stromal cells of the basal endometrium but was negative in 6 ESSs tested. Additionally we found that CD34-staining was absent in 10 fibrous and myxoid ESTs. In contrast, Rizeq and colleagues found CD34 positivity in 36% of 22 conventional smooth muscle tumors with a spindle cell morphology and 6% of 36 epithelioid smooth muscle neoplasms, although normal myometrium in most cases did not stain for CD34. Furthermore, as previously noted in the rare cases in which the differential diagnosis includes a gastrointestinal stromal tumor, the latter frequently is positive for CD34 in contrast to EST.

c-kit, a well known marker for gastrointestinal stromal tumors and it has been to be the most useful immunohistochemical marker for gastrointestinal stromal tumors and it is typically positive in 72-100% of these tumors. It has been recently tested in endometrial stromal and smooth muscle neoplasms. In our study all endometrial stromal tumors where negative for c-kit and Klein and Kurman found that only 1/10 endometrial stromal sarcomas and 3/6 endometrial stromal nodules were positive for c-kit but no more than 5% of the cells stained with the antibody. In contrast to the

homogenous results obtained in endometrial stromal tumors, the literature on smooth muscle tumors and c-kit is confusing. Some studies have shown that leiomyosarcomas are c-kit negative while others have reported variable degrees of positivity in malignant smooth muscle tumors and have even found correlation with prognosis.

Oxytocin, a neurohypophyseal peptide associated with muscle contraction during labor, is expressed in smooth muscle tumors but not in endometrial stromal tumors. In the study conducted by Loddenkemper and colleagues they found that oxytocin was present in all conventional and highly cellular leiomyomas as well as in all leiomyosarcomas while all nine ESS (9) were oxytocin negative. These authors postulate that this antibody may be used as part of the panel to distinguish ESTs from smooth muscle tumors.

Aromatase, participates in the extraovarian estrogen production via conversion of androgen to estrogen through the aromatase enzyme complex. Aromatase has been described in stromal cells of endometriosis, adenomyosis, endometrial carcinomas as well as ESSs. Reich and Regauer found that most low-grade ESSs expressed aromatase and little or no expression of aromatase tended to correlate with stage I disease.

Finally, numerous studies have shown that ESTs frequently contain estrogen and progesterone receptors, a finding that may have therapeutic and prognostic implications, although the presence of these receptors has limited utility in differential diagnosis inasmuch as these receptors may be found in many other epithelial and mesenchymal tumors of the uterus

- ✍ It is important to remember that one should not rely in one antibody but on a panel when trying to interpret mesenchymal tumors of the uterus.

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MESENCHYMAL UTERINE TUMORS

Jaime Prat, M.D.

SMOOTH MUSCLE TUMORS

The diagnosis of uterine **leiomyosarcoma** is not usually problematic because most clinically malignant smooth muscle tumors in this site have the microscopic constellation of hypercellularity, marked degrees of nuclear pleomorphism, and high mitotic rates that usually exceed 15 mitotic figures per 10 high-power-fields (MFs/10HPFs).[1-4] One or more supportive clinical or pathological features are also commonly present, including peri- or postmenopausal age, extrauterine extension of tumor, a diameter over 10 cm, an infiltrating border, necrosis, and atypical mitotic figures.[1-4] In contrast, the minimal pathologic criteria that justify a diagnosis of leiomyosarcoma are more problematic and the differential diagnosis in such cases is not only with benign smooth muscle tumors that exhibit a variety of atypical histologic features but also with "smooth muscle tumors of uncertain malignant potential".

Zaloudek and Norris,[1] combining the results of 8 series in the literature, found that 75% of cellular smooth muscle tumors with mitotic rates of 5 or more MFs/10HPFs were clinically malignant (i.e. leiomyosarcoma), whereas those with 4 or fewer MFs/10HPFs were almost invariably benign; all of the clinically malignant tumors were cytologically atypical. The criteria for leiomyosarcoma therefore proposed by these authors were the simultaneous presence of 5 or more MFs/10HPFs and cytologic atypia.

Subsequently, it has been shown that otherwise typical or cellular leiomyomas with up to 15 MFs/10HPFs have a benign course (even when treated by myomectomy), providing that they are benign by other clinical and pathologic criteria. Such tumors are typically small (<10 cm) and have a grossly benign appearance. The terms **mitotically active leiomyoma** (MAL)[4-6] or **leiomyoma with increased mitotic figures**[2] have been suggested for such tumors. In two studies, a diagnosis of MAL was allowable only in the absence of nuclear pleomorphism,[5,6] whereas in a third, mild or even moderate nuclear pleomorphism did not exclude the diagnosis[4]. In contrast to leiomyosarcomas, MALs almost invariably occur in women of reproductive age, are associated with the secretory phase of the menstrual cycle, pregnancy, or the use of exogenous progestins. These observations suggest that the mitotic activity in at least some MALs is due to an exogenous or endogenous progestational effect.[5-7] At least 60% of mitotically active leiomyomas were submucosal in one study.

Other findings in clinically benign leiomyomas that may result in confusion with leiomyosarcoma are increased cellularity and nuclear atypia. Leiomyomas that are unusually cellular but otherwise typical, i.e. **cellular leiomyomas**, have a behavior that is identical to the usual leiomyoma.[8,9] On gross examination, cellular leiomyomas may resemble typical leiomyomas but often have a fleshier, tan-brown to yellow sectioned surface. Hemorrhage or infarct-type necrosis or both are present in a minority of cases.

Cellular leiomyomas may resemble endometrial stromal nodules. Findings that help in the differential diagnosis with an endometrial stromal neoplasm are:

- Coexistence of highly cellular areas with fascicular growth pattern typical of smooth muscle tumors.
- Vessels of large caliber with thick muscular walls in contrast to a prominent network of small blood vessels typical of endometrial stromal tumors.
- Strong and multifocal or diffuse immunoreactivity for smooth muscle markers including desmin and h-caldesmon.

These tumors almost always have < 5MFs/10HPFs and are cytologically bland. Occasionally, brisk mitotic activity may be found. When this occurs in a highly cellular leiomyoma, the designation of "mitotically active cellular leiomyoma" is used.[8,9]

Occasional leiomyomas contain cells with bizarrely shaped, multilobated or multinucleated, hyperchromatic nuclei. These tumors are variously referred to as "symplastic", "atypical", or "bizarre" leiomyoma, or **leiomyoma with bizarre nuclei**.[1-3,10] A diagnostic impression of leiomyosarcoma can be enhanced in such cases when degenerating or karyorrhectic nuclei are mistaken for atypical mitotic figures. The largest series of these tumors (24 cases) was reported by Downes and Hart.[10]

? Gross features: These tumors usually resemble conventional leiomyomas, but they may show yellow to tan areas, hemorrhage, focal softening, cavitation, or myxoid change.

? Microscopic features: Cellularity ranges from slight, as seen in conventional leiomyomas (21%), to high as seen in highly cellular leiomyomas (21%). The defining feature is the presence of bizarre pleomorphic cells usually with abundant eosinophilic cytoplasm, prominent nuclear pseudoinclusions and atypical nuclei, which can be distributed throughout the tumor, or may form discrete foci. Most of these cells are multinucleated but they also can be mononucleated. The nuclei are often pyknotic with dense smudged chromatin. Karyorrhectic nuclei simulating abnormal mitotic figures are often seen. A worrisome feature in some tumors is the finding of mitotic counts up to 7MFs/10HPF by the highest count method. By the average method, however, it ranged from 0 to 2.8 MFs/10HPFs (mean 0.8). In such cases it is important to recognize that the areas not involved by the bizarre cells show bland cytologic features.[10]

Leiomyomas with bizarre nuclei are distinguished from leiomyosarcomas by an absence of tumor cell necrosis and mitotic counts of < 10MFs/10HPFs. The combination of aneuploidy and high MIB-1 activity is rare in bizarre leiomyomas, and in such cases the diagnosis should be made with caution.[11] Several studies in the literature have shown that leiomyomas with bizarre nuclei have a benign clinical course.[1-3,10]

A variety of sometimes worrisome morphologic changes may be seen in **leiomyomas from pregnant women** and those on **progestin therapy**. These include hemorrhage, edema, myxoid change, focal hypercellularity, nuclear pleomorphism, and increased mitotic activity. Because of the rarity of leiomyosarcomas in the reproductive age group, a diagnosis of uterine leiomyosarcoma should be rendered with caution in a pregnant patient or one on hormonal medication. There may be a history of rapid growth of the leiomyoma (which may also occur with clomiphene or tamoxifen therapy), causing a clinical suspicion of sarcoma. The designations **"apoplectic leiomyoma"**[12] and **"hemorrhagic cellular leiomyoma"**[13] have been used to refer to a constellation of changes occurring within leiomyomas in women taking oral contraceptives or who are pregnant. Patients may present during pregnancy or the puerperium with acute abdominal signs secondary to rupture of the tumor into the peritoneal cavity. On gross examination, hemorrhage within one or more leiomyomas, which may be accompanied by cystic change, is the cardinal feature. Microscopic examination reveals densely cellular proliferations of smooth muscle cells surrounding stellate zones of recent hemorrhage. The cells lack malignant nuclear features, but as many as 8 MFs/10HPFs have been encountered in some cases.[12] Vascular alterations, including intimal myxoid change and fibrosis, medial hypertrophy, fibrinoid necrosis, and thrombosis, may be encountered within the leiomyomas or the surrounding myometrium.

Some of the findings in apoplectic leiomyomas also occur in leiomyomas treated with **gonadotropin-releasing hormone agonists (GnRHa)**, agents that are used to reduce the size of

leiomyomas prior to their removal. Most studies have found: irregular borders, focally increased cellularity, hyalinization, infart-type necrosis, and vascular changes including fewer vessels, decreased vessel diameter, mural thickening, myxoid change, fibrinoid change, luminal narrowing, and thrombosis. Surprisingly, no study has demonstrated any difference in the mitotic rate between leiomyomas removed during treatment and those from untreated women. In contrast, leiomyomas removed several weeks after withdrawal of GnRHa treatment may have increased mitotic activity.

Fibrosis or hyalinization, is a very common finding in leiomyomas of all types, especially in postmenopausal women in whom the tumors shrink in size and can be replaced by fibrous tissue. In such cases, dystrophic calcification is common.

Hydropic degeneration is another common degenerative change that can result in diagnostic problems, especially if confused with myxoid change. On gross examination, the watery edematous change may simulate the picture of myxoid leiomyosarcoma or intravenous leiomyomatosis.

Myxoid leiomyomas are characterized by abundant, acellular, pale staining material rich in acid mucins that stains with alcian blue or colloidal iron stains. They may be encountered during pregnancy. They are usually well circumscribed and resemble extrauterine myxomas, being composed of soft, gray, jelly-like material. Microscopically, they have well-circumscribed margins. The neoplastic cells may be elongated or stellate in shape and widely separated by the extracellular material. The cytologic features are bland and mitotic figures are rare. Distinction between myxoid leiomyoma and myxoid leiomyosarcoma may be difficult in curettage specimens. In a recent study conducted by Atkins et al.,[14] in the absence of tumor cell necrosis or severe cytologic atypia, a mitotic index of <2 MFs /10 HPFs favored a benign myxoid smooth muscle tumor.

Epithelioid leiomyomas are composed of polygonal cells containing abundant eosinophilic cytoplasm. These tumors are also known as clear cell leiomyomas and "leiomyoblastomas".[15]

Grossly, they may resemble typical leiomyomas or may appear fleshy due to their high cellularity; they may be poorly circumscribed, and may show foci of hemorrhage and necrosis.

Microscopically, epithelioid leiomyomas often exhibit a diffuse growth pattern, but nests, cords or pseudoglandular spaces may be found. The cell cytoplasm is usually eosinophilic and granular, but it may be clear, and in about 25% of the cases the entire tumor is composed of clear cells (clear cell leiomyoma). The round or angular nuclei are typically central but may be eccentric, occasionally resulting in a signet-ring appearance. Immunohistochemically these tumors are more frequently positive for cytokeratins and less often positive for muscle markers than nonepithelioid smooth muscle tumors.[16,17]

Because of the rarity of these tumors, criteria predictive of their malignant behavior, which occurs in 12-40% of cases, are less well established than for spindle-cell smooth muscle tumors. Kurman and Norris[15] studied a series of 26 epithelioid smooth muscle tumors and concluded that the presence of clear cytoplasm, expansile margin, extensive hyalinization, and lack of extensive necrosis were parameters associated with a favorable prognosis, whereas tumors that exhibited 5 or more MFs/10 HPFs should be designated as epithelioid leiomyosarcomas.

Prayson et al.[16] did not find a single histologic feature predictive of outcome. In their series, clinically malignant tumors showed grade 3 nuclei, mitotic activity higher than 3/10 HPFs, and tumor cell necrosis. Atkins et al.[17] recently studied 32 epithelioid smooth muscle tumors and found that in the absence of tumor cell necrosis, cytologic atypia or a mitotic index >5 MFs/10 HPFs warranted a diagnosis of malignancy.

The differential diagnosis of epithelioid smooth muscle tumors includes primary endometrial or metastatic carcinoma (especially those composed of eosinophilic or clear cells), placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT), and low-grade endometrial stromal sarcoma. Desmin immunoreactivity, absence of the characteristic features of PSTT and ETT, and lack of the characteristic vascular-space invasion seen in low-grade endometrial stromal sarcoma facilitate the correct diagnosis.

Plexiform tumorlets are typically microscopic and frequently multiple. Although they occur more common in the myometrium, may occasionally involve, or be confined to the endometrium.[18]

Recently, a low-grade mesenchymal tumor of the soft tissues and uterus thought to derive from perivascular epithelioid cells has been described as **PEComa**.[19] The tumor cells are arranged in sheets or solid nests, contain oval to round nuclei, exhibit abundant clear or eosinophilic cytoplasm, and often express smooth muscle markers. PEComas are characteristically positive for HMB-45 and may express other melanocytic markers. Some tumors may be associated with lymphangioleiomyomatosis and the tuberous sclerosis syndrome. As experience with these tumors is very limited, the long-term prognosis is unknown. Some cases have followed an aggressive behavior.

Leiomyosarcomas

Leiomyosarcomas account for approximately 45% of all uterine sarcomas. The vast majority affect women over 40 years. Patients frequently present with abnormal vaginal bleeding, pain or both. Occasionally, the presenting manifestations are related to tumor rupture (and hemoperitoneum), extrauterine extension (present in one-third to one-half of cases), or metastases.

Gross features: Typically large solitary masses with a mean diameter of 10 cm. Approximately 25% of the tumors are < 5 cm. About 2/3 of leiomyosarcomas are intramural, 1/5 submucosal, and 1/10 subserosal; 5% arise in the cervix. They are almost always less circumscribed than leiomyomas and cannot be shelled-out from the adjacent myometrium. The cut surface is typically bulging, fleshy, and focally necrotic and hemorrhagic. Thorough sampling is recommended when a myometrial tumor has an unusual gross appearance (at least one section per cm in diameter). Leiomyosarcomas are either the only mass or, when associated with leiomyomas, the largest mass. Examples of leiomyosarcoma arising in a typical leiomyoma are rare.
Microscopic features: Most uterine leiomyosarcomas are obviously malignant on microscopic examination, and exhibit:

- At least **moderate hypercellularity**
- **Moderate to marked nuclear atypia**, which is usually diffuse
- **High mitotic rate** (10 or more MFs /10 HPFs; 90% have > 15 MFs/10 HPFs)
- **Tumor cell necrosis**, characterized by an abrupt transition from the viable cells to the necrotic cells without an interposed zone of granulation tissue or fibrous tissue. Preserved nuclei with marked pleomorphism and hyperchromasia can still be seen within the necrotic areas and often there is a perivascular growth of viable tumor cells. Tumor cell necrosis is highly characteristic of leiomyosarcomas.

This type of necrosis should be distinguished from **infart-type necrosis** (which may be seen in benign or malignant smooth muscle tumors) and is characterized by a transition zone composed of granulation or fibrous (hyalinized) tissue depending upon the age of the infarct. The necrotic tissue has a mummified and homogeneous appearance, areas of hemorrhage are common, and no perivascular growth of tumor cells is seen. According to Bell et al.[20] the presence of 2 of the last three criteria warrants a diagnosis of leiomyosarcoma.

Rare leiomyosarcomas contain numerous **giant cells** of the **osteoclastic type** resembling a giant cell tumor of bone or the giant cell variant of malignant fibrous histiocytoma. Rare **xanthomatous leiomyosarcomas,** which can be focally or diffusely yellow, contain large cells with abundant cytoplasm, lipid vacuoles, and multiple or multilobulated nuclei.

Leiomyosarcomas are aggressive tumors.[21-24] In a large Gynecology Oncology Group (GOG) study, the recurrent rate was 71%.[25] The first recurrence was in the lung in 40% of the patients, and in the pelvis in only 13%. The survival rate ranges from 15% to 25%, with a median survival of only 10 months in one study. There has been no consistency among various studies with respect to showing a correlation between survival and patient age, clinical stage, tumor size, type of border (pushing vs infiltrative), the presence or absence of necrosis, mitotic rate, degree of nuclear pleomorphism, and vascular invasion. One study, however, found tumor size to be a major prognostic parameter: five of eight patients with tumors < 5 cm in diameter survived, whereas all patients with tumors > 5 cm in diameter died of tumor. A recent study of 208 uterine leiomyosarcomas concluded that the only parameters predictive of prognosis were tumor grade and stage.[23]

Rare malignant smooth muscle tumors lacking the high mitotic activity of typical leiomyosarcomas include those of epithelioid and myxoid type.

Epithelioid leiomyosarcomas are composed predominantly or entirely of round or polygonal cells with eosinophilic or clear cytoplasm.[15, 16, 26] The neoplastic cells grow diffusely, in nests, cords, or in a plexiform pattern; Nuclear pleomorphism in epithelioid smooth muscle tumors is usually slight, but occasionally is moderate to marked, and the mitotic rate is generally <3 MFs/10 HPFs. Most of the tumors infiltrate the adjacent myometrium but vascular invasion is rare. Three of 26 tumors in one series recurred or metastasized.[15] The malignant tumors exhibited one or more of the following features: a component of eosinophilic cells, an infiltrating margin, necrosis, a diameter greater than 6 cm, and an absence of hyaline stroma.[15]

Myxoid leiomyosarcomas are usually grossly gelatinous and are characterized microscopically by a sparsely cellular, myxoid appearance.[27] Such tumors are almost always clinically malignant despite low mitotic rates (0-2 MFs/10 HPFs) and bland nuclear features; they are diagnosable as sarcomas on the basis of their highly infiltrative borders. Occasionally, leiomyomas, with hydropic change exhibit such a change in the surrounding myometrium, simulating a myxoid leiomyosarcoma.

Recently, immunohistochemical and molecular genetic studies on uterine leiomyosarcomas have been reported.[28-31]

Uterine smooth muscle tumors that are unclassifiable by current criteria as unequivocally benign or malignant have been referred to as "**smooth muscle tumors of uncertain malignant potential**" (STUMP) although as yet there is no uniform definition of these tumors. Criteria used by Bell et al.[20] include the presence of moderate to severe cytologic atypia and <10 MFs/10 HPFs in absence of tumor necrosis. In contrast, O'Connor and Norris[5] render a diagnosis of STUMP in the presence of 5-9 MFs/10 HPFs and mild (grade 1/3) nuclear atypia.

SMOOTH MUSCLE TUMORS WITH UNUSUAL GROWTH PATTERNS

The designation **leiomyoma with vascular invasion** refers to an otherwise typical leiomyoma with microscopic intravascular growth confined to the tumor.[1,2] Although most of these tumors are clinically benign, several cases have been associated with benign smooth muscle nodules in the lungs ("benign metastasizing leiomyoma", see below) while other cases may represent an early stage of intravenous leiomyomatosis.

It is important to distinguish leiomyomas with vascular invasion from **intravenous leiomyomatosis**, another lesion characterized by the presence of grossly visible intravenous proliferations of benign-appearing smooth muscle outside the confines, or in the absence, of a leiomyoma[32,33] Extrauterine extension within pelvic veins has been reported in 80% of the cases, and in 40% of such cases the tumor has reached the right side of the heart, sometimes with fatal consequences.[32]

Grossly, the uterus is usually involved by multiple leiomyomatous nodules, some in the form of worm-like extensions of tumor within vessels; the latter finding, however, is not always appreciated on initial examination of the hysterectomy specimen. On histological examination, the intravascular growth usually resembles a typical leiomyoma, but occasionally it resembles one or other variant of leiomyoma, including cellular leiomyoma, leiomyoma with bizarre nuclei, lipoleiomyoma, or epithelioid leiomyoma.[33] The intravascular tumor often has a clefted or lobulated contour, and its appearance may be altered by extensive hydropic change or hyalinization, and numerous thick-walled vessels. Usually, mitotic figures are rare, but cellular intravenous leiomyomatosis may contain up to 4 MFs/10 HPFs. In contrast to cellular intravenous leiomyomatosis, low-grade endometrial stromal sarcoma, lacks thick-walled vessels, lobulation, and hydropic degeneration in its intravascular extensions; furthermore, it involves the endometrium as well as the myometrium.

In women in whom the diagnosis of intravenous leiomyomatosis is made on a hysterectomy specimen, postoperative ultrasonic or magnetic resonance imaging studies may be useful in detecting and monitoring the growth of residual intravascular tumor. GnRH-agonists may be useful in controlling unresectable tumor.

Diffuse leiomyomatosis is a rare lesion characterized by symmetrical uterine enlargement from innumerable, confluent, leiomyomatous nodules within the myometrium.[34] Microscopic examination reveals that the nodules, including many not appreciable grossly, consist of cytologically benign, typically cellular, mitotically-inactive smooth muscle. The differential diagnosis includes rare cases of uterine involvement by lymphangioleiomyomatosis, usually in patients with tuberous sclerosis. In such cases, the myometrium is usually grossly normal but involved by numerous microscopic ill-defined nodules of smooth muscle surrounding lymphatics and protruding into their lumens. The smooth muscle cells of lymphangiomyomatosis are immunoreactive for HMB-45.[35]

Benign metastasizing leiomyoma is also a rare disorder; it is characterized by extrauterine nodules of benign-appearing smooth muscle in women who have had typical uterine leiomyomas[36-38] The benign glands composed of entrapped respiratory epithelium are typically found within the lesions. Less commonly, the retroperitoneal and mediastinal lymph nodes or other sites (bone, soft tissue) may be involved. The extreme rarity of primary pulmonary smooth muscle tumors, the association with uterine leiomyomas, and the occasional involvement of extrapulmonary sites, suggest that the pulmonary nodules in this disorder are metastatic. Additional evidence includes an occasional paradoxical reduction in their size during pregnancy and a cessation in their growth after the menopause, suggesting hormone dependence.

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MIXED EPITHELIAL AND MESENCHYMAL TUMORS OF THE UTERUS

Esther Oliva, M.D.

CLASSIFICATION:

Mullerian Adenofibroma
Mullerian Adenosarcoma
a) Homologous
b) Heterologous
Malignant Mixed Mullerian Tumor
a) Homologous
b) Heterologous
Mullerian Carcinofibroma and Carcinomesenchymoma
Mullerian Adenomyoma
a) Endometrioid type
b) Endocervical type
c) Atypical polypoid adenomyoma

The body of the uterus develops from the paramesonephric (mullerian) ducts, which in turn are derived from the mesenchyme of the urogenital ridge and the celomic lining epithelium. The term mixed mullerian tumors refers to a group of tumors that are composed of a combination of mesenchymal and epithelial elements and their classification is based on whether these elements are benign or malignant. The commonest mixed epithelial mesenchymal tumors are the malignant mullerian mixed tumor and the mullerian adenosarcoma, being the mullerian carcinofibroma; carcinomesenchymoma and adenofibroma rare entities.

MALIGNANT MULLERIAN MIXED TUMOR (MMMT).

These are the most common tumor in this category of neoplasms and account for almost half of all uterine sarcomas.

CLINICAL FEATURES:

These tumors occur typically in post-menopausal women although a small number have been documented in patients less than forty years of age, including children. Risk factors including obesity, exogenous estrogens, and nulliparity are similar to those found for endometrial adenocarcinoma. A history of prior pelvic irradiation is found more often in patients with carcinosarcoma that with any other type of uterine cancer. Between 7 and 37% of women with carcinosarcoma have previous radiation, and those tend to develop in younger women, contain more often heterologous elements and they have more extensive disease at the time of diagnosis. Most women present with abnormal vaginal bleeding and an enlarged uterus. The serum level of CA125 is elevated in most cases. Extrauterine spread (Stage III-IV) is reported in up to 1/3 of cases.

GROSS FEATURES:

These tumors are typically large, bulky polypoid masses, filling the uterine cavity and prolapsing through the endocervical canal into the external os. The cut surface is usually fleshy and often shows areas of hemorrhage, necrosis and secondary cyst formation. Myometrial invasion is frequently seen. Rare tumors may arise in the uterine cervix.

MICROSCOPIC FEATURES:

On microscopic examination, these tumors are characterized by an intimate but at the same time haphazard admixture of carcinomatous and sarcomatous elements, although one component may predominate. In most MMMTs, both components are high grade but in rare instances, one or both components may be low grade.

- The **carcinomatous component** is usually serous or endometrioid but it can also be clear cell, mucinous, squamous or undifferentiated carcinoma (including small cell carcinoma, although this is rare). MMMTs arising in the uterine cervix frequently have a non-glandular carcinomatous component that is exclusively or predominantly composed by squamous or basaloid carcinoma, or resembles adenoid cystic carcinoma and may have overlying intraepithelial squamous neoplasia. The carcinoma is well differentiated in less than 20% of cases. In up to ½ of these tumors the typical endometrial hyperplasia or even pure endometrial carcinoma (endometrioid or serous) is identified in the uninvolved endometrium.

- The **sarcomatous component** may be either of homologous or heterologous type. The homologous sarcomatous component is composed of cell types that are normally found in the uterus and resemble endometrial stromal sarcoma, malignant fibrous histiocytoma, leiomyosarcoma and undifferentiated sarcoma, or any combination thereof. In heterologous MMMTs the most common components are rhabdomyosarcoma, benign appearing cartilage or chondrosarcoma and less often show osteoid formation (osteosarcoma) or adipose tissue (liposarcoma). These heterologous components merge with the more undifferentiated homologous sarcomatous component. About 50% of MMMTs are heterologous, the relative percentage will vary depending on the extent of sampling and a thoroughness of searching for those elements with or without the use of immunochemistry. Rarely, neuroectodermal, melanocytic, yolk sac and rhabdoid differentiation has been observed. The presence of eosinophilic hyaline droplets is common and they are immunoreactive for alpha-1-antitrypsin. This should not be confused with the eosinophilic appearance of the cytoplasm seen in rhabdomyoblast and this finding has not specific significance. Those tumors arising in the uterine cervix usually show homologous sarcomatous component only.

IMMUNOHISTOCHEMISTRY:

The carcinomatous elements are typically positive for epithelial markers (cytokeratin, epithelial membrane antigen (EMA)) and vimentin as seen in endometrial carcinomas. The sarcomatous elements are typically positive for vimentin and frequently for actin. They also frequently express epithelial markers reflecting a common mesodermal origin of these tumors. The sarcomatous component can also express CD10, a marker used initially for the diagnosis of endometrial stromal tumors. The rhabdomyosarcomatous component stains for desmin, myoglobin, myogenin, and MyoD1. Both carcinomatous and sarcomatous elements may show positivity for neuroendocrine markers including synaptophysin, NSE and Leu-7. In most cases, immunohistochemistry is not needed to establish the diagnosis of MMMT as it can be based on microscopic findings.

HISTOGENESIS:

Because MMMTs have such an intimate admixture of epithelial and mesenchymal malignant elements their histogenesis has been for long time a matter of speculation. Four main theories exist to explain this diverse histologic appearance. The "collision" theory, where two independent tumors seem to have collided; the "composition" theory, where the spindle cell component is a pseudosarcomatous stromal reaction to the presence of carcinoma; the "combination" theory where the two components have arisen from the same pluripotential cell; and finally the "conversion"

theory where the sarcomatous component evolves from the carcinomatous component by a metaplastic process. The "combination" and "conversion" theories (which are not mutually exclusive) are the most widely accepted. In fact molecular data have shown that most of these tumors are monoclonal in origin based on patterns of X chromosome inactivation, loss of heterozygosity and p53 and K-ras mutations. There is still a small proportion of tumors that represent true collision tumors.
Some tumors arising in the cervix have been shown to contain HPV-DNA by polymerase chain reaction and have integrated HPV 16 in the carcinomatous and sarcomatous components by in situ hybridization.

DIFFERENTIAL DIAGNOSIS:

1. **Sarcomatoid endometrioid carcinoma**. In these cases there is transition from typical carcinomatous to spindled cell areas with absence of clear-cut heterologous components as well as absence of reticulin fibers around the neoplastic cells.
2 **High-grade endometrioid sarcomas and pure heterologous sarcomas**. These tumors may cause problems in differential diagnosis in cases where the carcinomatous component of the MMMT is minor and for that reason difficult to identify. In those cases extensive sampling is needed to exclude the presence of an epithelial component.
3 **Endometrial adenocarcinomas with heterologous elements**. These are rare tumors characterized by otherwise typical endometrial carcinoma associated with minor foci of benign heterologous components (cartilage, fat, bone) but without a sarcomatous component.

BEHAVIOR AND PROGNOSTIC FACTORS

The 5-year year survival rates range from 5 to 40% for patients with tumors of all stages, and 40 to 60% for those Stage I and II tumors. The depth of myometrial invasion and the stage of the tumor are the most important prognostic factors. Myometrial invasion beyond the inner third is seen in 80% of tumors, 40% have deep myometrial invasion. Confinement of the tumor to a polyp with absence of myometrial invasion, however, does not preclude extrauterine spread. Lymphatic and blood vessel invasion is found in most cases and typically shows the carcinomatous component. Metastatic and recurrent tumor may be exclusively carcinomatous, sarcomatous or carcinosarcomatous, but often is mainly carcinomatous. Some studies have shown that that within the epithelial elements, high-grade carcinoma and serous and clear cell carcinoma are associated with higher frequency of metastases, deep myometrial invasion, lymphatic or vascular space invasion and cervical involvement, all parameters indicative of an aggressive behavior. Within the sarcomatous component, grade, mitotic index or presence of heterologous elements do not affect the overall prognosis.

MULLERIAN ADENOSARCOMA.

Mullerian adenosarcomas of the uterus are uncommon neoplasms characterized by an admixture of a benign but sometimes atypical glandular epithelium and a sarcomatous stromal component. Adenosarcomas, in contrast to malignant mullerian mixed tumors, typically have a low malignant potential, manifested predominantly by local recurrence in approximately 25% of cases; distant metastases occur in less than 5% of cases.

CLINICAL FEATURES:

Adenosarcoma typically occurs in postmenopausal women, but 30% are found in premenopausal patients. Frequently they present with abnormal vaginal bleeding, often accompanied by pelvic pain and enlarged uterus. In ½ of the cases, the tumor protrudes through the external os. In occasional

cases the diagnosis is made in retrospect in patients that have a history of recurring endometrial or endocervical "polyps". Associated risk factors include hyper-estrogenic states (including tamoxifen therapy) and prior radiation therapy.

GROSS FEATURES:

Mullerian adenosarcomas are typically polypoid intracavitary tumors. Most adenosarcomas arise in the endometrium, but occasionally they may develop in the cervix (9%) or within the myometrium (4%). In rare cases the uterine corpus and the cervix may be involved by separate primary tumors. They are typically broad-based and polypoid but sometimes they have a villous appearance. The cut surface is commonly spongy due to cystic spaces containing watery or mucoid material that are surrounded by white to tan tissue. Those tumors with a villous appearance often have a clefted cut surface reminiscent of the phyllodes tumors of the breast. Myometrial invasion is seldom evident on gross examination.

MICROSCOPIC FEATURES:

On **low-power examination**, the tumors show a biphasic growth of typically benign glandular epithelium and malignant stroma. The epithelial component forms glands, often dilated, showing glandular polypoid projections of the stroma and/or a papillary or leaf-like shape resembling on low power a phyllodes tumor of the breast. The stroma concentrates around the glands forming periglandular cuffs and/or intraglandular protrusions. This low-power appearance even without cytologic atypia or mitotic activity should suggest the diagnosis of adenosarcoma.

On **high-power examination:**

- **The glands** are lined by a variety of benign or atypical mullerian epithelia, most commonly of proliferative endometrioid type but mucinous, ciliated, hobnail or indifferent types alone or in combination may be seen. It can also show metaplastic squamous epithelium. In 1/3 of the tumors one can see focal architectural and cytologic atypia of the glandular epithelium and in a minority of cases even small foci of adenocarcinoma. In those cases, the endometrium elsewhere in the uterus may show a typical hyperplasia or adenocarcinoma.

- **The stromal component** is usually a low-grade sarcoma, resembling low-grade endometrial stromal sarcoma, fibrosarcoma or combinations thereof. Some tumors may show areas of smooth muscle differentiation. This sarcomatous component is typically more cellular around the glands, and in these areas 4 or more mitotic figures per 10 high power fields are present in over 80% of the tumors. In areas away from the glands the tumors may be hypocellular, or even replaced by myxoid or hyalinized fibrous tissue, showing low mitotic index and giving the impression of deceptively benign tumor. Heterologous components with striated muscle, cartilage, and adipose tissue occur in up to 25% of the cases. Sex cord-like elements as seen in endometrial stromal tumors are found in approximately 7% of the cases. These sex cord-like elements consist of epithelial-like cells arranged in solid nests, trabeculae, and solid or hollow tubules. The cells typically have eosinophilic or foamy, lipid-rich cytoplasm and a small round to oval nuclei and they have an appearance similar to that seen in Uterine Tumors Resembling Ovarian Sex Cord Tumors. This component may occupy as much as 50% of the tumor and tends to merge imperceptibly with the conventional sarcomatous component.

Mitotic activity of the stromal component is variable. A cut of point of 4 or more mitotic figures per 10 high power fields has been used by some authors, however, mitotic figures in adenosarcomas often are restricted to the periglandular cuffs, making mitotic counts difficult to perform. In the

largest series of adenosarcomas published by Clement and Scully, about 24% of their adenosarcomas had 3 or fewer mitoses per 10 high power fields.

Myometrial invasion is found in only 1/6 of tumors and is superficial (in ½ of the myometrium) in 80%. The invasive front is usually well circumscribed and rarely these tumors invade myometrial vessels in contrast to low-grade endometrial stromal sarcomas.

Stromal overgrowth is defined as by the presence of at least 25% of the tumor being composed of pure sarcoma and occurs in 10% of tumors. The overgrowing sarcoma is typically of a higher grade that is seen in the adenosarcoma although in some cases may be of low grade. The tumors with a stromal overgrowth invade the myometrium more often and more deeply than typical adenosarcomas, leaving to a more aggressive behavior with a poor outcome for these patients.

Useful criteria in diagnosing mullerian adenosarcoma alone or in combination include:

- Two or more stromal mitotic figures/10 high power fields
- Marked stromal cellularity
- Significant stromal cell atypia

DIFFERENTIAL DIAGNOSIS:

1. **Endometrial Polyp:** They are characterized by hypocellular stroma with no periglandular cuffing, stromal atypia nor mitotic activity. Some endometrial polyps are cellular but still show the typical features described above. However, on occasion adenosarcomas may arise in endometrial/endocervical polyps.

2. **Adenofibroma**: Those account for approximately 5% of tumors in the adenofibroma-adenosarcoma spectrum. These are characterized by diffuse hypocellularity, no periglandular stromal condensation, no stromal atypia, and mitotic activity <2 per 10 high power fields.

3. **Atypical Polypoid Adenomyoma**: They typically have a much more prominent glandular component with squamous morules. The stromal component contains prominent benign smooth muscle, the latter is unusual in adenosarcomas.

4. **MMMT**: In those cases the carcinomatous component is overtly malignant in contrast to mullerian adenosarcoma where the glandular component show at the most a well-differentiated carcinoma.

5. **Endometrial Stromal Sarcoma with Glandular Differentiation or Sex Cord-like Differentiation**: These tumors show the typical tongue-like infiltrative growth pattern as well as prominent myometrial and lymphovascular invasion. In most cases the epithelial elements are scant, without the typical low-power appearance of an adenosarcoma. The same applies to endometrial stromal tumors with sex cord-like differentiation.

BEHAVIOR AND PROGNOSTIC FACTORS:

Adenosarcomas frequently have an indolent growth rate, with recurrences at 5 years or months and long-term follow-up is therefore essential in those patients. Recurrences are primarily vaginal or pelvic in 1/3 of the cases. Hematogenous spread occurs in less than 10% of the cases. The only morphologic features that have associated with a high rate of recurrence are deep myometrial invasion and the presence of sarcomatous overgrowth. The histology of the recurrent tumor is pure sarcoma in70% of cases, adenocarcinoma in 30% and a carcinosarcoma in rare cases. Recurrent

tumor rarely contains heterologous elements or foci of carcinoma not present in the primary tumor. Blood-borne metastases have been purely sarcomatous. Sarcomatous overgrowth is associated with recurrence, hematogenous metastases, and death from tumor in 780%, 40%, and 60% of patients, respectively.

MULLERIAN CARCINOFIBROMA AND CARCINOMESENCHYMOMA

These are rare tumors characterized by a malignant epithelial component and a benign mesenchymal component. Carcinofibromas are defined as tumors where the mesenchymal composed of abundant fibromatous stroma, although it is difficult to prove that the mesenchymal component is neoplastic and not reactive to the carcinomatous component. The term carcinomesenchymoma has been used for a more convincing example of carcinoma associated with benign smooth muscle, cartilage and adipose tissue. This tumor was described in a 50-year-old woman that presented with an intramural mass and on microscopic examination the epithelial and mesenchymal components of the tumor were intimately admixed.

MULLERIAN ADENOFIBROMA

This is an extremely rare tumor composed of benign epithelial and mesenchymal components and at least some of these cases represent mullerian adenosarcomas. The most common presenting symptom is vaginal bleeding. They occur typically in postmenopausal women, more often in the uterine corpus and rarely in the cervix. Their gross appearance overlaps with that of mullerian adenosarcomas. On microscopic examination the epithelial elements are similar to those seen in adenosarcomas. The stromal cells resemble fibroblasts or endometrial stroma. The most helpful features for the diagnosis of adenofibroma are the absence cuffing around the glands, absence of cellular atypia and minimal or absent mitotic activity (<2 mitosis/10 high power fields). The presence of heterologous elements has been rarely reported and includes the finding of fat (lipoadenofibroma) and skeletal muscle (adenomyofibroma).

MULLERIAN ADENOMYOMA OF ENDOMETRIOID TYPE

CLINICAL FEATURES:

Women range from 26 to 64 years of age and frequently they present with abnormal vaginal bleeding. In some cases the tumor may be an incidental clinical or microscopic finding.

GROSS FEATURES:

The tumors are mores frequently located in the uterine corpus but they may be seen in the cervix. In the corpus they have a submucosal location. They may reach 17 cm in largest dimension. On sectioning they are firm are often show small cysts sometimes filled with blood. The firm areas have a similar appearance of that seen in leiomyomas. The tumors are well circumscribed from the surrounding tissues.

MICROSCOPIC FEATURES:

On low-power examination these tumors are well circumscribed.

- **The glands** are variable in density and outlines, but usually well spaced and range from small simple glands to more irregularly shaped glands and large cysts. They are predominantly lined by proliferative endometrioid-type epithelium, but ciliated, endocervical-type mucinous and squamous epithelium may be found. Cytologic atypia is absent and scattered mitotic figures may be seen.

- **The stroma** consists of endometrial-type stroma and smooth muscle, and the latter typically predominates. The endometrial-type stroma always has a periglandular distribution and the smooth muscle component is present surrounding the stromal-type component. The endometrial stromal component is characterized by small oval to spindle cells with scant cytoplasm and benign nuclear features. It may show sex cord-like differentiation. The smooth muscle component may be hyper or hypocellular with areas of edema and/or hyalinization. They may contain cells with bizarre nuclei, but there is no cytologic atypia of the background smooth muscle cells. Thick-walled blood vessels are typically found. Mitotic activity if present is more often seen in the endometrial stromal component than in the smooth muscle component.

DIFFERENTIAL DIAGNOSIS:

1. **Leiomyoma with entrapped endometrial glands.** The glands are usually present at the periphery of the tumor and there are not surrounded by endometrial-type stroma.

2. **Atypical polypoid adenomyoma**. In contrast to the typical endometrioid adenomyoma, atypical polypoid adenomyoma is characterized by irregular crowded endometrioid glands with cytologic atypia and, in 90% of cases, squamous morules, embedded in a cellular, sometimes mitotically active stroma composed, in large part, of smooth muscle.

3. **Typical endometrial polyps**. These lack a prominent smooth muscle component, having instead fibrous and endometrial stromal components and the latter does not uniformly surround the glands as in adenomyomas.

4. **Endometrioid adenocarcinoma, diffusely infiltrating**. These are not well circumscribed and show cytologic atypia of the glandular component.

5. **Adenosarcoma with smooth muscle differentiation**. They show the characteristic low-power appearance of dilated or leaf-like glands with periglandular condensation of the stroma.

6. **Mixed endometrial stromal-smooth muscle tumors**. No glandular differentiation has been described in those tumors yet and there is a different distribution of the stromal and smooth muscle components than that described in adenomyomas.

BEHAVIOR:

These are benign tumors with no recurrence or spread reported to date.

MULLERIAN ADENOMYOMA OF ENDOCERVICAL TYPE

These are frequently an incidental finding in women of reproductive age or postmenopausal.

GROSS FEATURES:

They are polypoid masses growing into the endocervical canal and sometimes protruding into the external os. On gross examination the tumors are well circumscribed and grey-white or tawny and frequently contain multiple mucin-filled cysts.

MICROSCOPIC FEATURES:

On microscopic examination:

- **The glandular component** forms glands and cysts lined by a single layer of endocervical-type mucinous epithelium. The glands have frequently a lobular architecture with a large irregular gland surrounded by smaller glands. One can also see tubal or endometrioid-type epithelium.
- **The smooth muscle** which represents the mesenchymal component of the tumor which is admixed with the glandular component. Both epithelial and mesenchymal components are uniformly bland.

DIFFERENTIAL DIAGNOSIS:

The main differential diagnosis is with **adenoma malignum** because of the finding of bland appearing endocervical glands admixed with muscle. The gross circumscription of the adenomyomas, their polypoid appearance, the frequent lobular arrangement of the glands, the absence of invasive glands with a desmoplastic stromal reaction, and lack of even focal atypia are helpful in this differential diagnosis.

BEHAVIOR:
These are benign tumors but if excision is incomplete they may recur.

ATYPICAL POLYPOID ADENOMYOMA (APA)

CLINICAL FEATURES:

Most of these tumors occur in women of reproductive age (mean, 39 years of age), but occasional tumors occur in postmenopausal women. Rare cases are associated with long-term estrogen therapy. The patients typically present with abnormal vaginal bleeding, pelvic examination is usually negative, but in some cases a polypoid mass protrudes from the external os.

GROSS FEATURES:

These tumors frequently involve the lower uterine segment, but they may arise in the corpus or cervix. They are typically solitary, well-circumscribed, pedunculated or sessile, and <2 cm in greatest dimension. The sectioned surfaces are yellow-tan to gray and white, solid and firm or rubbery.

MICROSCOPIC FEATURES:

- **The epithelial component** has endometrioid glands with varying degrees of architectural and cytologic atypia and mitotic activity are separated by myofibromatous stroma. Squamous morules, present in 90% of cases may fill glandular lumens and occasionally have areas of central necrosis. Keratin liberated from these morules rarely may implant on the peritoneum and result in keratin granulomas. Rare findings include a cribriform pattern, severe cytologic atypia, or both. Foci resembling well-differentiated adenocarcinoma may be seen in APAs. Some APAs are contiguous to and appear to be the origin of a well-differentiated adenocarcinoma.
- **The stromal component** contains interlacing bundles of cellular smooth muscle, proliferating myofibroblasts, or both. The stromal cells exhibit mild to moderate atypicality in a minority of cases. Occasional mitotic figures are usually seen.

APAs usually are non-invasive, with a well-circumscribed border in hysterectomy specimens, although some involve the superficial myometrium. In one study no typical APAs invade the myometrium, but rare APAs associated with foci resembling well-differentiated adenocarcinoma superficially invaded the myometrium.

DIFFERENTIAL DIAGNOSIS:

1. **Endometrial Adenocarcinoma**. In a curetting specimen features favoring adenocarcinoma include a postmenopausal age and the presence of glands with overt malignant features.

2. **MMMT**. These usually lack a prominent smooth muscle component and overtly malignant appearance of the epithelial and stromal components.

3. **Low-grade Mullerian Adenosarcoma**. They usually lack a prominent smooth muscle component and periglandular condensation of the stromal component around the glands.

4. **Typical Adenomyoma of the Endometrioid Type**. There is absence of architectural and cytologic atypia.

GENETICS:

These lesions share some of the molecular alterations seen in endometrial hyperplasia as some of them exhibit MLH-1 promoter hypermethylation with focal lack of MLH-1 immunostaining, a molecular abnormality involved in the transition from complex atypical hyperplasia to endometrioid adenocarcinoma.

BEHAVIOR:

There is a recurrence index of 45% in patients treated conservatively and those treated in this manner rarely may progress to adenocarcinoma. Those APAs with foci resembling well-differentiated carcinomas have a higher recurrence rate (60% versus 33%).

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INFECTIONS OF THE UTERUS

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INFECTIONS

In the past, uterine infections were divided into two main pathogenetic groups, ascending infections and descending infections based on the prevalence of gonorrhea and tuberculosis. Gonorrhea was the prototype of ascending infection leading to cervico-vaginitis, endometritis and salpingitis; if not adequately treated the late event was hydrosalpinx and infertility. Tuberculosis is a systemic disease and only secondarily involves the genital tract with the development of salpingitis and endometritis. By time, the prevalence of infections changed and development of new tests allowed the discovery of other etiologic agents but the approach may be considered still valid. Inflammation may also develop following treatments, such as radiation and endometrial ablation.

The vaginal pool is the main source of uterine infections; some of them don't cause severe symptoms and the condition is designated vaginosis. Symptomatic infection is defined as vaginitis and cervico vaginitis. Most of these infections have the potential to extend to the uterine cavity producing endometritis and, in pregnancy, chorionamniositis and villositis. A brief comment on the vaginal ecosystem is necessary to understand the development of some uterine infections.

The cervico-vaginal ecosystem

The cervico-vaginal ecosystem includes the vaginal and cervical epithelium, microbial flora, vaginal fluid, and cervical mucus. The vaginal environment is hormone-dependent and is influenced by several biologic factors including individual characteristics, normal physiologic states, changes caused by systemic disease or treatment and other health practices, such as sexual and hygiene measures. The prevalence of certain bacteria in the vaginal flora depends by the oxidation-reduction potential and pH; when the oxidation reduction potential is low, anaerobic bacteria are favored. The pH may affect the viability of many organisms (for example, HIV does not survive in an acid pH), and certain enzyme systems (for example, some strains of lactobacilli can break down glycogen at a low pH but not at a higher one) and it may also affect the solubility of nutrients.

The relationship between genital tract infection risk and use of intravaginal products, such as vaginal barrier contraceptives, treatment of vaginitis, and products for vaginal hygiene are difficult to understand. The products may have direct effects on microbial pathogens, alter endogenous microbial flora, cause alterations in the vaginal environment, or have a direct effect on vaginal epithelium. For example, nonoxynol-9 (N-9) is toxic to Lactobacillus acidophilus, but has little or no direct effect on colis and may result in an increase in vaginal (and urethral) colonization by this pathogen.

Vaginitis and bacterial vaginosis

All the major types of organisms (bacteria, fungi, viruses, and parasites) have been found to abnormally colonize the vagina and produce invasive infection. Some of them are included in the list of the Sexually Transmitted Pathogens. The diagnosis of vaginitis includes the presence of vaginal discharge (color, odor, quality and quantity). Typical vaginitis is caused by Candida and Trichomonas.

In the past bacterial vaginosis was designated as non-specific vaginitis when the clinical evidence of vaginitis was absent. Actually it is considered an overgrowth of multiple colonizing bacteria including

Gartnerella and anaerobes. Gartnerella, a Gram negative bacillus, was firstly related to vaginosis; however, these bacteria alone do not seem sufficient to be the cause of all cases of vaginosis and may be found in a high number of asymptomatic women.

Anaerobes include Prevotella bivia, Mycoplasma hominis, Mobiluncus muliebri and curtisii. Diagnosis can be done if there are three of the four criteria: 1) homogeneous thin malodorous discharge, 2) vaginal pH > 4,5, 3) presence of "clue cells" (cells with bacteria), 4) fish odor on alkalinization of vaginal secretions. Confirmation needs the exclusion of other pathogens and the combination of Gram negative to Gram variable bacilli and "clue cells" on smears. Pap smear is specific (even less sensitive). The major complications include endometritis, salpingitis and PID, and premature onset of labor and chorioamniositis

Infections on histologic material

Non specific infections. Chronic cervicitis is a common finding in women with ectopion. The severity of the inflammatory infiltrate is variable and usually mild; more severe form is associated with lymphoid follicles (follicular cervicitis). Chronic endometritis is defined by the presence of plasma cells in the stroma. In the mild form, it may be an occasional and unexplained finding; however, more prominent endometritis is associated with rests of the placental site (postabortive endometritis and postpartum or puerperal endometritis). In other cases polyps, submucosal leiomyomas and IUD may be tresent and may explain the finding.

Most common infections. Cervicovaginitis plays a central role for the dissemination of some agents to the upper genital tract with the development of endometritis, salpingitis, and pelvic inflammatory disease (PID). Major complications are postabortal and postpartum or puerperal endometritis, chorion amniositis that are among the major causes of fetal morbidity. Symptoms include mucopurulent discharge; histologically, cervicitis may be chronic or follicular and endometritis is similar to non-specific endometritis. Among the etiologic agents the most frequent are Chlamydia trachomatis and Neisseria gonorrhea, anaerobic gram-negative bacteria and Mycoplasma hominis. Some of the last agents may be associated with lymphoid aggregates in the basal endometrium.

Actinomycosis. Actinomycosis may be found in pap smears from asymptomatic women; in histologic material may be found in women with endometritis particularly those with IUD. Infection spreads to the tubes with development of purulent salpingitis and PID. Usually the agent is found is surgical specimens from the tubes and infrequent in the material from the abdominal cavity.

Granulomatous infections. Tuberculosis is the most frequent granulomatous infection. On biopsy material endometritis is by far more frequent than cervicitis and is usually associated with salpingitis. Sarcoidosis is histologically similar with tuberculosis, but is rare. Other granulomatous infections include syphilis, lymphogranuloma venereum, granuloma inguinale which may simulate cancer on gross examination. However, they are more typical in the vulva (and vagina), rarely occur in the cervix with the exclusion of syphilis, and do not reach the endometrium. Foreign body reaction is common following surgical procedures and may associated with granulation tissue and fibrosis.

Viral infections. Human papillomavirus (HPV) infection is the most frequent viral infection of the cervix and is followed in frequency by Herpes virus (HSV) and Cytomegalovirus (CMV) infection. Clinically, HSV presents with painful vesicles in the cervix and vagina, which on smears and biopsy show the typical intranuclear inclusion bodies. Cytomegalovirus infected cells also show a typical cytopatic effect. Although HSV and CMV infections are frequent in STD clinics, it may be encountered in asymptomatic women. HSV and CMV infection may be found in the endometrium.

Fungal infections. Candida albicans is frequently involved in vulvitis and vaginitis and diagnosis may be done on smears.

Protozoal infections. Another common form of vaginitis, which is associated with yellow-green discharge, is caused by Trychomonas vaginalis and diagnosis is merely cytologic.
Parasitic infections. They are rare in developed countries

Xanthogranulomatous inflammation. May be seen in the endometrium and is rare in the cervix.

Other inflammatory conditions include giant cell arteritis, Langherhans cell histiocytosis. A rare lesion is known as colpitis or cervicitis emphysematosa for the development gas containing cysts.

MISCELLANEOUS LESIONS OF THE CERVIX

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RARE TUMORS

Rare primary tumors analogous to those arising in the ovary, including teratoma, yolk sac tumor, and Brenner tumor, have been describe in the uterus. Angiomas and so called hemangiopericytomas may also be found. Some other tumors tumors deserve particular mention: embryonal rhabdomyosarcoma (sarcoma botryoides), rhabdomyoma, alveolar soft part sarcoma, melanocytic lesions, melanomas and the group of tumors characteristically positive for S-100 and/or HMB45.

Sarcoma botryoides.

Unlike the vaginal tumor, which is usually encountered in the first two decades, the cervical sarcoma botryoides develops more frequently in the second to the fourth decade. It is characterized by polypoid edematous or myxoid masses with condensation around the larger blood vessels and particularly in the subepithelial stroma. Tumor tissue is analogous to the embryonal rhabdomyosarcoma of other non gynecologic location., however, fetal-type cartilage in the stroma is a frequent finding. Progosis is by far better than the vaginal type with a high cure rate after hysterectomy and, in favorable cases even after conservative treatment.

Rhabdomyoma.

This cervical tumor is composed of fetal rhabdomyoblasts often associated with areas of edema. It should be differentiated from embryonal rhabdomyosarcoma particularly by the absence of the subepithelial immature cambium layer.

Alveolar soft part sarcoma.

It is a solid usually well circumscribed tumor composed of nests of epithelioid cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Pas positive intracytoplasmatic crystals are frequent in tumor cells. Although suspected a skeletal muscle differentiation has not been clearly demonstrated. Prognosis seems to be better than that of extragenital tumors.

Melanocytic lesions and melanomas

Aggregates of dendritic pigmented Schwann cells laying in superficial endocervical mucosa, and rarely in the superficial myometrium of the fundus, are designated “blue nevi”. The exocervical epithelium may contain dendritic melanocytes in the condition known as “melanosis” which is more frequent in the vagina. This condition should be differentiated from in situ malignant melanoma. Primary melanoma may occur on the cervix and should be differentiated from metastatic melanoma.

S-100 and HMB-45 positive tumors.

Spindle cell tumors with S100 positive cells include melanomas and Schwannomas similar to soft tissue tumors. Recently a HMB-45 positive tumor has been described and designated perivascular epithelioid cell tumor (PECOMA) for the suspected origin from perivascular epithelioid cells. These tumors may resemble epithelioid smooth muscle tumors or low grade endometrial stroma

sarcomas; tumor cells, however, exhibit clearer cytoplasm. Smooth muscle differentiation may also be present.

PSEUDOTUMORS

Rare examples of pseudotumor include inflammatory pseudotumor (inflammatory myofibroblastic tumor), spindle cell nodule and arteriovenous malformations. Another pseudotumoral lesion is represented by pseudolymphoma. Severe inflammatory infiltrate with numerous activated lymphocytes may appear atypical and should not misinterpreted as lymphoma being polyclonal. Unlike the cervix, the endometrium may contain numerous follicles, which represent a form of MALT.

POLYPS

Endocervical polyps are benign lesions associated with spotting or bleeding. They should be examined because they may be involved by more serious lesions including CIN or adenocarcinoma. Moreover, rare polyps are characterized by multinucleated or atypical stroma cells.

Endometrial polyps are another frequent finding particularly around menopause and are frequently sent as cervical polyp. Some have a fibrous stroma surrounding the glands; in others the stroma is similar to the uninvolved endometrium. Such polyps are recognized mainly for the presence of thick walled vessels and irregular distribution and shape of the glands. They are called functional polyps when they resemble functioning endometrium and hyperplastic polyps when they are similar to simple hyperplasia. In some cases there is extensive mucinous metaplasia and the polyp is interpreted as cervical. Moreover, the polyps may contain areas of complex or atypical hyperplasia and adenocarcinoma.

Mullerian papilloma is a variant of cervical polyp occurring in the first decades; it is characterized by more papillary fronds lined by mullerian type epithelium.

Mesodermal stromal polyps are similar to the more frequent vaginal polyps and are lined by native squamous epithelium.

HETEROTOPIC TISSUES

The finding of heterotopic tissues, is more frequent in the uterus and glia, cartilage, bone, adipose tissue, and prostate have been described. Skin and skin appendages may occur in the cervix.

MESONEPHRIC REMNANTS AND HYPERPLASIA

Mesonephric (or Wolffian or Gartner) duct rests are a common finding in the cervix particularly in serially sectioned specimens. They are usually bilateral and deep into the lateral wall of the cervix. There is one main duct (rarely there are few main ducts) and tubules with colloid-like eosinophilic secretion in the lumen. The tubules are lined by cuboidal cells with scanty amphophilic cytoplasm and round nuclei. Mitotic activity is null.

When glands around the ducts are numerous the condition is called mesonephric hyperplasia. Rare carcinomas arise from these remnants and are purely epithelial carcinomas in the great majority of the cases. However, few mixed tumors have been described and should be differentiated from the mullerian mixed tumors.

ENDOCERVICAL GLANDULAR HYPERPLASIA

The changes and the proliferation of benign endocervical glands may be so exuberant or unusual for architectural and cytologic features that interpretation can be difficult particularly with regard to differential diagnosis with adenocarcinoma.

These proliferations are usually an incidental microscopic finding, but when florid they may be grossly visible simulating a neoplasm. They consist of glandular aggregates, displaced glands, enlargement and or increased number of glands, irregular crowding of glands and atypical cell changes. In spite of the worrisome architectural features there is no evidence of stromal invasion, desmoplastic reaction, severe cell atypia, or increased mitotic activity, all features of malignant tumors.

Nabothian cysts

Nabothian cysts represent cystically dilated endocervical glands and are a common incidental finding on pathologic examination of the uterus. Usually they correspond in location to that of normal endocervical glands, but may be extended through two thirds of the cervical mucosa and in extreme examples they penetrate deeper reaching the paracervical tissues or the perimetrium. In the last cases they should be differentiated from a cystic form of well differentiated adenocarcinoma particularly minimal deviation adenocarcinoma (MDA) or "adenoma malignum". However in MDA cystic glands are only an occasional and focal finding. The pathogenesis of Nabothian cysts is related to the endocervical tunnels that lose their connection with the clefts from which they originate and accumulate mucus

Tunnel clusters (TC)

They consist of aggregates of closely packed glands which at the periphery are quite circumscribed from the surrounding cervical stroma. They are located in the lower half of the cervix, preferentially within the posterior wall and are grossly visible depending upon the size and the degree of cystic dilatation of the glands. Microscopically there are two types, types A and B.

Type A TC is a lobular proliferation of closely packed small glands usually around a central endocervical cleft. Typically, the glands varying in shape from rounded to elongated are lined by mainly cuboidal cells with minimal degree of atypia.

Lobules of dilated glands are characteristic of type B TC; they are grossly visible in about 40% of the cases for the cysts and may protrude in a polypoid fashion. Nabothian cysts are usually present in the specimen. The cysts are lined by flattened epithelium and contain inspissed mucin. This type of tC is quite common and has been observed retrospectively in 6% to 10% of surgical specimens (hysterectomy vs cone).

Microglandular hyperplasia (MGH)

In MGH the proliferating glands are closely packed with little intervening stroma. They vary little in shape and size and the lumen is not always clearly evident. The glandular epithelium is cuboidal to tall columnar and vacuolized. The complexity is enhanced by basal reserve cell hyperplasia or immature squamous metaplasia. Inflammatory cells are frequent. MGH is usually a microscopic finding in cervical biopsies and polyps but can be identified grossly as a sessile polyp and colposcopically because is usually located around the external os of the cervix.

Diffuse laminar endocervical glandular hyperplasia (DLEGH)

DLEGH is a superficial not lobulated glandular proliferation which is confined to the inner third of the cervical wall and sharply demarcated from the underlying cervical stroma. The glands are closely packed, but clearly separated by the intervening stroma. Inflammation is common.

Lobular endocervical glandular hyperplasia, not otherwise specified (LEGH)

LEGH consists of a poorly circumscibed increased number of typical endocervical glands with lobular architecture. In the lobular aggregates the glands are of small to medium size and rarely cystic and a central dilated gland surrounded by smaller glands is characteristic. Occasionally the glands are crowded suggesting a cribriform growth or may show papillary infoldings. The lining epithelium is unremarkable (tall columnnar mucinous cells), but reactive changes (increased nuclear size, irregular chromatin, and enlarged nuceoli) and increased mitotic activity (up to 2 MF per 10 HPF) may occur. Stromal extravasation of mucin secondary to cyst rupture may be associated with chronic inflammatory response, but elsewhere prominent inflammatory infiltrate and evidence of stromal invasion are typically absent.

LEGH is usually an incidental microscopic finding in hysterectomy specimens and in most cases it is confined to the inner half of the cervical wall; on rare instances deeper extension, incresed fibrous stroma, polypoid growth, and large cysts may occur producing a grossly visible mass. An interesting observation is the pyloric-type intracytoplasmic secretion based on PAS and Alcian blue and HIK 1083. CEA is almost always uniformly negative, but p16 is positive in about half of the cases. Unlike LEGH, "adenoma malignum" is usually deeply infiltrative and only occasionally may show a lobular architecture. Generous sampling discloses atypical glands and evidence of desmoplastic stromal response.

Patients were premenopausal in most cases but age range was wide (37 to 71 years); symptoms (vaginal or cervical discharge) occurred in about 30 % of the cases and the presence of a cervical mass was rare. One fourth of the patients had a history of hormone intake.

Adenomyomas of endocervical type and florid deep glands of the endocervix

The presence of endocervical glands deep in the stroma should always be differentiated from adenoma malignum. In some cases the glands are surrounded by smooth muscle resembling adenomyomas of the cervix.

METAPLASIAS

In the cervix, besides the common squamous metaplasia, two types of metaplasia need to be mentioned. One is glandular and include tubal and tuboendometrial metaplasia and the other is transitional metaplasia.

Transitional cell metaplasia resembles urothelium. The absence of CK20 and the common occurrence after menopause suggest that the similarity with the urothelium is only histological. Transitional metaplasia develops near the transformation zone usually in the postmenopause and may involve the crypts similarly with CIN.

Tubal metaplasia consists of the lining of the surface of the canal or cripts and glands by ciliated cells, which on Pap smears may be of difficult interpretation. Tuboendometrial metaplasia shows more endometrioid features and should not be confused with endometriosis.

Superficial endometriosis (and stromal endometriosis) are occasional findings on colposcopic biopsies. Pathogenesis of this condition seems to be related to previous trauma (curettage, abortion …) and implies implantation of menstrual endometrium and is not associated with pelvic endometriosis a condition associated with deep cervical endometriosis.

ARIAS STELLA CHANGE

Arias-Stella change is a typical finding in the "spongiosa" of the first trimester of pregnancy. It may occur in other sites including the cervix and also in non pregnant women. This change is characterized by an high degree of glandular complexity due to the prominent "ferning" (secretory hyperplasia) and enlargement of the lining cell. The nuclei are objectively "atypical" if compared with the nuclei of non pregnant endometrium. The absence of mitoses, chromatin clumping, and prominent nucleoli helps to interpret the changes as benign "atypia". Differential diagnosis with clear cell carcinoma is particularly difficult in the uterine cervix where the glands with the Arias-Stella change can be microcystic resembling one microscopic type of clear cell carcinoma. One should look also for other findings associated with pregnancy such as decidua in the surrounding stroma and the socalled optically clear nuclei, due to nuclear pseudoinclusions resembling herpes virus infection, in the adjacent glands. Clinical information is essential and immunostaining for p53 and Ki 67 is necessary in some cases.

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