Pathology of the Uterine Corpus

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Abstract

Endometrial cancer is the fourth most common cancer in women in the United States. Endometrial carcinomas can be divided into two types based primarily on association with excess estrogen. Endometrioid adenocarcinoma is the prototypical type 1 endometrial carcinoma, well known for its association with excess estrogen. It is the most common uterine malignancy and usually occurs in postmenopausal women. Endometrial hyperplasia is widely recognized as a non-obligate precursor to endometrioid adenocarcinoma. Type 2 endometrial carcinomas are not associated with excess estrogen and include serous and clear cell carcinomas. A wide variety of other neoplasms occur in the uterus. More common entities include biphasic tumors like malignant mixed Mullerian tumors (MMMT) and mesenchymal malignancies such as endometrial stromal sarcoma and leiomyosarcomas. More rare uterine tumors include perivascular epithelioid cell tumor (PEComa), primitive neuroectodermal tumor (PNET), lymphoma, and gestational trophoblastic disease.

Keywords

Endometrial hyperplasia • Endometrial intraepithelial neoplasia • Endometrioid adenocarcinoma • Clear cell carcinoma • Endometrial stromal sarcoma • Leiomyosarcoma • Malignant mixed Mullerian tumor • Gestational trophoblastic disease • Hydatidiform mole

Contents

1 Introduction 1042

2 Histology of Normal Uterine Corpus 1042

3 Endometrioid Adenocarcinoma Precursors 1042
3.1 Endometrial Hyperplasia 1042
3.2 Endometrial Intraepithelial Neoplasia 1043
3.3 Metaplastic Change 1044
3.4 Progestin Effect 1044

4 Uterine Tumors 1044
4.1 Endometrial Carcinoma 1044
4.2 Mesenchymal Lesions 1050
4.3 Mixed Epithelial-Mesenchymal Tumors 1053
4.4 Other Uterine Tumors 1054

5 Gestational Trophoblastic Disease 1055
5.1 Hydatidiform Mole 1056
5.2 Malignant Gestational Disease 1056

6 Conclusion 1057

7 Cross-References 1058

References 1058

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1 Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States, of which endometrioid adenocarcinoma is the most common type. Endometrial hyperplasia is a widely recognized non-obligate precursor to endometrioid adenocarcinoma. Other types of endometrial carcinomas include serous, clear cell, and malignant mixed Mullerian tumors (MMMT), among others. In addition to carcinomas, many different neoplasms can be found in the uterus. Leiomyoma is the most common tumor of the uterus; mesenchymal malignancies, such as endometrial stromal sarcoma and leiomyosarcomas, are less common. Other tumors that can be encountered in the uterine corpus include perivascular epithelioid cell tumor (PEComa), primitive neuroectodermal tumor (PNET), lymphoma, and gestational trophoblastic disease, all of which are rare. In this chapter, the histology of various tumors of the uterine corpus will be described with explanations of workup and differential diagnosis.

2 Histology of Normal Uterine Corpus

The uterine corpus consists of the endometrium, myometrium, and serosa. The endometrium is divided into stratum functionalis, the superficial portion that sheds into the uterine cavity, and stratum basalis, the deeper portion that abuts the myometrium. The appearance of the stratum functionalis varies depending on the time of the menstrual cycle while the basalis remains constant. Normal endometrium is composed of glands and stroma in an approximately 1:1 ratio. The stroma consists of a uniform population of small, round to spindled blue cells. In the proliferative phase, the glandular epithelium shows columnar cells with pseudostratification, and the stroma ranges from cellular to edematous. Both the glands and stroma show mitoses. The hallmark of secretory phase is vacuoles in glandular cells. Secretory phase shows features distinct enough to date day by day. In late secretory phase, a sawtooth pattern, the presence of neutrophils, and stromal predecidualization are seen. In predecidualization, the stromal cells become larger, plumper, and rounder, showing increased eosinophilic cytoplasm. During menstruation, glandular and stromal breakdown is seen with fibrin and necrosis. In postmenopause, the endometrium becomes atrophic, characterized by glands with a single layer of cuboidal or flat epithelial cells without stratification and without mitoses.

The myometrium is the thickest layer of the uterus and is composed of smooth muscle cells. The serosa is the outermost layer of the uterus and is composed of a single layer of mesothelial cells.

3 Endometrioid Adenocarcinoma Precursors

3.1 Endometrial Hyperplasia

Endometrial hyperplasia is a well-known non-obligate precursor to endometrioid adenocarcinoma. The most widely used classification system for endometrial hyperplasia is one that the World Health Organization (WHO) adopted in 1994, dividing endometrial hyperplasia into four categories: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, (4) and complex hyperplasia with atypia. In 2014, WHO revised this system, simplifying classification into two categories: hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN) (Kurman et al. 2014). Both systems will be described below.

In endometrial hyperplasia, proliferative type endometrium is seen with an increased gland-to-stroma ratio with architectural complexity. Architectural complexity is defined as irregularity in gland size and shape. In simple hyperplasia, glandular crowding is present with mild to moderate architectural complexity, sometimes with cystic glands (Fig. 1). Complex hyperplasia shows increased glandular crowding and increased architectural complexity, including branching and outpouching of glands. Atypia refers to cytologic

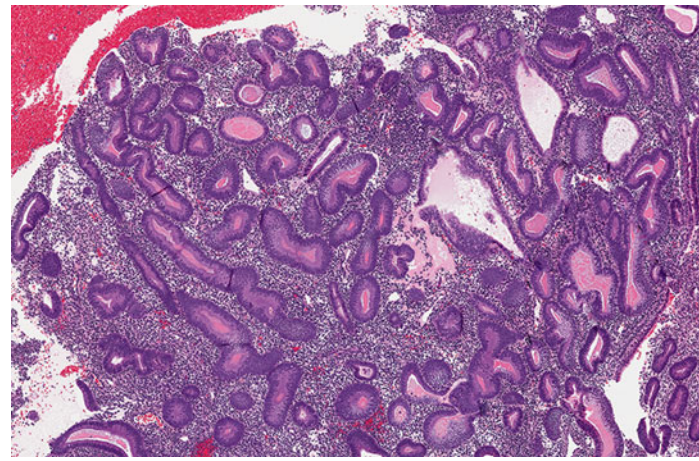

Fig. 1 Simple hyperplasia without atypia. Glandular crowding with proliferative type endometrial glands showing irregular shapes

atypia defined by nuclear enlargement, loss of polarity with rounding of the nucleus rather than ovoid nuclei, irregular nuclear borders, pleomorphism, and prominent nucleoli. Among the four categories, simple hyperplasia without atypia and complex hyperplasia with atypia are most commonly seen while simple hyperplasia with atypia is very rare.

While widely used, this classification system is known to suffer from interobserver variability with suboptimal reproducibility. The binary system proposed in the most recent WHO aims to reduce interobserver reproducibility by simplifying classification. It is also based on the finding that cytologic atypia is the most significant factor in progression to endometrioid adenocarcinoma. The majority of hyperplasia without atypia regresses while 8% of simple hyperplasia with atypia and 29% of complex hyperplasia with atypia progress to endometrioid adenocarcinoma (Kurman et al. 1985).

3.2 Endometrial Intraepithelial Neoplasia

Endometrial intraepithelial neoplasia (EIN) is a monoclonal precursor lesion that was originally identified based on morphometric analysis and finding genetic alterations similar to that seen in grade 1 endometrioid adenocarcinomas (Mutter et al. 2000). The histologic criteria for EIN are (1) gland-to-stroma ratio greater than 1:1,

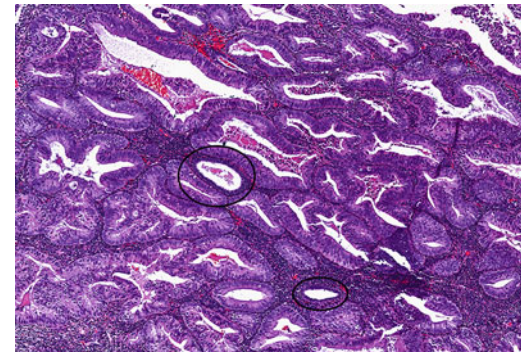

Fig. 2 Endometrial intraepithelial neoplasia (EIN). Marked glandular crowding with architectural complexity and enlargement and rounding of cells. Note that background glands (*circled*) are different from the neoplastic glands

(2) cytology of cells in lesional area is different from background glands or cytology is clearly abnormal, (3) greater than 1 mm focus, (4) and exclusion of benign mimics such as polyps, basalis, disordered proliferative endometrium, metaplastic change, and carcinoma (Fig. 2).

While most cases of atypical hyperplasia would fit the definition of EIN, these two categories are not interchangeable, as cases previously diagnosed as simple hyperplasia without atypia and complex hyperplasia without atypia have been reclassified as EIN.

The differential diagnosis of endometrial hyperplasia includes, but is not limited to, endometrial polyps, disordered proliferative endometrium,

stratum basalis, metaplastic change, and endometrioid adenocarcinoma. Endometrial polyps may show disorganized glands resembling hyperplasia. Recognizing characteristic features of endometrial polyps such as thick-walled vessels and fibrotic stroma or polypoid architecture can help to distinguish between the two, although in an endometrial biopsy, distinction can be challenging at times. Disordered proliferative endometrium can also show irregular glands; however this change is more focal than in hyperplasia. The basalis may show glandular crowding; however the glands should be inactive, not proliferative type.

3.3 Metaplastic Change

The endometrium can demonstrate different types of metaplastic change, including eosinophilic, ciliated, squamous, mucinous, and clear cell change. Metaplasia can occur in benign endometrium, hyperplasia, and carcinoma, which can obfuscate the underlying process. Eosinophilic change, for example, shows rounding of cells that can be mistaken for cytologic atypia. Squamous differentiation is fairly common and has traditionally been thought to manifest in morular or non-morular forms. In morular metaplasia, round nests of bland oval or spindled cells are seen that resemble squamous epithelium, hence the name "squamous" morules. Morular metaplasia has been proposed as an alternative name as the squamous nature of these cells has been questioned recently due to different staining patterns than non-morular squamous differentiation. Morular metaplasia expresses CDX2 (a marker often associated with gastrointestinal differentiation) and does not express p63 (a marker of squamous differentiation) while non-morular squamous differentiation demonstrates the opposite staining pattern. Morular metaplasia is often seen with hyperplasia, and its presence should raise suspicion for possible hyperplasia or carcinoma. Distinguishing atypical hyperplasia from adenocarcinoma is discussed in the Sect. 4.1.1.

3.4 Progestin Effect

Progestin is commonly used to treat atypical hyperplasia as well as some cases of well-differentiated endometrioid adenocarcinoma. The characteristic histologic feature of progestin treatment is pseudodecidualized stroma where the stromal cells become large, round, and plump, with abundant pink cytoplasm. The glands may be inactive or show eosinophilic change that should be distinguished from residual atypia.

4 Uterine Tumors

4.1 Endometrial Carcinoma

Endometrial carcinomas occur more often in postmenopausal women and usually present with abnormal vaginal bleeding. They can be divided into two types: type 1 and type 2. Type 1 tumors are associated with unopposed estrogen and are usually low grade. Endometrioid adenocarcinoma is the prototypical type 1 tumor. Type 2 tumors are not associated with unopposed estrogen, tend to be high grade, and occur more frequently in an older age group than those who develop type 1 tumors. Serous carcinoma is an example of a type 2 carcinoma. Different types of endometrial carcinoma will be discussed below.

4.1.1 Endometrioid Adenocarcinoma

Endometrioid adenocarcinomas comprise 60–80% of endometrial carcinomas. Grossly, these tumors may be unifocal or multifocal and often present as an exophytic, friable mass (Fig. 3). However, in some cases, particularly in small, atrophic uteri, the tumor manifests primarily as thickened endometrium and myometrium and may be difficult to identify grossly. Identifying the tumor grossly is clinically significant since intraoperative consultation is often performed for staging purposes and the pathologist must identify the point of deepest invasion (whether tumor involves more than half of the myometrium) which may not always be evident on gross examination.

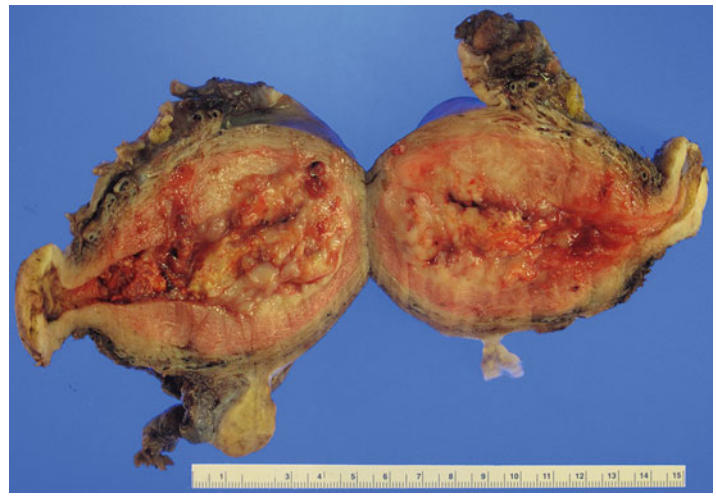

Fig. 3 Endometrioid adenocarcinoma. Gross photograph of a bivalved uterus showing a large, friable, tan-white mass filling the uterine cavity and invading into the myometrium

Microscopically, endometrioid adenocarcinoma consists of proliferative type endometrium with pseudostratified columnar cells showing crowded glands with complex architectural patterns and cytologic atypia. The extent of architectural and cytologic atypia should be greater than that seen in atypical hyperplasia/EIN. Differentiating between these two entities is further discussed below. The presence of invasive glands in the myometrium is pathognomonic for adenocarcinoma.

Endometrioid adenocarcinoma is graded using the International Federation of Gynecology and Obstetrics (FIGO) grading system. The tumor is divided into three grades based on both architecture and nuclear atypia. Architectural grade is based on the degree of gland formation: grade 1 = solid areas comprise less than 5% of the tumor, grade 2 = solid areas comprise 5–50% of the tumor, and grade 3 = solid areas comprise more than 50% of the tumor (Table 1) (Figs. 4 and 5). Nuclear grade is defined as follows: nuclear grade 1 = uniform round and oval nuclei, nuclear grade 2 = irregular nuclei with chromatin clumping, and nuclear grade 3 = large, pleomorphic nuclei that may show prominent nucleoli.

The nuclear grade of the tumor is usually consistent with the architectural features, e.g., endometrioid adenocarcinoma with low-grade architecture usually has low-grade nuclei. Under the FIGO grading system, if a tumor with grade

Table 1 Grading of endometrioid adenocarcinoma

	Architectural grade	Nuclear grade
Grade 1	Less than 5% solid areas	Uniform, round to oval nuclei; inconspicuous nucleoli
Grade 2	5–50% solid areas	Irregular nuclei with chromatin clumping
Grade 3	Greater than 50% solid areas	Large, pleomorphic nuclei with prominent nucleoli

Overall grade is based on both architecture and nuclear grade. Tumor grade is increased by one if nuclear grade is discordant with architectural grade, e.g., a tumor should be upgraded from grade 1 to 2 if it has grade 1 architecture and grade 2 nuclei

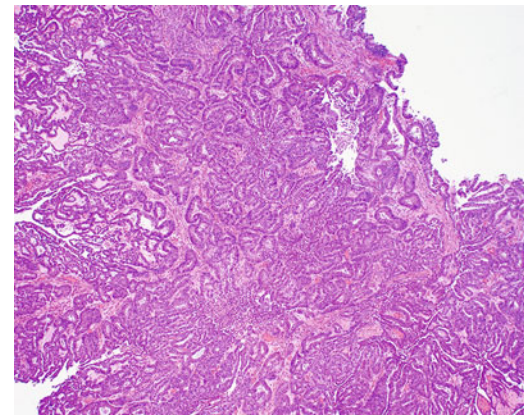

Fig. 4 Endometrioid adenocarcinoma, grade 1. The tumor is composed entirely of glands that are back to back and confluent with cytologic atypia

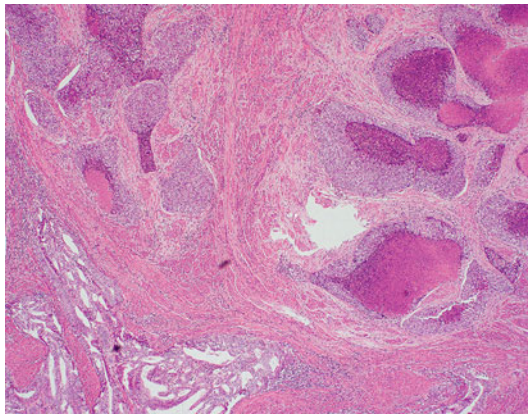

Fig. 5 Endometrioid adenocarcinoma, grade 3. The tumor shows predominantly solid nests of cells with central necrosis, invading the myometrium. In the lower left corner, gland formation is seen

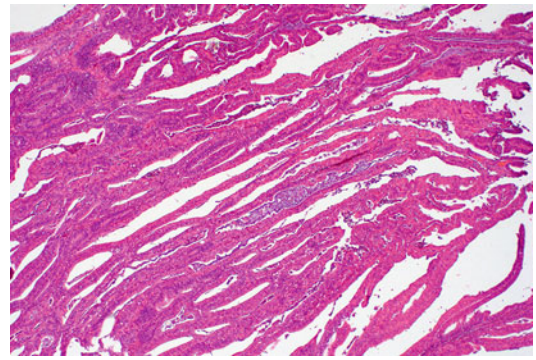

Fig. 6 Villoglandular carcinoma. The tumor shows long, villous papillae with low-grade nuclei

1 architecture shows grade 2 nuclei, the tumor should be upgraded to an overall grade 2 tumor. Caution should be used in upgrading though as the presence of marked architectural/nuclear atypia dyssynchrony should raise suspicion that the tumor is actually serous carcinoma rather than endometrioid type as serous carcinomas show high-grade nuclei with gland formation. When evaluating tumor architecture, areas of squamous differentiation should not be included as solid areas.

4.1.2 Villoglandular and Secretory Carcinoma

Several variants of endometrioid adenocarcinoma exist. Two distinctive ones that can mimic serous and clear cell carcinomas are villoglandular and secretory carcinomas, respectively.

Villoglandular carcinomas are characterized by long, villous papillae with fibrovascular cores and bland, columnar cells (Fig. 6). The percentage of the tumor that should show villoglandular features in order to be classified as villoglandular carcinoma is not well-defined, but should be at least the majority of the tumor. Villoglandular carcinomas can resemble serous carcinomas due to papillary architecture; however marked nuclear atypia is not typical in villoglandular carcinomas as it is in serous carcinomas. The prognosis of villoglandular carcinomas is based primarily on grade and stage as in other endometrioid adenocarcinomas and because these tumors are primarily low grade, they tend to have a good prognosis.

Secretory adenocarcinoma is rare and defined by the presence of cytoplasmic vacuoles as seen in secretory phase glands. It is a low-grade tumor with bland, uniform cells and is associated with a good prognosis. Secretory carcinoma is further discussed under clear cell carcinoma, a tumor it can mimic.

Other subtypes of endometrioid adenocarcinoma can show metaplastic change such as ciliated and clear cell change. The significance of recognizing variant features is to not misdiagnose endometrioid adenocarcinoma as a different tumor such as clear cell carcinoma. Mentioning such features also helps to identify the tumor on an excisional specimen or recurrence. Metaplastic change in endometrioid adenocarcinoma is not prognostically significant.

4.1.3 Commonly Encountered Problems in Pathologic Diagnosis and Staging of Endometrioid Adenocarcinoma

Several areas in diagnosis and staging of endometrioid adenocarcinoma can be problematic, with some issues more frequently encountered than others. The issues are enumerated below:

1. Endometrioid adenocarcinoma versus atypical hyperplasia/EIN

The line between atypical hyperplasia and adenocarcinoma can be blurry, and the diagnosis is subject to interobserver variability. Confluent glands, back-to-back glands with little to no intervening stroma, increased architectural complexity such as cribriforming or papillary architecture in more than a minute focus, greater nuclear atypia than that seen in atypical hyperplasia, and the presence of desmoplasia favor a diagnosis of adenocarcinoma. Desmoplasia however is rarely seen in endometrioid adenocarcinoma. In endometrial biopsy specimens, a diagnosis of "atypical hyperplasia bordering on low-grade endometrioid adenocarcinoma" may be appropriate in certain cases with the final diagnosis deferred to the excisional specimen.

2. Myometrial invasion

Myometrial invasion is measured from the endomyometrial junction to the deepest point of invasion. Several issues must be considered in determining both the presence of myometrial invasion and depth of invasion.

(a) The endomyometrial junction is irregular making it difficult to assess for invasion. Superficial myometrial invasion tends to be overdiagnosed. Clues to invasion are jagged, angular glands and desmoplasia. The diagnosis of superficial invasion can be highly subjective as borne out by data showing no difference in prognosis between those with tumors confined to the endometrium and those with tumors involving the upper half of the myometrium. Based on this evidence, in 2009, FIGO changed the staging system so tumors confined to the endometrium and involving the upper half of the myometrium are both now staged as Ia.

(b) Myometrial invasion can manifest as glands infiltrating the myometrium or as a pushing border. In cases of a pushing border, without the presence of normal endomyometrial junction for comparison, it can be difficult to diagnose invasion.

(c) Myometrial invasion should not be diagnosed when malignant glands involve adenomyosis. Adenomyosis is when benign endometrial tissue, both glands and stroma, are found in the myometrium. Adenocarcinoma involving adenomyosis is not true myometrial invasion. The rounded contour of adenomyosis versus the angulated glands of true invasion, the presence of benign glands adjacent to malignant glands, areas of uninvolved adenomyosis elsewhere, and the presence of endometrial stroma in adenomyosis favor a diagnosis of tumor involving adenomyosis. In some tumors, there can be both tumor involving adenomyosis and true myometrial invasion.

(d) An unusual type of invasion, microcystic, elongated, and fragmented (MELF) invasion, has been described. In this type of invasion, glands are surrounded by inflamed fibromyxoid stroma that can almost obscure the glands. The glands themselves may be flat and resemble lymphovascular spaces. The significance of MELF however is still controversial.

4.1.4 Serous Carcinoma

Serous carcinomas of the uterus are aggressive tumors that have a propensity to spread to peritoneal surfaces and commonly present at a late stage. They comprise 5–10% of endometrial cancers and are usually found in women over 65. Serous carcinomas of the uterus are by definition high grade. They can be found in pure form, admixed with other high-grade carcinomas such as high-grade endometrioid carcinoma or clear cell carcinoma, or found as a component of MMMT.

Grossly, serous carcinomas usually present as a friable, exophytic mass. Microscopically, serous carcinomas classically exhibit papillary or micropapillary architecture with fibrovascular cores; small glands and solid areas can also be seen. The cells often show tufting into the lumen and exfoliated cells are present. Cytologically, the cells are round to cuboidal, with large, pleomorphic, often vesicular nuclei and prominent nucleoli (Fig. 7). Brisk mitotic activity is common and hobnailing is not infrequent. Psammoma bodies

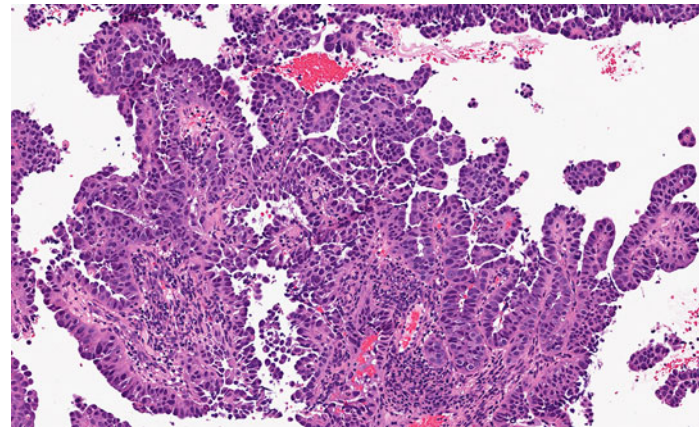

Fig. 7 Serous carcinoma. Papillary architecture is seen with markedly atypical nuclei and detached cells

are another feature classically associated with serous carcinomas.

The differential diagnosis of serous carcinoma includes clear cell carcinoma, MMMT, villoglandular carcinoma, high-grade endometrioid carcinomas, and eosinophilic syncytial change. Distinguishing serous carcinoma from some of these other lesions is discussed in the pertinent sections of the aforementioned lesions. Serous carcinomas tend to be either diffusely positive or completely negative or "null" for p53 and diffusely positive for p16 while endometrioid carcinomas show heterogeneous staining with p53 and p16. The combination of morphology and pattern of immunostaining should help to distinguish serous carcinoma from its mimics. Eosinophilic syncytial change, also referred to as eosinophilic syncytial metaplasia, is seen in association with endometrial breakdown. The epithelial cells are eosinophilic and can show enlarged nuclei with pseudopapillary architecture that can mimic serous carcinoma. The background of breakdown and minimal pleomorphism should help to distinguish this change from malignancy.

Another problem that can be encountered with serous carcinomas is determining the primary site. When there is widespread tumor involving the uterus, ovaries, and fallopian tubes, a fallopian tube primary would be favored. Synchronous primaries should also be considered. The absence of uterine serosal involvement would be more consistent with a uterine primary.

The precursor to serous carcinoma is serous endometrial intraepithelial carcinoma (EIC). Serous EIC involves only the surface epithelium, showing markedly atypical cells lining the epithelium. An intraepithelial or in situ lesion should by definition have no capacity to metastasize as it has not yet invaded the stroma. In other tumors, such is the case but serous EIC behaves differently than other in situ lesions, demonstrating a propensity to spread just like invasive serous carcinoma (Sherman et al. 1992). Serous carcinoma confined to endometrial polyps also demonstrates aggressive behavior (Silva and Jenkins 1990).

4.1.5 Clear Cell Carcinoma

Clear cell carcinomas are high-grade, aggressive tumors that comprise less than approximately 5% of uterine malignancies. They tend to occur in women older than 65 and, like serous carcinoma, are high-grade tumors by definition (Abeler and Kjorstad 1991).

Grossly, clear cell carcinoma presents as a uterine mass without any distinctive features. Microscopically, the tumor shows papillary, tubulocystic, and solid architecture, usually exhibiting a mixture of patterns. Per its name, cells with clear cytoplasm due to glycogen are often seen (Fig. 8). Another characteristic feature is hobnail cells. Hobnail refers to a cell with bulbous nuclear protrusion and a narrow base; hobnail is literally a short nail with a wide head. The hobnail cells may have either clear or eosinophilic cytoplasm. The cells show high-grade

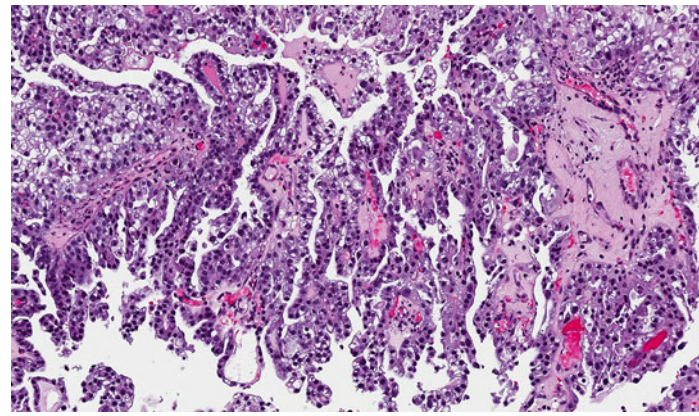

Fig. 8 Clear cell carcinoma. Papillary architecture is seen with clear cells and stromal hyalinization

features such as pleomorphism and large nuclei with prominent nucleoli. Hyalinized stroma and hyaline bodies (homogeneous eosinophilic droplets) are also commonly seen.

Clear cells are not pathognomonic for clear cell carcinoma as clear cells can be encountered in a variety of lesions, both benign and malignant. Clear cell carcinomas should be distinguished from Arias-Stella reaction, secretory carcinoma, endometrioid carcinoma with clear cell change, and serous carcinoma.

Arias-Stella reaction is a benign change that usually occurs during pregnancy. It is characterized by atypical clear and hobnail cells mimicking malignancy. Features of Arias-Stella reaction that help to distinguish it from clear cell carcinoma include the following: it occurs in premenopausal women, does not show invasion, shows little to no mitotic activity, and is an incidental finding. Secretory carcinoma may show solid areas with clear cells that resemble clear cell carcinoma. The low-grade cytology of secretory carcinoma should help to distinguish it from the marked nuclear atypia seen in clear cell carcinoma. Serous carcinomas exhibit high-grade nuclei just as in clear cell carcinomas; however presence of extensive clearing or other features associated with clear cell carcinoma such as hyalinization would favor clear cell carcinoma. Endometrioid carcinoma with clear cell change is not likely to show marked nuclear atypia.

Immunostains have limited utility in the diagnosis of clear cell carcinomas, as these tumors do not show a specific pattern of immunostaining. However, it can help in some instances. Clear cell carcinomas tend to be estrogen receptor/progesterone receptor (ER/PR) negative versus endometrioid adenocarcinomas that are clear cell carcinomas also tend to show heterogeneous expression of p53 which may help to differentiate them from serous carcinomas that tend to be diffusely positive or completely null for p53.

4.1.6 Undifferentiated Carcinoma

Undifferentiated carcinomas are rare tumors that, despite their name, have distinctive histologic features and should not be used as a wastebasket diagnosis for tumors that cannot be classified (Altrabulsi et al. 2005). Microscopically, these tumors are characterized by sheets of monotonous, epithelioid, medium-sized cells with cytokeratin expression in usually less than 10% of cells. Prominent nucleoli, vesicular nuclei, brisk mitoses, and necrosis are usually seen. A marked lymphoid infiltrate may also be present.

The differential diagnosis includes grade 3 endometrioid carcinoma, endometrial stromal sarcoma, high-grade sarcoma, neuroendocrine carcinoma, and lymphoma. Immunostains can help to differentiate between these entities: cytokeratin will show greater expression in pure endometrioid carcinomas, endometrial stromal sarcoma tends to be CD10 positive, high-grade sarcoma should show a pattern of immunostaining consistent with the differentiation seen, and lymphoma tends to be CD45 positive. Synaptophysin and chromogranin are

markers of neuroendocrine differentiation that can be focally (usually less than 10%) expressed in undifferentiated carcinomas (Taraif et al. 2009) while neuroendocrine carcinomas should show greater expression of these two markers and also show neuroendocrine histology. Undifferentiated carcinomas are aggressive tumors with a poor prognosis.

4.1.7 Mixed-Type Carcinoma

Mixed carcinomas refer to tumors showing carcinomas of at least two different types. The most commonly encountered mixed carcinomas are endometrioid adenocarcinoma with serous carcinoma, endometrioid adenocarcinoma with clear cell carcinoma, and endometrioid adenocarcinoma with undifferentiated carcinoma. Endometrioid adenocarcinoma and its variants, such as secretory carcinoma, are not considered mixed carcinomas. When endometrioid adenocarcinoma is seen with variant features, it should be diagnosed as endometrioid adenocarcinoma with clear cell features, for example, rather than a mixed tumor. The percentage of each histologic type should be stated in mixed carcinomas as this can have prognostic value.

4.1.8 Lynch Syndrome

Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder with incomplete penetrance that increases the risk of various cancers, particularly colorectal and endometrial cancer. The lifetime risk for endometrial cancer has been found to be as high as 60% in Lynch syndrome. Endometrial cancers in Lynch syndrome demonstrate microsatellite instability (MSI) which is excessive repetition of short DNA sequences secondary to a defective DNA repair system. Twenty-five to 30% of sporadic endometrial tumors also exhibit MSI. Both endometrioid and non-endometrioid carcinomas can show MSI. Screening guidelines for Lynch syndrome are not standardized, but some groups recommend routine screening in women under the age of 50 who are diagnosed with endometrial carcinoma. Screening for MSI in Lynch-associated endometrial carcinomas can be performed with a panel of immunostains for the mismatch repair proteins, MLH1, MSH2, MSH6, and PMS2. Loss of expression in one or more of these stains suggests MSI and further genetic testing is then indicated.

4.2 Mesenchymal Lesions

4.2.1 Endometrial Stromal Tumors

Endometrial Stromal Nodule

Endometrial stromal nodules are the benign counterpart of endometrial stromal sarcomas. They are composed of small round to ovoid blue cells as seen in endometrial stromal sarcoma but are confined to the endometrium without myometrial involvement while endometrial stromal sarcoma involves the myometrium.

Endometrial Stromal Sarcoma

Endometrial stromal sarcomas were traditionally divided into low- and high-grade types. In 2003, WHO classified these tumors into two groups, endometrial stromal sarcoma, with no designation of low or high grade, and undifferentiated endometrial sarcoma. In the most recent WHO, these group of tumors are divided into low-grade and high-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma based on recent evidence showing a common translocation in the tumors now designated high-grade endometrial stromal sarcoma (Kurman et al. 2014).

Low-Grade Endometrial Stromal Sarcoma

Low-grade endometrial stromal sarcomas are low-grade malignant tumors that tend to occur in premenopausal women (median age 40). Women present with abnormal vaginal bleeding or abdominal pain.

Grossly, endometrial stromal sarcoma is classically described as showing a "wormlike" appearance that is primarily due to nodules of tumor in vascular spaces. It can also manifest as a solid mass with diffuse involvement of the myometrium.

Microscopically, the tumor consists of highly cellular, monotonous, small round to ovoid blue

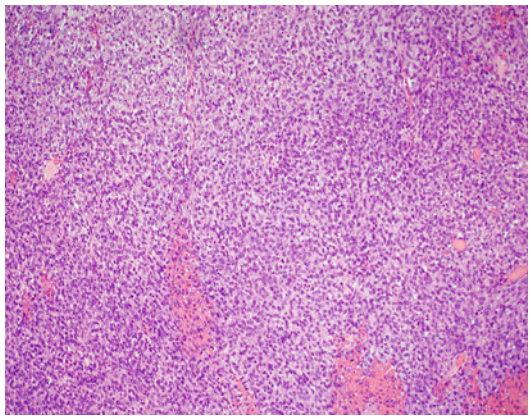

Fig. 9 Endometrial stromal sarcoma. Sheets of monotonous, small, round blue cells are seen

cells that forms large irregular nests and invades the myometrium as irregular tongues (Fig. 9); spindle cell forms can also be seen. Mitotic activity is usually low. A classic feature of endometrial stromal sarcoma is the presence of numerous small vessels resembling endometrial spiral arterioles. Vascular invasion is common. Endometrial stromal sarcoma can exhibit different elements, including smooth muscle differentiation, sex cord-like elements, and gland formation.

CD10 is the immunostain typically associated with endometrial stromal sarcoma; however it is not very specific. Endometrial stromal sarcomas also tend to express ER and PR. In the majority of typical endometrial stromal sarcomas, JAZF1-SUZ12 fusion is present secondary to t(7;17)(p15;q21) (Kurman et al. 2014).

The differential diagnosis of endometrial stromal sarcoma includes endometrial stromal nodule, smooth muscle lesions, adenomyosis, and adenosarcoma. As stated previously, the main difference between endometrial stromal sarcoma and endometrial stromal nodule is the presence of myoinvasion. In an endometrial biopsy, distinguishing between the two may be impossible, but endometrial stromal sarcoma would be more likely. In some cases, it can be difficult to distinguish endometrial stromal sarcoma from smooth muscle tumors, particularly cellular leiomyoma and intravenous leiomyomatosis. Since both endometrial stromal sarcomas and smooth muscle tumors can express CD10 and smooth muscle markers, a panel of immunostains, rather than one or two immunostains, is recommended to differentiate between the two (see IHC chapter). Adenomyosis can be gland-poor such that only nests of endometrial stroma are seen in the myometrium that can raise suspicion for endometrial stromal sarcoma. Unlike endometrial stromal sarcoma, however, a mass should not be apparent, the stromal cells may appear atrophic, and adenomyosis with sparse glands is more likely to occur in postmenopausal women while endometrial stromal sarcoma is more common in premenopausal women. Adenosarcoma is discussed below.

High-Grade Endometrial Stromal Sarcoma

Recently, a specific genetic alteration was identified in a subset of tumors that are now designated as high-grade endometrial stromal sarcoma by WHO. High-grade endometrial stromal sarcoma exhibits a specific translocation, t(10;17)(q22;p13), which causes YWHAE-FAM22 fusion (Lee et al. 2012). Microscopically, the tumor consists of large, round cells with frequent mitoses and necrosis. Bland spindled cells may also be present. CD10 is negative in the high-grade round cells but tends to be expressed by the low-grade spindled cells. Cyclin D1 staining has also been found in these tumors.

Undifferentiated Endometrial Sarcoma

Undifferentiated endometrial sarcomas are aggressive, high-grade sarcomas. They are rare, occur primarily in postmenopausal women, and present with either abnormal vaginal bleeding or systemic symptoms related to late stage disease.

Microscopically, sheets of pleomorphic oval or spindled cells are seen, usually with necrosis and brisk mitoses. The tumor tends to replace the myometrium, rather than infiltrating it as endometrial stromal sarcoma does. The immunoprofile of undifferentiated endometrial sarcomas is not specific. Undifferentiated endometrial sarcoma may express CD10 and ER like endometrial stromal sarcoma but exhibits much weaker expression. Due to the fairly nonspecific histology of this tumor, the differential is broad, including other

high-grade tumors such as high-grade leiomyosarcoma, sarcomatous component of MMMT, and undifferentiated endometrial carcinoma. Undifferentiated endometrial sarcoma is therefore a diagnosis of exclusion after ruling out other lesions.

4.2.2 Smooth Muscle Tumors

Leiomyoma

Leiomyomas are not only the most common tumor in the uterus; uterine leiomyomas are the most common neoplasm in humans. Grossly, classic features of uterine leiomyomas are circumscribed, tan-white solid masses with a whorled appearance on cut surface. Microscopically, leiomyomas show fascicles of uniform cigar-shaped spindle cells with little to no nuclear atypia, low to moderate cellularity, and little to no mitotic activity.

Leiomyosarcoma

Leiomyosarcomas are rare, aggressive tumors that are the most common pure mesenchymal malignancy of the uterus. It is most common in women in their 50s. Diagnosing a leiomyosarcoma requires recognition of two elements: (1) smooth muscle differentiation and (2) that it is malignant. Clinically, leiomyosarcoma may be suspected versus a leiomyoma when there is a single large mass versus multiple masses (leiomyomas) or a dominant large mass among multiple masses.

Grossly, leiomyosarcomas are usually large (10 cm or greater) and have a fleshy variegated appearance with infiltrative margins and necrosis. Microscopically, conventional leiomyosarcomas consist of fascicles of spindled cells with high cellularity, nuclear atypia, and brisk mitoses. Tumor cell necrosis may or may not be seen. The criteria for malignancy in smooth muscle tumors are moderate to marked nuclear atypia, mitotic rate $\geq$10 mitoses/10 HPF, and tumor cell necrosis. Leiomyosarcoma should be diagnosed when two of the three criteria are met.

Distinguishing between tumor cell necrosis and infarct-type necrosis is a well-known problematic issue in uterine smooth muscle neoplasms. Tumor cell necrosis is a criterion of malignancy while infarct-type necrosis is not. Infarct-type necrosis can be seen in leiomyomas but tumor cell necrosis should not be present, while one or both types of necrosis may be present in leiomyosarcomas, but only tumor cell necrosis qualifies as a criterion of malignancy. Tumor cell necrosis shows abrupt transition from necrotic cells to viable tumor while infarct-type necrosis shows granulation tissue or fibrosis between necrosis and viable cells. Sometimes, the type of necrosis present is indeterminate and such cases, in combination with other features, may best be classified as smooth muscle tumors of unknown malignant potential (STUMP). Another confounding factor is that treated leiomyomas can be necrotic. Another criterion of malignancy, mitotic count, is also not always straightforward. Mitotic count can be overestimated if some cells showing nuclear condensation or smudging that can resemble mitotic figures are counted.

Two variants of leiomyosarcoma are epithelioid and myxoid types. The criteria for malignancy in these variants are somewhat different from conventional type, with both variants only requiring $\geq$5 mitoses/10 HPF rather than $\geq$10 mitoses/10 HPF. Epithelioid leiomyosarcomas have epithelioid or round cells, rather than spindled cells, that demonstrate smooth muscle differentiation by immunohistochemistry. Myxoid leiomyosarcomas, as their name states, show diffuse myxoid change and can have a deceptively bland appearance with low cellularity that may be construed as a benign lesion.

Smooth muscle differentiation can be confirmed with various smooth muscle markers if necessary. The most commonly used immunostains are smooth muscle actin (SMA), desmin, and h-caldesmon. In addition, ER/PR expression may be seen.

Several variants of leiomyomas are recognized that can be mistaken for leiomyosarcomas. They include cellular leiomyoma, leiomyoma with bizarre cells, mitotically active leiomyoma, among others. Cellular leiomyomas, per their name, show high cellularity. Mitotically active leiomyomas can have greater than 10 mitoses/10 HPF but should not show atypical mitoses. Leiomyomas with bizarre cells have also been referred to as symplastic leiomyomas or atypical

leiomyomas and show scattered markedly atypical or bizarre cells that can show multinucleation. The aforementioned variants demonstrate a feature that is suspicious for malignancy or a criterion for malignancy; however, they do not have other criteria for malignancy.

The differential diagnosis of leiomyosarcoma depends on its type. Spindled or conventional leiomyosarcomas should be differentiated from cellular leiomyomas, MMMT, endometrial stromal sarcoma, spindle cell rhabdomyosarcoma, undifferentiated sarcoma, and other sarcomas. The differential diagnosis of epithelioid leiomyosarcoma is broad and includes carcinomas, PEComa, malignant melanoma, and other sarcomas. The differential diagnosis of myxoid leiomyosarcoma includes myxoid leiomyoma, myxoid variant of endometrial stromal sarcoma, and myxoid change within the myometrium. Careful attention to histologic features, immunostaining, and clinical information can help in differentiating between the different entities.

Smooth Muscle Tumor of Unknown Malignant Potential

Smooth muscle tumors with equivocal features between leiomyoma and leiomyosarcoma are best classified as smooth muscle tumor of unknown malignant potential or STUMP. Some have also referred to these lesions as atypical smooth muscle tumors, a designation that can be confusing as the term atypical leiomyoma has also been applied to a different lesion, leiomyoma with bizarre cells. STUMP shows some criterion for malignancy that is insufficient to render an unequivocal diagnosis of malignancy. An example would be a lesion with moderate nuclear atypia but no tumor cell necrosis and less than 10 mitoses/10 HPF.

4.3 Mixed Epithelial-Mesenchymal Tumors

4.3.1 Adenosarcoma

Adenosarcoma is a malignant biphasic tumor with a malignant mesenchymal component (sarcoma) and benign epithelial component. It can occur in all ages and usually presents with abnormal vaginal bleeding. Grossly, a polypoid mass is usually seen. Microscopically, adenosarcoma is morphologically similar to phyllodes tumor of the breast and classically shows broad polypoid fronds. The tumor consists of malignant spindled cells and dilated glands of varying shape lined by proliferative type endometrium. The sarcomatous component most often resembles endometrial stromal sarcoma but can exhibit heterologous differentiation. The mesenchymal component should show nuclear atypia, $\geq$2 mitoses/10 HPF, and periglandular cuffing. Periglandular cuffing refers to increased cellularity or condensation of cells around glands and is a distinctive feature of adenosarcomas. The epithelium can show metaplasia such as squamous and ciliated change and may exhibit some cytologic atypia but is not frankly malignant.

The differential diagnosis includes adenofibroma, adenomyoma, MMMT, and sarcomas. Adenofibroma is the benign counterpart of adenosarcoma. Adenomyoma is another polypoid lesion consisting of benign glands with benign stroma with a predominant smooth muscle component. Lack of malignant features of the mesenchymal component should help to identify both adenofibromas and adenomyomas. MMMT will show malignant epithelium, unlike adenosarcomas. A biopsy of an adenosarcoma may mimic pure sarcoma if the epithelial component is not evident; in some cases, diagnosis is best made on the excisional specimen. Immunostains are usually not necessary for diagnosis; if performed, the sarcomatous component will usually stain like endometrial stromal sarcomas, expressing CD10, ER, PR, and WT1.

Adenosarcomas may recur in 25% of cases. Cases with sarcomatous overgrowth ($\geq$25% high-grade sarcomatous component) tend to be more aggressive (Clement 1989).

4.3.2 Malignant Mixed Mullerian Tumor

Malignant mixed Mullerian tumor (MMMT) or carcinosarcoma is a biphasic tumor with both epithelial and mesenchymal elements. They

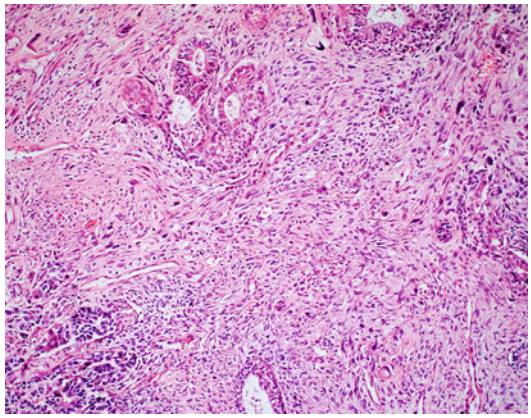

Fig. 10 Malignant mixed Mullerian tumor (MMMT). Biphasic pattern with glands and pleomorphic spindle cells is seen

comprise less than 5% of uterine malignancies and occur almost exclusively in postmenopausal women.

Grossly, MMMT may present as a polypoid mass and exhibit a fleshy appearance. Microscopically, the presence of malignant glands admixed with high-grade spindled cells is essentially diagnostic of MMMT (Fig. 10). These tumors however can exhibit varying histology. The epithelial component may show elements of endometrioid, serous, or other high-grade carcinomas, including unclassifiable carcinoma, while the mesenchymal component can be homologous and/or heterologous. Homologous elements refer to finding cells showing differentiation indigenous to the uterus, such as smooth muscle, while heterologous elements refer to the presence of tissue not usually found in the uterus, such as skeletal muscle. The homologous component in MMMT is often high-grade spindled or pleomorphic cells, while the heterologous component is often rhabdomyosarcoma (skeletal muscle differentiation) or chondrosarcoma (cartilaginous differentiation). The proportion of the epithelial to the mesenchymal component can vary. In some cases, the epithelial component may so predominate in an endometrial biopsy that MMMT can only be diagnosed on the excision. Lymphovascular invasion is common.

In MMMT, cytokeratin immunostains are not only expressed by the epithelial component but also tend to stain the mesenchymal component. The differentiation of the mesenchymal component can be demonstrated if necessary with stains such as desmin and myogenin for rhabdomyosarcoma but is usually not necessary.

The differential diagnosis of MMMT includes endometrioid carcinoma with spindle cells, endometrioid adenocarcinoma with heterologous elements, mixed endometrioid and undifferentiated carcinoma, and adenosarcoma. Endometrioid carcinoma with spindle cells should not show immunostaining for a mesenchymal component, heterologous elements in endometrioid adenocarcinoma should not be malignant as they are in MMMT, mixed endometrioid and undifferentiated carcinoma will usually show a low-grade epithelial component compared with the high-grade epithelial component seen in MMMT, and in adenosarcoma, the epithelial component is benign.

MMMT are aggressive tumors with a poor prognosis. Heterologous tumors had been thought to have a poorer prognosis at one time; however that is currently controversial. When MMMT metastasize, the epithelial component is more likely to be seen.

4.4 Other Uterine Tumors

4.4.1 Perivascular Epithelioid Cell Tumor

Perivascular epithelioid cell tumors (PEComas) are rare tumors of unclear origin that express both melanocytic (HMB-45, Melan-A) and smooth muscle markers (SMA, desmin). In some cases, PEComas are associated with tuberous sclerosis and lymphangioleiomyomatosis (LAM). Microscopically, fairly uniform, epithelioid or spindled cells with clear and eosinophilic cytoplasm are seen that classically show a nested growth pattern (Fig. 11). A prominent capillary pattern is usually present. Uterine PEComas may behave in a benign or malignant manner. One system proposed the following criteria for malignancy: size greater than 5 cm, high-grade nuclear atypia, necrosis, vascular invasion, $\geq$1 mitosis/

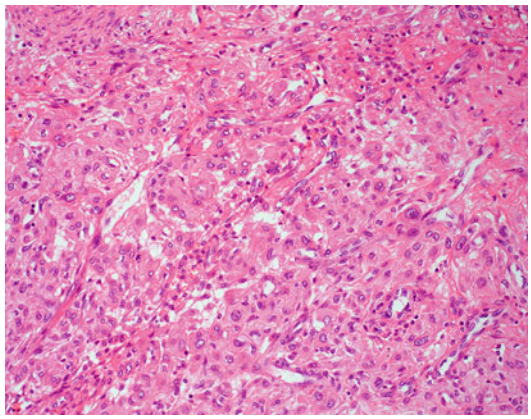

Fig. 11 Perivascular epithelioid cell tumor (PEComa). Nests of eosinophilic, epithelioid cells with mild pleomorphism are seen

50 HPF, and infiltrative growth pattern (Folpe et al. 2005). The differential diagnosis includes smooth muscle tumors, secondary involvement by gastrointestinal stromal tumors, malignant melanoma, and alveolar soft part sarcoma. Immunostains can help in diagnosis although smooth muscle neoplasms can also show expression of HMB-45 which can be a pitfall in diagnosis.

4.4.2 Primitive Neuroectodermal Tumor

Primitive neuroectodermal tumor (PNET) is an aggressive small round blue cell tumor thought to be of neuroectodermal origin that rarely occurs in the uterus. PNET is also referred to as Ewing sarcoma. Microscopically, sheets of monotonous, small, round cells are seen with brisk mitoses. A feature classically associated with PNET is rosettes; however they are not that commonly seen. Like PNET at other sites, uterine PNET tends to show membranous CD99 staining and FLI1 staining. They may also express neuroendocrine markers (synaptophysin, chromogranin). A characteristic translocation of these tumors is t(11;22) that leads to the fusion of EWS and FLI-1 genes. The differential diagnosis includes other round blue cell tumors such as small cell carcinoma, lymphoma, rhabdomyosarcoma, and endometrial stromal sarcoma.

4.4.3 Lymphoma

Non-Hodgkin lymphoma rarely involves the gynecologic tract. The female genital tract is the primary site of extranodal lymphomas in less than 2% of cases (Cohn et al. 2007). Secondary involvement is more common. Most cases are diffuse large B-cell lymphoma. Patients may be asymptomatic or present with abnormal vaginal bleeding or nonspecific complaints such as bloating. Lymphoma is a round blue cell tumor that shows a diffuse growth pattern. It tends to expand the endometrium and grows around the endometrial glands. The differential diagnosis includes other round blue cell tumors such as undifferentiated carcinoma, neuroendocrine carcinoma, particularly small cell carcinoma, PNET, and endometrial stromal sarcoma. Benign processes such as reactive lymphoid infiltrates and chronic endometritis should also be considered. Ancillary testing with immunohistochemical staining is necessary for a correct diagnosis; flow cytometry would also be helpful.

5 Gestational Trophoblastic Disease

Gestational trophoblastic diseases are diseases that occur related to pregnancy. Some understanding of normal placental histology is necessary to understand gestational trophoblastic diseases. The placenta is composed of amnion and chorionic villi. Chorionic villi consist of a core of stroma and capillaries lined circumferentially by cytotrophoblasts and syncytiotrophoblasts. Cytotrophoblasts are mononuclear, epithelioid cells with clear to eosinophilic cytoplasm. Syncytiotrophoblasts are multinucleated cells with hyperchromatic, smudgy nuclei. Intermediate or extravillous trophoblasts are another type of cell that helps anchor the placenta to the uterus and is usually found in the decidua. They can be epithelioid or spindled, have eosinophilic or amphophilic cytoplasm, and are usually mononuclear but can show multinucleation. Intermediate trophoblasts are thought to give rise to several gestational diseases, including exaggerated placental site, placental site nodule,

placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

5.1 Hydatidiform Mole

Hydatidiform moles are products of abnormal fertilization and consist of partial and complete moles. Grossly, moles have a characteristic appearance often described as a "bunch of grapes" that consist of clear to opaque, small, delicate vesicles.

5.1.1 Complete Mole

Most complete moles develop when a single sperm or two sperm fertilize an egg that has lost its DNA, i.e., empty egg; hence all chromosomes in complete moles are usually paternally derived. Most complete moles have no fetal tissue and consist entirely of enlarged edematous villi or hydropic villi with circumferential trophoblastic proliferation. Cisterns or cavities are a characteristic feature. The stroma shows the absence of nucleated red blood cells that are seen in normal villi.

5.1.2 Partial Mole

Partial moles develop when a viable egg is fertilized by two sperm or by one sperm that duplicates itself leading to a triploid karyotype (69XXY or 69XXX). Partial moles have some fetal tissue and consist of a mixture of enlarged and normal-sized villi. Cisterns and nucleated red blood cells may be present. Fibrotic villi may be seen. Trophoblastic hyperplasia occurs but is less prominent than in complete moles.

Complete and partial moles need to be differentiated from hydropic villi of non-molar abortion or hydropic abortus as molar pregnancy has significant clinical implications. If histology is equivocal, ancillary studies can help to confirm the diagnosis. A fairly simple and cost-effective next step is p57 immunostaining. p57 is a biomarker expressed only in the maternal genome as it is paternally imprinted. In complete moles, p57 should be absent in cytotrophoblasts and villous stromal cells while in partial moles and hydropic villi, p57 is expressed. In some cases, p57 immunostaining may be equivocal and in these cases, further testing may be required.

DNA ploidy analysis can also be performed to determine whether a triploid (partial mole or hydropic abortus) or diploid (complete mole or hydropic abortus) population is present. Flow cytometry and fluorescent in situ hybridization (FISH) are two common methods of analysis; however one major limitation of these tests is that they will not distinguish hydropic abortus from partial moles. Currently, the best method for differentiating between the three entities is molecular genotyping with polymerase chain reaction (PCR) which requires maternal endometrial tissue.

Sequelae of molar pregnancy include persistent gestational disease (retained molar tissue and invasive moles), recurrence, and malignant gestational disease. Persistent and invasive moles occur in 15–20% of complete moles and less than 4% of partial moles (Conran et al. 1993). Beta-hCG is followed to monitor for persistent gestational disease, and methotrexate is used for treatment. As medical treatment is highly effective, histologic diagnosis of invasive moles is infrequent. However, if seen, invasive moles will show villi invading the myometrium. Distant metastasis can occur with invasive moles.

5.2 Malignant Gestational Disease

Choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) are all rare malignancies that are associated with previous gestation, particularly with molar pregnancy. Choriocarcinoma is more strongly associated with molar pregnancy than the other two tumors. Choriocarcinoma tends to occur months after pregnancy, while PSTT and ETT usually occur many years afterwards. Abnormal vaginal bleeding is commonly the presenting symptom. In cases of choriocarcinoma and PSTT, the tumor may have already metastasized at the time of presentation so the presenting symptoms will be related to metastasis. Beta-hCG is elevated in all three tumors; however it is

much higher in choriocarcinoma than in PSTT and ETT.

5.2.1 Choriocarcinoma

Less than 3% of molar pregnancies lead to choriocarcinoma while half of choriocarcinomas are related to molar pregnancy. Twenty-five percent follow intrauterine gestation and 25% follow abortion or tubal pregnancy.

Grossly, choriocarcinoma presents as a markedly hemorrhagic mass with necrosis. Microscopically, a solid proliferation of cells consisting of three cell types, cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts, is seen. A "biphasic" pattern of cytotrophoblasts alternating with syncytiotrophoblasts is characteristic of this tumor. Both cytotrophoblasts and syncytiotrophoblasts show pleomorphism. In some cases, syncytiotrophoblasts may not be apparent and beta-hCG staining can be performed to identify their presence as syncytiotrophoblasts are necessary to render a diagnosis of choriocarcinoma. Hemorrhage is typical, necrosis is often seen, and villi are not present.

5.2.2 Placental Site Trophoblastic Tumor

Grossly, an ill-defined mass is seen deeply invading the myometrium. Microscopically, sheets of pleomorphic, mononuclear, epithelioid cells with clear, eosinophilic, or amphophilic cytoplasm are seen. The cells tend to split smooth muscle fibers of the myometrium. Nuclear grooves may be seen. Brisk mitoses are typical and necrosis and hemorrhage frequent. Sometimes, the neoplastic cells can show multinucleation that should not be mistaken for syncytiotrophoblasts.

5.2.3 Epithelioid Trophoblastic Tumor

Grossly, a well-circumscribed tumor that deeply invades the myometrium with hemorrhage and necrosis is seen. Microscopically, mononuclear epithelioid cells with abundant clear or eosinophilic cytoplasm are seen like in PSTT but are less pleomorphic than in PSTT. Multinucleated cells may be seen. Necrosis and lymphocytic infiltrate are often seen.

The differential diagnosis of both PSTT and ETT are placental site nodule, exaggerated placental site, choriocarcinoma, and squamous cell carcinoma. Placental site nodule is a benign lesion that can be found years after pregnancy as residue of gestation. It is most often an incidental finding. Small hyalinized nodules of intermediate trophoblasts with variable nuclear atypia and clear and eosinophilic cytoplasm are seen. Placental site nodule should not form a mass like PSTT and ETT, and it also should have low Ki67 (less than 10%) compared with Ki67 greater than 10% in PSTT and ETT. Exaggerated placental site can show similar morphology to these tumors but is usually found after recent gestation. It also should have Ki67 less than 1 (Kurman et al. 2011). Beta-hCG staining can be used to differentiate choriocarcinoma from these two entities. To distinguish squamous cell carcinoma from PSTT and ETT, immunostains can be used to identify squamous cells of squamous cell carcinoma versus the trophoblasts of PSTT and ETT. Both PSTT and ETT can show recurrence and metastasis, however do not appear to be as aggressive as choriocarcinoma.

6 Conclusion

Various lesions, both benign and malignant, occur in the uterus. The most common are benign leiomyomas and malignant endometrial carcinomas while more rare entities include gestational trophoblastic diseases. The mainstay of pathologic diagnosis is morphology; however, ancillary studies such as immunohistochemical staining can be instrumental in diagnosing a lesion. Advances in molecular pathology have led to the identification of certain mutations such as the recently identified translocation in tumors now designated high-grade endometrial stromal sarcomas; undoubtedly, more mutations will be discovered creating a larger role for molecular testing to better classify and possibly treat uterine tumors.

7 Cross-References

- Abnormal Vaginal Bleeding During the Early Reproductive Years
- Conservative Management of Endometrial Cancer
- Diagnosis and Management of Gestational Trophoblastic Disease
- Diagnosis and Management of Postmenopausal Bleeding
- Diagnosis and Management of the Cancer of the Uterus
- Endometrial Hyperplasia
- Management of Abnormal Uterine Bleeding: Later Reproductive Years

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