Introduction:

Among the various categories of diagnostic pitfalls in evaluation of endometrial biopsies, one of the most significant is the category of under-diagnosis of malignancy since this may lead to under-treatment of the patient. This category consists of three scenarios. Selected examples in each category are addressed:

1.) non-neoplastic alterations that may be associated with un-sampled malignancy.
   - Papillary proliferation of endometrium (associated with atypical hyperplasia / endometrioid adenocarcinoma).
   - Morular metaplasia of endometrium (associated with atypical hyperplasia / endometrioid adenocarcinoma, atypical polypoid adenomyoma).

2.) atypia / malignancy that resembles a benign lesion
   - Mucinous adenocarcinoma (may resemble endocervical microglandular hyperplasia).
   - Residual progestin treated adenocarcinoma (may resemble benign endometrium).

3.) high grade cancer that resembles a lower grade cancer:
   - Dedifferentiated endometrial carcinoma (may resemble grade 2 endometrioid adenocarcinoma or endometrioid adenocarcinoma, cored and hyalinized type)
   - Pseudo-glandular serous carcinoma (may resemble grade 1 endometrioid adenocarcinoma).

Papillary Proliferation of Endometrium (PPE)

**Definition:** PPE is an uncommon alteration that consists of simple or complex papillary branching of endometrium without significant nuclear atypia. PPE frequently involves endometrial polyps and has a slight predilection for post-menopausal women. At the lower end of the spectrum of architecture are short non-branching papillary structures growing at the surface of a polyp or endometrium. At the higher end of the spectrum are complex branching papillary structures, often growing within cystically dilated glands; this end of the spectrum may be viewed by some pathologists as equivalent to papillary hyperplasia. Epithelial metaplasia commonly involves PPE, mostly in the form of mucinous metaplasia, however ciliated cells, eosinophilic and squamous metaplasia can also be present.

**Clinical significance:** Although PPE itself does not meet criteria for atypical endometrial hyperplasia or adenocarcinoma, patients may concurrently have or subsequently develop either of these. The extent of PPE (focal distribution, simple architecture versus diffuse distribution, complex architecture) appears to predict this risk. In the single contemporary study with outcome (Ip et al., cited below), 12% of patients with simple PPE had atypical hyperplasia or grade 1 endometrioid adenocarcinoma. In contrast, 81% of patients with complex PPE had concurrent or subsequent non atypical hyperplasia, atypical hyperplasia, and/or endometrioid adenocarcinoma (most of which was grade 1). Patient age and menopausal status do not appear to predict outcome of PPE. Therefore, if PPE is identified in a biopsy, curettage or polypectomy specimen, there is a possibility of un-sampled hyperplasia / carcinoma. Even though the risk seems to be much smaller for simple versus complex PPE, the distinction between these two may be challenging in a biopsy, curettage or polypectomy. For this reason, complete curettage merits consideration to determine whether the entire PPE lesion has been removed and whether any hyperplasia / carcinoma is present; follow up for development of hyperplasia/ carcinoma should also be considered.

- Management of endometrial polypectomy specimens. The discussion of PPE raises an important point about endometrial polypectomy specimens: complete submission of the entire specimen is advised, particularly in post-menopausal women. Concurrent endometrioid adenocarcinoma may be found in other parts of a polyp involved by PPE. Unrelated to PPE, occult microscopic foci of serous carcinoma or clear cell carcinoma may occasionally be present in polyps from post-menopausal women. In some cases, these small foci of cancer may only be present in 1 of several blocks of a large polyp. Therefore, complete examination of polypectomy specimens is worth considering.
- Minimal serous carcinoma  Microscopic foci of endometrial serous carcinoma may exhibit the papillary architecture of PPE however the key distinction between the two is the presence of severe nuclear atypia and brisk/atypical mitoses in serous carcinoma.  PPE does not exhibit the constellation of cytologic malignancy seen in serous carcinoma: increased nucleus to cytoplasm ratio, nuclear size/shape variability, nuclear hyperchromasia, macronucleoli, or brisk/atypical mitoses.  Nor does PPE exhibit aberrant immunophenotype (aberrant p53 and p16) that is characteristic of endometrial serous carcinoma.

- Papillary variant endometrioid adenocarcinoma  Papillary branching can be present as a variant morphology (either the villoglandular type or the small non-villose papillae type) in endometrioid adenocarcinoma.  These tumors usually will exhibit areas that fulfill conventional criteria for endometrioid adenocarcinoma (i.e. complex gland crowding with loss of intervening endometrial stroma) and those areas distinguish it from PPE.

- Syncytial papillary change  The endometrium overlying areas of stromal breakdown may undergo syncytial papillary change, consisting of tufts, buds, stratification, and papillary formation.  Often there is eosinophilic metaplasia.  The cells also usually exhibit syncytial growth and loss of polarization.  The extent of papillae is usually limited and is less well-developed as that of PPE.  The presence of stromal condensation, stromal breakdown, fibrin, neutrophils and other evidence of endometrial breakdown are further clues of syncytial papillary change.  Since this is a reactive, degenerative alteration and does not carry an increased association with hyperplasia or carcinoma, it should be distinguished from PPE.

- Telescope artifact  Mechanical artifact in biopsy or curettage specimens may result in pseudo-papillary structures floating within otherwise simple endometrial glands.  These structures are usually not attached to the lining of the endometrial glands that they are floating in.  Nor will they usually exhibit the degree of mucinous metaplasia, or other metaplasia, seen in PPE, or association with an underlying endometrial polyp.

References:

Morular Metaplasia of Endometrium (MME)

Definition:  MME consist of intraglandular round nests or syncytial sheets of epithelial cells with eosinophilic cytoplasm and round, oval, or slightly spindle shaped nuclei.  The epithelium is often arranged in concentric distribution within the nest.  These so-called morules can not only completely fill the lumen of the endometrial gland but they can also significantly expand and enlarge the diameter of the involved gland, creating a noticeable solid nest, visible at scanning magnification.  There is no nuclear atypia or abnormal mitotic activity.  Central comedonecrosis can be present.  Although some authors refer to MME as squamous morules, there are no features of squamous differentiation such as keratinization or intercellular bridges or immunoeexpression of the squamous marker p63.  MME usually lack immunoeexpression of estrogen receptors but often are positive for CDX2, CD10 and beta-catenin.

In one study (Lin et al, cited below) of 66 cases of MME, 61% of the cases contained benign endometrium (some had focal gland crowding) while 39% contained atypical endometrial hyperplasia.  Among the cases of MME in benign endometrium, 5% subsequently were found to have endometrial cancer compared to 19% among the cases of MME in atypical hyperplasia.  Another study (Houghton et al, cited below) reported that nearly all cases of MME were in the setting of atypical hyperplasia, endometrioid adenocarcinoma, or atypical polypoid adenomyoma.

Clinical significance:  MME on its own does not meet criteria for atypical hyperplasia or carcinoma, however it often occurs in the setting of atypical hyperplasia, endometrioid adenocarcinoma or atypical polypoid adenomyoma.  Therefore it should be considered a diagnostic red flag when identified in a biopsy, curettage or polypectomy specimen and should prompt thorough evaluation for atypical hyperplasia or endometrioid adenocarcinoma.  Complete submission of the biopsy, curettage, polypectomy specimen for microscopic examination should be confirmed.  Even if there are no atypical features in the specimen, the possibility of unsampled atypical hyperplasia or carcinoma cannot be excluded.  Complete curettage should be considered to exclude this possibility.

Differential diagnosis:

- Solid pattern endometrioid adenocarcinoma  Nuclear atypia and mitotic activity of endometrioid adenocarcinoma that grows in a solid pattern distinguishes it from MME, as does large sheets or fragments since MME tends to be small, discrete nests.  Conversely there is usually more cytoplasm in the cells of MME than in solid pattern endometrioid adenocarcinoma.  Concentrically streaming distribution of cells favors MME over adenocarcinoma.
- **Cervical squamous dysplasia or squamous cell carcinoma** Detached fragments of high grade squamous intraepithelial lesion or squamous cell carcinoma can occasionally appear in an endometrial sampling either as an artifact of the sampling procedure capturing cervical tissue during the endometrial sampling procedure or as biologic extension of the cervical pathology into the endometrium. Nuclear atypia, increased nucleus to cytoplasm ratio, and mitotic activity distinguish high grade squamous intraepithelial lesion / squamous cell carcinoma from MME as does diffuse strong p16 immunohistochemical expression.

- **Primary squamous cell carcinoma of endometrium** This is an exceedingly rare entity. Nuclear atypia, mitotic activity and large sheets or fragments distinguishes this tumor from MME. Most primary endometrial squamous cell carcinomas are not associated with high risk HPV so they do not exhibit diffuse, strong p16 immunohistochemical staining. (Bures et al. Int J Gyn Pathol. 2013; 32: 566).

- **Trophoblastic lesion or tumor** Placental site nodule (PSN), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) can exhibit a solid growth pattern and epithelioid appearance that mimics MME. The trophoblast of PSN are embedded in a hyalinized stromal background that is not seen in MME and the distribution of the trophoblast tends to be as scattered individual cells rather than as a cohesive, syncytial aggregate of trophoblast. Nuclear atypia and mitotic activity distinguish PSTT and ETT from MME. Trophoblast, both benign and malignant, are positive for GATA3 nuclear immunohistochemical expression whereas MME is not.

**References:**


**Microglandular hyperplasia (MGH)- like features in Endometrioid Adenocarcinoma**

**Definition:** Features that mimic endocervical MGH may be seen on the surface or at the periphery of some endometrioid adenocarcinomas. Often these are grade 1 tumors with prominent mucinous differentiation. There is a predilection for post-menopausal women.

**Clinical significance:** There is no clinical significance to MGH-like features in an endometrioid adenocarcinoma; it is not a feature that needs to be reported for prognostic or predictive purposes. The significance is purely to pathologists from the standpoint of differential diagnosis in biopsy or curettage specimens because undersampling of this type of tumor may simulate benign endocervical MGH. The biopsy may only contain fragments of a mucinous glandular proliferation that looks exactly like benign endocervical MGH. There may not be any nuclear atypia or mitotic activity. These fragments may not fulfill criteria for either adenocarcinoma or hyperplasia. There may not be any morphologic feature present that suggests concern for anything other than benign endocervical MGH. The only clue may be the patient age, and in some cases the clinical history of an endometrial tumor, endometrial thickening or uterine bleeding. The usual patient age for benign endocervical MGH is pre-menopause. It is not commonly present post-menopause. Conversely, many MGH-like endometrioid adenocarcinomas arise in post-menopause. Therefore, an important diagnostic rule of thumb is to consider the patient age when considering a diagnosis of endocervical MGH in an endometrial sampling: if peri- or post-menopausal age, then the possibility of undersampled adenocarcinoma with MGH-like features should be considered.

A descriptive diagnosis is advised in this setting, such as “complex mucinous glandular proliferation”, with a discussion of the differential diagnosis of undersampled adenocarcinoma versus endocervical MGH. These patients should undergo further clinical and radiologic evaluation to exclude undersampled cancer, including thorough endometrial curettage. The likelihood of finding adenocarcinoma on subsequent hysterectomy is partly related to the degree of architectural complexity. Although some studies have reported a correlation between architectural complexity and likelihood of undersampled cancer, this can be challenging in actual practice. The presence of MGH-like glands in an endometrial sampling in peri- or post-menopausal woman, regardless of the degree of complexity, should be mentioned and discussed.

**References:**


Residual Progestin-Treated Endometrioid Adenocarcinoma

Context: Hysterectomy is the primary treatment for endometrial cancer, however, a subset of pre-menopausal patients who wish to preserve fertility may potentially delay hysterectomy by using high dose progestin treatment, delivered in any of a variety of methods including oral, intramuscular, vaginal delivery, or by progestin-coated intrauterine device (IUD). This strategy may potentially work in clinically stage IA, grade 1 endometrioid adenocarcinoma or atypical hyperplasia but not in any higher stage or grade tumor. The strategy works by suppression of the estrogen pathway via several mechanisms: down-regulation of estrogen receptors; increased conversion of estradiol to estrone, which is a weaker estrogen, and promotion of a secretary, non-mitotic state (Gressel et al. Int J Gynecol Ob; 2015; 131: 234). Successful progestin treatment (e.g. complete suppression of cancer or atypical hyperplasia) is defined as complete absence of any abnormal endometrial glandular architecture or atypical nuclear features on surveillance endometrial sampling. About 65% to 75% of appropriately selected patients may achieve complete suppression on progestin treatment. Those patients may then proceed with pregnancy plans and delay hysterectomy until afterwards (2016 NCCN Guidelines, www.nccg.org). Complete suppression does not equate to complete cure because most of these patients who ultimately elect for hysterectomy will be found to have atypical hyperplasia or cancer in the hysterectomy specimen; thus, the progestin-induced suppression is temporary (Gunderson et al; 2014). Overall, about 50% of patients achieve durable complete suppression. The time required to achieve complete suppression is difficult to define based on the literature but may take around 7 to 9 months (Wheeler et al 2007). In the interim, surveillance endometrial sampling is essential to this strategy. The 2016 NCCN Guidelines recommend surveillance sampling at 3 to 6 month intervals (www.nccn.org). The purpose of surveillance is to determine if there is a progressive reduction in the extent of cancer or atypical hyperplasia, compared to the prior sampling. If so, then this suggests that there is response to the progestin treatment strategy and justifies continuation of progestin-treatment and further surveillance sampling. However, if there is progression at any point, then hysterectomy should be considered. Similarly, if there is no response by approximately 7 to 9 months, then this approach is unlikely to be successful (Wheeler et al 2007) and hysterectomy should be considered.

Morphologic Findings: Progestin-therapy causes changes in the non-neoplastic endometrium and in the neoplastic endometrium. The non-neoplastic endometrium shows features similar to those in patients on long term oral contraception: glandular atrophy and stromal pseudo-decidualization. The neoplastic endometrium, if responsive, may show reduction in gland complexity, gland cellularity, nuclear grade, mitotic activity, and nucleoli. The tumor cells may acquire eosinophilic cytoplasm and produce luminal secretions. Squamous differentiation may also be prominent. Therefore, partially-treated cancer or atypical hyperplasia may not exhibit features that fulfill conventional diagnostic criteria. The presence of any degree of abnormal gland architecture (crowding, cribriform or papillary growth) or abnormal nuclei (nucleoli, enlargement) should be interpreted as residual partially suppressed neoplasm. Immunohistochemistry is usually not necessary for evaluation of these types of specimens but it is known that partially suppressed cancer will exhibit decrease in Ki-67 index and decrease in estrogen receptors (ER) and/or progesterone receptors (PR) (Zaino et al, 2014). There are no pathologic predictors of response of atypical hyperplasia / grade 1 endometrioid adenocarcinoma to progestin therapy. The degree of pre-treatment immunohistochemical expression of ER or PR does not appear to be associated with response to progestin therapy.

The pathology report of surveillance samples should document findings in both the non-neoplastic endometrium and the state of the neoplastic lesion, relative to the most recent sampling in terms of quantity and quality. Therefore, it is important to review the slides of the pre-treatment endometrial sampling and any surveillance samplings in the interim. If the findings fulfill standard criteria for cancer or atypical hyperplasia then the report should document those diagnoses as such.

Example diagnosis:
1. Residual grade 1 endometrioid adenocarcinoma.

If the findings do not fulfill standard criteria but are atypical, then the report should communicate the presence of the abnormality as well as provide a comparison relative to most samplings.

Example diagnosis:
1. Residual atypical glandular proliferation, consistent with partially suppressed endometrioid adenocarcinoma; see comment.
Comment: Some fragments exhibit endometrial gland crowding with focal papillary branching; although these findings do not meet criteria for adenocarcinoma, in this particular setting of progestin treatment, they represent partially suppressed cancer. Compared to the most recent surveillance sampling, the amount of atypical lesion is less in the current specimen. The remainder of the fragments exhibit features of benign endometrium with progestin treatment effect.

If there are no residual atypical findings, then the report should communicate this specifically and, ideally, provide comparison to the most recent sampling.

*Example diagnosis:*
1. No residual gland abnormalities; see comment.

Comment: There is no residual abnormal glandular architecture or abnormal cytologic features. Slides of the patient's most recent sampling containing residual abnormality were reviewed and none of those features are present in the current specimen. The entire sampling consists of benign endometrium with features of progestin treatment.

Because some patients who achieve complete suppression while on progestin treatment may subsequently develop endometrial cancer if the progestin treatment is stopped (Wheeler et al; 2007; Gunderson et al; 2014), complete suppression should not be equated to a complete cure. Clinical consideration of hysterectomy is still indicated after fertility goals have been achieved (2016 NCCN Guidelines, www.nccn.org).

*Diagnostic Pearl:* On occasion, the clinical history of progestin-treatment of endometrial cancer may not be communicated to the pathologist evaluating an endometrial sampling. This may result in under-diagnosis of glandular abnormalities that fall short of a criteria for atypical hyperplasia or cancer. However, if there is evidence of progestin-treatment in the benign endometrium in the sampling, then that should prompt inquiry into the clinical history. In other words, a sampling that contains focal endometrial gland crowding or branching plus background atrophy and stromal pseudo-decidualization is a scenario that should raise concern that the patient has a prior diagnosis of cancer or atypical hyperplasia. The significance of focal gland crowding in this setting is very different than in a patient with no prior history of cancer or progestin treatment.

*References:*

**Glandular-pattern Serous Carcinoma**

*Definition:* Endometrial serous carcinoma can occasionally grow in a pure tubuloglandular pattern that mimics the architectural pattern of atypical endometrial hyperplasia or grade 1 endometrioid adenocarcinoma.

*Clinical Significance:* The surgical management of a patient with an endometrial sampling is strikingly different between these two scenarios (2016 NCCN Guidelines, www.nccn.org). Endometrial serous carcinoma, regardless of the growth pattern or size in an endometrial sampling, is a high grade cancer that generally is managed by total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para aortic lymph node dissection and omentectomy. While hysterectomy is the mainstay treatment for grade 1 endometrioid adenocarcinoma, the same extent of additional surgery is not necessarily indicated in every patient. Total hysterectomy without extensive surgical staging may be appropriate for certain carefully selected patients. Therefore, under-diagnosis of glandular pattern serous carcinoma in a biopsy may result in incomplete surgical management.

The key diagnostic finding in glandular pattern serous carcinoma is the discordance between the low grade architecture (simple tubuloglandular growth) and the high grade cytology: moderate to severe nuclear pleomorphism, hyperchromasia, high nucleus to cytoplasm ratio, macronucleoli, brisk and atypical mitotic figures. This constellation of cytologic features is not seen in grade 1 endometrioid adenocarcinoma. Thus, a good practice is confirmation of cytologic features at high magnification when contemplating a diagnosis of atypical hyperplasia or grade 1 endometrioid adenocarcinoma. If the cytologic features are low grade, then the diagnosis is confirmed. If they are high grade, the possibility of serous carcinoma should be considered.
Immunohistochemical confirmation of endometrial glandular pattern serous carcinoma is similar to conventional patterns: aberrant p53 and p16. Aberrant p53 is defined as either strong diffuse nuclear staining in more than 80% of the tumor cells or as complete absence of any staining in any nuclei. In the latter case, it is important to verify the stain is working by identifying wild-type staining (patchy weak staining) in the background stroma, lymphocytes and benign epithelium. Aberrant p16 is defined as strong diffuse cytoplasmic staining.

**Diagnostic Pearl:** Large endometrial polyps are one of the settings in which glandular pattern serous carcinoma may be found. The growth pattern may subtend and, at low magnification, may resemble normal gland crowding within a polyp or atypical hyperplasia in a polyp, or grade 1 endometrioid adenocarcinoma in a polyp. High magnification evaluation of the cytology is advised in evaluation of any glandular abnormality within a polyp. In addition, microscopic examination of the entire polypectomy specimen is advised since the size of the serous carcinoma in a polyp may be microscopic.

**References:**


**Dedifferentiated Endometrial Carcinoma**

**Definition:** Dedifferentiated endometrial carcinoma (DDEC) is a tumor that contains well-differentiated endometrioid adenocarcinoma plus undifferentiated endometrial carcinoma (UEC). Although uncommon, it is an important entity to be aware of because it can be under-recognized, especially in endometrial samplings, and misinterpreted as grade 2 endometrioid adenocarcinoma. This is problematic since DDEC is an aggressive cancer that requires management as a high grade cancer.

The main pattern of UEC is diffuse sheets of monomorphic, moderately atypical cells that lack cell-cell adhesion, admixed with extensive geographic necrosis. There are no tubulo-glandular, papillary or squamous features. The tumor cells may contain rhabdoid cytoplasm. Another pattern of UEC is corded and trabecular growth of tumor cells within myxoid stroma. Both patterns of UEC may be present, or just one. The areas of UEC directly abut areas of lower grade endometrioid adenocarcinoma, without blending or merging between the two components; this combination is referred to as DDEC. Pure UEC (i.e. without any component of lower grade endometrioid adenocarcinoma) may also occur, albeit less frequently than DDEC.

The diagnosis of UEC (whether pure or mixed as DDEC) can be confirmed by immunohistochemical loss of epithelial differentiation (negative or focal EMA, keratin), loss of Mullerian differentiation (usually negative PAX, CK7, ER), loss of cell-cell adhesion (negative E-cadherin), loss of SWI-SNF complex proteins (about half are negative for BRG1 (SMARCA4); BRM (SMARCA2) or INI1/ BAF47 (SMARCB1), and loss of mismatch repair protein (about half show loss of MLH1/PMS2).

**Clinical Significance** An otherwise low grade endometrioid adenocarcinoma that contains only a minority component of UEC may still carry the same poor prognosis as pure UEC and should be classified as DDEC regardless of how little UEC is present. The main diagnostic pitfall is misinterpretation of the solid pattern of UEC as solid pattern endometrioid adenocarcinoma and therefore an overall diagnosis of pure grade 1 or grade 2 endometrioid adenocarcinoma. The key diagnostic features that distinguish UEC from grade 2 endometrioid adenocarcinoma are tumor cell discohesion, rhabdoid cytoplasm, geographic necrosis, and lack of direct merging of the solid and glandular components. Presence of any of these features should prompt consideration of a component of UEC and immunohistochemical confirmation.

Conversely, the corded and hyalinized type of endometrioid adenocarcinoma (so-called CHEC) can be misinterpreted to be DDEC due to the presence of corded growth and myxoid stroma. A key feature of CHEC is the direct blending of the endometrioid adenocarcinoma component with the corded and hyalinized component, in contrast to the lack of merging of patterns in DDEC. Keratin and EMA immunohistochemistry will be positive in CHEC but absent or focal in DDEC.

**Diagnostic Pearl:** The presence of notable necrosis in an endometrial sampling that otherwise contains lower grade endometrioid adenocarcinoma should raise diagnostic concern for unsampled components of a higher grade tumor, such as DDEC or carcinosarcoma and concern for unsampled high stage growth, such as myoinvasion or cervical invasion. A benign explanation for the necrosis, such as degeneration of a polyp or submucosal leiomyoma, is possible. Degeneration of a low grade endometrioid adenocarcinoma could also possibly result in necrotic debris. Therefore, necrotic debris in an endometrial sampling is important to recognize but is not pathognomonic for an aggressive tumor. Abundant necrosis is worth documenting in the pathology report and then discussing the differential diagnosis. Doing so permits the clinician to decide whether additional sampling (i.e. curettage) is needed before making a treatment decision.
References:


